group of patients with TIA's exists in whom the sole cause of the attack is an abnormality of platelet function. The less stenotic group in our study may correspond to Al-Mefety's specific group of TIA patients.

An important question remains to be answered. Is enhanced platelet aggregation in the less stenotic group a true risk factor for cerebral thrombosis? In order to reply it is necessary to study a control group matched for the same degree of vessel stenosis, age and sex. We selected a group of non-stroke hypertensive subjects. Platelet aggregation in hypertensive stroke patients in the less stenotic group was significantly increased from those of hypertensive control subjects without stroke. From these observations, it is suggested that a combination of enhanced platelet aggregation and hypertension increases the risk of a specific type of infarction characterized by mild stenotic changes of major cranial arteries and small infarction in the deep structures of the brain.

Acknowledgment

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THE RELATIONSHIP BETWEEN ELECTROCARDIOGRAPHIC CHANGES associated with subarachnoid hemorrhage (SAH) has been documented since 1947 when Byer et al.1 described large upright T-waves and prolonged Q-T intervals in a patient with subarachnoid hemorrhage that occurred secondary to a ruptured aneurysm. Since that time reports have appeared that suggest an association between SAH and electrocardiographic abnormalities,2-5 although the realization regarding the life threatening nature of these cardiac arrhythmias is a fairly recent one.6 Moreover, when there is a concomitant impairment of consciousness and no clinical history, the disturbances of the cardiac rhythm may appear to be the primary illness of these patients.6

In order to be able to study the electrocardiographic changes occurring secondary to a sudden SAH and the mechanisms involved in producing these changes, an
The present study was undertaken to investigate the suitability of the rat (a smaller, less expensive and easily available laboratory animal) for studying the acute effects of a non-invasive simulated SAH produced by the introduction of blood into the subarachnoid spaces in the vicinity of the circle of Willis on the electrocardiogram, blood pressure and intracranial pressure. The approach mentioned above for experimental SAH was taken primarily, to ensure a constant blood volume in the animal and secondly, to minimize local brain damage that may occur if SAH was produced by puncture of a cerebral blood vessel. Dextran 40 and Gentran 75, substances of different molecular weights which are iso-osmolar to blood, and 0.9% saline were also used instead of blood in simulating a SAH in the area of the circle of Willis to determine the specificity of blood in producing hypertension and electrocardiographic abnormalities. Saline or blood was also introduced into the cisterna magna to determine if the electrocardiographic abnormalities so generated were also agent-specific.

**Methods**

Male Sprague-Dawley rats between 300–350 g in weight were anesthetized with urethane (1.2–1.6 g/Kg ip). Data was obtained from thirty-six animals. Electrocadiogram was recorded from lead II using rust proof safety pin 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). For simulating a SAH and for recording intracranial pressure a small hole was drilled using a dental burr in the left lateral frontal bone 10 mm anterior to the interaural line (slightly posterior to the os frontale in the rat) on the dorsal surface of the skull. 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 corresponds to the level of the junction of the olfactory lobes and frontal lobes. Adjustments may be needed in the coordinates used for determining the position of the hole for different weights, ages and strains. Approximately 1.6 cm of a 15 cm long piece of silastic tubing was led through the burr hole along the left lateral surface of the brain until it touched the base of the skull and was then directed medially so that the tip of the cannula rested in the area of the circle of Willis. It is important that the silastic tubing fits tightly in the hole. The hole with the silastic tubing in place, was sealed and held in place with five-minute epoxy that was applied on a 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 needed more than 0.5 ml of blood to generate heart rate and rhythm changes were excluded from this study. Usually when more than 0.5 ml of blood was required to produce electrocardiographic abnormalities it was observed on autopsy that the tip of the cannula was either epidural, had been misdirected so that the tip rested inside brain tissue or was pushed too far backwards so that little accumulation of blood was seen inside the cranial cavity evidently draining the blood down the spinal cord. The rat was held in the stereotaxic apparatus throughout the experiment. 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 intracranial pressure. The same silastic tubing was therefore used for introducing blood and for recording intracranial pressure from the subarachnoid spaces. 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 blood pressure. Electrocardiogram, intracranial pressure and blood pressure were recorded on photosensitive rapid access type instrumentation recording paper (Eastman Kodak Co., Rochester, N.Y.). The intracranial pressure and blood pressure recorded were calculated from a calibration curve.

