INTRODUCTION

Myocardial infarction (MI) has a major impact on overall mortality across the world especially in western countries [42]. Left ventricular remodeling (LVR) is caused by a set of phenomenon occurring after MI leading to increased myocardial wall stress and deleterious increased of left ventricular (LV) volumes. His relationship with mortality is well established [7, 17, 43] as is the positive relationship between intervention' effects on LVR and clinical outcomes [25, 43-45]. So to predict LVR is a key point and a challenging issue after MI. Even if some major determinants are now identified - such as infarct size (IS) [8], microvascular obstruction (MVO) [16], left ventricular ejection fraction (LVEF), TIMI flow, and patency of the related artery [12, 46, 47]) - various patterns of LVR have been observed and could implicate diverse pathophysiological processes [7]. Diverse timing of LVR should result in diverse timing of LVR evaluation and risk assessment. The aim of the study was to assess diverse patterns of LVR and their determinants during the first year after MI with a serial cardiac magnetic resonance imaging (CMR) approach.

METHODS:

Study population

161 patients with a first ST-elevation MI admitted to the University Hospital of Angers (France) were prospectively evaluated. Inclusion criteria were as follows: primary or rescue percutaneous coronary intervention for first ST-elevation MI within 12 hours of symptom onset; age above 18 years; culprit coronary artery with proximal occlusion, *i.e.*, proximal or mid-left anterior descending coronary artery, proximal dominant circumflex coronary artery, or proximal right coronary artery; thrombosis in myocardial infarction-flow Grade 0 or 1 prior to PCI, and successful revascularisation with a flow Grade 3 after stenting. Exclusion criteria were cardiogenic shock, initial cardiac arrest, history of myocardial infarction or aorto-coronary bypass surgery, and contraindication to CMR. This study conformed to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent for completion of the CMR, and the study protocol was approved by the hospital's ethics committee (CHU Angers).

All patients underwent detailed assessment of medical history as well as clinical evaluation during the index hospitalization, at 3 months and one year. Medication doses were collected at 24 hours after hospital admission, at discharge and at 3 months as previously described by Grall *et al*.[48]

CMR protocol

Baseline scan was scheduled between 3 to 5 days after reperfusion and follow-up at 3 months and 1 year after index infarction. CMR was performed using either a 1.5 or 3 Tesla imager (Avanto and Skyra, Siemens, Erlangen, Germany) with the application of an 8-element phased-array cardiac receiver coil. Left ventricular function was analyzed using the steady-state free precession sequence performed on contiguous short-axis slices covering the entire left ventricle. The typical in-plane resolution applied was similar among imagers: 1.6x1.9mm, with a 7mm section thickness (matrix: 256x208; temporal resolution: 35-45 msec).

Late gadolinium enhancement sequences were performed 12 to 15 minutes after the injection, at a dose of 0.2mmol/Kg, by means of a 2D segmented inversion recovery gradient-echo pulse sequence. Contiguous short axis slices covered the entire ventricle. The typical in-plane resolution used was similar among imagers: 1.68x1.68mm, with a 7mm section thickness (imaging was triggered to every other heartbeat; matrix: 256x208). Steady-state free precession pulse sequences and late gadolinium enhancement sequences were acquired in breathhold state, each with identical section positioning.

Image Analysis

The CMR images were transferred to a workstation for analysis and calculation (Qmass 7.1, Medis, Leiden, The Netherlands).

Left ventricular function

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, such as LV mass, were determined.

Infarct size measurement

Infarct size (IS) was quantified on late gadolinium enhancement images by means of the FWHM (full width at Half Maximum)[49], corresponding to the sum of the hyperenhanced area measured on all sections, given in grams.

Microvascular obstruction assessment

If present, central hypoenhancement was manually delineated for quantification, and its extent was systematically added to the hyperenhanced area. The variability assessment for LV volumes, infarct size, and MVO extent produced good results, published elsewhere [49].

Systolic Wall stress measurement

Global systolic wall stress was calculated by means of a dedicated software, specially built by our laboratory, using a 3D model analysis [50-52] In brief, a median border between endo- and epicardial borders was generated on each slice. The barycenter of the section was then defined as the mass center of the median border. Each short axis was centered on the barycenter. The radius of curvature and wall thickness were calculated on end-systole in a series of contiguous short-axis slices (5-12 sections, depending on heart size) in order to compute the SWS. All apical slices absent of ventricular cavity and basal slices presenting open borders were excluded from the analysis. The SWS was calculated on each slice, with the SWS of the whole heart (global wall stress) defined as the average value of all slices, then used for the statistical analyses. Three measurements were taken from the systolic blood pressure cuff during the acquisition of cine-MRI.

Data analysis

Outcomes

LVR was considered as ≥10% increase in LV end-systolic volume (LVESV)[53]. EarlyLVR was defined a volume increase between baseline and 3 months and LateLVR as volume increase between baseline and 1 year (excluding patients with EarlyLVR). Regarding of LVR patterns, 3 groups of patients were defined: NoLVR (patients without ventricular remodeling as defined previously), EarlyLVR and LateLVR.

Clinical events (cardiovascular deaths, heart failure, infarction, stenting) were tabulated per subject.

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 mean ± standard deviation for continuous variables and as frequency with percentage for categorical variables. ANOVA with the Tukey post-oc test or chi-squared test where appropriate were used to test for differences among the three subgroups at each time point. Change in imaging parameters over time were assessed with paired t-tests. Univariate and multivariate logistic regression analyses with stepwise binomial logistic regression analysis were performed to identify independent predictors of LVR patterns. EarlyLVR patients were excluded of the analysis of predicting factors of LateLVR at 3 months. Variables that were significant ($p<0.05$) in univariate analyses were entered in the multivariate models. A two-tailed $p <0.05$ was set to indicate statistical significance.

RESULTS

A total of 193 patients were included in the study and 160 patients underwent all CMR examinations (Figure 1). 161 patients were included in the final analysis (one patient presented a sudden death between 3 months and one year and was included in the final analysis). The first CMR examination was performed at 6 days (IQR 4;9) following MI, the second at 98 days (IQR 94;107) and the last at 371 days (367;379). In total, LVR occurred in 38 patients (24%), including 19 Early LVR patients and 19 Late LVR patients.

Baseline characteristics

Baseline characteristics are shown in table 1. Compared to NoLVR, EarlyLVR patients presented higher prevalence of diabetes (26.3% vs 9%; p=0.027), anterior MI (78.9% vs 52.8%; p=0.033) and greater maximum Killip class during hospital stay (p<0.001). EarlyLVR patients had greater peak of creatin kinase (5079±2231 vs 2544±1958 UI/l; p<0.001). No difference for baseline characteristics was observed between NoLVR and LateLVR groups. When comparing the two groups of patients with LVR, we observed more anterior MI in Early LVR group (78.9% vs 47.3%; p=0.044) and more inferior MI in LateLVR group (5.3% vs 31.6%; p=0.036). Abdominal perimeter was higher in EarlyLVR group (105±10 vs 85±40; p=0.014).

