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PROGNOSIS OF LEFT ATRIAL REMODELING AFTER A MYOCARDIAL INFARCTION: A CMR STUDY

Rôle pronostique du remodelage de l'oreillette gauche en post infarctus du myocarde: étude IRM

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Liste des abréviations

LA :	Left atrial
LAVI :	Left atrial volume index
MI :	Myocardial infarction
CMR :	Cardiac magnetic resonance
HR :	Hazard ratio
LVEF :	Left ventricular ejection fraction
LVR :	Left ventricular remodeling
HF :	Heart failure
LAD :	Left anterior descending artery
STEMI :	ST-Elevation Myocardial Infarction
CI :	Confidence interval
AF :	Atrial fibrillation
MACE :	Major adverse cardiac events

Plan

INTRODUCTION

Following myocardial infarction (MI), molecular, cellular and histological changes in structure and function of the heart may occur, defining left ventricular remodeling (LVR). At a certain point, these phenomena relate to adaptative mechanisms, secondary to the loss of contractile function. Nevertheless, when outreached, LVR might lead to left ventricle (LV) dilation and depressed function, and has been identified to be a frequent (1), and a major cause of heart failure (2,3) following MI.

Left atrial (LA) size is known to be a prognostic predictor across a wide spectrum of cardiac diseases (4,5,9,12). Out of many methods of measurements, maximal LA volume indexed to body surface area is the most strongly associated with cardiovascular disease (5). Moreover, there are strong evidence of the implication of the LA dilation in the prediction of outcomes, in particular for developing heart failure (6). As the left atrium (LA) is connected to the left ventricle, it is affected by the same constraints as the LV, but only a small number of studies focused on the LA remodeling after MI.

We sought to evaluate, by the use of cardiac magnetic resonance (CMR), the prognostic impact of LA dilatation and remodeling after a first STEMI.

METHODS

In this study, 446 patients presenting a first STEMI were enrolled consecutively and prospectively between May 2006 and February 2018 in one single university hospital. All patients were treated with percutaneous coronary intervention, and a TIMI flow grade 3 was obtained. All patients gave written informed consent and underwent CMR at baseline (day 6 [IQ range 4;8]), at 3-month follow-up (day 98 [IQ 93;105]). Exclusion criteria were a coronary bypass grafting, age <18 years, a major comorbidity limiting life expectancy in the year and a contra indication for CMR. The protocol was approved by the local institutional ethics committee, and the study was conducted in accordance with the declaration of Helsinki and local regulatory requirements. CMR at 3 months was not performed for various reasons: one death, one defibrillator implantation and 16 refusals. Left atrial volume could not be assessed in some patients due to CMR acquisition.

1. Cardiovascular magnetic resonance

CMR was performed using either 1.5 or 3.0 T imager (Avanto or Skyra, Siemens, Erlangen, Germany) with the application an 8-element phased-array cardiac receiver coil. Cine CMR was performed using the steady-state free precession sequence in multiple short-axis, and four chamber long-axis views covering the entire left ventricle (LV). The typical in-plane resolution applied was 1.2 mm x 1.2 mm with a 7 mm section thickness and no gap (matrix : 155 x 288 ; temporal resolution : 45-50 msec).

All CMR exams were injected with gadolinium contrast agents at a dose of 0.2 mmol/kg (gadoterate meglumine, DOTAREM, Guerbet, Aulnay-Sous-Bois, France).

Late gadolinium enhancement (LGE) sequences were performed 12-15 min after the injection, by means of a standard 2D segmented inversion recovery gradient-echo pulse

sequence. An initial inversion time scout sequence was conducted to determine the optimal inversion time. Contiguous short axis and four-chamber long-axis slices covered the entire ventricle. Typical parameters used were : in-plane resolution of 1.6 mm x 1.6 mm, with a 7 mm section thickness ; TE 4.66 msec ; flip angle 30° ; image acquisition triggered at every other heartbeat.

