Myocardial Damage and Cardiac Arrhythmias After Intracranial Hemorrhage. A Critical Review

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Abstract: Evidence is presented which supports the theory that intracranial hemorrhage may secondarily cause myocardial damage and cardiac arrhythmias.

Fatal intracranial hemorrhage occasionally is accompanied by ECG changes which are consistent with myocardial infarction; histological examination of the heart revealed a variable amount of myocardial damage. After intracranial hemorrhage in animals, myocardial damage was frequent. Similar myocardial damage was produced in animals by intravenous infusion of norepinephrine or acetylcholine and by electrical stimulation of the stellate ganglia, vagus nerve or mesencephalic reticular formation.

Atrial and ventricular arrhythmias and various degrees of A-V block were reported in patients suffering from subarachnoid hemorrhage. Similar cardiac arrhythmias were found in animals after intracranial hemorrhage, and with electrical stimulation of the vagus nerve, stellate ganglia or CNS centers. Available data suggest that increased or altered autonomic activity may be the mechanism whereby intracranial hemorrhage produces myocardial damage and cardiac arrhythmias.

The efficacy of autonomic blockade in preventing myocardial damage, which was secondary to experimental intracranial hemorrhage in animals, was demonstrated. It is suggested that the initiation of therapy with autonomic blocking drugs, as soon as possible after the onset of intracranial hemorrhage in patients, may be useful in preventing myocardial damage and cardiac arrhythmias.

Additional Key Words sympathetic nervous system intracerebral hemorrhage parasympathetic nervous system autonomic blockade

The purpose of this review is to present the evidence for the theory that intracranial hemorrhage secondarily causes myocardial damage and cardiac arrhythmias. It is anticipated that this review will alert the practicing clinician to these two possible complications of intracranial hemorrhage, and suggest an acceptable plan of management to prevent them. Hopefully, this review also will serve to stimulate needed research in a relatively neglected area, when one considers the morbidity and mortality in the large patient population affected.

Little information exists about the actual mechanism of death in patients who have suffered a fatal intracranial hemorrhage.1 In a study of 100 stroke patients, who died within seven days after the onset of symptoms, 14% had no important pathological findings outside of the nervous system at the time of postmortem examination.1 Subsequent discussion will indicate that cardiac arrhythmias should be considered as a highly probable cause of death in this group of patients, as well as in patients in the same study who had demonstrable myocardial lesions. In a study of 135 stroke patients, cardiac arrhythmias were observed in 61% during the first three days after the stroke.2 Some of these arrhythmias probably were due to pre-existing cardiac disease, since 69% of these patients also had known heart disease. However, it seems unlikely that the latter finding is sufficient to explain such a high frequency of arrhythmias.

Myocardial Damage in Patients

Intracranial hemorrhage has been reported to produce myocardial damage in both patients and experimental animals. Greenhoot and Reichenbach3 reported six cases of fatal subarachnoid hemorrhage, in which there were no complicating factors such as prolonged hypoxia, cardiac arrest, vasopressor treatment, or severe electrolyte changes; they found cardiac lesions which consisted of subendocardial hemorrhages, focal

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Myocardial Damage in Animals

Better controlled studies on the capability of intracranial hemorrhage in producing myocardial damage have been possible in animals. Burch et al. reported three fatal cases of subarachnoid hemorrhage, in which subendocardial hemorrhages were demonstrated at necropsy; ECG changes resembled those frequently documented in subendocardial infarction. Apparently, even less obvious cardiac lesions in subarachnoid hemorrhage may result in markedly altered cardiac performance. For example, Hammermeister and Reichenbach reported a case of fatal subarachnoid hemorrhage in which the ECG first was consistent with subendocardial ischemia and later developed Q waves in leads II, III, and aVF; at the time of admission, the patient was in pulmonary edema, but at postmortem examination only multiple foci of myocytolysis were found in the myocardium.

