Cardiac functional remodeling indices in acute experimental infarction under the influence of inotropic agents

Dimitrios I. Chaniotis, Evangelos Papademitriou, Stavroula Galani, Petros Petropoulos, Eleni Eftichidou, Michael Maximiadis, Frangiskos I. Chaniotis

Athens Institute of Technology and Technological Educational Institution of Epirus
Foundation of Biomedical Research, Academy of Athens
Address for correspondence: Dimitrios I. Chaniotis, MD PhD, Tel. +6973049444
E-mail: chaniotisdimitris@gmail.com

Abstract

Objective: To study the time course changes of cardiac left ventricular (LV) geometry in acute experimental infarction by coronary artery ligation under the influence of inotropic agents. **Methods:** Cardiac remodelling indices depicted in the LV functional geometry such as lengths of LV long axis (LongAxL) and short axis (ShortAxL), their fractional shortening (LongAxFS and ShortAxFS) and a new recommended "function index" (FI=LongAxFS/ShortAxFS) were monitored echocardiografically in 20 anesthetized swines. Measurements were obtained before (control) and during a 75 min period following left anterior descending coronary artery (LAD) ligation. **Results:** In the initial 11 animals studied ejection fraction (EF), LongAxFS and FI decreased significantly below control values all over the 75 min period after LAD ligation and ShortAxFS increased progressively above control values and maximized at the 45th min. In order to investigate the underlying mechanism of these changes, LAD ligation was performed under dobutamine infusion in the remaining 9 animals: EF, LongAxFS and FI failed initially into a decline and EF returned to control values at the 45th min and LongAxFS, FI at the 75th min. ShortAxFS remained unchanged vs control under dobutamine throughout the 75 min period. The changes in FI obtained under dobutamine infusion after ligation were best bivariately correlated (r=0.72, p<0.001) and independently associated in a multiple regression model (b=0.45, p<0.001) with the changes in EF. **Conclusion:** The echocardiography remodelling adaptation of LV functional geometry observed in acute experimental infarction consists in deterioration contractility across the LV Long Axis and in compensatory increase contractility of the Short Axis. Dobutamine infusion at a rate of 5 μg/kg/min was correcting both EF and LongAxFS and eliminating compensatory ShortAxFS changes to prevent the acute, unfavourable remodelling of the LV. Furthermore as manifested by all indices in this study, the new "function index" FI in early post myocardial infarction period predicts the complex LV functional geometry, cardiac remodelling and EF changes.

Key Words: Experimental infarction, Coronary artery ligation, Ventricular geometry, Cardiac remodelling, function index, dobutamine infusion, echocardiography.

INTRODUCTION

Changes in left ventricular (LV) structural and functional geometry may occur very early following acute myocardial infarction [1,2,3] and can be visualized echocardiographically in seconds after a coronary artery occlusion [4]. Most of the

studies are dealing mainly with LV structural remodeling and the effect of various interventions but scarcely with changes in LV functional remodeling [5,6,7,8,9,10].

This study was performed to evaluate the acute LV structural geometry changes during experimental myocardial infarction and examine to what extent the dobutamine infusion may modify and recovery these changes. Established echocardiography indices were used to assess LV structural and functional changes, such as EF, long axis length (LongAxL), short axis length (ShortAxL) at end-systole and end-diastole [11,12,13,14], long axis fractional shortening (LongAxFS) and short axis fractional shortening (ShortAxFS). A new called "function index" (FI) defined as the ratio of LongAxFS to ShortAxFS was used to comparative estimation.

MATERIAL AND METHODS

The experimental animals included in this study received human care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health (NIH publication 85-23, revised 1985).

A. Surgical preparation

Twenty healthy swines weighing between 18 and 27 Kg were submitted to preanesthetic administration of Ketamin (20 mg/Kg) and Diazepam (1 mg/Kg) both given intramuscularly. Fifteen minutes later, they were supine positioned and anesthetized by intravenous injection of phenobarbital (6.5 mg/Kg), pankuroniun bromide (0.2 mg/Kg) and fentanyl (0.1 μg/mg). A central venous catheter was inserted in the superior vena cava via the left subclavian vein for fluid administration and central venous pressure monitoring. The trachea was then cannulated and positive pressure respiration applied under electrocardiography and O_2 saturation monitoring. Surgical approach was achieved by median sternotomy. The thymus gland was excised and the pericardium opened. A ring-shaped probe connected to a Biotronex Pulsed-Logic flowmeter (Biotronex Laboratory, Inc., Silver Spring, Maryland) was placed around the aortic root [15].