2. Image analysis

The CMR images were transferred to a workstation for analysis and calculation (Qmass 7.1, Medis, Leiden, The Netherlands). On all short-axis cine slices, the endocardial and epicardial borders were outlined manually, on end-diastolic and end-systolic images, excluding the trabeculae and papillary muscles. LV end-diastolic and end-systolic volumes, hence LV mass, were determined. Mean intra-observer reproducibility was published elsewhere (7). Infarct size was quantified on late gadolinium enhancement images by means of the full-width at half-maximum method (8), corresponding to the sum of the hyper-enhanced area measured on all sections, given as a percentage of total LV mass. The variability assessment for LV volumes and infarct size, produced good results, published elsewhere (7).

3. Left atrial measurement

Maximal left atrial volume index (LAVI) was assessed using the contiguous four-chamber views with manual delineation at the end of the left ventricular systole (figure 1). Data were reported to body surface area. Among the 446 patients, 356 were included with a valuable measure of LA volume at baseline, and 323 at 3 months (figure 2).

4. Outcomes

Cardiovascular outcomes were prospectively recorded up to 5 years after MI and were adjudicated after consultation of medical records and the computer database by two physicians (who were unaware of clinical and CMR data).

Major adverse cardiac event (MACE) was a composite outcome including Death, HF, AF and stroke.

5. Statistical analysis

All statistical tests were conducted by means of a commercially available statistical program (SPSS 15, SPSS Inc., Chicago, Illinois, USA).

Data are expressed as frequency, with percentage for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous variables.

For the analysis, baseline represents the period of the MI and 3-months the delay from MI in the follow-up. Reverse remodeling correspond to a decrease in LA volume at 3-months.

Changes in CMR parameters over time were compared by using a Wilcoxon rank-sum test.

Changes in LA and LV volumes over time were compared using Pearson's correlation test.

Cox regression models were applied for the purposes of explaining long-term MACE, and 3-month to long-term MACE afterwards. We tested specific interactions between LAVI and gender, prior history of hypertension, coronary artery disease, anterior infarction, CPK peak and heart failure during hospitalization. Only significant interactions were included into the multivariate Cox models. The proportional-hazard assumptions were tested by analyzing the Schoenfeld residuals. A p-value <0.05 was considered significant for all analyses.

RESULTS

1. Characteristics of the population

In our cohort, 368 patients (82.5%) were men, with a mean age of 58.4±6.4. 46.6% were current smokers, 32.7% had hypertension, and 11.9% had diabetes mellitus. Table I shows the baseline characteristics of the study population.

Optimal medical treatment was used with 88% of patients having a angiotensin-converting-enzyme inhibitor (ACEI) and 95.5% a beta blocker.

2. CMR parameters

Table II represents the baseline and follow-up CMR parameters.

Mean LVEF was 46.6±9.7% at baseline and 50.1±10.3% at 3 months.

Infarct size (% of LV mass) was 15.9±10.8% at M0 and 14.4±9.6% at M3.

3. LA volume

There was a significant decrease in the mean LAVI over time, with respectively 43.9 ± 10.4ml vs 42.8 ± 11.1ml, p=0.003, at baseline and 3-month (figure 2).

This reverse remodeling was absent in HF patients at baseline: LAVI was 45.7±11.8 ml at baseline vs 45.9±12.2 ml at 3-month, p=0.81.

4. LA remodeling and outcome

During a median follow-up of 850 days, a total of 31 patients (9,6%) experienced MACE : 1 death, 19 hospitalization for heart failure, 5 atrial fibrillation, 8 stroke (17 MACE during the first 3-month and 14 MACE after 3 months).

LAVI at baseline was related to MACE: hazard ratio [HR] 1.393 [95% confidence interval (CI) : 1.010-1.922, p= 0.044 after multiple adjustments including LVEF, age, level of CK and the presence of heart failure at baseline (Table III).

A significant interaction between LAVI and HF during initial hospitalization was clearly distinguished, with a higher LAVI proving predictive of excessive MACE solely in HF patients (HR: 2.046 with 95%CI: [1.278;3.274] ; p=0.003).

Figure 4. represents Kaplan-Meier plots analysis concerning the risk of MACE according to follow-up for total population (A), patients with (B) and without (C) heart failure at baseline.

