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

Stefania Funaro[1], Giuseppe La Torre[2], Mariapina Madonna[3], Leonarda Galiuto[4], Antonio Scarà[4], Alessandra Labbadia[3], Emanuele Canali[3], Antonella Mattatelli[3], Francesco Fedele[3], Francesco Alessandrini[1], Filippo Crea[4], and Luciano Agati[1]*, on behalf of AMICI Investigators

[1]Department of Cardiology, Catholic University of the Sacred Heart, Campobasso, Italy; [2]Epidemiology and Biostatistics Unit, Catholic University of the Sacred Heart, Rome, Italy; [3]Department of Cardiology, 'La Sapienza' University of Rome, Italy; and [4]Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

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[6,7] 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.[7] r-LVR was also observed after ST-elevation acute myocardial infarction (STEMI).[8–10] 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.[11]

Thus, we analysed the Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study database[3] 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[2–5,12,13] 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.[3] 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 consensus 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 as previously described (3.12.13). A percentage of the extent of wall motion abnormalities (WMA%), as an index of the ischaemic damage, was also calculated by dividing the number of akinetic and dyskinetic segments by the total number of segments evaluated.[3,12,13] Regional LV dysfunction area was arbitrary defined as large when WMA% was >50, intermediate when WMA% was between 25 and 50, and small when WMA% was <25%. Reverse remodelling was defined as >10% reduction in LVESV at 6 months follow-up compared with 24 h echocardiogram.[7]

Myocardial contrast echocardiography

Microvascular perfusion was assessed by real-time myocardial contrast echocardiography (MCE) using continuous infusion of Sonovue® (Bracco Imaging) as previously described.[3,12,13] In brief, a rotating infusion pump (Vueject, Bracco Imaging, 2–4 vials at 78–180 mL/h infusion rate) was used. Commercially available ultrasound systems equipped with a real-time imaging package were used. A compromise between power gain, dose and rate of contrast injection, and flash duration was achieved to obtain a completely dark myocardium after the flash. The settings of the echocardiograph were adjusted to optimize myocardial opacification and minimize attenuation artefacts. Instrument settings, including power, gray-level compression (dynamic range), gain, and frequency were kept constant until the end of the session. For each patient, the previously optimized contrast settings were carefully matched for control MCE studies. MCE images were digitally stored in a magneto-optical disk. The best MCE images were selected for quantitative analysis of perfusion defect.

Qualitative analysis

The dysfunctional LV segments at baseline 2DE represented the area at risk of necrosis. For analysis of myocardial perfusion, each initially hypo, akinetic, or dyskinetic LV segment was graded using MCE during simultaneously performed 2DE, 4-2-3-chamber apical views. Poor or no opacification was defined as delayed, low, or absent contrast enhancement in the evaluated segment when compared with adjacent segments with adequate opacification. A 17-segment model of the left ventricle was used to assign the following contrast scores: 1—homogeneous enhancement; 2—patchy enhancement; 3—no enhancement. A Regional Contrast Score Index (RCSI) was calculated by dividing the sum of the contrast scores for each dysfunctional segment by the number of dysfunctional segments analysed. In case of disagreement over scoring, a consensus was reached after open discussion.

Quantitative analysis

Quantitative analysis was performed on MCE images after coronary reflow and at pre-discharge using Qontrast® Software (Bracco Imaging), as previously described.[3,12,13] In brief, from native MCE images, the length of the endocardial border corresponding to the segment of the myocardium with no or poor opacification was measured in the 2-4- and 3-chamber views. The sum of endocardial border length measurements defined the size of the perfusion defect. The following formula was used to assess the relative contrast defect length (CDL%): (total length of residual contrast defect after reperfusion)/(total length of endocardial border) × 100.

Percutaneous coronary intervention and medications

In all patients, PPCI and stenting of the infarct-related artery (IRA) was performed according to the clinical protocol used at our institutions.[3,13] TIMI grade and myocardial blush grade were semi-quantitatively scored as previously described.[3,13] Number of coronary vessels showing significant CAD was calculated.

