Coronary Vascular Response to the Cerebral Ischemia Reflex

Stefan L. De Boel and David D. Gutterman

Most centrally mediated sympathoexcitatory reflexes produce increases in arterial pressure, heart rate, and peripheral vascular resistance, including coronary vasoconstriction. Cerebral ischemia also causes large increases in arterial pressure and peripheral vasoconstriction but with modest or variable changes in heart rate. To examine the effect of cerebral ischemia on coronary vascular resistance, we produced cerebral ischemia in 14 cats by occluding the right brachiocephalic and left subclavian arteries for 30 seconds. After vagotomy and \( \beta \)-blockade, a marked increase in arterial pressure (89±14%) and coronary vascular resistance (52±7%) was seen. After inhibition of the carotid baroreceptor reflex by surgical denervation and application of topical lidocaine, the increase in arterial pressure to cerebral ischemia was not affected, but the increase in coronary vascular resistance was attenuated (33±6%; \( p<0.05 \) versus before denervation) to a level expected with autoregulation. To evaluate the possible contribution of the chemoreflex on coronary blood flow during cerebral ischemia, we conducted separate experiments in which nicotine was injected into both carotid arteries. Coronary constriction was not observed. Adrenalectomy and upper extremity ischemia likewise did not alter coronary vascular resistance. We conclude that cerebral ischemia elicits neurally mediated coronary vasoconstriction as a result of baroreceptor hypotension rather than directly. The relative absence of neurogenic coronary constriction and changes in heart rate suggest that sympathoexcitation during cerebral ischemia is directed more toward the peripheral vasculature than the heart. (Hypertension 1993;21:216–221)

Key Words • vasoconstriction • pressoreceptors • sympathetic nervous system • cerebral ischemia

A variety of reflex stimuli produce \( \alpha \)-adrenergic-mediated coronary vasoconstriction. Baroreceptor hypotension, \(^1\) activation of carotid chemoreceptors, \(^2\) and nociceptive reflexes, \(^3\) as well as static and dynamic exercise, \(^4\) all increase systemic arterial pressure, heart rate, and coronary vascular resistance through sympathetic activation.

Cerebral ischemia, produced by interruption of perfusion to the head, is a potent stimulus for sympathetic discharge. However, unlike most sympathoexcitatory reflexes, tachycardia is not a consistent feature of the ischemic response. The effect of cerebral ischemia on coronary flow is difficult to predict. The large pressor response to cerebral ischemia suggests that neurogenic coronary constriction accompanies the sympathoexcitation. However, other sympathoexcitatory reflexes producing coronary constriction include tachycardia. Bradycardia typically accompanies cerebral ischemia. This dissociation between cardiac and peripheral vascular responses suggests that coronary vasoconstriction may not occur as a result of cerebral ischemia. Therefore, we tested the hypothesis that coronary vasoconstriction is a component of the cerebral ischemic response.

Methods

Preparation

General. Experiments were performed on 14 mongrel cats (weight, 3.5–5 kg) of either sex. Anesthesia was induced with halothane and maintained with \( \alpha \)-chloralose (100 mg/kg i.v. with 30 mg/kg supplements as needed). The trachea was cannulated and cats were mechanically ventilated (Harvard respirator). Ventilatory rate, intravenous sodium bicarbonate, and supplemental oxygen were used to maintain pH between 7.35 and 7.45, Po\(_2\) between 80 and 100 mm Hg, and Pco\(_2\) between 35 and 45 mm Hg. A polyethylene catheter was placed in a femoral artery for continuous recordings of blood pressure and heart rate (derived from a cardiotachometer). A right brachial arterial catheter was used for measurements of arterial pressure during aortic constriction using an aortic snare. Core temperature was maintained at 37°C by a thermostatically regulated heating pad. The vagal nerves were sectioned in the neck, and propranolol was administered (1.5 mg/kg i.v.) to exclude efferent parasympathetic and \( \beta \)-adrenergic influences on the myocardium and coronary vasculature, respectively.
A left thoracotomy was performed and the pericardium incised to expose the epicardium. The right brachiocephalic and left subclavian arteries were identified, and vascular occluders were loosely secured around the proximal segments of these arteries. Umbilical tape was placed around the descending thoracic aorta to form a snare. Coronary blood flow velocity was measured with a specially designed Doppler flow probe described previously. This probe consists of a 20-mHz piezoelectric crystal housed in a Silastic dome and is attached to the left anterior descending coronary artery by suction. Changes in coronary blood flow velocity are recorded on-line with an electronic signal analyzer (University of Iowa Bioengineering). Previous studies have shown that changes in coronary blood flow velocity measured by Doppler correlate well with changes in volumetric flow measured by electromagnetic flow probes, radiolabeled microspheres, and timed venous sampling in several species. Percent changes in coronary resistance index were calculated from simultaneous measurements of mean arterial pressure and coronary blood flow velocity, $\%CVRI = \left(\frac{\%AAP + 100}{\%ACBFV + 100} - 1\right) \times 100$, where CVRI is the coronary vascular resistance index, AAP is the change in mean arterial pressure, and CBFV is coronary blood flow velocity.

