Impaired Cardiac Functional Reserve and Left Ventricular Hypertrophy in Adult Sheep After Prenatal Dexamethasone Exposure

Miodrag Dodic, Chrishan Samuel, Karen Moritz, E. Marelyn Wintour, John Morgan, Leanne Grigg, James Wong

Abstract—We have shown that exposure of pregnant ewes to dexamethasone (11.5 mg/d for 2 days) at 27 days of gestation (term, 150 days) led to increased blood pressure and cardiac output in adult offspring. In this study, we hypothesized that dexamethasone-induced hypertension is associated with left ventricular hypertrophy and a reduced cardiac functional reserve (\(\text{CO}_{\text{max,0}}\)). Six control animals (group C) and five dexamethasone-exposed animals (group D) were volume-loaded with Hemaccel until the wedge pressure was 13 mm Hg (baseline). The wedge pressure was held constant during an infusion of dobutamine at incremental doses (0.4 to 12 \(\mu\)g/kg/min) while blood pressure and cardiac output were measured. The same protocol was repeated in each animal 5 days later under mild general anesthesia (1.5% isoflurane), when transthoracic echocardiography (M-mode) was obtained. Group D showed a reduced \(\text{CO}_{\text{max,0}}\) in response to dobutamine during both conscious (89±22 versus 150±25 mL/kg/min in control; \(P<0.01\)) and anesthetized states (91±38 versus 156±56 mL/kg/min in control; \(P<0.05\)). Reduced \(\text{CO}_{\text{max,0}}\) in group D was associated with higher left ventricular mass index compared with group C (2.6±0.67 versus 1.8±0.51 g/kg; \(P<0.05\)). In addition, group D showed a reduced cardiac contractility reserve (\(\text{FS}_{\text{max,0}}\)) in response to dobutamine (21±22% versus 54±34% in group C; \(P<0.05\)). An impaired cardiac functional reserve in group D was associated with increased left ventricular type I collagen content. In conclusion, brief prenatal exposure to dexamethasone led to the development of hypertension, left ventricular hypertrophy, and reduced cardiac functional reserve in adult life. (Circ Res. 2001;89:623-629.)

Key Words: dexamethasone ▪ hypertension ▪ left ventricular hypertrophy ▪ sheep

There is now strong and coherent epidemiological evidence that reduced growth in utero and in years 1 through 5 is linked with higher incidence of known cardiovascular risk factors, including hypertension, non–insulin-dependent diabetes mellitus, raised serum lipids, increased left ventricular mass, and reduced arterial compliance in later life.1–4 In a study of human subjects between 8 and 24 years of age, it was found (by M-mode echocardiography) that the left ventricular mass (adjusted for gender, present age, weight, and height) was associated with reduced infant growth; ie, the highest ventricular mass was found in the subjects whose weights at 9 months and 2 years were lowest. This was independent of the level of systolic blood pressure.5 The suggestion is that some factors predisposing to intrauterine growth retardation (maternal malnutrition and anemia, placental malfunction, and excess exposure to stress hormones) cause adaptations to be made by the fetus, which allow for survival in utero but lead, ultimately many years after birth, to increased risk of cardiovascular and metabolic disease.6

There are several animal experiments in which cardiovascular and metabolic disease have been programmed by different treatments, such as maternal undernutrition, maternal anemia, and exposure to excess natural or synthetic glucocorticoids.7–11 Most interestingly, in some of these cases, there is no evidence of fetal growth retardation.7–11 Regardless of the experimental perturbation applied to the mother causing long-term programming of the fetus, there is good evidence that one common factor, which may mediate the effect, is exposure of the fetus to excess glucocorticoid.12

There is some evidence that disturbance of the intrauterine environment, particularly early in pregnancy, can have profound effects on the health of the adult. Exposure to malnutrition during the Dutch famine, especially during the first gestational trimester, led to a greater occurrence of coronary heart disease, an atherogenic lipid profile, and obesity in 50-year-old adults.13–15 An early origin for programming of cardiovascular disease was also documented in some experimental models in rats.16,17 We were the first to show that very brief exposure of pregnant ewes to high levels of dexamethasone for only 2 days very early in gestation (at a mean age of 27 days of the 150-day gestation period) results

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in hypertensive offspring at 3 to 4 months of age. This type of hypertension amplifies with age and is associated with increased cardiac output (CO) (attributable to increase in stroke volume). Therefore, we consider it of interest to evaluate additionally cardiovascular function in these animals with prolonged elevation of blood pressure as a result of a brief prenatal exposure to dexamethasone. Specifically, we tried to assess whether hypertension in this model is associated with cardiac hypertrophy and reduced cardiac functional reserve. We used a dobutamine challenge test and transthoracic echocardiography (M-mode) to assess cardiac function and left ventricular mass. In addition, we measured collagen content in the left ventricle of the heart.

