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Research Article

REGIONAL CONTRACTILITY AS PREDICTOR FOR LEFT VENTRICULAR REVERSE REMODELING AFTER REVASCULARIZATION FOR CHRONIC TOTAL OCCLUSIONS - A 3D ECHOCARDIOGRAPHIC STUDY

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ABSTRACT

The present study aims to identify 3D echocardiography-derived parameters to predict regression of LV remodeling in patients with chronic total occlusion (CTO) of Left Anterior Descending Artery (LAD), based on 3D assessment of regional and global contractility. In total, 38 subjects with successful reopening of an LAD chronic total occlusion were enrolled. Regression of ventricular remodeling (RR) was defined as >15% reduction of LV end-diastolic diameter at 3 moths after reopening of the occluded LAD. Patient groups were: gr.1 - 22 pts with RR, gr.2 - 16 pts without RR. All patients underwent computerized 3D echocardiography with complex assesment of global and regional function and remodelling, based on classic parameters (EF, ventricular volumes) and on 3D regional index of contraction amplitude (RICA), defined as the sum of maximum contraction amplitude for those segments irrigated by the infarct-related artery divided by the number of these segments. Group 1 presented lower baseline values for EF (46.60 %+/- 6.09% vs 49.39% +/- 3.46, p=0.008) and higher baseline values for EDV (164.50 +/- 19.9346 ml versus 156.93 +/- 16.46 ml, p=0.2), ESV (87.09+/- 8.41 ml vs 79.37 +/- 9.46 ml, p= 0.01), and RICA (2.70 versus 2.05, p=0.01) compared with no RR group. Linear regression showed a statistically significant correlation between the index of regressive remodeling and the RICA (p = 0.02) at 3 months post-revascularization. The logistical analysis based on ROC curve characteristics showed a good predictive value of RICA for prediction of regression of ventricular remodeling after revascularization, with a good area under the curve (AUC) of 0.72 (p = 0.003). The cut-off point of 2.6 for the RICA had a sensitivity of 77%, and a specificity of 69% in predicting regression of ventricular remodeling after revascularization. This study demonstrates the correlation between changes in global and regional ventricular contractility and the regression of ventricular remodeling after revascularization of a chronic total LAD occlusion. A less severe impairment of regional contractility was associated with regression of the ventricle's remodeling process, while the regional index of contraction amplitude shows a good predictive value for prediction of left ventricular remodeling regression.

Key Words: *Remodeling, 3D Echocardiography, Acute Myocardial Infarction, Ventricular Dysfunction*

INTRODUCTION

One of the main complications of an acute myocardial infarction (AMI) is the development of a deletorious ventricular remodeling and consecutive heart failure, which has an extremely negative impact on the further evolution of these patients. It has been demonstrated that the degree of ventricular remodeling is one of the most important predictor for worse outcomes in the postinfarction period (Sutton *et al.*, 2000). Ventricular remodeling is more frequent in cases of large anterior infarctions caused by obstructions of the left anterior descending artery (LAD) and in those cases where no revascularisation procedures have been performed in the acute phase (Barletta *et al.*, 2008). However, several studies tried to reveal a potential role of late revascularization of infarcted-related artery, proving that this late revascularization, beyond the acute phase, could play a role in stopping the remodeling process and regression of the already-installed ventricular remodeling on long term (Carluccio *et al.,* 2006). The studies on the so-called "late open-coronary" hypothesis showed contradictory results, indicating that some categories of patients respond to late revascularisation while others do not. However, all the studies have failed so far to identify significant predictors associated to regression of cardiac remodeling following late revascularization in myocardial infarction (Silva *et al.,* 2005; Rizzello *et al.,* 2004). Indication for late reopening of coronary arteries after Acute Myocardial Infarction (AMI) is mainly based on identification of viable, hibernated myocardium. Identification of hibernated myocardium (areas of viable myocardium, located in the peripheral areas of the infracted zone myocardium) (Wenk *et al.,* 2012), able to recover its contractility after different methods of revascularization, as well as identification of ischaemic myocardium which could seem normal at rest but present a contractility disfunction at stimulation with dobutamine, could play an important role because these area of myocardium represents the target area for revascularisation therapy (Ghanem *et al.,* 2008). It is well known that stress concentration around a region of infarction depends more strongly on the inotropic state of the noninfarcted tissue than on the infarct size, and different loading conditions and the tethering effect of the infarct-related myocardium may reduce function in the remote myocardium (Bodí *et al.,* 1999). Therefore in this study we aimed at demonstrating the role of regional contractility, in the region including not only the infarcted segments but also the surrounding territories, irrigated by the distal part of the infarcted artery, in regression of ventricular remodeling following revascularization of the infarct related artery.