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 (defined as sudden death caused by AMI or arrhythmia or heart failure), non-fatal AMI (typical chest pain and increased troponin I), and hospitalization for congestive heart failure. The diagnosis of heart failure was based on clinical symptoms (limitation of activity, fatigue, and dyspnoea), physical signs (oedema, elevated jugular venous pressure, rales, or third heart sound with gallop), or radiological evidence of pulmonary congestion.[7] 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 different value 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 χ^2 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 $P \leq 0.05$ (two-sided tests), and for multiple testing we used a statistical significance of $P \leq 0.01$.

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 (L.G.), 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.[14] 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.[15]

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 led to an overfitting. As one of the main point 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 technique was used.[16] In order to validate our final logistic model, we used the bootstrapping procedure performing a non-linear regression, programming a maximum number of 999 iterations. This procedure released the beta-coefficients of the variables inserted in the model, and we back-calculated the OR (and 95% CIs) through an exponential transformation. The non-linear regression used in the bootstrapping procedures was a generalized linear model for the logistic regression. For the Cox analysis, we performed the boosting procedure described by Li and Luan,[17] using the R package *mboost* and the call gamboost (x, y, family = CoxPH()) as suggested by Hothorn and Buhlmann.[18]

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*).

Table 1 Mean difference and 95% limits of agreement (95% confidence intervals) of values from echo analysis comparing inter- and intra-observer variability at two different time and for each observer (L.G. and L.A.)

	Mean difference	95% Limits of agreement (95% CIs)
CDL% 1	0.76	−1.92 (−2.13 to −1.70)−3.44 (3.21−3.66)
CDL% 2	−0.42	−2.34 (−2.51 to −2.18)−1.50 (1.34−1.66)
CDL-LG	−0.47	−2.25 (−2.49 to −2.02)−1.31 (1.09−1.54)
CDL-LA	0.71	−1.83 (−2.01 to −1.67)−3.25 (3.06−3.45)
LVESV 1	0.25	−2.08 (−2.12 to −2.04)−2.57 (2.53−3.62)
LVESV 2	1.00	−1.82 (−2.15 to −1.50)−3.82 (3.50−4.15)
LVESV-LG	−0.75	−5.13 (−5.34 to −4.92)−3.63 (3.45−3.80)
LVESV-LA	0	−2.82 (−2.93 to −2.71)−2.82 (2.69−2.94)
LVEDV 1	0.13	−4.30 (−4.47 to −4.12)−4.45 (4.30−4.61)
LVEDV 2	−0.5	−5.16 (−5.26 to −5.05)− 4.16 (4.07−4.26)
LVEDV-LG	−0.63	−5.41 (−5.54 to −5.27)−4.15 (4.03−4.28)
LVEDV-LA	0	−3.20 (−3.27 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.

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

	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 (%)			
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 (lul)	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 (%)			
LAD	30 (70)	52 (78)	0.571
RCA	4 (9)	6 (9)	
LCX	9 (21)	9 (13)	
Vessels disease, n (%)			
One	36 (83)	45 (68)	0.121
Two	4 (9)	15 (20)	
Three	3 (7)	8 (12)	
Time to reperfusion (h)	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
LVEDV-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; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; CAD, coronary artery disease. P-values in bold are significant.

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

Table 3 Temporal changes of echocardiographic parameters in reverse LV remodelling (r-LVR) when compared with no reverse LV remodelling (no r-LVR) group

	r-LVR				No r-LVR			
	T1	T2	T3	P	T1	T2	T3	P
CDL%	13 ± 17	8 ± 13		**0.001**	21 ± 16	19 ± 17		0.080
RCSI	1.7 ± 0.6	1.5 ± 0.5		**0.000**	2 ± 0.6	1.9 ± 0.6		0.136
WMA%	35 ± 21	25 ± 21	21 ± 22	**0.010**	41 ± 21	39 ± 21	38 ± 22	0.169
RWMSI	2.6 ± 0.7	2 ± 0.8	1.7 ± 0.4	**0.013**	2.7 ± 0.5	2.6 ± 0.6	2.6 ± 0.7	0.182
LVEF%	48 ± 8	51 ± 9	55 ± 8	**0.047**	46 ± 9	46 ± 9	45 ± 8	0.329
LVEDV	110 ± 27	102 ± 27	94 ± 27	**0.004**	105 ± 28	113 ± 32	121 ± 38	0.000
LVESV	58 ± 21	49 ± 19	41 ± 14	**0.048**	56 ± 20	60 ± 26	68 ± 31	0.000

