

HYPONATREMIA, VOLUME STATUS AND
BLOOD PRESSURE FOLLOWING
ANEURYSMAL SUBARACHNOID HEMORRHAGE

HYPONATRIEMIE, VOLUMESTATUS EN BLOEDDRUK NA EEN SUBARACHNOIDALE
BLOEDING DOOR EEN ANEURYSMA

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“It must be recognised that one is not treating the disease of subarachnoid haemorrhage but a selection of surviving patients with that disorder.”

Michael Briggs (16)

*Aan Bar, Coen en Marilou
Aan de nagedachtenis van mijn ouders*

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GENERAL INTRODUCTION

Patients who survive an aneurysmal subarachnoid hemorrhage (SAH) are endangered by complications, which especially occur during the first weeks after the hemorrhage. These complications have a high mortality and morbidity, and the outcome of patients with SAH will improve if these complications can be prevented or if the neurological deterioration caused by these complications can be reversed. To achieve this, it is of the utmost importance to distinguish between the different causes of deterioration after SAH. For instance, if a patient has an impaired level of consciousness a few days after the initial hemorrhage, while there were no abnormalities during the days before, this patient might have had a rebleed, cerebral ischemia, hydrocephalus or other, less common complications.

In our department all such patients were under continuous observation in an intensive care unit. If a deterioration had occurred, the time course was documented, the patient was examined and a CT scan was repeated. The serum sodium levels were also measured in these patients, since it is known that hyponatremia may occur after SAH and can lead to neurological deficits. A low serum sodium level never appeared to be the direct cause of a deterioration, probably because the sodium levels decreased gradually and were never under 120 mmol/liter. However, we had the impression that patients with hyponatremia did worse than others.

I decided to investigate whether SAH patients with hyponatremia did indeed have a particularly poor outcome, how and why hyponatremia develops and how it can be prevented. These questions are the subject of this thesis.

Chapter I reviews the natural history and complications after a subarachnoid hemorrhage. Aneurysmal subarachnoid hemorrhage is a life-threatening disorder with an incidence of between 11 and 19 per 100,000 inhabitants per year. The neurological complications are discussed in part 2 and the medical complications, of which cardiac abnormalities, pulmonary edema and hyponatremia are the most important, in part 3. Part 4 is dedicated to the regulation of body water, sodium homeostasis, and the pathogenesis of hyponatremia. Initially it was thought that hyponatremia after SAH was caused by excessive sodium loss in the urine, accompanied by hypovolemia. This was termed cerebral salt wasting. Later, hyponatremia was attributed to the inappropriate secretion of antidiuretic hormone, causing expansion of the intravascular volume.

The cause of poor outcome in patients who developed hyponatremia was studied in a consecutive series of 134 patients with SAH. The results of this study are described in Chapter II.

An important question was whether hyponatremia following subarachnoid hemorrhage was caused by primary salt wasting, resulting in a decrease in plasma volume, or by a dilution as a result of volume expansion, caused by inappropriate secretion of antidiuretic hormone. To elucidate the cause of hyponatremia a prospective study on plasma volume, sodium balance and secretion of antidiuretic hormone was done (Chapter III).

Cerebral ischemia after SAH may be reversed by volume expansion and induced hypertension. Induced hypertension is probably effective because it increases cerebral perfusion pressure, resulting in improved blood flow in regions with ischemia. However, this treatment might be dangerous in patients in whom the aneurysm is still unoperated, as hypertension might increase the chance of rebleeding. I investigated in a large and consecutive series of patients whether the level of blood pressure or the institution of antihypertensive treatment was related to the incidence of cerebral ischemia and rebleeding. In addition, the relationship between antihypertensive treatment and cerebral ischemia was studied after adjustment for other factors that predispose to cerebral ischemia (Chapter IV).

Recently, it was demonstrated that an association exists between acute hydrocephalus and the development of hyponatremia. It has been suggested that the key event is enlargement of the third ventricle which would interfere with hypothalamic function. I investigated if the development of hyponatremia was related to enlargement of the third ventricle on the admission CT scan in a consecutive series of 133 patients who were seen within 72 hours of aneurysmal hemorrhage (Chapter V).

Before the description of the syndrome of inappropriate secretion of antidiuretic hormone, hyponatremia after SAH was attributed to a putative natriuretic factor. An endogenous substance cross-reacting with antibodies to digoxin has been demonstrated in patients with hypertension, renal failure or atrial arrhythmias, in newborn infants, and after fluid and salt loading. This substance appeared to have natriuretic properties. By means of a radioimmunoassay, plasma digoxin was measured in 25 patients with SAH not receiving digoxin therapy. The results of this part of the study are described in Chapter VI.

A final question was whether patients who are at risk of developing volume depletion and natriuresis benefit from treatment with fludrocortisone acetate. Fludrocortisone acetate has a mineralo-corticoid action and therefore enhances sodium absorption. This was studied in a consecutive series of 21 patients with SAH treated with fludrocortisone acetate and large fluid intake. I aimed to define the effect of this regimen on sodium balance and plasma volume, and at the same time to study the possible complications (Chapter VII).

Chapter I

NATURAL HISTORY AND COMPLICATIONS AFTER SUBARACHNOID HEMORRHAGE

Part I

ANEURYSMAL SUBARACHNOID HEMORRHAGE

The most common cause of subarachnoid hemorrhage is rupture of a saccular aneurysm of the circle of Willis. Its annual incidence lies between 11 and 19 per 100,000 (14, 37, 92, 96). Aneurysmal rupture is extremely uncommon in the first decade of life. The incidence gradually increases for each decade and peaks in the sixth decade (92).

As a result of the initial rupture, about one third of the patients die or become severely disabled, and of the remaining patients, another half will die or become disabled as a result of rebleeding, cerebral infarcts, and medical or surgical complications (52, 54, 62, 71). As a result, only one third of the patients who suffer an aneurysmal subarachnoid hemorrhage will survive without major disability. Even then, despite the lack of overt neurological deficits, these patients may have severe cognitive incapacities (107). These figures show that aneurysmal subarachnoid hemorrhage is a catastrophic event from which only few patients recover without sequelae. Unfortunately, the prognosis has hardly improved for many years, despite medical and surgical advances (126). This is largely explained by the high morbidity and mortality within the first 24 hours following the initial hemorrhage, which is difficult to influence. Early death (within 24 hours of admission) is caused in most patients by an intracerebral hematoma, intraventricular hemorrhage or both. A small proportion of the patients who died from the initial hemorrhage might perhaps have been saved by resuscitation as they had only subarachnoid blood on CT, although secondary brain damage caused by hypoxia cannot explain death in similar patients with rebleeding who are resuscitated in hospital (55).

The majority of the patients who die early can be saved only if earlier warning bleeds occur and if these are recognized. It has been suggested that massive destructive hemorrhages are preceded by minor ones. Recognition of these minor warning bleeds might improve the outcome following SAH (30).

CLINICAL PRESENTATION AND DIAGNOSTIC INVESTIGATIONS

The clinical syndrome of SAH is marked by a sudden onset of headache, overwhelming in intensity, generalized or sometimes more located in the neck. It may be accompanied by a brief loss of consciousness, but half of the patients remain alert (136). Nuchal rigidity is almost always present but takes time to develop in the first hours after the ictus. These signs and symptoms may be associated with transient neurological deficits or a third-nerve palsy. Preretinal hemorrhage is a classic sign but may not immediately appear after SAH and is present in only 20% of the patients (1).

When admitted, every patient with suspected SAH should undergo CT scanning as a first investigation. CT may confirm the diagnosis by showing blood at the classical aneurysm sites in the basal cisterns or interhemispheric fissure (86). CT evidence of blood in the basal cisterns almost certainly indicates a ruptured aneurysm (130). Even five days after the onset, blood in the basal cisterns or fissures is still present in 85% of the patients. After that time, it rapidly clears from the basal cisterns and even intracerebral hematomas are no longer present after three weeks (132). CT may show other causes of bleeding than a ruptured aneurysm and readily shows the presence of acute hydrocephalus which might have immediate therapeutic implications (131, 133).

Recently, a non-aneurysmal and benign form of subarachnoid hemorrhage has been reported. On early CT, blood was seen mainly or only in the cisterns around the midbrain (133). The cause of this hemorrhage is not known, but a venous or capillary source seems likely.

Only when CT fails to ascertain the presence of subarachnoid blood, spinal fluid must be obtained. However, bloody spinal fluid can be confused with a traumatic puncture, even by experienced neurologists. Spectrophotometric screening of the supernatant must be carried out. Only if no bilirubin can be detected, twelve hours or more after the hemorrhage, subarachnoid hemorrhage can be ruled out. Conversely, the presence of bilirubin in spinal fluid is highly indicative of subarachnoid hemorrhage, but cannot definitely distinguish between a traumatic tap and a subarachnoid hemorrhage. CSF cytology can be of additional value, but only if erythrophages can be demonstrated. Negative CSF cytology cannot exclude the presence of subarachnoid blood (18).

Four-vessel angiography to demonstrate the aneurysm is necessary if surgery is to be undertaken. With a good technique and adequate projections, a false-negative rate of less than 2% can be achieved, irrespective of the presence of vasospasm (38).

Part 2 NEUROLOGICAL COMPLICATONS

Following the initial hemorrhage patients may deteriorate from many causes. Rebleeding and cerebral infarction are the leading causes of morbidity and mortality.

The incidence of *rebleeding* has been overestimated in the past (58, 76, 129, 137). In a prospective CT-scan study on episodes of acute clinical deterioration, rebleeding could be confirmed in 68%; other causes were epilepsy, acute onset of ischemia and ventricular fibrillation. In 16%, the acute events remained unexplained. In a series of 176 patients who survived the first 24 hours, the incidence of rebleeding was 22% (58). Rebleeding has a mortality of 56%. The overall outcome of patients who rebled is poor: 82% had died within three months (136). The clinical features on admission and the severity of the initial hemorrhage on CT are not correlated with the incidence of rebleeding. The peak time for rebleeding of the patients who survived the first 24 hours is in the second and at the end of the third week. When patients are included who died within 24 hours, there is a peak incidence on the first day (58).

Fibrinolysis of the clot surrounding the ruptured aneurysm is an important factor in the pathogenesis of rebleeding, as antifibrinolytic treatment considerably decreases the incidence of rebleeding (136). Patients at a high risk of rebleeding cannot be identified by clinical or radiological features on admission (58), nor by measuring fibrin degradation products (FDP), since FDP's reflect a damaged blood-brain barrier rather than fibrinolytic activity in the CSF (139).

Rebleeding can be prevented by clipping of the aneurysm. The mortality and morbidity of this operation has considerably decreased during the last decades, thanks to microsurgical techniques. The timing of surgery and the selection of patients are points of major controversy. Some neurosurgeons operate on all patients within three days after the initial hemorrhage, irrespective of the neurological condition of the patients (117). Others delay operation at least two weeks and never operate on patients with an impaired level of consciousness (84), while other neurosurgeons prefer to operate on days 7-9 (121).

Antifibrinolytic agents decrease the incidence of rebleeding (136). However, the outcome of patients treated with antifibrinolytics did not improve by a concomitant increase in the incidence of cerebral infarcts.

Cerebral infarcts after SAH differ from atherosclerotic brain infarcts. In atherosclerotic brain infarcts, the clinical signs and symptoms have an acute onset, consciousness is rarely impaired, ischemia is confined to a single arterial territory, and the cause is in most cases thrombo-embolism from extracranial arteries or the heart.

Cerebral ischemia after SAH develops gradually, and approximately 75% of the patients have an impaired level of consciousness. Most patients have focal deficits, but a gradually developing decrease in consciousness can be the only sign. In the majority of patients with cerebral ischemia, the lesions are multifocal or diffuse, mainly in cortical areas and boundary zones (57).

