ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR HYPERTROPHY AND FUNCTION IN RENAL HYPERTENSIVE DOGS

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To investigate the performance of the hypertrophied left ventricle, M-mode echocardiographic measurements were performed 2 to 3 times weekly on 8 unanesthetized dogs for several weeks before and for 6 months after the induction of perinephritic hypertension. Four dogs with sham-wrapping and contralateral nephrectomy served as the controls. From a baseline value of 7.7 ± 0.4 mm (mean ± SD), left ventricular wall thickness increased to 9.0 ± 0.6 mm (p < 0.001) by the 4th week after the induction of hypertension and reached a plateau of 10.2 ± 1.2 mm (p < 0.001) by week 10. Fractional shortening of left ventricular dimension (%ΔD) increased during early left ventricular hypertrophy and remained elevated for 6 months in the surviving 6 hypertensive dogs. In hypertensive dogs, left ventricular concentric hypertrophy became detectable by week 6 of hypertension. Control dogs did not show these changes. At autopsy, the left ventricular weight of hypertensive and normotensive control dogs was 6.2 ± 1.4 g/kg and 4.3 ± 0.5 g/kg (p < 0.05). In summary, during the early stage of left ventricular hypertrophy in renal hypertensive dogs cardiac performance increased. There is no evidence for deterioration of left ventricular performance as concentric left ventricular hypertrophy develops and becomes chronic.

The functional capacity of the hypertrophied heart associated with arterial hypertension has been the subject of considerable controversy! Myocardial contractility or cardiac performance in the experimental models of left ventricular hypertrophy induced by hypertension has been variably reported as depressed2,3 normal or enhanced4–6. There are also some reported discrepancies regarding left ventricular function in patients with systemic arterial hypertension7–10. Since Meerson11 has described 3 stages in the natural history of cardiac hypertrophy, it is likely that the duration of hypertrophy may be an important factor in determining the functional response. Nevertheless, no studies have examined the sequential changes in left ventricular function during the development and maintenance of left ventricular hypertrophy in hypertension.

The adaptation of surface M-mode echocardiography to the study of unanesthetized dogs12,13

Key Words:
Cardiac hypertrophy and function
Echocardiography
Experimental renal hypertension

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has made long-term sequential measurements of left ventricular wall thickness and function possible. In the present study, we have used serial M-mode echocardiography to assess the course of development of left ventricular hypertrophy in renal hypertensive dogs and the function of the hypertrophied heart in the early and chronic stages of hypertension.

MATERIALS AND METHODS

Twelve mongrel male dogs, weighing 17 to 34 kg, were trained to lie quietly during echocardiographic examinations and arterial blood pressure measurements. After 4 weeks of baseline studies, the dogs were anesthetized with sodium pentobarbital, 30 mg/kg iv, and a left flank incision was made using sterile techniques. In 8 dogs, the left kidney was wrapped in silk to induce perinephritic hypertension. Four dogs were sham-operated as the controls. Two weeks later, the right kidney was removed surgically from all 12 dogs. Operative procedures have been described in detail previously.14

Arterial blood pressure was measured by percutaneous puncture of the femoral artery with a 19G needle, using a P23ID pressure transducer and a Hewlett Packard Model 7758D recorder. Mean arterial pressure measurements were performed once a week during the baseline period and for 4 weeks following the initial surgery. Thereafter, mean arterial pressure was measured every 2 weeks for the rest of the study.

Echocardiographic Measurements

M-mode echocardiographic measurements were performed on unanesthetized, unsedated dogs placed in the right lateral decubitus position according to the techniques developed in our laboratories.12 The ultrasonic transducer was placed over the point of maximal impulse on the right anterior chest wall and the beam was directed medially and inferiorly so that clear echoes from the interventricular septum and the left ventricular posterior wall could be obtained simultaneously with fragments of the mitral valve echoes in the left ventricular cavity. M-mode scanning was used in order to standardize the recording of the left ventricular echocardiograms (Fig. 1). Echocardiograms were recorded with an Ekoline 20A ultrasonoscope (Smith-Kline) and a Honeywell 1856 strip chart recorder, using a 2.25 MHz, 0.5 inch transducer focused at 7.5 cm, at a paper speed of 50 mm/sec. Echocardiograms were recorded simultaneously. In each dog, left ventricular echocardiograms were recorded 4 to 8 times during the baseline period, and 2 to 3 times weekly during the rest of the study. Echocardiographic measurements were made by the leading edge method.15 End-diastolic left ventricular internal dimension (Dd) and end-diastolic left ventricular posterior wall thickness (WTd) were measured at the peak of the R wave of the electrocardiogram; end-systolic left ventricular internal dimension (Ds) at the nadir of the interventricular septal motion. These measurements were made over 10 consecutive cardiac cycles in each recording and were averaged to minimize the effects of respiration and of sinus arrhythmia. Percent fractional shortening of left ventricular dimension (%ΔD) was calculated by the formula:

\[
\%\Delta D = \left( \frac{Dd - Ds}{Dd} \right) \times 100
\]
<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline period</th>
<th>Post-wrap</th>
<th>Post-nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-3 to -2</td>
<td>-1 to 0</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>Hypertensive Dogs (n = 6)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>89 ± 23</td>
<td>86 ± 18</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>128 ± 10</td>
<td>118 ± 11</td>
<td>135 ± 9</td>
</tr>
<tr>
<td>Dd (mm)</td>
<td>45.3 ± 3.6</td>
<td>44.9 ± 4.0</td>
<td>45.4 ± 3.8</td>
</tr>
<tr>
<td>Ds (mm)</td>
<td>32.7 ± 2.8</td>
<td>32.4 ± 2.8</td>
<td>31.3 ± 2.9</td>
</tr>
<tr>
<td>%ΔD</td>
<td>27.8 ± 1.0</td>
<td>27.8 ± 1.4</td>
<td>31.0 ± 2.2</td>
</tr>
<tr>
<td>WTd (mm)</td>
<td>7.7 ± 0.4</td>
<td>7.8 ± 0.4</td>
<td>8.1 ± 0.7</td>
</tr>
<tr>
<td><strong>Control Dogs (n = 4)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75 ± 8</td>
<td>91 ± 16</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>131 ± 14</td>
<td>131 ± 13</td>
<td>130 ± 11</td>
</tr>
<tr>
<td>Dd (mm)</td>
<td>44.9 ± 1.7</td>
<td>44.8 ± 2.9</td>
<td>44.7 ± 2.4</td>
</tr>
<tr>
<td>Ds (mm)</td>
<td>31.5 ± 1.3</td>
<td>32.1 ± 1.6</td>
<td>32.4 ± 1.8</td>
</tr>
<tr>
<td>%ΔD</td>
<td>29.8 ± 2.7</td>
<td>28.2 ± 3.7</td>
<td>27.6 ± 4.0</td>
</tr>
<tr>
<td>WTd (mm)</td>
<td>7.8 ± 0.3</td>
<td>7.8 ± 0.3</td>
<td>7.8 ± 0.1</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. * = p < 0.05; ** = p < 0.01; *** = p < 0.001, for comparison of values for each measurement period with baseline values. HR = heart rate; MAP = mean arterial pressure; Dd = end-diastolic left ventricular dimension; Ds = end-systolic left ventricular dimension; %ΔD = fractional shortening of left ventricle; WTd = end-diastolic left ventricular wall thickness.
Left ventricular mass (LVM) was calculated as follows:

\[
LVM = \left( \frac{7.0}{2.4 + (Dd + 2WTd)} \times (Dd + 2WTd)^3 \right) - \left( \frac{7.0}{2.4 + Dd} \times Dd^3 \right)
\]

**Post-mortem Examination of the Heart**

At the completion of the study, the dogs were anesthetized with sodium pentobarbital and then sacrificed with an overdose of potassium chloride iv. The hearts were removed immediately and rinsed in saline. Both atria and the right ventricular free wall were removed and the left ventricle, including the interventricular septum, was weighed.
Fig. 3. Left ventricular echocardiograms recorded in a hypertensive dog during the baseline period (A), and 4 weeks (B) and 18 weeks (C) after nephrectomy. Note the development of concentric left ventricular hypertrophy after nephrectomy. Abbreviations are the same as in Fig. 1.

**Statistical Method**

The reported values are expressed as means ± standard deviation. For purposes of statistical analysis, the study has been subdivided into 2 baseline periods and periods of 2 or 4 weeks' duration (Table I). Measurements obtained during each measurement period were compared by analysis of variance for repeated measurements on the same elements. Linear correlations were calculated by standard statistical techniques. The left ventricular weight of hypertensive and control dogs was compared by the unpaired Student's t-test. The body weight of dogs at the beginning and at the end of the study was compared by the paired Student's t-test.

**RESULTS**

The 8 dogs that underwent wrapping of one kidney in silk and contralateral nephrectomy (hypertensive dogs) were studied for 6 months after the induction of hypertension. In the 4 dogs that underwent sham-wrapping and contralateral nephrectomy (control dogs), measurements were discontinued 10 weeks after sham-wrapping since no significant changes in mean arterial pressure and left ventricular wall thickness were found.

