Anesthesiology
73:1179–1185, 1990

Subarachnoid Clonidine Reduces Spinal Cord Blood Flow and Glucose Utilization in Conscious Rats

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The authors investigated the spinal blood flow and metabolic effects of subarachnoid clonidine in conscious rats prepared with chronically implanted subarachnoid catheters. For the blood flow experiments, rats received saline (n = 7) or clonidine 20 nmol (7 μg; n = 6), 100 nmol (27 μg; n = 5), or 400 nmol (107 μg; n = 7) intrathecally. Another group of rats received clonidine 400 nmol intravenously (n = 4). Spinal glucose utilization was measured in rats that received either saline (n = 5) or clonidine 100 nmol (n = 5) intrathecally. Spinal cord blood flow (SCBF) and glucose utilization were measured in five gray and three white matter areas of lumbar spinal cord 15 min after drug administration with the autoradiographic iodo-[^{14}C]-antipyrine and 2-[^{14}C]-deoxyglucose methods, respectively. Physiologic differences between the groups were minor. Rats in the blood flow experiments that received clonidine 100 nmol had a slightly lower arterial P_{O_2} level (70 ± 1 *vs.* 82 ± 3 mmHg; $P < 0.05$), whereas those in the glucose utilization group were mildly hypocarbic (P_{CO_2} 27 ± 1 *vs.* 32 ± 2 mmHg; $P < 0.01$) relative to control animals. Only animals that received 400 nmol clonidine intrathecally had significant analgesia, as assessed by the tail-flick test. One control animal for the metabolism experiments was technically unsatisfactory and was excluded from data analysis. Subarachnoid clonidine reduced both SCBF and glucose utilization. In spinal gray matter, the largest decreases in flow (32–44%; $P < 0.01$) occurred with 20 nmol clonidine, whereas flow decreased least (12–27%) with the 400-nmol dose. On the other hand, white matter blood flow decreased (17–39%) only at the two higher doses. Intravenous clonidine 400 nmol reduced SCBF to the same extent as the same dose administered intrathecally. At the single dose studied, subarachnoid clonidine reduced glucose utilization 11–42% in spinal gray and white matter, although the changes were significant in only five of eight areas. Neither the blood flow nor the glucose utilization changes were confined to areas of spinal cord known to contain high concentrations of alpha-2 receptors. These results indicate that, even at subanalgesic doses, subarachnoid clonidine reduces SCBF substantially and that the decrease is associated with, and perhaps caused partially by, a decrease in spinal metabolic rate. Accordingly, these data suggest that the blood flow and analgesic effects of clonidine occur by different mechanisms and support the hypothesis that spinal vasoconstriction may contribute to subarachnoid clonidine's ability to prolong spinal anesthesia. (Key words: Alpha-2 receptor agonist: clonidine. Analgesics: clonidine. Anesthetic techniques: spinal. Metabolism: glucose; regional; spinal cord. Spinal cord: blood flow, regional; clonidine; glucose utilization, regional; metabolism, regional. Sympathetic nervous system.)

CLONIDINE, a highly lipid-soluble, alpha-1- and alpha-2-adrenergic receptor agonist, is a potent subarachnoid and epidural analgesic[1–7] that has also recently proved to be more effective than epinephrine at prolonging the duration of spinal anesthesia.[8,9] The mechanism by which clonidine prolongs spinal anesthesia is unclear but probably represents either a direct analgesic action[10] or constriction of the spinal vasculature. The possibility of vasoconstriction is relevant not only because it would help explain clonidine's ability to prolong spinal anesthesia, but also because clonidine has been administered intrathecally in larger doses as the sole analgesic,[6,7] during which circumstance the potential for spinal vasoconstriction may be greater.

