

Vascular

# Reversal of cerebral vasospasm by sphenopalatine ganglion stimulation in a dog model of subarachnoid hemorrhage<sup>☆</sup>

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## Abstract

**Background:** Sphenopalatine ganglion stimulation dilates the ipsilateral arteries of the normal dog anterior circle of Willis. This experiment tested whether similar stimulation would reverse cerebral vasospasm.

**Methods:** Six dogs underwent baseline angiography followed by creation of subarachnoid hemorrhage (SAH) by injection of autologous blood into the cisterna magna. Two days later, subarachnoid blood injection was repeated. Seven days later, angiography was repeated and the left sphenopalatine ganglion was exposed microsurgically. Angiography was repeated 15 minutes after exposure of the ganglion. The ganglion was then stimulated electrically 3 times and angiography repeated during, and 15 and 30 minutes after stimulation. The protocol was repeated again. Adequacy of stimulation was confirmed by the presence of immediate ipsilateral nasal mucus production.

**Results:** Subarachnoid hemorrhage was associated with significant vasospasm of both middle cerebral arteries ( $11\% \pm 4\%$  and  $18\% \pm 7\%$ ,  $P < .05$ , paired  $t$  tests). Exposure of the ganglion and sham stimulation produced no substantial changes in arterial diameters compared with the diameter before stimulation and after ganglion exposure ( $n = 2-6$  per measurement, paired  $t$  tests). Ganglion stimulation produced significant dilatation of the ipsilateral extracranial and intracranial internal carotid, middle cerebral, and anterior cerebral arteries compared with the contralateral arteries ( $13\% \pm 6\%$  to  $32\% \pm 14\%$ ,  $P < .05$ , paired  $t$  tests).

**Conclusions:** The mild to moderate vasospasm that results from SAH in dogs was reversed by sphenopalatine ganglion stimulation. Since this method carries a potential for human application, additional studies are warranted to determine the effects on more severe vasospasm.

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## Keywords:

Cerebral arteries; Models, Animal; Sphenopalatine ganglion; Subarachnoid hemorrhage; Vasospasm

## 1. Introduction

Cerebral vasospasm is a common complication of aneurysmal subarachnoid hemorrhage (SAH), occurring radio-

graphically in nearly 70% of patients and clinically in 30% to 40% during the first 2 weeks after the hemorrhage. Among the approximately 3500 patients with aneurysmal SAH entered into randomized, controlled trials of tirilazad, 30% developed symptomatic neurological deterioration that was attributed to vasospasm [6,8-10]. Sixteen percent of deaths were due to vasospasm. This high impact on outcome has motivated the development of many therapeutic regimens over the years in an attempt to prevent or reverse

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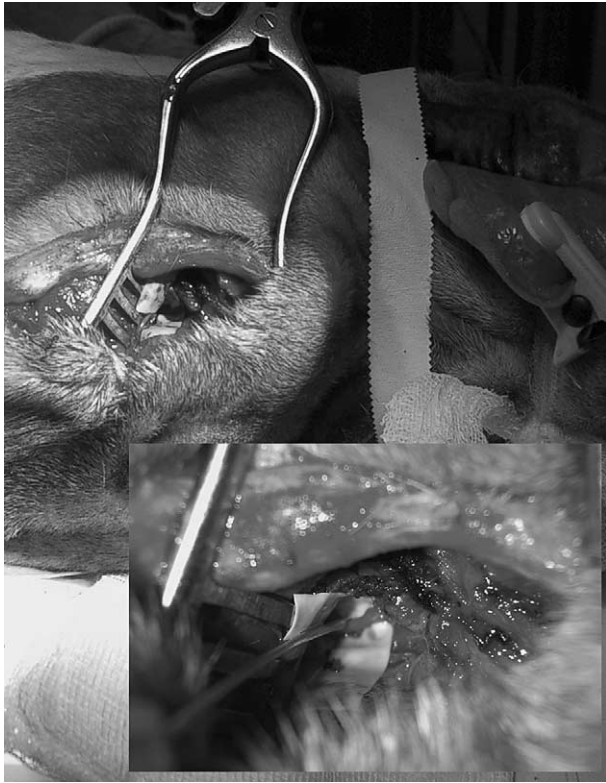