LAVI change between baseline and 3 months showed predictive for events that occurred after the 3rd month. It remained significant after adjustments with baseline LAVI (HR 1.031, 95%IC: [1.003;1.06], p=0.027), but significance was lost after adjustments to LVEF, CPK, anterior infarction : HR 3.045, 95%IC: [0.826;11.227], p=0,094 (Table IV). Only 3-month LVEF<40% was related to MACE with a HR at 5.555 and 95%IC [1.577;19.607], p=0.008 in multivariate analysis.

DISCUSSION

In this study concerning a prospective cohort of STEMI patients with successful reperfusion and optimal medical therapy, the major findings were:

1) Baseline LAVI is a powerful correlate for long-term MACE among patients who presented HF during hospitalization.
2) LA remodeling between baseline and 3-months is a risk marker for long-term prognosis but failed to reach significance after adjustments for cofounders.

LA maximum volume is a well-known predictor in various diseases (11). Dilation of the LA (one of the aspects of LA remodeling) is mediated by the increase of LA pressure or volume(11). LA remodeling is influenced by the same mechanisms as LV diastolic function because the LA is directly exposed to LV pressure through the open mitral valve (12). Abnormal LV relaxation and filling pressure may be related to the formation of scar tissue following MI. LA dilatation occurs in 15% to 45% of patients post MI (9, 20). In our cohort, we found a global decrease in LA volume at 3 months. This finding may be related to a pressure overload in the LV at the acute phase. Successful reperfusion and wide use of optimal medical therapy (beta blockers and ACEI), may explain the decrease in LA volume at 3 months (13,14). In a cohort of hypertensive patients, Kokubu and al (15) showed improvement in LA volume and function when treated by ACEI or ARB. This reverse remodeling was absent in the context of HF at baseline.

LA as a risk factor

LAVI has been shown to predict outcomes in several cardiovascular pathology such as: AF, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy and ischaemic heart disease (4,7,9). Most of these studies concerned echocardiographic evaluation of the LA. Only a small number used CMR to analysis LA remodeling. Kyhl and al (16) a CMR study, showed that LA maximal and minimal volume at the acute phase of MI, were related to major adverse cardiac events (all-cause mortality, reinfarction, heart failure and implantation of cardiac defibrillator) but did not adjust to confounders. In our study, each 10ml/m² increase in LA volume at baseline, increased the risk of MACE by 39.3%. The interaction we described between LAVI and HF suggest that baseline LAVI is, at least influenced by hemodynamic condition of the MI, but present a pejorative incremental impact on prognosis.

Yamaguchi and al (17) in 2013, showed, in an echocardiographic study, LA reverse remodeling in ~50% of patients after diagnosis of acute heart failure and this remodeling was predictor for recurence of heart failure. As a chronic marker of diastolic dysfunction, baseline LAVI also reflects prior cardiac disease of the patients and was not only reliable to acute MI (11). After an acute MI, patients with higher chronic LV filling pressure and worse previous diastolic dysfunction have lower haemodynamic cardiac reserve that helps to withstand an acute decrease in myocardial contractility (8).

Change in LAVI between baseline and 3-month were associated with MACE but only in univariate analysis. Meris and al (18) in an echocardiographic study (VALIANT) with high risk MI, found a significant increase in major adverse cardiac event when studying LA remodeling between baseline and 1-month. An increase in LAVI of 9mL/m² was the cut-off value associated with death or hospitalization for heart failure. In our study we included unselected STEMI patients (large or trivial infarction and with or without HF) and we aslo found a prognostic role of LAVI. Moreover, our cohort was most recent with successful

reperfusion in all cases and large optimal medical treatment. It could explain the small number of events and why we didn't found a significant relation between LAVI remodeling at 3 months and MACE but only a trend.

This findings, in a large cohort of STEMI patient with wide use of reperfusion therapy, support the interest of systematically analyzing and quantifying the dimensions of the left atrium in the context of MI. It could help in tailoring individual follow-up considering risk markers to develop MACE after MI. This is consistent with the majority of articles in the literature that support assessment of left atrial volume in many cardiovascular diseases (19,20,21). This evaluation seems all the more necessary in patients at risk, namely those who presented with heart failure at the initial phase of MI.

