Discussion

Automatic sampling of end-tidal $^{18}$Xe has a number of distinct advantages over manual or computer analysis of continuously sampled curves. Because the sample remains within the radiation-counting cell for a finite period of time, counts can be accumulated between breaths. This results in higher count rates, improved counting statistics, and a possible reduction in the isotopic dose needed to achieve a statistically reasonable number of counts. Also, automated sampling provides on-line computation of rCBF and renders editing of "bad" points a rather simple process. While computer programs can be written to select samples from a continuous curve, the programming may be quite cumbersome.

Our automatic sampling timer can be easily constructed for approximately $100. A detailed circuit diagram is presented in figure 5. It provides variable controls to match conditions existing in patients with widely differing patterns of ventilation. The inhibit control rejects poorly timed samples and reduces the need for excessive data editing, while the delay control permits synchronization with a respirator. In contrast to previous instruments that are limited to spontaneous breathing, the present system can be readily adapted to mechanical ventilation.

References


Cardiac Arrhythmias in Experimental Subarachnoid Hemorrhage

BRUNO V. ESTANOL, M.D., MAURO V. LOYO, M.D., J. HUMBERTO MATEOS, M.D., ENRIQUE FOYO, M.D., ALFREDO CORNEJO, M.D., AND JAVIER GUEVARA, M.D.

SUMMARY Experimental subarachnoid hemorrhage (SAH) in dogs was produced by introducing blood into the subarachnoid space through a catheter connected to an artery of the animal. The intact animals and those with preserved vagi and heart sympathetic innervation, developed arrhythmias with short latencies which correlated with the sudden increase in the intracranial pressure. The animals with sections of both vagi and heart sympathetic innervation, but with an intact spinal cord, developed arrhythmias that were delayed and did not correlate with the changes in intracranial pressure. These arrhythmias were preceded by changes in the QT interval, T wave and ST segment. It was concluded that the arrhythmias could be produced either by direct autonomic discharges to the heart or by increased circulating and tissue catecholamines. The clinical implications of these findings are discussed.

IN 1930, BEATTIE et al. published a series of remarkable observations showing that extrasystolic arrhythmia, induced by chloroform anesthesia in the cat, could be prevented either by the combination of sectioning sympathetic nerves to the heart and removal of the adrenal glands or by destruction of the hypothalamus. This important work was largely ignored and it is only now that its relevance can be fully appreciated. That cardiac arrhythmias could occur as a consequence of acute cerebral lesions, was suspected in 1936 when Bramwell published a paper with the question: "Can head injury cause auricular fibrillation?" Although later reports mentioned the presence of cardiac arrhythmias in subarachnoid hemorrhage the fact that these could be life threatening was not emphasized until 1973 when Parize described two patients with ventricular tachycardia. He made the point that these patients might have died had they not been correctly diagnosed and treated in a coronary care unit when the arrhythmia occurred. A recent report has emphasized the severity of subarachnoid hemorrhage (SAH) with associated cardiac dysrhythmia and the high incidence of sudden unexpected death in primary subarachnoid hemorrhage presumably due to arrhythmia. In 1947, Byer et al demonstrated that abnormal ECGs characterized by large upright T waves and prolonged QT intervals, could be seen in patients suffering from acute intracranial diseases, particularly subarachnoid hemorrhage secondary to ruptured aneurysms. Since that time, several authors have confirmed and extended their observations. Since the original description by Beattie et al., a number of experimental observations have confirmed the fact that sympathetic and perhaps vagal discharges were responsible for the disorders of the cardiac rhythm. The arrhythmias have been produced by electrical stimulation to different parts of the brain, including hypothalamus, mesencephalon, the orbital surfaces of the frontal lobes, insula and other areas. Arrhythmias can also be induced by stretching vessels of the circle of Willis or by producing sudden increase in the intracranial pressure with subdural balloons. It has been shown that acute hypoxia during mesencephalic stimulation precipitates these changes.

It has been shown that patients and animals dying after intracranial hemorrhage had subendocardial lesions presumably secondary to excessive sympathetic stimulation.
that following intracranial hemorrhage there was an increase in tissue catecholamines in the heart. Most of the experimental work has focused on the nature of the cardiac lesions or on the increase of tissue catecholamines rather than on the mechanisms of the arrhythmias or the arrhythmias themselves. We believed there was a need for an experimental model that resembled subarachnoid hemorrhage in humans. The dog was chosen because the vagi and sympathetic nerves to the heart run together in the neck where they can be readily dissected. In addition, the sympathetic and vagal innervation of the dog’s heart is well known. Most of the parasympathetic nerve distribution is to structures above the coronary sinus, whereas sympathetic fibers innervate mostly the ventricles.

