Intrathecal Clonidine and the Response to Hemorrhage

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Intraspinaly administered α₂-adrenergic agonists are being examined for postoperative analgesia, yet their effects on the hemodynamic response to acute hemorrhage have not been examined. In this study chronically prepared conscious sheep received thoracic intrathecal saline or clonidine 300 μg followed in 15 min by rapid removal of 1,000 ml blood. In saline-treated ewes blood pressure was maintained and heart rate steadily increased during hemorrhage of up to 700 ml blood, with further blood removal resulting in rapid decreases in both variables. In contrast, heart rate never increased and blood pressure was maintained only up to 400 ml blood loss in animals receiving intrathecal clonidine. Compared to saline controls, clonidine did not alter blood pressure or heart rate at the end of hemorrhage or during blood pressure restitution during the next hour. Clonidine inhibited the increase in plasma epinephrine at the end of hemorrhage without altering plasma norepinephrine, vasopressin, renin, or atrial natriuretic factor. Intrathecal idazoxan, a specific α₂-adrenergic antagonist, reversed clonidine's effect on blood pressure during hemorrhage. Intravenous DG-5128, a poorly lipid-soluble α₂-adrenergic antagonist, also reversed clonidine's effect and additionally completely blocked any reduction in blood pressure and heart rate during hemorrhage. These data suggest that intrathecal clonidine interferes with maintenance of blood pressure during hemorrhage, likely because of a spinal sympatholytic effect, but does not affect the ultimate decrease in blood pressure after rapid removal of 1,000 ml blood. This difference in effect during the two phases of hemorrhage can be explained by the relative importance of the sympathetic nervous system in each. (Key words: Anesthetic technique: spinal. Hormones: atrial natriuretic factor; renin; vasopressin. Physiology: hemorrhagic shock. Sympathetic nervous system, α₂-adrenergic agonists: clonidine.)

INTRASPINAL ADMINISTRATION OF α₂-adrenergic agonists produces analgesia, and epidurally administered clonidine has been shown to treat postoperative pain effectively. A major advantage of clonidine over opioids is lack of respiratory depression. However, epidurally administered clonidine decreases blood pressure (BP) and heart rate (HR). This effect occurs acutely, unlike delayed respiratory depression from intraspinaly administered opioids; is easily treated; and is probably of minor consequence in healthy adults. Such cardiovascular depression may be far more dangerous, however, during acute postoperative hemorrhage, yet the hemodynamic effects of intraspinaly administered α₂-adrenergic agonists have not been examined in this setting.

Hemorrhage activates a complex array of interacting neural and hormonal reflexes, typified in awake animals and humans by two distinct phases. BP is maintained in the first phase by a progressive increase in systemic vascular resistance (SVR) and HR, primarily due to activation of the sympathetic nervous system and the renin–angiotensin system. We postulate that intraspinaly administered α₂-adrenergic agonists, by inhibiting spinal preganglionic sympathetic neurons, will affect this phase by decreasing the amount of blood loss that will be tolerated before BP reduction begins.

With continued hemorrhage, there is an abrupt decrease in BP, SVR, and HR, accompanied by withdrawal of sympathetic tone and increased concentrations of arginine vasopressin (AVP), renin, and adrenally released epinephrine. The actions of intraspinaly administered α₂-adrenergic agonists during this second, hypotensive phase are less certain, since sympathoinhibition by these agents may be less important during this phase of general withdrawal of sympathetic tone. Indeed, systemically administered α₂-adrenergic agonists decrease BP in rats under resting conditions but increase BP during hypotensive hemorrhage, presumably by direct peripheral vasoconstriction.

The purpose of this study is to examine the hemodynamic and neurohumoral effects of intrathetically administered clonidine during progressive hemorrhage in conscious sheep and to determine the role of spinal and peripheral α₂-adrenoceptors in clonidine's effects.