This type of lesion may be caused by arterial spasm, as spasm can be multivascular or even generalized. It is unlikely that vasospasm is the only factor that leads to cerebral ischemia, since more than half of the patients with ruptured aneurysms have angiographic evidence of vasospasm, whereas about 27% of all patients develop clinical signs and symptoms of cerebral ischemia (2).

Other factors such as brain swelling, acute hydrocephalus, increased intracranial pressure and hemoconcentration may also impair cerebral perfusion. The peak incidence of ischemia occurs within four to ten days of the initial hemorrhage (53, 57, 71, 105). When clinical signs of cerebral ischemia appear, the prognosis is poor. Thirty-seven per cent of the patients with cerebral infarcts die from brain swelling with herniation. Patients who survive a cerebral infarct may eventually die from other complications that occur after SAH. In a series of 95 patients who had an infarct, 58% had died within three months of the initial hemorrhage (136). Prognostic factors for cerebral ischemia are the amount of subarachnoid blood on CT (65), intraventricular hemorrhage and antifibrinolytic treatment (56).

Many treatments for cerebral ischemia after SAH have been proposed. Improvement after volume expansion has been reported (98), induced hypertension might also be beneficial (17, 68), or a combination of both treatments (63). The use of extracranial-intracranial bypass surgery might reverse ischemia (104). Calcium-entry blockers might prevent vasospasm or limit the extent of ischemia, according to one clinical trial (2), but the results were not convincing (138). Other clinical trials about the effectiveness of calcium-entry blockers are in progress. It has also been suggested that removal of blood clots from the basal cisterns during an early operation might prevent cerebral ischemia (80).

The incidence of *intracerebral hematomas* varies from 4 to 35% (94), and they are associated with a high mortality (30-50%). Ruptured middle cerebral artery aneurysms cause an intracerebral hematoma more frequently than aneurysms at other sites (94, 145). Patients admitted with signs of brainstem compression do poorly, regardless of treatment (145).

Acute hydrocephalus occurs in 20% of the patients admitted early after the hemorrhage and is in most cases associated with impaired consciousness (134). This incidence is higher than in a series from a neurosurgical unit (135), probably because many patients with acute hydrocephalus never reach the neurosurgeon as they are considered in too bad a condition for operation.

In patients with an impaired level of consciousness from the time of the hemorrhage and with enlarged ventricles on CT, the clinical signs can be a direct effect of the hemorrhage or of hydrocephalus. In such a situation it is difficult to decide whether or not a shunt should be placed.

More specific for acute hydrocephalus is a history of gradually progressive impairment of consciousness within the first days of the hemorrhage, or the presence of small non-reactive pupils with otherwise intact brainstem reflexes (134). The cause of impaired consciousness in patients with acute hydrocephalus is probably a reduction of cerebral blood flow by the enlarged ventricles. This might explain why the immediate effect of shunting was invariably impressive. However, the outcome of patients in whom a shunt was placed, was poor (81, 134). Cerebral ischemia or rebleeding was the cause of death in most patients. It seems, however, illogical not to treat patients with acute hydrocephalus, as rapid improvement of cerebral blood flow may yet lessen the risk of developing cerebral ischemia. Moreover, when patients remain in a state of impaired consciousness, they run an increased risk of extracranial complications (134).

Seizures occur in about one quarter of the patients and may be easily confused with rebleeding. In one series, 63% of the seizures was observed soon after the initial hemorrhage (50).

Part 3 MEDICAL COMPLICATIONS

Electrocardiographic abnormalities are frequently seen in association with aneurysmal subarachnoid hemorrhage. The incidence is estimated at approximately 50% (73). The most consistent ECG findings are inverted T waves, ST segment depression or elevation, QT prolongation and pathological Q waves (23). Pathological Q waves or a raised ST segment indicate a poor prognosis (23). Diffuse myofibrillar degeneration accounts for these ECG changes (100). These lesions are not specific for SAH as they have been observed in both ischemic and hemorrhagic strokes (91). The lesions were dispersed throughout the myocardium and were not seen in areas normally associated with coronary artery occlusion. They were not present in patients suddenly dying from a violent cause, nor were they present more than two weeks after the acute intracranial event (67).

The myocardial damage correlates with changes in serum cardiac enzymes, including cardiospecific CPK-MB. Unlike the acute rise and fall of serum CPK-MB levels within 36 hours seen in patients with acute myocardial infarction, the enzyme levels in SAH rise gradually over the first few

days, reach their peak by about seven days and return to normal by the second week (91). It has been suggested that increased levels of catecholamines lead to hypertension, ventricular strain and subsequent ischemia of subendocardial tissues; also a direct tissue toxic effect has been proposed (20). Hypothalamic hemorrhages might be responsible for this increased sympathetic drive (13, 29, 87). Patients with SAH might therefore benefit from β -blocking agents, which counteract the hyperactivity of the sympathetic nervous system. This was investigated in a randomized clinical trial (140). The mortality was not significantly different between patients treated with placebo or with β -blocking agents, but this study was too small to be conclusive.

Dangerous ventricular dysrhythmias which have been linked with prolongation of the Q-T interval, have been found in 20% of patients following SAH (31). However, of all acute cardiorespiratory complications, most are primary disorders of respiratory rhythm and not cardiac arrhythmias. In a prospective series of 264 patients, only 2 patients had symptomatic cardiac arrhythmias (59).

Neurogenic pulmonary edema is a dramatic and dangerous complication with an extremely rapid onset, although rarely a delayed course has been reported (34). The typical clinical picture is unexpected dyspnea, cyanosis and production of pink and frothy sputum. In addition, pallor, sweating and a rapid, weak pulse may occur. Many cases were fatal, but mortality has decreased especially by the introduction of positive end-expiratory pressure (141). Pulmonary edema is not rare; a postmortem study revealed that in patients with fatal SAH, 71% had pulmonary edema and of these, 31% had a clinical diagnosis of pulmonary edema (142). Neurogenic pulmonary edema might be caused by a massive sympathetic discharge, mediated by the hypothalamus (5). This results in a rise of systemic and pulmonary vascular pressure and pulmonary capillary damage. Therefore, pulmonary edema persists despite the return of systemic and pulmonary pressures to normal in a later phase (122). Pulmonary wedge pressures were found to be normal in these patients (49).

Gastrointestinal bleeding in the preoperative period is rare. It may occur during the course of the illness in 0.02 to 3% of patients with SAH (119, 143).

Infections and septicemia are frequently encountered. In a series of 100 patients, 39% developed serious infections, of which 41% were caused by urinary infections (143).

Hyperglycemia with glycosuria is a well recognized finding following subarachnoid hemorrhage. Abnormal glucose tolerance tests and increased insulin levels were found in 15 of 20 patients (48).

Many patients with SAH develop *hypertension* immediately following the acute event. It is therefore understandable that hypertensive encephalopathy is a common misdiagnosis (1). It is, however, difficult to make an accurate estimate of its incidence, because of the lack of criteria for hypertension in patients who are severely ill and stressed. The Cooperative Aneurysm Study Group (125) found that hypertension was associated with higher mortality. A systolic blood pressure of 170 mm Hg or more was significantly related to recurrent hemorrhage, a diastolic blood pressure of 100 mm Hg or more was not.

In the study of Winn et al. (146) systolic hypertension was defined as 160 mm Hg or greater and diastolic hypertension as 110 mm Hg or greater. They found that, at least in their series, high diastolic blood pressure was associated with a worse prognosis, but only in patients with an anterior communicating artery aneurysm; the influence on rebleeding was not mentioned.

It is impossible to conclude from these studies how hypertension after SAH ought to be managed.

Hypertension might increase the incidence of rebleeding and also of cerebral infarcts. Experimental studies showed that hypertension produced vibratory damage of the wall of the aneurysm by increased turbulence within the aneurysm, which damage may result in rerupture (32). Hypertension may also aggravate cerebral ischemia by edema formation (114).

However, treatment of hypertension in patients with impaired autoregulation can reduce cerebral blood flow as in these patients cerebral blood flow is dependent on arterial pressure.

Hyponatremia is a frequent electrolyte disturbance. In a series of 290 patients with SAH, 10% developed hyponatremia, fulfilling laboratory criteria of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Other causes of hyponatremia were not found. Half of the patients had severe hyponatremia leading to an impaired level of consciousness (27). Several additional case reports on SIADH in patients with SAH were reported in the literature (61, 118, 148). Unfortunately, all reports lack detailed descriptions of the deterioration which was attributed to hyponatremia, nor do they provide data on sodium and fluid balances before the development of hyponatremia, which makes the interpretation of hyponatremia difficult.

The concept of the notion of SIADH in patients with SAH merits a separate discussion.

Part 4
HYPONATREMIA, SIADH AND REGULATION OF
SODIUM BALANCE

REGULATION OF BODY WATER AND SODIUM HOMEOSTASIS

The most important mechanism for the control of body water is osmoregulation via the antidiuretic hormone (103). In the internal carotid artery and probably in the hypothalamus osmoreceptors are present, which respond to changes in plasma osmolality. The plasma osmolality is an expression of the number of osmotically active particles per kilogram of water. As sodium is the most important osmotically active particle, plasma osmolality is practically a reflection of the serum sodium concentration. The osmoreceptors respond to an increase in plasma osmolality (of about 2%) by stimulating the neurohypophysis to secrete antidiuretic hormone, which results in reabsorption of water by the kidneys and dilution of the plasma, back to normal osmolality. ADH secretion may also respond to changes in intravascular volume (108) as a decrease in plasma volume may stimulate ADH secretion even though plasma osmolality is low. Other non-osmotic stimuli of ADH secretion are pain, stress, emotion and certain drugs (82).

The control of sodium balance is mediated by the kidney. When functioning appropriately, the kidney corrects volume expansion and volume depletion with natriuresis and increased sodium reabsorption, respectively (111). For instance: an increase in sodium intake leads to increased water intake (by thirst mechanism), expansion of extracellular volume, decrease of renin production and decrease of the sodium retaining hormone aldosterone, eventually resulting in natriuresis. The kidney regulates urinary sodium excretion in such a way that sodium excretion eventually equals sodium intake and a steady state is achieved. Normally, osmoregulation and volume regulation work in harmony (69).

Recently, an additional natriuretic mechanism was introduced (69, 85): digoxin-like substances, later followed by the discovery of a group of peptides from atrial tissue (atrial natriuretic hormone).

It has been suggested that this atrial natriuretic hormone opposes the renin-aldosterone system in situations involving high blood pressure and sodium surfeit (69, 85).

FROM CEREBRAL SALT WASTING TO SIADH, A HISTORICAL REVIEW

In 1950, Peters et al. described three patients with central nervous system disease (encephalitis, stroke, brainstem tumor), in whom balance studies revealed excessive sodium loss in the urine at the time of severe hypona-

tremia. This was termed cerebral salt wasting syndrome (95). The hyponatremia could not be corrected by high salt intake or mineralocorticoid administration. Adrenal and pituitary function tests were normal. Clinically, these patients exhibited dehydration. After volume expansion, the loss of sodium in the urine was increased. Later, similar case histories were reported (21, 144). It was suggested that the most probable explanation for urinary sodium loss was a decreased proximal tubular reabsorption of sodium.

After the syndrome of inappropriate antidiuretic hormone (SIADH) had been defined in 1957 by Bartter and Schwartz, who described it in two patients with bronchogenic carcinoma (11), cerebral salt wasting has seldom been reported.

In SIADH there is a continuing secretion of ADH, not appropriate to changes of plasma osmolality. Because of the secretion of ADH, extracellular volume and intravascular volume increase. As a result of expansion of the intravascular volume, dilutional hyponatremia occurs. Natriuresis takes place because volume expansion increases the glomerular filtration rate and inhibits the secretion of aldosterone. Balance studies showed that natriuresis is small and approximately equals intake. The high urinary sodium concentration in SIADH is explained by the fact that the sodium intake must be excreted in a small volume of urine (11).

