Central Neural Control of Blood Pressure and Cardiac Arrhythmias During Subarachnoid Hemorrhage in Rats

P.S. Lacy, Ph.D., and A.M. Earle, Ph.D.

SUMMARY Sudden death may follow subarachnoid hemorrhage which indicates involvement of neural mechanisms connected with the cardiovascular system. Since various regions of the brain mediate blood pressure and heart rate changes, these parameters and heart rhythm could be affected due to a subarachnoid hemorrhage near the circle of Willis which surrounds the hypothalamus, the highest center for autonomic control. To investigate this in the control group, intracranial pressure, blood pressure, and electrocardiogram were measured before and after a simulated subarachnoid hemorrhage; blood pressure and electrocardiogram were measured following midcollicular lesions in the decerebrate group both before and after a subarachnoid hemorrhage. The results demonstrate that an increase in systemic arterial blood pressure and premature ventricular contractions (with respect to unlesioned group, p < 0.04) are mediated by forebrain areas and require the integrity of neuroanatomical connections with structures that are caudal to the midbrain. Since bradycardia and other electrocardiographic abnormalities could still be produced after midcollicular lesioning it is suggested that they can be mediated via the brainstem only without involvement of more rostral areas and may occur due to increased intracranial pressure.

METHODS

Male Sprague-Dawley rats between 300–350 g in weight were anesthetized with 1.2–1.6 g/kg of urethane administered intraperitoneally. The animals were divided into two groups. Group 1 contained sixteen animals from whom ECG was recorded from lead II using rust proof brass safety pins as electrodes that were pinned onto the muscle from over the skin on the chest. The ground electrode was placed over the neck. The femoral artery was cannulated with a 6 inch long piece of polyethylene tubing (Intramedic, PE50 Clay Adams). SAH was experimentally produced as described earlier. The animal was placed in a stereotaxic apparatus. A small burr hole was drilled in the left lateral frontal bone at its widest point, approximately 10 mm anterior to the interaural line (slightly posterior to the os frontale in the rat) on the dorsal surface of the skull in order to simulate a SAH and to record ICP. The hole was drilled as far laterally on the dorsal surface of the skull as was possible (3.4 mm lateral to the mid-sagittal line). The position of the hole corresponded to the junction of the olfactory lobes with the frontal lobes. Approximately 1.6 cm was marked on a 15 cm long piece of silastic tubing (0.020 inch I.D. × 0.037 inch O.D.) which was led through the burr hole along the left lateral surface of the brain until it touched the base of the skull. Using the base of the skull as an indicator of appropriate depth and direction 1.6 cm of the silastic tubing was then manually pushed posteromedially to direct the tip of the cannula in the area of the circle of Willis. The burr hole was just large enough (approximately 1 mm. diameter) so that the silastic tubing could fit tightly in the hole. The hole with the silastic tubing in place was sealed and held in place with five-minute epoxy or super glue applied on the dry skull. Blood was drawn into a heparinized syringe by cardiac puncture from a littermate and was
introduced through the silastic tubing in the region of the circle of Willis. Between 0.2–0.5 ml of blood was required to produce bradycardia and arrhythmias, the volume needed differed with individual rats. Rats that did not respond to up to 0.5 ml of blood by producing heart rate and rhythm changes were excluded from this study as experience showed that nonresponsiveness was due to misplacement of tip of the cannula. If the tip is not directed postero-medially blood tends to flow towards the orbit with subsequent bulging of eyeball and no change in heart rate or rhythm. Using this model three other situations have been observed which do not generate bradycardia and arrhythmias; these are the following positions of the tip of the cannula; 1) epidural 2) intracerebral and 3) in the posterior cranial fossa thereby draining blood into the spinal subarachnoid space. The silastic tubing through which blood was introduced into the cranial cavity was connected via a three-way stopcock to a Hewlett-Packard 780-9 transducer and patient monitor which was in turn connected to a Honeywell 1508B Visicorder for recording ICP. The same silastic tubing was therefore used for introducing blood and for recording ICP from the subarachnoid space. The PE50 cannula in the femoral artery was similarly connected to a Hewlett-Packard 780-9 transducer and patient monitor as well as to the Honeywell 1508B Visicorder for recording arterial BP. ECG and BP were recorded on photosensitive rapid access type instrumentation recording paper (Eastman Kodak Co., Rochester, N.Y.). The transducers used for recording ICP and BP were calibrated via a three-way stopcock to a Hewlett-Packard 780-9 transducer and patient monitor which was in turn connected to a Honeywell 1508B Visicorder for recording ICP. The same silastic tubing was therefore used for introducing blood and for recording ICP from the subarachnoid space. The PE50 cannula in the femoral artery was similarly connected to a Hewlett-Packard 780-9 transducer and patient monitor as well as to the Honeywell 1508B Visicorder for recording arterial BP. ECG and BP were recorded on photosensitive rapid access type instrumentation recording paper (Eastman Kodak Co., Rochester, N.Y.). The transducers used for recording ICP and BP were calibrated using a sphygmomanometer. Group 2 contained fifteen rats who were to receive midcollicular lesions. ECG and BP were recorded before making midcollicular lesions. ECG and BP was recorded in eight animals while only ECG was recorded in the remaining seven rats. The details for recording ECG and BP and for simulating an acute SAH were the same as described for animals in Group 1. In order to produce lesions across the midcollicular region many burr holes placed adjacent to each other in the coronal plane were drilled in the skull anterior and adjacent to the lambdoid suture extending approximately 3 to 4 mm laterally on both sides of the midline. The depth of the lesion to be made was calculated by directing a needle electrode to the base of the skull and then retracting the electrode 1.5 mm from the base. The base of the brain was not lesioned. An uninsulated, monopolar, nickel-steel electrode of 0.7 mm diameter was connected to a Grass LM4 lesion maker. A lesioning current of 10 milliamperes for 10 seconds was delivered through the electrode. The electrode was then moved 1 mm laterally and another electrolytic lesion was made. This procedure was repeated over the entire area to be lesioned, extending from the left side to the right side of the brain to ensure complete destruction of the fibers. The hole was then filled with gelfoam and bone wax. ECG and BP was recorded after 15 minutes after making midcollicular lesions. Blood was then introduced into the subarachnoid space as described for animals in Group 1.