Scott reported a case of fatal intracranial hemorrhage, in which ECG changes indicated probable acute anterior myocardial infarction. However, postmortem examination revealed no evidence of myocardial infarction, and only microscopic foci of ischemic necrosis were present. A similar case of fatal subarachnoid hemorrhage was reported by Pfister and de Pando, the ECG changes were consistent with an acute anterior transmural myocardial infarction, but on a routine pathological study the cardiac histology was interpreted as entirely normal. In contrast to these findings, Wasserman et al. reported on a patient who had a fatal subarachnoid hemorrhage, and who secondarily developed a myocardial infarction clinically and electrocardiographically. Postmortem examination verified the infarction. From these studies, it appears that a whole spectrum of cardiac damage may occur secondary to subarachnoid hemorrhage; in the presence of ECG changes which are consistent with myocardial infarction, myocardial changes on routine pathological examination range from no detectable damage to frank myocardial infarction. In another study of patients with subarachnoid hemorrhage, myocardial damage was probable, based on serum enzyme elevations and ECG changes.

Myocardial Damage and Catecholamines

Continuous intravenous infusion of l-norepinephrine in therapeutic doses for one to two weeks or at much higher doses for up to ten hours resulted in focal myocarditis in association with subpericardial hemorrhages in dogs. Similar results were obtained with rabbits and cats. Although subcutaneous injection of isoproterenol produced the most severe myocardial necrosis in rats, similar lesions of lesser magnitude were produced by l-epinephrine, l-arterenol, or ephedrine. Further indirect evidence that the sympathetic nervous system may be instrumental in the production of myocardial damage secondary to CNS lesions is provided by experimental activation of the peripheral sympathetic nervous system. Focal myocardial necrosis developed in rats after the stellate ganglia were mechanically traumatized bilaterally; these myocardial lesions were very similar to those produced by parenteral administration of epinephrine and norepinephrine. Electrical stimulation of the stellate ganglia in dogs produced subendocardial hemorrhage and focal myocardial necrosis which was most marked in the inner one-third of the left ventricle and in the papillary muscles.
dial damage. Hall et al. administered 50 mg of an acetylcholine halide daily intravenously to dogs for a month or more. Progressive myocardial failure and death always ensued; autopsy revealed myocardial damage in the form of frank myocardial infarction and focal necrosis in 75% of experimental animals. Similar myocardial damage was produced by electrical stimulation of the vagus nerve in unanesthetized dogs; furthermore, myocardial damage was increased by the concurrent administration of eserine and prevented by atropine. The studies by Hall et al. and Manning et al. were criticized as being unphysiological and of little clinical significance because large doses of acetylcholine were used in the former and nearly continuous vagal stimulation for up to seven days' duration was utilized in the latter. Groover and Stout avoided these objections in a similar study on baboons by applying stimuli to the vagus nerve, which were just sufficient to cause visible cardiac slowing; 12 such consecutive stimulations were repeated with a one-minute recovery period after each stimulation. Histological study of these baboons four weeks later revealed multiple foci of fibrosis in the septum and adjacent ventricular wall; under the same experimental conditions, the administration of atropine prevented the development of myocardial damage.

Cardiac Arrhythmias in Patients
Smith reported a case of subarachnoid hemorrhage in which ventricular bigeminy and quadrigeminy occurred. Parizel reported the occurrence of circulatory arrest due to ventricular fibrillation in two patients with subarachnoid hemorrhage. In patients with subarachnoid hemorrhage, the following arrhythmias also have been reported: wandering atrial pacemaker, nodal extrasystoles, nodal rhythm, premature ventricular beats, sinus bradycardia, sinus arrhythmia, atrial fibrillation, premature atrial beats, and left bundle branch block.

Cardiac Arrhythmias in Animals
Cardiac arrhythmias, which are secondary to intracranial hemorrhage, also have been reported in animal studies; as was the case in studies on patients, arrhythmias were usually incidental findings in studies designed to investigate other parameters. Misra and Prasad injected 5 ml of blood into the orbitofrontal region of dog's brain; 100% of animals had a sinus irregularity, and 57% had cardiac extrasystoles as a result of this lesion. McIntyre et al. reported sinus arrhythmia, nodal rhythm and premature ventricular beats after the production of experimental subarachnoid hemorrhage in rhesus monkeys. In one of a series of excellent papers, van Bogaert and Selosse produced subarachnoid hemorrhage in dogs, which had previously undergone partial frontal lobectomy, including the olfactory area but not the orbital and motor areas. Under these conditions, they observed nodal bradycardia, complete AV block, and ventricular tachycardia, all of which disappeared after bilateral vagotomy. Smith and Ray observed sinus bradycardia, premature ventricular beats, nodal tachycardia and nodal bradycardia after experimental elevation of intracranial pressure in dogs.