Fig. 1. Photograph of surgical exposure of the left sphenopalatine ganglion. The view is of the left side of the head of a dog that is positioned supine. The inset shows the ganglion separated from the underlying tissues by a strip of latex. A bipolar electrode consisting of 2 hook-shaped wires can be seen around the ganglion.

the vasospasm and thereby prevent ischemic cerebral damage. These include nimodipine, hemodynamic therapy, and interventional neuroradiological procedures such as intra-arterial papaverine infusion and balloon angioplasty [17]. To date, no remarkable success has been achieved with any of these approaches.

The sphenopalatine ganglion is the source of parasympathetic innervation to most of the anterior part of the cerebral vasculature [2]. Stimulation of this ganglion induces vasodilation of the ipsilateral, intradural arteries of the anterior circle of Willis in normal rats [12], cats [5], dogs [14], and monkeys [16]. The extracranial arteries dilate as well. The purpose of this study was to determine whether this vasodilation would also be effective on vasospastic cerebral arteries.

Table 1  
Percent change in angiographic arterial diameters, day 0 to day 7

Artery	Right (%)	Left (%)
Extracranial ICA	$-1 \pm 7$	$-1 \pm 8$
Intracranial ICA	$0 \pm 10$	$-3 \pm 14$
MCA	$-11 \pm 4^*$	$-18 \pm 7^*$
ACA	$-8 \pm 13$	$-16 \pm 10$

Values are means  $\pm$  SEM.  $n = 6$  per measurement.

\*  $P < .05$ , paired  $t$  test.

## 2. Methods

### 2.1. Angiography, creation of subarachnoid hemorrhage, and protocol

Female mongrel dogs ( $n = 6$ ) weighing 15 to 20 kg were sedated by intravenous injection of sodium pentothal (15 mg/kg) and then intubated and ventilated on oxygen and 1% to 2% isoflurane. They underwent baseline cerebral angiography by catheterization of a vertebral artery to visualize the basilar artery and posterior circulation and by catheterization of one or both internal carotid arteries (ICAs) to visualize the anterior circulation (day 0). Dogs were then turned prone, the cisterna magna was punctured percutaneously with a spinal needle, and 0.3 mL/kg cerebrospinal fluid was allowed to drain spontaneously. Fresh, autologous, arterial, nonheparinized blood (0.5 mL/kg) was injected into the cisterna magna. The cisternal injection was repeated 2 days later. Seven days later (day 7), dogs were placed under general anesthesia and angiography of the