The *Criteria of SIADH* include hyponatremia, serum hypo-osmolality, a urine osmolality which is higher than serum osmolality, continued urinary excretion of sodium in spite of hyponatremia, absence of hypovolemia, normal renal and adrenal functions, no diuretic medication and correction of hyponatremia after fluid restriction. However, the correction of hyponatremia after fluid restriction may also occur in hyponatremia from other causes (11, 36).

It has been suggested that hypouricemia is of diagnostic value in patients with SIADH, since only these patients have low levels of serum uric acid, whereas normal levels were found in patients with hyponatremia of other causes (12).

SIADH may occur in SAH but also in various other neurological disorders (70).

Head injury with and without skull fractures	Subdural hematoma
Herpes simplex encephalitis	Hydrocephalus
Tuberculous meningitis	Multiple sclerosis
Brain abscess	Central pontine myelinolysis
Systemic lupus erythematosus	Guillain-Barré syndrome
Cerebral infarction	Wernicke encephalopathy
Brain tumors	

Some authors think that SIADH is diagnosed too often, without a valid basis (36, 47). Zerbe et al. reported normal ADH levels in 80% of a group of 79 patients with various diseases who were thought to have SIADH (150). In a study of 17 patients with severe hyponatremia who met the criteria of SIADH, high levels of ADH were found only in patients with infections or carcinoma of the lung (123). In a large prospective study on the causes of hyponatremia, plasma ADH levels in patients who met the criteria of SIADH were significantly lower than in patients with hyponatremia from other causes (4).

In subarachnoid hemorrhage plasma ADH levels have seldom been measured in patients with hyponatremia. Gupta described two patients with SAH and SIADH with normal plasma ADH levels (47). Mather found elevated plasma ADH levels in only five of nine patients with hyponatremia caused by SIADH (75).

Nelson et al. (1981) further questioned the existence of SIADH. In a study of 12 patients with intracranial disease (6 with SAH), 10 had decreased intravascular blood volumes despite fulfilling the criteria for SIADH (88). In a monkey model of subarachnoid hemorrhage they observed primary natriuresis as the cause of hyponatremia rather than SIADH (89).

HYPONATREMIA, CLASSIFICATION AND DIAGNOSTIC APPROACH

The causes of hyponatremia vary according to the patients' volume status. In most cases of hyponatremia the total body sodium is constant, but the water content of the extracellular volume is at fault (109, 111).

Hyponatremia can be categorized in relation with extracellular volume status (109).

- I. *Hyponatremia associated with diminished extracellular fluid volume*
 - gastrointestinal losses
 - diuretic therapy
 - a variety of renal disorders
 - adrenal insufficiency
- II. *Hyponatremia associated with modest extracellular volume excess*
 - hypothyroidism
 - pain, emotion and antidiuretic drugs
 - SIADH
- III. *Hyponatremia associated with profound extracellular volume excess*
 - cardiac failure
 - nephrotic syndrome
 - cirrhosis
 - iatrogenic fluid loading (15)

Other causes of hyponatremia are pseudo hyponatremia caused by hypoproteinemia or paraproteinemia, hyperglycemic hyponatremia and laboratory error (3, 4).

CLINICAL FEATURES OF HYPONATREMIA

The signs and symptoms of hyponatremia are mostly manifestations of disturbed CNS functions and depend upon the severity and rapidity of the development of hyponatremia (7). Signs and symptoms do usually not occur until plasma sodium is less than 125 mmol/L. In general, no predictable correlation exists between the degree of hyponatremia and the alteration in consciousness. The signs consist of impaired consciousness, apathy, ataxia, asterixis, hemiparesis, seizures and coma.

MANAGEMENT OF HYPONATREMIA

Many patients with moderate degrees of hyponatremia are asymptomatic. The therapeutic approach must be directed towards the cause of the hyponatremia (e.g. discontinuation of diuretics; sodium and water restriction in the edematous hyponatremic patient). Rapid correction of hyponatremia is therefore justified only when central nervous system symptomatology *rapidly* develops.

Hyponatremia, whatever the cause, can always be corrected by infusion of hypertonic salt solution, but this effect is only transient because the sodium is rapidly excreted.

Fluid restriction is recommended in SIADH or other causes of water intoxication. However, one should keep in mind that a careful water balance is needed as the patient may be pushed into rapid dehydration. Rapid decline of the plasma sodium under 125 mmol/liter is associated with considerable mortality (about 50%) and morbidity (3-15%). On the other hand, rapid correction of hyponatremia is associated with central pontine myelinolysis. Ayus et al. concluded that this condition particularly occurred in alcoholic patients and that it was not related to the speed of correction of hyponatremia, but probably caused by the effect of the underlying disorder (10). Sterns et al. reviewed reports on patients with very severe hyponatremia and found neurological sequelae to be associated with correction of hyponatremia by more than 12 mmol per liter per day (115). However, acute symptomatic hyponatremia is a medical emergency and ought to be treated with hypertonic NaCl at a rate of infusion such that plasma sodium is raised at a rate of 2 mmol/liter per hour until a serum sodium of 125 to 130 mmol is achieved (6, 10). Recently, good results were reported with intravenous

29.2% saline (149), although complications such as heart failure and pulmonary edema may be associated with this therapy.

The treatment of hyponatremia in SAH is controversial. When a clinical deterioration in SAH occurs, together with hyponatremia, it is hard to tell which causes which, or whether there is a common cause. On the other hand, when hyponatremia occurs in a patient in good clinical condition, it is not known if "masterly inactivity" (36) or an aggressive approach is necessary. This controversy was one of the incentives for the studies reported in this thesis.

Chapter II

HYPONATREMIA AND CEREBRAL INFARCTION. IS FLUID RESTRICTION HARMFUL?

Following aneurysmal subarachnoid hemorrhage (SAH), patients are likely to develop hyponatremia, frequently attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (27, 61, 70, 129, 148). Because the hyponatremia of SIADH is often attributed to dilution caused by expansion of the extracellular volume, fluid intake is usually restricted (110).

Recently, Nelson and colleagues (88) questioned whether volume expansion occurs in SIADH. It has been further suggested that fluid restriction can cause hypovolemia and subsequent ischemia if vasospasm is present (53, 116). To elucidate this problem, we studied the relationship between hyponatremia and cerebral infarction in patients with subarachnoid hemorrhage.

PATIENTS AND METHODS

We studied 134 consecutive patients with signs and symptoms of SAH and with computed tomographic (CT) evidence of extravasated blood in the basal cisterns, suggesting a ruptured aneurysm. All patients were without evidence of another cause of SAH (130). Patients with normal angiographic findings or another cause of SAH were not included in the study.

All patients were admitted within 72 hours of the initial hemorrhage and took part in a randomized, double-blind, placebo-controlled trial of tranexamic acid (136) (65 patients were given tranexamic acid and 69 were given placebo).

In 99 of the 134 patients an aneurysm was demonstrated by angiography or at postmortem examination. In the other 35 angiography was not performed because surgical treatment of the aneurysm was not considered; these patients for whom operation was ruled out were those over 65 years of age and those exhibiting an impaired level of consciousness or ischemic cerebral deficits.

During the study period, which lasted four weeks or until death or operation, all patients were under continuous observation in an intensive care unit.

Most operations were carried out on the twelfth day after the presenting hemorrhage.

CT scanning was performed on admission and repeated at least weekly. Clinical deteriorations were studied prospectively. When a patient's condition deteriorated, the patient was reexamined and the CT scan was repeated.

Infarction was diagnosed by two criteria: (1) if a patient gradually developed a focal neurological deficit, with or without evidence of infarction on repeated CT scanning, and (2) if a gradual deterioration of consciousness occurred at least 1 point on the motor score of the Glasgow coma scale (120), with CT confirmation of ischemic changes.

Hyponatremia was defined as a sodium level lower than 135 mmol/L on at least two consecutive days, in the absence of hyperlipemia and paraproteinemia (conditions that may falsely suggest hyponatremia) (36).

Serum sodium levels were measured on admission and at least three times a week and reviewed retrospectively. The criteria for SIADH were hyponatremia (as just defined), serum osmolality lower than 280 mmol/L, urine osmolality higher than serum osmolality, continued urinary excretion of sodium in spite of hyponatremia, normal findings on renal function tests (blood urea nitrogen, serum creatinine), and absence of hypotension or severe hypothyroidism (36, 42). We defined fluid restriction as an intake of 1,000 ml or less per 24 hours. Patients with temperatures between 37 and 38°C were considered to have a restricted fluid intake when intake fell below 1,500 ml per 24 hours; in patients with temperatures between 38 and 39°C the crucial level was 1,750 ml per 24 hours.

RESULTS

Hyponatremia (sodium level of 120 to 134 mmol/L) developed in 44 (33%) of the 134 patients. It was mild (130 to 134 mmol/L) in 18, moderate (125 to 129 mmol/L) in 20, and severe (120 to 124 mmol/L) in 6. In all instances the hyponatremia developed between days 0 and 10 (median 4) after the hemorrhage. Twenty-five patients with hyponatremia fulfilled the laboratory criteria for SIADH (18% of 134). Twelve patients had other conditions that might have contributed to hyponatremia, sepsis (2 patients), severe vomiting (3 patients), renal disease (3 patients), Addison's disease (1 patient), and diuretics (3 patients). In 7 cases the cause remained unknown because of incomplete laboratory investigations.

Cerebral infarction was diagnosed in 46 of the 134 patients and confirmed by CT scan or postmortem study in 41. Infarction occurred 2 to 24 days (median 9 days) after the presenting hemorrhage.

Twenty-seven of the cerebral infarctions occurred in the 44 patients who developed hyponatremia, and 19 in the 90 patients who maintained normal sodium levels (χ^2 test, $p < 0.001$) (Table 1). When these abnormalities coincided, hyponatremia always preceded the signs and symptoms of

Table 1. Relationship between hyponatremia and cerebral infarction in 134 patients with subarachnoid hemorrhage

Serum sodium level	No. of patients		
	With infarction	Without infarction	Total
≥135 mmol/L	19*	71*	90
<135 mmol/L	27	17	44
Total	46	88	134

*Significantly different from number in hyponatremic group by chi-square test ($p < 0.001$).

cerebral infarction. Cerebral infarction occurred 2 to 14 days (mean 6 days) after the development of hyponatremia.

Infarction was more often fatal in patients with hyponatremia; 12 of the 27 infarctions in patients with hyponatremia resulted in death, in contrast to 6 of the 19 infarctions in patients with normal sodium levels (χ^2 test, $p < 0.01$).

The incidence of infarctions was higher in patients with fluid restriction, with or without sufficient evidence of SIADH (Table 2) (Fisher's exact test; $p = 0.004$). Seventeen patients with SIADH were fluid restricted; of these, 15 developed infarction. Nine patients with other causes of hyponatremia were fluid restricted; of these, 6 developed infarction.

Table 2. Relationship between fluid restriction and cerebral infarction in 44 patients with hyponatremia.

Patients with hyponatremia	No. of patients		
	With infarction	Without infarction	Total
Fluid restricted*	21**	5**	26
Normal fluid intake	6	12	18
Total	27	17	44

*See Methods section for criteria.

**Significantly different from number in group with normal fluid intake by Fisher's exact test ($p = 0.004$).

Tranexamic acid did not increase the incidence of hyponatremia. Among patients with infarction, 16 of the 27 with hyponatremia and 11 of the 19 with normal serum sodium levels were given tranexamic acid (Fisher's exact test; $p_2 = 1.0$). The level of consciousness on admission did not differ in patients with low and with normal sodium levels.

Of the 5 patients in whom cerebral infarction was inferred from focal signs without CT changes, 3 had normal sodium levels and 2 had hyponatremia.

Focal signs indicating cerebral infarction that developed during the course of hyponatremia persisted in all instances after correction of the electrolyte imbalance.