Materials and Methods

ANIMAL PREPARATION

The study was approved by the Animal Care and Use Committee, and a total of 12 nonpregnant ewes of mixed western breeds, weighing 42–46 kg, were studied. Food was withheld for 48 h and water for 24 h. Anesthesia then was induced with ketamine 15 mg/kg intravenously (iv) and pentobarbital 15 mg/kg iv, the trachea intubated, and anesthesia maintained with halothane 1–1.5% in oxygen. Polyvinyl catheters were inserted under direct vision into both femoral arteries and veins and advanced to the distal aorta and inferior vena cava, respectively. An 8.5-Fr vascular introducer was inserted percutaneously into the right jugular vein and a 7.5-Fr pulmonary artery
catheter inserted under pressure waveguide guidance into the
distal pulmonary artery. The animal was turned prone,
a hemilaminectomy performed at the lumbosacral junction,
and a polyvinyl catheter inserted 28 cm cephalad
through a small nick in the dura. Catheter tip location
was not confirmed in this study, but in previous experi-
ments in this laboratory with this technique, the catheter
tip was at the T4–T6 dermatomal level.

All incisions were closed and catheters tunneled sub-
cutaneously and maintained in a canvas pouch at the flank,
and anesthesia was discontinued. Animals were observed
closely for any signs of postoperative pain. Meperidine
75 mg iv was to be administered postoperatively to treat
behavioral signs of pain. All animals were standing within
2 h of completion of surgery, and in no cases were ab-
normal behaviors noted. Kanamycin 1 g was administered
intramuscularly for the first 3 postoperative days. At least
3 days passed before study.

HEMORRHAGE PROTOCOL

On the day of the study a sling was placed under the
ewe in the metabolic cart. Femoral arterial and pulmonary
arterial catheters were connected to Viggo-Spectramed
pressure transducers connected to a Grass model 7
Polygraph and an on-line computer data acquisition sys-
tem for the continuous measurement of mean arterial
pressure, pulmonary artery pressure, right atrial pressure,
and HR. These variables were recorded at 1-min intervals
and values obtained at the same minutes as cardiac output
determinations used for data analysis. Following 30 min of
discontinuance, intrathecal idazoxan (an α2-adrenergic antagonist), iv DG-5128 (a hydrophilic α2-adrenergic antagonist), or intrathecal saline was injected. Fifteen minutes later, intrathecal clonidine (300 μg) or saline was injected. Fifteen minutes later, blood was with-
drawn from a femoral arterial catheter as quickly as pos-
sible (75–120 ml/min) until 1,000 ml blood was with-
drawn. Blood was transferred into heparinized blood col-
lection bags (total 5,000 U heparin in 1,000 ml blood)
and transfused via a femoral venous catheter 60 min later.

In addition to continuous monitoring of pressures and
HR, cardiac output was determined in triplicate (5 ml
iced injections of 5% dextrose) before each injection, be-
fore the beginning of hemorrhage, at the end of hem-
orrhage, and 5, 10, and 60 min thereafter. Arterial blood
was sampled before each injection, before the beginning
of hemorrhage, at the end of hemorrhage, and 60 min
thereafter (prior to blood reinfusion) and analyzed for
catecholamines, AVP, renin, atrial natriuretic factor
(ANF), blood gas tensions, and pH. Catecholamines were
analyzed using high-pressure liquid chromatography with
electrochemical detection; AVP, renin, and ANF were
analyzed by specific radioimmunoassays; and blood gas
tensions and pH were analyzed with a Radiometer BMD
analyzer.

INJECTION PROTOCOL

Animals were assigned randomly to one of four injec-
tion protocols. Control experiments consisted of two in-
trathecal saline injections (n = 6). The clonidine experi-
ment consisted of first a saline injection and then clonidine
300 μg intrathecally (n = 7). To ascertain the role of
spinal α2-adrenergic receptors in clonidine’s effects, ani-
mals received idazoxan 1 mg intrathecally and then clo-
 nidine 300 μg intrathecally (n = 6). This dose of idazoxan
has been shown to have no detectable effects on peripheral
actions but to inhibit spinal actions of clonidine. To
ascertain the role of peripheral α2-adrenergic receptors
in clonidine’s effects, animals received DG-5128 1 mg/
kg iv and then clonidine 300 μg intrathecally (n = 6). DG-
5128 does not cross the blood–brain barrier, and this dose
has been shown to antagonize the peripheral actions of
clonidine. Each animal was studied a maximum of four
times, with experiments separated by a minimum of 3
days and performed in random order. Two animals were
studied four times; five animals were studied three times;
and two animals were studied twice.