Materials and Methods

Animals

In this study, we used animals previously reported to become hypertensive after prenatal treatment with dexamethasone (Decadron; Merck, Sharp and Dohme NSW) given intravenously (11.5 mg/d) for 2 days at 27 days of gestation (group D). Only female lambs were included in additional studies, for practical purposes, there being fewer male offspring. Six female lambs served as the control group of animals. Surgery (ophorectomy and carotid artery loops) was performed on all lambs at 50 days of age. Oophorectomy was performed to eliminate potential effects of oestrus cycles. Sheep are seasonal breeders and usually spend a prolonged period in anestrous. At the time these experiments were conducted, animals were 7 years of age. All experiments were performed using a protocol approved by the Howard Florey Institute Animal Ethics Committee. Animals were supplied by Beverley Stud, Redesdale 3444, Victoria, Australia.

One day before the experiment, animals were instrumented with an Arrow Hands-Off infusion port thermodilution catheter (Arrow International) inserted via the jugular vein using a percutaneous sheath Introducer set (Baxter) under local anesthesia (0.5 mL of 0.5% Xylocaine; Astra). Pulmonary artery and pulmonary artery wedge pressures (WPs) were obtained. CO readings were taken from a CO computer (9520A, American Edwards Laboratories) after each bolus of 10 mL saline injected through the proximal lumen of the catheter. Mean arterial pressure (MAP) and heart rate (HR) were measured using a Tygon cannula (inner diameter, 1 mm; outer diameter, 1.5 mm) inserted into a carotid artery connected to a pressure transducer (TD XIII, Cobe) and recorded on a Gould 3000 series chart recorder (Gould Inc.).

Experimental Protocols

On the day of the experiment, basal MAP, CO, HR, mean pulmonary pressure (PAM), WP, and central venous pressure (CVP) were measured in conscious animals for at least 1 hour (baseline). Cardiac functional reserve was evaluated by the CO response to β-adrenergic stimulation (dobutamine challenge). To eliminate the differences in preload pressures between the animals, before dobutamine challenge each animal was infused with a plasma volume expander (Hemaccel; infusion rate of 20 mL/min), 200 mL steps or until the WP was 13 mm Hg. At each incremental load level, MAP, CO, HR, PAM, WP, and CVP were measured for 3 to 5 minutes. Once the desired WP was reached, MAPp, COp, HRp, PAMp, WPp, and CVPp were measured to establish a new baseline before commencing the dobutamine challenge. Dobutamine (dobutamine hydrochloride, Lilly) was infused in 6 to 8 incremental stages (each running for 10 minutes) with the dose ranging from 0.4 to 12 μg/kg/min or until the CO response reached a plateau. During each incremental stage of dobutamine infusion, MAP, CO, HR, PAM, and WP were recorded. WP was maintained at 13 mm Hg during the entire dobutamine challenge.

Transthoracic echocardiography was performed using the same protocol in each animal at least 5 days later under mild general anesthesia. General anesthesia was induced with 5% thiopentone sodium (Pentothal; Rhone Merieux) via the jugular vein, an endotracheal tube was inserted, and anesthesia was maintained on an isoflurane anesthetic (Isoflo inhalation anesthetic; Abbott). The animal was maintained on 1.5% Isoflo/high oxygen mixture (4:1 oxygen to air). M-mode measurements of the heart size (see below) were obtained to derive the fractional shortening (an index of the cardiac contractile reserve). All animals were studied in the left lateral decubitus position for serial echocardiographic examinations. At the conclusion of all in vivo experiments, animals were killed with an overdose (100 mg/kg) of pentobarbitone sodium (Lethabarb, Arnolds of Reading) for tissue collection.