Medication

At discharge**,** three patients were not administered beta-blocker treatment owing to a history of asthma and two patients did not receive angiotensin convertase enzyme inhibitors (ACEi) due to symptomatic hypotension. No difference was observed between NoLVR and EarlyLVR group. At baseline and at 3 months, patients without betablockers or ACEi were more frequent in LateLVR group (15.8% vs 1.6%; p=0.002) (table 2).

CMR findings

Change of LV CMR parameters over time according to LVR patterns (figure 2)

In NoLVR group, LV volumes and LVEF depicted inverse positive variation between baseline and 3 months with no further variation thereafter while LV mass and IS decreased during follow-up at each time point. SWS slightly increased between baseline and 1 year. In EarlyLVR group, LVEF did not significantly decreased during follow-up (LVEF: 45.4%±9.9, 43.9%±9.6, 43.4%±10.4 at baseline, 3 months and 1 year, respectively) while LV mass and volumes showed inverse variation during follow-up with significant changes between baseline and 3 months and then a stabilization of LV volume associated to a non-significant increase of LV mass between 3 months and 1 year. SWS presented a relative increase of 56% during the first three months and stopped thereafter. In LateLVR group, LV volumes remained stable during the first three months and then significantly increased while LVEF presented a biphasic pejorative course (LVEF: 48.0%±11.4, 50.7%±11.1, 46.3%±11.2 at baseline, 3 months and 1 year, respectively) and LV mass decreased during follow-up. SWS significantly increased all along follow-up.

Baseline CMR parameters and during follow-up (table 3)

NoLVR, EarlyLVR and LateLVR group depicted similar baseline LV volumes and LVEF whereas EarlyLVR group presented larger IS and higher prevalence and extent of MVO. Compared to NoLVR group, LVESV was greater, LVEF was lower and SWS was higher at three months and one year in EarlyLVR group and in LateLVR group at one year. EarlyLVR group had higher LV mass than both other groups at 1 year.

Predictors of LVR patterns

Results of univariate analysis are shown in table 4. In multivariate analysis (table 5), independent predictors of EarlyLVR were diabetes mellitus (OR=5.079 [95%CI:1.276-20.213]; p=0.021) and baseline infarct extent (OR:1.104 [95%CI: 1.055-1.156], p<0.001). Independent predictors of

LateLVR were SWS at 3 months (OR:1.08 [1.02-1.15]; p=0.011) and the absence of ACEi or betablockers at baseline or 3 months (OR: 14.98 [2.21-101.42]; p=0.006).

Outcomes

12 patients underwent stenting during follow-up, 2 in EarlyLVR group, 2 in LateLVR group and 8 in NoLVR group. Recidive of infarction occurred in 1 patient of NoLVR group. 1 patient had a cardiovascular death during follow-up (from EarlyLVR group) and 6 patients had congestive heart failure (2 from EarlyLVR group and 4 from NoLVR group).

DISCUSSION

In this study concerning a large sample of patients of modern era with infarct on each coronary territory, optimal reperfusion techniques and optimal medical management, the major findings were: 1) We observed two different patterns of adverse LVR after MI. 2) IS remained a strong predictor of EarlyLVR but was not predictive of late LVR 3) Late LVR can occur in patients with intermediate sized MI whatever the coronary territory 4) SWS increased rapidly in EarlyLVR patients and progressively in LateLVR patients.

EarlyLVR

Changes in LV characteristics in EarlyLVR patients

These patients experienced an intense adverse LVR during the first 3 months associating an increase of LVESV, with dramatic increase of SWS (+56%). Interestingly, there were no further significant increase in LVESV and SWS between 3 months and one year probably due to a compensatory increase of myocardial mass between 3 months and one year, that was only seen in EarlyLVR patients.

Predictors of Early LVR

Our study demonstrated that patients with severe myocardial damage experienced more intense LVR during the first 3 months after MI. This is concordant with the major part of previous study showing IS as the main predictor of LVR [8, 15]. MVO was also described as related to LVR [16, 54], with MVO presence related to higher degree of infarct shrinkage during follow-up [16] and multivariate analysis

even favoring MVO [54] in a study involving 63 patients. Regarding diabetes mellitus, it is known that patient with diabetes mellitus are at increased risk of adverse outcomes after myocardial infarction [55], that might be independent to infarct size [56], but literature is more controversial about the mechanisms mediating this higher risk. One echocardiographic study reported more pronounced baseline concentric remodeling and long term elevation of LV diastolic pressure [57] and a recent CMR study [56] found similar IS and rates of MVO yet higher MVO/IS ratio among diabetics patients, suggesting specific response to injury notably at the microvascular level. Our study raised that's diabetes mellitus could expose patients to EarlyLVR independently of IS, and it could participate to the greater risk of adverse cardiac outcomes after MI in this population.

This temporal profile of LVR is probably close to LVR assessed in many studies evaluating LVR between baseline and 1 to 6 months [8, 54, 58] and a baseline assessment of CMR infarct characteristics, mainly MVO and IS, appear to be adequate to predict this LVR temporal profile. There remains still of interest in the assessment of very early LVR (that happened during the first hours or days, that means before our first assessment) that is possibly directly related to LV damage and extent of compromised myocardium. Yet in our study the so-defined EarlyLVR happened after that period and presented no dissimilar values in LV volumes and ejection fraction, but in infarct size and SWS.

Late LVR

Changes in LV characteristics in LateLVR patients

LVEF depicted a 2-step pejorative decrease in this group. Contrary to EarlyLVR group, SWS described a progressive increase during follow-up mediated by initial stability of LV volumes with late increase between 3 months and one year associated with a decrease of LV mass all along follow-up. It remains to determine if those patients will continue to increase their LV volume or will develop a compensatory hypertrophy, as EarlyLVR patients did.

Predictors of LateLVR

To our knowledge, we report the first analysis aiming to describe the determinants of LateLVR by a multiparametric and quantitative CMR analysis. LateLVR patients are of interest because despite similar baseline characteristics and similar baseline infarct characteristics, they underwent adverse LVR at 1 year follow-up. Particularly, there was no specific coronary territory in this group and no predictive value of IS or MVO contrary to EarlyLVR patients (table I). It underlines that LVR may not be exclusively determined by the initial intensity of myocardial damage. We found a progressive increase of SWS between baseline and 3 months, mediating deleterious LVR at 1 year. SWS offers a mechanistic insight covering a broad panel of parameters such as wall thickness, radius of curvature, and systolic blood pressure. This functional approach outmatched IS for the prediction of post discharge heart failure after MI [59]. Intensity of neuro-hormonal activation is playing a central role in LVR [1] and its blockage was successfully targeted [43, 60, 61]. Chronic activation of the adrenergic and renin–angiotensin–aldosterone systems is closely related to SWS and LVR by acting on wall thickness (myocardial thinning induced by myocyte apoptose, interstitial fibrosis and shrinkage phenomenon of remote myocardium), LV volume (fluid retention) or systolic blood pressure (breakdown of bradykinin, fluid retention). Interestingly, we observed a relation between the absence of betablockers or ACEi use and LateLVR. For now, individual susceptibility was not addressed by genetic analysis [62], but by angiotensin II type 1 receptor density [63]. More, Bolognese *et al* [7] described LateLVR pattern as LVR between 1 to 6 months after MI by echocardiography and found IS to be the main determinant but underlined the potence of multivessel coronary disease. They suggested chronic ischemia to be a trigger of LateLVR.

