
Depressed Responsiveness to Vasoconstrictor and Dilator Agents and Baroreflex Sensitivity in Conscious, Newborn Lambs

W. THOMAS MANDERS, B.S., MASSIMO PAGANI, M.D., AND STEPHEN F. VATNER, M.D.

SUMMARY The effects of vasoconstrictors and vasodilators were compared in conscious, newborn lambs and adult sheep instrumented with electromagnetic flow probes on the ascending aorta and catheters in the thoracic aorta. Methoxamine, angiotensin II, norepinephrine, nitroglycerin and isoproterenol were administered intravenously to evaluate their effects on arterial pressure, cardiac output and systemic vascular resistance (SVR). The difference in response between adults and newborns was most apparent with methoxamine. Methoxamine, 400 μg/kg, i.v., which increased mean arterial pressure by 57 ± 6% and SVR by 278 ± 27% in newborn lambs, caused greater increases (p < 0.01) of 81 ± 8% and 1418 ± 141%, respectively, in the adults. Responses also differed significantly between newborn and adult animals to norepinephrine, angiotensin II, nitroglycerin and isoproterenol. In a second group of animals in which smaller amounts of methoxamine and isoproterenol were injected directly into the terminal aorta, changes in terminal aortic flow and resistance were examined. Again, both vasoconstrictor and vasodilator responses were more marked in adults than in newborns. Finally, the sensitivity of the arterial baroreceptor reflex was evaluated by comparing the regression of pulse interval (PI) on systolic arterial pressure (SAP) after an intravenous dose of methoxamine in conscious, adult and newborn animals. The PI/SAP slopes in adult sheep, 45.4 ± 3.5 msec/mm Hg, were significantly greater (p < 0.01) than in newborn lambs, 11.7 ± 2.2 msec/mm Hg.

THE REQUIRED therapeutic dose of digitalis is relatively greater in the newborn patient than in the adult.1-3 While the responsiveness to vasoactive drugs might also demonstrate age-dependent differences, results of prior studies have conflicted. For instance, studies conducted in anesthetized animal preparations4 9 or isolated vessel strips10-12 have shown both an increased4, 7, 10 and decreased4, 9, 11, 12 responsiveness of the neonatal peripheral circulation to vasoactive agents.

In this investigation we compared the peripheral vascular responses to pharmacological agents that constrict or dilate peripheral vessels in conscious newborn lambs and adult sheep, with all control mechanisms intact and the complicating influences of a general anesthetic absent.13-15 Since several reflex adjustments are likely to be induced by the changes in arterial pressure after systemic drug administration, two groups of animals were studied. In one group, drugs were administered i.v. and responses were examined in terms of changes in systemic arterial pressure (SAP), blood flow and systemic vascular resistance (SVR). In a second group smaller amounts of the drugs were injected intra-arterially into the ter-
minal aorta and responses were examined in terms of changes in terminal aortic pressure, blood flow and SVR. Under these conditions, heart rate and SAP were essentially unaltered, indicating that reflex adjustments were probably not involved.

We also analyzed the development of arterial baroreceptor reflex sensitivity. To accomplish this, the technique of Smyth et al.\textsuperscript{16} was used, i.e., the extent of cardiac slowing induced by an abrupt elevation in arterial pressure was examined. In this investigation, methoxamine, a potent $\alpha$-adrenergic agonist with trivial $\beta$-adrenergic properties,\textsuperscript{19} was administered to raise arterial pressure.

**Methods**

Twelve adult sheep (32–62 kg) and 10 lambs 1–5 days old (2.9–5.0 kg) were anesthetized with sodium thiamylal (Surital), 20 mg/kg, intubated and placed on a Harvard respirator and then maintained on 1–2% halothane for operation. Through an incision in the fourth left intercostal space, an electromagnetic flow probe (Zepeda Instruments, Seattle, Washington) was placed around the ascending aorta to measure cardiac output. A heparin-filled Tygon catheter was implanted in the descending thoracic aorta. In two of the lambs a hydraulic occluder was placed around the ductus arteriosus. In a second group of 10 adult sheep and 10 newborn lambs, similarly anesthetized, two heparin-filled Tygon catheters were implanted in the terminal aorta, i.e., distal to the renal arteries and just proximal to the bifurcation, through a left flank incision. An electromagnetic flow probe and a hydraulic occluder, distal to the probe, were also placed around the terminal aorta.

