

Experimental myocardial hypertrophy induced by a minimally invasive ascending aorta coarctation

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Abstract

Ascending aorta coarctation was produced by a minimally invasive technique in rabbits. Animal mortality was 5%. Morphometric and hemodynamic parameters were evaluated. A parabiologically isolated heart model was used to assess the hemodynamic parameters. Left ventricular weight/body weight ratio and muscle area showed clear evidence of hypertrophy when compared to control. The hemodynamic changes in the isolated heart model suggested decreased diastolic and systolic function in the coarcted group. The present model produced hypertrophy with low mortality rates as a result of its less invasive nature.

Key words

- Ventricular hypertrophy
- Ventricular function
- Experimental model

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Experimental models producing myocardial hypertrophy and ventricular dysfunction are of interest in heart research. These models permit the evaluation of drug effects, of myocardial protection methods, and of stunned myocardium recovery methods, among other possibilities. Several models have been proposed and different animals have been used. Several authors have described cardiac hypertrophy induced by drugs, coarctation of aorta or coarctation of the pulmonary artery (1-6). Aorta coarctation is frequently used in either the ascending or descending position. Ascending aorta coarctation is more similar to clinical conditions such as supraaortic congenital aortic stenosis. This technique, however, requires full sternotomy which is associated with up to 20% animal mortality (7,8). Minimally invasive methods are those which use small inci-

sions by the endovascular technique or assisted video, and allow complex procedures to be carried out with less trauma (9). Our objective was to standardize a minimally invasive technique for ascending aorta coarctation in order to induce left ventricular anatomic and functional changes in rabbit hearts, with low surgical mortality.

For the proposed technique, after sodium pentobarbital anesthesia, a small transverse cervical incision is made above the sternal bone. After retrosternal dissection, the ascending aorta and its branches are identified and, under pericardiotomy, aorta coarctation is carried out according to the classic technique of Bregagnollo et al. (4). This technique was applied to 10 animals and the results were compared with those for age-matched, sham-operated rabbits (N = 10). After 5 weeks, the animals were euthanized

with an anesthetic overdose for morphometric and functional study of the left ventricle according to the parabiotic model (use of a support animal). After the functional study, the atria were discarded and the right and left ventricles (including the septum) were separated and weighed. A 3-mm thick coronal section of the left ventricle was obtained, corresponding to the median portion of the chamber at the papillary muscle level. The transverse section area occupied by the myocardium was obtained by scanning, using the Sigma Scan Pro[®] software. The following functional parameters were analyzed: dP/dt+, defined as the maximum rate of systolic pressure increase; Dpmax, defined as maximum developed pressure, corresponding to the difference between systolic pressure and a diastolic pressure of 30 mmHg; Dstress, defined as developed stress, corresponding to the difference between systolic and diastolic stress, calculated when diastolic pressure was 30 mmHg; Kmyo, defined as the passive myocardial stiffness constant, which was determined for each animal by fitting the diastole stress (σ_d)-strain (ϵ) data to an exponential relation, and ΔV , defined as the balloon volume required to increase diastolic pressure from zero to 30 mmHg, which is used as an index of ventricular compliance (10). All of these indexes are often used in similar preparations reported in the literature (11,12). The Student *t*-test was used for comparison of the two

groups, with the level of significance set at 5%.

A mortality rate of 5% for the animals undergoing ascending aorta coarctation by this minimally invasive technique was considered low enough to demonstrate a technical advantage when compared to the traditional surgical approach (7,8).

The 5-week period of coarctation allowed the development of significant left ventricular concentric hypertrophy, which showed a mass increase of 50% compared to the sham-operated group. Myocardial growth was partially due to the reduction of the ventricular chamber (Table 1).

The objective of induced myocardial hypertrophy with ventricular dysfunction was reached as demonstrated by the results shown in Table 1. The studies performed on the isolated heart permitted the identification of systolic and diastolic function impairment.

Dpmax and dP/dt+ were maintained and Dstress was decreased in the hypertrophied ventricle. Although these results may seem conflicting, two factors should be taken into consideration: first of all, it has been reported that compensatory myocardial hypertrophy increases systolic function rates (13). Therefore, the findings of systolic function compared to control might indicate early decompensation. Secondly, left ventricular concentric hypertrophy provides favorable geometric conditions for the development of high isovolumetric pressure, overestimating

Table 1 - Morphometric and functional parameters of animals in the coarcted group (Coa) and in the sham-operated (Sham) group.

Lvw/Bw: Left ventricular and body weight ratio; area: cardiac muscular area; Dpmax: maximum value of developed pressure; dP/dt+: maximum rate of systolic pressure increase; Dstress: developed stress; ΔV : difference between ventricular volume for a diastolic pressure of 30 and 0 mmHg; Kmyo: passive myocardial stiffness constant. * $P < 0.05$, and ** $0.05 < P < 0.10$ compared to the sham-operated group (Student *t*-test).

| Groups | Lvw/Bw (mg/g) | Area (cm ²) | Dpmax (mmHg) | dP/dt+ (mmHg/s) | Dstress (g/cm ²) | ΔV (ml) | Kmyo (g/cm ² %) |
|--------|------------------|----------------------------|-----------------|--------------------|---------------------------------|--------------------|-------------------------------|
| Coa | 0.0021 ± 0.0001* | 2.8 ± 0.1* | 67.9 ± 18.5 | 888.9 ± 93 | 68.6 ± 16.6* | 0.97 ± 0.2* | 0.08 ± 0.02** |
| Sham | 0.0014 ± 0.0001 | 2.0 ± 0.2 | 70.6 ± 13.8 | 930.0 ± 100 | 91.1 ± 19.7 | 1.14 ± 0.2 | 0.06 ± 0.01 |

the actual contractile condition of the myocardium (14). In this case, the most adequate contractility index would be D_{stress} . Therefore, we conclude that the coarcted animals presented ventricular systolic dysfunction. Moreover, diastolic function, evaluated by the ventricular compliance index (ΔV), was decreased and the passive myocardial stiffness constant (K_{myo}) was abnormal, although with a significance level of 10%. This means a statistical trend to higher myocardial passive stiffness in this experimental model, indicating a biological significance which agrees with several studies of pressure-overload myocardial hypertrophy (15). The major cause of diastolic impairment is

reported to be myocardial fibrosis (13), which was not evaluated in the present study. The decreased ventricular compliance might be caused by either the increased myocardial stiffness or the altered ventricular geometry. Thus, the decreased cavity surrounded by a thick wall is less capable of accommodating a given diastolic volume.

In conclusion, ascending aorta coarctation by a minimally invasive technique was effective in producing myocardial hypertrophy and ventricular dysfunction. In addition, the technique is easily performed and may become an optional method for surgical ascending aorta coarctation.

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