The rats were divided into four groups and were subjected to a subarachnoid hemorrhage using blood, 0.9% saline, Dextran 40 and Gentran 75 respectively. Group I consisted of sixteen rats of which six were used for recording electrocardiogram, blood pressure and intracranial pressure both before and after inducing a subarachnoid hemorrhage in the same animal. In the remaining ten rats only electrocardiogram and intracranial pressure were recorded. The accumulation of blood within the cranial cavity was confirmed in each animal at autopsy. Group II consisted of eight rats who were given 1.0 ml of 0.9% saline mixed with trypan blue instead of blood. Intracranial pressure and electrocardiogram were recorded in six rats while blood pressure, intracranial pressure and electrocardiogram were recorded in two animals. Group III consisted of six rats and this group was given 1.0 ml of Dextran 40 mixed with trypan blue in the subarachnoid spaces instead of blood. Intracranial pressure and electrocardiogram were recorded in four animals in this case.
group. Blood pressure, intracranial pressure and electrocardiogram were recorded in the remaining two rats. Group IV consisted of six rats who were given 1.0 ml of Gentran 75 mixed with trypan blue instead of blood. Intracranial pressure and electrocardiogram were recorded in four rats. Blood pressure, intracranial pressure and electrocardiogram were recorded in the remaining two rats. The presence of 0.9% saline, Dextran 40 and Gentran 75 in the cranial cavity was confirmed on autopsy in each animal by the presence of the blue dye which was present all over the cranial cavity.

Agents under investigation were administered in doses of 0.1 ml over a period of approximately 6 seconds. Each dose was administered 1 minute apart and each animal received only one of the above mentioned four agents. Electrocardiogram, intracranial pressure and blood pressure were recorded both before and after administration of blood, 0.9% saline, Dextran 40 and Gentran 75 so that each animal served as its own control. Injections of 0.5 ml of whole heparinized blood and 1.0 ml of 0.9% saline were also made into the cisterna magna. Four animals were used for each of the two agents used, namely blood and saline. Cerebral perfusion pressure was calculated as the difference between mean arterial blood pressure and intracranial pressure.

Results

In normal rats, the heart rate varied from 300 beats/minute to 420 beats/minute. An example of a normal electrocardiogram, blood pressure and intracranial pressure record from a male adult rat is shown in figure 1. Also included in figure 1 are examples of electrocardiographic abnormalities and changes in intracranial pressure observed in different animals after a SAH. Figure 2 and 3 show other examples of electrocardiographic abnormalities, increased intracranial pressure and hypotension in a dying animal after an experimental SAH.

Electrocardiographic abnormalities were seen in 89% of the rats subjected to an experimental subarachnoid hemorrhage. Electrocardiographic abnormalities did not appear in animals in which the cannula used for introducing the blood into the subarachnoid spaces had pierced and rested within brain tissue or when the tip of the cannula had been misdirected towards the spinal cord. In these cases it appeared that the blood introduced into the subarachnoid spaces had drained into the spinal cord which was observed on autopsy. All animals which showed electrocardiographic changes first developed bradycardia. Table 1 is an example of the changes seen in intracranial pressure, blood pressure and cerebral perfusion pressure before and after simulating a SAH in a rat. Table 1 shows that as intracranial pressure rose with the addition of 0.1 ml increments of heparinized blood introduced into the subarachnoid spaces with a waiting period of 1 minute between each addition of blood, arterial blood pressure also rose and when the intracranial pressure approached the diastolic blood pressure but was still below the mean arterial blood pressure, bradycardia appeared. The cerebral perfusion pressure had decreased to 15 mm Hg at the time bradycardia appeared in this animal. Table 2 shows the mean changes in intracranial pressure, arterial blood pressure and cerebral perfusion pressure seen in six rats. Using the paired t test, the mean arterial blood pressure rose significantly ($p < 0.05$) before any decrease in heart rate was observed. After bradycardia was observed, the blood pressure decreased and the difference then was not statistically significant. The decrease in heart rate was also significantly different from the control state ($p < 0.02$).