Methods

Thirty healthy mongrel dogs, weighing 11 to 15 kg were anesthetized with 50 mg/kg of body weight of chloralose 1% given intravenously; the animals were intubated and respiration controlled with a respiratory pump. A twelve-lead ECG was taken before and after the introduction of blood into the subarachnoid space. Leads II, V5 and V6 were taken continuously. Arterial pressure was monitored through a catheter placed in the femoral artery. Bilateral burr-holes were made in the parieto-occipital regions two cm above the ears and the dura was carefully opened. A small polythylene catheter for ventricular shunting (radiopaque end with side slits) was introduced approximately three cm into the subarachnoid space. It was checked to assure that the cerebrospinal fluid flowed freely and was positioned to avoid damage to the cerebral cortex. Through a symmetrical burr-hole a similar tube was introduced into the subarachnoid space for monitoring intracranial pressure. A peripheral artery was isolated and a polyethylene catheter flushed with heparin was introduced through an arteriotomy and connected to a three way stopcock. Blood was introduced into the subarachnoid space by opening the stopcock. On three occasions normal saline instead of blood was introduced rapidly (3 or 4 seconds). A Van Gogh Universal Physiological Amplifier was used for recording. The module IEN-20 was utilized for recording of the ECG and two modules IBBD-2A for recording intracranial and arterial pressure. A Statham transducer (Model CB SER 5163) was used for recording arterial and intracranial pressure. The animals were sacrificed after the experiment and the brain extracted. All had blood in the subarachnoid space. In two there was also a subdural collection. The animals were divided in six groups. 1) Five served as controls. 2) Five had section of the cervical cord between C2 and C3 with vagi and heart sympathetic innervation intact. 3) Five had bilateral section of vagi with an intact spinal cord and heart sympathetic innervation intact. 4) Five had sectioned vagi and cervical cord with intact heart sympathetics. 5) Five had section of heart sympathetic innervation and cervical cord with intact vagi. 6) Five had section of vagi and sympathetic nerves with cervical spinal cord intact.

Results

In the control animals the introduction of blood into the subarachnoid space invariably produced a disturbance of cardiac rhythm. Arrhythmias developed immediately (1- to 3-seconds) after the introduction of blood into the subarachnoid space. There was a close correlation between the appearance of the arrhythmias and the increase of intracranial pressure. The arrhythmia usually started with sinus bradycardia or arrest followed by premature ventricular
contractions (PVCs) and runs of ventricular tachycardia. Blood pressure usually increased. Arrhythmias lasted for a relatively short period of time (30 seconds to 3-4 minutes) and thereafter the incidence sharply declined (fig. 1). The group of animals with cervical spinal cord section but intact neural innervation also developed arrhythmias that were related to the increase in intracranial pressure. They were less likely to develop delayed arrhythmias or changes in the morphology of the ECG.

The third group of animals with vagal section, intact spinal cord and sympathetic innervation did not develop sinus bradycardia, sinus arrest or junctional rhythms. They usually had ventricular arrhythmias; bigeminal rhythm was the most frequent abnormality in this group. The arrhythmias appeared in two periods: a) those correlated with changes in intracranial pressure, and b) those occurring several minutes after the hemorrhage. Propranolol (0.5 mg/kg/wt) abolished the arrhythmia effectively (figs. 2, 3). The fourth group of animals with intact sympathetic innervation, spinal cord and vagi section developed ventricular arrhythmias without initial slowing of the heart rate. The arrhythmias were ventricular and usually of short duration. They correlated in time with changes in intracranial pressure. The fifth group with intact vagi but sectioned cervical spinal cord and sympathetic innervation usually had sinus arrest (fig. 4) sinus bradycardia or junctional rhythms that correlated with the changes in intracranial pressure (fig. 5). No ventricular arrhythmias were seen. There were no changes in blood pressure. The sixth group with sectioned vagi and sympathetic innervation and intact cervical spinal cords showed quite different behavior. There were no changes in cardiac rhythm immediately after introduction of blood into the subarachnoid space. There was no correlation between the onset of increased intracranial pressure and arrhythmias. These animals developed arrhythmia from 3 to 10 minutes after inducing subarachnoid hemorrhage and it was usually (although not invariably) preceded by changes in the morphology of the ECG. This type of arrhythmia tended to persist longer and recur. They could also be abolished with propranolol (figs. 6, 7, 8, 9).