NoLVR

Changes in LV parameters in patients without LVR provided some interesting insights about positive adaptative LV remodeling leading to cardiac healing after MI. A decrease in LV mass and volumes was observed during follow-up, especially during the first 3 months associated with an increase of LVEF. Decrease of LV volumes during the first 3 months was exclusively observed only in NoLVR

group and the absence of decrease of LV volume during the first three months could be a simple criteria to detect patients at risk of adverse LVR.

Clinical implications

This study provided some new insights on LVR raising some issue. First, regarding the prediction of LVR, we cannot restrict our concern to IS as half of patients presenting LVR depicted only intermediate IS. Second we observed that usual CMR tools demonstrate some accuracy at baseline to predict EarlyLVR but failed to predict LateLVR. Accordingly, a 2-step assessment should be considered, including one during follow-up. Third, our study emphasize SWS, that was shown more accurate to predict LateLVR than usual CMR parameters. This parameter is easy to use, derived from end-systolic delineation and offer the opportunity to assess new insights into LV mechanistic.

Limitations

Even if the total amount of patients included was substantial, we performed statistical analysis on 2 groups of 19 patients. More, the follow-up was limited to one year, and we cannot exclude that LVR may affect other individuals thereafter [11]. A comprehensive CMR analysis may seek to analyze some other potential determinants of LVR, including edema, and interstitial fibrosis as assessed by T1 mapping [64]. They were also no systematical echocardiography assessment during follow-up and absence of confounders cannot be excluded such as ischemic mitral regurgitation, diastolic dysfunction and atrial dilation.

CONCLUSION

Two clinical patterns of LVR were distinguished in our study. Initial infarct severity was the major determinant of EarlyLVR whereas SWS at 3 months and long-term medications were the only determinants of LateLVR, intimating more general and progressive processes. Our results suggest the use of a 2-step assessment of LVR and underline the clinical interest for a mechanistic approach including SWS quantification.

BIBLIOGRAPHIE

1. Cohn, J.N., R. Ferrari, and N. Sharpe, *Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling.* J Am Coll Cardiol, 2000. **35**(3): p. 569-82.
2. Thygesen, K., et al., *Third universal definition of myocardial infarction.* Eur Heart J, 2012. **33**(20): p. 2551-67.
3. Whittaker, P., D.R. Boughner, and R.A. Kloner, *Role of collagen in acute myocardial infarct expansion.* Circulation, 1991. **84**(5): p. 2123-34.
4. Weisman, H.F., et al., *Cellular mechanisms of myocardial infarct expansion.* Circulation, 1988. **78**(1): p. 186-201.
5. Hutchins, G.M. and B.H. Bulkley, *Infarct expansion versus extension: two different complications of acute myocardial infarction.* Am J Cardiol, 1978. **41**(7): p. 1127-32.
6. Mitchell, G.F., et al., *Left ventricular remodeling in the year after first anterior myocardial infarction: a quantitative analysis of contractile segment lengths and ventricular shape.* J Am Coll Cardiol, 1992. **19**(6): p. 1136-44.
7. Bolognese, L., et al., *Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications.* Circulation, 2002. **106**(18): p. 2351-7.
8. Masci, P.G., et al., *Relationship between location and size of myocardial infarction and their reciprocal influences on post-infarction left ventricular remodelling.* Eur Heart J, 2011. **32**(13): p. 1640-8.
9. McKay, R.G., et al., *Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion.* Circulation, 1986. **74**(4): p. 693-702.
10. Giannuzzi, P., et al., *Heterogeneity of left ventricular remodeling after acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3 Echo Substudy.* Am Heart J, 2001. **141**(1): p. 131-8.
11. Springeling, T., et al., *Late cardiac remodeling after primary percutaneous coronary intervention-five-year cardiac magnetic resonance imaging follow-up.* Circ J, 2013. **77**(1): p. 81-8.
12. Gaudron, P., et al., *Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors.* Circulation, 1993. **87**(3): p. 755-63.
13. Tarantini, G., et al., *Influence of transmurality, infarct size, and severe microvascular obstruction on left ventricular remodeling and function after primary coronary angioplasty.* Am J Cardiol, 2006. **98**(8): p. 1033-40.
14. Wu, E., et al., *Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study.* Heart, 2008. **94**(6): p. 730-6.
15. Orn, S., et al., *Effect of left ventricular scar size, location, and transmurality on left ventricular remodeling with healed myocardial infarction.* Am J Cardiol, 2007. **99**(8): p. 1109-14.
16. Orn, S., et al., *Microvascular obstruction is a major determinant of infarct healing and subsequent left ventricular remodelling following primary percutaneous coronary intervention.* Eur Heart J, 2009. **30**(16): p. 1978-85.
17. White, H.D., et al., *Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction.* Circulation, 1987. **76**(1): p. 44-51.
18. Gaudron, P., et al., *Time course of cardiac structural, functional and electrical changes in asymptomatic patients after myocardial infarction: their inter-relation and prognostic impact.* J Am Coll Cardiol, 2001. **38**(1): p. 33-40.
19. Grines, C.L., et al., *A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group.* N Engl J Med, 1993. **328**(10): p. 673-9.

20. Prunier, F., et al., *The RIPOST-MI study, assessing remote ischemic perconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction.* Basic Res Cardiol, 2014. **109**(2): p. 400.
21. Staat, P., et al., *Postconditioning the human heart.* Circulation, 2005. **112**(14): p. 2143-8.
22. Botker, H.E., et al., *Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial.* Lancet, 2010. **375**(9716): p. 727-34.
23. Savoye, C., et al., *Left ventricular remodeling after anterior wall acute myocardial infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group).* Am J Cardiol, 2006. **98**(9): p. 1144-9.
24. Dargie, H.J., *Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial.* Lancet, 2001. **357**(9266): p. 1385-90.
25. Doughty, R.N., et al., *Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy.* Circulation, 2004. **109**(2): p. 201-6.
26. Kober, L., et al., *A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group.* N Engl J Med, 1995. **333**(25): p. 1670-6.
27. Kuvin, J., et al., *Images in cardiovascular medicine. Primary lymphoma of the heart.* Circulation, 2005. **112**(1): p. e5-6.
28. Pfeffer, M.A., et al., *Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators.* N Engl J Med, 1992. **327**(10): p. 669-77.
29. Pfeffer, M.A., et al., *Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both.* N Engl J Med, 2003. **349**(20): p. 1893-906.
30. Pitt, B., et al., *Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction.* N Engl J Med, 2003. **348**(14): p. 1309-21.
31. Weir, R.A., et al., *Left ventricular remodeling after acute myocardial infarction: does eplerenone have an effect?* Am Heart J, 2009. **157**(6): p. 1088-96.
32. Udelson, J.E., et al., *Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction.* Circ Heart Fail, 2010. **3**(3): p. 347-53.
33. Hayashi, M., et al., *Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction.* Circulation, 2003. **107**(20): p. 2559-65.
34. Bozkurt, B., et al., *Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure.* Circulation, 2001. **103**(8): p. 1044-7.
35. Schachinger, V., et al., *Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction.* N Engl J Med, 2006. **355**(12): p. 1210-21.
36. Hudson, M.P., et al., *Effects of selective matrix metalloproteinase inhibitor (PG-116800) to prevent ventricular remodeling after myocardial infarction: results of the PREMIER (Prevention of Myocardial Infarction Early Remodeling) trial.* J Am Coll Cardiol, 2006. **48**(1): p. 15-20.
37. Cazeau, S., et al., *Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay.* N Engl J Med, 2001. **344**(12): p. 873-80.
38. Abraham, W.T., et al., *Cardiac resynchronization in chronic heart failure.* N Engl J Med, 2002. **346**(24): p. 1845-53.
39. Daubert, C., et al., *Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from*