The experiment (Group I and Group II) was terminated by perfusing the animal through the left ventricle with 0.9% saline followed by 10% formalin. The position of the tip of the cannula and accumulation of blood in the subarachnoid space on the ventral aspect of the brain was verified on autopsy in each animal. To determine the position of the lesion in Group II animals all brains were removed and stored in a jar containing 10% formalin for a week and subsequently sectioned in the sagittal plane to determine both the position and the depth of the lesion. These sections were not stained as the depth and position of the lesion could be visually determined.

Statistical Analysis: Data obtained on the incidence of cardiac arrhythmias from the control group and the decerebrate group of rats was analyzed by Fisher's exact test, which was used for determining the probability values. The significance was determined by a p value of 0.05 or less.

Results

Heart rate varied from 300 beats/minute to 420 beats/minute before simulating a SAH. Mean heart rate in the control group was 350 ± 40.98 beats/minute and 340 ± 45.28 beats/minute in the midcollicularly lesioned (decerebrate) group prior to SAH. All animals subjected to midcollicular lesioning were moribund 30 minutes after a SAH. Resting arterial BP, heart rate and rhythm showed no change or abnormality after the brain was lesioned between the superior and inferior colliculi in the same animal (figs. 1A and 1B), and in the decerebrate group (n = 7, BP prior to decerebration = 83.65 mm ± S.D. 9.07, BP following decerebration = 81.77 mm ± S.D. 9.5). Only a decrease in blood pressure was observed after SAH in the decerebrate group (statistically not significant from pre-decerebrate values) in contrast to the controls of Group I which showed a hypertensive response (n = 6, BP pre-SAH = 97.71 mm ± S.D. 22.42, BP after SAH = 119.33 mm ± S.D. 22.16, p < 0.05). Figure