DRUGS AND SOLUTIONS

Halothane, kanamycin, ketamine, and pentobarbital
were obtained from Barber Veterinary Supply Co. (Rich-
mond, VA). The following drugs were generous gifts:
clonidine (Fujisawa Pharmaceutical Co., Deerfield, IL),
DG-5128 (Seiyaku Pharmaceutical Co., Kyoto, Japan), and
idazoxan (Reckitt and Colman, Kingston-Upon-Hull,
England). Drugs were dissolved in sterile saline, and in-
trathecal injections were administered in a volume of 0.5
ml followed by flush of 0.5 ml (two times catheter dead
space) of sterile saline.

STATISTICS

Data are expressed as mean ± SEM. Although for clarity
some data are expressed as percent change from values
immediately before hemorrhage, all data analyses were
performed on the raw data. Groups were compared to
baseline using a one-way analysis of variance (ANOVA)
for repeated measures, followed by a Newman-Keuls test.
Difference between groups was assessed by two-way ANO-
VA for repeated measures. AVP, norepinephrine, epi-
nephrine, and renin data were log-transformed for sta-
tistical analysis. Effect of duration of hemorrhage on
measured variables was assessed by Pearson correlation,
and effect of order of experiments on measured variables
within groups was assessed by two-way ANOVA. P < 0.05
was considered significant.
TABLE 1. Mean Arterial Pressure and Heart Rate Immediately Prior to Hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Arterial Pressure (mmHg)</th>
<th>Heart Rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>101 ± 2</td>
<td>112 ± 6</td>
</tr>
<tr>
<td>Clonidine</td>
<td>111 ± 11</td>
<td>105 ± 8</td>
</tr>
<tr>
<td>Idazoxan + clonidine</td>
<td>105 ± 5</td>
<td>121 ± 6</td>
</tr>
<tr>
<td>DG-5128 + clonidine</td>
<td>98 ± 2</td>
<td>116 ± 7</td>
</tr>
</tbody>
</table>

Groups do not differ in either variable.

Results

The 1,000-ml hemorrhage (22–24 ml/kg) was achieved in 10.1 ± 0.4 min (range 8–13 min). In a separate analysis by Pearson correlation, there was no effect of duration of hemorrhage on hemodynamic or hormonal variables. Similarly, there was no effect of the order of experiments within each animal on baseline hemodynamic or hormonal variables or on response to hemorrhage. All animals tolerated hemorrhage well, eating and drinking normally at the conclusion of each experiment.

HEMODYNAMIC EFFECTS

The groups did not differ in resting BP (table 1). In saline-treated animals BP was not decreased until hemorrhage of 800 ml of blood, and then BP declined rapidly (fig. 1). In contrast, animals receiving intrathecal clonidine exhibited a linear decrease in BP during hemorrhage, which became significant beyond 400 ml of blood loss (fig. 1). Despite this difference in BP response during hemorrhage (P < 0.01), BP did not differ between saline- and clonidine-treated animals at the end of the 1,000-ml hemorrhage (fig. 1). Similarly, clonidine and saline groups did not differ in cardiac output, stroke volume, or SVR at the end of the 1,000-ml hemorrhage (table 2).

HR progressively increased during hemorrhage in saline-treated animals, differing from baseline after 500–900-ml blood loss, but HR decreased to a value not different than baseline at the end of the 1,000-ml hemorrhage (fig. 2). In contrast, HR did not change significantly from baseline at any time during hemorrhage in clonidine-treated animals (fig. 2; P < 0.05 vs. saline controls in which HR did increase).

HORMONAL EFFECTS

The groups did not differ in plasma catecholamines, AVP, renin, or ANF at rest. In saline-treated animals, hemorrhage increased circulating concentrations of AVP, renin, and epinephrine (table 3). The hormonal response to hemorrhage was similar in clonidine-treated animals, except for plasma epinephrine, which did not increase above baseline (table 3).