As soon as the experimental set up described above was completed, two 3:0 prolene sutures were placed around the anterior descending branch of the left coronary artery as close as possible to its origin. Care was taken not to include the vein in the sutures loop. The ends of the sutures were then passed through the 3 mm lumen of a 5 cm long rigid plastic tube. Holding the four ends of the two sutures, the rigid tube was advanced towards the epicardium until its proximal end was 3-5 mm close to the anterior descending coronary branch. Thus, the origin of this branch was surrounded by a loose suture loop which was not affecting its patency until the next stage of the experiment.

Subsequently the sternum was approximated and closed with five No 0 Dexon sutures. Care was taken to stabilize the plastic tube between two sutures, keeping it vertically to the axis of the left anterior descending coronary branch. Its proximal end approached the coronary branch at a distance of 3 to 4 mm, yet not affecting the patency of the artery. The distal end through which the four ends of the two prolene sutures were emerging was kept outside the chest. The 3.5 MHz transducer of a Hewlett-Packard 77.600 echocardiography system was also stabilized by the sutures closing the sternum; it was positioned at the subxiphoid area, facing the apex of the

heart at an angle providing a stable, well defined four-chamber view, as described below.

B Echocardiographic measurements
Two-dimensional echocardiography was performed by using the Hewlett-Packard 77.600 imaging system equipped with a 3.5 MHz phased array transducer. The ECG was simultaneously recorded. Echocardiographic images were recorded on AG7330E-P VSH video tape for subsequent playback and analysis.

Two-dimensional apical four chambers views were obtained using epicardial echocardiographic images to end-diastolic and end-systolic phases consecutive to the cardiac cycle (fig.1). All echocardiograms were randomly numbered at a blinding time sequence, as well as, all other data of the experiments. Two observers reported on each echocardiogram. End diastole was defined as the point in cardiac cycle coinciding with the onset of the Q wave on the ECG. End systole was defined as the time of apparent minimal LV chamber size. The echocardiographic long axis (in the apical four chamber view) was measured from the mid - point of the mitral valve to the apex. The short axis (in the apical four chamber view at valve level) was measured at the tips of the mitral valve leaflets about from one-third the length of the long axis from the base perpendicularly to it [16]. No hypokinetic region in the inferior wall exists in any of the experiments included in the study. Fractional shortenings (FS) for both axes were then calculated. Four consecutive cycles were measured by each observer. The mean of the four measurements for each of the above variables in each echocardiogram was recorded. The average of the recorded values from each reader was used for further analysis.
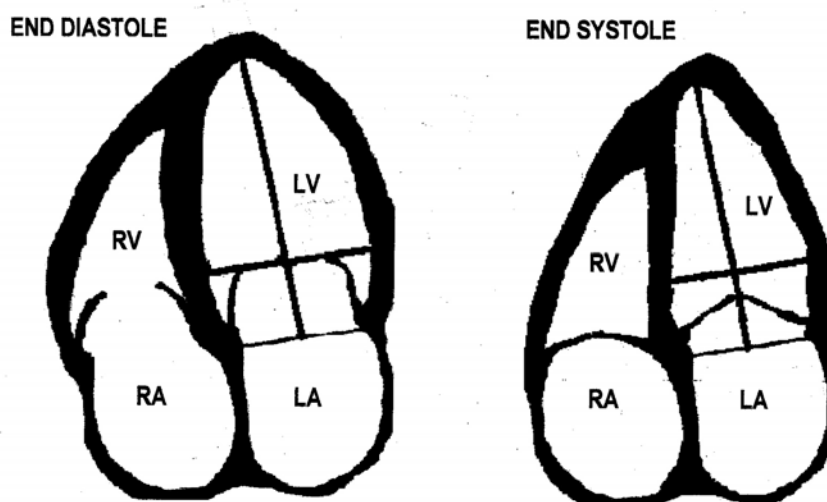

Fig.1. Measurement of LV dimensions: The major long-axis measurement is obtained from the apical four-chamber view from the apical endocardium to the mid - point plane of the mitral valve. The minor short axis is measured at the tips of the mitral valve leaflets about from one-third the length of the long axis from the base and orthogonal to it.

A new index expressing left ventricular functional geometry is introduced in this study: The ratio of long axis FS to short axis FS defined as "function index" was calculated in all instances.