the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol, 2009. **54**(20): p. 1837-46.
40. Starling, R.C., et al., *Sustained benefits of the CorCap Cardiac Support Device on left ventricular remodeling: three year follow-up results from the Acorn clinical trial.* Ann Thorac Surg, 2007. **84**(4): p. 1236-42.
41. Jones, R.H., et al., *Coronary bypass surgery with or without surgical ventricular reconstruction.* N Engl J Med, 2009. **360**(17): p. 1705-17.
42. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.
43. St John Sutton, M., et al., *Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril.* Circulation, 1994. **89**(1): p. 68-75.
44. Doughty, R.N., et al., *Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group.* J Am Coll Cardiol, 1997. **29**(5): p. 1060-6.
45. Kramer, C.M., et al., *Multimodality imaging of myocardial injury and remodeling.* J Nucl Med, 2010. **51 Suppl 1**: p. 107S-121S.
46. Jeremy, R.W., et al., *Infarct artery perfusion and changes in left ventricular volume in the month after acute myocardial infarction.* J Am Coll Cardiol, 1987. **9**(5): p. 989-95.
47. Bolognese, L. and G. Cerisano, *Early predictors of left ventricular remodeling after acute myocardial infarction.* Am Heart J, 1999. **138**(2 Pt 2): p. S79-83.
48. Grall, S., et al., *Relationship between Beta-blocker and Angiotensin-converting enzyme inhibitor dose and clinical outcome following acute myocardial infarction.* Circ J, 2015. **79**(3): p. 632-40.
49. Bière, L., et al., *Longitudinal strain is a marker of microvascular obstruction and infarct size in patients with acute ST-segment elevation myocardial infarction.* PLoS One, 2014. **9**(1): p. e86959.
50. Balzer, P., et al., *Regional assessment of wall curvature and wall stress in left ventricle with magnetic resonance imaging.* Am J Physiol, 1999. **277**(3 Pt 2): p. H901-10.
51. Delepine, S., et al., *3-D MRI assessment of regional left ventricular systolic wall stress in patients with reperfused MI.* Am J Physiol Heart Circ Physiol, 2003. **284**(4): p. H1190-7.
52. Prunier, F., et al., *Three-dimensional MRI assessment of regional wall stress after acute myocardial infarction predicts postdischarge cardiac events.* J Magn Reson Imaging, 2008. **27**(3): p. 516-21.
53. Zhang, Y., et al., *Left ventricular systolic dyssynchrony is a predictor of cardiac remodeling after myocardial infarction.* Am Heart J, 2008. **156**(6): p. 1124-32.
54. Nijveldt, R., et al., *Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury.* J Am Coll Cardiol, 2008. **52**(3): p. 181-9.
55. Berger, A.K., et al., *Effect of diabetes mellitus and insulin use on survival after acute myocardial infarction in the elderly (the Cooperative Cardiovascular Project).* Am J Cardiol, 2001. **87**(3): p. 272-7.
56. Eitel, I., et al., *Prognostic impact of hyperglycemia in nondiabetic and diabetic patients with ST-elevation myocardial infarction: insights from contrast-enhanced magnetic resonance imaging.* Circ Cardiovasc Imaging, 2012. **5**(6): p. 708-18.
57. Shah, A.M., et al., *Cardiac structure and function, remodeling, and clinical outcomes among patients with diabetes after myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both.* Am Heart J, 2011. **162**(4): p. 685-91.
58. Larose, E., et al., *Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction traditional measures compared with microvascular*

obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance. J Am Coll Cardiol, 2010. **55**(22): p. 2459-69.
59. Clerfond, G., et al., *End-systolic wall stress predicts post-discharge heart failure after acute myocardial infarction.* Arch Cardiovasc Dis, 2015.
60. Weir, R.A., et al., *Aldosterone and cortisol predict medium-term left ventricular remodelling following myocardial infarction.* Eur J Heart Fail, 2011. **13**(12): p. 1305-13.
61. Doughty, R.N., et al., *Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy.* Circulation, 2004. **109**(2): p. 201-6.
62. Bauters, C., et al., *A prospective evaluation of left ventricular remodeling after inaugural anterior myocardial infarction as a function of gene polymorphisms in the renin-angiotensin-aldosterone, adrenergic, and metalloproteinase systems.* Am Heart J, 2007. **153**(4): p. 641-8.
63. Maczewski, M., et al., *Late ventricular remodeling in non-reperfused acute myocardial infarction in humans is predicted by angiotensin II type 1 receptor density on blood platelets.* Int J Cardiol, 2008. **127**(1): p. 57-63.
64. Chan, W., et al., *Acute left ventricular remodeling following myocardial infarction: coupling of regional healing with remote extracellular matrix expansion.* JACC Cardiovasc Imaging, 2012. **5**(9): p. 884-93.

