Incidence, determinants, and prognostic value of reverse left ventricular remodelling after primary percutaneous coronary intervention: results of the Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study

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Aims Few data are available on the extent and prognostic value of reverse left ventricular remodelling (r-LVR) after ST-elevation acute myocardial infarction (STEMI). We sought to evaluate incidence, major determinants, and long-term clinical significance of r-LVR in a group of STEMI patients treated with primary percutaneous coronary intervention (PPCI). In particular, the role of preserved microvascular flow within the infarct zone in inducing r-LVR has been investigated.

Methods and results Serial echocardiograms (2DE) and myocardial contrast study were obtained within 24 h of coronary recanalization (T1) and at pre-discharge (T2) in 110 reperfused STEMI patients. Follow-up 2DE was scheduled after 6 months (T3). Two-year clinical follow-up was obtained. Reverse remodelling was defined as a reduction >10% in LV end-systolic volume (LVESV) at 6 months follow-up. r-LVR occurred in 39% of study population. At multivariable analysis, independent predictors of r-LVR were an effective microvascular reflow within the infarct zone, the in-hospital improvement of myocardial perfusion, an initial large LVESV, and a short time to reperfusion. Cox analysis identified r-LVR as the only independent predictor of 2-year event-free survival. Combined events rate was significantly higher among patients without compared to those with r-LVR (log-rank test \( P < 0.05 \)).

Conclusion r-LVR frequently occurs in STEMI patients treated with PPCI and it is an important predictor of favourable long-term outcome. A preserved microvascular perfusion within the infarct zone is the major determinant of r-LVR.

Keywords Myocardial contrast echocardiography • Acute myocardial infarction

Introduction

Left ventricle remodelling (LVR) is a relatively common and unfavourable event occurring after acute myocardial infarction (AMI).\(^1\) The extent of microvascular damage after reperfusion has been identified as one of the main determinant of this process.\(^2\)–\(^5\)

On the other hand, the opposite phenomenon, LV volume reduction after coronary reperfusion, known as reverse LVR
(r-LVR), has been poorly investigated. A significant r-LVR has been recently described after cardiac resynchronization therapy (CRT) in patients with chronic heart failure and it is a strong predictor of longer long-term survival and less adverse cardiac events. r-LVR was also observed after ST-elevation acute myocardial infarction (STEMI). However, few data are available on the extent, determinants, and clinical significance of r-LVR after STEMI in modern clinical practice with a systematic use of primary percutaneous coronary intervention (PPCI) and ‘antiremodelling’ medications. This information might have important clinical implications for the design and interpretation of trials aimed at evaluating the efficacy of new therapeutic options in patients with STEMI.

Thus, we analysed the Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study database to investigate incidence, major determinants, and long-term prognostic impact of r-LVR in a group of STEMI patients treated with PPCI. Furthermore, as the extent of microvascular damage is one of the key determinants of LVR, we assessed the role of microvascular flow changes after reperfusion in inducing r-LVR.

Methods

Study population
Details of AMICI study have been previously published. In brief, consecutive patients referred to the catheterization laboratories of the three centres involved in the study between January and November 2005, who underwent successful PPCI within 6 h of onset of STEMI entered the AMICI trial. The Ethical Committee of the three Institutions involved approved the study, and all patients gave written informed consent to participate in the study.

Two-dimensional echocardiography (2DE) followed by myocardial contrast study (MCE) was performed within 24 h of coronary recanalization (T1) and at pre-discharge (T2). Follow-up 2DE was scheduled after 6 months (T3).

Echocardiography study
Two experienced observers analysed the echocardiographic data; disagreement was resolved by consensus. The observers were blind as for the time of echo images acquisition (admission, pre-discharge, or follow-up) and for the patient’s identity. Regional LV Wall Motion Score Index (RWMSI), end-diastolic (LVEDV) and end-systolic (LVESV) LV volumes, and LV ejection fraction (LVEF) were calculated for each patient.