In every one of the experiments included in this paper the 3.5 MHz transducer remained in a stable position throughout the experimental procedure. The transducer was stabilized by the sutures closing the sternum. After the closure of the chest no further manipulations took place. A stable well defined four-chamber view was thus obtained. Throughout the period of measurements an experienced echocardiographist was watching the screen for any change in the apical four chamber view echo imaging if any translocation of the transducer was accidentally happened. In all animals included in the study no such change was seen. Data from experiments in which the position of transducer had changed due to manipulations during the procedure were not further analyzed and these experiments were not included in this study.

C. Experimental protocol

Control values of left ventricular pressure, aortic flow and lead II of the ECG were simultaneously recorded immediately before coronary artery occlusion on a multichannel photographic recorder (Electronics for Medicine, White Plains, New York). A two-dimensional apical four chambers echocardiographic view was obtained as described above.

The 3:0 prolene sutures ends being outside the chest were snuggled occluding the left anterior descending coronary branch. Thus, the artery was occluded by minimal manipulations not affecting the quality and the stability of the four chamber echocardiographic view.

The 20 animals were divided in two groups:1) A control group (n=11) in which the above mentioned hemodynamic and echocardiographic variables were recorded at 15 min intervals for 75 min and 2) The dobutamine group (n=9) in which a dobutamine iv infusion of 5μg/Kg/min was established immediately after ligation and the same variables were recorded exactly as in the previous group, at 15 min intervals for 75 min.

The flow probe was calibrated at the end of each experiment. Mean flows were measured from flow recordings by planimetry.

D. Statistical analysis

Data are expressed as mean± SE and were analysed by using one-way analysis of variance (ANOVA) post hoc multiple comparison least significant difference test. Statistical correlation between indices was performed by using linear regression analysis. Multiple linear regression analysis with collinearity statistics was used to identify independent predictive variables [17]. A level of $P < 0.05$ was considered as statistically significant.

RESULTS

Group A (n=11 animals with LAD ligations):
The echocardiographic changes (fig. 2) in EF, LongAxFS and FI of infarcted left ventricular myocardium, all over the 75 min period after LAD ligation, were decreased below the control value by 30.4±2.7%, 56.5±6.2% and 62.1±7.6%, respectively (ANOVA: F=16.44, F=7.84, F=7.99, p<0.001). ShortAxFS was noted a maximum increase above control values by 40.6±14.5% (ANOVA: F=4.13, p=0.025) at the 45th min. End-systolic LongAxL and end-diastolic LongAxL was significantly

increased vs control (5.5±0.3cm vs 4.5±0.4cm, p<0.001 and 6.2±0.2cm vs 5.4±0.5cm p=0.002, respectively). End-systolic and end-diastolic ShortAxL remained unchanged vs control throughout the 75 min period after LAD ligation.
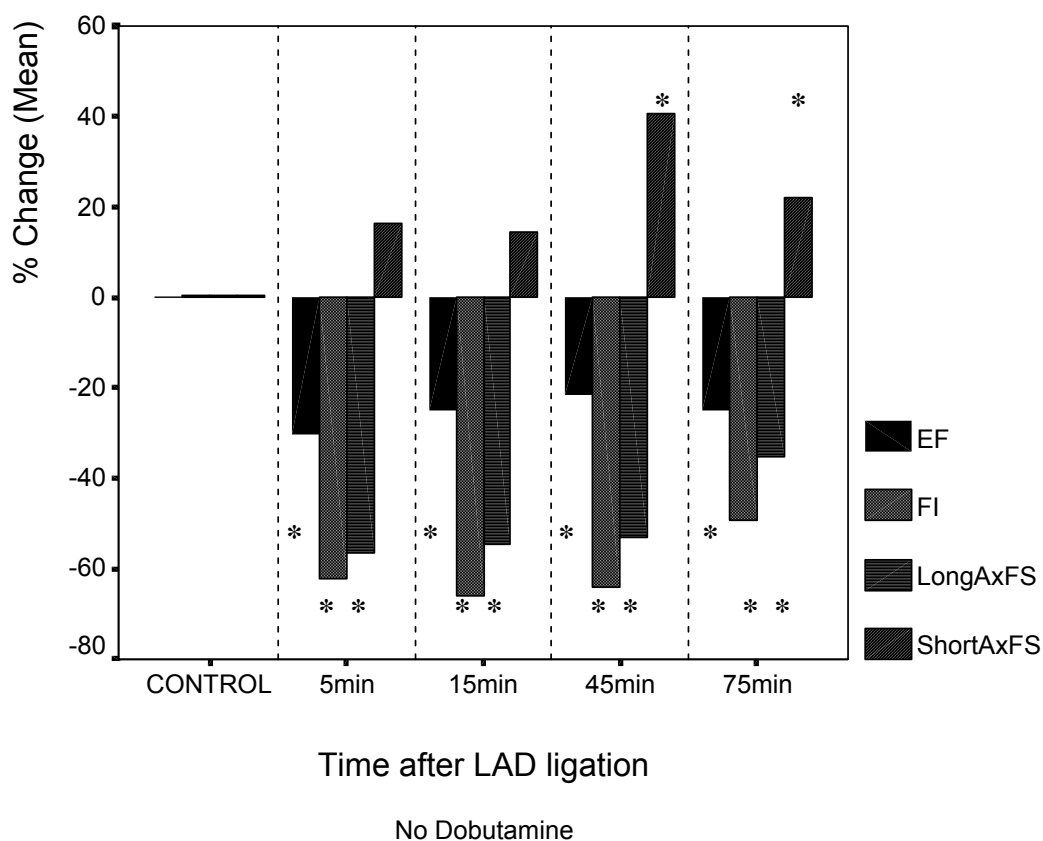