Controversy continues, however, as to whether the practice of administering adrenergic agonists into the subarachnoid space produces important changes in spinal cord blood flow (SCBF). This is in large part because results of studies directly measuring SCBF are inconsistent. For instance, clonidine is reported to increase SCBF in anesthetized dogs after subarachnoid administration[11] but, when administered epidurally, may decrease SCBF in pigs[12] and has no effect in sheep.[13] These results are at variance with data from studies of systemic administration, which demonstrate consistently that clonidine decreases cerebral blood flow (CBF)[14,15] and increases cerebrovascular resistance.[16] Because of such inconsistencies, we designed a study to reexamine whether subarachnoid clonidine affects SCBF. To this end, the SCBF effects of analgesic as well as subanalgesic doses of subarachnoid clonidine were examined in conscious rats so as to eliminate one source of confusion in previous work,[11,12] namely, use of background general anesthesia. Furthermore, because one hypothesis[15] advanced previously to explain intravenous clonidine's CBF effect asserts that clonidine is a central nervous system depressant, we investigated directly whether subarachnoid clonidine reduces spinal cord metabolic rate.

Materials and Methods

Experiments were performed, with approval of the Subcommittee on Animal Care, in 39 conscious, male,

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Received from the Anesthesia Services, Massachusetts General Hospital, and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts. Accepted for publication July 11, 1990. Supported by NIH grant R01-GM 30502 (G.C.).

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325–375-g Sprague-Dawley rats, and local SCBF and glucose utilization were measured in lumbar spinal cord with quantitative autoradiographic techniques.

Experimental Design

Animals were prepared approximately 48 h in advance with lumbar subarachnoid catheters, according to the method of Yaksh and Rudy.[17] With the animals under halothane–nitrous oxide anesthesia, a 15-cm length of polyethylene tubing (PE 10) was advanced 8 cm caudally into the subarachnoid space from a slit in the cisternal membrane. This procedure places the distal tip of the catheter near the rostral portion of the lumbar enlargement. The catheter was brought out the back of the animal's neck and secured in place. Rats were evaluated clinically (regarding ability to walk, groom, stand on hind limbs) on awakening and again at 48 h after the initial surgery. Only neurologically normal animals were included in the study. These animals were reanesthetized on the day of the experiment for about 15 min with 1% halothane–70% nitrous oxide for femoral artery and vein catheterization. The rats were then partially immobilized with a pelvic plaster cast and allowed at least 2 h to recover from general anesthesia.

Spinal cord blood flow was measured in five groups of rats. Animals received either saline (n = 7) or clonidine in dosages of 20 nmol (7 μg; n = 6), 100 nmol (27 μg; n = 5), or 400 nmol (107 μg; n = 7) intrathecally. The fifth group (n = 4) received clonidine 400 nmol intravenously to determine whether the SCBF effects of intravenous and subarachnoid administration differ. The metabolic effects of clonidine were evaluated in separate groups of rats. Spinal glucose utilization was measured in rats that received either clonidine 100 nmol (n = 5) or saline (n = 5) intrathecally. Clonidine doses were selected on the basis of previous studies in rats to include analgesic as well as subanalgesic doses. The drug was prepared and administered in 10 μl of preservative-free saline, followed by an additional 10 μl of saline to flush the catheter.

Analgesia in control and clonidine-treated rats was quantified before autoradiographic tracer administration with the tail-flick test. For this purpose, the tail was placed over a slit 1.5 cm from a 150-W focused projection bulb. The end point of the test was removal of the tail; a 6-s cut-off point was used to avoid thermal damage to the tail. Mean arterial blood pressure (MAP), arterial blood gases and pH, and rectal temperature were also monitored. Temperature was maintained with a thermal blanket and heat lamp. Measurement of local SCBF or glucose utilization began 10–15 min after administration of clonidine.

Spinal Blood Flow and Metabolism Measurement

Local spinal blood flow was measured with the autoradiographic iodo-[^{14}C]-antipyrine (IAP) technique.[18] IAP (Amersham, Arlington Heights, IL), 50–60 μCi in 1.5 ml physiologic saline, was infused intravenously at an increasing rate over 45 s. Timed arterial blood samples were collected and weighed and the volume determined by assuming a specific gravity of 1.05 g/ml blood. Animals were killed by decapitation, and the lumbar spinal cord was removed within 2–3 min, frozen in isopentane (−50° C), and processed for autoradiography. Serial sections 20 μm thick were later cut at −22° C in a cryostat and autoradiographed along with a set of previously calibrated ^{14}C methylmethacrylate standards (Amersham). Optical density measurements were made bilaterally in a minimum of five autoradiographic sections with the aid of a computerized image-processing system. These measurements were made in five gray and three white matter areas approximating the laminae and tracts of the spinal cord. Local tissue ^{14}C concentration was determined from the optical density measurements and the calibrated ^{14}C standards. Local SCBF was calculated from the tissue and arterial blood concentrations of the tracer, a tissue–blood partition coefficient of 0.8, and the appropriate correction for lag and washout in the catheter as described by Sakurada *et al.*[18]