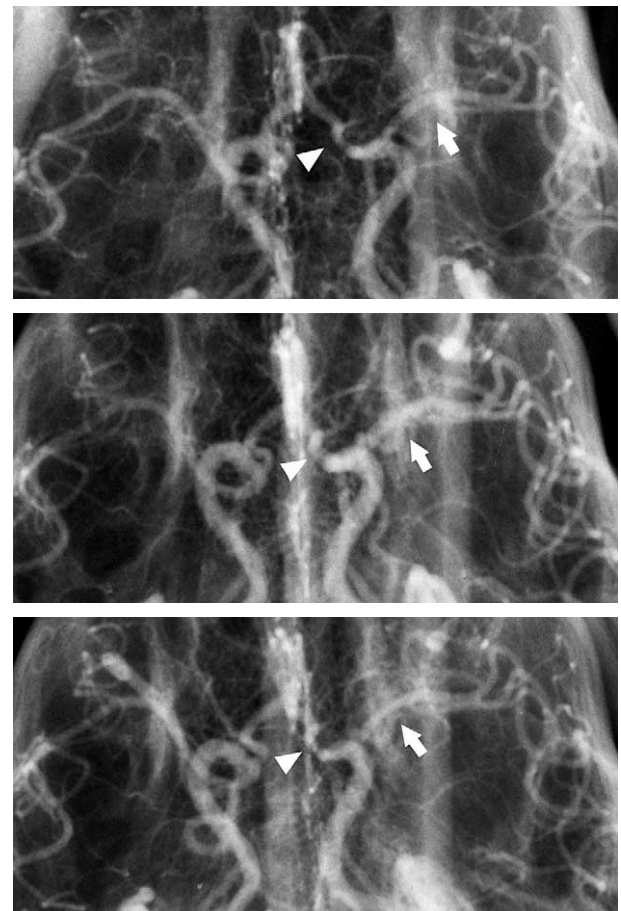


Fig. 2. Photographs of representative anteroposterior cerebral angiograms of a dog taken before stimulation and before exposure of the sphenopalatine ganglion (top), during the second series of stimulations (middle), and 70 minutes after the beginning of stimulation (30 minutes after cessation of the last stimulation, bottom). Arrows show the left MCA, which dilates during stimulation and then returns to a vasospastic diameter after stimulation. Similar changes are observed in the anterior cerebral artery (arrowheads).