Abbreviations as in *Table 2*.

LVESV when compared with LVEDV was observed ($-26 \pm 13\%$ vs. $-13 \pm 14\%$, 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 $\geq$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 $\geq$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].

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

Table 4 Receiver-operating characteristic curve analysis

	Cutoff value (95% CI)	Sensitivity (%)	95% CI (*)	Specificity (%)	95% CI (*)	AUC	95% CI	P-value
Age	<64 (<59 to <69)	74	58.8−86.5 (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
CDL%-T1	**<20 (<15 to <26)**	**70**	**53.9−82.8 (50−91)**	**61**	**48.5−72.9 (44−83)**	**0.635**	**0.538−0.725**	**0.0110**
RCSI-T1	**<2 (<1.1 to 3)**	**60**	**44.4−75.0 (38−85)**	**53**	**41.1−66.0 (35−74)**	**0.626**	**0.529−0.717**	**0.0182**
WMA%-T1	<41 (<28 to <55)	65	49.1−79.0 (44−88)	56	44.0−68.8 (36−78)	0.580	0.482−0.674	0.1458
RWMSI-T1	<2.82 (<1.23 to <4.44)	46	31.2−62.3 (25−70)	73	60.9−83.2 (58−89)	0.579	0.481−0.672	0.1522
LVEF%-T1	>42 (>39 to >45)	81	66.6−91.6 (65−98)	31	20.6−43.8 (11−55)	0.557	0.459−0.651	0.3182
LVEDV-T1	>104 (>82 to >127)	58	42.1−73.0 (37−82)	56	44.0−68.8 (21−58)	0.554	0.457−0.649	0.3380
LVESV-T1	>60 (>33 to >86)	44	29.1−60.1 (23−68)	67	54.6−78.1 (50−83)	0.526	0.428−0.622	0.6532
CDL%-T2	**<19 (<16 to <23)**	**81**	**66.6−91.6 (64−99)**	**54**	**41.1−66.0 (35−75)**	**0.682**	**0.586−0.767**	**0.0003**
RCSI-T2	**<1.8 (<1.5 to 2)**	**74**	**58.8−86.5 (55−95)**	**58**	**45.5−70.1 (40−77)**	**0.695**	**0.600−0.780**	**0.0001**
WMA%-T2	**<41 (<38 to <44)**	**83**	**69.3−93.2 (68−99)**	**48**	**35.4−60.3 (28−69)**	**0.654**	**0.558−0.742**	**0.0031**
RWMSI-T2	**<2.1 (<1.5 to <2.8)**	**58**	**42.1−73.0 (37−81)**	**80**	**69.1−89.2 (66−94)**	**0.659**	**0.563−0.747**	**0.0021**
LVEF%-T2	**>49 (>40 to >58)**	**67**	**51.5−80.9 (45−92)**	**60**	**47.0−71.5 (39−80)**	**0.639**	**0.542−0.729**	**0.0114**
LVEDV-T2	<105 (<89 to <120)	70	53.9−82.8 (50−92)	57	44.0−68.8 (33−81)	0.603	0.505−0.695	0.0579
LVESV-T2	**<50 (<36 to <55)**	**60**	**44.4−75.0 (38−84)**	**62**	**50.0−74.2 (47−79)**	**0.627**	**0.530−0.718**	**0.0170**
ΔCDL%	**<−15 (<−21 to <−10)**	**71**	**47.8−88.6 (44−99)**	**75**	**61.1−86.6 (58−92)**	**0.731**	**0.612−0.830**	**0.0002**

*95% bootstrap bias-corrected confidence interval.
Abbreviations as in *Table 2*.