**Figure 1.** Sections A, B and C each represents BP and ECG in a rat recorded before and after decerebration and following SAH respectively. (Time scale is the same for A, B and C.) A and B show that heart rate and BP do not change after midcollicular lesioning. C shows junctional rhythm and decrease in blood pressure after SAH in the same animal.
TABLE 1  Incidence of Cardiac Arrhythmias in Normal and Decerebrate Rats after a Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control group n = 16</th>
<th>Decerebrated group n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Biphasic P and absent P</td>
<td>10</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Sinus arrhythmia</td>
<td>5</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>ST elevation</td>
<td>4</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Changes in T wave</td>
<td>8</td>
<td>6 (54%)</td>
</tr>
<tr>
<td>Inverted T wave</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Premature atrial contractions</td>
<td>7</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Premature ventricular contractions</td>
<td>6</td>
<td>0*</td>
</tr>
<tr>
<td>Junctional rhythm</td>
<td>9</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>2° heart block</td>
<td>4</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>A-V dissociation</td>
<td>4</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>QT/QRS prolongation</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>QT/QRS shortening</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Idioventricular rhythm</td>
<td>2 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.04.

1C, a record from the same animal as Fig. 1A and 1B shows that after midcollicular lesioning and SAH, only a decrease in blood pressure with junctional rhythm occurred; no increase in systemic arterial BP was observed to precede the decrease in heart rate. Systemic blood pressure decreased in both the intact and decerebrate animals e.g., figure 1C from one decerebrate animal after onset of bradycardia and other ECG abnormalities following SAH. A variety of ECG changes were observed in both the control animals and decerebrate rats after SAH (table 1). Thirteen (87%) of the decerebrate rats showed ECG abnormalities after SAH (table 1). Figure 2 shows examples of some of the ECG abnormalities seen in decerebrate animals after an experimental SAH. Table 1 shows the relative incidence of ECG abnormalities seen in intact and decerebrate animals after a SAH. The only statistically significant difference between the two groups regarding the occurrence of any one type of arrhythmia was that no premature ventricular contractions (PVCs) were observed after SAH in the decerebrate group whereas 6 (37%) animals developed it in the control group. The difference was statistically significant at p < 0.04 for PVCs only for the two groups. It is unlikely that the absence of hypertension and premature ventricular contractions was due to non-specific effects of the lesion on the central nervous system since bradycardia and other arrhythmias observed in the control group could be produced in the decerebrate animals.

Spontaneous pulsations in intracranial pressure or plateau waves were occasionally observed in the control group in which ICP was monitored. Examples are shown in figures 3A and 3B. Figure 3A shows a slight increase in BP which was initiated following an ICP pulse. Figure 3B shows a premature ventricular contraction that follows a spontaneous pulsation in ICP in a non-decerebrate animal.

The position and depth of the midcollicular lesion is shown in figure 4. The results reported here are of those animals in whom the tip of the cannula rested in the subarachnoid space near the circle of Willis under the ventral aspect of the brain. The brains did not show parenchymal injury on visual examination.

Discussion
Suprabulbar 3, 6, 10, 11, 27, 32 and bulbar 5, 20, 26, 29, 31, 32 neural regions have been implicated in cardiovascular function.7 Severance of cardiovascular connections between the brainstem and more rostral regions by midcollicular lesioning showed in this study that the sys-

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Examples of cardiac arrhythmias in decerebrate animals after SAH. A shows sinus bradycardia, B shows complete heart block, C shows the appearance of sinus bradycardia again with a widening of QRS complexes, and D shows idioventricular rhythm in the first portion of the record followed by junctional rhythm which again reverts to idioventricular rhythm.