Follow-up
After discharge, the clinical follow-up was achieved by means of a visit at 6 months and a new visit or a phone interview at 2 years. Major adverse cardiac events (MACE) were defined as cardiac death, non-fatal AMI (typical chest pain and increased troponin I), or hospitalization for congestive heart failure. The diagnosis of heart failure was based on clinical symptoms (limitation of activity, fatigue, and dyspnea), physical signs (oedema, elevated jugular venous pressure, rales, or third heart sound with gallop), or radiological evidence of pulmonary congestion. For purposes of survival analyses, only one event (the first which occurred) was tabulated for each patient.
Statistical analysis

The study sample size was powered to demonstrate a difference of CDL% in predicting reverse LV remodelling. We calculated that 100 patients had to be enrolled to have an alpha error of 0.05, a power of 0.80, a pooled variance of 320, and a mean difference of 5 in a prospective cohort study. Mean and standard deviations were calculated for quantitative variables and percentages for qualitative variables. All variables were not normally distributed and therefore differences between groups were tested by Mann–Whitney test for quantitative variables and by χ² test for percentages of qualitative variables. A repeated-measure analysis of variance was performed for all variables using the generalized linear model, using the F-test (Pillai’s Trace) as a statistical significance test. The statistical significance was set at P ≤ 0.05 (two-sided tests), and for multiple testing we used a statistical significance of P ≤ 0.01.

All images were independently analysed by two experienced observers (L.A. and L.G.) who were blinded to the clinical data and of each other’s results. To assess intra-observer variability of MCE and LV volume analyses, 16 echo studies were independently reviewed by the same observer (LG.), 40 ± 10 days after initial scoring. Inter-observer variability was assessed by comparing the reading of the two observers (L.G. and L.A.). Bland–Altman analysis was used.

For quantitative variables that showed a statistical significant difference between the two groups (r-LVR vs. no LVR), receiver-operating characteristic (ROC) curves were obtained to calculate the cutoff values optimized to reach the best compromise in the prediction of r-LVR. Optimal cutoff was defined as the threshold where the sum of sensitivity and specificity was maximum. We used the bootstrap method in order to characterize the variability of the adjusted estimates of sensitivity and specificity using 95% confidence intervals (CIs) according to the methods developed by Efron and Tibshirani. A multivariable logistic regression analysis was conducted considering as dependent variable the occurrence of reverse remodelling at follow-up. All the variables presenting a significant value < 0.25 at univariate analysis were included in the model. The stepwise method with backward elimination was used, and odds ratios (ORs) with 95% CIs were calculated. The model was evaluated with Hosmer and Lemeshow test.

We have to consider that the results from any model could be too optimistic when the model is used on the data set from which it has been developed, and this could lead to an overfitting. As one of the main points of a research is the external validity, our aim was to develop a model that can be used also for future patients. In order to validate the final model and to adjust (shrink) the regression coefficients (log ORs and log hazard ratio) for overfitting, a bootstrapping procedure was a generalized linear model for the CoxPH() as suggested by Li and Luan, using the R package mboost and the call gamboost(x, y, family = CoxPH()) as suggested by Hothorn and Buhlmann.

Considering the follow-up period, we were interested in identifying baseline and pre-discharge predictors of MACE. We fitted Cox proportional-hazards models to estimate the unadjusted hazard ratios (HRs) of all variables. All variables were considered with P < 0.25 as the inclusion level. We analysed the incremental associations of each variable to MACE beyond clinical variables (family history of CAD and age). First of all, we built a multivariable Cox proportional-hazards regression clinical model by a stepwise forward strategy to select the strongest predictors associated with MACE. To assess the incremental prognostic information from the ‘cardiac’ parameters (r-LVR, WMA%-T1, LVESV-T1, and LVEDV-T1), we entered each of these variables into the clinical models (for MACE) and used likelihood-ratio (LR) tests to assess any significant incremental prognostic information beyond the clinical variables. In each of the final models, the validity of the proportional-hazards assumption was tested by adding a time-dependent interaction variable for each of the predictors in the models. This assumption was tested valid for all the variables in the final models. Finally, we validated our final model using the bootstrapping procedure, as described below for the logistic regression model. Event-free survival curve for MACE was constructed by use of the Kaplan–Meier method, and statistical differences between curves were assessed by log-rank test. Statistical analysis was performed with the use of the SPSS software package for Windows 12.0 (SPSS, Inc., Chicago, IL).

Results

A total of 115 patients were enrolled, out of which five patients were lost to 6-month follow-up. The remaining 110 patients were considered for the final analysis, and a 2-year follow-up was obtained. No MACE occurred up to 6-month follow-up. T1-2DE and MCE were performed 15 ± 4 h from hospital admission and T2-2DE and MCE at 6 ± 2 days from admission. T3-2DE control was repeated at 22 ± 3 weeks. Adequate MCE was achieved in 95% of overall LV segments analysed at T1 and T2 (3553 out of 3740). All artefacts were excluded from the analysis. More than half of the artefacts preventing assessment of MCE occurred in the basal infero-posterior (16%), lateral (11%), and anterior (28%) walls. There was high inter-observer and intra-observer agreement in MCE and LV volume analyses according to the Bland–Altman analysis (Table 1).