The 2-[^{14}C]-deoxyglucose (2DG) method[19] was used to measure local spinal glucose utilization. Animals received a 125 μCi/kg intravenous bolus of 2DG (Amersham), and timed arterial blood samples were taken during the 45-min experiment for plasma glucose and 2DG determinations. Animals were killed with an overdose of pentobarbital, and the lumbar spinal cord was removed and processed for autoradiography as described for the blood flow experiments. Optical density measurements were made with a computerized image-processing system in a minimum of five autoradiographic sections. Local spinal glucose utilization was calculated from the tissue ^{14}C concentrations, plasma glucose and 2DG concentrations, and the rate and lumped constants of normal rat brain according to the operational equation of the method. Because oxygen is used in the central nervous system almost entirely for the oxidation of glucose and the stoichiometry of this relationship is known, under steady-state conditions the rate of glucose utilization directly reflects the rate of oxidative metabolism.[20]

Statistics

Data from the blood flow experiments were subjected to a one-way analysis of variance, followed by Bonferroni's correction of a *t* test. Four pairwise comparisons were

TABLE 1. Physiologic Data: Blood Flow

	Control (7)	Subarachnoid Clonidine			Intravenous Clonidine†
		20 nmol (6)	100 nmol (5)	400 nmol (7)	400 nmol (4)
Arterial *p*H	7.45 ± 0.01	7.48 ± 0.03	7.46 ± 0.01	7.46 ± 0.02	7.45 ± 0.01
Pa_{CO_2} (mmHg)	31 ± 1	28 ± 1	31 ± 2	32 ± 2	31 ± 2
Pa_{O_2} (mmHg)	82 ± 3	77 ± 2	70 ± 1*	70 ± 6	78 ± 15
Rectal temperature (° C)	36.7 ± 0.2	36.4 ± 0.2	35.2 ± 0.6	36.4 ± 0.5	35.7 ± 0.5
Map (mmHg)					
Preinjection	122 ± 3	113 ± 4‡	118 ± 3	112 ± 5	113 ± 4
15 min postinjection	120 ± 5‡	105 ± 3	119 ± 4	136 ± 6	140 ± 6
Tail flick latency (min)	0.03 ± 0.002	0.042 ± 0.005	0.05 ± 0.008	0.7 ± 0.008*	—

Data are mean ± SEM for the number of animals in parentheses.
* $P < 0.05$ compared to control.
† Compared only to subarachnoid clonidine 400 nmol.
‡ n = 4.

made: each group treated with subarachnoid clonidine was compared with a control and the two groups that received clonidine 400 nmol were compared with each other. An unpaired *t* test was applied to data from the two glucose utilization experiments.

Results

Blood Flow Studies

There were few physiologic differences between the groups (table 1). Although the Pa_{O_2} level of animals treated with 100 nmol clonidine was lower than that of control rats ($P < 0.05$), the change was small and probably of no physiologic significance. Subarachnoid administration of all three doses of clonidine produced hypertension initially, but at the time of SCBF measurement 15 min later blood pressure had returned to control levels. Such transient hypertension has been reported previously[21] after intrathecal administration of clonidine and presumably results from vascular uptake and an action on peripheral alpha receptors. In fact, MAP changes were similar regardless of whether animals received clonidine 400 nmol intrathecally or intravenously. Subarachnoid clonidine increased the latency of the tail-flick response only in animals treated with 400 nmol (table 1; $P < 0.05$).

All doses of subarachnoid clonidine reduced SCBF (table 2), but gray and white matter responded differently. In spinal gray matter, for instance, the largest decreases in flow (29–44%) occurred with 20 and 100 nmol clonidine, whereas the highest dose produced lesser effects (12–27% decreases) that achieved statistical significance in only two of five areas. In white matter, on the other hand, clonidine's SCBF effect appears to be dose dependent; the two highest doses produced the largest reductions in flow (17–39%), whereas 20 nmol clonidine had no effect. The SCBF effects of clonidine 400 nmol administered intrathecally and intravenously were virtually identical (table 2).

