

Original Research

Effect of Dobutamine on Left Ventricular Functional Geometry After Acute Myocardial Infarction: Experimental Study

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Key words:

Acute myocardial infarction, post-infarction remodelling, dobutamine, echocardiography.

Manuscript received:

October 4, 2006;

Accepted:

January 15, 2007.

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Introduction: Acute myocardial infarction causes left ventricular (LV) remodelling, which forms the substrate for its early and late complications. The aim of this experimental study was to evaluate the acute changes in LV functional geometry after acute myocardial infarction using echocardiography and to investigate the effect of continuous intravenous dobutamine administration on those changes.

Methods: In 22 pigs acute myocardial infarction was induced by ligation of the anterior descending branch of the left coronary artery. In 11 animals dobutamine was administered at a rate of 5 µg/kg/min (Group B), while the remainder (Group A) served as controls. Before infarction and 5, 15, 45 and 75 minutes after, the fractional shortening of the long (FSL) and short (FSS) axes of the LV were measured echocardiographically and the ejection fraction (EF) was calculated.

Results: In Group A FSL and EF reduced significantly after infarction ($p < 0.0001$), while FSS increased significantly ($p < 0.05$). In Group B FSL and EF reduced significantly 5 minutes after infarction and then returned progressively to normal values after 15 min (EF) and 45 min (FSL). FSS did not change significantly during 75 minutes after infarction.

Conclusions: Dobutamine, administered at a rate of 5 µg/kg/min during acute experimental anterior myocardial infarction, before the appearance of early complications, may prevent the acute, unfavourable remodelling of the LV, as manifested by a decrease in FSL and EF and a compensatory increase in FSS.

Acute myocardial infarction triggers structural, geometric, biochemical and functional changes in both the infarcted and non-infarcted regions of the left ventricular (LV) myocardium.¹⁻⁴ Changes in LV structure and function after acute infarction can be recorded echocardiographically a few seconds after coronary artery ligation. These changes form the substrate for the early and late complications of acute infarction.^{5,6} Heart failure, severe arrhythmias and sudden death are some of the main manifestations of LV remodelling after acute myocardial infarction.

Clinical and experimental studies⁷ have shown that certain types of therapy (phar-

maceutical⁸⁻¹⁰ or invasive^{11,12}) can prevent or reverse the acute, unfavourable post-infarction remodelling of the LV. The effect of dobutamine on acute myocardial infarction has not been adequately studied. It is likely that the improvement it causes in myocardial contractility could contribute to positive LV remodelling, overcoming the negative consequences of acute myocardial infarction.

The aim of this experimental study was to evaluate the acute changes in LV

[†]Nikolaos S. Saridakis passed away while this paper was being written.

functional geometry after acute myocardial infarction using echocardiography, and to investigate the effects of continuous dobutamine administration on those changes.

Material and methods

The study material comprised 22 healthy pigs weighing 18 to 37 kg. The protocol complied with the "Principles for the Care of Experimental Animals" and the "Guidelines for the Care and Use of Experimental Animals" issued by the US National Academy of Sciences and National Institute of Health (version 85-23, revision 1985) and was approved by the Scientific Committee of the "Alexandra" hospital.

Surgical preparation

The animals were initially given intramuscular ketamine (20 mg/kg) and diazepam (1 mg/kg), followed by general anaesthesia. A central line catheter was placed in the superior *vena cava*, via the left subclavian vein, for the delivery of drugs and fluids and monitoring of central venous pressure. Electrodes were then applied to the animal's limbs for continuous ECG monitoring, and a peripheral oximeter was connected to the tail for monitoring haemoglobin oxygen saturation. The animals were anaesthetised with intravenous phenobarbital (6.5 mg/kg), pancuronium bromide (0.2 mg/kg) and phentanyl (0.1 mg/kg). Endotracheal intubation was then performed with a 5.5 mm tube and respiratory support was provided by a ventilator, delivering a mixture of atmospheric air and 40% oxygen, with a ventilatory volume of 10 ml/kg per breath, at a rate of 15-16 breaths/minute and with positive end-expiratory pressure.