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

Variables	Cutoff value (95% CI)	Univariable analysis		Multivariable analysis	
		OR (95% CI)	P	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**		
ΔCDL%	<−15	2.22 (0.93–5.32)	**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; ΔCDL%, in-hospital contrast defect length changes. Other abbreviations as in *Table 2*.

late reopening of an occluded IRA[9] 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.[22] 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 (ΔCDL −38%). Similar improvement in microvascular flow after reperfusion has

been previously reported.[23,24] 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.[23,24] 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.[25] 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.[26]

Similar data have been recently reported by Ndrepepa *et al.*[27] They showed in the majority of STEMI patients treated by PPCI a substantial improvement in LVEF at 6-month follow-up mainly
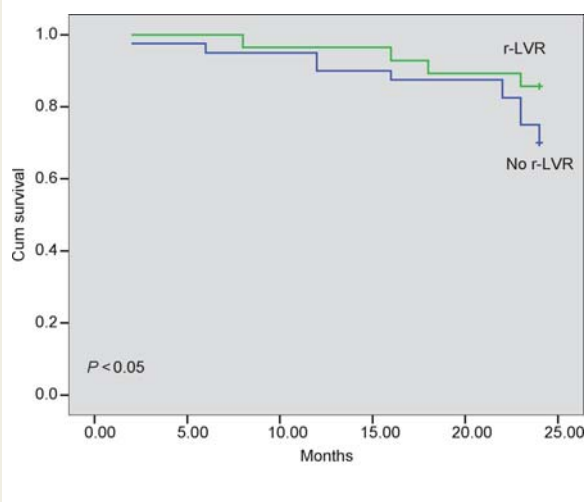
Figure 1 Kaplan–Meier curves showing patients with r-LVR had a significantly higher 2-year event-free survival rate (log-rank test $P < 0.05$) than those without r-LVR.

Table 6 Unadjusted hazard ratios for major adverse cardiac events

Variables	MACE ($n = 16$)	
	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
Anterior wall AMI	1.576 (0.653–2.153)	0.576
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	1.024 (1–1.049)	**0.053**
RWMSI-T1	0.994 (0.460–2.148)	0.987
CDL%-T1	1.011 (0.985–1.037)	0.411
RCSI-T1	1.240 (0.647–2.377)	0.517
LVEF%-T1	0.947 (0.896–1.001)	0.556
LVESV-T1	1.025 (1.006–1.045)	**0.012**
LVEDV-T1	1.015 (1–1.030)	**0.054**
r-LVR	0.605 (0.230–1.593)	**0.240**

CI, confidence interval; HR, hazard ratio; r-LVR, reverse left ventricular remodelling; AMI, acute myocardial infarction. 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)	3.81 (1.36–10.69)	3.64 (1.29–10.22)	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)				0.50 (0.18–1.38)
WMA%-T1			1.02 (0.99–1.05)			
LVESV-T1				1.02 (1.00–1.04)		1.02 (1.00–1.05)
LVEDV-T1					1.01 (0–99–1.02)	
LR model χ^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 LVESV of 10% has recently identified[7] 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 LVESV of $26 \pm 13\%$ and in LVEDV of $13 \pm 14\%$ 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[11] 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 randomized 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.[2–5,12,13,24] 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 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.