A variety of electrocardiographic abnormalities were observed in our study after introduction of blood into the subarachnoid spaces similar to those observed clinically in patients\textsuperscript{13} and experimentally in animals.\textsuperscript{8} The electrocardiographic abnormalities in a decreasing order of incidence were absence or inversion of P waves, junctional rhythm, changes in the shape and
FIGURE 2. A, B and C are tracings taken from different animals after SAH. (A) Sinus arrhythmia, second degree heart block, ST elevation, a premature atrial contraction with a retrograde P wave. ICP is raised. (B) Bradycardia, A-V dissociation, biphasic P waves, ST elevation and raised ICP. (C) Bradycardia, junctional rhythm, non-conducted beats, and raised ICP.

The size of T wave, premature atrial contractions, premature ventricular contractions, sinus arrhythmia, 2:1 atrioventricular block, A-V dissociation, ST segment elevation, inverted T wave and QT interval changes. Electrocardiographic abnormalities were also observed after blood or saline was injected into the cisterna magna.

The rationale for introducing 0.9% saline in the subarachnoid spaces was as a "control" agent to blood. It was observed that none of the three agents, i.e., 0.9% saline, Dextran 40 and Gentran 75 produced any changes in heart rate and rhythm when they were introduced into the subarachnoid spaces. Intracranial pressure rose above normal, but did not equal the diastolic blood pressure and returned to normal values or close to normal values in the waiting period between the consecutive additions of 0.1 ml of the agent being used, namely, saline, Dextran 40 and Gentran 75.

Blood pressure rose slightly with Dextran 40 (figure 4), but did not when saline and Gentran 75 were used (records not shown). Addition of a total volume of 1.0 ml of saline, Dextran 40 or Gentran 75 which is two times the total volume of blood used for simulating SAH, did not produce any changes in heart rate and rhythm. Table 3 shows the incidence of bradycardia and other electrocardiographic abnormalities seen after introduction of blood, 0.9% saline, Dextran 40 and Gentran 75.

Discussion

The myriad of information available on the production of electrocardiographic abnormalities that often occur after a subarachnoid hemorrhage in patients does not clearly point to one mechanism which could explain the disturbances in heart rate and rhythm. Changes involving the cardiovascular system are of particular relevance to clinicians who make decisions on anesthetics, surgical procedures and other procedures that may be required during surgery, e.g., hypotension, hypothermia, blood transfusions, etc. The situation is complicated by the appearance of cardiac arrhythmias in patients after SAH which may constitute a fatal complication. An association between increased intracranial pressure as may be seen in spontaneous human subarachnoid hemorrhage and systemic arterial blood pressure and heart rate was established by Cushing who observed that when the intracra-
Pressure and Cerebral Perfusion Pressure Before and After a Subarachnoid Hemorrhage in a Rat

TABLE 1  An Example of Changes in Intracranial Pressure. Blood Pressure and Cerebral Perfusion Pressure Before and After a Subarachnoid Hemorrhage in a Rat

<table>
<thead>
<tr>
<th>Blood volume injected (ml) into the subarachnoid spaces</th>
<th>Intracranial pressure (mm Hg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Cerebral perfusion pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None*</td>
<td>10</td>
<td>95/75</td>
<td>75</td>
</tr>
<tr>
<td>0.1*</td>
<td>35</td>
<td>100/80</td>
<td>55</td>
</tr>
<tr>
<td>0.2*</td>
<td>40</td>
<td>110/90</td>
<td>60</td>
</tr>
<tr>
<td>0.3*</td>
<td>40</td>
<td>150/110</td>
<td>90</td>
</tr>
<tr>
<td>0.4†</td>
<td>90</td>
<td>120/90</td>
<td>15</td>
</tr>
</tbody>
</table>

*Normal heart rate = 330 beats/min.
†Appearance of bradycardia approximately 5 seconds later was followed by other electrocardiographic abnormalities. Heart rate = 240 beats/min.

