Renin-Angiotensin II Response to the Hemodynamic Pathology of Ovines With Ventricular Septal Defect

Mark M. Boucek, Richard Chang, and David P. Synhorst

We studied the response of the renin-angiotensin system (RAS) to a surgically created ventricular septal defect (VSD) in immature ovines and also the role of angiotensin II in the pathophysiology of VSD in the chronically instrumented ovine. Plasma renin activity (PRA) was increased from 2.39±1.1 to 3.78±1.4 ng/ml/hr (p<0.05, n=17) after VSD but not after sham procedure. The change in PRA was positively correlated with the amount of left-to-right shunt through the VSD (r=0.74, p<0.05). Inhibition of angiotensin II effect with saralasin (10 μg/kg/min) or angiotensin II production with captopril (2 mg/kg) lowered systemic resistance (Rsj by 14% and 34%, respectively (p<0.05), and raised pulmonary resistance (Rpj by 35% and 77%, respectively (p<0.05). Thirty minutes following captopril, the ratio of pulmonary to systemic flow (Qp/Qs) decreased from 3.31±0.18 to 2.15±0.18 (p<0.05) while total pulmonary flow fell from 7.15±0.38 to 5.92±0.34 l/min/M2 (p<0.05, n=11). Systemic flow increased from 2.17±0.14 to 2.86±0.33 l/min/M2 (p<0.05) despite a reduction in left atrial pressure (17.3±1.0 vs. 13.0±1.7, p<0.01). Reinfusion of angiotensin II (0.02 μg/kg/min) into the central aorta after captopril returned the hemodynamics to baseline including a rise in Rj and fall in Rpj. Exogenous angiotensin II alone (0.08 μg/kg/min) or a threefold stimulation in PRA with furosemide (2 mg/kg) caused little hemodynamic effect. The flow disturbance with a large VSD causes near maximal stimulation/effect of the RAS as indicated by the rise in PRA, the lack of response to further increases in PRA, and the response to exogenous angiotensin II. The RAS appears to promote the pathophysiology of VSD, demonstrated with RAS antagonists, by increasing Rpj, lowering Rpj, and causing a redistribution of left ventricular output to the pulmonary circulation. (Circulation Research 1989;64:524–531)

The renin-angiotensin system (RAS) is thought to be more important in regulating systemic arterial resistance in the normal infant than the adult. Furthermore, the RAS is known to respond to pathologic alterations in cardiac performance. Adult humans and probably children show a stimulation in RAS activity with congestive heart failure. Inhibition of angiotensin II production in adults with congestive heart failure may improve cardiac performance, and in dogs with high output failure, sodium balance is enhanced. With a structural cardiac defect, the cardiac performance may be normal but flow distribution is abnormal. Since the infant is more reliant on the RAS to maintain normal blood pressure, pathologic lesions with flow mal-distribution may amplify the RAS response in the infant leading to further systemic vasoconstriction.

A ventricular septal defect (VSD) results in redistribution of left ventricular output to the pulmonary circuit, left ventricular volume loading, and supranormal left ventricular stroke volume. The low resistance pulmonary vascular bed is included in the total left ventricular afterload, and thus the ratio of pulmonary to systemic resistance determines relative flow. If the RAS is stimulated by these flow alterations with VSD, the resulting increase in systemic resistance would tend to promote the pathologic cascade of increasing pulmonary flow and decreasing systemic flow. How the immature RAS responds to the hemodynamic pattern with a VSD is unknown. The pulmonary vascular bed is particularly important with a VSD. The effects of the RAS on pulmonary resistance may either magnify or reduce the effects of angiotensin II on the systemic bed. The pulmonary vascular bed in the adult is
responsive to angiotensin II or converting enzyme inhibitors, but the magnitude is usually small and may depend on the resting tone.9-12 The response of the immature, hypertrophied pulmonary bed with a VSD to angiotensin II is unknown and it may be pharmacologically more responsive compared with the adult.13,14

To study the interaction of a VSD with the RAS, we surgically created a VSD in lambs and serially determined plasma renin activity (PRA) while maintaining a fixed sodium intake. The contribution of angiotensin II effect to the pathologic hemodynamics was assessed by infusing angiotensin II and the angiotensin antagonist [Sar1,Ala8]-angiotensin II (saralasin) in chronically instrumented lambs with VSD. Also, captopril was used to block angiotensin I conversion to angiotensin II in the instrumented lambs. Since with VSD left atrial blood can both reenter the pulmonary circulation and the systemic circulation, we selectively infused angiotensin II, after captopril administration, into either the left atrium (to mimic pulmonary conversion to angiotensin II) or into the central aorta (to mimic peripheral conversion to angiotensin II). This selective infusion was used to determine the site of conversion of angiotensin I to angiotensin II and whether the site was important to the effect. Finally, to determine the relative degree of RAS activity, in vivo stimulation of renin secretion was induced with furosemide while monitoring the hemodynamic effect and the change in PRA.