The surgical preparation of the animals included exposing and preparing the large vessels of the neck, a median sternotomy using a cauter, excision of the thymus gland and opening of the pericardium. A 6 F pigtail catheter for continuous pressure monitoring and recording was advanced to the LV cavity via the right carotid artery. The anterior descending branch of the left coronary artery was surgically exposed and two 3:0 proline sutures were placed after the origin of the first diagonal. The four ends of the two sutures were passed through an inflexible plastic tube 5 cm in length. While the ends of the sutures were secured, the tube was advanced towards the epicardium until its proximal part was 3-5 mm from the anterior descending artery. In this way a suture loop tourniquet was created around the artery, after the origin of the

first diagonal, without ligation, ready for the next stage of the experiment. An annular Biotronex pulsed-logic flowmeter (Biotronex Laboratory, Inc., Silver Spring, MD, USA) was placed around the aortic root for monitoring of the cardiac output.¹²

The edges of the sternum were then brought together and fixed with Dexon No. 0 sutures. Special care was taken with the stabilisation of the plastic tube enclosing the sutures, so that: a) it was placed perpendicular to the anterior descending branch; b) its proximal part remained 3-4 mm from the anterior descending, without affecting its patency; and c) the distal part of the tube, from which the four suture ends protruded, was outside the chest. During closing of the chest the ultrasound transducer was introduced, stabilised and immobilised by the sternal closure sutures in a sub-xiphoid position, opposite the apex of the heart, so that the four-chamber view could be visualised continuously. Displacement of the transducer from its stable position was grounds for exclusion of the particular experiment from the study.

On the completion of the surgical part, 2500 IU intravenous heparin were administered for the prevention of intravascular thrombi.

Experimental protocol

Throughout the experiment, ECG lead II and LV pressure were monitored and recorded simultaneously at a speed of 100 mm/s by a multi-channel device (Electronics for Medicine, White Plains, NY, USA). At the same time the two-dimensional four-chamber echo image and the ECG were recorded by the ultrasound device and cardiac output was monitored by the electromagnetic flowmeter.

Pulling on the four ends of the two sutures that were outside the sternum achieved ligation of the anterior descending branch, about 1 cm after the origin of the first diagonal. Ligation was performed with gentle manipulations so as to avoid any movement of the transducer.

In alternate animals (11 of 22: Group B) intravenous dobutamine was given immediately after ligation of the anterior descending artery, at a rate of 5 µg/kg/min. The other 11 animals (Group A) received no dobutamine and served as controls. Echocardiographic recordings were made before coronary artery ligation (baseline) and 5, 15, 45 and 75 minutes after the induction of acute myocardial infarction.

Ultimately, the study material included 18 animals, since 2 of Group A died before completion of the pro-

tocol (one from ventricular fibrillation, the other from cardiogenic shock), while two animals of Group B were excluded because of displacement of the ultrasound transducer during the experiment.

Echocardiography

The echocardiographic study was performed using a Hewlett-Packard Sonos 1000 device (Andover, MA, USA) and a 3.5 MHz phased-array transducer. Data from the ultrasound examination and the simultaneous ECG recording at 100 mm/s were stored on super VHS tape using a Panasonic AG-7350 video recorder for later processing and analysis.

Two-dimensional imaging of the LV was obtained epicardially in the four-chamber view. At each stage of the experiment, with or without dobutamine administration, the following parameters were measured¹³ and evaluated:

1. The length of the long axis of the LV, from the middle of the mitral valve to the LV apex, at end-diastole (EDL) and end-systole (ESL).
2. The length of the short axis of the LV, about a third of the way along the long axis from the base of the LV and perpendicular to it, at the level of the tips of the mitral valve leaflets, at end diastole (EDS) and end-systole (ESS).