Arterial pressure was measured with a Statham P23Db strain gauge manometer (Statham Instruments, Oxnard, California). Ascending aortic flow (cardiac output minus coronary blood flow) and terminal aortic flow were measured with an electromagnetic flowmeter (Benton Instruments, Cupertino, California). The electromagnetic flow probes were calibrated in vitro before implantation, using timed collections of blood. Zero for ascending aortic blood flow was assumed to occur during late diastole. Zero for terminal aortic flow was obtained by inflating the implanted aortic occluder.

The adult animals were studied 2–4 weeks after recovery from operation, while the newborn lambs were studied 2–10 days after operation, when the animals were vigorous and healthy and when their resting levels of heart rate and arterial pressure were similar to those of noninstrumented lambs of comparable ages. The drugs were administered in random sequence over a 3-day period, which allowed sufficient intervals between drug injections for full recovery from the prior injection. Bolus injections of methoxamine (Vasoxyl, Burroughs Wellcome), angiotensin II (Hypertensin, Ciba Pharmaceuticals), norepinephrine (Levophed, Winthrop Laboratories), isoproterenol (Isuprel, Winthrop Laboratories) and nitroglycerin (Eli Lilly Company) were administered in graded doses i.v. to animals in which cardiac output and arterial pressure were measured. These drugs were also administered i.v. to two newborn lambs before and after inflation of the occluder on the ductus arteriosus. Smaller doses of methoxamine and isoproterenol were administered directly in the terminal aorta through one of the implanted Tygon catheters in the animals in which terminal aortic flow and arterial pressure were measured. To assess the concentration of drug administered, the dose of drug in $\mu$g/kg was multiplied by the weight of the animal. The quotient of this product and blood flow rate was used to provide an approximation of drug concentration.

To test the sensitivity of the arterial baroreceptor reflex, the technique of Smyth et al.\textsuperscript{16} which has also been used previously in our laboratory,\textsuperscript{18} was used. The cardiac slowing in terms of pulse interval (PI) was plotted against the rise in SAP in response to a bolus i.v. injection of methoxamine, 200 $\mu$g/kg. The relationship PI/SAP (msec/mm Hg) was treated as a linear function. The slope (regression coefficient) was taken as a measure of baroreflex sensitivity and calculated by the method of least squares.\textsuperscript{19} ECG was measured simultaneously to insure that all beats originated in the sinus node.

Pressure and flow data were recorded on magnetic tape and played back on a multichannel oscillograph (Gould Brush Company, Cleveland, Ohio). Electronic resistance-capacitance filters with 2-second time constants were used to derive mean arterial pressure, while a filter with a 6-second time constant was used to derive mean ascending and terminal aortic blood flows. SVR was calculated as the quotient of mean arterial pressure and mean aortic blood flow. Terminal aortic resistance was calculated as the quotient of mean arterial pressure and terminal aortic blood flow. The mean $\pm$ SEM for the changes from control were calculated and compared between the adult and newborn groups using the analysis of variance.\textsuperscript{18} The relationship between SAP and PI after methoxamine