DISCUSSION

This study found the incidence of cerebral infarction after aneurysmal SAH to be significantly higher in patients who developed hyponatremia. Furthermore, patients with cerebral infarction and hyponatremia had a higher mortality than patients with cerebral infarction and normal sodium values.

We did not find episodes of clinical deterioration that could be attributed to hyponatremia alone, without clinical or radiological signs of cerebral ischemia. This pattern may be explained by the gradual development of hyponatremia and by the absence of sodium levels below 120 mmol/L (7).

The incidence of hyponatremia in our series was higher than that in the report of Döczi and colleagues (27) (33% versus 9%), a difference that may be explained by the more frequent determinations of sodium levels in our study. In addition, we found causes of hyponatremia other than SIADH.

Fluid restriction to correct hyponatremia was introduced after the description of the SIADH by Schwartz and co-workers (110). The action of antidiuretic hormone is believed to lead to an expansion of extracellular volume. Normally, the osmotic receptors depress the secretion of antidiuretic hormone after expansion of the extracellular volume, but in SIADH they function inappropriately as a result of osmotic resetting. This leads to a sustained secretion of antidiuretic hormone and a further increase in the extracellular volume, with subsequent suppression of secretion of aldosterone, hyponatremia, and natriuresis. In fact, in true SIADH, hyponatremia is a dilutional hyponatremia and not a true sodium depletion; therefore, fluid restriction is a recommended therapy (36, 42).

In patients with SAH (27, 61, 148), an inappropriate secretion of antidiuretic hormone was initially thought to explain the hyponatremia and natriuresis. Zerbe and colleagues (150), however, reported normal levels of antidiuretic hormone, and volume expansion could not always be demonstrated in patients with SIADH. Nelson and associates (88) even found a significant decrease in both plasma and total blood volume in patients who fulfilled the criteria for SIADH.

Before the description of SIADH, hyponatremia in patients with SAH was attributed to a natriuretic hormone that caused true sodium depletion. This phenomenon was termed cerebral salt wasting (21, 95), but the natriuretic hormone has not yet been identified. Nevertheless, recent evidence suggests that hyponatremia, after all, is caused by a true sodium loss and not by a dilution resulting from an increased extracellular volume (88, 89). If so, fluid restriction may be harmful rather than beneficial. If our patients with hyponatremia had a decrease in plasma volume, as Nelson and associates (88)

found in their patients, fluid restriction might have aggravated a hypovolemic state, leading to hemoconcentration and changes in blood viscosity. Hemoconcentration may be especially dangerous in patients with vasospasm and other characteristics that decrease cerebral perfusion pressure and result in prolonged ischemia. Hyponatremia developed between the second and the tenth day after the initial hemorrhage. Fluid intake was restricted in many of these patients at a time when they were at especially high risk of ischemic complications.

Many authors insist on an adequate volume status in patients with SAH, and others even advise volume expansion if signs and symptoms of ischemia develop (53, 63, 74). Until the incidence of hyponatremia and infarction in patients with a normal volume status is known more precisely, we conclude that fluid restriction to correct hyponatremia is potentially dangerous in patients with aneurysmal SAH.

Chapter III

VOLUME DEPLETION AND NATRIURESIS

INTRODUCTION

Many conditions can lead to hyponatremia, but if associated with a decreased serum osmolality and increased natriuresis, it is generally attributed to inappropriate secretion of antidiuretic hormone (27, 61, 110). In this syndrome, continued secretion of antidiuretic hormone results in increased extracellular fluid volume, increased body weight, and dilutional hyponatremia. Natriuresis is increased as volume expansion causes suppression of aldosterone, and possibly as a result of a decrease in tubular sodium reabsorption, but this need not necessarily result in a negative sodium balance (36, 110).

Originally, hyponatremia in cerebral diseases was thought to be caused by salt wasting (21, 95). Primary loss of sodium with a concurrent loss of extracellular fluid volume would result in a decrease in plasma volume and body weight, an increase in blood urea nitrogen, and a negative salt balance. This explanation was recently reintroduced (88) and indirectly supported by our observation that fluid restriction to correct hyponatremia in patients with subarachnoid hemorrhage increases the incidence of cerebral infarction (Chapter II). It is likely that fluid restriction impairs cerebral perfusion by aggravating preexisting hypovolemia.

To elucidate the cause of hyponatremia in subarachnoid hemorrhage - depletion or dilution - we performed a prospective study of plasma volume, sodium balance, and secretion of antidiuretic hormone in these patients.

PATIENTS AND METHODS

Patients

Twenty-one patients with subarachnoid hemorrhage were studied. Patients with signs and symptoms of subarachnoid hemorrhage and with computed tomographic (CT) evidence of blood in the basal cisterns suggesting a ruptured aneurysm, but without evidence of another cause of subarachnoid hemorrhage, were included (130, 133).

All patients were admitted within 48 hours of the initial hemorrhage. Patients with any of the following conditions were excluded: endocrine dis-

turbances, heart failure, renal failure, neoplasm, and treatment with diuretic drugs. We treated no one with diuretics, steroids, or antifibrinolytic agents.

In 18 of the 21 patients an aneurysm was demonstrated by angiography. In the other 3 patients angiography was not performed; surgical treatment was not indicated because of age (over 70) or impaired level of consciousness. However, rupture of an aneurysm in these patients was considered highly probable because of the presence of blood in the interhemispheric, suprasellar, or sylvian cisterns without evidence of another lesion (130).

During the study period, which lasted 10 days, all patients were under continuous observation in an intensive care unit. CT scan was performed on admission and repeated if a patient's clinical condition deteriorated.

Infarction was diagnosed if a patient had gradually developed a focal deficit and if CT scanning showed one or more areas of hypodensity. Rebleeding was diagnosed if sudden deterioration occurred and if CT scanning showed an increased amount of blood compared with the previous scan (137).

Fluid and sodium balance

We obtained daily measurements of electrolytes, blood urea nitrogen, creatinine, serum osmolality, and hematocrit. Hyponatremia was defined as a sodium level lower than 135 mmol/L on at least two consecutive days. When hyponatremia occurred, we measured creatinine clearance, thyroid function, and plasma cortisol concentrations. The criteria for inappropriate secretion of antidiuretic hormone were hyponatremia as defined above, serum osmolality lower than 280 mmol/L, a urine osmolality value higher than that of serum osmolality, continued urinary secretion of sodium in spite of hyponatremia, and absence of hypotension, hypothyroidism, Addison's disease, or renal failure (70, 110).

All patients had a minimal fluid intake of 1,500 ml per 24 hours. None were fluid restricted, even when hyponatremia occurred.

The sodium intake was calculated from the sodium content of the food, which was specially prepared, and from the sodium content of the fluids that were given intravenously for 5 days. Sodium excretion was measured in 24-hour urine samples. Salt balance was considered negative when sodium excretion in the urine was larger than the daily sodium intake. Loss of sodium from the skin or in the feces was not included in the calculations of sodium balance.

Plasma volume determinations

The patients studied underwent plasma volume determinations on admission and again on the sixth day after the initial hemorrhage or when hyponatremia occurred. Body weight was measured at the same time.

Plasma volume was determined by the isotope dilution technique with ^{131}I labeled to human serum albumin (HSA) (41). We injected intravenously 5 mg HSA labeled with a total dose of 158 kilobecquerels ^{131}I in 5 ml of physiological saline. Blood samples were taken before injection of the tracer substance and at 8 and 13 minutes after injection. Between 8 and 13 minutes, a given dose is evenly distributed throughout the blood volume and there is no disappearance into extravascular spaces (41). Plasma volume was calculated on a Gammatrac 1191 (Tracor Analytic).

In normal subjects, plasma volume has an average value of 40 ml per kilogram of body weight (41), but because most patients showed changes in body weight, we expressed the results in total plasma volume and calculated the percentage of change between the first measurements and the measurements taken after 6 days. Because bed rest alone may cause a decrease in plasma volume after 1 week (45), we considered only a decrease of more than 10% to be substantial.

Arginine vasopressin

We measured serum vasopressin concentrations in 19 of the 21 patients. The patients studied were selected for practical reasons and not because of clinical or biochemical features. As controls, we used plasma from 10 healthy volunteers. Vasopressin samples were taken every time plasma volume was determined. Plasma volume determinations did not affect the measurements of arginine vasopressin. Blood samples were taken without the use of a tourniquet and were immediately frozen at -70°C . Extraction of plasma samples and subsequent radioimmunoassay were carried out as described in detail elsewhere (28). Briefly, 20 mg of Vycor glass powder was added to the samples and after vigorous shaking the samples were centrifuged. Supernatants were discarded and the pellets were washed with cold water and 1 N hydrochloric acid. Pellets were resuspended in an aqueous acetone solution. After shaking and centrifugation, the supernatants were evaporated under a mild nitrogen stream. Residues were redissolved in a barbital buffer, pH 8, containing 5 mg human serum albumin per millimeter for subsequent measurements of arginine vasopressin by radioimmunoassay using a specific antiserum, W1E, which showed almost no cross reactivity (0.01%) with oxytocin. The inter-assay and intra-assay coefficients of variation were 11.9% and 14.8%, respectively. Tracer arginine vasopressin was prepared using the iodogen method, which is described elsewhere (106). The whole procedure, except the iodination, was carried out at 4°C .

RESULTS

Hyponatremia and Changes in Plasma Volume

Hyponatremia developed in 9 of the 21 patients on an average of 7 days after subarachnoid hemorrhage (range 3 to 9 days). In these 9 patients the serum sodium levels dropped to a median of 131 mmol/L (range 129 to 134 mmol/L). The sodium levels declined gradually and then normalized again without any therapeutic measure after an average interval of 4.5 days (range 2 to 9 days).

The plasma volume decreased between 10 and 20% in 6 of the 9 patients with hyponatremia, decreased less than 10% in 2, and increased 4% in 1. Of the 12 patients in whom sodium levels remained normal, plasma volume decreased more than 10% in 5 and less than 10% in 3. In 4 of these 12 patients plasma volume increased from 5 to 28% (Figure 1). The proportion of patients with a decrease in plasma volume of more than 10% was not significantly different in patients with normal sodium values (5 of 12 patients) compared with patients with hyponatremia (6 of 9 patients) (Fisher's exact test, $p_2 = 0.3$).

Sodium Balance

The actual fluid and sodium intake and output in patients with hyponatremia and patients with normal sodium values are illustrated in Figures 2 and 3. In 8 of the 9 patients who developed hyponatremia, we found a negative sodium balance, which always preceded the development of hyponatremia; 4 patients without hyponatremia also had a negative sodium balance. There was no difference in sodium intake between patients who had normal sodium values and patients who developed hyponatremia.

Plasma volume decreased more than 10% in 10 of the 12 patients with a negative sodium balance, and in only 1 of the 9 patients with a positive sodium balance. The difference is statistically significant (Fisher's exact test, $p < 0.01$).