Technical issues and limitations

Our study has limitations inherent to retrospective measurement of LA volumes. We did not quantify LA fibrosis because of the need of dedicates sequences of CMR. This may be an important point because it reflects LA dysfunction, which is not totally explain by the LA dilatation. LA volume is only one parameter that reflect the LA complex function.

LA function was not evaluated in this study. It could have been interesting to compare LA dilatation with LA minimal volume and LA ejection fraction by CMR, in order to explore the different components of atrial function (booster pump, reservoir and conduit). Diastolic echocardiographic parameters such as Doppler-derived mitral deceleration time, Doppler tissue analysis and atrial strain, could have been useful to compare with CMR measures. Nevertheless, Losi and al (22) in a echocardiographic study of patients with HCM, found only a correlation with LAVI and not with Doppler parameters to predict AF. In a same manner, Montserrat in a cohort of patient treated by ablation for paroxysmal AF, showed that only LA maximal volume at baseline was correlated with recurrence of AF after ablation (23).

Moreover, we did not assess the presence of mitral regurgitation which could have influenced LA remodeling. Recently, in a swine model of MI, Aguero and al (24) showed deleterious effect of MI, in particular with proximal occlusion of the proximal left circumflex artery (which contain LA branch), on volume and function of the LA. Mitral regurgitation seemed also to be involved in LA remodeling. This results highlight the complex physiopathology of LA dilation and dysfunction. Biomarkers (like the brain natriuretic peptide) were not available in our cohort.

CONCLUSION

In our modern cohort of reperfused STEMI with optimal medical treatment, baseline LAVI was a prognostic marker for major cardiovascular events, specifically among patients who presented HF during initial presentation. LAVI volume change between baseline and 3-month tended to predict long-term outcomes.

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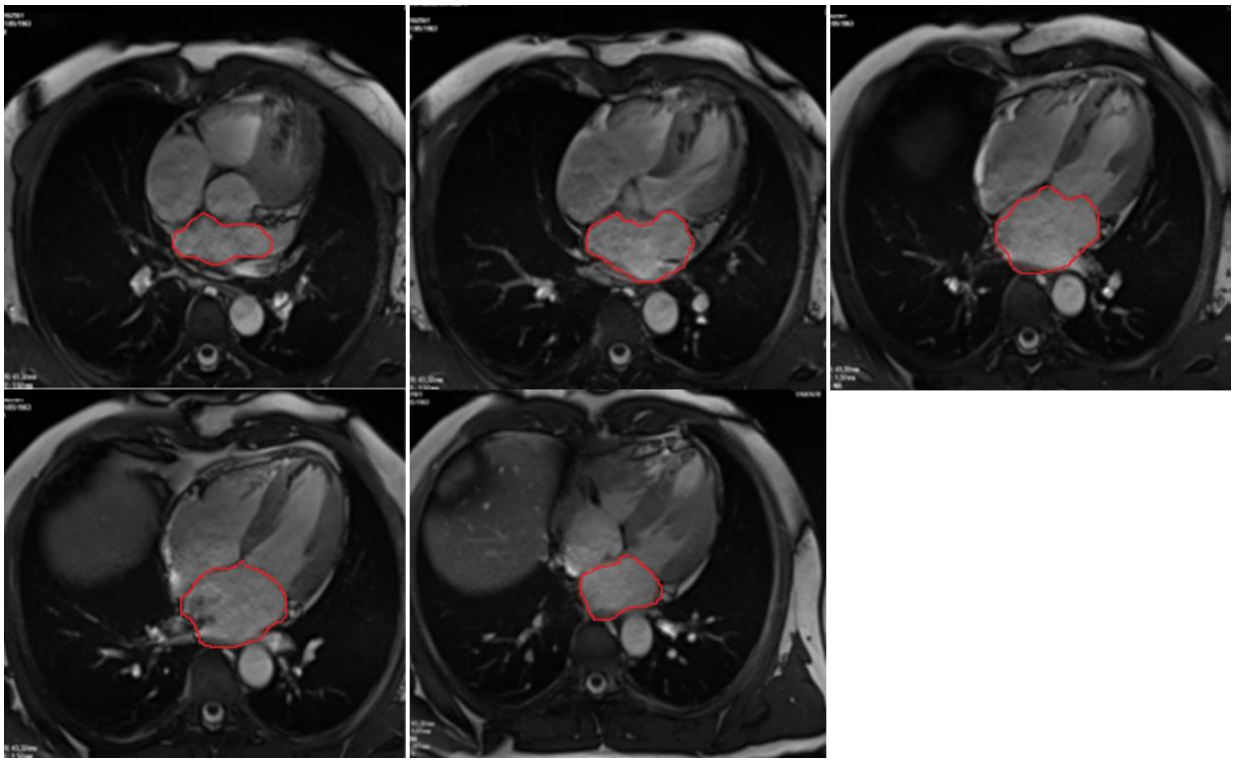
LISTE DES FIGURES