Bradycardia was suddenly increased in excess of systemic arterial blood pressure, transient bradycardia and systemic hypertension ensued.

Cushing16 and others17,18 observed cardiac slowing as a transient response (ten to twenty seconds). These investigators used either saline or artificial cerebrospinal fluid which was injected into the medulla, parietal or parieto-occipital region in rabbits and dogs to increase intracranial pressure. The bradycardia observed in rats in our study after introduction of blood in the area of the circle of Willis19 was usually not transient, if and when it was so, it could be made to persist for as long as two hours by adding an additional 0.1 ml of blood. Most animals, however, were sacrificed within one hour after the onset of bradycardia and arrhythmias in order to localize the tip of the cannula that was used for introducing blood into the subarachnoid spaces and recording intracranial pressure. Some animals died within one hour of inducing an experimental subarachnoid hemorrhage. The second phase of the Cushing response which is represented by an increase in heart rate that usually follows the initial bradycardia was never observed in Sprague-Dawley rats. The rats in our study showed an increase in arterial blood pressure followed by a progressively worsening bradycardia, with or without the appearance of a variety of other electrocardiographic abnormalities. With the appearance of electrocardiographic abnormalities a progressive fall in blood pressure was observed.

In this study the latency of the hypertensive response was usually about 2–5 seconds with a concomitant increase in intracranial pressure after the addition of the first 0.1 ml of blood into the subarachnoid spaces which was delivered over approximately 6 seconds. However, bradycardia did not appear till about 5 seconds after another 0.1 to 0.4 ml of blood was introduced into the subarachnoid spaces which made the latency of the bradycardic response approximately 1½ minutes to 5 minutes after hypertension was first observed. Since both the latencies of the hypertensive and bradycardic responses in this study were very short once the respective thresholds were reached, it is possible that these responses were evoked by distortion of brain tissue as suggested by Doba and Reis20 and Reis et al.21

The specificity of blood in evoking electrocardiographic changes appears to be related to its ability to raise intracranial pressure and maintain it at levels high enough to generate cardiac arrhythmias in contrast to 0.9% saline, Dextran 40 and Gentran 75. No change in heart rate with little or no increase in blood pressure was seen with these non-blood agents in rats used in our study. Nevertheless, both saline and blood could produce electrocardiographic changes when introduced into the cisterna magna. The possibility that blood itself may, by mechanical irritation, be at least partly responsible for generating electrocardiographic changes, apart from its ability to influence intracranial pressure cannot be ruled out. Some evidence that supports this idea has come from the work of Clower et al.7 who observed that dogs subjected to a subarachnoid hemorrhage over the circle of Willis suffered cardiorespiratory distress both when blood or saline was used. Total cardiorespiratory failure occurred only following blood injection which could not be demonstrated after injection of saline either at normal intracranial pressure or when it was increased eight times above normal.

The electrocardiographic abnormalities observed in our study appear to be due to an "interplay" of both the parasympathetic and the sympathetic nervous systems and were similar to those observed in patients with subarachnoid hemorrhage.3,13,14,22–26 More spe-
cifically, in patients, bradycardia and rhythm disturbances, e.g. varying degrees of heart blocks indicative of overactivity of the parasympathetic nervous system have been observed and repolarization abnormalities (ischemic changes) e.g. deeply inverted T waves, minimal ST elevation or depression, prominent upright T waves, changes in QT interval are also reported to be of common occurrence.

The increase in blood pressure in our study, after introduction of blood into the subarachnoid spaces is indicative of sympathetic hyperactivity. The appearance of supraventricular premature beats and premature ventricular contractions would also be indicative of dysfunction of the sympathetic nervous system and were observed both in our study as well as in patients with a subarachnoid hemorrhage.