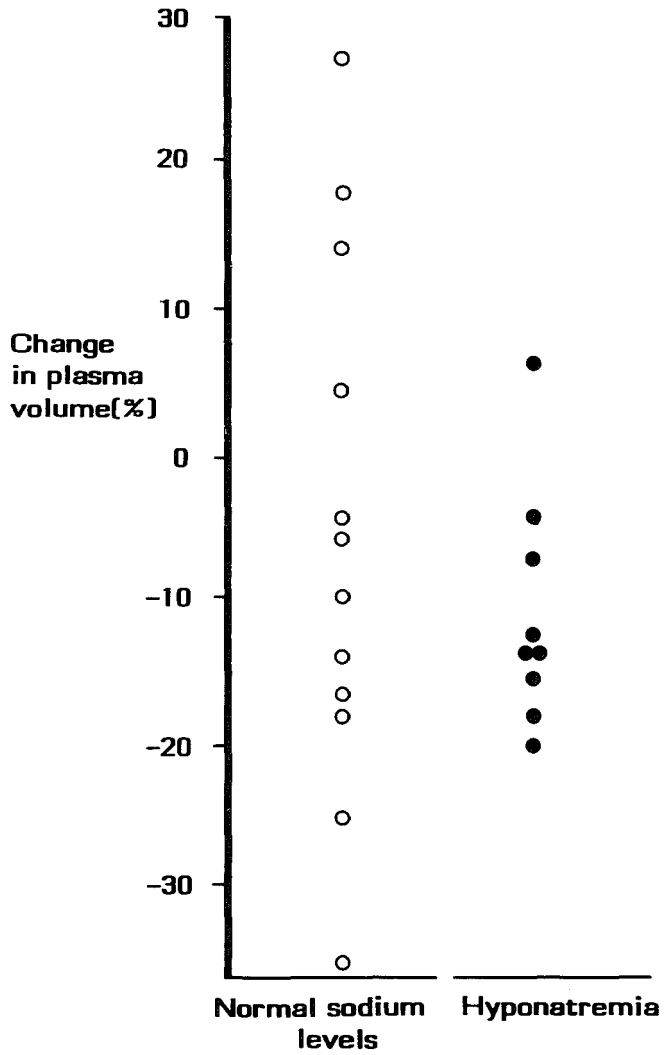


Figure 1. Plasma volume changes in 21 patients with a ruptured aneurysm. (open circles = normal sodium level; closed circles = hyponatremia).

mmol	DAY					CUMULATIVE			HYPO-NATRE-MIA ▲
	1	2	3	4	5	SODIUM INTAKE *	SODIUM BALANCE *	FLUID BALANCE °	
150 0 -150						850	+82	7.000	
200 0 -150						750	+497	4.720	▲
150 0 -150						502	+204	4.275	
150 0 -150						830	+115	4.800	
150 0 -150						327	+206	7.085	
150 0 -150						656	+205	5.470	
150 0 -150						583	-150	3.650	▲

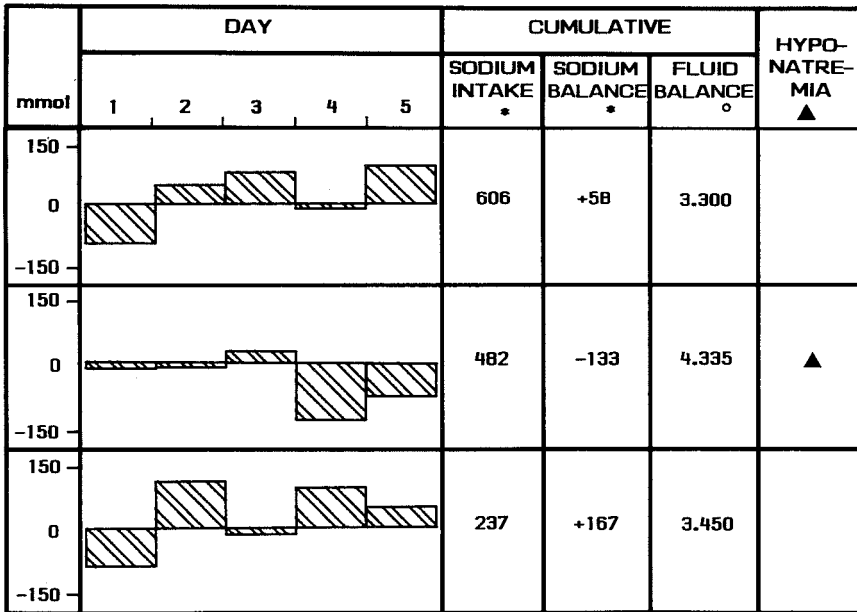


Figure 2. Sodium balance in patients with a plasma volume decrease of less than 10% (stars = data expressed in mmol, circles = data expressed in liters).

mmol	DAY					CUMULATIVE			HYPO-NATRE-MIA ▲
	1	2	3	4	5	SODIUM INTAKE *	SODIUM BALANCE *	FLUID BALANCE °	
150 0 -150						677	-251	3.255	▲
150 0 -150						583	-110	4.800	
150 0 -150						874	-100	3.825	▲
150 0 -150						988	+325	5.030	
150 0 -150						783	-87	4.450	▲
150 0 -150						636	-146	3.585	
150 0 -150						356	-255	3.705	

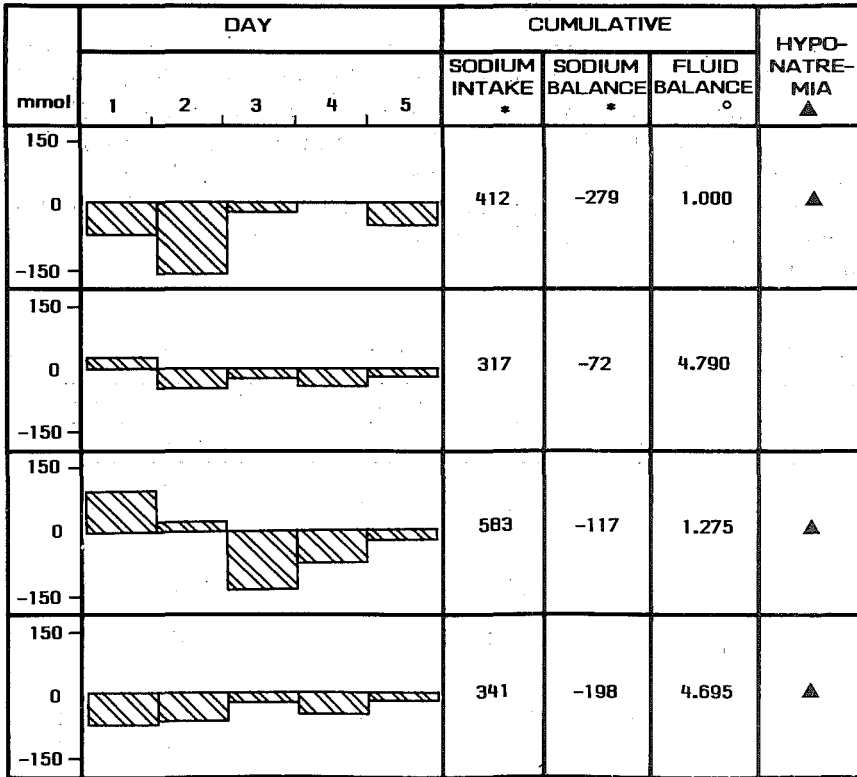


Figure 3. Sodium balance in patients with a plasma volume decrease of more than 10%. (stars = data expressed in mmol; circles = data expressed in liters).

Hyponatremia and Other Laboratory Findings

We have summarized in the Table the results on admission and at the time of the second plasma volume determination. The thyroxine values ranged from 75 to 124 nmol/L (median 110). The cortisol values ranged from 215 to 717 nmol/L (median 496). The creatinine clearance ranged from 79 to 189 ml/minute (median 124). These values are within normal limits.

In none of the patients high glucose levels were observed. In 3 of the 21 patients a temporary glucosuria was observed during the first days of observation.

Table 1. Laboratory findings in patients with normal sodium levels and hyponatremia*

Laboratory measurement	Normal sodium		Hyponatremia	
	Range	Median	Range	Median
Hematocrit (%)	35-47	41	35-46	42
	37-49	46	35-47	42
Blood urea nitrogen (mmol/liter)	3.6-7.7	5.8	2.8-8.3	5.7
	2.7-9.7	7.1	2.7-8.4	7.9
Creatinine (μ mol/liter)	58-103	70	49-98	68
	61-99	86	52-124	69
Plasma osmolality (mOsm)	276-298	289	273-306	287
	266-300	280	272-300	275
Urine osmolality (mOsm)	356-1064	767	501-805	671
	280-805	570	456-927	794

*Top number = values on admission; bottom number = values at the time of the second plasma volume determination.

Hyponatremia and Body Weight

Body weight was repeatedly measured in patients who developed hyponatremia and decreased in all (range 1 to 2.2 kg; median 2 kg). The caloric intake ranged from 1,67 kilojoules to 7,350 kilojoules (median 4,691 kilojoules), so weight loss in this short time span cannot have resulted from caloric insufficiency. Body weight loss in patients who developed volume depletion and did not develop hyponatremia was within the same range.

Hyponatremia and Arginine Vasopressin Levels

Of the 19 patients in whom arginine vasopressin was measured, 8 developed hyponatremia, with levels ranging from 1.1 to 14.3 pg/ml (median 2.3 pg/ml). The 11 patients without hyponatremia showed similar or even higher values. On second measurement (6 days after subarachnoid hemorrhage or earlier if hyponatremia developed), the arginine vasopressin levels had decreased whether hyponatremia occurred or not (range 0.1 to 2.6 pg/ml; median 1.6 pg/ml). Levels remained slightly elevated compared with control levels (range 0.6 to 2.5 pg/ml; median 0.7 pg/ml) (Figure 4). There was no association in the second week between changes in plasma volume and levels of arginine vasopressin.

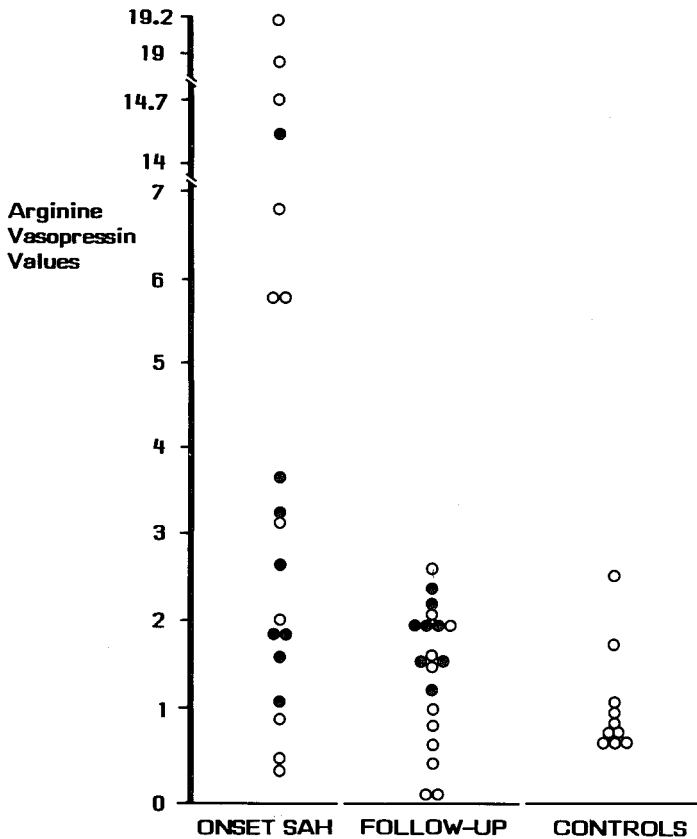


Figure 4. Arginine Vasopressin values in 19 patients with a ruptured aneurysm (open circles = normal sodium values, closed circles = hyponatremia, SAH = subarachnoid hemorrhage).

Clinical Features

The level of consciousness on admission, measured with the Glasgow coma scale (120), was not different in patients with continuously normal sodium values and in patients who later developed hyponatremia.

Ten of the 21 patients deteriorated clinically, 9 from rebleeding and 1 from cerebral infarction, which was confirmed by CT scan. None of the deteriorations was related to low serum sodium values.

DISCUSSION

This study demonstrates that hyponatremia in patients with an aneurysmal subarachnoid hemorrhage is associated with a decrease in plasma volume in most patients and with a decrease in body weight in all. The combination of hyponatremia and decreased plasma volume was always preceded by a negative sodium balance. In addition, the blood urea nitrogen increased in patients with hyponatremia. Serum vasopressin levels were increased on admission in most patients and decreased during the first week whether or not hyponatremia developed. The initial rise of vasopressin levels may be related to a sudden increase in intracranial pressure or to the onset pain of subarachnoid hemorrhage (9, 75, 82). All these findings are consistent with a salt wasting syndrome rather than with inappropriate secretion of antidiuretic hormone. On the other hand, 3 patients with hyponatremia did not show a fall in plasma volume (it even increased in one). It is possible that in these patients natriuresis was followed by a renal compensation of water excretion.