Materials and Methods

Mixed Western breed lambs were obtained in the first month of life and weaned to bottle feeding with a fixed caloric and sodium intake (4 meq Na+/kg/day). Between 14–21 days of age, a control peripheral venous sample was obtained for PRA before anesthesia and after an overnight fast. The lamb was then anesthetized with ketamine (20 mg/kg i.m.) intubated, and a right thoracotomy was performed. The right atrial appendage was exposed and encircled with a pursestring suture. After the appendage was opened, an introducer and grommet were passed to the apex of the right ventricle and thrust across the interventricular septum. The introducer was then withdrawn, leaving the grommet in place to create a ventricular septal defect (Figure 1). The size of the grommet was 8.0–9.0 mm i.d. compared with an aortic anulus that measured 10–11 mm. The atrial pursestring was tied, the pericardium was closed, the ribs approximated, and the chest was closed in layers. The lamb was then weaned from the ventilator. The surgical success was greater than 85%. Feedings were resumed the same day as surgery. After a 10-day recovery period with the same formula intake, the lamb was restudied with a fasting peripheral venous sample for PRA. The lamb was then anesthetized with ketamine, and through a left thoracotomy, electromagnetic flow probes (Biotronix, Kensington, Maryland) were placed on the main pulmonary artery and ascending aorta. Catheters were inserted into the left atrium, pulmonary artery, aorta, and right atrium. The chest was then closed and the catheters and flow probe cables exteriorized. After a 1-week recovery period, physiologic data were recorded. Small variations in shunt size (Figure 3) were primarily caused by variations in grommet size. In the animals with a very low ratio of pulmonary to systemic flow (Qp/Qs), the explanation was found to be a grommet placed too far toward the apex and partially buried in myocardium. Four lambs underwent sham VSD placement, which included all steps up to the placement of the grommet. These animals were used as controls for the renin data. For control hemodynamic data, six 1–2-month-old lambs were chronically instrumented with arterial and thermodilution pulmonary arterial catheters. These animals were then given captopril and angio-

![Figure 1. Schematic representation of the technique used to create the ventricular septal defect. The arrow depicts left-to-right shunting of blood. (Not drawn to scale.)](image)

![Figure 2. Comparison of the plasma renin activity response in sham and lambs with ventricular septal defect (VSD).](image)
Results

Plasma Renin Activity

The PRA was elevated, compared to normal values for ewes, under basal conditions as expected for immature lambs. The sham-operated lambs showed no change in PRA (Figure 2). Following creation of the VSD ($n=17$), the PRA increased from $2.39±1.1$ to $3.8±1.4$ ng/ml/hr ($p<0.05$). In the 12 lambs with a $Q_p/Q_s$ ratio greater than 3:1, the PRA increased by greater than 100% ($2.13±0.9$ vs. $4.49±1.6$) despite the presence of the surgically created VSD. When the $Q_p/Q_s$ ratio was plotted against the change in PRA, a significant relation was evident with a correlation coefficient of 0.74 ($p<0.05$, Figure 3). The PRA also was increased following the administration of 2 mg/kg of furosemide. By 30 minutes,
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TABLE 1. Vascular Effects of Captopril and Angiotensin in Control Lambs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Ao (mm Hg)</th>
<th>Mean PA (mm Hg)</th>
<th>Mean RA (mm Hg)</th>
<th>R_s (units/m²)</th>
<th>R_p (units/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=6)</td>
<td>81±12</td>
<td>17±2.6</td>
<td>3.4±1.3</td>
<td>23.5±6</td>
<td>2.69±0.19</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>109±14 (35%)*</td>
<td>19.2±1.3</td>
<td>5.7±2.2 (+68%)*</td>
<td>33±6 (40%)*</td>
<td>2.88±0.28</td>
</tr>
<tr>
<td>(0.02 µg/kg/min)</td>
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<tr>
<td>(n=6) (10 min)</td>
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<td></td>
</tr>
<tr>
<td>Captopril (2 mg/kg)</td>
<td>76±12</td>
<td>18.3±4.9</td>
<td>1.8±1.6 (-48%)*</td>
<td>20.4±4</td>
<td>3.14±0.61</td>
</tr>
<tr>
<td>(n=6) (30 min)</td>
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</tbody>
</table>

Ao, aortic pressure; PA, pulmonary artery pressure; RA, right atrial pressure; R_s, systemic resistance; R_p, pulmonary arteriolar resistance.