<table>
<thead>
<tr>
<th>Table 1. Control Values</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
</tr>
<tr>
<td>(beats/min)</td>
</tr>
<tr>
<td>Adult: 86 ± 4</td>
</tr>
<tr>
<td>Newborn: 142 ± 10*</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong></td>
</tr>
<tr>
<td>(mm Hg)</td>
</tr>
<tr>
<td>Adult: 78 ± 2</td>
</tr>
<tr>
<td>Newborn: 70 ± 2*</td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
</tr>
<tr>
<td>(ml/min)</td>
</tr>
<tr>
<td>Adult: 5303 ± 256</td>
</tr>
<tr>
<td>Newborn: 965 ± 90*</td>
</tr>
<tr>
<td><strong>Systemic vascular resistance</strong></td>
</tr>
<tr>
<td>(mm Hg/ml/min)</td>
</tr>
<tr>
<td>Adult: 0.015 ± 0.001</td>
</tr>
<tr>
<td>Newborn: 0.080 ± 0.008*</td>
</tr>
<tr>
<td><strong>Terminal aortic flow</strong></td>
</tr>
<tr>
<td>(ml/min)</td>
</tr>
<tr>
<td>Adult: 682 ± 20</td>
</tr>
<tr>
<td>Newborn: 158 ± 9.1*</td>
</tr>
<tr>
<td><strong>Terminal aortic resistance</strong></td>
</tr>
<tr>
<td>(mm Hg/ml/min)</td>
</tr>
<tr>
<td>Adult: 0.121 ± 0.017</td>
</tr>
<tr>
<td>Newborn: 0.439 ± 0.031*</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
</tr>
<tr>
<td>Adult: 47 ± 2</td>
</tr>
<tr>
<td>Newborn: 3.8 ± 0.3*</td>
</tr>
</tbody>
</table>

All values are mean $\pm$ SEM.

*Newborn significantly different from adult ($p < 0.01$).
**ARTERIAL PRESSURE** (mmHg)

**MEAN PRESSURE** (mmHg)

**AORTIC FLOW** (L/min)

**MEAN FLOW** (L/min)

**SYSTEMIC VASCULAR RESISTANCE** (%Δ)

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**FIGURE 1.** The effects of methoxamine (MX), 400 µg/kg, i.v., are compared in a newborn (left panel) and an adult (right panel) on phasic and mean arterial pressure, phasic and mean ascending aortic blood flow, and calculated systemic vascular resistance, shown as percent increase from control in the bottom panel. The same dose caused much more striking vasoconstriction and a slower heart rate in the adult.

injection was determined using standard linear regression techniques. The PI/SAP slopes were compared in newborns and adults using the analysis of variance.

**Results**

Control values for the adult and newborn animals are in table 1, while changes from control for all doses of the drugs are in the figures.

**Systemic Circulation**

**Vasoconstrictors**

Methoxamine administered at the same dose per kilogram body weight caused greater increases in mean arterial pressure and SVR and decreases in cardiac output in the adults compared with newborns (fig. 1). The 400 µg/kg dose of methoxamine increased mean arterial pressure (81 ± 8%) and SVR (1418 ± 141%) in adults, significantly more ($p < 0.01$) than in the newborn for SAP (57 ± 6%) and SVR (278 ± 27%) (fig. 2). Conversely, this dose of methoxamine reduced cardiac output more ($p < 0.01$) in the adults (−87 ± 2%) than in the newborns (−57 ± 3%). With increasing doses of methoxamine the differences in responses of SVR between the newborns and adults were more apparent (fig. 2). When the results from the 100 µg/kg dose in the adults were compared with those from the 200 µg/kg dose in the newborns, significantly greater vasoconstriction was observed in the adult at equivalent drug concentrations (table 2). Norepinephrine (fig. 3) and angiotensin II (fig. 4) also increased SVR significantly more ($p < 0.01$) in adults than newborns.

In two lambs, the responses to these drugs were not modified by inflating a hydraulic occluder implanted around the ductus arteriosus. For instance, methoxamine 100 µg/kg increased mean arterial pressure
**Table 2. Peripheral Vascular Responses to Vasoactive Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (µg/ml/min)</th>
<th>%Δ Systemic vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic methoxamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (100 µg/kg)</td>
<td>1.06 ± 0.11</td>
<td>357 ± 27</td>
</tr>
<tr>
<td>Newborn (200 µg/kg)</td>
<td>1.03 ± 0.07</td>
<td>134 ± 12*</td>
</tr>
<tr>
<td>Systemic isoproterenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (0.5 µg/kg)</td>
<td>5.4 ± 0.5 × 10⁻³</td>
<td>−63 ± 1.4</td>
</tr>
<tr>
<td>Newborn (1.0 µg/kg)</td>
<td>4.3 ± 0.5 × 10⁻³</td>
<td>−54 ± 2.0*</td>
</tr>
<tr>
<td>Intra-arterial methoxamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (10 µg/kg)</td>
<td>0.58 ± 0.06</td>
<td>533 ± 91</td>
</tr>
<tr>
<td>Newborn (50 µg/kg)</td>
<td>0.87 ± 0.09†</td>
<td>371 ± 75</td>
</tr>
<tr>
<td>Intra-arterial isoproterenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (0.01 µg/kg)</td>
<td>0.80 ± 0.12 × 10⁻³</td>
<td>−74 ± 2.2</td>
</tr>
<tr>
<td>Newborn (0.1 µg/kg)</td>
<td>1.54 ± 0.29 × 10⁻²</td>
<td>−48 ± 1.9*</td>
</tr>
</tbody>
</table>

