Reduced renal reserve and increased cardiac output in adult female sheep uninephrectomized as fetuses

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Background. Removal of one kidney during the period of nephrogenesis in the sheep leads to offspring with elevated blood pressure and reduced glomerular filtration rate (GFR) at 6 and 12 months of age. The mechanisms underlying the hypertension and the degree of renal impairment are not known.

Methods. Changes in GFR were measured in response to an infusion of amino acids and cardiac output was measured by thermal dilution in female offspring at 2 years of age in eight control (sham-operated) and seven animals that had been unilaterally nephrectomized at 100 days of gestation.

Results. Animals uninephrectomized as fetuses had significantly higher blood pressure (91 ± 2 mm Hg) compared to control animals (86 ± 2 mm Hg) (P < 0.05). Cardiac output was significantly higher in the uninephrectomized group (148 ± 10 ml/kg/min) compared to the control group (124 ± 6 ml/kg/min) (P < 0.05). Heart rate and stroke volume were similar in the two groups although both parameters tended to be higher in the uninephrectomized group. Uninephrectomized animals had a lower basal GFR (P < 0.05). An infusion of amino acids caused a significantly different response in GFR in the two groups (P < 0.01 between the groups) with the uninephrectomized animals having significantly lower GFRs during the infusion period.

Conclusion. The increased blood pressure observed after fetal uninephrectomy is due to an increase in cardiac output. Thus, formation of a low number of nephrons in utero may predispose an individual to later renal failure and elevated blood pressure.

The formation of a low nephron number in utero has been suggested to be linked to elevated blood pressure in adulthood [1]. The process of nephrogenesis is completed before birth in the human [2] and thus a healthy intrauterine environment is critical for the normal development of the kidney and the formation of an adequate number of nephrons [3]. Suboptimal in utero conditions may predispose an individual to development of adult disease in a process termed fetal programming [3]. We have shown in the sheep, a species in which nephrogenesis is also complete before birth, that removal of one kidney during the period of active nephrogenesis results in the offspring developing elevated blood pressure by 6 months of age [4]. Unilateral nephrectomy of the rat also causes high blood pressure in the adult when the kidney is removed soon after birth, prior to completion of nephrogenesis in that species [5]. Furthermore, in a different sheep model, where the fetus is exposed to high levels of dexamethasone early in gestation and the offspring go on to develop high blood pressure [6], we have recently demonstrated a nephron deficit [7]. These studies demonstrate that formation of a low nephron number may result in a higher blood pressure in the adult.

Unilateral nephrectomy during fetal development in the sheep also resulted in impaired renal function with animals having a lower glomerular filtration rate (GFR) at both 6 months and 1 year of age [4]. These results indicate a degree of renal insufficiency is present in early adulthood as a result of a prenatal reduction in nephron number. Renal ability to increase GFR in response to vasodilatory stimulation such as amino acid infusion is known as the functional renal reserve (FRR). It is well established that FRR is greatly diminished in patients with renal disease particularly in patients with essential hypertension [8], chronic renal failure [9], or diabetic nephropathy [10]. Based on these results, we hypothesized in this study that the unilaterally nephrectomized sheep would have a reduced FRR. We aimed to determine the changes in GFR in response to an infusion of amino acids.

In addition, we aimed to investigate further the basis of the elevated blood pressure. In adult female sheep that have elevated blood pressure due to early prenatal exposure to dexamethasone, it was shown that the increased blood pressure was associated with an increase in cardiac output [11] and a significant reduction in cardiac

Key words: cardiac output, fetal uninephrectomy, functional renal reserve.

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GENETIC DISORDERS – DEVELOPMENT
LVH may precede the development of end-stage renal dialysis [14, 15]. This suggests that the development of cases of chronic renal failure but it has also been found in children with mild renal insufficiency not requiring dialysis [14, 15]. This suggests that the development of LVH may precede the development of end-stage renal disease (ESRD). Furthermore, the sheep made hypertensive due to prenatal dexamethasone exposure have LVH present at 7 years of age [12].

Ours aims were thus to test the following hypotheses: (1) the FRR would be blunted in the uninephrectomized sheep; (2) the elevated blood pressure seen in the uninephrectomized animals would be due an elevated cardiac output; (3) increased cardiac output would be due to an increase in stroke volume rather than heart rate as the uninephrectomized animals had not shown elevated heart rates at 6 and 12 months of age; and (4) evidence of LVH would be present in these animals as they had been moderately hypertensive for at least 18 months and although not exhibiting signs of renal failure, they do have reduced renal function.

