Echocardiographic Assessment of Myocardial Infarction Evolution in Young and Adult Rats

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Summary

Background: The regeneration of cardiomyocytes after a myocardial infarction (MI) is more evident in young animals; however, it is not known whether it is associated with functional improvement.

Objective: To perform the functional analysis by echocardiography (echo) of young adult rats submitted to MI.

Methods: Seventy-two animals were included in the study: 35 young rats (group Y) that were 28 days old and 37 adult rats (group A) that were 153 days old. The rats were subdivided in two subgroups: infarcted (YI and AI) and control (YC and AC). The animals were assessed by echocardiogram on the 7thand 30th postoperative days for the analysis of the ejection fraction (EF) and the final systolic (FSV) and diastolic volume (FDV) of the left ventricle. Only animals with EF < 40% were included in the study.

Results: The comparison of the FDV and FSV between infarcted and control animals showed that there was a significant increase in infarcted adult animals at the two analyzed phases. Among young animals only the FSV was significantly higher on the 7th day. The intragroup evolution analysis showed an increase in FDV and FSV in the two young subgroups, which was proportional to growth and only increase in FDV in the infarcted adult group. There was an improvement in EF in young rats, whereas EF remained decreased in adult rats when compared to controls.

Conclusion: The infarcted young rats presented improvement in the systolic function and ventricular volumes 30 days after the infarction, whereas the adult rats presented increased FDV with no improvement in systolic function. (Arq Bras Cardiol 2008; 91(5) : 295-300)

Key words: Echocardiography; myocardial infarction; clinical evolution; rats.

Introduction

The clinical evolution of adult and pediatric patients with ventricular dysfunction due to myocardial ischemic disease shows to be distinct, as well as its etiologies[1,2]. Among adults with myocardial infarction (MI) submitted to coronary artery reperfusion, only a small number of patients presents full recovery of the cardiac function; however, in children with significant ventricular dysfunction secondary to ischemic diseases, a better evolution is observed[1-3]. The proliferation of new cardiomyocytes can be one of the compensation mechanisms that needs to be better understood.

During the gestational phase and for a short time after the birth, the growth of cardiomyocytes occurs by hyperplasia and, subsequently, by hypertrophy[4,5], which can contribute to a better recovery in young individuals. Anversa and cols. suggest that the cardiomyocytes are constantly renewed, even in adult individuals; however, this is not enough for full function recovery[6].

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Considering the hypothesis that the heart of young animals submitted to myocardial infarction, with significant left ventricle dysfunction, presents better recovery of the systolic function, this echocardiographic study was designed to compare the functional evolution of the heart of young and adult rats submitted to surgical ligature of the left coronary artery.

Methods

The initial study sample consisted of 168 male Wistar rats (*Rattus Norvegicus Albinus, Rodentia, Mammalia*): 98 young rats (28 days old) and 70 adult rats (153 days old). The final sample consisted of 72 rats, being 35 young and 37 adult animals.

The young (group Y) and adult (group A) rats were subdivided in two subgroups: 1) infracted animals, called YI and AI; and 2) controls, called YC and AC. The experimental group was submitted to myocardial infarction through surgical ligature of the left coronary artery and the control group, to sham operation.

To undergo the surgery and echocardiogram, the animals were anesthetized with a basal dose of ketamine (Ketalar®) of 50 mg/kg and xylazine (Xylazine®) of 10 mg/kg, intramuscularly. In order to ascertain the anesthetic effect, the absence of neuromuscular reflex was observed. In young rats, a lower dose of ketamine was

used, corresponding, on average, to half the adult dose.

For the surgical procedure, the animals were submitted to orotracheal intubation and mechanical ventilation, with a Harvard 683 volume respirator, with 68 cycles per minute, with 21% oxygen. The MI was carried out according to what was described by Tarnavski et al[7]. For the sham operation, the same surgical phases were performed, except for the ligature of the left coronary artery.

The echocardiographic studies were performed on the 7th and the 30th postoperative days. The parasternal longitudinal image was used for the planimetry of the left ventricle (LV) by the Simpson method to obtain the final diastolic volume (FDV) and the final systolic volume (FSV) and the ejection fraction (EF) was calculated by the equipment software[8]. The FDV was obtained at the R wave peak of the electrocardiogram and the FSV, at the smallest LV diameter, both aided by the visualization of the closed mitral and aortic valves.