*Newborn significantly different from adult (p < 0.01).
†Newborn significantly different from adult (p < 0.005).

**Figure 2.** The effects of graded doses of i.v. methoxamine are compared in adults (triangles) and newborns (squares) as percent change from control on mean arterial pressure, cardiac output and systemic vascular resistance.

**Figure 3.** The effects of graded doses of i.v. norepinephrine are compared in adults (triangles) and newborns (squares) as percent change from control on mean arterial pressure, cardiac output and systemic vascular resistance.

**Figure 4.** The effects of graded doses of i.v. angiotensin II are compared in adults (triangles) and newborns (squares) as percent change from control on mean arterial pressure, cardiac output and systemic vascular resistance.
Resistance
Systemic
Output
Cardiac
Pressure
Arterial
change from control
percent
compared
are
diac
FIGURE 5. The effects of graded doses of i.v. isoproterenol
are compared in adults (triangles) and newborns (squares) as
percent change from control on mean arterial pressure, car-
diac output and systemic vascular resistance.

(23%) and SVR (29%) before inflating the occluder
and by 21% and 26% for pressure and SVR, respec-
tively, after inflation of the occluder. This was not sur-
prising, since the ductus arteriosus was closed at post-
mortem in the animals in this study.

Vasodilators
Isoproterenol resulted in significantly greater
decreases in SAP and SVR and conversely in a greater
rise in cardiac output in adults than newborns (fig. 5).
When the results from the 0.5 μg/kg dose in the adult
were compared with the 1.0 μg/kg dose in the new-
born, i.e., at equivalent drug concentrations, signifi-
cantly greater vasodilatation occurred in the adult
(table 2). Nitroglycerin induced greater decreases in
SVR and greater increases in cardiac output in adults,
but the decreases in arterial pressure were only
significantly greater at the lower doses (fig. 6).

Hindlimb Circulation
The injection into the terminal aorta of methox-
amine and isoproterenol in doses 1–2 orders of magni-
tude less than in the experiments in which drugs were
administered i.v. did not alter mean arterial blood
pressure or heart rate substantially either in the adult
or in the newborn sheep (fig. 7).

Vasoconstrictor
Methoxamine administered at the same dose per
kilogram body weight significantly reduced terminal
aortic flow in the adults compared with the newborns
(fig. 8). Likewise, terminal aortic resistance increased
more in the adults, with differences more apparent
with increasing doses (fig. 8). An example of the
effects of the 10 μg/kg dose of methoxamine injected
intra-arterially in the terminal aorta is shown in figure
7. This dose did not alter mean arterial blood pressure,
but increased terminal aortic resistance in the adults
significantly more (p < 0.05) than with twice the dose
in the newborn, (fig. 9). Moreover, when the results
for the 10 μg/kg dose in the newborn, slightly but not
significantly greater vasoconstriction was observed in
the adult at a significantly lower drug concentration
than in the newborn (table 2).

Vasodilator
Isoproterenol resulted in a significantly greater in-
crease in terminal aortic blood flow and decrease in
resistance in the adults than in the newborns (fig. 8). In
fact, the newborn showed less vasodilation even when
time five times the dose per kilogram body weight was
administered in the terminal aorta (fig. 9). Moreover, the
0.01-μg/kg dose in the adults compared with those
of the 0.1-μg/kg dose in the newborns resulted in
significantly greater vasodilatation in the adult at a
significantly lower drug concentration (table 2).