3. The fractional shortening of the long axis of the LV (FSL), given by the formula:

$$FSL (\%) = (EDL - ESL) / EDL \times 100.$$

4. The fractional shortening of the short axis of the LV (FSS), given by the formula:

$$FSS (\%) = (EDS - ESS) / EDS \times 100.$$

5. The LV ejection fraction (EF) calculated using Simpson's rule (Figures 1, 2).

End-diastole was defined as the point in the cardiac cycle that coincided with the appearance of the Q wave on the ECG, while end-systole was the point at which the LV cavity was minimised.

Statistical analysis

Variables are expressed as mean ± standard deviation. The regularity of distributions was checked using the Kolmogorov-Smirnov test. Between-group comparisons of echocardiographic parameters were made using repeated measures ANOVA and Tukey's *post hoc* test. A p-value <0.05 was the criterion for significance.

Results

In Group A (9 animals, no dobutamine), FSL and EF decreased significantly 75 minutes after coronary artery

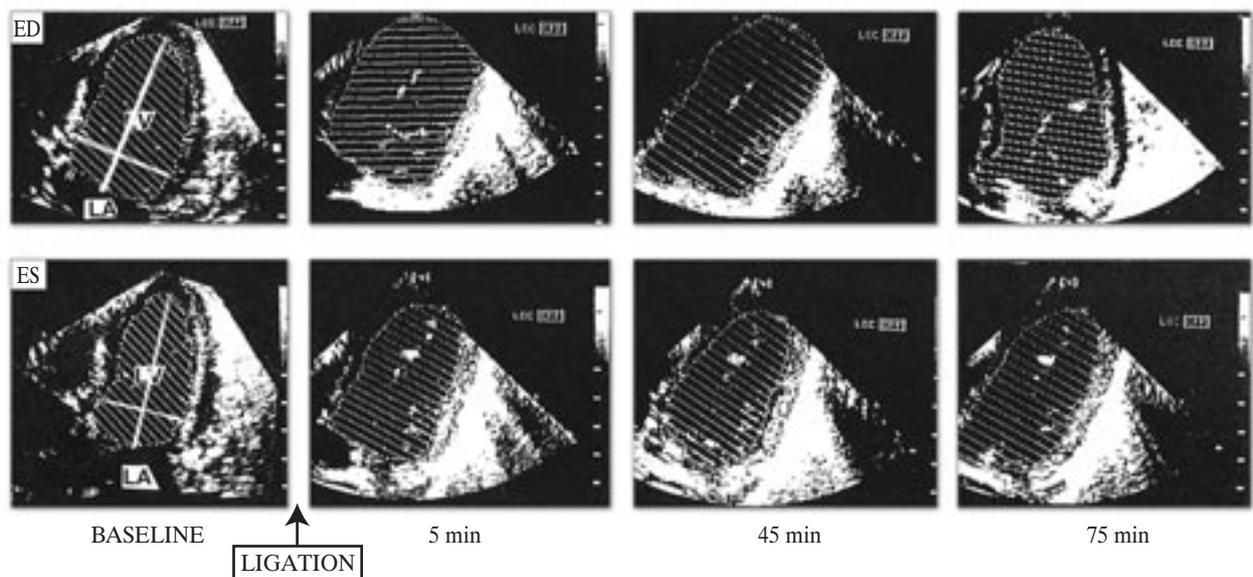


Figure 1. Echocardiographic image showing the estimation of end-diastolic (ED, upper series) and end-systolic (ES, lower series) left ventricular volume for the calculation of ejection fraction from the epicardial four-chamber view, using Simpson's rule, before infarction (BASELINE) and 5, 15, 45 and 75 minutes after ligation (LIGATION) of the anterior descending coronary artery. Representative example from Group A (no dobutamine, 1st experiment).