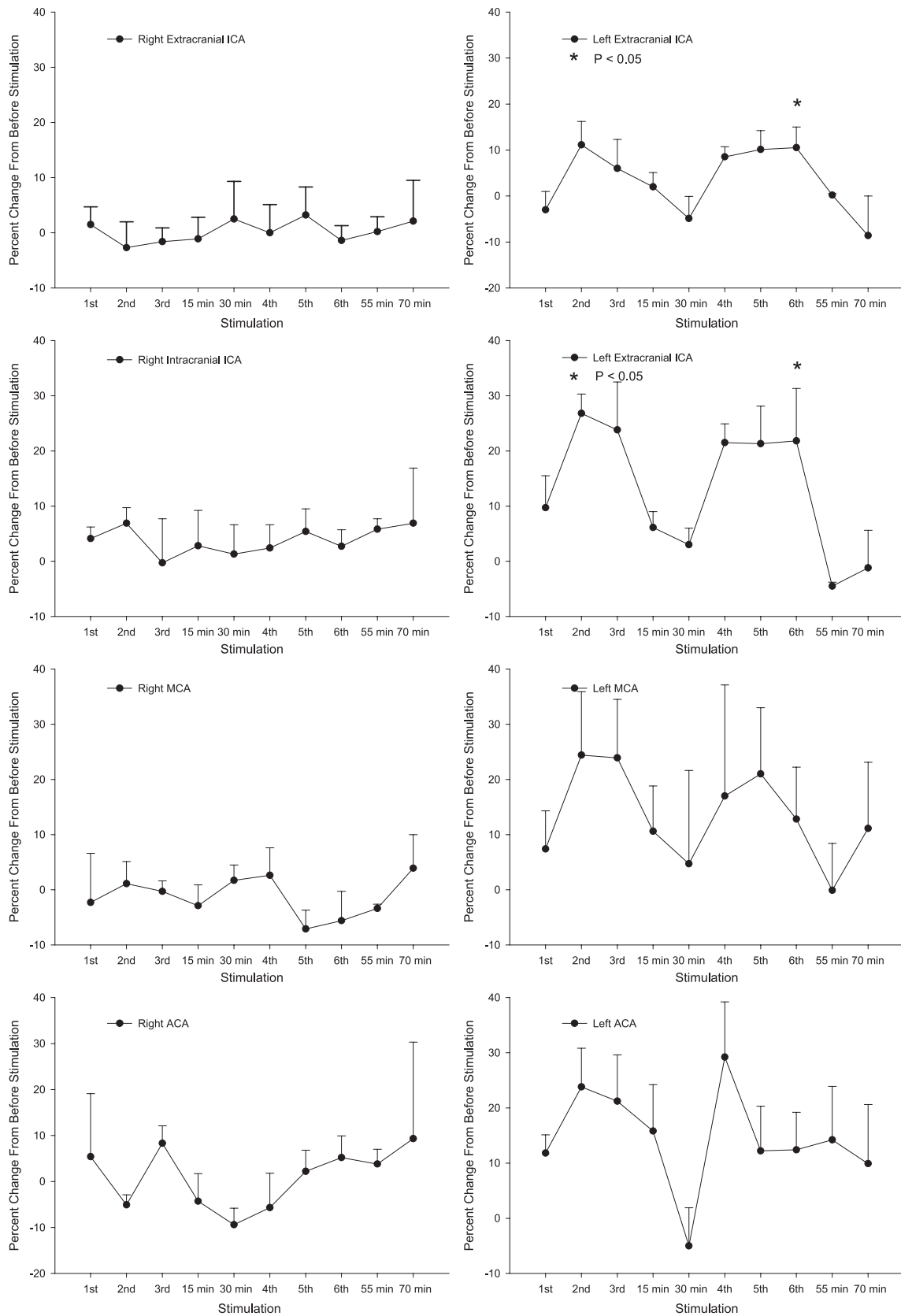


Fig. 3. Graphs of percent change in diameter from before stimulation on day 7 of left (stimulated, left) and right (unstimulated, right) cerebral arteries vs time. There is dilation of the stimulated left arteries during each epoch of stimulation (values are means  $\pm$  SEM,  $n = 4-6$  per point; see text for details).

basilar artery was repeated. Each ICA was catheterized with a Tracker 18 microcatheter (Boston Scientific Cork, Cork, Ireland) and angiography of the anterior circulation was performed by simultaneous injection of contrast into each carotid catheter. Internal carotid angiography was repeated but vertebral angiography was not repeated during the stimulation protocols.

The left sphenopalatine ganglion was then exposed. Angiography was repeated 15 minutes later and the stimulation protocol was then performed. After stimulation, animals were euthanized by perfusion with ice-cold phosphate-buffered saline. Blood pressure, heart rate, arterial blood gases, and body temperature were monitored throughout all procedures and maintained in the physiological range. All radiographs were taken at constant magnification and with uniform exposure factors. All procedures were approved by the Institutional Animal Care and Use Committee.

## 2.2. Exposure of the sphenopalatine ganglion

The left zygomatic arch was exposed and resected and a portion of the underlying retroorbital fat and parotid gland was removed using microsurgical technique. The sphenopalatine fossa was thus exposed and the infraorbital nerve identified. This was retracted inferiorly, exposing the sphenopalatine ganglion. The ganglion was stimulated under direct vision using either a fine, bipolar, concentric stimulating electrode inserted precisely into the ganglion or a bipolar electrode with hooklike ends (Fig. 1).

## 2.3. Stimulation protocol

Stimulation was given at 10 Hz with voltage adjusted continuously in a range of 4 to 6 V to keep the current between 0.8 and 1.4 mA. Two sets of three 90-second sti-

mulations separated by 60-second intervals were administered 30 minutes apart with angiography performed at the end of each 90-second stimulation and 15 and 30 minutes after each cycle (corresponding to 55 and 70 minutes for the second recovery period). The ipsilateral nostril was observed for watery secretion during stimulation.

## 2.4. Measurement of vascular diameters and statistical analysis

Arterial diameters were measured at predetermined points by 2 blinded observers and the results averaged. Data were compared using paired *t* tests (Sigmaplot, SPSS, Chicago, IL) or analysis of variance (ANOVA, Prism, GraphPad Software, San Diego, CA). If significant variance was found, pairwise comparisons were made by Tukey test. A *P* value < .05 was considered significant. Linear regression was performed using the least squares method and fits to lines were performed using the Levenburg-Marquardt algorithm in Sigmaplot. All data are presented as means  $\pm$  SEM.