MATERIALS AND METHODS

Patients

In total, we enrolled 38 subjects with recent anterior myocardial infarction treated conservative in the acute phase due to the late presentation (more than 12 hours after the onset of symptoms) in whom coronarography performed at 6 weeks following the infarction revealed a chronic total occlusion of the left anterior descending artery (LAD) and in whom dobutamin echocardiography revealed existence of viable myocardium in the territory irrigated by the LAD.

Chronic total occlusion was defined as a total occlusion of the LAD older than 6 weeks.

Viable myocardium was defined as an akinetic myocardial segment at rest, which presents a partial or total recovery of its contractility following infusion of Dobutamin in increased doses, as evaluated by 3D echocardiography.

In all patients percutaneous revascularization of the LAD was successfully achieved, with TIMI III flow postintervention, at 6 weeks after the infarction. All patients received complex medical therapy (ACE inhibitors, clopidogrel, aspirin, statins) before the intervention which was continued on long term.

3D echocardiography was performed at baseline immediately after the infarction and repeated at 6 weeks, before revascularization, to assess the development of ventricular remodeling. At 3 months after revascularization, 3D echocardiography was repeated to assess the regression of ventricular remodeling following reopening of the LAD.

According to the 3D echocardiographic results at 3 months, patients were restrospectively divided in two groups: group 1 - 22 patients who developed regression of left ventricular remodeling (RR) 3 months after revascularization, and group 2 - 16 patients in whom 3D echocardiography did not reveal a regression of left ventricular remodeling (no RR).

All patients gave written informed consent for the study, and the study protocol was approved by the ethics committee of the center where the study was conducted.

The demographic data, history and risk factors (age, gender, smoking status, presence of diabetes, hyperlipidemia, obesity and hypertension) were recorded for every patient.

3D Echocardiographic Analysis

All echocardiographic examinations were carried out at the baseline (day 2+/-3 postinfarction) at 6 weeks after the infarction (to assess the postinfarction ventricular remodeling) and during follow-up at 3 months postrevascularization (to assess the postrevascularization regression of remodeling), using a Sonos 7500 equipment (Philips, Netherlands). All acquired images were transferred to the QLab workstation for data processing, measurements and interpretation.

3D echocardiographic analysis started with delineation of the endocardial border followed by definition of ventricular segments (Figure 1A). Based on recommendations by the American Heart Association, left ventricle was divided into 17 segments. Therefore, in the 38 patients, 646 ventricular segments were analyzed and for each of the segments a contractility curve was obtained (figure 1 B and C). Than a polar map of contractility was automatically generated, indicating the region with wall motion abnormality as a spot on the polar map of contraction (figure 1D)

For each segment the following parameters were determined using the QLab workstation: maximum contraction amplitude (endocardial excursion), maximum and minimum volume during the cardiac cycle and segmental ejection fraction. After summation of these data from all the 17 segments, we obtained the 3D-determined left ventricular end-diastolic (LVED) and end-systolic volumes (LVES) and ejection fraction (EF).

Remodeling was assessed by measuring serial changes in global LV volume using 3D echocardiography at baseline immediately after the infarction and after 6 weeks, immediately before the revascularization.

Positive remodeling (PR) was defined as an increase in LV end-diastolic global volume with >15% compared with baseline, while ***regression of ventricular remodelling*** (RR) was defined as a >15% reduction of LVED volume at 3 months

Regression remodeling index (RI) was defined as the % reduction of LVED volume a 3 months following revascularization divided by the LVED volume immediately after revascularization.