Mean±SD (percent change from control).

*p<0.05 compared with control.

The PRA increased by greater than 300% (1.9±1.23 vs. 6.73±3.3, p<0.05) in eight lambs.

Hemodynamic Data

Control lambs. The control animals were studied at a mean weight of 8.2 kg. There was no significant change in cardiac index with either captopril or angiotensin II. The effects on the vascular pressures and resistance are shown in Table 1. Angiotensin II caused a significant increase in systemic pressure and resistance (R_s). However, there was no significant change in pulmonary resistance (R_p) or pressure. Captopril did not significantly change either systemic or pulmonary arterial pressures and resistance. There was a significant fall in right atrial pressure and a rise in heart rate (140±43 vs. 170±42) with captopril.

Ventricular septal defect lambs. All lambs had a normal arterial blood gas and hemoglobin concentration at the time of study. The mean weight at initial surgery was 6.4±1.1 kg, and this had increased to 9.3±1.0 kg by the time of the hemodynamic data gathering. Infusions of angiotensin II were performed through the left atrium and central aorta. No difference in effect on systemic or pulmonary resistance was seen regardless of infusion site under these control conditions, but the hemodynamic effects were quite small and differences may have been obscured. Under basal conditions, angiotensin II produced a maximal degree of elevated systemic resistance (22%, p<0.01) at a dose of 0.04 µg/kg/min. A dose of 0.08 µg/kg/min produced no further increase in R_s. At 0.02 µg/kg/min, angiotensin II increased R_s by 16% (p<0.01). Associated with the increase in R_s, there was a 21% (p<0.05) decrease in R_p/R_s ratio, a 16% (15.6±2.5 vs. 18.1±3.6, p<0.05) increase in the mean left atrial pressure, an 11% increase in Qp/Q_s ratio, and an 11% increase in mean aortic pressure (n=10, p<0.01). The pulmonary pressure and resistance were not significantly increased.

TABLE 2. Angiotensin II Infusion and Saralasin (Ventricular Septal Defect)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Qp/Q_s</th>
<th>Mean Ao (mm Hg)</th>
<th>Mean PA (mm Hg)</th>
<th>R_s (units/m²)</th>
<th>R_p (units/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>0.02 µg/kg/min</td>
<td>Base 10 min</td>
<td>Base 10 min</td>
<td>Base 10 min</td>
<td>Base 10 min</td>
</tr>
<tr>
<td>(n=10) (10 min)</td>
<td>3.28</td>
<td>3.63</td>
<td>70.8</td>
<td>78.9</td>
<td>28.2</td>
</tr>
<tr>
<td>Saralasin (10 µg/kg/min)</td>
<td>0.65</td>
<td>0.78*</td>
<td>8.7</td>
<td>10*</td>
<td>4.8</td>
</tr>
<tr>
<td>(n=8) (10 min)</td>
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<tr>
<td>Angiotensin II</td>
<td>(0.05 µg/kg/min)</td>
<td>± ± ± ± ± ± ± ±</td>
<td>± ± ± ± ± ± ± ±</td>
<td>± ± ± ± ± ± ± ±</td>
<td>± ± ± ± ± ± ± ±</td>
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<tr>
<td>+ (n=10) (10 min)</td>
<td>3.11</td>
<td>2.66</td>
<td>74.3</td>
<td>72.5</td>
<td>28.4</td>
</tr>
<tr>
<td>Saralasin (10 µg/kg/min)</td>
<td>0.28</td>
<td>0.37*</td>
<td>4.6</td>
<td>5.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Qp/Q_s, ratio of pulmonary to systemic flow; Ao, aortic pressure; PA, pulmonary artery pressure; R_s, systemic resistance; R_p, pulmonary arteriolar resistance.

Mean±SD.