FIGURES

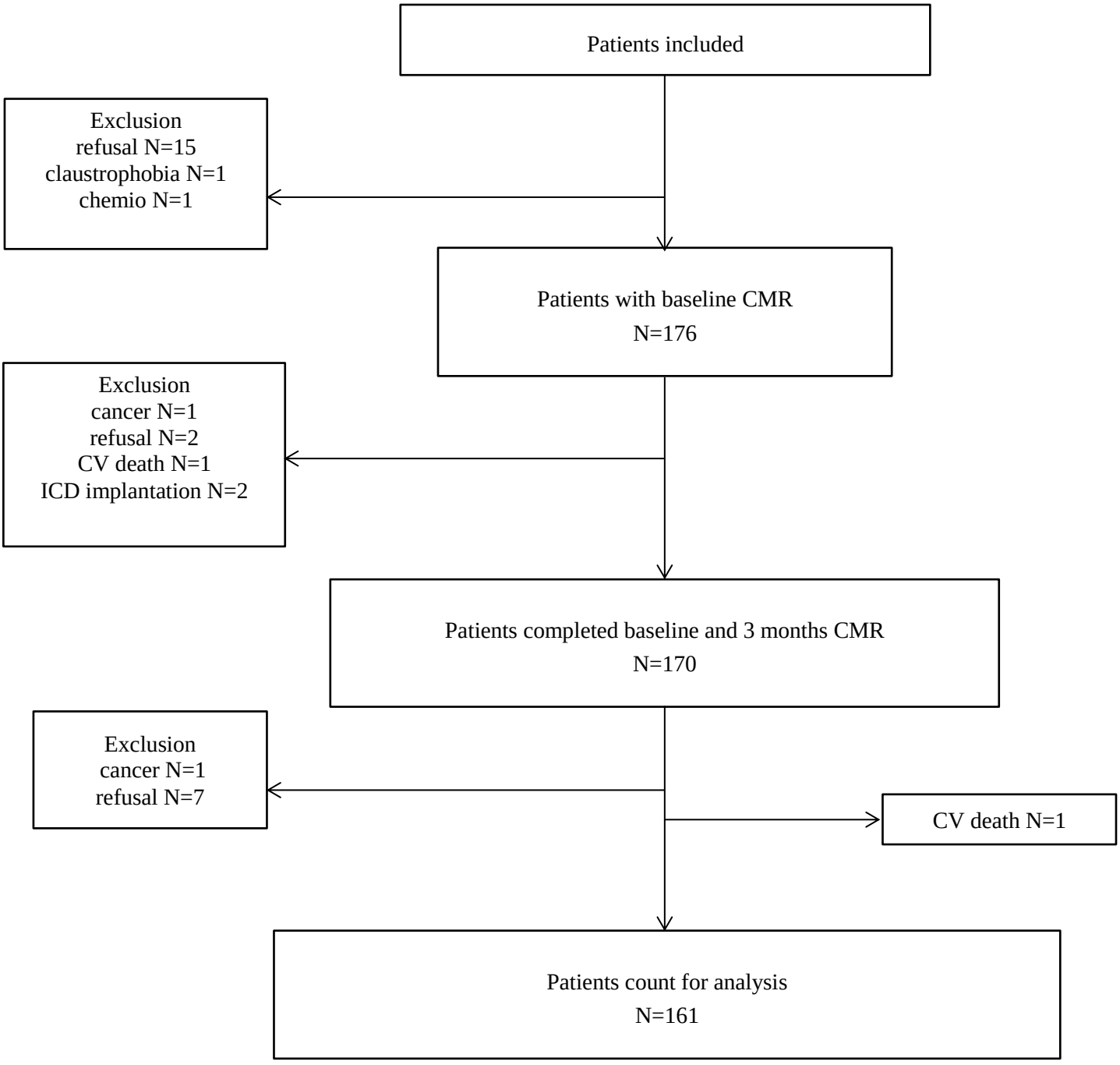


Figure 1: Flow chart of the study; ICD: Implantable cardioverter-defibrillator, CMR: Cardiovascular Magnetic Resonance

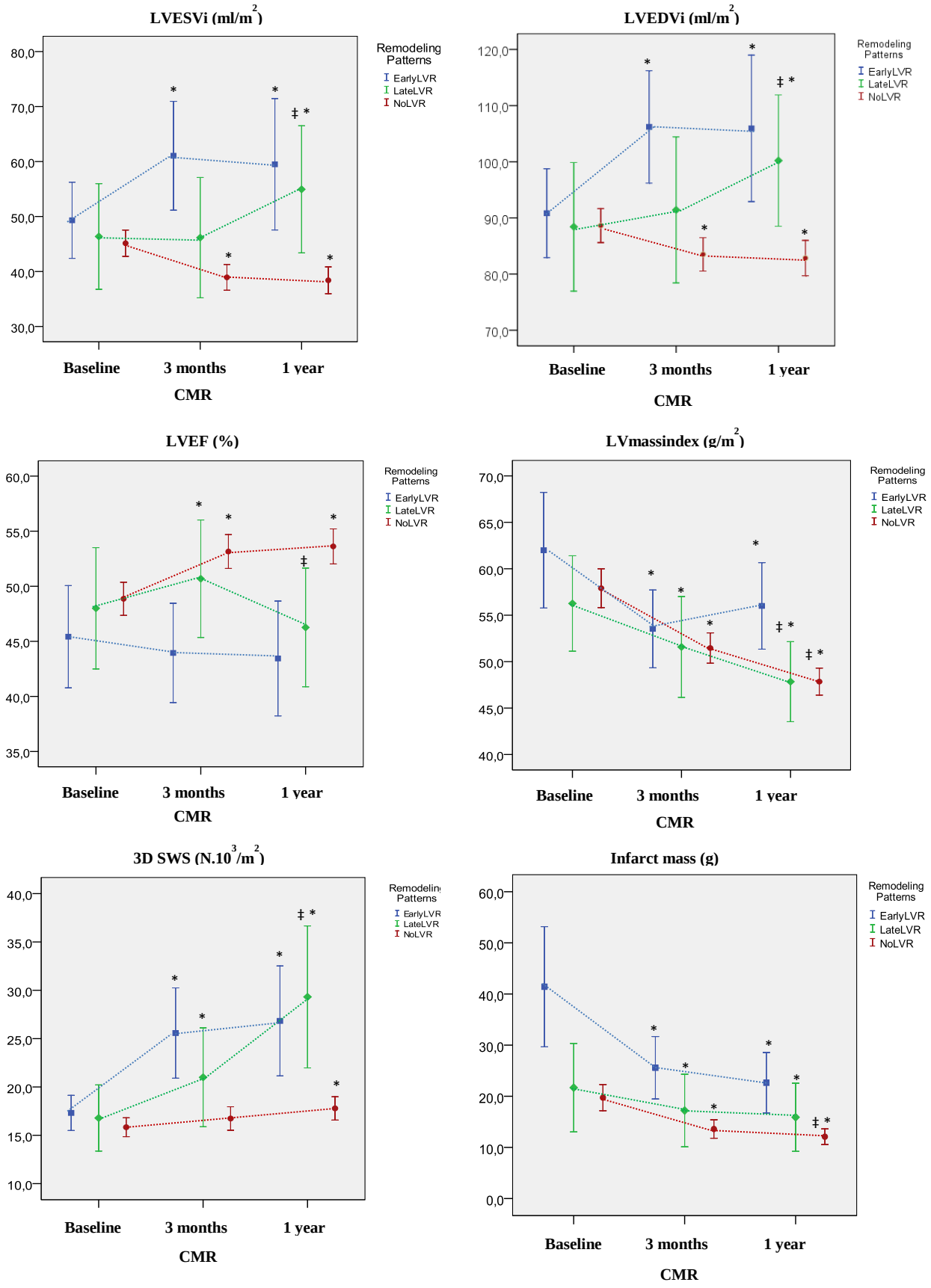


Figure 2: Variation during follow-up of CMR parameters according to LVR patterns; Error bar represent * p<0.05 vs baseline; ł p<0.05 vs 3 months; 3DSWS: 3D systolic wall stress; LVESVi: left ventricular end-systolic volume index; LVMasseindex: Diastolic left ventricular mass index; LVEF: left ventricular ejection fraction; LVR: left ventricular remodeling; CMR: Cardiovascular Magnetic Resonance