One dog developed features of malignant hypertension manifested by mean arterial pressures of 200 to 240 mmHg and inability to stand and to feed itself. The dog was sacrificed 46 days after nephrectomy. Another dog developed heart failure manifested by progressive left ventricular dilatation and decreased fractional shortening and also had to be sacrificed 45 days after nephrectomy.

The mean arterial pressures of the remaining 6 hypertensive dogs and of the 4 control dogs are shown in the Table I and Fig. 2. The mean arterial pressure of hypertensive dogs rose by 14 mmHg during the 2 weeks after wrapping (NS) and by 31 mmHg during the first 2 weeks after nephrectomy (p < 0.001). Thereafter, the mean arterial pressure of hypertensive dogs remained at that level. In control dogs, mean arterial pressure did not change during the study. There were no changes in the heart rate of either hypertensive or control dogs. The body weight of the 6
hypertensive dogs at the end of the study, 26.4 ± 4.5 kg, was not different from baseline values, 25.3 ± 2.8 kg (NS, paired t-test).

Echocardiographic Measurements

Good quality echocardiograms were obtained from all dogs. In Fig. 3, left ventricular echocardiograms obtained from a hypertensive dog during the baseline period, and 4 weeks and 18 weeks after nephrectomy are shown. The results of echocardiographic measurements in hypertensive and control dogs are summarized in the Table I and Fig. 2. In hypertensive dogs, left ventricular hypertrophy was detectable by the 4th week after the induction of hypertension and was progressive, reaching a maximal level by the 14th week. End-diastolic left ventricular dimension did not change during the early phase of left ventricular hypertrophy. End-diastolic and end-systolic left ventricular dimensions in hypertensive dogs decreased by the 6th week after the induction of hypertension, indicating the development of concentric left ventricular hypertrophy.

Fractional shortening of left ventricular dimension (%ΔD) in hypertensive dogs was increased during the early phase of left ventricular hypertrophy and remained elevated during the entire study except for a small dip at week 5–6 after the induction of hypertension (Table I and Fig. 2). %ΔD in control dogs changed in the opposite direction during the same period.

In the dog that developed malignant hypertension, %ΔD increased from 35 to 39% during the 2 weeks after wrapping and returned to within the normal range by the 4th week after nephrectomy. End-diastolic left ventricular dimension of this dog did not change during the study. In the dog that developed heart failure, %ΔD rose from 24 to 26% after wrapping. After nephrectomy, %ΔD dropped to 12% within 7 weeks, at which time the dog had to be sacrificed. Its end-diastolic left ventricular dimension rose gradually from 48 to 53 mm by the end of the study (Fig. 4). The left ventricular mass of this dog was the biggest among all dogs (Fig. 5).

Post-mortem Examination of the Heart

At autopsy, the left ventricular weight of the 8 hypertensive dogs, 6.2 ± 1.4 g/kg, was significantly increased compared to that of the 4 normotensive control dogs, 4.3 ± 0.5 g/kg (p < 0.05, unpaired t-test). Correlation between the measured left ventricular weight and the one calculated from echocardiograms obtained during the last week of the study is shown in Fig. 5. Although the calculated left ventricular weight underestimated the actual weight by 12%, the 2 measurements were closely correlated (r = 0.95).

DISCUSSION

Echocardiographic Measurements in Dogs

Echocardiography has been proved to be one of the most reliable methods for measuring wall thickness and for evaluating left ventricular function in clinical cardiology. However, its use in experimental cardiology has been confined to open-chest dogs, because it has been considered difficult to obtain good quality echocardiograms from unanesthetized, closed-chest dogs. The technique of echocardiographic measurements in unanesthetized, closed-chest dogs was developed by Mashiro et al. The authors found that in dogs the ultrasonic beam traversed the right ventricle, the interventricular septum and the left ventricle when the transducer was placed 3 to 5 cm to the right of the sternum in the 3rd to 5th intercostal space with the dog in the right lateral decubitus position. The echocardiograms obtained in this way were similar to those obtained in human beings in the left lateral decubitus position. In the present study, using the method of
Mashiro et al., good quality echocardiograms could be obtained in all 12 dogs. Measurements of left ventricular dimension and wall thickness on successive days in the same dogs are highly reproducible. As further validation of the method, left ventricular mass calculated from echocardiograms was found to be highly correlated with the post-mortem measurements. Being a noninvasive, reproducible and accurate technique that can be applied as often as necessary, surface echocardiography is an ideal method for the long-term study of left ventricular hypertrophy and function in hypertensive dogs.