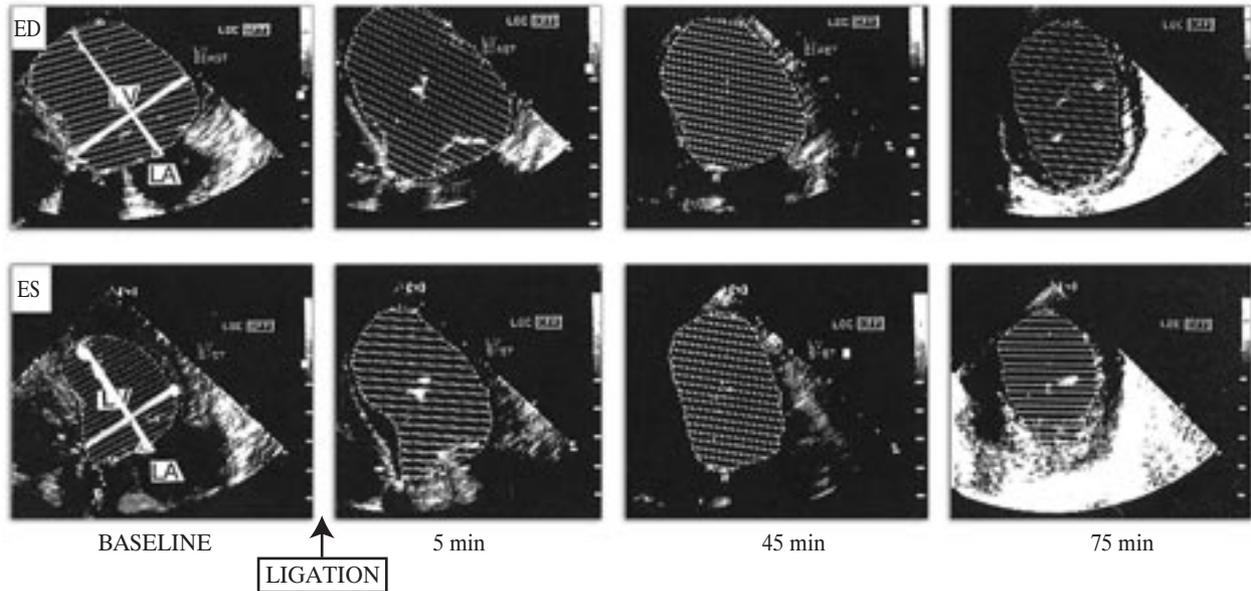


Figure 2. As figure 1. Representative example from Group B (dobutamine, 10th experiment).

ligation (repeated measures ANOVA, $F=19.54$, $F=15.64$, respectively, $p<0.0001$) (Table 1). In contrast, FSS increased progressively, reaching its peak value compared to baseline ($24.67 \pm 2.74\%$ before infarction) at the 45th minute ($39.89 \pm 12.03\%$, $F=2.82$, $p<0.05$) (Figure 3).

In Group B (9 animals, continuous intravenous dobutamine), FSL and EF decreased significantly during the first 5 minutes at coronary artery ligation ($4.33 \pm 0.71\%$ and $39.89 \pm 4.57\%$, respectively) (Table 2). EF began to improve at the 15th minute ($45.22 \pm 5.49\%$), and FSL at the 45th minute ($7.78 \pm 1.72\%$). Values of these parameters were restored to normal 75 minutes after coronary artery ligation ($17.67 \pm 4.44\%$ and $57.22 \pm 2.39\%$, respectively; repeated measures ANOVA $F=31.04$ and $F=34.87$, respectively, $p<0.0001$). FSS did not change significantly

($p<0.06$) during the first 75 minutes of acute myocardial infarction (Figure 4).