Heart Size

The assessment of the heart size was performed by M-mode scanning in the short parasternal axis at the papillary muscle level using a Hewlett-Packard Sonos 1000 echocardiographic machine with a 5-MHz transducer. The images were stored on VHS magnetic tapes. At least 5 cardiac cycles were averaged for each data point. Measurements of the left ventricular diastolic diameter (LVD) and the thickness of posterior wall (PWd) and interventricular septum (IVSd) were performed in diastole (defined by the frame exhibiting the largest left ventricular cavity dimension). The left ventricular systolic diameter (LVS) and the thickness of posterior wall (PW) and interventricular septum (IVS) were measured during systole (defined by the frame exhibiting the smallest left ventricular cavity dimension). These measurements allowed estimation of the left ventricular mass using the following formula: LV mass (Penn conversion)=1.04[LVd+(LWd+LWd)−[LVD]−13.6 g and were indexed for animal body weight.

At autopsy, the left ventricle together with interventricular septum was dissected free of the right ventricle and separated from the aorta, mitral valve, and left atrium. The gross epicardial fat was removed, and the resulting left ventricle myocardium was weighed (wet weight).

Calculations

Left ventricular fractional shortening, FS = [LVD − LVS]/LVD × 100, and relative wall thickness, RWT = [PWd + IVSd]/LVD, were calculated. In addition, CO and FS were corrected for the prevailing total peripheral resistance (TPR) or meridional end-systolic wall stress (MWS) and HR using the following formulae:

(1) $\frac{CO}{TPR} = \frac{CO}{MWS} = \frac{FS}{TPR}$

(2) $\frac{CO}{\sqrt{\frac{R}{R}}} = \frac{CO}{\sqrt{\frac{R}{R}}} \times \frac{TPR}{FS}$

(3) $MWS = \left[0.334 \times SBP \times LVs \times (0.5 + 0.5) \times \frac{1}{2} (IVS + PW) \times 0.5 \right]$

where SBP is the peak systolic blood pressure.

For each animal, CO and FS responses to dobutamine were plotted individually, and maximal CO response (COmax) maximal FS response (FSmax), and EC50 (the negative logarithm of the concentration required to produce 50% of the maximal response) were obtained from sigmoid plot (nonlinear fit) using GraphPad Software. Cardiac functional reserve (COmax,p) and cardiac contractile reserve (FSmax,p) were then defined as a maximal change in CO or FS from respective values obtained at WP of 13 mm Hg.

Determination of Collagen Content

The collagen content in the left ventricle of the heart from 6 group C and 5 group D animals was determined as previously described. Triplicate 10-μL aliquots from each sample were analyzed for hydroxyproline content using a scaled-down procedure. Hydroxyproline values were then converted to collagen content by multiplying by a factor of 7.46.
Determination of Collagen Types

Collagen was extracted from 0.2% of the overall wet-weight tissue (from each of the control and dexamethasone-treated animals) as described. The maturely cross-linked collagen was extracted by limited pepsin digestion (enzyme to substrate ratio, 1:10; 24 hours) before aliquots of each sample were analyzed by SDS-PAGE on 5% (wt/vol) acrylamide gels containing 3.5% (wt/vol) acrylamide stacking gels. Interrupted electrophoresis with delayed reduction of the disulfide bonds of type III collagen was used to separate the $\alpha_1$(I) chains from the $\alpha_1$(III) collagen chains. The gels were stained overnight with 0.1% (wt/vol) Coomassie blue R-250 and destained with 30% (vol/vol) methanol containing 7% acetic acid.

Statistical Analysis

The results are presented as mean±SD. Results were analyzed by two-tailed Student’s $t$ test using Ryan-Holm step-down Bonferroni adjustment for testing multiple hypotheses. The strength of correlation between transthoracic echocardiography (M-mode) and autopsy measurements was assessed by linear regression analysis (GraphPad Software).

Results

Studies Performed on Conscious Animals

At the time of experiment, body weights of animals were similar (group C, 52±5 kg versus group D, 53±2 kg). As shown in Table 1, under basal conditions, group D animals showed a higher MAP, CO, stroke volume (SV), PAM, and WP but similar CVP compared with animals from group C.

MAP, CO, SV, HR, TPC, CVP, PAM, and WP at baseline taken for 1 hour during either conscious or anesthetized states and FS and MWS during anesthetized state in group C and group D animals. Results are expressed as mean±SD.

$^*P<0.01$, †$P<0.001$, and ‡$P<0.05$.