Arterial Baroreceptor Reflex Sensitivity (table 3)
The average PI/SAP slope after injection of
methoxamine in the adult sheep was 45.4 ± 3.5
The effects of intra-arterial methoxamine (MX) 10 μg/kg, on phasic and mean arterial pressure, phasic and mean terminal aortic blood flow, heart rate and calculated terminal aortic resistance are compared in a conscious newborn lamb (left panel) and an adult sheep (right panel). This intra-arterial dose had little systemic effect, i.e., change in arterial pressure or heart rate, but induced a greater decrease in terminal aortic flow and a greater increase in terminal aortic resistance in the adult than in the newborn.

Discussion

The responsiveness of newborn vessels to adrenergic stimuli is controversial. Ljung et al. support the concept that newborn responses are depressed. In a rat portal vein preparation, they demonstrated decreased sensitivity to norepinephrine in the newborn compared with the adult. However, Boatman et al. found that isolated hindlimb preparations of newborn puppies and adult dogs behaved similarly in response to identical total doses of vasoconstrictors, and thus concluded that the newborn peripheral vascular responses were subsensitive. Moreover, peripheral vasoconstrictor responses elicited by sciatic nerve stimulation have been observed to be depressed in newborn pigs. Ad-
DEPRESSED DRUG RESPONSES IN NEWBORN/Manders et al.

Figure 8. The effects of graded doses of intra-arterial methoxamine (upper panel) and isoproterenol (lower panel) are compared in adults (triangles) and newborns (squares) as percent change of terminal aortic resistance from control.

Additionally, isolated strips of aortic muscle from newborns stimulated with adrenergic agents produced less tension than similar preparations from adult animals. Cox et al. observed in isolated vessels that the maximum smooth muscle stress response to norepinephrine increased with age. Finally, a recent study from our laboratory demonstrated significantly less shift in the stress-radius relationship of the aorta in response to methoxamine in the conscious newborn as compared with adult sheep.

Studies supporting the opposing point of view include those of Ericsson and Lundholm, showing enhanced relaxation of aortic strips of newborn rats in response to isoproterenol, and of Gerova et al., demonstrating enhanced vasoconstriction of peripheral vessels in puppies in response to sympathetic nerve stimulation. Hutchinson et al. found that newborns required smaller doses of i.v. norepinephrine and epinephrine than adults to produce equivalent increases in arterial pressure. Finally, Woods et al. compared responses of arterial pressure to norepinephrine and isoproterenol in conscious, newborn lambs and adult sheep, and noted similar sensitivity in both groups. Since the blood volume is larger in the newborn, the fact that identical doses per kilogram body weight elicited similar responses would imply supersensitivity.

The wide discrepancy in findings and interpretations
may be the result of differences in species, specific age and animal preparation, particular model or vessel studied, as well as the reflection of the effects of anesthesia and recent surgery. The latter are known to disrupt physiological cardiovascular control mechanisms and to interfere directly with smooth muscle tone.

In the present investigation when identical doses per kilogram of body weight were administered, vasoconstrictors induced smaller pressor and constrictor responses, while vasodilators induced smaller dilator responses in the conscious newborn as opposed to the adult. We cannot explain the differences between the results in the present investigation and those in the recent study by Woods et al., who also studied conscious sheep, but found that differences between responses of arterial pressure to i.v. norepinephrine and isoproterenol in adult sheep and newborn lambs were not significant. In the present investigation differences in response of arterial pressure, although present, were not as clearly defined as those for vascular resistance.