REVERSAL STUDIES

Neither idazoxan nor DG-5128 pretreatment altered hemodynamic or hormonal variables immediately before hemorrhage (tables 1–3). Both intrathecal idazoxan and iv DG-5128 pretreatments inhibited clonidine's effect on BP during hemorrhage (fig. 3; P < 0.01 vs. clonidine). In

TABLE 2. Cardiac Output, Stroke Volume, and Systemic Vascular Resistance Before and Immediately After 1,000-ml Hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiac Output</th>
<th>Stroke Volume</th>
<th>Systemic Vascular Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Saline</td>
<td>6.5 ± 0.4</td>
<td>3.2 ± 0.6*</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>Clonidine</td>
<td>6.2 ± 0.7</td>
<td>2.5 ± 0.4*</td>
<td>62 ± 8</td>
</tr>
<tr>
<td>Idazoxan + clonidine</td>
<td>6.3 ± 0.5</td>
<td>3.5 ± 0.6*</td>
<td>51 ± 4</td>
</tr>
<tr>
<td>DG-5128 + clonidine</td>
<td>7.2 ± 0.7</td>
<td>4.6 ± 0.6*</td>
<td>60 ± 7</td>
</tr>
</tbody>
</table>

Cardiac output in liters per minute; stroke volume in milliliters; systemic vascular resistance Hg·l⁻¹·min. *P < 0.05 versus value before hemorrhage. No difference among groups in any variable either before or after hemorrhage.
CLONIDINE AND HEMORRHAGE

Fig. 2. Change in heart rate (HR) during hemorrhage in ewes after intrathecal saline (open circles) or clonidine (filled circles) injection. Each point represents the mean ± SEM of six or seven animals. *P < 0.05 versus baseline. The two curves differ by two-way ANOVA (P < 0.05).

In contrast to idazoxan pretreatment, which did not differ in BP response to saline controls, DG-5128 pretreatment abolished all hypotension during hemorrhage, with BP never differing from baseline in this group. This may have been due to differences in SVR, which increased from resting level at the end of hemorrhage only in DG-5128-treated animals (table 2). Compared to clonidine alone, idazoxan and DG-5128 pretreatments did not alter the HR, cardiac output, or stroke volume response to hemorrhage (fig. 4 and table 2), nor did they alter hormonal responses (table 3).

BLOOD PRESSURE RESTORATION

Hemodynamic and hormonal variables returned rapidly toward normal, with most variables not differing from baseline 60 min after the end of hemorrhage (table 4). In contrast to saline-treated animals, cardiac output decreased compared to prehemorrhage values and SVR increased in clonidine-treated animals 60 min after hemorrhage. These effects were inhibited by DG-5128 pretreatment (table 4).

Discussion

These data demonstrate a significant difference in the effect of intrathecal clonidine on the two hemodynamic phases of hemorrhage. The hormonal data suggest that this difference may be due to the relative importance of the sympathetic nervous system and clonidine's inhibition of this system in each of these phases.

The BP response to progressive hemorrhage observed in control experiments in this study agree well with previous examinations in sheep and other species, including humans. For example, in a recent study of similar design in sheep, BP was maintained until the removal
### Table 3. Hormonal Effects of Hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Vasopressin</th>
<th>Renin</th>
<th>Atrial Natriuretic Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Saline</td>
<td>150 ± 21</td>
<td>330 ± 55*</td>
<td>270 ± 90</td>
<td>370 ± 160</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>Clonidine</td>
<td>120 ± 44</td>
<td>170 ± 67</td>
<td>180 ± 59</td>
<td>280 ± 86</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Idazoxan + clonidine</td>
<td>120 ± 18</td>
<td>150 ± 53</td>
<td>240 ± 68</td>
<td>150 ± 52</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>DG-5128 + clonidine</td>
<td>182 ± 52</td>
<td>150 ± 62</td>
<td>170 ± 30</td>
<td>120 ± 71</td>
<td>1.7 ± 0.7</td>
</tr>
</tbody>
</table>

All values expressed in picograms per milliliter.

* $P < 0.05$ versus value before hemorrhage. Groups differ only in epinephrine concentration after hemorrhage, with saline greater than other groups ($P < 0.05$).