### Table 1. Basal Cardiovascular Function in Adult Control Animals and Animals Exposed to Dexamethasone for 48 Hours at the End of the First Month of Gestation

<table>
<thead>
<tr>
<th></th>
<th>Conscious</th>
<th>Anesthetized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group C</td>
<td>Group D</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>73±5</td>
<td>83±4*</td>
</tr>
<tr>
<td>CO, mL/kg/min</td>
<td>106±10</td>
<td>125±6†</td>
</tr>
<tr>
<td>SV, mL/kg/beat</td>
<td>1.35±0.3</td>
<td>1.57±0.2‡</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>79±10</td>
<td>80±4</td>
</tr>
<tr>
<td>TPC, mL/kg/min</td>
<td>1.5±0.3</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>−1.9±1.5</td>
<td>0.5±3.4</td>
</tr>
<tr>
<td>PAM, mm Hg</td>
<td>10.7±1.5</td>
<td>15.9±1.1†</td>
</tr>
<tr>
<td>WP, mm Hg</td>
<td>3.8±1.2</td>
<td>7.2±2.0†</td>
</tr>
<tr>
<td>FS, %</td>
<td>33±10</td>
<td>25±7</td>
</tr>
<tr>
<td>MWS, mm Hg</td>
<td>57±29</td>
<td>62±16</td>
</tr>
</tbody>
</table>

MAP, CO, SV, HR, TPC, CVP, PAM, and WP after plasma expander Haemaccel was given to raise PAM (PAM=23 mm Hg) and WP (WP=13 mm Hg) during either conscious or anesthetized states and FS and MWS during anesthetized state in group C and group D animals. Results are expressed as mean±SD.

$^*P<0.05$.
same level in all animals by Hemaccel infusion (Table 2). Interestingly, the total volume of Hemaccel required to raise WP to 13 mm Hg was significantly lower in group D compared with the control group (940 ± 6219 versus 1171 ± 44 mL, respectively; \( P, 0.05 \)). However, both groups required a similar volume of Hemaccel to maintain the WP at 13 mm Hg.

The \( \text{CO}_{\text{max}} \) to dobutamine infusions were not significantly different between group D compared with the control group (232 ± 45 versus 269 ± 22 mL/kg/min, respectively). However, \( \text{CO}_{\text{max},0} \) was found to be significantly reduced in group D (89 ± 22 mL/kg/min) compared with group C (150 ± 25 mL/kg/min; \( P < 0.01 \)) (Figure 1). As shown in Table 3, after indexing \( \text{CO} \) for the prevailing TPR or HR, there was still significant reduction in \( \text{CO}_{\text{max},0} \) in the group D animals. There was similar rightward shift in the \( \text{CO} \) response to dobutamine in group D (EC\(_{50} \) 6.5 ± 1.34 \( \mu \)g/kg/min) compared with group C (EC\(_{50} \) 4.7 ± 1.23 \( \mu \)g/kg/min; \( P < 0.05 \)). In addition, maximal HR response to dobutamine was not different between group D compared with group C (141 ± 18 versus 142 ± 7 bpm, respectively).

**Studies Performed on Anesthetized Animals**

Animals were allowed at least 1 week to recover before the same experiments were performed under general anesthesia so that transthoracic echocardiography (M-mode) could be performed. There were no significant differences in pH, \( \text{PCO}_2 \), and \( \text{PO}_2 \) between the animals from group D and group C before and after the infusion of dobutamine. Before the infusion of dobutamine started in the 6 animals from group C and the 5 animals from group D, these values were as follows: pH, 7.417 ± 0.10 (group C) and 7.450 ± 0.02 (group D); \( \text{PCO}_2 \), \( 39 \pm 7 \) mm Hg (group C) and \( 39 \pm 5 \) mm Hg (group D); and \( \text{PO}_2 \), \( 285 \pm 101 \) mm Hg (group C) and \( 314 \pm 22 \) mm Hg (group D).

As shown in Table 1, under anesthesia the basal values for \( \text{MAP}, \text{CO}, \text{SV}, \text{HR}, \text{TPC}, \text{CVP}, \text{PAM}, \text{WP}, \) and \( \text{FS} \) were similar between groups C and group D. A similar amount of Hemaccel was required to raise and maintain WP to 13 mm Hg in group C and group D. In addition, when the WP was standardized, there was also no difference in \( \text{MAP}_{0}, \text{CO}_{0}, \text{SV}_{0}, \text{HR}_{0}, \text{TPC}_{0}, \) and \( \text{CVP}_{0} \) between the two groups of animals (Table 2).