Assessment of myocardial viability was performed using dobutamine stress test associated with 3D echocardiography. For this, we repeatedly acquired the 3D cineloops of ventricular contraction at rest and after each 3 minutes of injection of Dobutamine in doses of 5, 10, 20, and 30 micrograms/kgc/min. The cineloops were than transferred to the 3D workstation and we obtained computerized contraction curves for each myocardial segment and polar maps of contraction corresponding to each dosage of the dobutamin infusion. A spot on the polar map represented an akinetic segment, and a viable segment was defined as a segment appearing akinetic on the polar map obtained at rest but with recovered contractility (regression of the spot) after stimulation with dobutamin (figure 1D and E).

In order to assess the regional contractility we defined the following contraction parameters based on the 3D echo assessment of ventricular contractility:

-Index of contraction amplitude (ICA) was defined as the sum of maximum contraction amplitude for all segments divided by the number of segments.

-Regional index of contraction amplitude (RICA) was defined as the sum of maximum contraction amplitude for those segments irrigated by the infarct-related artery divided by the number of these segments.

We followed the correlation between these 3D-echo derived parameters and the regression of cardiac remodeling following revascularization of viable myocardium, which was assessed by measuring serial changes in global LV volume using 3D echocardiography at baseline and after 3 months follow-up.

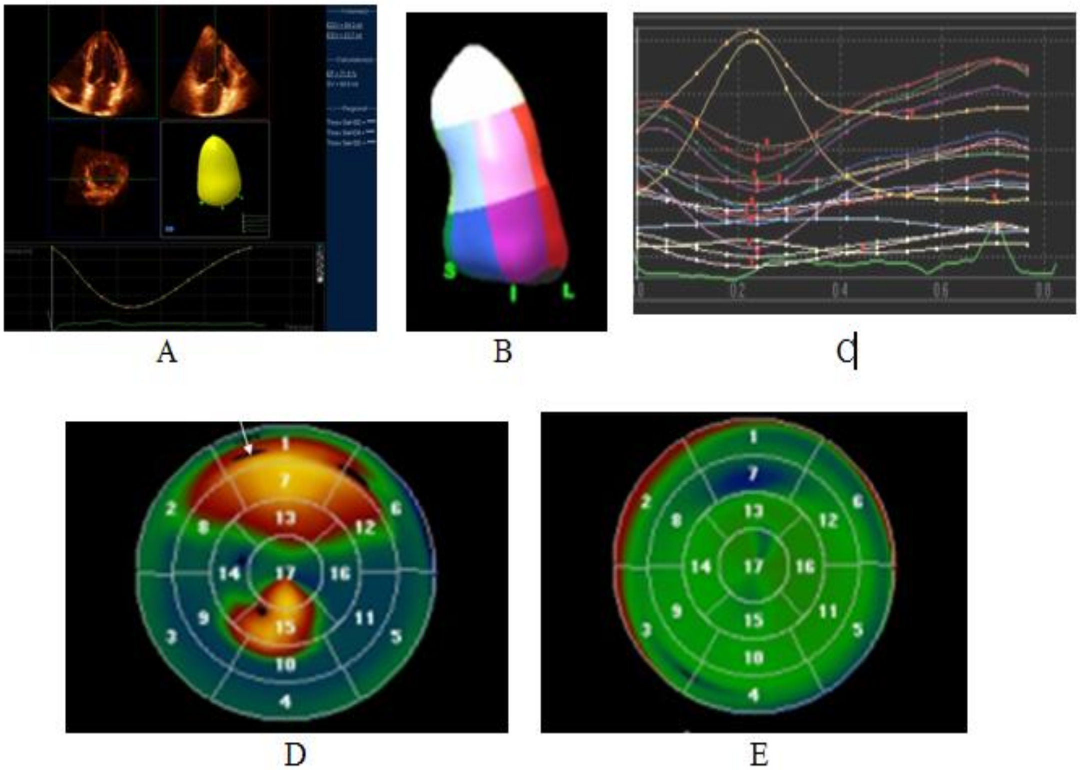

Figure 1: 3D echocardiography - (A) endocardial border detection and automated cuantification of ventricular volumes and ejection fraction; (B) segmentation of a remodeled left ventricle; (C) wall motion analysis using contractility curves of endocardial excursion for each of the 17 segments; (D) - polar map of ventricular contraction with a spot indicating an akinetic segment; (E) regression of the spot on the polar contraction map after stimulation with dobutamine, indicating the presence of a viable myocardium