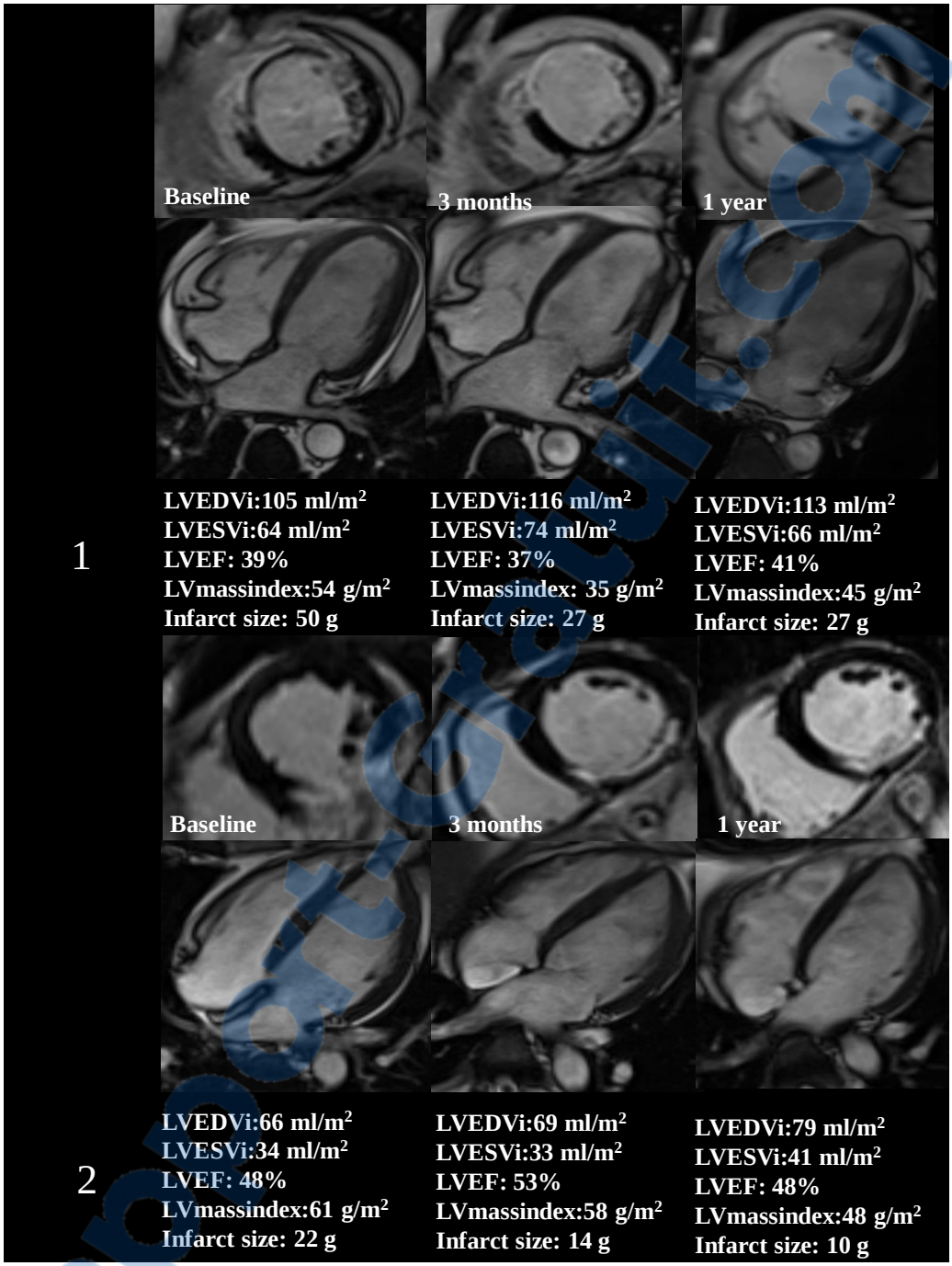


Figure 3: Example of EarlyLVR and LateLVR patients with CMR parameters; **1**: EalyLVR patients with massive anterior infarction and expansive MVO at baseline; quick increase of LV volumes associated with slight decrease of LVEF at 3 months and increase of LV mass – there is a stabilization of LV volumes associated with slight increase of LVEF at 1 year. **2**: LateLVR patients with inferior infarction of intermediate size without MVO; stability of LV volumes at 3 months with improvement of LVEF in a first step and increase of LV volumes at 1 year associated with decrease of LVEF in a second step ; LVEDVi:left ventricular end-diastolic volume index; LVESVi: left ventricular end-systolic volume index; LVEF: left ventricular ejection fraction

TABLES

Table I : Baseline characteristics

	All patients (n=161)	**NoLVR (n=123)**	**EarlyLVR (n=19)**	**LateLVR (n=19)**	**p-value**
Age	58±10	59±10	57±12	56±10	0.50
Male	136 (84%)	102 (82.9%)	16 (84.2%)	17 (89.5%)	0.94
Body Mass Index (kg/m2)	27±4	27±4	28±3	26±4	0.27
Abdominal perimeter (cm)	95±22	95±19	105±10 §	84±40	0.02
Cardiovascular risk factors					
Current smoking	70 (43.2%)	54 (43.9%)	7 (36.8%)	9 (47.4%)	0.79
Hypertension	58 (36%)	46 (35%)	9 (47.4%)	6 (31.6%)	0.52
Diabetes mellitus	18 (11%)	11(9%)	5 (26.3%) ł	2 (10.5%)	0.08
Hypercholesterolemia	74 (46%)	52 (42.3%)	11 (57.9%)	11 (57.9%)	0.18
Heredity	42 (26%)	30 (24.4%)	6 (31.6%)	6 (31.6%)	0.67
Maximum Killip class during hospital stay					<0.001
1 or 2	*155 (96.1%)*	122 (99.2%)	15 (78.9%)	18 (94.7%)	
3 or 4	*6 (3.7%)*	1 (0.8%)	4 (21.1%) ł	1 (5.3%)	
Time to reperfusion (min)	*282±144*	281±151	290±93	282±143	0.96
Number of diseased coronary artery					0.26
1	*93 (58%)*	75 (61%)	10 (52.6%)	8 (42.1%)	
2	*45 (28%)*	30 (24.4%)	8 (42.1%)	7 (36.8%)	
3	*23 (14%)*	18 (14.6%)	1 (5.3%)	4 (21.1%)	
Infarct-related artery					0.20
Left anterior descending	89 (55%)	65 (52.8%)	15 (78.9%) ł §	9 (47.3%)	
Left circumflex	31 (19%)	24 (19.5%)	3 (15.8%)	4 (21.1%)	
Right coronary	41 (26%)	34 (27.7%)	1 (5.3%)ł §	6 (31.6%)	
Peak Creatin Kinase (UI/L)	2959±2285	2544 ±1958	5079±2231 ł	3483±3020	<0.001

Values are reported as mean ± standard deviation or as percentage.
p-value: ANOVA or qui-square test among three groups; ł: p<0,05 EarlyLVR vs NoLVR ;
* :p<0,05 LateLVR vs NoLVR ; §: p<0,05 EarlyLVR vs LateLVR