Practically all animals developed cardiac dysrhythmia, but only those that had intact cervical sympathetics, spinal cord or both had arrhythmias of ventricular type. None of the dogs died as a consequence of these disorders. In the in-
CARDIAC ARRHYTHMIAS IN SAH/Estanol el al.

Figure 5. Animal with section of both sympathetics and high cervical cord. Vagi intact. The production of subarachnoid hemorrhage only induced sinus bradycardia.

tact animals and those with intact vagi, atropine was needed, in addition to propranolol, to abolish the arrhythmias effectively. The arrhythmias could be induced equally by the introduction of saline into the subarachnoid space rapidly enough to produce a sudden elevation of intracranial pressure. There was no consistent relationship between changes in the morphology of the ECG and the disorders of cardiac rhythm except in those animals that had sectioning of the cervical sympathetics and vagi, leaving the cord intact. The arrhythmias in these animals were preceded by prolongation of QT interval, deep inversion of the T wave and elevation of the ST segment. These ECG changes could not be reversed by the administration of propranolol. The most common type of arrhythmias seen were: a) sinus arrest, b) sinus bradycardia, c) atrial and nodal tachycardia, d) premature atrial contractions (PACs), e) premature ventricular contractions (PVCs), f) bigeminal rhythm, and g) ventricular tachycardia.

Blood pressure increased almost immediately after the introduction of blood into the subarachnoid space in the control animals and those with an intact spinal cord. The elevation of blood pressure was sustained for several minutes. The rise in systemic arterial pressure was the same in the intact animals and those with sectioned vagi and heart sympathetic innervation but with an intact spinal cord. On the other hand, animals with a sectioned cervical cord did not elevate their systemic arterial pressure, either immediately or several minutes after production of SAH. The rise in arterial pressure in all animals was effectively blocked by administration of propranolol (figs. 10, 11, 12). Supraventricular arrhythmias did not cause a fall in the blood pressure unless cardiac rate was higher than 220 per minute. Ventricular tachycardias and fibrillation induced an immediate fall in blood pressure. Sinus arrest without nodal escape also produced a sudden drop in blood pressure.

Discussion

One of the most important questions regarding the genesis of arrhythmias of neurogenic origin is the role of increased intracranial pressure. Although Cushing in his original paper had described sinus bradycardia and elevation of the arterial pressure, he did not observe supraventricular or ventricular tachycardias. Smith and Ray induced a variety of arrhythmias by sudden inflation and deflation of a subdural balloon in the dog. They also found in the intact animal that sinus bradycardia, sinus arrhythmia and sinus arrest were most prominent. We have confirmed the observations of Smith and Ray regarding the role of increased intracranial pressure. Intracranial pressure must be raised acutely in order to produce these changes; this is likely to occur in spontaneous human subarachnoid hemorrhage. The blood per se does not appear necessary because the same changes can be induced by rapid injection of saline into the subarachnoid space. This is an important finding as it confirms reports in the literature suggesting that sudden increases in the intracranial pressure are of importance in the development of the arrhythmias.

In the intact animal, vagal influences are stronger than the sympathetic at the SA node level and are therefore responsible for the bradycardia. All of our intact animals and those with vagi intact had sinus arrest or bradycardia immediately after the elevation of the intracranial pressure. Most of the intact animals, however, also developed ventricular arrhythmias during the episode of raised intracranial pressure. This can be explained by assuming that there are massive vagal and sympathetic discharges and although the vagus predominates over the sympathetic at the SA node, the effect of sympathetic stimulation on the ventricular system increases its excitability and probably induces the ventricular arrhythmias. There was a close temporal relationship between the onset of arrhythmias and the raised
intracranial pressure in the intact animal and those with intact vagi and heart sympathetic innervation. This indicates that the direct sympathetic and vagal discharges upon the structures of the heart are responsible for arrhythmias that have a short latency. It has been speculated that in some clinical cases these types of arrhythmias may be responsible for a fatal outcome. Although Crompton has shown that hypothalamic lesions attributable to arterial spasm are frequently encountered in the brains of patients who died with SAH, it appears that the arrhythmias that have a time locked relationship with raised intracranial pressure are not necessarily related to the presence of blood in the subarachnoid space. These lesions, however, may be of importance in the production of those arrhythmias that have a close temporal relationship to the intracranial pressure. How increased intracranial pressure induces the sympathetic and vagal discharges is not clear, but it may possibly be due to compression of the brain stem or diencephalic structures. Rodbard has proposed that the increase in systemic arterial pressure seen with cerebral compression is due to activation of specific arterial baroreceptors localized in the cerebral blood vessels. The arterial baroreceptors in turn activate hypothalamic and brainstem centers. The fact that arrhythmias are seen with traction on the vessels of the circle of Willis supports this hypothesis.