Neural Mechanisms of Cardiac Arrhythmias
The hypothesis that intracranial hemorrhage secondarily may cause cardiac arrhythmias required the following two pieces of evidence in order that it be plausible. First, functional pathways from the central nervous system to the heart were shown to exist. Second, activation of CNS centers was shown to result in the production of arrhythmias. Excellent reviews of the research on these concepts were published by Mauck, Hockman and Hoff.

With electrical stimulation of the posterior hypothalamus in cats, various investigators have reported premature ventricular beats, AV block, nodal rhythm, and ventricular tachycardia. Similarly, electrical stimulation of the hypothalamus in rabbits resulted in premature beats. In dogs, electrical stimulation of the posterior hypothalamus, thalamus, and midbrain produced sinus bradycardia, premature ventricular contractions, AV block, nodal beats, ventricular tachycardia, and ventricular fibrillation. Electrical stimulation of the mesencephalic reticular formation resulted in premature ventricular beats and ventricular tachycardia in dog and cat; in AV block in cat; in WPW-like complex, nodal beats, wandering atrial pacemaker, and atrial fibrillation in the dog. Stimulation of the posterior hypothalamus, substantia nigra and subiculum in the rhesus monkey caused premature atrial and ventricular beats. In cats, stimulation of the lateral hypothalamic produced premature ventricular beats and ventricular tachycardia. Stimulation of the cingulate gyrus resulted in sinus bradycardia and sinus arrest in monkeys, and in sinus bradycardia and premature ventricular beats in man. In cats and monkeys, electrical stimulation of the amygdaloid region produced premature ventricular beats and AV block; furthermore, sinus arrhythmia, premature atrial beats and nodal beats also were seen in monkeys and ventricular tachycardia and ventricular fibrillation were produced in cats.

Both the parasympathetic and sympathetic nervous systems appear to be important in the production of neurogenic arrhythmias. Cardiac arrhythmias have been produced by the electrical stimulation of vagus nerve in cats; in baboons stimulation of the vagus nerve produced intractable ventricular fibrillation. Electrical stimulation of the distal end of the cut right vagus nerve slowed the sinus rate, and electrical stimulation of the right stellate ganglion elevated sinus.
rate in anesthetized cats; but neither of these procedures alone produced arrhythmias. However, simultaneous stimulation of both of them produced the same spectrum of arrhythmias which were obtained with stimulation of the midbrain and posterior hypothalamus; furthermore, the arrhythmias produced by stimulation of the latter two structures were abolished by bilateral vagotomy or extirpation of the stellate ganglia.

The ventricular arrhythmias produced by experimentally elevated intracranial pressure in dogs are presumably of vagal origin, because they were eliminated or prevented by vagotomy or the administration of atropine. Finally, stimulation of the nucleus ambiguus and the afferent solitarius nuclei in both cats and dogs resulted in sinus bradycardia, sinus arrest, AV block, nodal rhythm, atrial fibrillation, and ventricular tachycardia.

The primary mechanisms by which natural catecholamines and sympathomimetic drugs produce cardiac arrhythmias are increased myocardial automaticity and ectopic pacemaker activity; other factors include enhancement of reentrant activity, induction of vagal reflexes and increased cardiac work and oxygen requirements. Of course, these same factors become operative with increased activity in the sympathetic nerves supplying the heart. Electrical stimulation of the left stellate ganglion in dogs produced a brief period of nodal tachycardia followed by a period of slowing; but right stellate stimulation resulted in a marked sinus tachycardia. Chronic cardiac denervation completely prevented the development of ventricular fibrillation after coronary artery ligation in dogs, whereas ventricular fibrillation occurred in 53% of dogs (controls) which were not protected by chronic cardiac denervation.