The volumes were measured in three consecutive cardiac cycles and after that, the arithmetic mean of these values was calculated. The myocardial infarction was established based on the longitudinal and transversal images of the LV.

The left ventricular dysfunction was characterized by the presence of EF < 40% at the echocardiogram on the 7th postoperative day. Therefore, the rats from the infarcted group that presented EF> 40% were excluded from the analysis.

The assessments and measurements were carried out in an Agilent echocardiogram equipment (model Sonos 5500; Andover, MA), equipped with S12 MHz and L15 MHz transducers, model 21390[A], Agilent, Palo Alto, CA. The equipment has the capacity of 120 pictures per second (Hertz).

Some animals were randomized for euthanization during the study.

All animals received humane care throughout the study in accordance with the "Guiding Principles for the Care and Use of Laboratory Animals in Research", following the "Ethical Principles in Animal Experimentation of the Brazilian College of Animal Experimentation" (Cobea). The study was approved by the Ethics Committee in Animal Research of the Pontificia Universidade Catolica do Paraná.

The statistical analysis was carried out with the software Statistica v.10. The results were expressed as means and standard deviations. The Student's t test was used to compare the study and the control groups for independent samples, considering the homogeneity of the variances. To compare the moments of evaluation, the Student's t test was used for dependent samples.

The condition of data normality was evaluated by the Shapiro-Wilks test and the condition of homogeneity of the variances was evaluated by Levene's test. The level of significance was set at 0.05, adjusted with Bonferroni correction. Thus, p values < 0.025 indicated statistically significant differences.

Results

The mortality rate of the study was 34.5%. In the infarcted subgroups, 18 young rats (33.9%) and 8 (17.3%) adult rats were excluded, as they presented EF > 40% on the 7th postoperative day, as well as 12 rats with identification problems. The final sample consisted of 72 rats, being 35 young and 37 adult animals.

The mean weight of the young animals in the beginning of the study was 186.4 ± 35.5 g, with no difference between the subgroups (YI and YC). There was a significant difference in weight on the 30th day echocardiogram, with p< 0.01, with values of 265.3 ± 8.7 g for YI and 312.3 ± 17.4 g for YC.

In the adult group there was no difference in weight between the subgroups at the two analyzed moments, as well as in the comparison of evolution in the subgroups. The animals' mean weight on the 7th postoperative day was 343.4 ± 24.4 g and 364.2 ± 22.4 g on the 30th day.

The heart rate (HR) of the young animals was 270 ± 66 bpm on the 7th day and 203 ± 36 bpm on the 30th day, and in the adult group, it was 204 ± 27 and 191 ± 27 bpm, on the 7th and 30th days, respectively. There was no statistical difference in the comparison between the infarcted and control animals of the same group at the two analyzed periods as well as during the evolution in the same subgroups.

The mean FDV in the young rats of the infarcted subgroup was similar to that of the control subgroup, in the two analyzed periods. The FSV was significantly higher in the infarcted subgroup, when compared to the control subgroup on the 7th postoperative day (p < 0.01); consequently, the ejection fraction was significantly decreased in this period (Table 1).

Table 1 – Distribution and comparison of the echocardiographic variables in the young rat group

		n	Infarcted	n	Controls	P*
FDV* (ml)	7 days	22	0.371 ± 0.179	13	0.404 ± 0.060	0.441
	30 days	14	0.557 ± 0.148	9	0.626 ± 0.146	0.286
FSV* (ml)	7 days	22	0.270 ± 0.143	13	0.169 ± 0.041	0.004
	30 days	14	0.347 ± 0.160	9	0.325 ± 0.072	0.665
EF* (%)	7 days	22	27.9 ± 7.6	13	58.6 ± 6.7	< 0.001
	30 days	14	40.6 ± 13.2	9	47.7 ± 4.2	0.079

FDV - final diastolic volume in milliliters; FSV - final systolic volume in milliliters; EF - percentage of ejection fraction; (*)Student t Test for independent samples (p < 0.025, Bonferroni correction); FDV - final diastolic volume; FSV - final systolic volume; EF - ejection fraction; (*)Student t Test for independent samples (p < 0.025, Bonferroni correction)

The analysis of evolution of the young animals carried out with the paired sample, showed a significant increase in the FDV and the FSV between the 7th and 30th postoperative days, associated with the animals' growth. The ejection fraction of the infarcted subgroup increased significantly ($p < 0.01$), whereas there was a significant decrease in the control group, $p < 0.01$ (Table 2).