METHODS

Animals

All experiments were approved by the Animal Ethics Committee of the Howard Florey Institute, in accordance with guidelines set down by the National Health and Medical Research Council of Australia. The animals used in this study have been reported on previously [4]. Briefly, at 100 days of gestation, the ewe underwent general anesthesia at which time the left kidney was removed from female fetuses (uninephrectomized) (N = 7) or left intact (control) (N = 8). Lambs were allowed to be born naturally at term (150 ± 1 days) and were of normal birth weight (uninephrectomized = 4.3 ± 0.2 kg, control = 4.3 ± 0.1 kg). At approximately 4 months of age, one carotid artery was exteriorized into a fold of skin to form a loop. In the current study, sheep were aged between 20 and 24 months. Animals were introduced into the laboratory at postmortem [12]. Due to technical difficulties, it was not possible to obtain echocardiography measurements in one of the control animals so results were calculated using N = 7 in this section.

Blood pressure

To measure blood pressure, a Tygon cannula (inner diameter 1.0 mm, outer diameter 1.5 mm) was inserted into the carotid loop. After a 24-hour equilibration period, blood pressure and heart rate were measured as described previously for 3 days [4, 6]. Data were collected on computer and mean values obtained for each 24-hour period. These values were then averaged to give a 3-day basal mean arterial pressure (MAP) and heart rate. Blood pressure data were also averaged into 4-hour periods for each animal to assess possible differences in diurnal rhythms.

Cardiac output

For measurement of cardiac output, an Arrow hands-off infusion port thermodilution catheter (Arrow International, Reading, PA, USA) was inserted into the jugular vein using a percutaneous sheath introducer set (Baxter, Sydney, Australia) under local anesthesia (0.5 mL of 0.5% xylocaine) (Astra Zeneca, Sydney, Australia). On the day following cannulation, basal MAP, heart rate, central venous pressure (CVP), pulmonary artery pressure (PAP), and pulmonary artery wedge pressures (PAWP) were measured. The cardiac output was measured after the bolus infusion of 10 mL saline injected through the proximal lumen of the thermodilution catheter. Measurements were obtained using a cardiac output computer (9520A) (American Edwards Laboratories, Irvine, CA, USA) and collected over a 2-hour period during which the animal was standing quietly in its cage. At least 20 to 25 measurements were made for each animal. These values were averaged to give a single cardiac output values for each animal. This method has been used previously in sheep [11].

Echocardiography

M-mode scanning echocardiography was used to determine heart size in the conscious animal as described previously [12]. Measurements were made at the level of the short parasternal axis papillary muscle using a Hewlett-Packard Sonos 1000 echocardiography machine with a 5 MHz transducer. Five cardiac cycles were obtained for each animal and then averaged for each data point. Left ventricular diameter (LVD), posterior wall thickness (PWd), and intraventricular septum diameter (IVSd) were obtained during diastole. Left ventricular mass (LVM) was then calculated using the formula:

\[
\text{LVM (Penn conversion)} = 1.04 \times ([\text{LVD} + \text{PWd} + \text{IVSd}]^3 - [\text{LVD}]^3) - 13.6\]

and indexed for body weight

This method has been shown to slightly overestimate LVM but values correlate well with weights obtained at postmortem [12]. Due to technical difficulties, it was not possible to obtain echocardiography measurements in one of the control animals so results were calculated using N = 7 in this section.

Kidney function

On the day prior to experimentation, a cannula was placed in a jugular vein (internal diameter 1.18 mm) under local anesthetic (0.5% xylocaine) (Astra...
Pharmaceuticals). A Foley catheter (size 12 F) (Bardia, Kedah, Malaysia) was inserted into the bladder to allow for continuous collection of urine. GFR was measured as described previously in sheep [16] using 51-chromium ethylenediaminetetraacetic acid (51Cr-EDTA). Basal GFR was measured for four 30-minute periods. Urine flow rate and urinary concentrations of ions (sodium, chloride, potassium, urea, creatinine, phosphate, and total protein) were measured. Excretion rates of these ions were then calculated.