In Feibel's study the level of catecholamine output correlated well with the frequency and severity of these arrhythmias. The appearance of cardiac arrhythmias secondary to cerebral infarction and possibly mediated by catecholamines have also been recently reported by Myers et al.

| Table 3 | Incidence of Cardiac Arrhythmias Observed After Subarachnoid Hemorrhage in Rats |
|---|---|---|
| Agent | N | ECG abnormality | Incidence |
| 1. Blood | 16 | bradycardia | 16 |
| 1. Blood | 16 | biphasic P and absent P | 10 (63%) |
| 1. Blood | 16 | junctional rhythm | 9 (56%) |
| 1. Blood | 16 | changes in T wave | 8 (50%) |
| 1. Blood | 16 | premature atrial contractions | 7 (44%) |
| 1. Blood | 16 | premature ventricular contractions | 6 (38%) |
| 1. Blood | 16 | sinus arrhythmia | 5 (31%) |
| 1. Blood | 16 | 2° heart block | 4 (25%) |
| 1. Blood | 16 | A-V dissociation | 4 (25%) |
| 1. Blood | 16 | ST elevation | 4 (25%) |
| 1. Blood | 16 | inverted T wave | 1 (6%) |
| 1. Blood | 16 | QR/QRS shortening | 1 (6%) |
| 2. Saline | 8 | bradycardia and other ECG changes | None (0%) |
| 3. Dextrans 40 | 6 | bradycardia and other ECG changes | None (0%) |
| 4. Gentran 75 | 6 | bradycardia and other ECG changes | None (0%) |

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We wish to thank Drs. Alan Forker and David McCall of the Cardiology Division for their assistance in confirming the cardiac arrhythmias and Mr. W.L. Brudon for his help with the illustrations.

References
Recurrent Ischemic Attacks in Two Young Adults with Lupus Anticoagulant

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PIER MUNNUCCIO MUNNUCCI, M.D.‡, AND LIVIA CANDELISE, M.D.*

SUMMARY Two young adults with lupus anticoagulant had multiple attacks of cerebrovascular ischemia in different arterial territories. Cerebral angiography was normal. One patient had a new episode during anticoagulant therapy, but has remained asymptomatic on antiplatelet treatment. In the other, further events occurred during treatment with platelet-inhibiting drugs, but there have been no recurrences with adequate anticoagulant therapy.

Lupus anticoagulants are possible causes of otherwise unexplained thromboembolic events. Due to the variable mode of action of these immunoglobulins, platelet-inhibiting drugs may in some cases be considered as a prophylactic alternative to anticoagulant treatment.

THROMBOEMBOLISM due to arteriosclerotic lesions accounts for most cases of ischemic cerebrovascular accidents, but other causes are not infrequent in young adults.1, 2 Among hemostatic abnormalities, lupus anticoagulants have been found in association with thrombotic events.3, 4 These acquired circulating anticoagulants are immunoglobulins, either IgG or IgM,5 and were initially described in patients with systemic lupus erythematosus (SLE).6 Although the paradox of thrombosis occurring in the presence of coagulant inhibitors has not been adequately explained, anticoagulant therapy has been used in order to prevent further episodes.4 We report the cases of two young women with lupus anticoagulant and recurring cerebrovascular accidents, who presented unusual therapeutic problems.

Case Reports

Case 1

A 39-year-old woman experienced one episode daily for three consecutive days of bilateral scintillating scotomata, without headache, lasting a few minutes each time. Seven months later she had a myocardial infarction. Coronary angiography was normal. Mild hypertension (150/100 mm Hg) was diagnosed and treated with diuretics. Six months later she had another attack of scintillating scotomata, this time followed by a persistent defect of the left visual field.

She had smoked 10 cigarettes daily until her myo-
A small animal model for electrocardiographic abnormalities observed after an experimental subarachnoid hemorrhage.

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