Fig. 2. Time course of mean percent (%) changes in ejection fraction (EF); function index (FI); long axis fractional shortening (LongAxFS) and short axis fractional shortening (ShortAxFS) at 5min, 15, 45 and 75min after artery ligation. All changes expressed as percent of the initial mean value before ligation (Control). *p<0.05 compared with control.

Group B (n=9 animals with LAD ligations and dobutamine infusion 5μg/kg/min).
The echocardiographic changes (fig. 3) in EF, LongAxFS and FI within the initial 5 min were significantly decreased below control values by 29.8±5.5%, F=12.43, 64.9±3.3%, F=13.39, 56.03±3.5%, F=29.66, p<0.001 respectively. EF returned to control values at the 45th min and LongAxFS, FI at the 75th min. No change was noted for the ShortAxFS within the 75 min period.
End-systolic LongAxL was significantly increased vs control within the initial 5 min (5.5±0.4cm vs 4.5±0.4cm, p<0.001). Restoration to the control values was noted at the 45th min, while a decrease in this variable was noted at the 75th min as well (3.8±0.1cm vs 4.5±0.4cm, p=0.002). End-diastolic LongAxL, end-systolic and end-diastolic ShortAxL remained unchainged during the initial 15 min after LAD ligation under dobutamine infusion and were significantly decreased at the 45th min (4.6±0.2 vs 5.4±0.5 cm, p=0.001, 2.2±0.1 vs 2.8±0.3cm, p<0.001 and 3.1±0.2 vs 3.7±0.4cm, p<0.001, respectively).
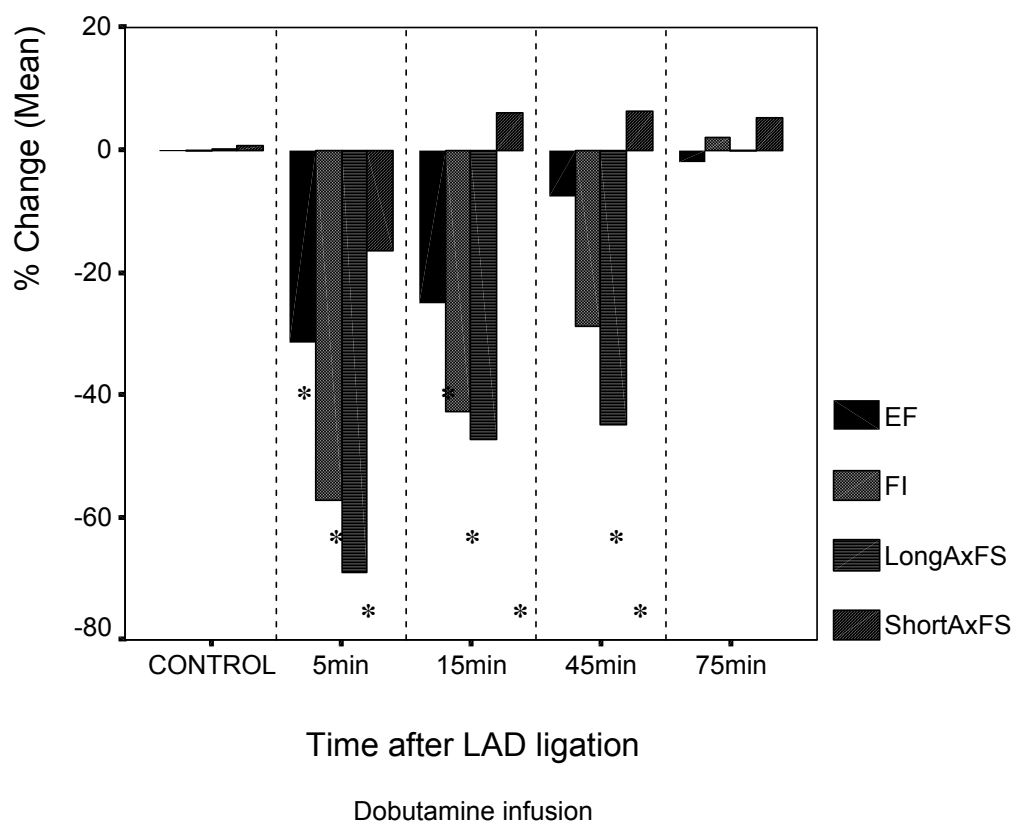
Fig. 3. Time course of mean percent (%) changes in EF, FI, LongAxFS and ShortAxFS at 5min, 15, 45 and 75min after artery ligation following dobutamine (5μg/kg/min) infusion . All changes expressed as percent of the initial mean value before ligation (Control). *p<0.05 compared with control.

