Effect of Exercise on Ventricular Remodeling after Experimental Myocardial Infarction in Rabbits

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SUMMARY
The effect of exercise on ventricular remodelling after myocardial infarction (MI) is under discussion. The aim was to evaluate whether moderate exercise initiated at early stages of MI modifies the degree of ventricular dilation.

New Zealand rabbits were used, considering 3 groups: Group 1, "sham group" (G1, n=7); Group 2 (G2, n=4), rabbits were subjected to the ligature of a prominent branch of the left coronary artery, and Group 3 (G3, n=6), group with MI and moderate exercise on motor-driven treadmill, after 18 days of evolution. Rabbits were sacrificed at day 56 post-surgery, and hearts were perfused using Langendorff technique. Left ventricular end diastolic pressure (LVEDP) -volume curves were recorded.

The size of MI was determined by morphometric analysis.

MI size was (8±SEM) G 1: 0±0.00, G 2: 20.55±0.94 and G 3: 19.15±1.47

Conclusion: Moderate exercise initiated at early stages of MI evolution has an unfavourable effect on ventricular remodelling.

*: P < 0.05

INTRODUCTION
Among ischemic cardiopathies, myocardial infarct (MI) is the most important due to its high morbidity and mortality rates both in its acute phase and in the long term.

The appearance of a MI can provoke structural changes in the ventricular walls and cavity, thus causing modifications in the shape and size of the ventricle and - therefore - in ventricular geometry. Such changes are known as ventricular remodeling (1).

This process is initiated rapidly postinfarct, allowing to compensate, sharply, for the abrupt loss of myocytes suffered, and may continue even after histopathologic healing is completed, provoking ventricular dilation (1-4). Thus, the evolution of ventricular remodeling can cause left ventricular dysfunctions, which can lead to heart failure (1-11).

During recent years, comprehension of the physiopathologic mechanisms involved in post myocardial infarction ventricular remodeling has become increasingly important. A key role has been attributed to parietal stress, both in early (5) and late (1) stages. Physical exercise could be capable of modifying the remodeling process, as it acts by altering the load conditions of the left ventricle.

OBJECTIVES
The aim of this study was to evaluate ventricular remodeling after myocardial infarction (MI), under resting conditions and in the presence of moderate exercise initiated at the early stages of evolution, considering infarct size and degree of ventricular dilation.

MATERIAL AND METHODS
1.- Experimental model:
Female New Zealand rabbits were used. A left lateral thoracotomy was performed under general anesthesia. After performing pericardietomy, a 6-0 type silk thread was passed around a prominent
branch of the left coronary artery (LCA) (equivalent to the anterior descending artery in human beings). In order to induce MI the LCA was ligated. Throughout the observation period, the animals were kept in a quiet and acclimatized environment, and were fed with standard rabbit chow and water ad libitum.

2.- Experimental groups:

- Sham group, n=7: surgery was performed on this group as described above, but without inducing MI. Rabbits were allowed to follow the natural course of evolution during 56 days.
- MI sedentary group, n=4: MI was induced as described above. Rabbits were allowed to follow the natural course of evolution during 56 days.
- MI with moderate exercise group, n=6: MI was induced as described above and rabbits were allowed to follow the natural course of evolution during 56 days. Moderate exercise on treadmill was added as from day 18 of evolution after MI. The moderate exercise protocol established 3 sessions per week of 2 minutes per session, at a speed of 17 m/min, avoiding physical adaptation (endurance training).
  Upon completion of the evolution period both ventricular functions and morphologic characteristics were studied.

3 - Ventricular function studies:

On completion of the period assigned to each protocol the animals were weighed and sacrificed by means of an overdose of thiopental sodium (35 mg/kg). Chests were quickly opened and the aortas isolated and cannulated. Hearts were immediately excised and placed in a perfusion system by means of the cannulae, and were perfused according to Langendorff's modified technique in Krebs - Henseleit solution at a constant temperature of 37 °C and balanced with 95% O2 - 5% CO2 for oxygenation and to keep pH close to 7.4.

A latex balloon tied to a rigid polyethylene tube was placed in the left ventricle and was connected to a Deltram II (Utah Medical System) pressure transducer, thus allowing to record inner pressure of the left ventricle. Also coronary perfusion pressure (CPP) was recorded by means of a pressure transducer connected to the perfusion line at a point immediately anterior to the aortic cannulae. Coronary flow was regulated to obtain a constant CPP close to 80 mm/Hg. Heart rate was kept constant at close to 180 beats per minute by means of two electrodes (Figure 1).

![Figure 1](image)

Ventricular functions were measured in the preparation thus obtained by recording pressure/volume curves of the left ventricle. Considering the diastolic component (left ventricular end-diastolic pressure,
LVEDP) of these curves it was possible to evaluate the degree of ventricular dilation.