## 3. Results

### 3.1. Physiological variables

There were no significant changes in blood pressure, heart rate, arterial pH, or PaCO<sub>2</sub> between day 0 and day 7 before, during, or after stimulation (ANOVA, data not shown). Body temperature varied significantly (ANOVA, *P* < .001) with significant pairwise differences between the temperature on day 0 vs on day 7 after stimulation and on day 7 before stimulation vs during stimulation and after stimulation. These changes were due to a decrease in body temperature during the prolonged anesthesia on day 7. The

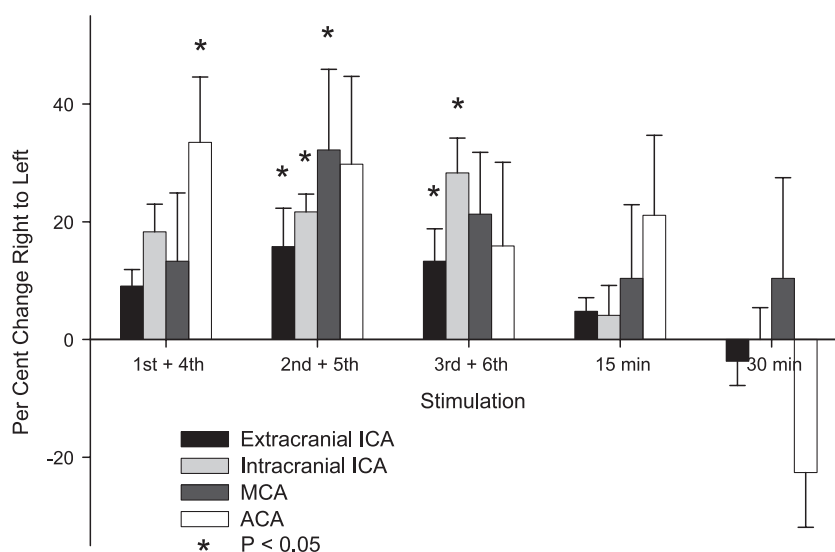


Fig. 4. Bar graph of percent difference in diameter between stimulated left and unstimulated right cerebral arteries for each stimulation and recovery. There was significant dilation of the ACA during the first stimulation (*P* = .05), of the extracranial ICA (*P* = .005), intracranial ICA (*P* < .001), and MCA (*P* = .043) during the second stimulation, and of the extracranial (*P* = .009) and intracranial (*P* < .001) ICA during the third stimulation (paired *t* tests, values are means  $\pm$  SEM, *n* = 8–12 per point).



decrease in temperature would not have a significant effect on angiographic arterial diameters.

### 3.2. Arterial diameters

Subarachnoid hemorrhage was associated with mild to moderate vasospasm of the arteries of the anterior circle of Willis (Table 1). There was significant vasospasm of the right and left middle cerebral arteries (MCAs,  $P < .05$ , paired  $t$  tests). Angiography 15 minutes after exposure of the left sphenopalatine ganglion and after a 3-epoch trial of sham stimulation did not produce any significant changes in arterial diameters (data not shown). Comparisons of diameters of each intracranial artery were made over time. When comparing diameters before exposure of the ganglion to those during the first and second series of stimulations, there was significant increase in diameter of the left extracranial and intracranial ICAs during the second series of stimulation ( $P < .05$ , ANOVA), with pairwise differences between the maximal dilations observed during stimulation and the diameter at 70 minutes (Figs. 2 and 3).

Comparisons between right and left sides at each time were also made. At baseline on day 0 and day 7, both before and after exposure of the ganglion, there were no significant differences between right and left sides. There were significant differences between the right and left sides during the third, fourth, fifth, and sixth stimulations for the intracranial ICA ( $P = .007$ ,  $.039$ ,  $.01$ , and  $.01$ , respectively; paired  $t$  tests), during the fourth stimulation for the anterior cerebral ACA, ( $P = .05$ ), and during the sixth stimulation for the extracranial ICA ( $P = .047$ ). When the 2 sets of stimulation were combined so there were only a first, second, and third stimulation and 15- and 30-minute recoveries, there

were significant differences for the ACA during the first stimulation ( $P = .05$ ); for the extracranial ICA ( $P = .005$ ), intracranial ICA ( $P < .001$ ), and MCA ( $P = .043$ ) during the second stimulation; and for the extracranial ( $P = .009$ ) and intracranial ( $P < .001$ ) ICA during the third stimulation (Fig. 4). The percent increases ranged from  $13\% \pm 6\%$  to  $32\% \pm 14\%$ .