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Spontaneous pulsations in intracranial pressure in non-decerebrate animals after SAH. A shows a small pulse in ICP which precedes an increase in systemic arterial BP indicated by a solid black horizontal line. Arrowhead indicates the peak increase in BP during the decline in ICP pulse. ECG and heart rate are normal. B shows bradycardia, a supraventricular premature beat during the ICP wave and a premature ventricular contraction which occurs after the ICP wave.
tomic arterial BP did not change significantly in decerebrate cats. These findings are in agreement with those of other investigators, among others, who observed that midcollicular lesioning alone (without SAH) did not change the resting arterial BP and an apparently normal control of BP was maintained if the communications were interrupted between the medulla oblongata and more rostral areas of the brain. The initial hypertensive response observed in the control group after SAH could not be elicited in the decerebrate group which showed hypotension only (statistically not significant). The abolition of the hypertensive response due to midcollicular lesions in rats indicates that areas more rostral to the midbrain are essential for its occurrence and require the integrity of the neuroanatomical connections between suprabulbar and bulbar structures after SAH in the area of the circle of Willis. Pressor and depressor effects are known to be mediated by noradrenergic neurons, in the suprabulbar and bulbar regions. Two central pathways having opposite effects, namely, an excitatory hypothalamic and an inhibitory bulbar pathway has been suggested by Haeusler. Our observations indicate an excitatory input from suprabulbar regions to be responsible for the increase in BP observed after SAH in 'control' rats which is abolished following decerebration. Besides the studies mentioned earlier, experimental studies that employed arrhythmogenic drugs, like cardiac glycosides and picrotoxin have shown that forebrain areas and most likely the posterior hypothalamus are involved in producing an increase in arterial BP. The absence of premature ventricular contractions after SAH in decerebrate cats indicates the participation of areas rostral to the midbrain in their occurrence (Table 1). The integrity of neuroanatomical connections between the suprabulbar and bulbar structures is therefore implicated in causing PVCs following SAH near the circle of Willis as 37% animals of the control group developed PVCs. The occurrence of PVCs via the sympathetic nervous system has been previously reported. Helke et al observed that decerebrate cats required a larger dose of deslanoside to produce ventricular arrhythmias than control animals which implicated forebrain noradrenergic mechanisms in the production of ventricular arrhythmias.

The bradycardia observed in rats after decerebration cannot be attributed to a reflex decrease as no increase in BP was observed in these animals. Other ECG abnormalities seen in control rats, e.g. absence and inversion of P waves, changes in the shape and size of T waves, junctional rhythms, second degree heart block and A-V dissociation were also seen in decerebrate rats after SAH. To our knowledge the base of the midbrain which was left intact during decerebration does not conduct autonomic fibers connected with the cardiovascular system. The above mentioned arrhythmias and bradycardia are therefore attributed to areas caudal to the midbrain e.g. pons and/or medulla. It is probable that the above changes may be due to a global increase in intracranial pressure only, since earlier observations showed that both saline and blood could induce bradycardia and ECG abnormalities when introduced into the cisterna magna. Evidence suggests that neural activity in the brain stem becomes suppressed following an increase in ICP produced by infusing blood and saline solution in the cisterna magna of rats with resultant bradycardia and supraventricular extrasystoles. Suppression of neural conductance and activity following an increase in ICP has also been reported by other workers. In this study since no neurophysiological recordings were made it is suggested that either suppression or excessive neural activity in the cardiovascular centers in the brainstem may be a probable cause of bradycardia and ECG abnormalities observed. Since the brainstem has both sympathetic and parasympathetic cardiovascular centers an imbalance in activity in the two divisions of the autonomic nervous system may be the cause of arrhythmias (except PVCs) which may not require the participation of the autonomic centers of the forebrain.

It is concluded that participation of areas rostral to the midbrain are essential for producing hypertension and premature ventricular contractions under conditions of a simulated SAH in the area of the circle of Willis in rats; the brainstem alone can produce bradycardia and other arrhythmias.

Acknowledgments

The help given by Drs. Alan Forker and David McCall of the Division of Cardiology in identification of arrhythmias is very gratefully acknowledged. The authors express appreciation to Mr. W.L. Bradon for assistance with the illustrations.

References

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FIGURE 4. A sagittal section of a fixed rat brain showing position and the vertical extent (arrows) of the electrolytic lesion at the midcollicular level sparing the base of the brain. SpC denotes spinal cord, CL is cerebellum, P is pons, IC is inferior colliculus and SC is superior colliculus.


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Central neural control of blood pressure and cardiac arrhythmias during subarachnoid hemorrhage in rats.
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Stroke. 1985;16:998-102
doi: 10.1161/01.STR.16.6.998

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