| Mean difference | 95% Limits of agreement (95% CIs) |
|-----------------|----------------------------------|
| CDL% 1          | 0.76                             | −1.92 to −1.70                        |
| CDL% 2 −0.42    | −2.34 to −2.18                    | 1.50 (1.34–1.66)                     |
| CDL-LG −0.47    | −2.25 to −2.02                    | 1.31 (1.09–1.54)                     |
| CDL-LA 0.71     | −1.83 to −1.67                    | 3.25 (3.06–3.45)                     |
| LVESV 0.25      | −2.08 to −2.04                    | 2.57 (2.36–3.62)                     |
| LVESV 1.00      | −1.82 to −1.56                    | 3.82 (3.50–4.15)                     |
| LVESV-LG −0.75  | −5.13 to −4.92                    | 3.63 (3.45–3.80)                     |
| LVEDV-LA 0      | −2.82 to −2.71                    | 2.82 (2.69–2.94)                     |
| LVEDV 0.13      | −4.30 to −4.12                    | 4.45 (4.30–4.61)                     |
| LVEDV-LG 0.5    | −5.16 to −5.05                    | 4.16 (4.07–4.26)                     |
| LVEDV-LA 0.63   | −5.41 to −5.27                    | 4.15 (4.03–4.28)                     |
| LVEDV-LA 0      | −3.20 to −3.12                    | 3.20 (3.11–3.30)                     |

CDL, contrast defect length; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; CIs, confidence intervals.
At 6-month follow-up, 43 out of 110 patients (39%) showed r-LVR (ΔLVESV = 26 ± 13%) with an incidence rate of 65.15/1000 person months (CI: 45.78–84.63). Baseline clinical, angiographic, and echocardiographic characteristics in r-LVR when compared with no r-LVR group were listed in Table 2. There was no significant difference in terms of age, gender, risk factors, Killip class on admission, prevalence of multivessel coronary artery disease, time from symptom onset to reperfusion, anterior infarct site, and peak CK between groups; ST-segment reduction after PCI was higher in the r-LVR group (P = 0.02). Medications throughout hospital stay and during the follow-up were similar between groups. No difference in TIMI and myocardial blush grade 3 flows after PCI was found. In particular, there were no significant differences between groups as for the initial regional LV dysfunction area (RWMSI and WMA%), LV volumes, and LVEF. The extent of microvascular damage (CDL%, RCSI) on day 1 after reperfusion was significantly lower in r-LVR group.

Changes in contrast defect extent, LV volumes, regional LV dysfunction, and LVEF over time were reported in Table 3. At pre-discharge, only patients with r-LVR showed significant improvement in microvascular flow with parallel decrease in dysfunctioning area and improvement in LVEF. This functional improvement was confirmed at follow-up. In particular, a higher reduction in

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Table 2 Baseline clinical, angiographic, and echocardiographic parameters in the reverse left ventricular remodelling (r-LVR) group when compared with the no reverse left ventricular remodelling (no r-LVR) group

| Parameter                                      | r-LVR (43 pts) | No r-LVR (67 pts) | p     |
|------------------------------------------------|----------------|-------------------|-------|
| Mean age (years)                               | 57 ± 9         | 60 ± 11           | 0.24  |
| Male, n (%)                                    | 38 (88%)       | 54 (81%)          | 0.861 |
| Hypertension, n (%)                            | 33 (77%)       | 39 (60%)          | 0.454 |
| Diabetes, n (%)                                | 4 (9)          | 19 (19%)          | 0.082 |
| Smokers, n (%)                                 | 30 (70%)       | 39 (58%)          | 0.671 |
| Hypercholesterolaemia, n (%)                   | 19 (44%)       | 25 (37%)          | 0.775 |
| Family history of CAD, n (%)                   | 12 (30%)       | 17 (25%)          | 0.991 |
| ST-segment reduction (%)                       | 65 ± 33        | 42 ± 51           | **0.02** |
| Killip Class >1, n (%)                         | 10 (24%)       | 17 (26%)          | 0.981 |

Concomitant medications, n (%)

| Medication            | r-LVR (43 pts) | No r-LVR (67 pts) | p     |
|-----------------------|----------------|-------------------|-------|
| ACE inhibitor/ARB     | 40 (94%)       | 64 (96%)          | 0.963 |
| β-Blocker             | 39 (92%)       | 62 (93%)          | 0.944 |
| Statins               | 40 (94%)       | 65 (98%)          | 0.992 |
| Peak CK (Iul)         | 2019 ± 1933    | 2505 ± 1923       | 0.22  |
| TIMI 3 flow after PCI, n (%) | 37 (87) | 50 (76)          | 0.732 |
| MBG 3 after PCI, n (%) | 13 (30)       | 21 (32)           | 0.310 |