### Table 4. Hemodynamic and Hormonal Variables 60 Min after Hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Arterial Pressure</th>
<th>Heart Rate</th>
<th>Cardiac Output</th>
<th>Stroke Volume</th>
<th>Systemic Vascular Resistance</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Vasopressin</th>
<th>Renin</th>
<th>Atrial Natriuretic Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Saline</td>
<td>98 ± 4.3</td>
<td>130 ± 12</td>
<td>5.9 ± 1.1</td>
<td>39 ± 7.7*</td>
<td>18 ± 2.9</td>
<td>210 ± 47</td>
<td>380 ± 100</td>
<td>25 ± 8.0*</td>
<td>1.8 ± 0.9*</td>
<td>89 ± 23</td>
</tr>
<tr>
<td>Clonidine</td>
<td>93 ± 8.6</td>
<td>103 ± 6.5</td>
<td>4.1 ± 0.5*</td>
<td>41 ± 3.5*</td>
<td>24 ± 3.7*</td>
<td>97 ± 22</td>
<td>255 ± 100</td>
<td>32 ± 14*</td>
<td>3.0 ± 0.7*</td>
<td>58 ± 51</td>
</tr>
<tr>
<td>Idazoxan + clonidine</td>
<td>99 ± 3.2</td>
<td>129 ± 11</td>
<td>5.4 ± 0.2*</td>
<td>41 ± 3.8*</td>
<td>17 ± 0.8</td>
<td>65 ± 32</td>
<td>220 ± 85</td>
<td>14 ± 3.6*</td>
<td>1.4 ± 0.4</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>DG-5128 + clonidine</td>
<td>92 ± 3.1</td>
<td>115 ± 6.7</td>
<td>6.1 ± 0.8</td>
<td>51 ± 7.7</td>
<td>16 ± 2.5</td>
<td>69 ± 26*</td>
<td>200 ± 33</td>
<td>17 ± 11*</td>
<td>7.4 ± 2.7*</td>
<td>54 ± 11</td>
</tr>
</tbody>
</table>

See Tables 1–3 for units of measure.

Groups differ only in renin concentration, with the value in DG-5128–treated animals greater than the others ($P < 0.05$), and epinephrine, with the value in saline-treated animals greater than the others ($P < 0.05$).

* $P < 0.05$ versus value before hemorrhage.
of 17 ml/kg blood (compared to 18 ml/kg in the current study), and then BP decreased rapidly to 50 mmHg (compared to 51 mmHg in the current study), accompanied by a decrease in cardiac output to 3.0 l/min (compared to 3.2 l/min in the current study).

Intrathecal clonidine practically abolished the animal's ability to maintain BP at baseline levels during the first phase of hemorrhage, in that it appeared that BP passively followed changes in intravascular volume during hemorrhage in clonidine-treated animals. This effect is similar to that observed with hemorrhage during general anesthesia. Although we measured neither sympathetic nervous system activity nor circulating catecholamines during progressive hemorrhage in this study, others have demonstrated a rapid, progressive, and preeminent role of sympathetic nervous system activation during this phase of BP maintenance. This activation is abolished by pentobarbital general anesthesia.

Clonidine can diminish sympathetic nervous system activity at three sites: reduction in bulbospinal drive to preganglionic sympathetic neurons by actions in the brainstem, direct inhibition of spinal preganglionic sympathetic neurons, and peripheral inhibition of norepinephrine release by a presynaptic mechanism. The spinal mechanism is likely the most important, for two reasons. First, hypotension following intrathecal clonidine injection is spinally mediated: it occurs in sheep only after injection at dermatomal sites that include the preganglionic sympathetic neurons. Second, intrathecal injection of the specific α2-adrenergic antagonist idazoxan, in a small dose that reverses clonidine's antinociceptive effect when injected intrathecally, but not iv, inhibited the effect of clonidine during the first phase of hemorrhage.

The abrupt decrease in BP during the second phase of hemorrhage is accompanied, in awake animals and humans, by a withdrawal of sympathetic tone and the importance of renin, angiotensin, and AVP in protecting against further reductions in BP. The rapid decline in both BP and HR and minimal increase in SVR observed in control animals in the current study typifies this response. Compared to a study of similar design in sheep, ewes in the current study also exhibited dramatic increases in circulating AVP and renin during hypotensive hemorrhage but minor (<25%) increases in norepinephrine.