Several problems inherent in comparing responses between the adult and neonatal peripheral circulations must be pointed out. First, there are marked differences between control conditions (table 1). Second, the associated reflex cardiovascular adjustments in response to the alteration in arterial pressure are likely to be different in the two age groups. Third, the response of different beds to the various substances might be different and variable with age. Finally, a conscious animal preparation was used to avoid the complicating influences of anesthesia and recent surgery; however, this dictates the use of a simplified model for the interpretation of data, since experimental conditions cannot be completely controlled. In an attempt to overcome these limitations, two groups of newborn lambs and adult sheep were studied. In the first group of animals the effects of intravenously administered vasoactive drugs were examined on arterial pressure, cardiac output and total peripheral resistance, while heart rate and arterial pressure were varying. In a second group, the effects of intravenously administered vasoactive drugs were examined on terminal aortic flow and resistance. In this group, in which a peripheral bed was examined, essentially no changes in heart rate or pressure occurred. Therefore, the problems that might be associated with calculation of peak resistance changes, when both pressure and flow are varying, were minimized.

Because of these limitations in our animal model, it is difficult to determine the mechanism of the differences between adult and newborn responses. Possibilities include differences in reflex attenuation of the direct effects of the vasoactive agents, differences in receptor population or affinity, differences in blood

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**Table 3. Baroreflex Sensitivity in Adults and Newborns**

<table>
<thead>
<tr>
<th></th>
<th>Control systolic Arterial pressure (SAP) (mm Hg)</th>
<th>Control pulse interval (PI) (msec)</th>
<th>Slope (PI/SAP) (msec/mm Hg)</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult sheep</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>126</td>
<td>710</td>
<td>39.8</td>
<td>0.90</td>
</tr>
<tr>
<td>2</td>
<td>119</td>
<td>750</td>
<td>27.2</td>
<td>0.94</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
<td>690</td>
<td>61.0</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
<td>810</td>
<td>51.9</td>
<td>0.98</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>660</td>
<td>50.0</td>
<td>0.93</td>
</tr>
<tr>
<td>6</td>
<td>128</td>
<td>700</td>
<td>46.6</td>
<td>0.87</td>
</tr>
<tr>
<td>7</td>
<td>95</td>
<td>720</td>
<td>42.3</td>
<td>0.96</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>1120</td>
<td>44.6</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>105.5 ± 5.62</td>
<td>770 ± 52.4</td>
<td>45.4 ± 3.48</td>
<td></td>
</tr>
<tr>
<td><strong>Newborn lambs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>80</td>
<td>760</td>
<td>11.91</td>
<td>0.60</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>400</td>
<td>13.50</td>
<td>0.74</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>430</td>
<td>7.50</td>
<td>0.81</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>600</td>
<td>9.60</td>
<td>0.88</td>
</tr>
<tr>
<td>5</td>
<td>94</td>
<td>610</td>
<td>6.60</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>108</td>
<td>600</td>
<td>10.42</td>
<td>0.86</td>
</tr>
<tr>
<td>7</td>
<td>98</td>
<td>850</td>
<td>14.10</td>
<td>0.83</td>
</tr>
<tr>
<td>8</td>
<td>112</td>
<td>460</td>
<td>3.55</td>
<td>0.98</td>
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<td>9</td>
<td>78</td>
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<tr>
<td>10</td>
<td>101</td>
<td>770</td>
<td>28.00</td>
<td>0.96</td>
</tr>
<tr>
<td>11</td>
<td>88</td>
<td>400</td>
<td>3.93</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>91.9 ± 3.98</td>
<td>600.9 ± 48.8</td>
<td>11.71 ± 2.16</td>
<td></td>
</tr>
</tbody>
</table>
volume distribution and differences in smooth-muscle contraction or relaxation.

The difference between adult and newborn responses are probably not the result of differences in reflex modulation of the direct effects of the drugs for two reasons. First, when the drugs were delivered to the terminal aorta, significant differences were still observed in the newborns and adults, while arterial pressure and heart rate were not altered substantially. Second, experiments with i.v. methoxamine indicated that the arterial baroreceptor reflex sensitivity, insofar as heart rate control is concerned, appears to be depressed in the newborn. Thus, in the absence of reflex effects, responses should be even more disparate in the newborn and adult animals.