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**Theories on Cardiac Complications**

Altered activity of the autonomic nervous system has been suggested as the mechanism whereby brain lesions cause myocardial damage, ECG changes, and altered myocardial function. Because of the location of the lesions in their series of patients with subarachnoid hemorrhage, Cropp and Manning hypothesized that the observed ECG changes were the result of increased vagal activity. Some investigators proposed that the ECG changes in subarachnoid hemorrhage result from activated sympathetic centers in the hypothalamus which in turn cause the release of catecholamines in the myocardium or systemically. Catecholamine release at the local tissue level has been suggested as a cause of myocardial damage secondary to experimental intracranial hemorrhage in animals. Other investigators suggest that ECG changes in patients with subarachnoid hemorrhage are due to autonomic imbalance resulting from irritation or depression of vagal or sympathetic centers or their pathways. Greenhoot and Reichenbach suggested that activation of sympathetic "centers" in the posterior diencephalon and upper midbrain, either by stimulation or by lesions more anteriorly which alter the balance of autonomic outflow, results in sympathetic discharge which produces myocardial necrosis after subarachnoid hemorrhage in patients. Connor proposed that myocardial damage after cerebrovascular accidents was the result of a stimulation of the autonomic nervous system and a rise in the level of circulating catecholamines.

**Possible Therapeutic Approaches**

Some animal studies have been done which demonstrate that blockade of autonomic activity partially prevents cardiac damage and arrhythmias secondary to experimental brain lesions or electrical stimulation. Subarachnoid and intracerebral hemorrhage in mice after the daily administration of reserpine for two weeks resulted in an incidence of myocardial damage of 0 to 8%, whereas the incidence in untreated mice was 48 to 80%. Cardiac damage produced by vagal stimulation in dogs and baboons was prevented by the administration of atropine. In mice treated with atropine prior to the production of experimental intracranial hemorrhage, the incidence of myocardial damage was 20%, whereas those mice which did not receive atropine had an 80% incidence of myocardial damage. Both the administration of atropine and vagotomy eliminated or prevented the cardiac arrhythmias which were secondary to an experimental increase in intracranial pressure in dogs. In rats subjected to experimental intracranial hemorrhage, the incidence of myocardial damage was significantly decreased by the administration of propranolol.

The findings in animals suggest that the initiation of therapy with atropine and propranolol as soon as possible after the onset of intracranial hemorrhage may be useful in the prevention of myocardial damage. The reduction in the incidence of myocardial damage by drug therapy probably would be accompanied by a reduction in the incidence of cardiac arrhythmias because myocardial damage is probably the anatomical basis for at least a portion of these arrhythmias. Furthermore, the institution of propranolol therapy may produce beneficial effects by mechanisms other than adrenergic beta-receptor blockade. Propranolol has been shown to reduce myocardial damage under ischemic conditions and it has additional antiarrhythmic activity by a mechanism other than beta adrenergic blockade.

**Conclusion**

To summarize, considerable evidence exists which supports the contention that subarachnoid hemorrhage may secondarily cause myocardial damage and life-threatening cardiac arrhythmias in patients. Furthermore, both subarachnoid hemorrhage and in-
tracerebral hemorrhage have been shown to produce myocardial damage and cardiac arrhythmias in animals. The experimental design of these animal studies was such that either animals with subarachnoid hemorrhage and tracerebral hemorrhage were grouped together for data analysis or only one form of intracranial hemorrhage was investigated in a given study. Unfortunately, these investigative approaches do not permit a distinction to be made between the adverse cardiac effects of subarachnoid hemorrhage and tracerebral hemorrhage. Both animal and patient studies are needed to determine the incidence and the severity of cardiac effects secondary to these two kinds of intracranial hemorrhage, since clinical data show differences in their pathogenesis, treatment and mortality.

It is probable that the myocardial damage and ECG changes (both arrhythmias and wave changes), which occur secondary to intracranial hemorrhage, are closely related in origin, and that arrhythmias are often the result of myocardial damage, either at the cellular or subcellular level. Further studies are needed to test this hypothesis.

The theory that the cardiac complications of intracranial hemorrhage are secondary to abnormally increased autonomic activity or an imbalance between parasympathetic and sympathetic input to the heart has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed. Despite a recent suggestion by Gillis et al.64 that the adrenergic neuroeffector junction has been discussed.

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