The comparison between the infarcted and control subgroups of the adult animal group showed that the FDV on the 30th day and the FSV on the 7th and 30th days were significantly higher in the infarcted subgroup, with $p < 0.05$, $p < 0.001$ and $p < 0.01$, respectively. The EF was significantly decreased in the two analyzed phases, with $p < 0.001$ and $p < 0.001$ (Table 3).

The evolution analysis showed that, in the adult rats, only the FDV of the infarcted subgroup increased significantly ($p < 0.01$) (Table 4).

When comparing the two infarcted subgroups, the FDV on the 7th day (YI 0.371 ± 0.179 ml and AI 0.802 ± 0.112 ml) and on the 30th day (YI 0.557 ± 0.148 ml and AI 0.919 ± 0.196 ml), was significantly different, with $p < 0.001$ in the analyzed periods. The same statistical difference was observed when comparing the FSV on the 7th day (YI 0.270 ± 0.143 ml and AI 0.588 ± 0.113 ml) and on the 30th day (YI 0.347 ± 0.160 ml and AI 0.668 ± 0.225 ml).

When comparing the EF, no significant difference was observed between the two infarcted groups on the 7th postoperative day. On the 30th postoperative day, there was a marked improvement in the young subgroup, whereas the EF remained unaltered in adult group ($p = 0.013$).

The young infarcted subgroup attained the normal range value for this EF study, on the 30th postoperative day (Figure 1).

Table 2 – Comparison of the echocardiographic values at the evolution with paired samples, of 7 and 30 days, in the young rat group

		n	7	30	p*
FDV (ml)	infarcted	14	0.290 ± 0.152	0.557 ± 0.148	<0.001
	controls	9	0.418 ± 0.059	0.626 ±0.146	0.006
FSV (ml)	infarcted	14	0.210 ± 0.122	0.347 ± 0.160	<0.001
	controls	9	0.169 ± 0.048	0.325 ± 0.071	0.001
EF (%)	infarcted	14	28.1 ± 8.8	40.6 ± 13.2	0.001
	controls	9	60.3 ± 6.7	47.7 ± 4.2	0.001

FDV - final diastolic volume; FSV - final systolic volume; EF - ejection fraction; (*)Student t Test for independent samples (p < 0.025, Bonferroni correction); FDV - final diastolic volume in milliliters; FSV - final systolic volume in milliliters; EF - percentage of ejection fraction; (*)Student t Test for independent samples (p < 0.025, Bonferroni correction)

Table 3 – Distribution and comparison of the echocardiographic variables in the adult rat group

		n	infarcted	n	Controls	P
FDV* (ml)	7 days	24	0.802 ± 0.112	13	0.724 ± 0.169	0.103
	30 days	15	0.919 ± 0.196	10	0.712 ± 0.173	0.013
FSV* (ml)	7 days	24	0.588 ± 0.113	13	0.407 ± 0.131	< 0.001
	30 days	15	0.668 ± 0.225	10	0.401 ± 0.111	0.001
EF* (%)	7 days	24	26.9 ± 6.6	13	44.6 ± 7.4	< 0.001
	30 days	15	29.0 ± 10.4	10	45.8 ± 4.1	< 0.001

FDV - final diastolic volume; FSV - final systolic volume; EF - ejection fraction; (*)Student t Test for independent samples (p < 0.025, Bonferroni correction)

Table 4 – Comparison of the echocardiographic values at the evolution with paired samples, of 7 and 30 days, in the adult rat group

		n	7	30	p
FDV	infarcted	15	0.796 ± 0.107	0.919 ± 0.196	0.009
	controls	10	0.667 ± 0.133	0.695 ± 0.168	0.410
FSV	infarcted	15	0.587 ± 0.117	0.668 ± 0.225	0.114
	controls	10	0.367 ± 0.110	0.389 ± 0.106	0.305
EF	infarcted	15	26.5 ± 7.5	28.9 ± 10.3	0.369
	controls	10	45.7 ± 7.9	46.1 ± 3.7	0.826

FDV - final diastolic volume in milliliters; FSV - final systolic volume in milliliters; EF - percentage of ejection fraction; (*)Student t Test for independent samples (p < 0.025, Bonferroni correction)