In our investigation the development of the baroreceptor reflex was evaluated using the technique described by Smyth et al.,16 which involves examining the reflex cardiac slowing induced by an injection of a peripheral vasoconstrictor. Methoxamine was chosen, since it is primarily an α-adrenergic agent with trivial β-adrenergic properties.17 There were marked differences in PI/SAP slopes in adult sheep and newborn lambs (fig. 10). The PI/SAP slopes observed in the newborns we studied were similar to those reported by Shinebourne et al.,28 who showed that the sensitivity of the baroreceptor reflex, determined by examining responses to mechanical instead of pharmacologic elevations of arterial pressure, increases in the fetus to the time of birth, and that there is little difference in sensitivity in the late gestational fetus and newborn. However, Shinebourne et al.28 did not compare responses to those in adults, and therefore could not discern that baroreceptor reflex sensitivity was depressed in the newborn.

A difference in receptor population or affinity should also be considered. The adrenergic nervous system is not completely developed at birth,29-31 and the effects of sympathetic activation increase rapidly early after birth.9 However, this cannot explain the depressed responsiveness in the newborn, since non-adrenergic agents, e.g., angiotensin II and nitroglycerin, also elicited smaller responses in newborns.

Another possible cause of the difference between newborn and adult responses to systemic pharmacologic agents would be a patent ductus arteriosus in the newborn, which would shunt a large fraction of the drug to the pulmonary circuit. To determine if the ductus arteriosus was patent, two newborn lambs were studied before and after inflation of the hydraulic occluder previously implanted on the ductus. Responses were similar in both conditions. Moreover, studies at autopsy in these lambs confirmed that the ductus was closed.

The most important reason for the different responses in newborns and adults is the difference in concentration of the drugs reaching the receptor sites. Cardiac output and terminal aortic flow per kilogram body weight are higher in the newborn than in the adult (table 1). Similarly, blood volume per kilogram body weight is greater in newborns than in adults, with reported values of approximately 60% greater in newborn lambs29 than the corresponding adult sheep.24 Glantz et al. found that the distribution space for ouabain was twice as great in young dogs as compared with adults.25 Therefore, the concentration of drug delivered to the receptor site must be significantly less in the newborn for any given dose administered on the basis of body weight. Since blood volume per kilogram body weight is approximately 60% greater in the newborn lamb than adult sheep, comparisons were
also made between newborns and adults, where the dose of drug per kilogram body weight administered to the newborn, was at least 100% greater than given to the adult. Changes in SVR in response to pharmacologic agents administered i.v. and changes in terminal aortic resistance in response to the agents administered into the terminal aorta were significantly greater in adults than newborns, although the dose per kilogram body weight was at least twice as great in the newborn (fig. 9).

To approximate the concentration of the administered drug, the quotient of the total amount of the drug delivered and the blood flow rate was calculated. Using this type of analysis we observed that adult responses to α- and β-adrenergic agonists were significantly greater than those in the newborn (table 2). Thus, while the major cause of the discrepancy between peripheral vascular responses to these drugs in adults and newborns appears to be related to differences in dilution and distribution in the two age groups, a component of depressed vascular response also appears to play a role.

A recent study from our laboratory supports the hypothesis that the arterial smooth muscle in the newborn might be capable of generating less tension than that of the adult in response to α-adrenergic stimulation. In that study, aortic stress-radius relationships were examined in conscious newborn lambs and adult sheep. Infusions of methoxamine shifted aortic stress-radius relationships significantly in adult animals but not in newborns. Thus, α-adrenergic stimulation was capable of increasing aortic stress at a given radius in adult sheep, but not in newborn or fetal animals. An increase with age in the tension generated by aortic smooth muscle in response to adrenergic stimulation has also been observed in in vitro experiments. Immaturity of arterial smooth muscle in the newborn has also been noted using histologic techniques.

Regardless of the mechanism, the striking difference in responsiveness between newborns and adults to vasoconstrictors and vasodilators is relevant in understanding the use of these agents in pediatric patients. Moreover, the depressed responsiveness to adrenergic agonists, and the finding that arterial baroreceptor reflex control of heart rate is depressed in the newborn, provide further support for the hypothesis that autonomic control of the circulation is incompletely developed in the newborn.

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