A surprising finding is that plasma volume decreased considerably in half of the patients, including some without hyponatremia. With one exception, all these patients had a negative balance caused by excessive natriuresis. Excessive loss of sodium in the urine may be caused by inhibition of tubular sodium reabsorption with a concurrent loss of extracellular fluid, resulting in a decrease in plasma volume. The factor that causes the inhibition of tubular reabsorption in subarachnoid hemorrhage is unknown. This natriuretic factor might be released after damage to the hypothalamus (95). Not all the patients with a negative sodium balance developed hyponatremia. It is possible that the concomitant renal fluid loss increased the serum sodium level and thereby prevented the development of hyponatremia.

Our observations confirm the previous reports of Nelson and associates (88, 89). In their clinical study, although done without serial measurements, they found subnormal plasma volumes in 6 of 8 patients with subarachnoid hemorrhage who had hyponatremia and who fulfilled the laboratory criteria for the syndrome of inappropriate secretion of antidiuretic hormone (88). The observations in their subsequent report, based on experiments in monkeys, clearly showed the development of a negative salt balance before hyponatremia occurred, but plasma volumes were not significantly decreased (89).

Maintenance of an adequate intravascular volume is important in the management of patients with aneurysmal subarachnoid hemorrhage (53). Patients with subarachnoid hemorrhage are threatened by vasospasm, which may lead to cerebral ischemia. Cerebral blood flow may be further impaired in patients with an increased blood viscosity caused by volume depletion. The importance of an adequate intravascular volume has been corroborated by reports describing improvements in signs attributed to cerebral ischemia when volume expansion was given (63, 98, 116). The effectiveness of volume expansion in increasing cerebral perfusion may be explained by an improvement in blood viscosity or by a rise in cardiac output.

Patients with hyponatremia are especially at risk of developing cerebral ischemia (Chapter II). This study confirms that these patients have volume depletion and therefore ought to be treated with volume expansion. In addition, we demonstrated that a decrease in plasma volume also occurs in patients with normal sodium levels. Therefore, monitoring salt balance becomes of great importance in patients with subarachnoid hemorrhage. When volume depletion coincides with a negative sodium balance, the administration of hypertonic sodium or volume replacement seems justified (63, 98, 116). However, it remains to be shown that such measures can effectively prevent cerebral ischemia.

Chapter IV

THE EFFECT OF ANTIHYPERTENSIVE TREATMENT

INTRODUCTION

Immediately after aneurysmal subarachnoid hemorrhage (SAH), a quarter to half of the patients without a previous history of hypertension have an elevated blood pressure (8, 43). The rationale for antihypertensive treatment in these patients is to reduce the chance of rebleeding by decreasing the pressure against the weakened wall of the aneurysm (43, 125). However, reduction of blood pressure might also decrease cerebral perfusion pressure in patients with an impaired autoregulation and in this way enhance the risk of cerebral ischemia (40, 53). This has been supported by the observation that neurological deterioration and a fall in cerebral blood flow occurred when dopamine treatment was withdrawn after aneurysm surgery (78). Conversely, ischemic deficits can sometimes be reversed by induced hypertension (17, 68, 83).

In this study we reviewed a prospectively collected series of patients to investigate the relation between the level of the blood pressure or the institution of antihypertensive treatment on the one hand and the development of rebleeding or ischemia on the other.

PATIENTS AND METHODS

Patients

We studied 134 consecutive patients with signs and symptoms of subarachnoid hemorrhage and with CT-scan evidence of extravasated blood in the basal cisterns, suggesting a ruptured aneurysm (130). Patients with normal angiography or another cause of SAH were excluded (133).

All patients had been entered into a double-blind, placebo-controlled trial on the effectiveness of tranexamic acid (136). Computerized tomography scanning was carried out on admission and was repeated every week and within six hours of any clinical deterioration.

Assessment of outcome and of events

Outcome was assessed at three months according to the five-point Glasgow outcome scale (60). For the purpose of analysis this scale was collapsed into three groups, viz. dead, persistent vegetative state/severe disability (i.e. dependent), and moderate disability/good recovery (i.e. independent).

Cerebral infarction was diagnosed if a patient had gradually deteriorated and developed a focal neurological deficit, with or without evidence of infarction on repeat CT scans, or if a gradual deterioration of consciousness had occurred (at least one point on the motor score of the Glasgow Coma Scale) with CT confirmation of ischemic changes (136).

Rebleeding was diagnosed if a sudden deterioration was associated with increased hemorrhage on a CT scan or at autopsy, on comparison with the previous CT scan, or when sudden deterioration and death occurred without the possibility of proof by CT scanning and when autopsy was refused (136).

All patients were under continuous observation in an intensive care unit. Blood pressures were measured and recorded every three hours by the usual manometric method, from the day of admission until the 14th day or until operation or death. The average of these daily measurements was calculated for both systolic and diastolic values from the values at 6, 12, 18 and 24 hours. In patients who had been on antihypertensive medication before the hemorrhage, this treatment was discontinued. Antihypertensive treatment was started if a single recording showed a diastolic blood pressure of 110 mm Hg or more. These patients were treated with at least 150 micrograms clonidine intramuscularly. The aim was to bring back the diastolic blood pressure to levels under 110 mmHg. When it was not possible to lower the blood pressure with doses of clonidine up to 900 micrograms daily, β -blocking agents or diuretics were added.

Some factors that were taken into account because they are known to be associated with an increased incidence of cerebral infarction were defined as follows:

Hyponatremia was defined as a sodium level lower than 135 mmol/L on at least two consecutive days, in the absence of hyperlipidemia and paraproteinemia. Serum sodium levels were measured at least three times a week.

The amount of cisternal and intraventricular blood was graded as described before (56, 133).

As a linear measurement of ventricular size, we used the bicaudate index, that is the width of the frontal horns at the levels of the caudate nuclei divided by the corresponding diameter of the brain. The width of the third ventricle was measured on the slice where the third ventricle had the maximal transverse diameter. The bicaudate index and the width of the third ventricle were converted into a relative size by dividing the absolute values by the upper limit for age, as described elsewhere (134) and in detail in Chapter V.

Statistical analysis

Distributions in 2×2 tables were analyzed with the Chi-square test. Combined 2×2 tables were analyzed with the Mantel-Haenzel test. The significance of the different factors that were associated with cerebral ischemia were assessed by means of logistic regression.

RESULTS

Eighty of the 134 patients (60%) were given antihypertensive medication soon after admission. To 53 of these 80 patients, only clonidine was given, in four to six intramuscular gifts per day. In the remaining 27 patients (34%) clonidine alone did not sufficiently reduce the blood pressure, for which reason it was combined with other antihypertensive drugs: β -blocking agents in 10, diuretics in nine, both β -blocking agents and diuretics in three, and β -blocking agents as well as other antihypertensives in five.

The Figure shows the comparison of average systolic and diastolic blood pressures among patients with and without antihypertensive treatment. Diastolic blood pressures in treated patients were kept below 110 mm Hg, but still remained around 100 mm Hg. The mean systolic blood pressure in the treated patients was about 160 mm Hg. On average, both diastolic and systolic pressures were still higher than in patients without antihypertensive treatment.

Antihypertensive treatment and outcome

Review three months after the hemorrhage showed that there was no significant difference in outcome between the patients who were given antihypertensive treatment and patients with normal blood pressures (Table 1).

Death occurred in 41 of 80 patients (51%) treated with antihypertensive drugs, and in 27 of 54 patients (50%) not treated with antihypertensive drugs.

Antihypertensive treatment and rebleeding

Rebleeding occurred in 30 (22%) of the 134 patients. Although the 80 patients treated with antihypertensive drugs had on average a higher blood pressure than patients without antihypertensive treatment (Figure), only 12 (15%) had a rebleed, whereas rebleeding occurred in 18 (33%) of the 54 patients without antihypertensive treatment ($\chi^2 = 6.23$, 1 df, $p = 0.012$).

The only other factor related to rebleeding was treatment with tranexamic acid, also in an inverse direction. Of the patients on antihypertensive treatment, slightly less than half were treated with tranexamic acid (38/80), versus precisely half of the remaining patients (27/54). Factors such as a

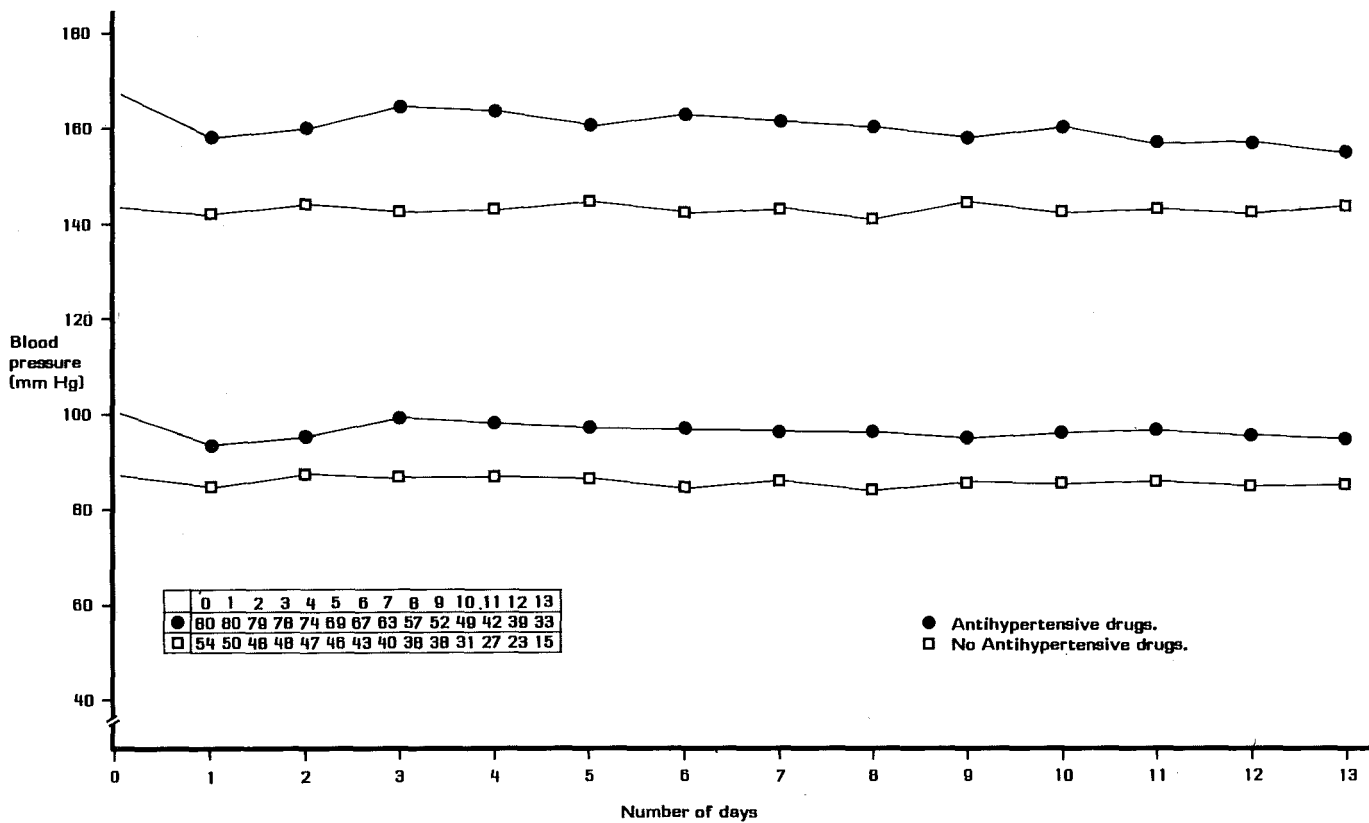


Figure: Average systolic and diastolic blood pressure values in the first two weeks after admission in 134 patients with SAH treated or untreated with antihypertensive drugs. (Inset shows numbers of patients (alive and unoperated) from day 0 to day 13.)