Statistical Analysis
All statistical analysis was performed using the JMP 10 statistical software (SAS Institute Inc., Cary, North Carolina).
We used the Fisher's exact test (or the Student's *t*-test for age) for comparing the baseline characteristics of patients between the PR and non-PR population. Continuous values are expressed as the mean and standard deviation, and statistical significance was determined using the Mann-Whitney test. Categorical variables are expressed as percentages. Statistical significance was considered for a p value <0.05 and all p values were 2-sided. For those variables with $p<0.05$, we performed logistic regression analysis to test their reliability in predicting the development of ventricular remodeling.

RESULTS AND DISCUSSION
Results
The clinical baseline characteristics of the study population showed no significant differences between the PR and non-PR group in respect to age ($p=0.66$), gender ($p=0.7$), the presence of diabetes ($p=0.7$), hypertension ($p=0.7$), obesity ($p=0.7$), or smoking status ($p=0.3$) (table 1).

Table 1: Baseline characteristics of study population

Characteristic	**Group 1 - RR n=22**	**Group I - no RR n=16**	***p***
Age	62.00 +/- 10.41	63.37 +/- 8.94	*0.66*
Sex, male	12 (54.54%)	8 (50.00%)	*0.7*
Diabetes	6 (27.27%)	6 (60.00%)	*0.7*
Hypertension	6 (27.27%)	3 (18.75%)	*0.7*
Obesity	6 (27.27%)	3 (18.75%)	*0.7*
Smoker (past of present)	7 (31.81%)	8 (50.00%)	*0.3*

Group 1 (patients who presented regression of remodeling following revascularization) presented lower baseline values for EF (46.60 %+/- 6.09% vs 49.39% +/- 3.46, p=0.008) and higher baseline values for LVED volume (164.50 +/- 19.93 ml versus 156.93 +/- 16.46 ml, p=0.2), LVES volume (87.09+/- 8.41 ml vs 79.37 +/- 9.46 ml, p= 0.01), and RICA (2.70 versus 2.05, p=0.01) compared with no RR group. However, only the regional index of contraction presented a statistically significant difference between the two groups (table 2).

Table 2: 3D echocardiography - derived parameters in patients with regression of LV remodeling versus those with no regression of remodeling following revascularization of LAD occlusion

	Group 1- regression of remodeling	***Group 2- no regression of remodeling***	***p value***
LV end-diastolic volume (ml)			**0.2**
Mean +/- SD	164.50 +/- 19.93	156.93 +/- 16.46	
95% confidence interval	*155.66 – 173.34*	*148.16 – 165.71*	
LV end-systolic volume (ml)			**0.01**
Mean +/- SD	87.09 +/- 8.41	79.37 +/- 9.46	
95% confidence interval	*83.36 – 90.82*	*74.33 – 84.41*	
Ejection fraction (%)			**0.008**
Mean +/- SD	46.60 +/- 6.09	49.39 +/- 3.46	
95% confidence interval	*43.09 – 49.03*	*47.54 – 51.23*	
ICA			**0.002**
Mean +/- SD	3.22 +/- 0.60	3.93 +/- 0.33	
95% confidence interval	*2.92 - 3.53*	*3.76 - 4.11*	
RICA			**0.01**
Mean +/- SD	2.70 +/- 0.42	2.05 +/- 0.85	
95% confidence interval	*2.51 – 2.89*	*1.59 – 2.89*	

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Linear regression showed a statistically significant correlation between the regression remodeling index and the RICA (r=0.31, p = 0.02) at 3 months post-revascularization. All the other echocardiographic parameters presented significantly lower correlation levels with the regression remodeling index (r=-0.2, p=0.2 for EF, r=0.23, p=0.1 for LVED volume, r=0.36, p=0.03 for LVES volume) (figure2).