Linear regression was performed to compare the percent reduction in arterial diameters due to vasospasm to the percent dilation that occurred for each stimulation. This was done to determine if stimulation was less effective on more severely vasospastic arteries. There was a significant correlation between degree of vasospasm and of dilation during the first stimulation with greater degrees of vasospasm associated with more dilation (Fig. 5,  $r^2 = 0.31$ ,  $P = .017$ ).

### 4. Discussion

The vasospasm that commonly develops after aneurysmal SAH remains a major clinical problem that causes substantial morbidity and mortality. Current therapeutic maneuvers, such as nimodipine and hemodynamic therapy, principally induced hypertension, may have some efficacy by reducing cerebral ischemia due to vasospasm, but they do not alter the diameters of the spastic arteries. Direct dilation of vasospastic arteries can be achieved by mechanical or pharmacological angioplasty, but these procedures are invasive, associated with substantial risk of complications, and require technical expertise that is not widely available. A simple, effective treatment for vasospasm still is awaited.

The anatomical distribution and functional role of the parasympathetic innervation of the cerebral vessels has been described [7,13,15]. The preganglionic parasympathetic fibers originate in the superior salivatory nucleus and travel first with the facial nerve, and then alone, as the greater superficial petrosal nerve and then the nerve of the pterygopalatine canal or vidian nerve [16]. The latter reaches the sphenopalatine ganglion, residing in the sphenopalatine fossa, where the fibers synapse. The sphenopalatine ganglion is synonymous with the pterygopalatine ganglion in the pterygopalatine fossa, which are the terms usually used to describe the anatomy in primates. The preganglionic neurotransmitter of these fibers is acetylcholine, which acts on nicotinic postganglionic cholinergic receptors. The postganglionic fibers reach the cerebral vasculature, in addition to the lacrimal gland, forehead skin, and nasal mucosa. In the rat, fibers from each ganglion innervate predominately the ipsilateral hemisphere with some innervation also reaching the contralateral hemisphere [13]. In higher animals such as dogs and monkeys, the innervation is only ipsilateral and only to the anterior cerebral circulation [4]. Parasympathetic fibers from the otic ganglion innervate the vertebral and basilar arteries, and this innervation is less dense than that in the anterior circulation. Functionally, stimulation of the sphenopalatine ganglion

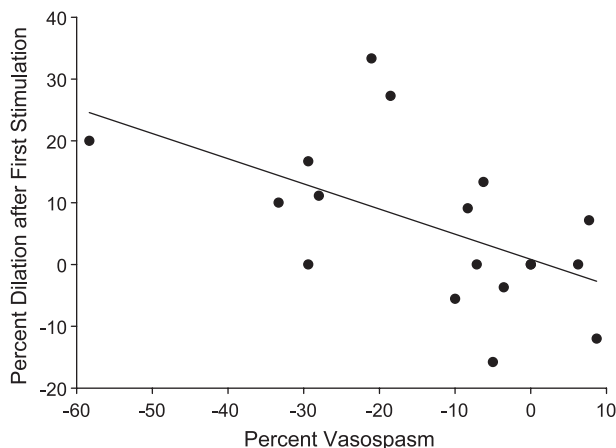


Fig. 5. Graph of correlation between the percent dilation from diameter on day 7 before stimulation of all left arteries during the first stimulation compared with the percent vasospasm present in the same artery. There is a significant positive correlation between the degree of vasospasm and the degree of vasodilation achieved ( $r^2 = 0.31$ ,  $P = .017$ ). Points represent maximal dilation of each measurable ipsilateral intracranial artery (internal, middle cerebral and anterior cerebral) during first stimulation for each of 6 days.

increases ipsilateral cerebral blood flow in cats and rats [3,12] and causes vasodilation of the ipsilateral arteries of the anterior circle of Willis in monkeys, increasing their diameters by 15% to 20% [16]. This dilatation is short-lived and reverses shortly after stimulation is halted. The neurotransmitters released by the postganglionic fibers include nitric oxide, vasoactive intestinal polypeptide, and acetylcholine, as well as other peptides of the vasoactive intestinal polypeptide family such as peptide histidine isoleucine and its human form, peptide histidine methionine [1,2,4,15]. Nitric oxide and vasoactive intestinal polypeptide are known vasodilators of cerebral arteries in vitro. Dilations in vitro and increases in cerebral blood flow in vivo in response to sphenopalatine ganglion stimulation are blocked by antagonists of nitric oxide and by vasoactive intestinal polypeptide antiserum [4].