Intrathecal clonidine did not alter BP during the hypotensive phase of hemorrhage and the period of BP restoration. Clonidine has been shown in some, but not all studies, to decrease AVP and renin and increase ANF. Most likely, the action of clonidine on these hormones would occur from systemic absorption and central redistribution, and the relatively low clonidine dose may have been inadequate to alter these hormones. Alternatively, minor inhibition in AVP and renin secretion by clonidine may have been overridden by the powerful stimulus of hypotensive hemorrhage. Clonidine did inhibit the increase in circulating epinephrine during hypotensive hemorrhage, perhaps through its spinal sympatholytic effect, but an absence of effect on hemodynamic response is in keeping with the minimal role of the sympathetic nervous system during this phase.

Systemically administered α2-adrenergic agonists are effective presoros during hypotensive hemorrhage in rats, presumably because of direct vasoconstricting actions, and have been proposed as effective therapy. It is unlikely that clonidine produced any meaningful vasoconstriction, and in the current study because of the low dose. Also, intrathecal idazoxan should have abolished the spinal hypotensive action of clonidine, uncovering its peripheral vasoconstriction, but BP was no greater in idazoxan/ clonidine- than in saline-treated animals.

Absence of a hypotensive phase in animals treated with DG-5128 is surprising. We reasoned, but did not observe, that iv DG-5128, by blocking any peripheral constriction produced by systemically absorbed clonidine, should worsen the decrease in BP during this phase. The only data supporting this hypothesis is inhibition of the late (60-min) increase in SVR in clonidine-treated animals by DG-5128. Although DG-5128 could have maintained BP and increased SVR by blocking presynaptic α2-adrenoceptors at sympathetic nerve endings, this argument is not supported by an increase in circulating norepinephrine in DG-5128–treated ewes. Whether the effect of DG-5128 during hemorrhage is due to actions at peripheral α2-adrenoceptors or other sites, and whether increased SVR by this treatment is beneficial during hemorrhage, are questions not addressed in the current study.

Also, whether intrathecal clonidine would be beneficial or detrimental during acute hemorrhage was not examined in the current study. On the one hand, upper thoracic epidural anesthesia decreases mortality during hemorrhagic shock in dogs, perhaps due to inhibition of sympathoadrenal reflexes, and clonidine may produce similar protection by the same mechanism. Unlike epidural anesthesia in humans, clonidine did not result in severe cardiovascular decompensation during hemorrhage in these sheep. On the other hand, BP declined after less blood loss in clonidine- than in saline-treated ewes in the current study. Although clonidine also reduced HR as a measure of myocardial work, in some individuals this decrease in BP may yield myocardial ischemia.

There are, of course, several limitations to extrapolation of these data to the clinical setting. BP decreases more during hemorrhage in sheep in the standing than prone position, and since the sheep were kept standing throughout this protocol, the degree of hypotension for any given blood loss may have been exaggerated. Intrathecal clonidine injection decreases BP less in sheep than in humans, and its effects during hemorrhage in
sheep may underestimate those observed clinically. For this reason, in this study we deliberately chose to inject clonidine at a site (thoracic intrathecal space) that would maximize cardiovascular depression in this species. Clonidine's effect on the hemodynamic response to hemorrhage may be more profound at this site than in the lumbar epidural space.\textsuperscript{10,125} Residual general or epidural anesthesia may alter clonidine's effect during hemorrhage in the acute postoperative setting as well.

In summary, in comparison to saline control, thoracic intrathecal clonidine injection in conscious sheep decreases the amount of acute blood loss tolerated before BP decreases during progressive hemorrhage. However, the final BP decrease after rapid removal of 1,000 ml blood, representing approximately 30\% of estimated blood volume in nonpregnant adult sheep,\textsuperscript{26} is not affected by clonidine injection. The distinct difference in clonidine's effects during the two phases of hemodynamic response to progressive hemorrhage and their reversal by intrathecal idazoxan can be explained by clonidine's sympathetic effect in the spinal cord. If applicable to humans, these data suggest that intrathecal clonidine may diminish the ability to maintain BP during acute postoperative hemorrhage.

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References