The \( \text{CO}_{\text{max}} \) to dobutamine infusions in the anesthetized state were not significantly different between group D compared with group C (209 ± 40 versus 263 ± 44 mL/kg/min, respectively) (Figure 2A). However, as found in the conscious state, \( \text{CO}_{\text{max},0} \) was found to be significantly lower in

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**TABLE 3. \( \text{CO}_{\text{max},0} \) and \( \text{FS}_{\text{max},0} \) After Adjustments for the Prevailing Afterload (TPR or MWS) and HR in Group C and Group D Animals**

<table>
<thead>
<tr>
<th></th>
<th>Conscious</th>
<th>Anesthetized</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CO}_{\text{max},0}/\text{TPR} ) (mL/kg/min)/mm Hg</td>
<td>423 ± 169</td>
<td>194 ± 110*</td>
</tr>
<tr>
<td>( \text{CO}_{\text{max},0}/\text{MWS} ), mL/kg/min/mm Hg</td>
<td>9.7 ± 1.5</td>
<td>4.9 ± 1.4†</td>
</tr>
<tr>
<td>( \text{CO}_{\text{max},0}/\sqrt{\text{R-R}} \times \text{TPR} ) (mL/kg/min)/mm Hg×ms</td>
<td>703 ± 262</td>
<td>391 ± 221*</td>
</tr>
<tr>
<td>( \text{FS}_{\text{max},0}/\text{TPR} ), %/mL/kg/min/mm Hg</td>
<td>157 ± 98</td>
<td>56 ± 27*</td>
</tr>
<tr>
<td>( \text{FS}_{\text{max},0}/\text{MWS} ), %/mm Hg</td>
<td>3.7 ± 0.6</td>
<td>1.7 ± 0.7†</td>
</tr>
<tr>
<td>( \text{FS}_{\text{max},0}/\sqrt{\text{R-R}} \times \text{TPR} ), %/mL/kg/min/mm Hg×ms</td>
<td>307 ± 167</td>
<td>127 ± 83*</td>
</tr>
</tbody>
</table>

*Results are expressed as mean ± SD.
†\( P < 0.01 \).
**TABLE 4. Heart Size and Thickness in Adult Control Animals and Animals Exposed to Dexamethasone for 48 Hours at the End of the First Month of Gestation**

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group D</th>
</tr>
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<tbody>
<tr>
<td>LVD, mm</td>
<td>349±40</td>
<td>400±36</td>
</tr>
<tr>
<td>LVS, mm</td>
<td>257±49</td>
<td>303±50</td>
</tr>
<tr>
<td>IVSd, mm</td>
<td>91±18</td>
<td>94±12</td>
</tr>
<tr>
<td>PWd, mm</td>
<td>89±16</td>
<td>95±10</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>106±15</td>
<td>120±4</td>
</tr>
<tr>
<td>PW, mm</td>
<td>116±18</td>
<td>116±3</td>
</tr>
<tr>
<td>RWT</td>
<td>0.53±0.13</td>
<td>0.52±0.10</td>
</tr>
<tr>
<td>LVM, g</td>
<td>98±29</td>
<td>134±32*</td>
</tr>
<tr>
<td>LVM/BW, g/kg</td>
<td>1.8±0.47</td>
<td>2.6±0.60*</td>
</tr>
</tbody>
</table>

Measurements of LVD, LVS, IVSd, and PWd during diastole and IVS and PW during systole were obtained by transthoracic echocardiography (M-mode) in 6 group C and 5 group D animals. In addition, RWT, left ventricular mass (LVM), and left ventricular mass indexed for body weight (LVM/BW) were calculated. Results are expressed as mean ± SD.

*P<0.05.

**Discussion**

The most interesting finding of this study is that high blood pressure occurring in adult sheep as a result of a very brief prenatal exposure to dexamethasone is associated with left ventricular hypertrophy (LVH) and reduced cardiac functional reserve. As previously reported, in these female sheep, a higher blood pressure was detected at 4 months of age. However, it was determined that compared with the control group of animals, this blood pressure difference was not only sustained but continuously increased at 10, 19, and 40 months of age. However, in the present study, we observed no additional increase in blood pressure difference...
between control and prenatally exposed dexamethasone animals, suggesting that blood pressure changes have reached a plateau. It has been shown that in spontaneously hypertensive rats that develop LVH before heart failure, blood pressure changes reach a plateau and may even decrease to a lower high level later because of reduction in cardiac contractility.24 Interestingly, in our animal model, LVH was associated with reduced cardiac functional reserve shown as an attenuated CO as well as fractional shortening response to dobutamine challenge.