Figure 1. LAVI assessment by CMR



Five contiguous and consecutive images were required to assess the LAVI.

Figure 2. Flow chart

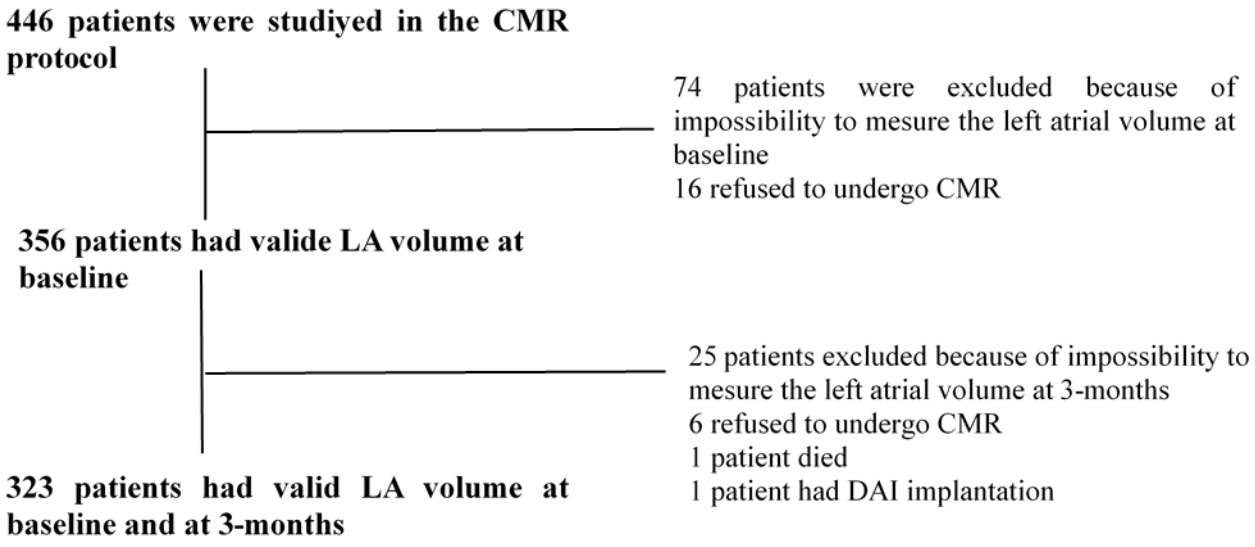
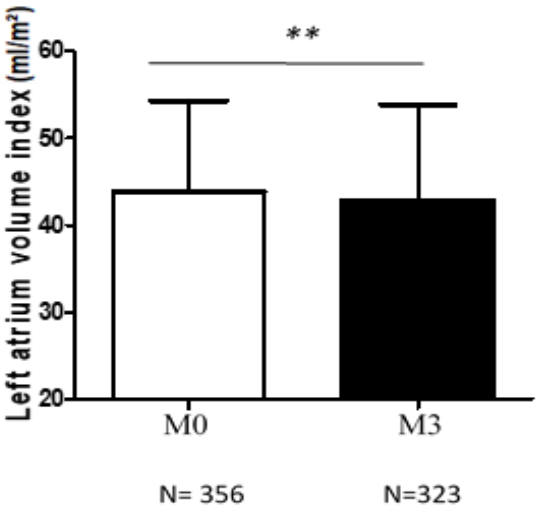