Discussion

The aim of this study was a dual one: first, to demonstrate the post-infarction remodelling of the LV during the 75 minutes following experimentally induced acute myocardial infarction, based on the echocardiographic parameters, fractional shortening of the long and short axes of the LV and EF; second, to assess the effect of dobutamine on LV remodelling during the early phase of acute myocardial infarction. In the present study, FSL decreased significantly during the first 45 minutes after coronary artery ligation in both groups, with and without dobutamine administration. The decrease in FSL and EF was accompanied by a

Table 1. Fractional shortening of the long (FSL) and short axis (FSS), and left ventricular ejection fraction (EF) in Group A (without dobutamine), before infarction (baseline) and 5, 15, 45 and 75 minutes after (mean \pm standard deviation).

Time (minutes)	FSL (%)	FSS (%)	EF (%)
Baseline	16.78 ± 1.79	24.67 ± 2.74	47.44 ± 1.74
5	$4.78 \pm 1.39^*$	29.89 ± 7.67	$30.67 \pm 3.46^*$
15	$7.67 \pm 4.64^*$	30.33 ± 15.35	$37.11 \pm 6.97^*$
45	$8.67 \pm 4.42^*$	$39.89 \pm 12.03^*$	$34.78 \pm 6.55^*$
75	$6.89 \pm 1.62^*$	32.89 ± 6.68	$33.56 \pm 3.54^*$

*Statistically significant difference ($p<0.05$) from baseline value.

Group A

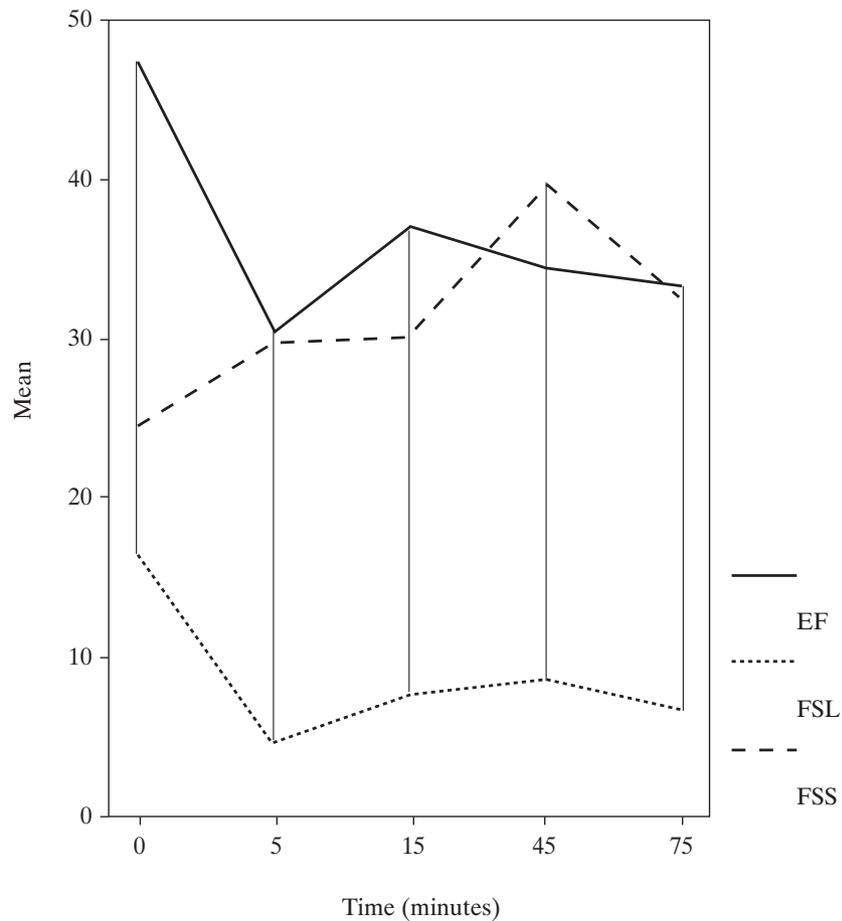


Figure 3. Graph of changes in left ventricular ejection fraction (EF), fractional shortening of the long (FSL) and short axis (FSS) at baseline (0) and during 75 minutes after acute anterior myocardial infarction in Group A (no dobutamine).