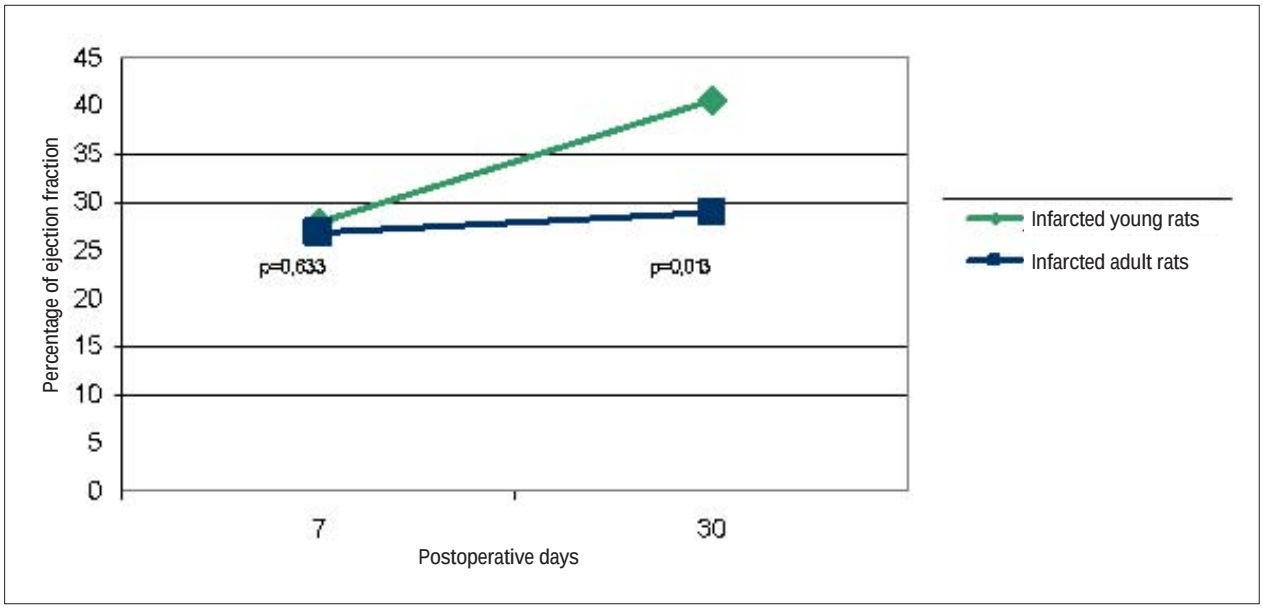

Figure 1 - Evolution of the ejection fraction throughout the study in the two infarcted subgroups.

Discussion

It was observed in the present study that the heart of the young infarcted rat showed a significant recovery of the systolic cardiac function when compared to the adult rat heart. The 28-day-old rats, considered young, reached, at the end of the study, a weight and cardiac development that was similar to that of the adult rats that started the study at 153 days old.

During the echocardiographic study, the heart rate of the animals was monitored with an echocardiographic tracing. On the 7th postoperative day, the number of beats was significantly higher in the group of young rats; however, on the 30th postoperative day, the numbers were similar.

As the animals were anesthetized, the heart rate was not the actual one, considering that the association of xylazine and ketamine produces bradycardia[9,10]. However, the mean values obtained in the adult rats were similar to those of other studies that used the same anesthetics[9]. The smallest dose used in the young rats can be the cause of the higher HR in these animals on the 7th postoperative day; however, this procedure was essential for the carrying out of the study, considering that many of young rats died at the beginning of the experiment, when there was an attempt to use the suggested total dose.

The general mortality of the study is similar to that reported by other authors. However, the mortality in the young group, alone, was the highest (49.3%)[11]. Additionally, the induction of significant infarction was more difficult in the young rats; therefore, the exclusion from the study due to an EF > 40% was higher in this group.

As the extension of the infarction cannot be controlled, the Simpson method was used for the echocardiographic analysis of the EF in the present study, as it allows the deformed area of the left ventricle to be included in the calculation of the systolic and diastolic volumes[8,12,13].

The LV final diastolic volume in the adult rat was increased when compared to that of the non-infarcted pairs. This alteration occurs as a consequence of the loss of contractile elements and the normal architecture of the ventricular wall, with a decrease in the contractile capacity of the affected region and, consequently, systolic function impairment[13,14].