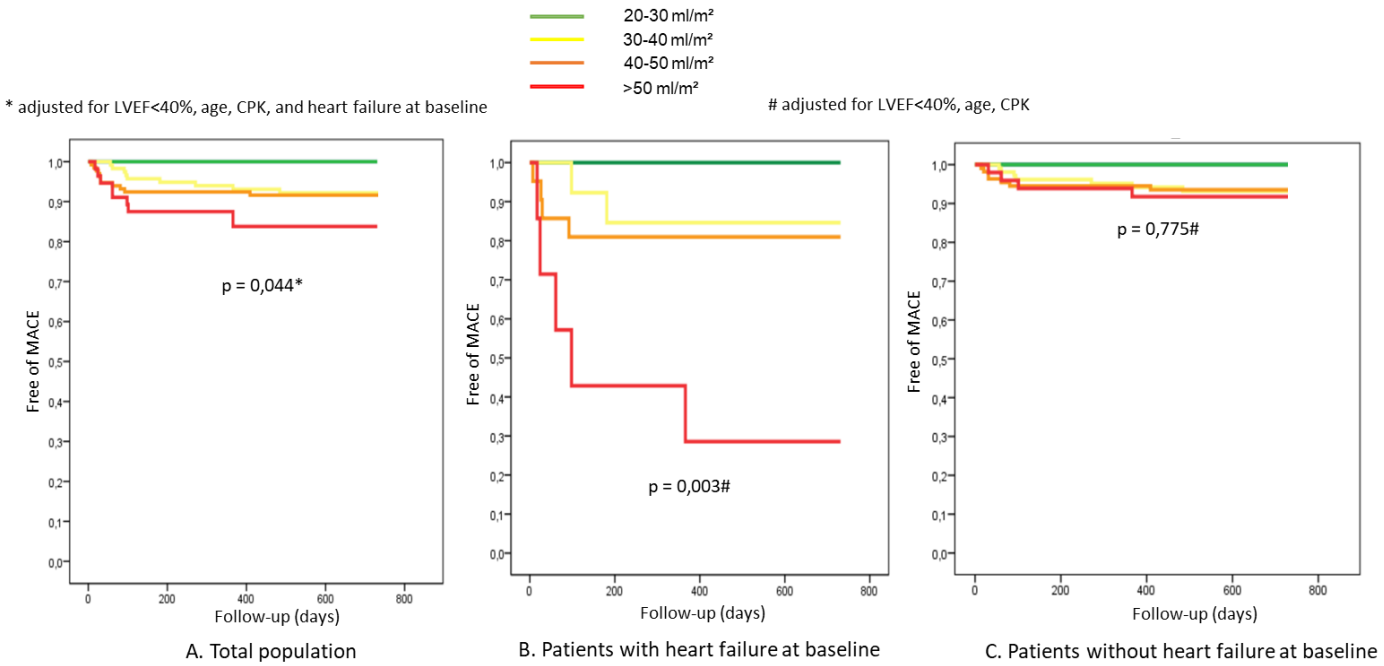


Figure 3. LA volume index (ml) at baseline and 3-months follow-up



LA : Left atrium ; M0 : baseline ; M3 : 3-month
LA volume at M0 : 43.9 ± 10.4 ml and at M3 : 42.8 ± 11.1 ml, p= 0.003