Renal reserve

After measurement of basal parameters, renal function was measured during an intravenous infusion of amino acids (0.065 mL/kg/hour of a 10% solution without electrolytes) (Synthamin®) (Baxter, Australia). Each 500 mL of this product contains 3.65 g L-leucine, 3 g L-isoleucine, 2.9 g L-valine, 2.8 g L-phenylalanine, 2.4 g L-histidine, 2.1 g L-threonine, 2 g L-methionine, 0.9 g L-tryptophan, 10.35 g L-alanine, 5.75 g L-arginine, 5.15 g glycine, 3.4 g L-proline, 2.5 g L-serine, and 0.2 g L-tyrosine. The dose was determined after preliminary experiments showed that this dose increased GFR in two control animals by approximately 10% to 15%. Measurements were made during the 2 hours of infusion and then for a further 2 hours after cessation of the treatment.

Sample analysis

A Beckman Synchron CX-5 clinical system (Beckman Instruments, Inc., Sydney, Australia) was used to measure concentrations of sodium, potassium, chloride, urea, and creatinine in urine and/or plasma. Osmolality was measured by freezing point depression using an Advanced Osmometer (Advanced Instruments, Norwood, MA, USA).

Statistics

Data are reported as mean ± SEM. A two-way analysis of variance (ANOVA) was used to test for differences between the groups over time (GFR data). Post hoc analysis (Tukey-Kramer test) was used to determine which points were significantly different. An unpaired t-test was used to test for differences in 3-day blood pressure, cardiac output, and parameters measured during echocardiography as well as basal renal parameters.

RESULTS

Blood pressure

Uninephrectomized animals had significantly elevated blood pressures (91 ± 2 mm Hg) (N = 7) compared to the control group (86 ± 2 mm Hg) (N = 8) (P < 0.05) when measured over 3 days but there was no difference in heart rates (uninephrectomized = 86 ± 3 beats/min and control = 77 ± 4 beats/min). MAP results collated in 4-hour intervals are shown in Figure 1. Uninephrectomized animals had significantly higher pressures at all times of the day. No consistent diurnal rhythm was observed over the 3 days.

Cardiac output and echocardiography

Intra-animal variation in cardiac output over the 20 to 25 measurements was 5 ± 2%. After correcting for body weight, cardiac output was significantly elevated in the uninephrectomized group (148 ± 10 mL/kg/min)
Kidney function

Food and water intake and urine output was similar in all animals during the 48 hours prior to GFR measurement (data not shown). Basal GFR varied by <5% during the control period and was significantly lower in the uninephrectomized group (see Table 3). Basal urinary concentrations and excretion rates of sodium, potassium, and creatinine were similar in both groups (Table 3). However, urinary protein concentrations tended to be higher in the uninephrectomized group (1248 ± 395 μmol/L) compared to the control group (632 ± 155 μmol/L) ($P = 0.1$) as did urinary protein excretion rates (74 ± 13 μmol/hour versus 51 ± 7 μmol/hour) ($P = 0.08$). A significant difference in urinary protein excretion was obtained with the removal of one animal from the uninephrectomized group which had a protein excretion less than half that of all others in the group [uninephrectomized = 83 ± 11 μmol/hour (N = 6) versus control = 51 ± 7 μmol/hour] ($P < 0.05$). This animal also had the lowest blood pressure in the uninephrectomized group. Basal plasma concentrations of sodium, potassium and urea were similar but the uninephrectomized animals had significantly elevated concentrations of creatinine ($P < 0.05$).

Table 1. Cardiovascular parameters in adult uninephrectomized ewes (N = 7) and sham-operated controls (N = 8) measured over a 2-hour period.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Uninephrectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output mL/kg/min</td>
<td>124 ± 6</td>
<td>148 ± 10*</td>
</tr>
<tr>
<td>Mean arterial pressure mm Hg</td>
<td>87 ± 3</td>
<td>91 ± 3</td>
</tr>
<tr>
<td>Heart rate beats/min</td>
<td>73 ± 4</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Stroke volume mL/kg/beat</td>
<td>1.73 ± 0.11</td>
<td>1.85 ± 0.10</td>
</tr>
<tr>
<td>Total peripheral resistance mm Hg/ml/kg/min</td>
<td>0.75 ± 0.07</td>
<td>0.65 ± 0.06</td>
</tr>
<tr>
<td>Mean pulmonary pressure mm Hg</td>
<td>13.8 ± 1.2</td>
<td>12.6 ± 0.8</td>
</tr>
<tr>
<td>Wedge pressure mm Hg</td>
<td>6.0 ± 1.0</td>
<td>5.1 ± 0.6</td>
</tr>
<tr>
<td>Central venous pressure mm Hg</td>
<td>4.0 ± 1.5</td>
<td>1.0 ± 1.6</td>
</tr>
</tbody>
</table>

*P < 0.05 between the groups.