The present report demonstrates that stimulation of the sphenopalatine ganglion can also induce vasodilation of the vasospastic anterior circle of Willis of the dog. The model used in the study is widely accepted as representative of the vasospasm that develops after SAH in humans [11]. This raises the possibility that stimulation of the sphenopalatine ganglion in humans could reduce cerebral vasospasm. The sphenopalatine ganglion lies in the sphenopalatine fossa in humans, immediately superior to the greater palatine canal. The greater palatine canal is a 2- to 3-cm long, straight bony canal that transmits blood vessels, and the greater and lesser palatine nerves to the palate. The distal foramen of the canal is in the hard palate immediately medial to the third molar.

Limitations of the present results must be acknowledged. The degree of vasospasm of the MCA produced in the dog model is mild to moderate in contrast to the severe vasospasm that occurred in every animal in this series in the basilar artery (unpublished observations). This raises the question as to whether sphenopalatine ganglion stimulation would reverse more severe vasospasm. The finding herein of a relatively direct relationship between the degree of reversal and the severity of vasospasm suggests stimulation might be efficacious against more severe vasospasm. There are additional questions, such as what effects more chronic stimulation would have as a possible preventive measure for vasospasm and whether a beneficial effect would occur by dilation of collateral and leptomeningeal pathways that would reduce the effects of vasospasm but not necessarily be observed angiographically. We did not measure cerebral blood flow in this study, so this remains a matter of speculation. In addition to vasodilation, we have shown that sphenopalatine ganglion stimulation increases the permeability of the blood-brain barrier [18]. While this might be a useful side effect for certain diseases, since it may allow introduction of drugs into the brain, in the context of SAH-induced vasospasm this is of some concern. There may be potential for systemically administered drugs to gain access to the brain. However, if the combination of induced hypertension and

hypervolemia is used in the presence of sphenopalatine ganglion stimulation-induced opening of the blood-brain barrier, it could increase cerebral edema and possibly intracranial pressure.

In conclusion, sphenopalatine ganglion stimulation reverses mild to moderate cerebral vasospasm after SAH in dogs. The robust vasodilatory effect and the potentially simple access to the pterygopalatine ganglion in humans make this approach worthy of investigation in models of vasospasm that produce more severe anterior circulation vasospasm and eventually in humans.

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## Commentary

In this tightly controlled and concisely described study, Yarnitsky et al have shown, at 7 days in a dog 2-hemorrhage model, that stimulation of the sphenopalatine ganglion produces an often significant dilatation of the spastic ipsilateral anterior circulation arteries. This effect is of presumably short duration, with a return more or less to baseline constriction on repeat angiography 15 minutes after each stimulus.

This research is in an early stage at present, but I strongly encourage the authors to continue it in the hope of an eventual clinical application. Future directions are well covered in the “Discussion,” and it would be particularly interesting to see the effect of ganglion stimulation on more severe spasm, whether the effect was maintained with chronic stimulation, and whether there was any effect on cerebral blood flow, or indeed any clinical effect.

The article is perhaps rather unfair on fluids and nimodipine. Although there is, as noted, certainly little influence of these on established angiographic spasm, the incidence of vasospasm and delayed ischemia with prophylactic fluid loading and nimodipine (Is the intravenous preparation, used more outside North America, more effective than oral?) is most probably lower, and outcome is definitely improved [1]. Certainly, most older neurosurgeons would agree that we now see very much less of the devastating deterioration that was common 25 years ago.

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If the doctors cure  
 then the sun sees it.  
 If the doctors kill  
 then the earth hides it.  
 The doctors should fear arrogance  
 more than cardiac arrest

—Anne Sexton (1928–1974), U.S. poet. “Doctors.”