Figure 4. Kaplan-Meier plots according to LAVI



A. Total population

B. Patients with heart failure at baseline

C. Patients without heart failure at baseline

n= 356

n=51

n=303

LISTE DES TABLEAUX

Table I. Study population

Parameters	Mean±SD
Age (years)	58.4±6.4
Gender, males	368 (82.5%)
Poids (kg)	78.4±14.6
Taille (cm)	170.4±8.1
BMI (kg/m²)	26.8±4
HTA (mmHg)	146 (32.7%)
Diabetes mellitus	53 (11.9%)
Dyslipidemia	238 (53.7%)
Current smoker	207 (46.6%)
Primary PCI	439 (100%)
Monotroncular lesion	267 (60%)
Success of revascularization	443 (100%)
In-hospoital heart failure	73 (16.5%)
Time to reperfusion (min)	229.2±190.1
SBP in cath lab (mmHg)	141.5±26.8
DBP in cath lab (mmHg)	88.3±18.6
HR in cath lab (bpm)	74.3±19.9
Creatinine (µmol/l)	80.8±22.5
CPK max (UI/l)	2884.1±2252.5
HbA1c (%)	5.9±1

Medication at discharge	Mean±SD
Statine	
Aspirine	436 (99.1%)
Other antiplatet agent	442 (100%)
ACEI	442 (100%)
Beta blocker	389 (88%)
	422 (95.5%)

Table II. CMR characteristics

Parameters	Baseline	3-month	
	Mean ±SD	Mean±SD	p
LV EDV (ml/m²)	90.3±20.1	89.6±26.1	0.52
LV ESV (ml/m²)	48.8±17,1	45.8±20.5	<0.001
LV mass (g/m²)	58.3±12.5	51.4±13	<0.001
LVEF (%)	46.6±9.7	50.1±10.3	<0.001
Infarct size (% of LV mass)	15.9±10.8	14.4±9.6	0.17
LAVI (ml/m²)	43.9±10.4	42.8±11.1	0.003

Table III. MACE after hospital discharge

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p	HR (95%CI)	p
Age (years)	1.045[1.017;1.073]	0.001	NS	NS
BMI (kg/m²)	1.014[0.944;1.089]	0.68	/	/
Sexe (male/female)	0.991[0.412;2.382]	0.98	/	/
LVEF <40%	0.165[0.089;0.306]	<0.001	2.551[1.104;5.882]	0.028*
Infarct size (%)	1.061[1.034;1.089]	<0.001	/	/
LV EDV index (mL/m²)	1.009[0.994;1.024]	0.19	/	/
CPK (per 500IU/L)	1.108[1.075;1.143]	<0.001	1.172[1.091;1.260]	<0,001*
LV ESV index (ml/m²)	1.025[1.012;1.038]	<0.001	/	/
LV mass index (g/m²)	1.024[1;1.048]	0.045	/	/
LAVI at baseline (all cohort)	1.378[1.029;1.845]	0.031	1.393[1.010;1.922]	0.044*
- LAVI in HF subgroup	1.547[1.047;2.285]	0.028	2.046 [1.278;3.274]	0.003$
- LAVI in no HF subgroup	1.143[0.761;1.716]	0.519	0.939[0.593;1.477]	0.775$
HTA	1.389[0.76;2.538]	0.28	/	/
Smoking	0.632[0,374;1.068]	0.087	/	/
Diabetes mellitus	1.387[0,629;3.059]	0.41	/	/
Anterior infarction	1.816[0,989;3.333]	0.054	/	/
Time to reperfusion (min)	0.999[0,998;1.001]	0.78	/	/
Heart failure in-hospital	4.384[2.365;8.125]	<0.001	NS	NS