Table 2. Heart size and wall thickness during diastole in uninuliniprectomized adult sheep (N = 7) and sham-operated controls (N = 7) as determined by M-mode echocardiography.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Uninephrectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight kg</td>
<td>44.6 ± 1.9</td>
<td>44.7 ± 2.3</td>
</tr>
<tr>
<td>Left ventricular diameter mm</td>
<td>37.9 ± 2.7</td>
<td>37.5 ± 1.5</td>
</tr>
<tr>
<td>Posterior wall diameter mm</td>
<td>7.5 ± 0.4</td>
<td>7.2 ± 0.2</td>
</tr>
<tr>
<td>Intraventricular septum diameter mm</td>
<td>8.2 ± 0.5</td>
<td>7.7 ± 0.1</td>
</tr>
<tr>
<td>Left ventricular mass g</td>
<td>94 ± 15</td>
<td>82 ± 5</td>
</tr>
<tr>
<td>Left ventricular mass/body weight g/kg</td>
<td>2.1 ± 0.2</td>
<td>1.9 ± 0.1</td>
</tr>
</tbody>
</table>

Table 3. Basal urinary and plasma parameters in uninephrectomized (N = 7) and sham-operated control (N = 8) ewes measured over a 2-hour control period at 2 years of age.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Uninephrectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight kg</td>
<td>46.7 ± 2.3</td>
<td>45.3 ± 2.8</td>
</tr>
<tr>
<td>Urinary filtration mL/kg/hour</td>
<td>2.2 ± 0.4</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Glomerular filtration rate mL/kg/hour</td>
<td>108 ± 4</td>
<td>84 ± 9*</td>
</tr>
<tr>
<td>Urinary filtration rate mmol/hour</td>
<td>711 ± 117</td>
<td>1051 ± 178</td>
</tr>
<tr>
<td>Urinary sodium mmol/L</td>
<td>77 ± 12</td>
<td>84 ± 21</td>
</tr>
<tr>
<td>Urinary sodium excretion mmol/hour</td>
<td>5.8 ± 0.9</td>
<td>5.1 ± 1.3</td>
</tr>
<tr>
<td>Urinary potassium mmol/L</td>
<td>168 ± 28</td>
<td>294 ± 42</td>
</tr>
<tr>
<td>Urinary potassium excretion mmol/hour</td>
<td>14.6 ± 1.1</td>
<td>16.3 ± 1.0</td>
</tr>
<tr>
<td>Urinary sodium/potassium ratio</td>
<td>0.49 ± 0.09</td>
<td>0.29 ± 0.06</td>
</tr>
<tr>
<td>Urinary protein μmol/L</td>
<td>632 ± 155</td>
<td>1248 ± 395</td>
</tr>
<tr>
<td>Urinary protein excretion μmol/hour</td>
<td>51 ± 7</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>Urinary creatinine mmol/L</td>
<td>6.7 ± 1.7</td>
<td>7.5 ± 1.4</td>
</tr>
<tr>
<td>Urinary creatinine excretion mmol/hour</td>
<td>0.41 ± 0.03</td>
<td>0.39 ± 0.04</td>
</tr>
<tr>
<td>Plasma osmolality mOsm/kg water</td>
<td>298 ± 2</td>
<td>301 ± 2</td>
</tr>
<tr>
<td>Plasma sodium mmol/L</td>
<td>148 ± 1</td>
<td>149 ± 1</td>
</tr>
<tr>
<td>Plasma potassium mmol/L</td>
<td>4.3 ± 0.1</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>Plasma urea mmol/L</td>
<td>6.1 ± 0.2</td>
<td>7.0 ± 0.4</td>
</tr>
<tr>
<td>Plasma creatinine μmol/L</td>
<td>77 ± 2</td>
<td>86 ± 3*</td>
</tr>
</tbody>
</table>

*P < 0.05 between treatment groups.
uninephrectomized group but levels excreted were actually lower than observed previously at 6 and 12 months [4].