*p<0.01.
†p<0.05 (compared with Base).
Table 3. Captopril and Angiotensin II Infusion (Ventricular Septal Defect)

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>Q_1</th>
<th>Q_2/Q_1</th>
<th>Mean Ao</th>
<th>Mean PA</th>
<th>R_p</th>
<th>R_p units/m²</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>2.17±0.46</td>
<td>3.31±0.59</td>
<td>73.2±6.1</td>
<td>28.6±6.2</td>
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<tr>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+32%</td>
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<td></td>
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<tr>
<td>30 min +</td>
<td>30</td>
<td>2.86±0.72</td>
<td>2.15±0.41*</td>
<td>62.4±11.9</td>
<td>30.1±6.7</td>
<td>+5%</td>
<td>-34%</td>
<td>2.91±0.41* +33%</td>
</tr>
<tr>
<td>% Change</td>
<td></td>
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<tr>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-35%</td>
<td>+5%</td>
<td>153±11</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>10 min Aorta</td>
<td>2.92±0.44</td>
<td>3.36±0.56</td>
<td>79.8±7.9</td>
<td>29.1±7.7</td>
<td>+2%</td>
<td>+9%</td>
<td>1.76±0.27 +7%</td>
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<tr>
<td>% Change</td>
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<tr>
<td>Captopril</td>
<td></td>
<td></td>
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<td></td>
<td>+4%</td>
<td>-2%</td>
<td>159±10</td>
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<tr>
<td>+</td>
<td>70</td>
<td>2.39±0.34</td>
<td>2.80±0.35</td>
<td>80.4±8.6</td>
<td>32.1±8.1</td>
<td>+12%</td>
<td>+3%</td>
<td>158±7</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>10 min Left Atrium</td>
<td>2.19±0.29*</td>
<td>67.4±9.1</td>
<td>31.3±8.8</td>
<td>24.3±1.9</td>
<td>-28%</td>
<td>+13%</td>
<td>160±10</td>
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<td>% Change</td>
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<tr>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+32%</td>
<td>-34%</td>
<td>54%</td>
</tr>
<tr>
<td>End Control</td>
<td>90</td>
<td>2.86±0.54*</td>
<td>2.19±0.29*</td>
<td>67.4±9.1</td>
<td>31.3±8.8</td>
<td>+32%</td>
<td>+54%</td>
<td>158±7</td>
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<td>% Change</td>
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Q_1, systemic flow; Q_2/Q_1, ratio of pulmonary to systemic flow; Ao, aortic pressure; PA, pulmonary artery pressure; R_p, systemic resistance; R_p, pulmonary arteriolar resistance; HR, heart rate.

Mean±SD.

*p<0.05 (compared to control).

Saralasin infused at a dose of 10 μg/kg/min produced maximal hemodynamic effect and abolished the response to exogenous angiotensin II (Table 2). There was a narrow dose response curve to saralasin. A dose of 5 μg/kg/min failed to inhibit exogenous angiotensin II completely, and a dose of 20 μg/kg/min appeared to show the partial agonist properties of saralasin causing an increase in R_p. At 10 μg/kg/min, saralasin produced a 16% (p<0.01) reduction in the Q_2/Q_1 ratio and the R_p was increased by 35% (n=8, p<0.05, Table 2). At this dose, saralasin blocked exogenous angiotensin II (Table 2).

Captopril (2 mg/kg) caused more striking alterations in the hemodynamic pattern than did saralasin. The effects of captopril are dose-related in lambs with a half-maximal effective dose of 0.5 mg/kg. Following a maximum inhibitory dose of captopril, there was a 34% reduction in R_p and a 35% decrease in Q_2/Q_1 ratio (n=11, p<0.01, Table 3). This was associated with a 25% decrease in mean left atrial pressure (17.3±1.0 vs. 13.0±1.7, p<0.01). Despite the fall in left atrial pressure, the systemic flow (Q_1) increased from 2.17±0.14 to 2.86±0.33 l/min/m² (p<0.05). Captopril also caused a significantly increased pulmonary vascular resistance (1.64 vs. 2.91, n=11, p<0.05) and a decreased total pulmonary blood flow (Q_p) (7.04±1.2 vs. 5.92±0.76) (Figure 4).

Reinfusion of angiotensin II. Following the administration of captopril to block the endogenous production of angiotensin II, infusion of exogenous angiotensin II into the central aorta for 10 minutes reestablished baseline hemodynamics at a dose of 0.02 μg/kg/min (Figure 4). However, the site of infusion varied the response of the pulmonary vascular bed but not the systemic vascular bed. Infusion of angiotensin II into the left atrium caused a similar increase in R_p as did aortic infusions (Table 3). But with left atrial infusion the R_p remained 54% (p<0.01) greater than baseline, whereas with aortic infusion the R_p returned to baseline values.