Carotid baroreceptor denervation. Interruption of neural input from the carotid sinuses was achieved by bilateral surgical transection of the exposed carotid sinus nerves and adjacent exposed nerve tissue. In addition, viscous 2% lidocaine was applied topically to the region of the carotid sinuses. Although the efficacy of carotid baroreceptor denervation was not directly tested, the method used was complete. Other studies using similar but less thorough denervation techniques have demonstrated effective baroreceptor denervation.

Provocation of cerebral ischemia. To produce cerebral ischemia, we used an approach modified from the method of Guyton in dogs. Vascular occluders were secured proximally around the right brachiocephalic and left subclavian arteries. During occlusion, all blood flow to the head, as well as most of the flow to the forelimbs, was interrupted. In preliminary experiments made to validate our technique for production of cerebral ischemia, we measured perfusion to the brain stem and cerebrum in two animals using radiolabeled microspheres. Measurements were made before vascular occlusion, after brachiocephalic and left subclavian artery occlusion, and after occlusion of both subclavian and vertebral arteries. Cerebral blood flow to all brain regions was virtually absent during vascular occlusion, validating these two methods of inducing cerebral ischemia (Figure 1).

Experimental Protocol

Cerebral blood flow was interrupted for 30 seconds by occlusion of the brachiocephalic and subclavian arteries. Coronary blood flow velocity, arterial pressure, and heart rate were measured and collected on computer at 1-second intervals for 40 seconds, beginning 5 seconds before cerebral ischemia. Changes from baseline in these parameters were measured, and the maximum change in coronary vascular resistance index was calculated (usually after 25 seconds of vascular occlusion). The peak increase in coronary vascular resistance (averaged over 4–5 seconds) was used for data analysis.

The carotid baroreceptors were then denervated, and hemodynamic responses to 30 seconds of cerebral ischemia were again recorded in all nine animals.

Statistics

Comparisons between baseline heart rates and arterial pressures were made using Student’s t test. Changes in coronary vascular resistance were compared with a nonparametric analysis (Wilcoxon rank sum test). Statistical significance was defined at a value of $p<0.05$. Data are presented as mean±SEM.

Results

After vagotomy and propranolol, interrupting cerebral blood flow for 30 seconds caused a marked and sustained increase in arterial pressure (peak, 89±14%) (Figures 2 and 3) and no significant change in heart rate. Coronary vascular resistance increased (52±7%), with the peak increase occurring between 20 and 25 seconds into the stimulus. The pressor response to cerebral ischemia was reproducible over multiple stimulations (Figure 4), indicating the absence of tachyphylaxis or functional collateral recruitment. Although in this example baseline arterial pressure decreased between the first and fifth occlusions, the baseline arterial pressures were similar before each of the inductions of cerebral ischemia at which statistical analyses were made (Figure 3).

After bilateral carotid sinus denervation, the pressor response to cerebral ischemia was preserved (75±11%).
FIGURE 2. Tracings show effect of carotid sinus denervation on the hemodynamic response to cerebral ischemia. Phasic tracings are shown in the first panel. Second panel shows the hemodynamic response to 30 seconds of right brachiocephalic and left subclavian artery occlusion (BSO), which includes coronary vasoconstriction. After bilateral carotid sinus denervation (third panel), the pressor response to cerebral ischemia is preserved, while the coronary constriction is greatly attenuated. HR, heart rate; bpm, beats per minute; AP, arterial pressure; CFV, coronary flow velocity; CR, coronary resistance.

Our method of inducing cerebral ischemia likely produced significant ischemia to the forelimbs. This could conceivably alter coronary blood flow, either through an ischemic reflex or through its effect on systemic vascular resistance. Therefore, in three separate experiments, we occluded only the brachial arteries, recording arterial pressure and coronary blood flow velocity. No change from baseline was observed (Figure 5). Thus, impairment of flow to the upper extremities does not account for the hemodynamic changes seen during cerebral ischemia.

In four animals, surgical adrenalectomy (Figure 6) reduced baseline mean arterial pressure (76±10 mm Hg before, 58±3 mm Hg after). During provocation of cerebral ischemia, the mean arterial pressure increased but the coronary constriction was markedly attenuated (33±6%). To test whether the remaining increase in resistance was due to a residual neural response or could be attributed to the concurrent elevation in arterial pressure, we accomplished mechanical elevation of arterial pressure using an aortic snare. By mimicking the same magnitude and rate of rise in arterial pressure with a snare, coronary resistance rose 31±5% (p<0.05 versus cerebral ischemia; p=NS versus cerebral ischemia after carotid sinus denervation). Thus, the increase in coronary resistance to cerebral ischemia after baroreceptor denervation can be fully accounted for by autoregulation to a level similar to that seen with mechanical elevation of arterial pressure (31±5%; p<0.05 versus cerebral ischemia; p=NS versus cerebral ischemia after carotid sinus denervation) (Figure 3).