Metabolism Studies

Because 100 nmol subarachnoid clonidine produced the largest percentage decrease in gray matter SCBF, we chose this dose to evaluate the spinal metabolic effects of the drug. One control animal had to be excluded from

TABLE 2. Spinal Cord Blood Flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)

	Control (7)	Subarachnoid Clonidine			Intravenous Clonidine†
		20 nmol (6)	100 nmol (5)	400 nmol (7)	400 nmol (4)
Lamina(e)					
I–III	62 ± 2	44 ± 3**	42 ± 6**	45 ± 3**	42 ± 5
IV–VI	100 ± 2	70 ± 4**	65 ± 8**	87 ± 5	86 ± 10
VII	129 ± 5	88 ± 5**	73 ± 10**	113 ± 7	106 ± 15
VIII	123 ± 5	80 ± 5**	69 ± 9**	102 ± 7	98 ± 12
IX	108 ± 3	68 ± 3**	60 ± 7**	83 ± 6**	80 ± 10
White matter					
Dorsal	23 ± 2	28 ± 2	19 ± 1	19 ± 2	19 ± 2
Lateral	36 ± 1	35 ± 3	26 ± 4*	22 ± 2**	23 ± 3
Ventral	31 ± 2	30 ± 2	21 ± 2**	20 ± 2**	19 ± 3

Data are mean ± SEM for the number of animals in parentheses.
* $P < 0.05$.
** $P < 0.01$ compared to control.
† Compared only to subarachnoid clonidine 400 nmol.

data analysis because of a technical problem in harvesting the spinal cord. Compared with animals in the blood flow experiments, these clonidine-treated rats were hypocarbic and slightly (but not significantly) hypotensive (table 3). In terms of metabolism, the results (table 4) indicate that subarachnoid clonidine reduced glucose utilization 11–42% in all areas of spinal gray and white matter, although a few changes failed to achieve statistical significance because of the small control group.

Discussion

These data indicate that, even in the absence of behavioral analgesia, subarachnoid clonidine reduces SCBF substantially in all gray matter regions of the lumbar spinal cord, not just those with high concentrations of alpha-2 receptors (*i.e.*, laminae I–II).[22] Accordingly, these results suggest that the blood flow and analgesic effects of clonidine do not share a common mechanism and lend support to the idea that vasoconstriction probably contributes to the ability of subanalgesic doses of intrathecal clonidine to prolong spinal anesthesia. These results are fundamentally consistent with previous work showing that intravenous clonidine reduces CBF in animals[15] and humans[14] and that intraarterial administration increases cerebrovascular resistance,[16] but they do not agree with previously reported SCBF effects of subarachnoid and epidural clonidine.[11–13] For instance, in the only other study involving subarachnoid administration, Mensink *et al.*[11] reported that intrathecal clonidine tends to increase SCBF in the lumbosacral cord of pentobarbital-anesthetized dogs. In contrast, Gordh *et al.*[12] reported that SCBF decreased 25–35% in the lumbar cord of anesthetized pigs receiving 10 or 30 μg/kg epidural clonidine but did not change in animals treated with 3 μg/kg. Finally, Eisenach and Grice[13] reported recently that epidural clonidine has no effect on SCBF in awake sheep.

Directly comparing the results of these studies is difficult because of substantial differences in experimental design. For example, the confounding variable of barbiturate anesthesia, which reduces vascular responsiveness,[23,24] was eliminated in our experiments but may have influenced the results of Gordh *et al.*[12] and Mensick *et al.*[11] The fact that different doses and routes of administration have been used further complicates the issue because epidural, but not subarachnoid, administration of clonidine could produce analgesia without decreasing SCBF. Such a theory does not account for discrepancies in the literature between studies using the epidural route,[12,13] however, and seems an unlikely explanation for variance with studies using subarachnoid administration[11] because, in both cases, the spinal cord is the common site of action. Finally, the possibility of important species differences must be considered seriously. The type and distribution of vascular receptors vary between species and even between different vessels in the same species.[25] Alpha-1 and alpha-2 receptors have been identified on central nervous system (CNS) intraparenchymal vessels of most species, but although the alpha-2 subtype predominates in cats, dogs, and pigs,[25,26] alpha-1 receptors are more numerous in rats and primates (including humans).[25] Thus, in terms of adrenergic receptor subtypes, the rat may more closely model primate cerebrovasculature than either dogs or pigs.