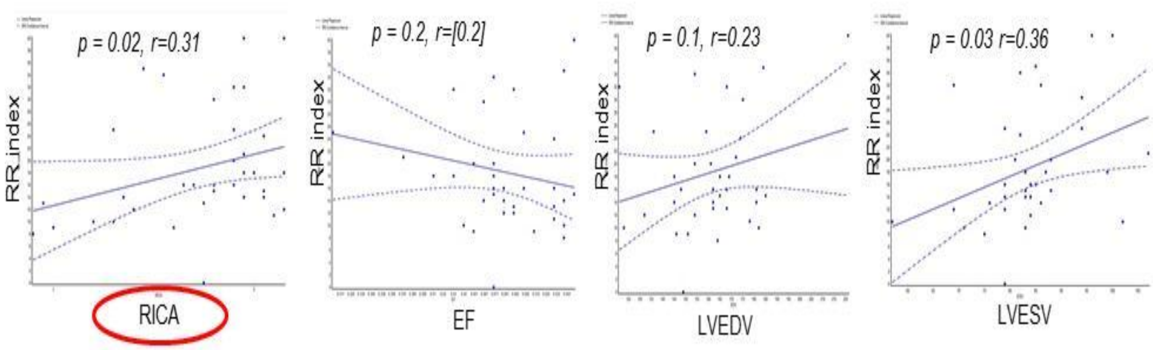

Figure 2: Correlation between Regression of Remodeling Index and 3D – echo derived parameters characterising LV function

The logistical analysis based on ROC curve characteristics (Receiver-Operator-Characteristics) showed a good predictive value of RICA for prediction of regression of ventricular remodeling after revascularization, with a good area under the curve (AUC) of 0.72 (p = 0.003). This was superior to the one recorded for other echocardiographic parameters such as Ejection fraction (AUC 0.62) or LVED volume (AUC 0.62) (figure3).

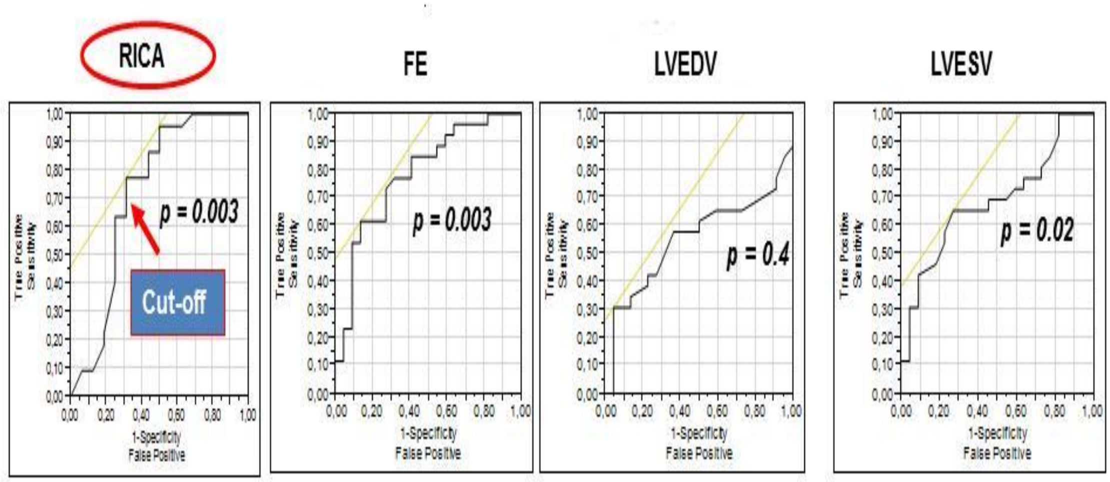

Figure 3: ROC analysis of different 3D echo-derived parameters for prediction of regression of LV remodeling

The cut-off point of 2.6 for the RICA had a sensitivity of 77%, and a specificity of 69% in predicting regression of ventricular remodeling after revascularization. However, ICA was characterized by a superior AUC (0.82) and a higher specificity (92%) but presented a lower sensibility for prediction of regression of left ventricular remodeling (table 3).