Table 1. Outcome at three months in 134 patients with SAH. (No. of patients (%)).

Outcome*	Antihypertensive drugs		No antihypertensive drugs	
Dead	41	(51)	27	(50)
Dependent	10	(13)	5	(9)
Independent	29	(36)	22	(41)
Total	80	(100)	54	(100)

*In our study the Glasgow outcome scale was collapsed into three groups, viz. dead, dependent (persistent vegetative state or severe disability) and independent (moderate disability or good recovery).

history of cardiovascular disease (TIA's, angina, myocardial infarction, brain infarcts), history of hypertension, loss of consciousness at ictus, the amount of blood on CT, level of consciousness on admission, age and sex, were all not significantly related with rebleeding.

Antihypertensive treatment and cerebral infarction

Cerebral infarction occurred in 46 (34%) of all patients in the series. Of those treated with antihypertensive drugs, 32 (40%) had a cerebral infarct, compared with only 14 (26%) of the patients without antihypertensive treatment ($\chi^2 = 6.07$, $p = 0.014$).

The factors associated with cerebral infarction in this group of patients are shown together in Table 2. Hyponatremia was the most powerful risk factor, and the other risk factors were also assessed after correction for hyponatremia (Table 2). Cerebral infarction occurred 2 to 14 days (mean 6 days) after the

Table 2. Factors associated with cerebral infarction.

Variable	χ^2 (1 d.f.)	P value	After adjustment for hyponatremia	
			χ^2 (1 d.f.)	P value
Loss of consciousness	5.35	0.021	6.12	0.013
History of cardiovascular disease	4.20	0.040	6.40	0.011
Enlarged lateral ventricles	1.76	0.185	0.35	0.554
Enlarged third ventricle	3.70	0.054	0.68	0.411
Cisternal blood	8.89	0.003	5.46	0.019
Intraventricular blood	7.66	0.006	4.25	0.039
Tranexamic acid treatment	4.85	0.028	3.12	0.077
Antihypertensive treatment	6.07	0.014	3.11	0.078
Hyponatremia	20.85	<0.001	—	—

development of hyponatremia. After adjustment for hyponatremia the incidence of infarction in patients treated with antihypertensive drugs is still higher than in patients without this treatment, but the difference is no longer statistically significant ($p = 0.078$). The confounding association between antihypertensive treatment and hyponatremia was not statistically significant in its own right ($p = 0.059$) and there was no relation between diuretic treatment and hyponatremia ($\chi^2 = 0.36$, 1 df, $p = 0.54$).

In the 104 patients who had no previous history of hypertension, the association between antihypertensive treatment and cerebral infarction was also statistically significant ($p < 0.02$, Table 3). In the 30 patients known to be hypertensive, this was not the case, but only three patients did not receive antihypertensive treatment. On the whole, the incidence of cerebral infarction was higher in patients with previous hypertension than in those without such history, although this difference did not reach statistical significance ($p = 0.11$).

Table 3. Incidence of cerebral infarcts related to history of hypertension and antihypertensive drugs.

	Antihypertensive drugs	No antihypertensive drugs	Total cases
History of hypertension			
total cases	27	3	30
no. infarcts	12	2	14
% infarcts	44	67	47
No history of hypertension			
total cases	53	51	104
no. infarcts	22	10	32
% infarcts	42	20	31
Totals			
total cases	80	54	134
no. infarcts	34	12	46
% infarcts	43	22	34

Blood pressure levels just before rebleeding or infarction

Because the blood pressures before rebleeding or infarction might show a temporary change, we also looked at the blood pressure levels just before these events. We compared the average blood pressures during the last 24 hours before rebleeding with the average values during the last 24 hours before the first signs of cerebral ischemia developed.

The pre-event blood pressure levels corresponded well with the levels in the

first week after admission, in that patients with infarcts had higher blood pressures – and more often antihypertensive treatment – than patients with rebleeds” (Table 4). In patients with rebleeds, 7 (23%) had an average systolic blood pressure higher than 160 compared with 21 patients (46%) with infarcts ($\chi^2 = 3.88$, $p = 0.048$). Similarly, four patients (13%) who rebled had an average diastolic pressure higher than 100, while 17 (37%) with infarcts had these values ($\chi^2 = 5.06$, $p = 0.024$).

Table 4. Average systolic and diastolic blood pressure values 24 hours before rebleeding and cerebral infarction. (No. of patients %).

Average systolic blood pressure	24 hours before rebleeding	24 hours before cerebral infarction
120-140 mm Hg	8 (27)	5 (11)
141-160 mm Hg	15 (50)	20 (43)
161-180 mm Hg	7 (23)	11 (24)
181-200 mm Hg	0	10 (22)
Total	30	46

Average diastolic blood pressure	24 hours before rebleeding	24 hours before cerebral infarction
≤ 80 mm Hg	5 (17)	3 (6)
81-100 mm Hg	21 (70)	26 (57)
101-120 mm Hg	4 (13)	16 (35)
121-140 mm Hg	0	1 (2)
Total	30	46

In addition, fluctuations in systolic and diastolic pressures (the difference between highest and lowest values) during the last 24 hours before a rebleed were compared with fluctuations during the 24 hours before the signs of cerebral ischemia developed (Table 5).

Fluctuations of more than 40 mm Hg of systolic values were more often found in patients with infarcts, but not statistically significant ($0.1 > p > 0.05$).

Table 5. Fluctuation of blood pressure (difference between highest and lowest value) during 24 hours before rebleeding or infarction. SBP = systolic blood pressure; DBP = diastolic blood pressure. (No. of patients %).

Fluctuation of blood pressure in mm Hg	24 hours before rebleeding		24 hours before cerebral infarction	
	SBP	DBP	SBP	DBP
0-20	16 (53)	17 (57)	16 (35)	19 (41)
21-40	8 (27)	12 (40)	11 (24)	21 (46)
41-60	4 (13)	1 (3)	10 (22)	4 (9)
> 60	2 (7)	0	9 (19)	2 (4)
Total	30	30	46	46

No dependence between cerebral rebleeding and infarction

To investigate if antihypertensive treatment decreased the incidence of rebleeds by increasing the number of deaths from infarction, which would leave fewer patients at risk of rebleeding, we compared the distribution of the times to the first event (rebleeding or infarction).

The times to rebleeding or infarction were similarly distributed (Wilcoxon test $t = 86.5$, $p > 0.05$). In addition, the reduced incidence of rebleeding with antihypertensive drugs was also evident in patients without infarction; 8 of 45 or 18% rebled with antihypertensive treatment, and 14 of 43 or 32% without these drugs.

DISCUSSION

This study demonstrates that antihypertensive treatment did not improve outcome at three months in patients with aneurysmal subarachnoid hemorrhage. The patients were not randomized to antihypertensive treatment, but treatment was started when diastolic blood pressures were higher than 110 mm Hg and our intention was to reduce the diastolic blood pressure below 110. Despite this, the average blood pressures in patients treated with antihypertensive drugs remained higher than in patients without this treatment. Although the outcome was similar, there was a significant difference in both rebleeding and infarction rates in patients with antihypertensive treatment: fewer rebleeds and more infarcts occurred, notwithstanding the higher blood pressures.

The higher incidence of rebleeding in the untreated group could neither be explained by temporarily high blood pressures during the last 24 hours before the rebleed, nor by marked systolic or diastolic fluctuations. The only other factor that showed a significant negative relation with rebleeding, treatment with tranexamic acid, proved to be independent.

The increased incidence of infarction (often with fatal outcome) after antihypertensive treatment might theoretically account for the reduction in the rebleeding rate, because fewer patients might be left at risk for rebleeding. However, the times to the onset of rebleeding and infarction were similar, and antihypertensive treatment reduced rebleeding also in patients without infarction.

The increased infarction rate in patients treated with antihypertensive drugs cannot simply be attributed to low blood pressures, because the average blood pressures in these patients were still higher than in patients without antihypertensive treatment. Pre-existing hypertension had to be discounted as an underlying factor, because antihypertensive treatment also increased the infarction rate in patients without such a history. When we related the association between antihypertensive treatment and cerebral infarction with other factors associated with cerebral infarcts, hyponatremia

proved to be the most significant of all. After adjustment for hyponatremia the rate of infarcts in patients treated with antihypertensive drugs is still higher but the significant association disappeared. The association between antihypertensive treatment and hyponatremia was weak, however. It could not be attributed to diuretic treatment.

Are the results of this study in keeping with those of others? Richardson et al. found a relationship between hypertension and rebleeding in patients with anterior communicating aneurysms, but not with posterior communicating aneurysms (101, 102). Nibbelink et al. found an increased rebleed rate in patients treated with drug-induced hypotension (90). Therefore, the common notion that high blood pressures predispose to rebleeding has little support from previous series, although rebleeding was poorly defined in these studies. The diagnosis was based mainly on clinical features, and it has been demonstrated that this results in an overestimation of the rebleeding rate (137).

What might be the explanation for the paradoxical finding that antihypertensive treatment, although resulting in blood pressures that are still higher than in untreated patients, yet increases infarction and decreases rebleeding? Hypertension itself or antihypertensive treatment might inhibit fibrinolysis. This would explain the decreased rate of rebleeding and perhaps also the increased rate of infarction, since inhibition of fibrinolysis - at least by tranexamic acid - is accompanied by an increased incidence of infarcts. However, such an effect of high blood pressure or of antihypertensive treatment (in particular clonidine, β -blocking agents and diuretics) has never been reported (79).

Many factors contribute to the pathogenesis of cerebral ischemia (56). Vasospasm, often identified with cerebral ischemia, could not be assessed in our study, because angiography was not repeated or even performed in all patients. Besides that, hyponatremia proved to be one of the most important determinants, probably by the concomitant decrease in plasma volume (Chapter III).

Hypertension might perhaps be considered a response to vasospasm, in order to maintain cerebral perfusion pressure, which effect can be negated if antihypertensive drugs are given. Nevertheless, the possible relationship between antihypertensive treatment and hyponatremia illustrates that the order and the interrelationship of these three factors remain obscure.

The results of this study have practical implications. Until we have further knowledge of the incidence of rebleeding and cerebral infarction in patients with untreated hypertension, there seems no need for antihypertensive treatment in aneurysmal subarachnoid hemorrhage, since reduction of rebleeding is achieved only at the expense of an increased incidence of infarction, with similar outcomes as the net result.

Chapter V

ENLARGEMENT OF THE THIRD VENTRICLE AND HYPONATREMIA

INTRODUCTION

Hyponatremia following aneurysmal subarachnoid hemorrhage (SAH) is not an infrequent finding and is associated with an increased risk of cerebral infarction (Chapter II).

Hyponatremia was previously attributed to an inappropriate secretion of antidiuretic hormone (27, 61, 70, 129, 148), but recently it was demonstrated that hyponatremia is a result of salt wasting (88, Chapter III). What factors mediate natriuresis after SAH remains to be established.

In a previous study, a relationship was found in patients with SAH between the development of hyponatremia and the presence of hydrocephalus on admission (134). A possible explanation was that enlargement of the third ventricle might interfere with hypothalamic function. In that study (134), however, the width of the third ventricle was not measured, as the diagnosis of acute hydrocephalus was based on the width of the lateral ventricles. Therefore, the relationship between hyponatremia and the size of the third ventricle was separately investigated.