Despite major differences in experimental design, the significant difference in results between our study and that of Eisenach and Grice[13] is still the most difficult to explain. Using conscious sheep, they[13] found no change in SCBF after a supramaximal dose (2.5 times the maximal antinociceptive dose) of epidural clonidine, whereas we found substantial decreases in flow with doses of subarachnoid clonidine only at or below the analgesic threshold. Part of the explanation for these differences may involve the relative dosages. The overall SCBF effect of clonidine almost certainly reflects a balance of several competing, and possibly opposite, effects of the drug on spinal vascular resistance. Some combination of local actions on vascular receptors, vascular smooth muscle, and tissue metabolism, as well as supraspinal effects, presum-

TABLE 3. Physiologic Data: Glucose Utilization

	Control (4)	Clonidine 100 nmol (5)
Arterial *p*H	7.49 ± 0.01†	7.46 ± 0.02
Pa_{CO_2} (mmHg)	32 ± 2	27 ± 1**
Pa_{O_2} (mmHg)	81 ± 4	80 ± 4
Rectal temperature (° C)	37.0 ± 0.4	35.9 ± 0.7
MAP (mmHg)	114 ± 6	98 ± 7
Tail flick latency (min)	0.038 ± 0.002	0.065 ± 0.014

Data are mean ± SEM for the number of animals in parentheses.
† n = 2.
** $P < 0.01$.

TABLE 4. Glucose Utilization ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$)

	Control (4)	Clonidine 100 nmol (5)
Lamina(e)		
I–III	35 ± 4	31 ± 1
IV–VI	48 ± 5	35 ± 1*
VII	57 ± 6	38 ± 1*
VIII	58 ± 6	35 ± 1**
IX	52 ± 5	35 ± 1**
White matter		
Dorsal	16 ± 2	10 ± 2
Lateral	26 ± 4	17 ± 1
Anterior	32 ± 4	14 ± 1*

Data are mean ± SEM for the number of animals in parentheses.
* $P < 0.05$; ** $P < 0.01$.

ably determines the actual rate of flow. Each such effect may be manifest at a different dose such that SCBF could decrease at a low dose of clonidine if vasoconstriction (resulting, for example, from metabolic depression) predominates, but at higher doses may not differ from baseline if vasodilatory influences supervene. This hypothesis could explain why gray matter SCBF changed least in our animals receiving the highest doses and why Eisenach and Grice,[13] using a supramaximal analgesic dose, found no SCBF effect with epidural clonidine. Although there is no direct evidence to support this hypothesis, biphasic effects on the cerebral vasculature of other adrenergic agonists have been reported.[27,28] An obvious and troublesome weakness of this hypothesis is that it does not account for the SCBF effect of clonidine in spinal white matter, where there is roughly a direct relationship between dose and percentage decrease in SCBF. Another difference, also unexplained, between spinal gray and white matter is that at 100 nmol clonidine, the percentage decrease in flow slightly exceeds that in metabolism for gray matter areas, whereas the converse is true in white matter.

One cannot assume that because clonidine is a relatively specific alpha-2 receptor agonist its SCBF effects are mediated by spinal alpha-2 receptors. Indeed, the fact that SCBF decreased in animals in which analgesia did not develop indicates that spinal alpha-2 receptors subserving analgesia are not involved in the SCBF effect, although definitive exclusion of an alpha-2 receptor mechanism requires evidence for inhibition by a specific antagonist. It is not likely that the decrease in SCBF results from systemic hemodynamic changes because blood pressure changes were minimal and intravenous clonidine does not alter cerebral autoregulation.[15] A direct vascular smooth muscle effect is possible, although evidence for a direct cerebral vasoconstrictor effect of clonidine is lacking.[15] However, a supraspinal effect occurring by vascular absorption or redistribution in the cerebrospinal fluid (CSF) almost certainly accounts for some of the SCBF changes we observed. For instance, clonidine is rapidly absorbed into the central circulation after subarachnoid administration and reduces activity in brain stem nuclei containing alpha receptors.[29] The fact that subarachnoid and intravenous clonidine produced very similar SCBF effects supports the notion that a supraspinal action at least contributes to the SCBF effect of subarachnoid clonidine. On the other hand, the fact that epidural clonidine has little effect on SCBF,[12,13] despite presumably higher blood concentrations, speaks against the importance of systemic absorption. Finally, the decrease in SCBF could reflect clonidine's sedative properties.[30] However, at the dose most likely to produce sedation (*i.e.*, the highest), gray matter SCBF was affected least. Thus, the question of whether subarachnoid clonidine acts locally or through supraspinal mechanisms to decrease SCBF is unresolved.