Table 2. Fractional shortening of the long (FSL) and short axis (FSS), and left ventricular ejection fraction (EF) in Group B (with dobutamine), before infarction (baseline) and during 5, 15, 45 and 75 minutes after (mean ± standard deviation).

Time (minutes)	FSL (%)	FSS (%)	EF (%)
Baseline	18.56 ± 4.28	30.22 ± 7.49	57.22 ± 3.03
5	4.33 ± 0.71*	21.11 ± 5.13	39.89 ± 4.57*
15	9.00 ± 4.03*	27.22 ± 9.98	45.22 ± 5.49*
45	7.78 ± 1.72*	23.44 ± 6.39	47.78 ± 3.03*
75	17.67 ± 4.44	28.33 ± 5.24	57.22 ± 2.39

*Statistically significant difference (p<0.05) from baseline value.

compensatory increase in FSS. This finding is compatible with the report by Anderson et al,⁸ that after myocardial infarction the longitudinal muscle fibres of the endocardium are damaged, being the most sensitive

layer of the LV myocardium to ischaemia. The macroscopic findings of Anderson et al are in accord with the microscopic findings of Cazorla et al.¹⁴ These authors attributed the lengthening of the muscle fibres in the

Group B

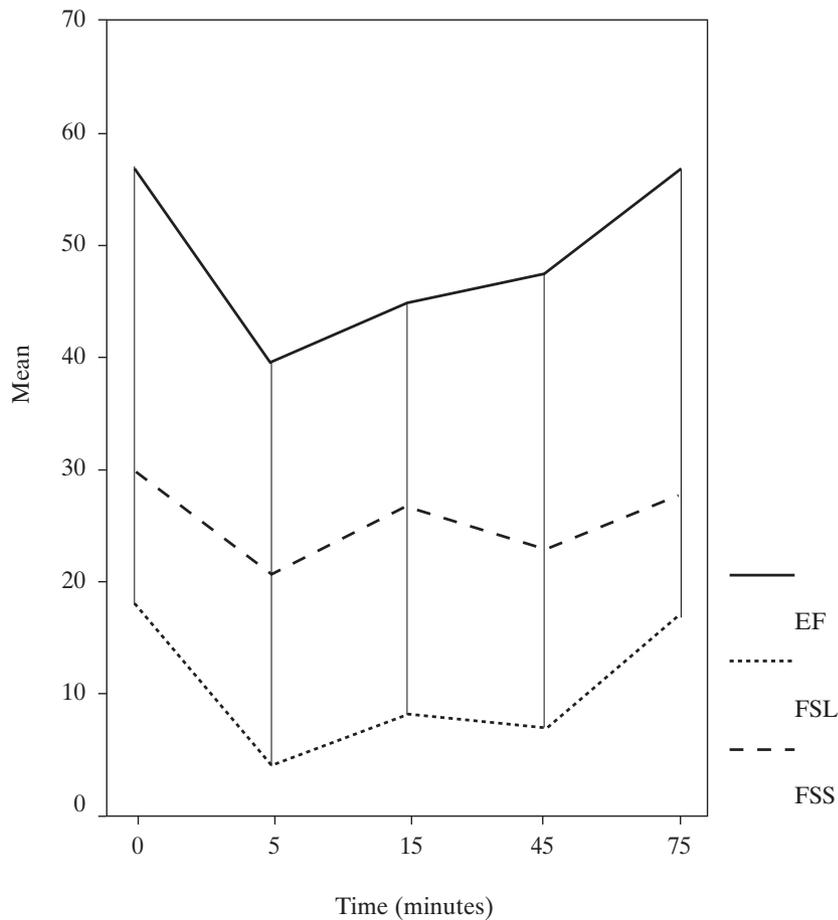


Figure 4. Graph of changes in left ventricular ejection fraction (EF), fractional shortening of the long (FSL) and short axis (FSS) at baseline (0) and during 75 minutes after acute anterior myocardial infarction in Group B (dobutamine).