Table II : Medications

	All patients (n=161)	NoLVR (n=123)	EarlyLVR (n=19)	LateLVR (n=19)	p-value
Medication at hospital discharge					
Beta blockers	*158 (98%)*	122 (99%)	19 (100%)	17 (89.4%)*	0.12
ACEi /AT-1 antagonist	*159 (99%)*	122 (99.2%)	19 (100%)	18 (94.7%)	0.23
Aspirin	*160 (99%)*	122 (99.2%)	19 (100%)	19 (100%)	0.85
Clopidogrel. prasugrel or ticagrelor	*161 (100%)*	123 (100%)	19 (100%)	19 (100%)	
Aldosterone antagonist	53 (33%)	39 (32%)	7 (37%)	7 (36.8%)	0.70
Statins	*160 (99%)*	123 (100%)	18 (94.7%)ł	19 (100%)	0.023
Target dose at discharge					
Betablockers					0.43
<50%	*35 (22%)*	24 (19.5%)	5 (26.3%)	6 (31.6%)	
≥50%	*126 (78%)*	99 (80.5%)	14 (73.7%)	13(68.4%)	
ACEi/AT-1 antagonist					0.43
<50%	*34 (21%)*	28 (22.7%)	2 (10.5%)	5 (26.4%)	
≥50%	*126 (79%)*	95 (77.3%)	17 (89.5%)	14(73.7%)	
No ACEi/AT-1 antagonist or betablockers	*5 (3%)*	2 (1.6%)	0	3 (15.8%) *	0.003
Target dose at 3 months					
Betablockers					0.61
<50%	*36 (24%)*	25 (20.3%)	5 (26.3%)	6 (31.6%)	
≥50%	*125 (78%)*	98 (79.7%)	14 (73.7%)	13(68.4%)	
ACEi/AT-1 antagonist					0.43
<50%	*24 (15%)*	17 (13.8%)	5 (26.3%)	2 (10.6%)	
≥50%	*137 (85%)*	106 (86.2%)	14 (73.7%)	17 (89.4%)	
No ACEi/AT-1 antagonist or betablockers	*5 (3%)*	2 (1.6%)	0	3 (15.8%) *	0.003

Values are reported as mean ± standard deviation or as percentage.
ACEi: Angiotensin Converting Enzyme inhibitor; AT-1: Angiotensine 1
p-value: ANOVA or chi-square test among three groups; ł: p<0.05 EarlyLVR vs NoLVR ; * :p<0.05 LateLVR vs NoLVR.

Table III : Cardiac magnetic resonance characteristics

	NoLVR (n=123)	EarlyLVR (n=19)	LateLVR (n=19)	p value
End-diastolic volume index (ml/m2)				
Baseline	88.6±13.3	90.8±16.4	88.4±23.7	0.87
3 months	83.5±13.1	106.2±20.8 ł §	91.4±26.9	<0.001
1 year	82.8±13.6	105.9±26.2 ł	100.2±24.3 *	<0.001
End-systolic volume index (ml/m2)				
Baseline	45.1±1.2	49.3±14.3	46.3±19.9	0.49
3 months	38.9±1.2	61±20.5 ł §	46.1±22.7	<0.001
1 year	38.3±8.9	59.5±24 ł	54.9±24 *	<0.001
Left ventricular mass index (g/m2)				
Baseline	57.9±9.5	62±12.9	56.2±10.6	0.28
3 months	51.4±9	53.5±8.6	51.5±11.2	0.67
1 year	47.8±9.2	56±9.4 ł §	47.8±8.9	0.001
Cardiac index (L/min/m2)				
Baseline	2.5±8.4	2.3±0.6	2.4±0.6	0.43
3 months	2.2±8.6	2.3±0.4	2.5±0.6	0.22
1 year	2.5±3.5	2.1±0.6	2.2±0.6	0.84
Left ventricular ejection fraction (%)				
Baseline	48.8±11.7	45.4±9.6	48±11.4	0.29
3 months	53.1±9.1	43.9±9.4 ł	50.6±11	<0.001
1 year	53.6±8.1	43.4±10.5 ł	46.2±11.2 *	<0.001
Infarct mass (% LV)				
Baseline	17±10.4	32.3±15.1 ł §	19.9±14.8	<0.001
3 months	13.6±9.9	23.9±10.8 ł	17.3±13.5	<0.001
1 year	13±9.2	20.1±9.5 ł	17.4±14.7	0.010
Microvascular obstruction	47 (38%)	16 (84.2%) ł §	8 (42%)	0.001
Microvascular obstruction extent (g)	1.2±4.6	5.1±6 ł §	1.8±3.5	<0.001
3D systolic wall stress ($N.10^3/m^2$)				
Baseline	15.0±16.6	16.6±5.3	16.0±6.5	0.47
3 months	16.7±17.6	25.5±9.7 ł	21±10.6	<0.001
1 year	17.8±6.7	26.8±11.4 ł	29.3±15.2 *	<0.001

Values are reported as mean ± standard deviation or as percentage.

LVR: Left ventricular remodeling

p-value: ANOVA or qui-square test among three groups; ł: p<0.05 EarlyLVR vs NoLVR ; * :p<0.05 LateLVR vs NoLVR ; §: p<0.05 EarlyLVR vs LateLVR.

Table IV: Unadjusted predictors of left ventricular remodeling patterns

	EarlyLVR			LateLVR		
	OR	**95 % CI**	**p-value**	**OR**	**95 % CI**	**p-value**
Age (years)	0.98	0.93-1.03	0.46	0.97	0.92-1.02	0.34
Male	0.91	0.26-3.29	0.93	1.46	0.35-6.01	0.59
Body mass index	1.10	0.97-1.24	0.10	1	0.88-1.13	0.96
Hypertension	1.71	0.65-4.48	0.27	0.85	0.30-2.41	0.77
Diabetes	3.52	1.09-11.32	0.03	1.18	0.24-5.82	0.84
Dyslipidemia	1.70	0.64-4.48	0.28	2.14	0.77-5.90	0.14
Current smoker	0.73	0.27-1.96	0.53	1.15	0.43-3.02	0.80
Time to reperfusion (min)	1	0.99-1.01	0.79	1	0.99-1.01	0.99
Maximum Killip class during hospital stay	2.80	1.43-5.50	0.003	1.93	0.81-4.57	0.13
LAD culprit lesion	3.45	1.09-10.89	0.03	0.80	0.30-2.11	0.66
Number of diseased vessels	0.92	0.46-1.79	0.80	1.52	0.83-2.79	0.17
Peak Creatin Kinase	1	1.00-1.01	<0.001	1	1.0-1.0	0.08
Peak PCR	1.01	0.99-1.02	0.07	1.01	0.99-1.02	0.49
Baseline LVEDVi (ml/m^2)	1.01	0.98-1.03	0.60	0.99	0.97-1.02	0.96
Baseline LVESVi (ml/m^2)	1.02	0.98-1.05	0.25	1.01	0.97-1.04	0.72
Baseline LVEF (%)	0.96	0.91-1.01	0.13	0.99	0.93-1.04	0.69
Baseline infarct mass (% LV)	1.10	1.05-1.14	<0.001	1.02	0.98-1.06	0.28
Baseline MVOmass (g)	1.21	1.09-1.34	<0.001	1.06	0.92-1.22	0.41
Baseline MVO	8.44	2.34-30.29	0.001	0.74	0.44-3.12	0.74
Baseline SWS (N.10^3/m^2)	1.04	0.96-1.13	0.31	1.03	0.91-1.17	0.54
3 months LVEDVi (ml/m^2)	-	-	-	1.02	0.99-1.04	0.08
3 months LVESVi (ml/m^2)	-	-	-	1.03	0.99-1.05	0.05
3 months LVEF (%)	-	-	-	0.97	0.92-1.02	0.26
3 months infarct mass	-	-	-	1.03	0.98-1.07	0.13
3 months SWS (N.10^3/m^2)	-	-	-	1.06	1.01-1.12	0.02
Betablockers Target dose at discharge	1.3	0.91-1.85	0.15	0.98	0.66-1.45	0.94
ACEi Target dose at discharge	1.30	0.84-2.00	0.27	0.88	0.55-1.41	0.61
No ACEi or betablockers at 3 months	-	-	-	11.25	1.17-72.53	0.01