Infarct-related artery, n (%)

| Artery | r-LVR (43 pts) | No r-LVR (67 pts) | p     |
|--------|----------------|-------------------|-------|
| LAD    | 30 (70%)       | 52 (78%)          | 0.571 |
| RCA    | 4 (9)          | 6 (9)             |       |
| LCX    | 9 (21%)        | 9 (13)            |       |

Vessels disease, n (%)

| Disease | r-LVR (43 pts) | No r-LVR (67 pts) | p     |
|---------|----------------|-------------------|-------|
| One     | 36 (83%)       | 45 (68%)          | 0.121 |
| Two     | 4 (9)          | 15 (20%)          |       |
| Three   | 3 (7)          | 8 (12%)           |       |

Time to reperfusion (h)

| Time | r-LVR (43 pts) | No r-LVR (67 pts) | p     |
|------|----------------|-------------------|-------|
| 4.2 ± 5 | 5.5 ± 7       |                   | 0.36  |
| CDL%-T1 | 13 ± 17       | 21 ± 16           | **0.02** |
| RCSI-T1 | 1.7 ± 0.6     | 2 ± 0.6           | **0.01** |
| WMA%-T1 | 35 ± 21       | 41 ± 21           | 0.13  |
| RWMSI-T1 | 2.6 ± 0.7    | 2.7 ± 0.5         | 0.17  |
| LVEF%-T1 | 48 ± 8        | 46 ± 9            | 0.35  |
| LVESV-T1 | 110 ± 27      | 105 ± 28          | 0.41  |
| LVESV-T1 | 58 ± 21       | 55 ± 20           | 0.57  |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CK, creatine kinase; TIMI, thrombolysis in myocardial infarction; MBG, myocardial blush grade; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; CDL, contrast defect length; RCSI, regional contrast score imaging; WMA, wall motion abnormality; RWMSI, Regional Wall Motion Score Index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; CAD, coronary artery disease. P-values in bold are significant.
LVESV when compared with LVEDV was observed (−26 ± 13% vs. −13 ± 14%, respectively) leading to a significant improvement in LVEF at follow-up.

The extent of wall motion abnormality size was small in 32 out of 110 (29%) patients, intermediate in 40 (36%), and large in 38 (35%). In these three groups, the prevalence of r-LVR was similar (34, 35, and 32% respectively).

**Independent predictors of reverse left ventricular remodelling**

Using the ROC curve analysis, optimal cutoff values of different parameters in the prediction of r-LVR were identified (Table 4).

The in-hospital reduction in CDL ≥15% is the parameter with the best sensitivity and specificity in predicting r-LVR (71 and 75%, respectively, AUC 0.731, \(P = 0.0002\)).

At multivariate analysis, age <64 years [OR 3.25 (95% CI: 0.9–11.68), \(P = 0.071\)], initial extent of microvascular damage after reperfusion <20% [OR = 15.59 (95% CI: 3.27–74.38), \(P = 0.001\)], initial LVESV >60 ml [OR = 7.93 (95% CI: 1.75–35.8), \(P = 0.007\)], time to treatment [OR = 3.35 (95% CI: 0.99–11.28), \(P = 0.051\)], and in-hospital CDL reduction ≥15% [OR = 4.57 (95% CI: 1.05–19.79), \(P = 0.042\)] were independently associated with r-LVR (Table 5). After bootstrapping procedure, only the following variables were associated with r-LVR: CDL-T1 [OR = 9.90 (95% CI: 3.34–29.27), LVESV-T1 [OR = 2.85 (95% CI: 0.93–8.64), time to treatment [OR = 2.74 (95% CI: 1.06–7.06), and ΔCDL [OR = 3.84 (95% CI: 1.02–14.44), \(P < 0.05\)].

For the logistic regression, the optimal solution was found after eight major iterations. The bootstrap statistics were based on 150 samples.

**Two-year survival**

In up to 2-year follow-up, four patients (3.6%) had non-fatal re-infarction, nine (8.2%) were hospitalized for heart failure, and three (2.7%) had cardiac death. According to the Kaplan–Meier curves, patients with r-LVR had a significantly higher 2-year event-free survival rate (log-rank test \(P < 0.05\)) than those without r-LVR (Figure 1). Hazard ratios of all variables entered into the Cox model were listed in Table 6. By multivariable Cox analysis, independent predictors of MACE were: family history of CAD [HR 3.42 (1.18–9.88), age [HR 3.15 (0.98–1018)], r-LVR [HR 0.50 (0.18–1.38)], and LVESV-T1 [HR 1.02 (1.00–1.05)] (Table 7).