Infusion of amino acids into healthy patients or animals, with no evidence of hypertension or renal disease, causes an increase in the GFR and renal blood flow commonly known as the FRR [8, 17]. In this study, the GFR response to an infusion of amino acids in control animals was very small (an increase in GFR of ~10%) or not present. This was surprising given the well-documented increase in GFR seen in other species in response to an amino acid infusion [18]. It has previously been reported that in the fetal sheep, infusions of amino acids cause an increase in GFR but this is not associated with increases in renal blood flow as seen in the adult of other species [18, 19]. There are scant data available on the effect of amino acid infusion on renal function in the adult sheep. One study has found that infusions of arginine but not glycine caused an increase in GFR in anaesthetized adult sheep [20]. At much higher doses, an infusion of alanine, glycine, proline, and serine (0.12 mmol/kg/min), sufficient to cause significant hypotension and tachycardia, caused no change in GFR in the adult sheep (Boyce, Gibson, and Lumbers, personnel communication). It would thus appear the sheep may differ from other nonruminant species in the renal response to an amino acid load. In simple stomached animals such as humans and dogs, removal of nitrogenous waste products occurs via the kidney following a protein load but in a ruminant the nitrogen can be used in protein synthesis by rumen bacteria.

Interestingly, although neither group showed a significant increase in GFR in response to amino acid infusion, there was a difference in responses between the groups. This may be related to the elevated blood pressure in the uninephrectomized group. In response to amino acid infusion some patients with essential hypertension exhibited a 10% decrease in GFR [8]. This occurred even though there was no change in systemic blood pressure or renal plasma flow [8] and may reflect preferential vasodilation of the efferent arterioles while afferent arteriolar resistance remains high. In other studies, high blood pressure has been shown to blunt the FRR [21]. In people with a family history of hypertension, the response was found to be significantly reduced prior to the development of elevated blood pressure [22]. The FRR was inversely dependent upon basal arterial pressure and GFR in patients with systemic sclerosis [23]. It should also be noted that there was considerable variation in the GFR response to amino acid infusion in both control and uninephrectomized animals. Two animals in the control group showed no significant increase in GFR while some increase was observed in other animals. As discussed above, this may be due to the sheep being a ruminant but this observation is also consistent with previous studies in humans [23] and baboons [24] that have demonstrated

**Fig. 3.** Changes in urinary protein excretion in sham operated control animals (N = 8) (●) and unilaterally nephrectomized animals (N = 7) (○) during an intravenous infusion of amino acids. Two-way analysis of variance (ANOVA). P < 0.05 between the groups.

**Amino acid infusion**

The GFR response to the infusion of amino acids can be seen in Figure 2. Two-way ANOVA showed there was a significant difference between the groups over time (P < 0.05). Post hoc analysis showed that after 60, 90, and 120 minutes of amino acid infusion, the difference in GFR was significantly greater than it had been under basal conditions (P < 0.01 at 60 and 90 minutes and P < 0.001 after 120 minutes). During the recovery phase, GFR values between the groups were not significantly different. Urinary sodium excretion decreased significantly in both groups over time; however, responses were similar in both groups. Excretion rates of chloride, urea, and creatinine were not different between the groups. The change in urinary protein excretion was significantly greater in the control than in the uninephrectomized animals (Fig. 3).

**DISCUSSION**

The most important finding in this study is that at 2 years of age, the animals uninephrectomized as fetuses are exhibiting signs of renal insufficiency, and along with the elevated blood pressure, it is possible these animals would develop renal failure in later life. The uninephrectomized animals had a significantly lower basal GFR and in response to an infusion of amino acids, the difference in GFR between the two groups increased significantly. Plasma creatinine concentrations were similar between the two groups when measured at 6 and 12 months [4]. However, in this study elevated basal plasma creatinine concentrations in the uninephrectomized animals were present indicating some degree of renal insufficiency. Urinary protein excretion tended to be higher in the
a wide range of renal responses to amino acids. A study of renal function in children after unilateral nephrectomy for Wilms’ tumor also showed that while FRR was normal in most patients, a significant number showed no change in GFR in response to the protein load [25]. The mechanisms through which amino acids mediate an increase in GFR are not completely understood but are thought to involve tubuloglomerular feedback [17]. It may also involve dopamine D2 receptors as central and peripheral inhibition of these receptors abolished the FRR [26]. We could speculate that there is a decreased level of the dopamine D2 receptor in the uninephrectomized animals although this is yet to be tested. Nitric oxide, a known renal vasodilator, may also be involved. In patients given the same amino acid composition as our sheep, a blunted FRR was associated with a diminished rise in the excretion of urinary nitric oxide suggesting an inability to convert the arginine (present in the amino acid load) to nitric oxide [18].