Correlation between changes in LV ejection fraction and functional geometry indices under dobutamine infusion.

Bivariate analysis indicated that changes in EF correlated with the changes in the LongAxFS, ShortAxFS and FI (r=0.51, r=0.42 and r=0.72 respectively, p<0.001) and inversely with changes in end-systolic LongAxL, (r=-0.40, p=0.001) and end-systolic ShortAxL, (r=-0.35, p=0.006). A multiple linear regression analysis model with collinearity diagnostics showed that the FI was the only variable which showed a strong independent (F=17.84, p<0.001, R=0.87, b=0.454, SE=0.057, p<0.001, Tolerance=0.54, VIF=1.85) association with EF changes (fig. 4).

DISCUSSION

Changes in functional geometry of the left ventricle immediately after experimental myocardial infarction has not been extensively studied. Recent trends for early myocardial revascularisation after acute coronary syndromes and prevention of remodeling make the investigation of this time period more significant.

Severe acute myocardial infarction initiates complex changes in the geometrical, structural and biochemical architecture of both infarcted and non-infarcted regions of the ventricular myocardium [9]. Data obtained in this study are concerning changes in EF in comparison to other LV functional geometry changes in systole and diastole occurring within the first critical hour following interruption of coronary flow. These

changes were examined with and without the administration of dobutamine. If was aiming to examine whether the use of dobutamine immediately following coronary artery occlusion may modify LV functional and structural geometry values altering the course of myocardial remodeling during the first hour.
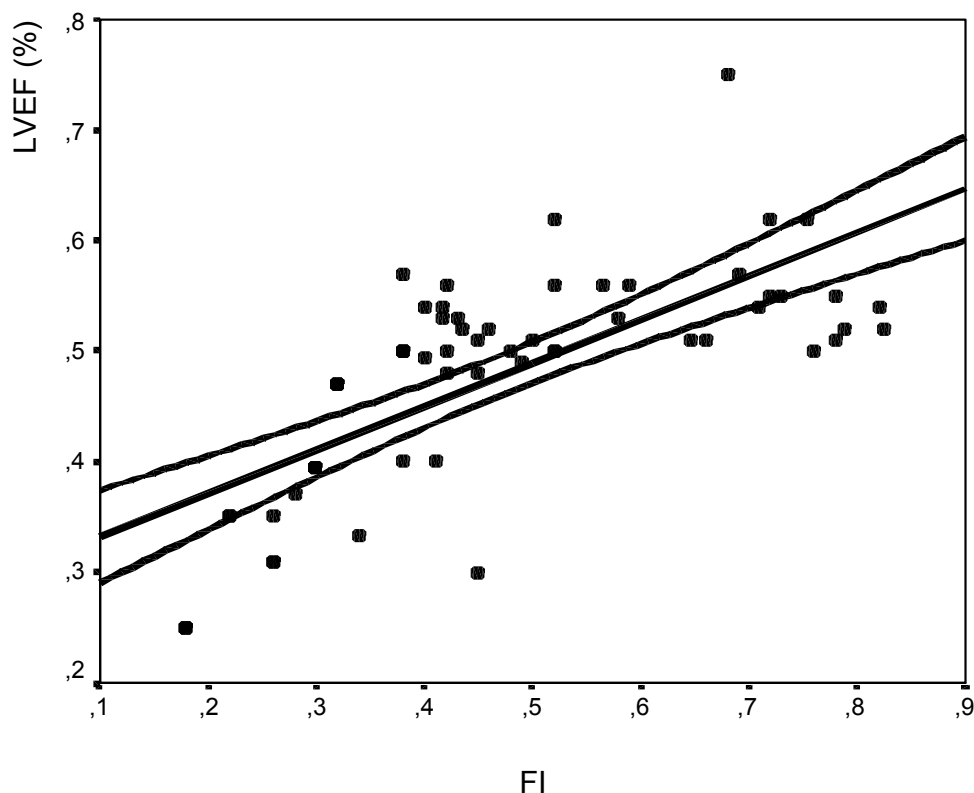