FIGURE 3. Bar graphs summarize the effect of cerebral ischemia on arterial pressure (AP) and coronary resistance before and after carotid sinus denervation, and effect of cerebral ischemia produced by ligation above the carotid baroreceptors. Left panel: There is no difference among pressor responses to right brachiocephalic and left subclavian artery occlusion (BSO) before or after carotid sinus denervation or to BSO above the baroreceptors. Right panel: When carotid sinus activity is not further deactivated (denervation; BSO above baroreceptor), the coronary vasoconstriction to BSO is at a level expected from autoregulation alone (see text). With the carotid baroreceptors intact and deactivated during BSO, coronary resistance rises. All data are mean±SEM. HR, heart rate; bpm, beats per minute.
by 75±17% before and by 58±9% after adrenalectomy (p=NS). Coronary resistance increased by 38±8% and 42±10% (p=NS), respectively.

After intracarotid injection of nicotine (n=4), a rise in arterial blood pressure of 54±7% (from a baseline mean arterial pressure of 80±6 mm Hg) and an increase in coronary resistance (27±6%) were observed. During mechanical elevation of mean aortic pressure to a similar degree (54±7% from a baseline of 82±7 mm Hg), the increase in coronary resistance was 28±4% (p=NS versus nicotine).

Discussion
The present study demonstrates two novel findings. First, coronary vasoconstriction does occur during cerebral ischemia. Second, coronary constriction to cerebral ischemia is the result of reflex inhibition of baroreceptors or is due to an interaction between baroreceptor activity and cerebral ischemia rather than to a direct effect of cerebral ischemia, because the constriction is attenuated to autoregulatory levels after carotid sinus denervation. The discussion will focus on several methodological considerations important to the interpretation of results as well as the physiological importance of these findings.

Statistical Analysis
Although the changes in arterial pressure and coronary resistance to bilateral brachial arterial occlusions were very small, it is possible that a type II error might exist. Similar caution in interpretation should be noted for studies involving intracarotid administration of nicotine and adrenalectomy.

Method of Inducing Cerebral Ischemia
The cerebral ischemic response has been elicited by occluding several combinations of cerebral blood vessels.10-13 A species-specific approach is mandated in view of the variation in vascular communications between the vertebral and carotid circulations. These connections are most extensive in dogs, less prominent in cats, and least developed in rabbits.14 Our approach of ligating the right brachiocephalic and left subclavian arteries interrupted all blood flow to the head. Perfusion to several brain regions (microspheres) was demonstrated to be nearly zero during this method of vascular occlusion. Thus, collateral flow from other arterial vessels was minimal.

Method of Measuring Coronary Blood Flow
Measuring coronary blood flow velocity through epicardial coronary vessels has two major advantages.
Physiological Importance

Cerebral ischemia elicits a powerful pressor response that is due to large increases in peripheral resistance secondary to neurogenic vasoconstriction. Other centrally mediated reflexes, including baroreceptor reflex, chemoreflex, nociceptor reflexes, exercise, cold pressor test, myocardial ischemia, and behavioral stress produce increases in arterial blood pressure and coronary vasoconstriction, which is often marked. In the present study, coronary vasoconstriction was observed during cerebral ischemia, but the neurogenic component of this vasoconstriction resulted from concurrent changes in baroreceptor activity and was not an independent effect of cerebral ischemia.

The reason for this lack of direct neurogenic coronary vasoconstriction to cerebral ischemia is not clear. It is of interest that most sympathoexcitatory reflexes activate both cardiac and vascular systems, resulting in tachycardia and peripheral vasoconstriction. Cerebral ischemia produces peripheral vasoconstriction often with bradycardia in anesthetized preparations. Thus, sympathoexcitation during cerebral ischemia appears directed relatively more toward the peripheral vasculature than the heart. This provides support for the idea that sympathetic innervation of the coronary arteries is more closely coupled to that of the heart than to that of the remaining peripheral vasculature. These findings support previous observations that tachycardia is a consistent finding during activation in central sites that produce coronary vasoconstriction.

In conclusion, neurally mediated coronary vasoconstriction occurs to experimentally induced cerebral ischemia. However, this coronary constriction is dependent on the concurrent baroreceptor response to carotid artery hypotension.

Acknowledgments

We acknowledge the excellent technical assistance of Angie Goodson and the secretarial support provided by Marlene Blakley.

References


Coronary vascular response to the cerebral ischemia reflex.
S L De Boel and D D Gutterman

Hypertension. 1993;21:216-221
doi: 10.1161/01.HYP.21.2.216

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/21/2/216

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/