After bootstrapping procedure, the only variable significantly associated with a 2-year event-free survival was r-LVR [HR = 0.28 (0.12–0.66)].

**Discussion**

The AMICI multicenter study demonstrates for the first time that r-LVR frequently occurs in STEMI patients treated with PPCI. The relatively short time to IRA recanalization with stenting implantation, the systematic use of downstream glycoprotein IIB/IIIa inhibitors with double-antiplatelet therapy, and the widespread use of statins and antiremodelling medications may explain these positive results. A significant reduction of LV volumes may be
observed even in patients with large risk area soon after reperfusion, thus showing that r-LVR is independent of initial dysfunctioning area extent. For the first time, we provide cutoff values of parameters able to offer the best diagnostic accuracy in the prediction of r-LVR. The major determinant of r-LVR is an effective microvascular reflow within the infarct zone (CDL% < 20%). Also the reduction in microvascular damage in the first week after recanalization (≥15%), an initial large end-systolic volume (>60 mL), and a short time to treat (<2.5 h) independently predict reverse remodelling, r-LVR has a strong clinical impact because only in this subset of patients a significant improvement in LVEF and a significant reduction in definitive infarct size have been observed at follow-up. Further, this subset of patients had a significantly lower combined events rate at 2-year follow-up than patients without r-LVR.

Future studies aimed at evaluating the effects of new therapeutic interventions in STEMI patients have to take into account this spontaneous improvement in myocardial perfusion and function occurring up to 6 months after myocardial infarction.

### Previous studies

Ventricular enlargement after myocardial infarction is an adaptive compensatory mechanism to maintain stroke volume after the loss of contractile function. Several studies show that the extent of subsequent LV volume enlargement reflects the magnitude of the primary microvascular damage. 2–5,8–10 Conversely, little information is available on the incidence, determinants, and clinical significance of r-LVR after STEMI. Previous large multicentre trials showed that pharmaceutical agents, including ACE inhibitors and β-blockers, attenuate rather than reverse LVR, with a few notable exceptions. 8–10 The GISSI 3 study showed for the first time a significant LV volume reduction after myocardial infarction. However, determinants and clinical significance of this phenomenon were not described. 10 The SAVE study 19 and most recently the VALIANT and the CAPRICORN studies 20,21 demonstrated the linkage between attenuation of LV enlargement by captopril, valsartan, or carvedilol after infarction and improved clinical outcomes. Recently, it has been demonstrated that r-LVR may occur after coronary revascularization in patients with ischaemic cardiomyopathy 8 or even after

### Table 4 Receiver-operating characteristic curve analysis

| Cutoff value (95% CI) | Sensitivity (%) | Specificity (%) | AUC | 95% CI | P-value |
|-----------------------|-----------------|-----------------|-----|-------|---------|
| Age <64 (<59 to <69) | 74              | 58.8–86.3 (57–93) | 39  | 27.1–51.5 (21–59) | 0.563 0.465–0.657 | 0.2585 |
| ST reduction >59 (>53 to >65) | 70              | 53.0–84.1 (51–90) | 58  | 43.2–71.3 (39–77) | 0.656 0.548–0.754 | 0.0088 |
| Peak CK <3026 (<2998 to <3055) | 85              | 70.2–94.3 (69–99) | 40  | 27.0–54.1 (21–60) | 0.590 0.485–0.690 | 0.1223 |
| Vessels disease =1 | 83              | 69.3–93.2 (68–99) | 27  | 17.0–39.6 (6–53) | 0.538 0.440–0.634 | 0.4993 |
| TIMI grade =3 | 87              | 72.6–95.7 (71–100) | 23  | 14.0–36.2 (5–48) | 0.556 0.454–0.654 | 0.3442 |
| MBG =2 | 70              | 51.3–84.4 (49–92) | 32  | 20.0–47.5 (13–56) | 0.535 0.422–0.646 | 0.5871 |
| Time to reperfusion ≤2.5 (<1.7 to ≤3.4) | 60              | 43.3–74.4 (39–83) | 65  | 51.6–76.9 (47–85) | 0.591 0.489–0.687 | 0.1074 |