* adjusted for LVEF<40%, CPK, age, heart failure at baseline

$ adjusted for LVEF<40%, CPK, age

Table IV. MACE after 3-month

Variables	Univariate analysis		Multivariate analysis*	
	HR (95%CI)	p	HR (95%CI)	p
Age (years)	1.046[1.005;1.09]	0.026	/	/
BMI (kg/m²)	0.98[0.875;1.098]	0.73	/	/
Sexe (male/female)	25.486[0.082;7885.22]	0.26	/	/
LVEF <40%	5.847[2.336 ;14.705]	<0.001	5.555[1.577;19.607]	0.008
Infarct size (% of LV mass)	1.065[1.026;1.106]	<0.001	/	/
CPK (range of 500UI/L)	1.136[1.044;1.247]	0.003	NS	NS
LV EDV index 3-month	1.015[0.997;1.034]	0.082	/	/
LV ESV index 3-month	1.027[1.01;1.045]	0.001	/	/
LV mass index 3-month	1.019[0.978;1.062]	0.35	/	/
LAVI index 3-month	1.043[1.001;1.087]	0.041	/	/
Variation of LAVI baseline-3-month	1.03[1.002;1.058]	0.033	3.045[0.826;11.227]	0,094
HTA	1.056[0.401;2.779]	0.91	/	/
Smoking	0.487[0.216;1.102]	0.08	/	/
Diabetes mellitus	1.368[0.392;4.773]	0.62	/	/
Anterior infarction	2.575[1.108;5.979]	0.028	NS	NS
Time to reperfusion	1[0.998;1.002]	0.78	/	/
Heart failure in-hospital	4.31[1.67;11.121]	0.002	/	/

* adjusted for CPK, LVEF<40%, anterior infarction

Table des matières

PASCAUD Adrien

Rôle pronostique du remodelage de l'oreillette gauche en post infarctus du myocarde : étude IRM

RÉSUMÉ

Introduction: L'infarctus du myocarde (IDM) peut conduire au développement d'un remodelage ventriculaire qui engendre dilatation et dysfonction ventriculaire gauche (VG). Ce remodelage est reconnu comme une cause majeure de développement d'insuffisance cardiaque (IC). L'oreillette gauche (OG) est aussi connue pour prédire les évènements cardiaques dans de nombreuses pathologies.
Nous avons analysé le remodelage de l'OG dans le contexte d'IDM par imagerie par résonance magnétique (IRM) et évalué son rôle pronostique.
Méthode: Analyse rétrospective du volume de l'OG par IRM à la phase initiale de l'IDM puis à 3 mois dans une cohorte d'IDM.
Résultats: Dans notre étude, 323 patients ont été analysés. On notait une diminution du volume de l'OG à 3 mois (43,9 ± 10,4 ml vs 42,8 ± 11,1 ml, p= 0,003). Le volume de l'OG initial était un facteur pronostique principalement chez les patients ayant présenté de l'IC à la phase initiale : HR 2.046, IC95% [1.278-3.274] p=0.003. Le remodelage de l'OG à 3 mois montrait une tendance à prédire également les évènements (p=0.094)
Conclusion: On retrouvait un remodelage inverse de l'OG à 3 mois. Le volume initial de l'OG constituait un facteur pronostique chez les patients ayant présenté de l'IC. Le remodelage de l'OG montrait une tendance à prédire les évènements à long terme.

Mots-clés : Infarctus du Myocarde ; imagerie par résonance magnétique ; remodelage ; oreillette gauche

Prognosis of left atrial remodeling after a myocardial infarction : a CMR study

ABSTRACT

Introduction: Myocardial infarction (MI) can lead to left ventricular (LV) remodeling. This remodeling can engender LV dilatation and dysfunction, known to be a major cause of heart failure. The left atrium (LA) dilatation is also known to predict poor outcomes in a wide spectrum of diseases.
Objectives: We sought to evaluate left atrial remodeling in the context of MI by cardiac magnetic resonance (CMR) and to evaluate its prognostic role.
Methods: Retrospective evaluation of left atrial volume index (LAVI) by using CMR at baseline and 3-months follow-up in a cohort of STEMI patients.
Results: In our study, 323 patients were analysed with valuable LA at 3 months. There was a decrease in LAVI between baseline and 3-months (43,9 ± 10,4 ml vs 42,8 ± 11,1 ml, p= 0,003). We identified LAVI at baseline to be a pronostic markor of major adverse cardiac events: HR 2.046, 95%CI [1.278-3.274] p=0.003 and a trend for LA remodeling between baseline and 3-month (p=0.094).
Conclusion: We found a reverse remodeling of the LA between baseline and 3-month. LAVI was a pronostic marker only in HF patients. LAVI volume change between baseline and 3-month tended to predict long-term outcomes.

Keywords : Myocardial infarction ; cardiac magnetic resonance ; remodeling ; left atrium

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