Metabolic demand is an important determinant of the rate of CNS blood flow. In fact, Kanawati *et al.*[15] hypothesized that a decrease in metabolic rate might explain the decrease in CBF seen with intravenous clonidine. Our work supports that suggestion. The minor decreases in blood pressure, temperature, and arterial P_{CO_2} levels are insufficient to account for the 25–35% decrease in spinal cord glucose utilization produced by subarachnoid clonidine.[31,32] Like blood flow, metabolic rate decreased diffusely throughout the lumbar cord, not just in areas with high concentrations of alpha-2 receptors. This metabolic depression presumably reflects clonidine's ability to reduce the activity of spinal sensory and motor neurons,[10,33] and the sedation seen clinically may reflect a decrease in CNS metabolism. However, not all anesthetics or analgesics that affect spinal neuronal activity decrease metabolism. For instance, Crosby[34] reported only minor (10–15%) decreases in spinal glucose utilization during spinal anesthesia with bupivacaine and Kuroda *et al.*[35] showed that epidural morphine produced analgesia but had no effect on spinal metabolic rate. Therefore, the presence or absence of analgesia after subarachnoid or epidural administration of local anesthetics and analgesics does not reliably predict whether SCBF and metabolic changes have occurred; SCBF may change in the absence of analgesia (*e.g.*, this study) and analgesia may occur without a change in spinal metabolism (*e.g.*, with morphine). It must be emphasized that the decrease in glucose utilization with subarachnoid clonidine is almost certainly not a consequence of reduced spinal blood flow. Measurement of glucose utilization with deoxyglucose is independent of the rate of blood flow[19] except during severe ischemia, when glucose utilization would increase, not decrease, because of anaerobic metabolism. Thus, the decrease in SCBF with subarachnoid clonidine may be a normal physiologic response to reduced spinal metabolic demand, although a firm cause–effect relationship cannot be established.

We conclude, therefore, that subarachnoid clonidine reduces SCBF in awake rats and that the decrease is associated with, and perhaps caused partially by, a reduction in spinal metabolic rate. These spinal vascular and metabolic effects may not be mediated locally; redistribution through the systemic or cerebrospinal fluid circulations to supraspinal structures could be involved. The vasoconstrictor effect of subarachnoid clonidine in spinal gray matter is substantial even at subanalgesic doses. This property may make clonidine a desirable adjunct for prolonging spinal anesthesia and help explain its superiority to epinephrine in that regard,[9] although preliminary clinical data indicate that clonidine does not alter the plasma

pharmacokinetics of intrathecally administered bupivacaine, as would be expected if spinal vasoconstriction occurred.[36] The capacity of subarachnoid clonidine to reduce blood flow should not be viewed as cause for alarm, however, because there is no evidence that subarachnoid clonidine produces a flow–metabolism imbalance that leads to ischemia. In fact, no evidence of neurotoxicity with acute intrathecal or epidural clonidine has been detected in studies involving several species,[37–40] perhaps because the decrease in SCBF is accompanied by a decrease in metabolism. Because those studies were performed in normal animals, they may not apply to patients concurrently receiving other anesthetics or to patients with vascular disease. Nevertheless, inasmuch as nearly all intravenous anesthetics reduce CNS blood flow without untoward CNS consequences (and some are even "protective")[41] and the weight of evidence against a systematically harmful effect of clonidine is substantial, we must agree with previous researchers[12,13] that a decrease in SCBF produced by subarachnoid clonidine is unlikely to be "dangerous" and may even be clinically useful.

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