Fig. 4. Linear correlation found between LV ejection fraction (LVEF, as estimated by using the modified Simpson method) and the newly introduced function index (FI) during the 75min period artery ligation following dobutamine (5μg/kg/min) infusion.

The long axis length changes following LAD artery ligation either with or without dobutamine infusion seem to be the most prominent effect of ischemia. This might be expected since the majority of the longitudinally arranged fibers of the left ventricle are located in the subendocardium which is very sensitive to ischemia [18]. Furthermore, Andersson's study demonstrates that the effects of β-adrenergic blockers seems greater on the longitudinal fibres than on the circumferentially fibres [19]. These findings are similar to those with intravenous milrinone in dilated cardiomyopathy, suggesting the great sensitivity of the subendocardial fibres to such drugs [20].

 In the group A (no dobutamine), LongAxFS reduction involves a compensatory delayed increase in ShortAxFS, after the 45th min. In the group B (dobutamine), although the LongAxFS was reduced only within the initial 5 min after LAD ligation it was restored to the control values, soon after. As a result the ShortAxFS was restored to the control levels 15min after starting dobutamine infusion following a short lasting initial decrease. These findings indicate that the post-ligation LongAxFS malfunction seen in this series of experiments was counterbalanced by ShortAxFS, with a time delay, but this effect was modified by inotropic drug infusion.

Changes in the fractional shortening observed with or without dobutamine infusion in any of the two axes taken separately were not paralleled and not statistically correlated to EF. On the contrary, changes in the newly introduced "function index" are best and independently correlated with an earlier restoration of EF changes. Changes observed under dobutamine infusion appear, thus, to be the result of complex functional geometry changes affecting both axes. This may explain why both EF and function index are simultaneously improving during dobutamine infusion.

Consequently, among all indices used to study the important changes in left ventricular function geometry and EF occurring within 75 min after LAD ligation, the introduced new "function index" changes were paralleled and best correlated with changes in EF. A study of long and short axis changes during systole and diastole and their derivatives versus EF changes indicates the primary importance of LongAxFS changes and the compensatory opposite changes in the ShortAxFS. Dobutamine infusion was correcting both EF and LongAxFS while the compensatory ShortAxFS changes are prevented. The changes in contractility across the LV Long Axis following acute experimental infarction by coronary LAD ligation with or without inotropic agents seem to be the most prominent effect of ischemia. The ShortAxFS preventive action into deterioration of LongAxFS was eliminated by dobutamine infusion. Furthermore among all indices studied, the new "function index" FI was closely following EF changes and seems to be a more sensitive index of the complex LV functional geometry changes occurring during acute ischemia and predict LV EF.

In conclusion, the echocardiography remodelling adaptation of LV functional geometry observed in acute experimental infarction consists in deterioration contractility across the LV Long Axis and in compensatory increase contractility of the Short Axis. Dobutamine infusion at a rate of 5 μg/kg/min was correcting both EF and LongAxFS and eliminating compensatory ShortAxFS changes to prevent the acute, unfavourable remodelling of the LV. Furthermore as manifested by all indices in this study, the new "function index" FI in early post myocardial infarction period predicts the complex LV functional geometry, cardiac remodelling and EF changes.

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