*95% bootstrap bias-corrected confidence interval. Abbreviations as in Table 2.*
Late reopening of an occluded IRA\(^2\) and is closely related to the extent of viable myocardium in the infarct zone. Similarly, a significant correlation was found between total scar burden at baseline and r-LVR after 6 months of CRT in patients with ischaemic cardiomyopathy.\(^2\) The total scar burden as detected by MCE is an independent predictor of long-term hard cardiac events in patients after AMI.\(^14\) Accordingly, our study showed that an effective microvascular reflow within the infarct zone soon after reperfusion is a key determinant of r-LVR and of long-term event-free survival. However, independently of dysfunctioning area soon after IRA reopening, the improvement of microvascular perfusion in the first week after hospital admission is a strong predictor of r-LVR at follow-up. In patients with r-LVR, a significant recovery of microvascular flow was detected during the first week after STEMI (\(\Delta CDL < -38\%) similar improvement in microvascular flow after reperfusion has been previously reported.\(^2\)\(^3\)\(^4\) Although there are no definitive explanations for this phenomenon, we can postulate that it might be the result of resolution of potentially reversible mechanisms of microvascular obstruction such as arteriolar spasm, tissue oedema, and cellular plugging.\(^2\)\(^3\)\(^4\) The improvement in microvascular flow may also be related to spontaneous angiogenesis occurring in the first week after reperfusion. An up-regulation of circulating endothelial progenitor cells (EPCs) known to be involved in vasculogenesis has been recently detected in the first week after primary stenting.\(^2\)\(^5\) The EPCs mobilized after AMI may contribute to new vessel generation and are closely related to a greater increase in myocardial salvage, decrease in LVESV, and recovery of LVEF.\(^2\)\(^6\)

Similar data have been recently reported by Ndrepepa et al.\(^2\)\(^7\) They showed in the majority of STEMI patients treated by PPCI a substantial improvement in LVEF at 6-month follow-up mainly

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**Table 5 Multiple logistic regression analysis for predictors of reverse left ventricular remodelling**

| Variables                  | Cutoff value (95% CI) | Univariable analysis OR (95% CI) | P     | Multivariable analysis OR (95% CI) | P     |
|----------------------------|----------------------|----------------------------------|-------|-----------------------------------|-------|
| Age                       | < 64                 | 1.845 (0.79–4.28)                | 0.155 | 3.25 (0.9–11.68)                  | 0.071 |
| Sex                       | Male                 | 1.83 (0.60–5.56)                 | 0.287 |                                   |       |
| Hypertension              | No                   | 0.042 (0.17–0.99)                | 0.049 |                                   |       |
| Diabetes                  | No                   | 2.34 (0.71–7.74)                 | 0.161 |                                   |       |
| Hypercholesterolaemia     | No                   | 0.752 (0.34–1.63)                | 0.473 |                                   |       |
| Smokers                   | No                   | 0.604 (0.26–1.35)                | 0.223 |                                   |       |
| Family history of CAD     | No                   | 0.878 (0.37–2.08)                | 0.769 |                                   |       |
| Time to treatment         | < 2.5                | 2.56 (1.13–5.82)                 | 0.024 | 3.35 (0.99–11.28)                 | 0.051 |
| Culprit lesion            | LAD                  | 0.66 (0.27–1.58)                 | 0.358 |                                   |       |
|                           | RCA                  | 1.04 (0.27–3.93)                 | 0.951 |                                   |       |
|                           | LCX                  | 1.70 (0.61–4.71)                 | 0.303 |                                   |       |
| ST reduction (%)          | > 59                 | 2.758 (1.131–6.723)              | 0.026 |                                   |       |
| Peak CK                   | < 3026               | 3.77 (1.36–10.49)                | 0.011 |                                   |       |
| TIMI grade after PCI      | = 3                  | 2.125 (0.70–6.40)                | 0.181 |                                   |       |
| MBG after PCI             | = 3                  | 0.89 (0.34–2.32)                 | 0.823 |                                   |       |
| Vessels disease           | 1                    | 2.4 (0.91–6.27)                  | 0.074 |                                   |       |
| WMA\% - T1                | < 41                 | 1.99 (0.91–4.33)                 | 0.082 |                                   |       |
| RWMSI - T1                | < 2.82               | 1.96 (0.87–4.41)                 | 0.104 |                                   |       |
| CDL\% - T1                | < 20                 | 3.639 (1.610–8.225)              | 0.002 | 15.59 (3.27–74.38)                | 0.001 |
| RCSI - T1                 | < 2                  | 1.776 (0.816–3.864)              | 0.148 |                                   |       |
| LVEF - T1                 | > 42                 | 1.99 (0.79–5)                    | 0.143 |                                   |       |
| LVESV - T1                | > 60                 | 1.619 (0.736–3.564)              | 0.231 | 7.93 (1.75–35.8)                  | 0.007 |
| LVEDV - T1                | > 104                | 1.820 (0.838–3.950)              | 0.130 |                                   |       |
| WMA\% - T2                | < 41                 | 3.38 (1.48–7.7)                  | 0.004 |                                   |       |
| RWMSI - T2                | < 2.18               | 5.769 (2.450–13.587)             | 0.000 |                                   |       |
| CDL\% - T2                | < 19.33              | 5.08 (2.05–12.57)                | 0.000 |                                   |       |
| DCDL\%                   | < –15                | 2.22 (0.92–5.32)                 | 0.072 | 4.57 (1.05–19.79)                 | 0.042 |
| RCSI - T2                 | < 1.8                | 4.052 (0.750–9.382)              | 0.001 |                                   |       |
| LVEF - T2                 | > 49                 | 3.069 (1.374–6.862)              | 0.006 |                                   |       |
| LVESV - T2                | < 50                 | 2.569 (1.170–5.643)              | 0.019 |                                   |       |
| LVEDV - T2                | < 105                | 3.024 (1.344–6.802)              | 0.007 |                                   |       |