4 - Macroscopic and microscopic morphologic studies:
Once the data corresponding to ventricular functions were obtained hearts were fixed in formalin in 10% and subsequently cut transversely in slices from apex to base, and slices were placed in paraffin and stained with hematoxylin-eosin and Masson's trichrome. All slices were then processed by means of a digital image analyzer (Image Pro® Plus 3.0) to calculate size of infarct area as a percentage of the compromised myocardial mass.

Data were calculated as the mean ± S.E.M., assessed by ANOVA and followed by a post-hoc test.

RESULTS
Table I shows the values corresponding to general parameters: animal weight and percentage of infarct area. There were no significant differences among the considered groups, with the exception of the non-existence of an infarct in the sham group.

<table>
<thead>
<tr>
<th>General data</th>
<th>&quot;Sham&quot; Group</th>
<th>MI Sedentary Group</th>
<th>MI + Moderate Exercise Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>2130±54</td>
<td>2270±60</td>
<td>1938±20</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>0.0±0.0</td>
<td>20.55±0.94</td>
<td>19.15±1.47</td>
</tr>
</tbody>
</table>

Figure 2 shows results corresponding to LVEDP at different intraventricular volumes (diastolic component of the pressure/volume curve of the left ventricle) of the three considered groups. It can be observed that the curves corresponding to the groups with MI are situated at the right of the sham group, indicating LV dilation, as a larger volume is required to reach the same pressure.

We noticed that this rightwards displacement was higher in the MI with moderate exercise group. (*: P<0.05)

DISCUSSION
Until about three decades ago, the early treatment of MI included a very prolonged rest period: patients were instructed to sharply reduce their physical activity, and rest in bed during at least two or three months.

Among the rational motives for such procedure was the objective of keeping myocardial oxygen consumption at a low level. At present physical activity is initiated during the early stages of convalescence and many patients are encouraged to participate in supervised programs of regular exercise; in certain cases, physical training is indicated. Among its beneficial effects there is an increase of vagal tonicity, restoration of a higher degree of heart rate variability, a favorable effect on peripheral resistance, a decrease of thrombolic phenomena and a feeling of well-being. However, there is a possibility that, within the population with recent MI, there may be some specific sub-populations for which physical training could prove to be harmful (12, 13).

Accordingly, it is extremely important to know the impact of exercise on post-MI ventricular remodeling. Notwithstanding, the available data are limited, and frequently contradictory. Studies in patients present several obstacles: certain variables are difficult to control, coexistence of MI with other pathologies or with different risk factors, the presence of concomitant treatments, non-scheduled abandonment, necessity of considering a large number of patients, etc.

Many of these drawbacks can be avoided through the use of animal models. On the other hand, although hearts of experimental animal models are different to human hearts, they allow a far more effective and strict control of variables, thus opening new possibilities for the better understanding of ventricular remodeling in MI (14-16).

In the last few years, rabbits have been used as suitable experimental models for the study of myocardial ischemia and for studies of exercise physiology. It has been pointed out (17) that this species could mimic myocardial ischemia of the human heart without previous episodes of angina, being a highly suitable experimental animal for the study of MI resulting from an acute occlusion of an artery without previous significant stenosis and with a viable myocardium.

In our study we have resorted to an experimental model of isolated rabbit heart, which, upon standardization of LV load conditions, allows to perform a detailed analysis of ventricular functions under the strict control of certain variables. We have used a protocol of moderate exercise (avoiding the generation of physiologic hypertrophy or "endurance training"), and such physical activity was incorporated at the early stages of the MI histopathologic evolution, when cicatrisation of infarct was still not consolidated.

In this study, the changes observed in the group with sedentary MI coincide with previous studies: the installation of a MI generates ventricular dilation when the size of the infarcted area exceeds a certain limit. Such dilation can be evidenced through the shifting of the diastolic component of the pressure-volume curves (9) towards the right. In this study, hearts of the group with sedentary MI show a degree of dilation that coincides with previous reports (6-10). Interestingly, the group of MI with moderate exercise shows a trend towards greater dilation than the group with sedentary MI.

In view of this trend towards greater dilation, and therefore greater parietal stress, such modifications in ventricular geometry represent an unfavorable effect with important functional and prognostic implications. Thus, exercise initiated at the early stages of MI could present some unfavorable aspects.

On one hand, exercise could aggravate infarct expansion. On the other hand, ventricular dilation can evolve slowly and progressively during months and even years, provoking hemodynamic impairment, and furthermore, it is linked to a decrease in the life-span, in both cases proportionately to infarct size (1-11). In another direction, the periodical increase in the consumption of systemic oxygen can increase the cardiac workload, thus favoring the appearance of ischemia in areas with a decreased coronary reserve, unleashing manifest episodes of heart failure or serious arrhythmia.
CONCLUSION

We have studied the degree of ventricular dilation reached as consequence of MI, under resting conditions and also in the presence of moderate exercise on treadmill initiated at the early stages of evolution. The data obtained indicate that ventricular dilation occurred in the MI sedentary group, and that moderate exercise initiated at the early stages of MI evolution has an unfavorable effect on ventricular remodeling.

REFERENCES


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