The ventricular dilation is one of the compensatory mechanisms to maintain the cardiac output and it is related to ventricular remodeling[14,15]. The increase in ventricular diameter results in higher ventricular wall stress and triggers compensatory mechanisms such as hypertrophy and hyperplasia[14,16,17].

In young rats, the FDV was similar between infarcted and control animals. This evolution was different in the group of adult rats, as the infarcted rats presented significantly higher values than the control animals on the 30th postoperative day. This fact is probably due to compensatory mechanisms such as hyperplasia and hypertrophy and to the lower infarction expansion, which are more evident in young animals and might have had an effect on the smaller dilation of the ventricular cavity[13,18,19].

The non-dilation of the ventricular cavity on the 7th day might be due to the hypertrophy and increased capacity of contraction of the non-infarcted areas.

The study by Litwin et al[13] showed that two infarcted rats presented smaller volumes than their controls among 11 observed animals, although the cause of this finding was not reported. This same fact occurred among the young rats, but with no statistical significance.

The final systolic volume in the young infarcted group was significantly higher than that of the control group on the 7th postoperative day and did not show any statistical difference on the 30th day. The hindering of the systolic dilation can also be due to mechanisms of hyperplasia, hypertrophy and lower infarction expansion in this age range[20].

The ejection fraction values established for this study are lower than the ones used by other authors[19,21], as the objective was that the animals would have not only myocardial infarction, but also ventricular dysfunction.

A cutoff of 40% for the EF showed to be adequate, as the rats with EF<40% on the 7th postoperative day presented significant infarction. Moreover, no control rat had an EF < 40%.

The EF in the infarcted adult rats showed to be significantly lower in the two analyzed periods. In the young group, however, there was an increase during the evolution, which was close to the values presented by the young controls. The differentiated capacity of cell proliferation and hypertrophy in the hearts of young rats might be one of the mechanisms of contractility recovery of these animals[22].

The regeneration of the cardiac muscle remains controversial, even with evidence of the formation of new cardiomyocytes in the adult heart. Thus, the persistence of a low EF in infarcted adult rats probably occurred due to the inadequate compensatory hypertrophy of the non-infarcted areas and by the lower rate of cardiomyocyte replacement[16,22].

The worsening in the cardiac function may also be due to the myocardial contractility depression in regions distant from the infarction[13,23,24]. It is suggested that, in the adult rats with myocardial hypertrophy, a disproportion between the development of new capillaries and the myocardial hypertrophy occurs. This anatomical alteration might be related to the depression of the contractile function of cardiomyocytes due to the longer distance for oxygen diffusion[25].

The pathological anatomy of an experimental model of myocardial infarction showed that the younger rat presented a higher capacity of cardiac cell replication when compared to the adult rat[26]. Gould et al[27] observed that the 2-month-old animals presented a better recovery than the 10- and 12-month-old animals.

The cardiomyocytes are constantly renewed to replace the losses caused by death and apoptosis. Studies have demonstrated that the adult heart contains a small cardiomyocyte population with proliferation capacity, but that is not enough to replace the number of cardiomyocytes lost at the infarction. The poorer replacement rate in older animals could explain the higher tendency to present heart failure in adverse situations[28,29].

Younger rats present a higher protein synthesis activity, necessary for the progression of the cell cycle and replication of cardiomyocytes; the myocardial infarction can be the stimulus for the cardiomyocyte to re-enter the cell cycle[6,22].

Study limitations

The echocardiogram was chosen as it is a non-invasive method of assessment of cardiac parameters, which allows the heart to be analyzed in series. In rats, however, this procedure has limitations, considering that it requires anesthesia, with risk for the animal. Additionally, the visualization of all cuts is not always possible.

In the group of young control rats, a decrease in the ejection fraction was observed at the evolution. It is known that the use of ketamine associated to xylazine, in addition to interfering with HR, significantly decreases the parameters of cardiac contractility[30]. The use of a lower drug dose in this group on the 7th day of postoperative evolution might have resulted in this difference. However, these differences do not modify the final study outcome, as the young infarcted subgroup received the same treatment during the procedures and on the 30th day, all were anesthetized, as the adult rats.

In conclusion, the adaptive processes of myocardial infarction remain to be further understood.

The present study shows that the myocardial infarction in the young rat shows a better recovery of the cardiac function than in the adult rat. Further studies, however, are necessary to verify whether the functional improvement in young rats is accompanied by cell recovery.

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