We observed that those animals with bilateral sectioned vagi and sectioned heart sympathetic innervation leaving an intact spinal cord did not develop an arrhythmia immediately after the elevation of intracranial pressure. The disturbance of the cardiac rhythm usually occurred several minutes (from three to ten) after production of the experimental SAH and correlated with the changes in the morphology of the ECG. We believe these changes are not mediated directly by neural influences but possibly by increased circulating or tissue catecholamines. Increased tissue catecholamines in the heart in experimental SAH has been
FIGURES 9A and B. (Same animal as figs. 6-8). The bigeminy persisted for several minutes. This arrhythmia could be abolished with propranolol 1 mg/kg/wt.

shown by Offerhaus and Van Gool. There are suggestions in the literature that increased circulating catecholamines are present in patients with SAH. The changes in the morphology of the ECG waves have also been reproduced by the administration of epinephrine and norepinephrine in

FIGURE 10. In control animals, experimental SAH induces an immediate bradycardia and an elevation of systolic blood pressure. The systolic arterial pressure and the heart rate reach normal levels in approximately one hour (mean values for two animals).

FIGURE 11. In animals with high cervical cord transection and intact vagi, the elevation of systolic arterial pressure secondary to the experimental SAH is absent. The initial bradycardia is present. The bradycardia is abolished by sectioning of the vagi (mean values for two animals).
normal subjects. These delayed arrhythmias were less predictable and less constant than those related to the sudden elevation of intracranial pressure. It is of interest that in the original paper of Beattie et al., it was necessary to remove both the sympathetic nerves to the heart and the adrenal glands in order to prevent the premature ventricular contractions. None of the experimental animals died as a consequence of these ECG changes, they all maintained good ventilation, normal arterial blood gases and electrolytes. In clinical cases, pre-existent heart disease, acute hypoxia secondary to respiratory arrest and perhaps electrolyte disturbances may all contribute to the severity of these disorders. The changes in the morphology of the ECG were not reversed by the administration of propranolol. They may reflect structural changes in the myocardium but more studies are necessary to make this correlation. It appears that the sympathetic discharges can produce supraventricular and ventricular tachycardias, probably on the basis of temporal dispersion of recovery of excitability upon atrium and ventricle. The parasympathetic discharges on the other hand probably act on the SA and AV nodes inducing changes in the slope of depolarization (phase 4) of the pacemaker and conductive system. The sympathetic system also acts upon these heart structures. Regarding the changes in arterial pressure we have largely confirmed the observation of Vander Ark et al. In control animals and vagotomized animals the initial bradycardia was absent but there was a higher rise in systemic blood pressure. The blood pressure elevation was absent in those animals that had section of the cervical cord. This finding indicates that the increase in blood pressure is mediated through the sympathetic nervous system that travels in the spinal cord. In our animals, propranolol blocked the elevation of the systemic blood pressure indicating that this response was induced by beta sympathetic stimulation. The elevation of blood pressure developed pari-passu with the arrhythmias and may be an easier index of sympathetic activity in clinical cases.

Acknowledgment

We are indebted to the members of the Department of Experimental Medicine of the National Medical Center. We are grateful for the editorial help given by Mrs. Lopez Negrete and Mrs. Mateos.

References

2. Bramwell C: Can head injury cause auricular fibrillation? Lancet 1: 8-9, 1934
10. Annand BKG and Dua S: Circulatory and respiratory changes induced by electrical stimulation of the limbic system. J Neuropsychirol 19: 393-400, 1956
26. Byer E, Ashman R, Toth LA: Electrocardiograms with large, upright T
waves and long Q-T intervals. Am Heart J 33: 796-806, 1947
Cardiac arrhythmias in experimental subarachnoid hemorrhage.
B V Estanol, M V Loyo, J H Mateos, E Foyo, A Cornejo and J Guevara

Stroke. 1977;8:440-449
doi: 10.1161/01.STR.8.4.440

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/8/4/440

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at: http://stroke.ahajournals.org/subscriptions/