Table 3: Sensitivity, specificity and predictive values of 3D echo- derived parameters for prediction of regression of ventricular remodeling

	AUC	(Cut-off)	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
RICA	0,72	2,60	69,00	77,00	77,27	68,75
ICA	0,82	3,50	94,00	68,00	93,75	68,18
EF	0,62	47%	69,00	63,00	73,68	57,89
LVEDV	0,62	165,00	75,00	54,00	75,00	54,55

RICA = regional index of contraction amplitude, ICA = index of contraction amplitude, EF = Ejection fraction, LVEDV - Left Ventricular ednd-diastolic volume, AUC = Area under the Curve, PPV = positive predictive value, NPV = negative predictive value

Discussion

Successful revascularization of a chronically occluded coronary artery following an acute myocardial infarction could restore the function of damaged myocardium if the areas irrigated by the coronary artery include viable myocardium, myocardium that could recover its contractility following a revascularization procedure. However, based on the current knowledge a clear distinction between future "responders" or "non-responders" to late revascularization is not possible (Epstein *et al*., 2007).

In a study published by Bogen *et al.*, (1984) in Circulation research (Bogen *et al.*, 1984), it has been proved that in case of a contracting segment which is not totally infarcted, stroke volume is impaired only when the contractility of the weak region is diminished below 50% of normal, and that the stress concentration around a region of infarction depends more strongly on the inotropic state of the noninfarcted tissue than on the infarct size. Also, Gotte *et al.*, (2001) proved that different loading conditions and the tethering effect of the infarct-related myocardium may reduce function in the remote myocardium, the myocardium located adjacent to the infarct region (Gotte *et al.*, 2001).

In this study we demonstrated that there is a strong correlation between preservation of regional viability and contractility in the border zone areas adjacent to infarction, after infarction, and the regression of left ventricular remodeling following a revascularization procedure. In our experience, 3D echo derived parameters characterizing regional contractility presented higher correlations with the index of remodeling regression than the parameters expressing global ventricular function. A high index of regional contraction was associated with regression of LV remodeling in a more significant extent than the global impairment of ventricular contractility.

Multiple parameters are involved in the maintenance of myocardial contractility in the border zone adjacent to myocardial infarction, among them development of collaterals in the period immediate following the infarction, anatomic variants, microcirculation and involvement of these territories in the ischaemic process. As all these could present various degrees of alterations after a non-revascularized myocardial infarction, a complex assessment in the postinfarction period should also include the condition of the border zone as a major contributor to the ventricular global and regional contractility and function.

Assesment of regional contractility was possible in this study due to the new 3D applications of echocardiographic techniques which allow semi-automated determination of endocardial systolic excursion or wall thickening and a therefore a more precise quantification of wall motion, providing a more objective and reliable basis for evaluation of ventricular volumes and regional wall motion. Also, in our study assessment of myocardial viability was based on a 3D echocardiography algorhythm, using quantitative assessment of wall motion before and after stimulation with dobutamine.

The index of regional contraction amplitude is a new parameter derived by 3D echocardiography, easy to be determined, which provides an objective basis for assessment of absolute regional contractility. A high index of regional myocardial contraction in the area of the infarction had the strongest association with

Research Article

the regression of LV remodeling following revascularization of a chronically occluded coronary artery, showing a superior correlation compared with classical parameters like ventricular volumes or ejection fraction at baseline. Our study opens a new perspective for complex assessment of ventricular function in the post infarction period, suggesting that regional contraction could be used to predict regression of remodeling following reopening of chronic total occlusions.

Conclusion

This study demonstrates the correlation between changes in global and regional ventricular contractility and the regression of ventricular remodeling after revascularization of a chronic total LAD occlusion. A less severe impairment of regional contractility was associated with regression of the ventricle's remodeling process, while the regional index of contraction amplitude shows a good predictive value for prediction of left ventricular remodeling regression. The regional index of contraction amplitude shows a good predictive value for prediction of left ventricular remodeling regression after revascularisation.

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