Hosmer–Lemeshow test \(\chi^2 = 9.151\) 0.242

CI, confidence interval; OR, odds ratio; \(\Delta CDL\%\), in-hospital contrast defect length changes. Other abbreviations as in Table 2.
Figure 1: Kaplan–Meier curves showing patients with r-LVR had a significantly higher 2-year event-free survival rate (log-rank test \( P < 0.05 \)) than those without r-LVR.

Table 6 Unadjusted hazard ratios for major adverse cardiac events

| Variables | HR (95% CI) | P-value |
|-----------|-------------|---------|
| Age       | 1.025 (0.978–1.074) | 0.240   |
| Male      | 0.799 (0.269–2.40)   | 0.690   |
| Hypertension | 0.763 (0.29–2.007) | 0.583   |
| Diabetes  | 0.739 (0.171–3.200) | 0.686   |
| Hypercholesterolaemia | 1.162 (0.457–2.951) | 0.755   |
| Smokers   | 0.846 (0.340–2.103) | 0.718   |
| Family history of CAD | 2.454 (0.987–6.105) | 0.053   |
| Time to treatment | 1.555 (0.356–6.801) | 0.558   |
| ST reduction (%) | 1.007 (0.991–1.022) | 0.720   |
| Peak CK    | 1.003 (1.012–1.034) | 0.881   |
| TIMI grade after PCI | 1.555 (0.356–6.801) | 0.558   |
| MBG after PCI | 1.120 (0.621–2.026) | 0.706   |
| Number of diseased vessels | 1.173 (0.651–2.113) | 0.595   |
| WMA%-T1   | 1.035 (0.651–2.113) | 0.595   |
| RWMSI-T1  | 0.994 (0.84–2.148)  | 0.987   |
| CDL%-T1   | 0.994 (0.84–2.148)  | 0.987   |
| RCSI-T1   | 0.994 (0.84–2.148)  | 0.987   |
| LVEF%-T1  | 0.994 (0.84–2.148)  | 0.987   |
| LVESV-T1  | 0.994 (0.84–2.148)  | 0.987   |
| LVEDV-T1  | 0.994 (0.84–2.148)  | 0.987   |
| r-LVR     | 0.605 (0.230–1.593) | 0.240   |

CI, confidence interval; HR, hazard ratio; r-LVR, reverse left ventricular remodelling; Other abbreviations as in Table 2.

Table 7 Cox regression building procedure, using a stepwise forward approach for major adverse cardiac events prediction

| Variables          | HR (95% CI) | Clinical model (CM) | CM + r-LVR | CM + WMA%-T1 | CM + LVESV-T1 | CM + LVEDV-T1 | CM + r-LVR + LVESV-T1 |
|--------------------|-------------|---------------------|-------------|---------------|---------------|---------------|-----------------------|
| Family history of CAD | 3.64 (1.32–10.04) | 3.64 (1.32–10.04) | 3.64 (1.32–10.04) | 3.20 (1.13–9.02) | 3.14 (1.09–9.03) | 3.42 (1.18–9.88) |
| Age                | 4.15 (1.41–12.20) | 4.15 (1.39–12.41) | 3.63 (1.19–11.05) | 3.47 (1.13–10.64) | 3.74 (1.24–11.28) | 3.15 (0.98–10.18) |
| r-LVR              | 0.60 (0.23–1.58)  | 1.02 (0.99–1.05)   | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) |
| WMA%-T1            | 0.60 (0.23–1.58)  | 1.02 (0.99–1.05)   | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) |
| LVESV-T1           | 0.60 (0.23–1.58)  | 1.02 (0.99–1.05)   | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) |
| LVEDV-T1           | 0.60 (0.23–1.58)  | 1.02 (0.99–1.05)   | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) | 1.02 (1.00–1.04) |
| LR model \( \chi^2 \) | 10.16         | 11.82               | 12.53        | 13.93         | 11.46         | 15.39         |

CI, confidence interval; HR, hazard ratio; r-LVR, reverse left ventricular remodelling; Other abbreviations as in Table 2.
related to a progressive decrease in the perfusion defect. These changes have a beneficial effect on long-term survival.