Function of the Hypertrophied Heart in Hypertension

The function of the hypertrophied heart in arterial hypertension has been a controversial subject in both clinical studies and animal experiments. Previous studies of cardiac performance in hypertension were mainly confined to the determination of cardiac output. With the recent development of noninvasive methods, more direct measurements of left ventricular function have become possible. Dunn et al. used echocardiography, found the left ventricular ejection fraction and fractional fiber shortening of hypertensive patients with apparent cardiac hypertrophy to be reduced. Karliner et al. also used echocardiography but found no evidence for depression of the basal inotropic state of the left ventricle in patients with hypertension and cardiac hypertrophy. Takahashi et al. studied the contractile state of the hypertrophied heart by simultaneously recording the echocardiogram and the brachial arterial pressure. The authors found that in hypertensive patients with left ventricular wall thickness of 1.0 to 1.2 cm the linear wall stress - diameter relationship at end-systole did not differ from that of normotensive control group, indicating a normal level of inotropic state. In patients with wall thickness of 1.3 cm or more, the end-systolic wall stress - diameter relationship was shifted to the right and had a less steep slope, indicating that myocardial contractility may be depressed in advanced left ventricular hypertrophy.

Controversy also exists in animal studies of left ventricular hypertrophy in arterial hypertension. Ferrario, Averill and coworkers evaluated the pumping ability of the hypertrophied heart in 2 experimental models of hypertension in rats, using the left ventricular end-diastolic pressure and stroke volume relationship as a measure of cardiac performance. They found that the peak pumping ability of the heart was depressed in hypertensive rats compared to that of normal controls at matched end-diastolic left ventricular pressure. In spontaneously hypertensive and normotensive control rats, Hållback-Norlander, Noresson and coworkers investigated the relationship between left ventricular filling pressure and stroke volume at different levels of aortic pressure. At higher arterial pressures, stroke volume was maintained in spontaneously hypertensive rats but fell in normotensive control rats, suggesting an increase in the pumping ability of the heart in hypertensive rats. Pfeffer et al. studied cardiac pumping ability during the natural development of left ventricular hypertrophy in spontaneously hypertensive rats. They demonstrated both a functionally stable stage of left ventricular hypertrophy and a later stage of functional deterioration in cases of massive left ventricular hypertrophy.

The studies of Pfeffer et al. raise the possibility that the duration of left ventricular hypertrophy is an important determinant of the function of the hypertrophied heart. In this regard, Meerson described 3 theoretical stages in the development of cardiac hypertrophy. At first, there is a phase of hyperfunction without hypertrophy, followed quickly by the development of cardiac hypertrophy. During the second stage of cardiac hypertrophy, myocardial mass increases to maintain normal function in the face of the increased demands imposed upon the heart. In the third stage, there is a progressive deterioration of myocardial function and eventually cardiac failure supervenes. There have been, however, no sequential studies of cardiac performance in experimental hypertension from the early hyperfunction stage through the established phase of cardiac hypertrophy.

In the present study, we have used surface M-mode echocardiography to investigate the cardiac performance in dogs with renal hypertension during the early and chronic stages of left ventricular hypertrophy. Fractional shortening of the left ventricular dimension increased significantly in all 8 hypertensive dogs during the early phase of hypertension. Contrary to Meerson's hypothetical first stage, this increased cardiac performance was accompanied by early left ventricular hypertrophy. Since end-diastolic left
ventricular dimension (preload), afterload and heart rate showed little change during this time, it is safe to assume that the increased fractional shortening was due to increased contractility of the left ventricular muscle. The fractional shortening in the 6 surviving hypertensive dogs remained above baseline levels during the established phase of concentric left ventricular hypertrophy. This phase of stable hyperfunction in the present study may correspond to Meerson's theoretical second stage of left ventricular hypertrophy. We have no explanation for the transient reduction in fractional shortening after the surgical interventions in the normotensive control dogs.

One of the hypertensive dogs developed features of heart failure manifested by progressive left ventricular dilatation and decreased fractional shortening after nephrectomy. This dog had the most severe cardiac hypertrophy of all dogs in the study. The findings in this dog suggest that Meerson's theoretical third stage may occur without the second stage of stable adaptation in the case of acute development of severe left ventricular hypertrophy.

In summary, the present study provides partial support for Meerson's theory of cardiac hypertrophy. In our dogs, hyperfunction and hypertrophy of left ventricle appeared to occur simultaneously. With the exception of one hypertensive dog that developed left ventricular hypertrophy acutely, there was no evidence for deterioration of left ventricular function for as long as 6 months of hypertension. It remains to be determined at which point in the course of left ventricular hypertrophy does deterioration of left ventricular function finally occur.

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