LV wall immediately after infarction to an increase in LV end-diastolic volume. The increase in end-diastolic volume, according to the Frank-Starling law, also increases end-diastolic wall stress, in order to improve LV contractility. The cellular mechanism of the Frank-Starling law, although not fully elucidated, is based on the heterogeneous transmural sensitivity of myocardial fibres to calcium. The sensitivity to calcium augments from the epicardium to the endocardium, and this augmentation is associated with the increase in wall stress (from epicardium to endocardium). According to the aforementioned study, the stretch of the subendocardial myocardial fibres induces phosphorylation of the light myosin chain (VLC2b), mainly in the endocardium. It is noteworthy that, immediately after infarction, the sensitisation of the myocardial fibres to calcium disappears and eliminates the aforementioned phosphory-

lation. Thus, the myocardial fibres lose their inotropic capability, resulting in a loss of LV contractility. In consequence, immediately after infarction, the longitudinal myocardial fibres, which are represented by the long (anatomical) axis of the LV, lose a part of their contractile capability, resulting in an increase of the end-diastolic and end-systolic length of this axis and a reduction in its fractional shortening.

The ability of dobutamine to stimulate the β_1 -adrenergic receptors of the heart and the β_2 -adrenergic receptors of the blood vessels causes an increase in the contractility of the ventricular myocardium and a decrease in peripheral vascular resistance (after-load). The effect of dobutamine on the myocardium, immediately after acute infarction and before the appearance of its early complications, has not been studied extensively. There are many conflicting views con-

cerning the safety of dobutamine in the acute phase of infarction. An arrhythmogenic effect of dobutamine has been reported during its administration in high dosages.¹⁵ However, in the present study we observed no notable ventricular arrhythmias in the animals that were given dobutamine, probably because of the low dosage that was used. Experimental studies have shown that the continuous administration of low-dose dobutamine immediately after induction of acute infarction can prevent acute, unfavourable LV remodelling. Miura et al¹⁶ administered dobutamine in continuous intravenous infusion at a rate of 10 µg/kg/min for 5 hours after acute experimental myocardial infarction. The extent of the infarct 48 hours later increased in some animals and decreased in others. Liang et al,¹⁷ administering dobutamine at a rate of 20 µg/kg/min after coronary artery ligation, observed that myocardial flow increased significantly in both infarcted and non-infarcted regions of the myocardium, while epicardial flow did not change significantly. In addition, the size of the infarct was smaller in the group of animals that received dobutamine. It should be noted, however, that the above findings refer to animals whose remaining coronary circulation was normal. In patients with coronary artery disease and hibernating myocardium it is likely that the action of dobutamine could prove damaging. In the present experimental study, continuous dobutamine administration at a rate of 5 µg/kg/min progressively reversed the decreased values of FSL (45 minutes after infarction) and EF (75 minutes after infarction). Also, it impeded the compensatory increase in FSS, which did not change significantly in the animals receiving dobutamine. The findings of this study differ significantly from those of Takehana et al,¹⁸ who found that the response of stunned myocardium to dobutamine was indicative of the size of the salvaged myocardium during reperfusion, whereas our findings demonstrate the beneficial effect of dobutamine on LV function during complete occlusion of the anterior descending artery.

Limitations of the study

Because of the experimental design (recording only the four-chamber view, epicardially) it is probable that the absolute values of fractional shortening thus measured deviated from the real ones. However, that limitation does not affect the results of the study, since the same methodology was used in both groups of animals.

Conclusions

Dobutamine, administered in continuous intravenous infusion at a rate of 5 µg/kg/min during the acute phase of experimental anterior myocardial infarction, before the appearance of early complications, could potentially prevent acute, unfavourable LV remodelling, as manifested by a reduction in FSL and EF and a compensatory increase in FSS.

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