It is generally agreed that LVH is an independent and powerful risk factor for coronary heart disease, stroke, and sudden death. More recently, it was reported that there was increased cardiovascular risk even for the left ventricular mass that is considerably lower than within the traditional upper normal limits.25 LVH is often accompanied by a reduced coronary vasodilator reserve, even in the absence of angiographic proof of coronary disease, which makes it a good marker of subclinical cardiovascular disease.26 Altered left ventricular geometry was also found to be a good predictor of extracardiac organ damage in people with essential hypertension.27 Although in this study estimates of the left ventricular mass found by transthoracic echocardiography (M-mode) were greater than the actual left ventricular mass (found at autopsy), there was a relatively close correlation between these two sets of values. A relatively higher degree of correlation between echocardiography and autopsy was reported for the human heart, although using a considerably bigger sample size and a wider range of left ventricular masses.28 In addition, we found that the LVH occurred in the absence of change in the relative wall thickness. This type of cardiac hypertrophy is generally associated with increased CO (attributable to increase in stroke volume) but with minimal or no elevation in peripheral resistance (volume load hypertrophy).29 Indeed, in our model of prenatally induced hypertension, high blood pressure has been shown to be associated with an increase in CO (attributable to an increase in stroke volume) and increase in both mean pulmonary artery and pulmonary WPs. Taken together, it would seem that in these animals there is a volume overload type of hemodynamic change, and its chronic impact on the heart may have resulted in the development of the LVH.

Our second major finding is that in our hypertensive animals, the LVH is associated with reduced cardiac functional reserve after exposure to the β-agonist dobutamine. A reduction in cardiac functional reserve was still present even after the preload, afterload, and HR adjustments had been made. In addition, these hypertensive animals have significantly lower fractional shortening in response to dobutamine challenge. It is therefore possible that in these animals a reduction of cardiac contractility is present (systolic dysfunction). In addition, in the spontaneously hypertensive heart failure rat, β-adrenoceptor numbers were reduced.24 In our study, there was a clear rightward shift in the CO response to dobutamine in the animals with the LVH, suggesting that reduced cardiac functional reserve might be caused by reduced β-adrenoceptor density. However, maximal change in the HR response to dobutamine challenge was similar between the two groups of animals. In addition, we found significantly increased left ventricular type I collagen (commonly associated with fibrosis) without type III collagen in animals with high blood pressure. Type III collagen (which usually forms a softer collagenous network) is increasingly expressed during early development but gradually decreases in proportion with age.30 Therefore, it is likely that the reduced cardiac functional reserve in our hypertensive animals may have resulted from structural changes of the myocardium (cardiac fibrosis) that have developed as a result of a chronic nontreated hypertension. It is well known that intense long-term physical training (athletes) also produces LVH. Whether the athlete’s heart carries an increased risk for cardiovascular events remains an intriguing clinical problem,31 but one distinct feature of the athletic heart (physiological LVH) is the absence of collagen deposition and ventricular fibrosis seen in pathological LVH.32 It is known that both aldosterone and angiotensin II can stimulate fibrosis in cardiac tissue.33,34

A limitation of this study is that we do not have any direct measure of the diastolic function in these animals. However, one interesting observation of this study is that in the control group of animals, the peak in CO response to dobutamine coincides with the peak in fractional shortening. On the other hand, in the hypertensive group of animals, the CO response to dobutamine peaks before the peak in fractional shortening. This might suggest that in these hypertensive animals there is an impairment in left ventricular relaxation (diastolic dysfunction). Diastolic dysfunction can be found in the presence of a normal fractional shortening32 and even in the absence of both hypertension and LVH,36 suggesting that abnormalities in diastolic function may precede or be independent of systolic dysfunction. However, it seems that in our study, impairment of systolic and diastolic function coexist and both might be attributable to impaired cardiac contractility.

In conclusion, short prenatal exposure to dexamethasone leads to high blood pressure in adult animals at least 7 years after the exposure. In these animals, reduced cardiac functional reserve is associated with LVH and an increased left ventricular type I collagen content.

Acknowledgments

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References


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