Stimulation of plasma renin activity. Furosemide (2 mg/kg) caused a marked increase (1.9±1.2 vs. 6.7±3.3 ng/ml/hr) in plasma renin activity at 30 minutes after infusion, but this was associated with only an 18% (23.8 vs. 28.1, p<0.05, n=7) increase.
in $R_\alpha$ and an increase in $Q_s/Q_\alpha$ ratio of 10% (NS). The $Q_s$ was also decreased by 9% and mean aortic pressure increased 8% (NS). The left atrial pressure was unchanged (19.8 vs. 20.5; NS), and these effects preceded a diuretic response.

Discussion

The plasma renin activity was increased in this ovine model of a structural heart defect, a VSD, which results in flow redistribution. The stimulation in renin activity appears to be the result of the flow maldistribution since the magnitude of change in PRA was related to the $Q_s/Q_\alpha$ ratio. In lambs undergoing identical surgical manipulation, care, and diet, but with lesser degrees of hemodynamic insult (or sham), the PRA either was unchanged or decreased. With increasing age, the normal immature ovine and human show a decrease in PRA.$^{19,20}$ Therefore, the increase in age between PRA values would tend to cause a decrease in PRA. This age-dependent change in PRA, if anything, would tend to minimize the effect of the VSD on PRA and lessen the association with shunt size. The significant increase in PRA following VSD may, therefore, be an underestimation of the true magnitude of PRA stimulation. The basal PRA activity was lower than the values reported by Siegel$^{16,19}$ but can be explained by the sodium intake, which is higher for formula-fed lambs than the suckling lamb, the older age, and the different pH used in the generation buffer. However, none of these factors would influence the effect of the VSD on the relative change in PRA.

The precise stimulus for the increase in PRA is unclear. The systemic output and mean aortic pressure measured in these lambs is low but falls within the normal range.$^{21}$ The possibility of a perceived reduction in renal perfusion or pressure$^{22}$ to explain the increased PRA could be explained by a systemic output relatively low compared with the demands of a hypermetabolic state observed with structural heart defects.$^{23}$ An elevated neurohumoral$^{24,25}$ state may, in fact, explain the increased metabolic demands and, perhaps also, the stimulation of PRA via $\beta$-receptor activation.$^{26}$ The VSD lambs were in congestive heart failure as demonstrated by the elevated left atrial pressure, and this could explain the increase in PRA.$^3$ The weak correlation of change in PRA with $Q_s/Q_\alpha$ ratio can be explained by the variability in $Q_s/Q_\alpha$ with changes in systemic resistance and the fact that PRA and $Q_s/Q_\alpha$ could not be determined simultaneously. Knowledge of the normal ontogeny of PRA and its rapid response to hemodynamic change makes the correlation more striking.

PRA is elevated in the infant, presumably in response to the relative sodium-wasting state,$^{27}$ and the subsequent generation of angiotensin II becomes a dominant factor in maintaining systemic resistance.$^{1,2}$ Stimulation of the renin-angiotensin system results in a hyposensitivity to additional exogenous angiotensin II.$^{16,28}$ Infusion of angiotensin II in lambs with VSD demonstrated a shifted dose response and blunted vasoconstriction. There was only an approximately 20% maximum increase in systemic resistance at a dose of angiotensin II of 0.04 $\mu$g/kg/min under basal conditions. These data, obtained in a sodium-replete state, would support a chronic stimulation of the RAS in lambs with a large ventricular level shunt.$^{28}$ Angiotensin II infusion in normal lambs increased systemic resistance by twice the level (40%) as in VSD lambs at a lower angiotensin dose (0.02 $\mu$g/kg/min) (Table I). Antagonists of angiotensin II effect or production caused a significant reduction in systemic resistance with a subsequent decrease in left-to-right shunt across the VSD, an increased systemic flow, and thus a smaller, insignificant reduction in mean aortic pressure. In normal lambs, converting enzyme inhibition lowers aortic pressure without changing organ blood flow.$^{29}$ In control lambs in this study, captopril lowered mean right and left atrial pressures, but the change in $R_\alpha$ was not significant.