In conclusion, the improvement of microvascular perfusion after STEMI is possible; it is independent of the initial extent of LV dysfunction and is a strong determinant of significant LV volume reduction and regional and global LV function improvement. Future studies aimed at assessing the efficacy of new angiogenetic drugs should take into account these spontaneous changes in microvascular flow occurring up to 6 months after STEMI.

**Clinical implications**

A reduction in LVEF of 10% has recently identified as the optimal cutoff value to predict long-term survival after CRT in patients with congestive heart failure thus signifying a clinically relevant reverse LVR. In our study population with AMI, a mean reduction at follow-up in LVEF of 26 ± 13% and in LVEDV of 13 ± 14% was observed, and was closely related to global and regional LV function improvement (ΔLVEF + 12%, ΔWMA −40%) and to long-term prognosis. These beneficial effects have been achieved in patients timely treated with primary IRA stenting and IIB/IIIA glycoprotein inhibitors. Further, large part of the study population received optimal medical therapy that includes ACE/ARBs, statins, and β-blockers and further support the importance of the use of these drugs after myocardial infarction. A recent meta-analysis showed a lesser efficacy of bone-marrow-derived cell therapy on cardiac function (mean reduction in infarct size −5.5%, in LVESV −4.8%, and in LVEDV −1.9%). Thus the effects of cell-based cardiac repair therapy may be masked by the powerful effect of reperfusion therapy and concomitant treatment.

**Study limitations**

The study population is relatively small and the 2-year event rate is low, thus the relationship between r-LVR and clinical outcome need to be confirmed in larger longitudinal studies. Patients enrolled in this study were optimally treated, thus the incidence or r-LVR in high-risk STEMI sub-optimally treated cannot be derived. However, the multicentre randomised design of the study adds strength to the results, and the data set collected allows drawing conclusions with sufficient statistical power. We have not performed quantitative analysis of the replenishment curves of MCE data because we believe that in the setting of AMI and for the purpose of the study these data did not add significant meaning to our results. On the other hand, we elected to quantify the length of MCE perfusion defect, which is the best indicator of the extent of microvascular damage and the ideal parameter able to influence LV remodelling. Finally, not all variables involved in determining dynamic changes in LV function and shape after AMI were considered in this study. In particular, the role of diastolic dysfunction, transmural extent of necrosis, and neurohormonal activation in preventing r-LVR need to be clarified by future studies.

**Conclusions**

A substantial number of STEMI patients treated according to the current guidelines show a significant reverse LVR. This volume reduction is an important predictor of favourable long-term clinical outcome.

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Cerebral embolism from subclinical carotid atherosclerotic lesion in a young woman with inflammatory Crohn disease

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A 39-year-old woman was hospitalized for sudden massive left haemiplegia. Her only risk factor was light smoking. She was diagnosed with Crohn disease 1 month before, and treated with corticoids. Early angio-computed tomographic (CT) scan and magnetic resonance imaging (MRI) showed large sylvian cerebral ischaemia, right sylvian artery thrombosis and suggested the existence of intraluminal right carotid bulb abnormality (Panel A). Ultrasound examination refined the abnormality as being a large mobile thrombus adherent to the posterior wall of the right bulb (Panel B). She was treated with heparin leading to lysis of the thrombus 7 days later (Panel C). A small plaque at the site of previous thrombus adhesion was visualized. After 1 month of Coumadin treatment, ultrasound confirmed the presence of a tiny ulcerated plaque (Panel D).

Laboratory investigations showed evidence of systemic inflammation. Traditional risk factors were normal. Serological examination for vasculitis-associated antibodies was negative.

Few cases of cerebrovascular complications in patients with Crohn disease have been published and were related to Crohn-associated vasculitis and/or consequence of hypercoagulability. Evidence of atherosclerotic aetiology has never been previously shown. Atherosclerosis is a chronic disease of the arterial wall where inflammation is central at all stages. This case illustrates the mechanism of stroke in a young woman with active inflammatory Crohn disease and high pro-thrombotic condition, due to small atherosclerotic plaque ulceration and thrombus embolization. It emphasizes the prominent role of carotid ultrasound in such cases.