Removal of one kidney at 100 days of gestation is likely to have caused compensatory changes within the remaining kidney that may have long-term sequelae and may result in some of the observed changes. We have demonstrated in male fetuses that underwent similar surgery and were killed at 130 days, a significant increase in kidney size as well as in the number of nephrons in the remaining kidney compared to controls [27]. In addition, uninephrectomy resulted in nephrogenesis continuing past the normal time of completion (130 days). After birth we would expect there to be hypertrophy of the remaining kidney and possibly chronic hyperfiltration. This occurs in some children who have a kidney removed early in life due to a Wilms’ tumor and contributes to further renal damage [28, 29]. Similar to some of these patients, the uninephrectomized sheep have a high single kidney GFR and a loss of the FRR suggesting there may be hyperfiltration.

The uninephrectomized animals used in the current study were shown to be moderately hypertensive compared to control animals when examined at 6 and 12 months of age [4]. To further understand the mechanisms underlying this elevated blood pressure we decided to investigate whether there were changes in cardiac output. In another model in sheep, where the fetus is exposed to 48 hours of high levels of maternal dexamethasone early in gestation, the elevated blood pressure seen after birth has been shown to be due to an increase in cardiac output [10]. The increase of approximately 10%, similar to that seen in this study, was associated with an increase in stroke volume but not heart rate [10]. In the current study there was also a significant increase in cardiac output which we attribute to small (although not statistically significant) increases in both heart rate and stroke volume. The heart rate measured during the period of cardiac output measurements, as well as the values obtained during the three day blood pressure measurements, was slightly increased in the uninephrectomized animals. As there were no differences in the indices of preload (PAWP, CVP, and PAP) it may suggest that small changes in stroke volume are not due to volume overload. It is possible that the changes in stroke volume and heart rate are due to increased sympathetic activity in the uninephrectomized sheep. There is now strong evidence that many hypertensive human patients have increased sympathetic drive to various tissues, including the kidney, skeletal muscle, and cardiac muscle [30]. This is particularly common in young, mildly hypertensive patients where the increased cardiac output was mainly due to increases in heart rate [31].

It should be noted that although the blood pressure was significantly increased when measured over a 3-day period in the uninephrectomized animals, when measured for a 2-hour period during the cardiac output measurements, the difference between the two groups did not reach statistical significance. This highlights the importance of chronic measurements as compared to acute measurements to detect small but significant changes in blood pressure. In rat studies, discrepancies have been found between acute (tail cuff) measurements and chronic (telemetry) recordings [32]. In children that have been uninephrectomized early in life, 24-hour blood pressure measurements were not different from controls; however, daytime systolic and diastolic pressures were elevated [33].

LVH has been demonstrated in sheep that are chronically hypertensive at 7 years of age [11]. In this study, there was no evidence that the left ventricle was enlarged. This may be due to the fact the animals are only relatively young (2 years) and there has not been sufficient time for any enlargement to occur or it may be that the hypertension and renal insufficiency, being only very moderate, was not enough to cause any heart changes. Children with renal insufficiency not requiring dialysis were found to have moderate LVH compared to healthy controls but severe hypertrophy was found in those in renal failure requiring dialysis [15]. It could be speculated that with possible further deterioration of renal function with age, LVH may develop.

**CONCLUSION**

Removal of one kidney during the period of active nephrogenesis in the sheep results in reduced renal function after birth. These animals have elevated plasma creatinine concentrations and an altered response to amino acid infusion suggesting a significant renal defect which may in the long term contribute to chronic renal failure. The increased blood pressure seen in this model was associated with an increase in cardiac output in adulthood. This study highlights the importance of formation of an adequate number of nephrons during development
and suggests any perturbation in utero affecting normal nephron endowment may “program” an individual for adult disease.

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