The effect of captopril at a maximum inhibitory dose with VSD was greater than saralasin at a fully antagonistic dose. Saralasin has a narrow dose response and may have inherent agonist properties in a high sodium intake environment with low angiotensin II levels.$^{30,31}$ Captopril also may have other effects, such as on bradykinin metabolism, which may explain the differences with saralasin. However, reinfusion of angiotensin II completely reversed the effects of captopril in this model. The fact that saralasin decreased systemic resistance despite a high sodium intake also argues for an important role of the RAS with elevated angiotensin levels since in normal animals that are sodium replete, saralasin would have little or opposite effect.$^{27,30}$ The normal suckling lamb would receive 1-2 meq Na$^+/kg/day$, whereas lambs in this study received 4 meq Na$^+/kg/day$ or at least twice the normal sodium intake.$^{27}$

It appears that the RAS is near maximally stimulated with a large VSD since both maximal pharmacologic doses of angiotensin II and a threefold stimulation of PRA with furosemide caused only an additional 20% increase in $R_\alpha$. If the RAS system was down regulated in terms of organ receptor response, the recovery must be short (10 minutes) since short-term inhibition of angiotensin II production with captopril restores responsiveness to exogenous angiotensin II.

With a VSD the left ventricular output is influenced by both systemic and pulmonary resistance.$^8$ Thus, the influence of the RAS on the pulmonary vascular bed becomes important. In the normal situation angiotensin II has little effect on the hemodynamics of the lesser circulation.$^9-11$ Normal neonatal lambs show a mild increase in pulmonary artery pressure from 12 to 18 mm Hg following angiotensin infusion.$^{14}$ Normal older lambs in this study did not show a significant change in pulmonary artery pressure or resistance with angiotensin
II (Table 1). Infusion of angiotensin II in lambs with VSD under basal conditions also had little effect on $R_p$. However, inhibition of endogenous angiotensin effect or production significantly raised $R_p$. Saralasin and captopril raised $R_p$ of 35% and 77%, respectively. Reinfusion of angiotensin II (0.02 μg/kg/min) after captopril lowered the $R_p$ back to control values, but the site of infusion was important. Following captopril, reinfusion of angiotensin II to the central aorta caused the $R_p$ to increase by 64%, and the $R_p$ was decreased by 40%. Reinfusion into the left atrium (mimicking pulmonary vascular conversion of angiotensin I to angiotensin II) caused a similar effect on $R_p$ (+53%), but the $R_p$ remained elevated in contrast to the fall seen with aortic infusion. With VSD, left atrial angiotensin II would recirculate to the lung, perhaps raising $R_p$ directly.12

These data would argue that with VSD the pulmonary bed is influenced by the stimulation in RAS in a manner (reduced $R_p$) that would promote the pathologic cascade of increasing left-to-right shunt. Furthermore, the reinfusion of angiotensin II after captopril may indicate that most of the functional angiotensin II is produced/metabolized in the peripheral bed and that the effects on the pulmonary bed are indirect. Similar data on the site of angiotensin II production in normal sheep have been obtained by direct measurements of angiotensin II.32 The high pulmonary arterial oxygen saturation, present with large VSD, may further influence the pulmonary endothelial converting enzyme activity.33 The rise in pulmonary resistance after captopril and the fall with reinfusion of angiotensin II may also be a nonspecific response (such as autonomic reflex with increased sympathetic pulmonary tone) to changes in systemic resistance and redistribution of flow. However, other systemic vasodilators studied in this model did not raise the calculated pulmonary resistance.15

The vascular effects of angiotensin II can be modulated by induced changes in prostaglandin production/secretion as shown by others.4.35 The present data do not allow a separation of factors that may contribute to the fall in $R_p$ with aortic-infused angiotensin II and the rise in $R_p$ with angiotensin II antagonism. Immaturity and hypertrophy of the pulmonary bed may be involved to explain the effects of angiotensin in this model versus the adult since age-related differences in responsiveness of the pulmonary bed to prostaglandins have been demonstrated.13,36

In summary, the presence of a VSD causes pulmonary vascular plethora and left ventricular volume overload that is dependent on the ratio of systemic vascular resistance to pulmonary vascular resistance. The RAS is stimulated in the infant and also by the flow disturbance due to VSD. The stimulation in RAS causes systemic vasoconstriction and, perhaps indirectly, pulmonary vasodilatation, which promotes the basic pathologic cascade. The ontogeny of angiotensin II responsiveness may in part explain the postnatal changes in the circulation described with a VSD.37

Acknowledgments
We sincerely appreciate the technical assistance of Kris Sjoblom in preparing the manuscript.

References

**KEY WORDS** • renin-angiotensin • ventricular septal defect
Renin-angiotensin II response to the hemodynamic pathology of ovines with ventricular septal defect.
M M Boucek, R Chang and D P Synhorst

Circ Res. 1989;64:524-531
doi: 10.1161/01.RES.64.3.524

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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