ACEi: Angiotensin Converting Enzyme inhibitor; LAD: Left anterior descending; LVEDVi: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESVi: Left ventricular end-systolic volume index; MVO: Microvascular obstruction; PCR: protein C-reactive; SWS: Systolic wall stress

Table V: Independent predictors of left ventricular remodeling patterns

	EarlyLVR			LateLVR		
	OR	**95 % CI**	**p-value**	**OR**	**95 % CI**	**p-value**
Baseline infarct size (% LV)	1,10	1,05-1,16	<0,001	-	-	-
Diabetes	5,08	1,28-20,21	0,021	-	-	-
3 months 3DSWS ($N.10^3/m^2$)	-	-	-	1,08	1,02-1,15	0,011
No ACEi or betablockers at 3 months	-	-	-	14,98	2,21-101,42	0,006

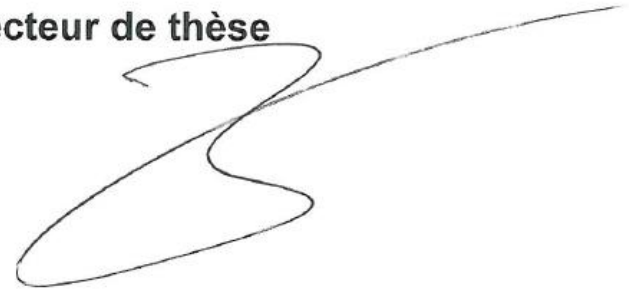
ACE: Angiotensin Converting Enzyme; LVR: Left Ventricular remodeling SWS: Systolic wall stress

Tables des matières

PERMIS D'IMPRIMER

THÈSE DE Monsieur DELAGARDE Hermeland

Vu, le Directeur de thèse



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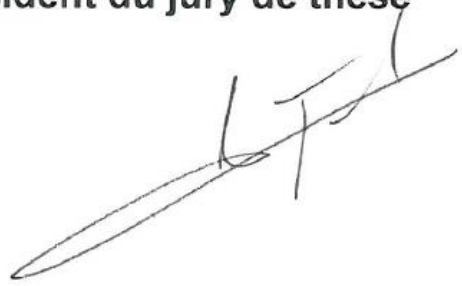

Vu, le Doyen de la Faculté de Médecine d'ANGERS

Professeur I. RICHARD

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ABSTRACT:

Background : Left ventricular remodeling (LVR) is a major concern after a myocardial infarction.

Purpose: To study various patterns of LVR during the first year after a myocardial infarction, with a serial CMR approach.

Methods: 161 patients with a first ST-elevation MI admitted to our University Hospital were prospectively enrolled. CMR was performed at baseline, and repeated at 3-month and 1 year follow-up in order to investigate left ventricular (LV) volumes and mass, ejection fraction (LVEF), infarct size (IS), microvascular obstruction (MVO), and systolic wall stress (SWS).

Results: LVR (>10% increase in end-systolic volume) occurred in 38 (24%) patients. 19 patients presented with early LVR (EarlyLVR) (volume increase during the first 3 months) and 19 others with late LVR (LateLVR) (volume increase between baseline and one year, excluding EarlyLVR patients). In patient without remodeling (NoLVR), LV volumes and mass decreased and ejection fraction increased during follow-up. In EarlyLVR patients, LVEF decreased during the first three months with no further changes (LVEF: 45.4%±±9.9, 43.9%±9.6, 43.4%±10.4 at baseline, 3 months and 1 year, respectively). In LateLVR patients, LV volumes remained stable during the first three months and then increased while LVEF presented a biphasic pejorative course (LVEF: 48.0%±11.4, 50.7%±11.1, 46.3%±11.2 at baseline, 3 months and 1 year, respectively). NoLVR and LateLVR patients depicted similar infarct characteristics (location and extent) and similar baseline LV volumes and LVEF whereas EarlyLVR patients presented larger IS, higher extent of MVO and greater creatin kinase peaks. In multivariate analysis, IS (OR:1.10 [95%CI: 1.05-1.16], p<0.001) and diabetes (OR:5.08 [95%CI:1.28-20.21]p=0.02) were independent predictors of EarlyLVR. SWS at 3 months (OR:1.08 [95%CI: 1.00-1.15], p=0.01) and the non-prescription of betablockers or angiotensin-converting enzyme inhibitors (OR:14.98 [95%CI:2.21-101.42], p=0.006) were independent predictors of LateLVR.

Conclusion: Two clinical patterns of LVR were distinguished in our study. Initial infarct severity was the major determinant of early remodeling whereas SWS and long-term medications were the only determinants of late remodeling, intimating more general and chronic processes

Keywords: left ventricular remodeling, myocardial infarction, cardiovascular magnetic resonance, systolic wall stress

RESUME

Objectif: Etudier les profils de remodelage ventriculaire dans la première année suivant un infarctus du myocarde (IDM), à l'aide d'une analyse par IRM en série.

Matériel et méthodes : 161 patients admis au CHU d'Angers pour un premier IDM ont été inclus prospectivement. Une IRM cardiaque a été réalisée à la phase initiale, et répétée à 3 mois et 1 an après l'IDM.

Résultats : 19 (12%) patients ont présenté un remodelage précoce (EarlyLVR) (> 10 % d'augmentation du volume télé-systolique dans les 3 premiers mois) et 19 (12%) patients ont développé un remodelage ventriculaire tardif (LateLVR) (>10% d'augmentation du volume télé-systolique à un an, excluant les patients EarlyLVR). Chez les patients EarlyLVR, la fraction d'éjection a diminué entre la phase initiale et 3 mois, sans variation significative ensuite. Chez les patients LateLVR, les volumes ventriculaires restaient stables pendant 3 mois puis s'élevaient à un an pendant que la fraction d'éjection décrivait une courbe bi-phasique. La taille d'infarctus (OR :1.10 [95%CI: 1.05-1.16], p<0.001) et le diabète (OR :5.1 [95%CI:1.28-20.21], p=0.02) étaient les prédicteurs indépendants du profil EarlyLVR. La contrainte télé-systolique à 3 mois (OR :1.08 [95%CI: 1.00-1.15], p=0.01) et la non prescription de bétabloquant ou d'inhibiteur de l'enzyme de conversion (OR :14.98 [95%CI:2.21-101.42], p=0.006) étaient les prédicteurs indépendants du profil LateLVR.

Conclusion : 2 profils de remodelage ventriculaire ont été observés. La sévérité initiale de l'infarctus était le principal déterminant du profil EarlyLVR; la contrainte pariétale et les médications au long cours étaient les déterminants du profil LateLVR, impliquant des mécanismes plus globaux.

MOTS CLES : INFARCTUS DU MYOCARDE, REMODELAGE VENTRICULAIRE, IRM CARDIAQUE, CONTRAINTE PARIETALE.