References

1. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. *Circulation* 1990;**81**:1161–1172.
2. Bolognese L, Carrabba N, Parodi G, Santoro GM, Buonamici P, Cerisano G, Antoniucci D. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. *Circulation* 2004;**109**:1121–1126.
3. Galiuto L, Garramone B, Scarà A, Rebuzzi AG, Crea F, La Torre G, Funaro S, Madonna MP, Fedele F, Agati L. The extent of microvascular damage at myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodelling: results of the multicenter study 'Acute Myocardial Infarction Contrast Imaging' (AMICI). *J Am Coll Cardiol* 2008;**51**:552–559.
4. Grayburn PA, Choi JW. Advances in the assessment of no-reflow after successful primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2008;**51**:566–568.
5. Hayat SA, Senior R. Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time? *Eur Heart J* 2008;**29**:299–314.
6. Rao RK, Kumar UN, Schafer J, Viloria E, De Lurgio D, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronisation therapy. *Circulation* 2007;**115**:2136–2144.
7. Yu CM, Bleeker CB, Fung JWH, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronisation therapy. *Circulation* 2005;**112**:1580–1586.
8. Rizzello V, Poldermans D, Boersma E, Biagini E, Schinkel AFL, Krenning B, Elhendy A, Vourvouri EC, Sozzi FB, Maat A, Crea F, Roelandt J, Bax JJ. Opposite patterns of left ventricular remodelling after coronary revascularization in patients with ischemic cardiomyopathy: role of myocardial viability. *Circulation* 2004;**110**:2383–2388.
9. Bellenger NG, Yousef Z, Rajappan K, Marber MS, Pennel DJ. Infarct zone viability influences ventricular remodeling after late recanalization of an occluded infarct related artery. *Heart* 2005;**91**:478–483.
10. Giannuzzi P, Temporelli PL, Bosimini E, Gentile F, Lucci D, Maggioni AP, Gavazzi L, Badano L, Stoian I, Piazza R, Geraci E, Nicolosi GL. Heterogeneity of left ventricular remodeling after acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-3 Substudy. *Am Heart J* 2001;**141**:131–138.
11. Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, Zuba-Surna EK, Al Mallah M, Dawn B. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med* 2007;**167**:989–997.
12. Agati L, Funaro S, Veneroso G, Volponi C, Tonti G. Clinical utility of contrast echocardiography in the management of patients with acute myocardial infarction. *Eur Heart J* 2002;**4**(Suppl. C):C27–C34.
13. Agati L, Funaro S, Madonna MP, Sardella G, Garramone B, Galiuto L. Does coronary angioplasty after timely thrombolysis improve microvascular perfusion and left ventricular function after acute myocardial infarction? *Am Heart J* 2007;**154**:151–157.
14. Dwivedi G, Janardhanan R, Hayat SA, Swinburn JM, Senior R. Prognostic value of myocardial viability detected by myocardial contrast echocardiography early after acute myocardial infarction. *J Am Coll Cardiol* 2007;**50**:327–334.
15. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy. *Stat Sci* 1986;**1**:54–77.
16. Harrell FE, Lee KI, Mark DB. Multivariable prognostic models: issue in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387.
17. Li H, Luan Y. Boosting proportional hazards models using smoothing splines, with applications to high-dimensional microarray data. *Bioinformatics* 2005;**21**:2403–2409.

18. Hothorn T, Buhlmann P. Model-based boosting in high dimensions. *Bioinformatics* 2006;**22**:2828–2829.

19. Sutton MJ, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas G, Rouleau J, Parker JO, Arnold MO, Sussex B, Braunwald E, for the SAVE investigators. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation* 1997;**96**:3294–3299.

20. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, Warnica W, Khrakoskaya M, Schwartz Y, Velazquez EJ, Califf RM, McMurray JV, Pfeffer MA. Changes in ventricular size and function in patients treated with Valsartan Captopril, or both after myocardial infarction. *Am Heart J* 2005;**111**:3411–3419.

21. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICON echo substudy. *Circulation* 2004;**109**:201–206.

22. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TAM, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007;**99**:657–660.

23. Galli M, Marcassa C, Bolli R, Giannuzzi P, Temporelli PL, Imparato A, Silva Orrego PL, Giubbini R, Giordano A, Tavazzi L. Spontaneous delayed recovery and contraction after the first 5 weeks following anterior infarction: evidence for the presence of hibernating myocardium in the infarcted area. *Circulation* 1994;**90**:1386–1397.

24. Galiuto L, Lombardo A, Maseri A, Santoro L, Porto I, Cianflone D, Rebuzzi AG, Crea F. Temporal evolution and functional outcome of no-reflow: sustained and spontaneously reversible patterns following successful coronary recanalization. *Heart* 2003;**89**:731–737.

25. Massa M, Rosti V, Ferrario M, Campanelli R, Ramaioli I, Rosso R, De Ferrari GM, Ferlini M, Goffredo L, Bertoletti A, Klersy C, Pecci A, Moratti R, Tavazzi L. Increased circulating hematopoietic and endothelial progenitor cells in the early phase of acute myocardial infarction. *Blood* 2005;**105**:199–206.

26. Numaguchi Y, Sone T, Okumura K, Ishii M, Morita Y, Kubota R, Yokouchi K, Imai H, Harada M. The impact of the capability of circulating progenitor cell to differentiate on myocardial salvage in patients with primary acute myocardial infarction. *Circulation* 2006;**114**:114–119.

27. Ndrepepa G, Mehilli J, Martinoff S, Schwaiger M, Schomig A, Kastrati A. Evolution of left ventricular ejection fraction and its relationship to infarct size after acute myocardial infarction. *J Am Coll Cardiol* 2007;**50**:149–156.

## CARDIOVASCULAR FLASHLIGHT

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

Marianne Lafitte[1]*, Sabrina Debruxelles[2], Igor Sibon[2], François Rouanet[2], and Thierry Couffinhal[1]

[1]CEPTA, CHU Haut Leveque, Pessac and Victor Segalen University, Bordeaux, France and [2]Stroke Unit, CHU Pellegrin and Victor Segalen University, Bordeaux, France

* Corresponding author. Tel: +33 557 656 270, Fax: +33 557 656 271, Email: marianne_lafitte@hotmail.com

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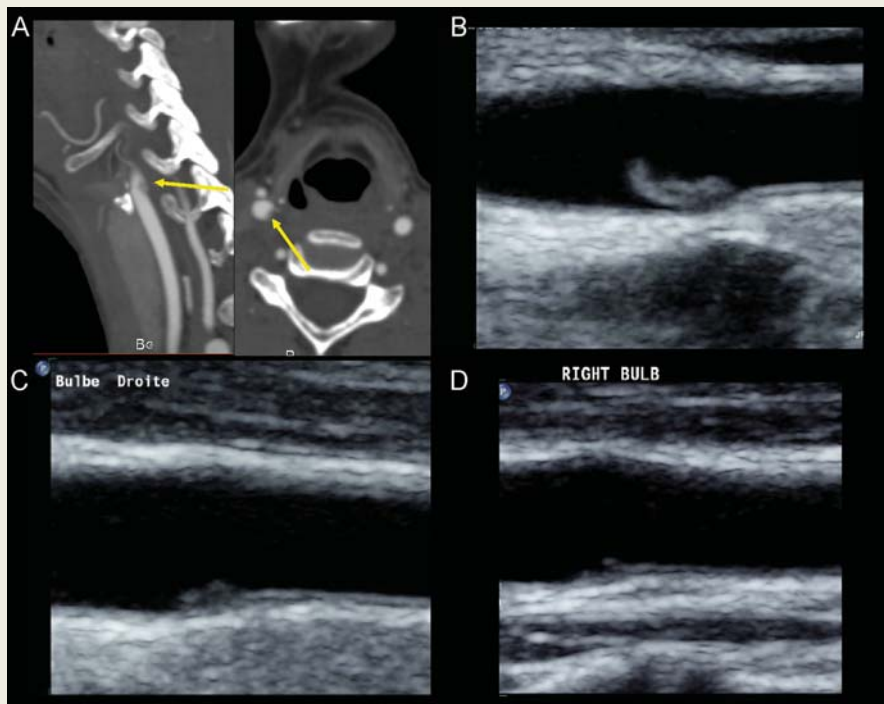
Laboratory investigations showed evidence of systemic inflammation. Traditional risk factors were normal. Serological examination for vasculitis-associated antibodies was negative.

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.