PATIENTS AND METHODS

A review was done of the CT scans of 134 consecutive patients with signs and symptoms of a subarachnoid hemorrhage and with computed tomographic evidence of extravasated blood in the basal cisterns, suggesting a ruptured aneurysm (130). Patients with causes other than a ruptured aneurysm or patients with a negative angiogram were excluded (133). CT scanning was performed on admission, always within 72 hours of the bleeding, and was repeated weekly and after any clinical deterioration. An aneurysm was confirmed by angiography or postmortem examination in 99 of the 134 patients. In 35 patients angiography was not performed because of age over 65, or poor clinical condition from the initial bleed or from secondary deterioration from any cause. In these patients the diagnosis was based on CT evidence only, particularly signs of blood in the basal cisterns (130) and absence of lesions other than an aneurysm (133). This consecutive series of

patients was part of a randomized, double-blind, placebo-controlled trial on the effectiveness of tranexamic acid (136). One patient died within 24 hours of massive intraventricular hemorrhage and was not included in the analysis. The remaining 133 patients were studied for a 4-week period after the presenting hemorrhage or until death or operation within this time. During this period all patients were under continuous observation in an intensive care unit. 52 patients underwent clipping of the aneurysm; most operations were carried out on the twelfth day after the presenting hemorrhage.

The width of the third ventricle on the initial CT scan was measured with a transparent ruler from X-ray films, and multiplied by the appropriate magnification factor – there were two CT machines – to obtain the real size. The slice where the third ventricle had the maximal transverse diameter was chosen. The normal values of the third ventricle were used as described by Meese (77). The upper limit of normal (90th percentile) was defined as: 5 mm at age 40 or under, 6 mm at age 50, 7 mm at age 60 and 9 mm at age 80. The width of the third ventricle was converted into a relative size by dividing the width of the third ventricle by the upper limit for age.

The bicaudate index was defined as the width of the frontal horns at the level of the caudate nuclei, divided by the corresponding diameter of the brain. The bicaudate index was converted into a relative size by dividing the bicaudate index by the upper limit for age for each half decade (95th percentile) as previously described (133).

At the time of measurement, the investigators had no knowledge of the clinical condition of the patients and, in particular, they were not aware which patients had developed hyponatremia.

The amount of cisternal blood on the initial CT scan was separately graded for ten cisterns and fissures. Patients were then distinguished into those with no cisternal blood or a small amount in only one cistern or fissure and those with frank cisternal hemorrhage. This dichotomy appeared to be related to the incidence of infarcts, according to our own data (56) and those of others (65).

Similarly, the amount of intraventricular blood on the initial CT scan was graded separately for each ventricle, on a scale of 0 to 3. A total score of 2 usually represented sedimentation of red blood cells in the dependent parts of the ventricular system, and only higher scores were regarded as frank intraventricular hemorrhage.

Hyponatremia was defined as a sodium level lower than 135 mmol/L on at least two consecutive days, in the absence of hyperlipemia or hyperproteinemia. Serum sodium levels were measured on admission and at least three times a week.

CT scanning was repeated weekly and after each clinical deterioration. Cerebral infarction was diagnosed if (1) there were new focal signs or a decrease in the level of consciousness, usually of gradual onset; and (2) CT showed a hypodense lesion compatible with the clinical signs, or there were no lesions other than infarction that could explain the clinical signs.

RESULTS

In this series of 133 patients, the admission CT scan showed enlargement of the lateral ventricles and also of the third ventricle in 26 patients (20%), of the third ventricle only (Figure 1) in 15 patients (11%), and of the lateral ventricles only (Figure 2) in 3 patients (2%). Hyponatremia developed in 44 of the 133 patients (33%), always between day 2 and day 10 (median day 4) after the hemorrhage. It was mild (130 to 134 mmol/L) in 18, moderate (125 to 129 mmol/L) in 20 and severe (120 to 124 mmol/L) in 6 patients.



Figure 1. Initial scan showing normal relative size of the lateral ventricles [bicaudate index (0.19) divided by the upper limit for age 57 (0.19) equals 1.00] and enlargement of the third ventricle [third ventricle size (8 mm) divided by the upper limit for age 57 (7 mm) equals 1.4].

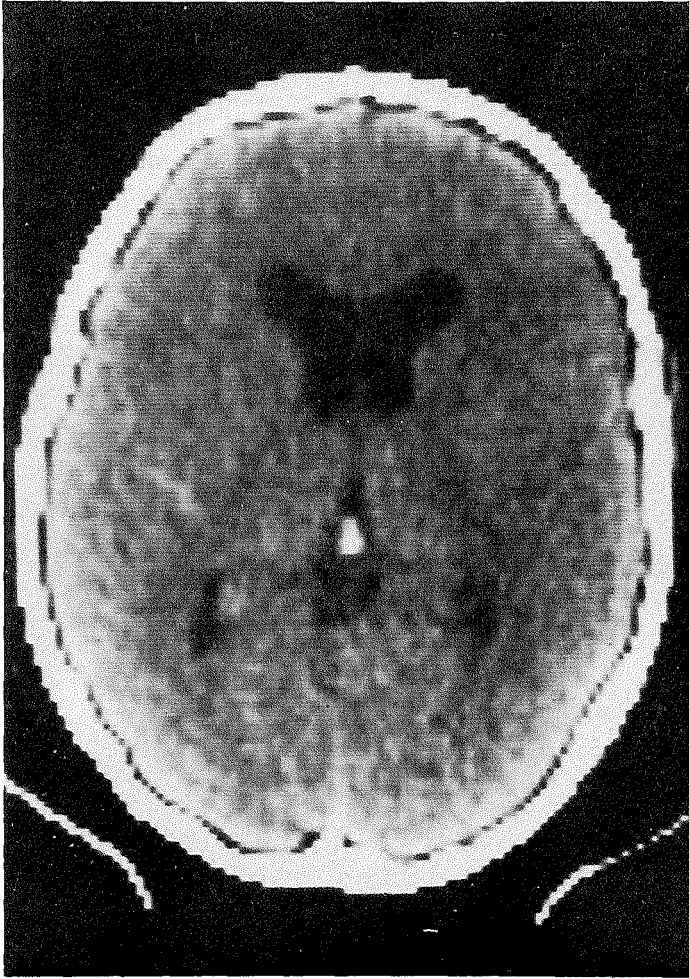


Figure 2. Initial CT scan showing increased relative size of the lateral ventricles [bicaudate index (0.19) divided by the upper limit for age 41 (0.17) equals 1.12] and normal size of the third ventricle [third ventricle size (6 mm) divided by the upper limit for age 41 (6 mm) equals 1.0].

Figure 3 illustrates the relative size of the third ventricle in patients with and without hyponatremia. It is clear that hyponatremia more often developed in patients with an enlarged third ventricle on admission (χ^2 -test, $p < 0.05$). However, the degree of hyponatremia (not shown) did not linearly correlate with the degree of ventricular enlargement.

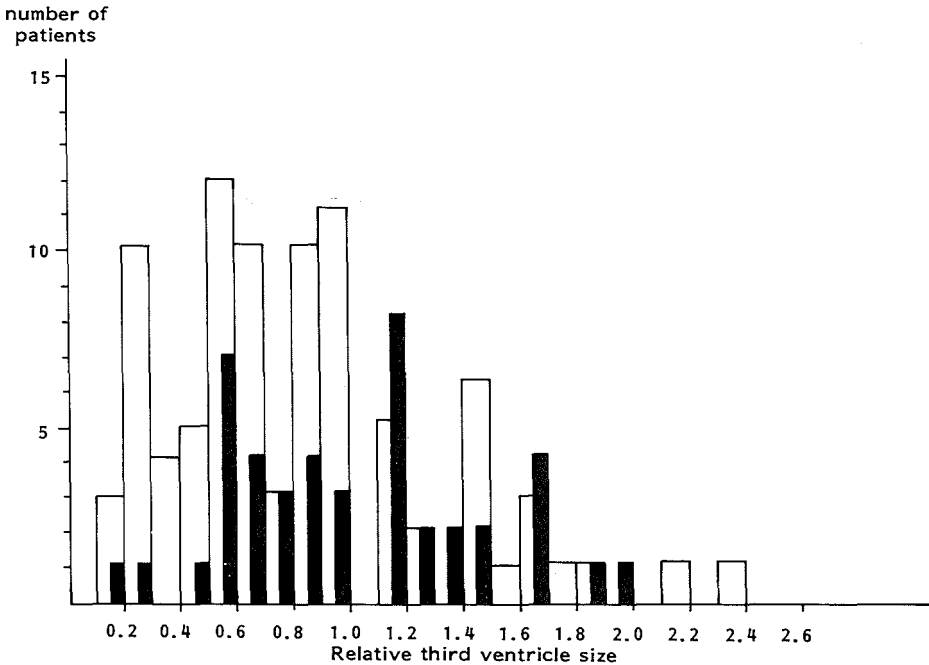


Figure 3. Diagram showing the distribution of relative third ventricle size (absolute width divided by upper limit for age) in patients with normal sodium values and in patients with hyponatremia (black bars).

The incidence of hyponatremia in the three subgroups of patients with hydrocephalus was compared with that in patients with normal ventricles (Table 1). Hyponatremia occurred significantly more often in patients with enlargement of the lateral ventricles as well as of the third ventricle, and also in patients with isolated enlargement of the third ventricle. An increased size of the lateral ventricles but not of the third ventricle was found in only three patients, which makes it impossible to draw conclusions about an association with hyponatremia in this category.

The relationship between hyponatremia and enlargement of the third ventricle was separately analyzed for the patients with marked hyponatremia (sodium levels 120-130 mmol/L). Fourteen of the 26 patients with marked hyponatremia had an enlarged third ventricle as opposed to 27 of the 107 patients with normal sodium levels or mild hyponatremia (130-135 mmol/L) (χ^2 test, $p < 0.01$).

Serial CT scans were done in 113 patients, including all 44 patients with hyponatremia. At the time of hyponatremia, the CT scan showed an enlarged third ventricle in 25 of the 44 patients, compared with 26 of the 69 patients who maintained normal sodium (χ^2 test, $p < 0.05$).

Table 1.

Ventricular size on the initial CT scan	Hyponatremia	Normal serum sodium	Total
Enlargement of third ventricle			
with enlarged lateral ventricles	12*	14	26
with normal lateral ventricles	8**	7	15
Normal third ventricle			
with enlarged lateral ventricles	2***	1	3
with normal lateral ventricles	22	67	89
Total	44	89	133

* $p_2 = 0.05$
 ** $p_2 = 0.03$
 ***N.S. } Fisher's exact probability test

The relationship between enlargement of the third ventricle and hyponatremia remained after adjustment for the amount of cisternal blood (Mantel-Haenzel test, $p = 0.02$ (see Table 2)). In keeping with this, an earlier study failed to show an association between the extent of cisternal hemorrhage and enlargement of the lateral ventricles (134).

Table 2.

	Amount of cisternal blood		Total cases
	Frank	Small or absent	
Enlarged third ventricle			
Total cases	35	6	41
no. hyponatremia	18	2	20
% hyponatremia	51	33	49
Normal third ventricle			
Total cases	76	16	92
no. hyponatremia	23	1	24
% hyponatremia	30	6	26
Totals			
Total cases	111	22	133
no. hyponatremia	41	3	44
% hyponatremia	37	14	33

Frank intraventricular hemorrhage was found in 18 of the 44 patients with hyponatremia versus 19 of the 89 patients with normal serum sodium levels (Fisher's exact test, $p = 0.02$).

After adjustment for intraventricular hemorrhage, the association between initial enlargement of the third ventricle and hyponatremia no longer reached statistical significance ($0.05 < p < 0.10$). This is explained by a separate but statistically weaker relationship between intraventricular hemorrhage and hyponatremia, after adjustment for initial enlargement of the third ventricle ($0.10 < p < 0.20$; Table 3).

Table 3.

	Intraventricular blood		Total cases
	Frank	Small or absent	
Enlarged third ventricle			
Total cases	21	20	41
no. hyponatremia	12	8	20
% hyponatremia	57	40	49
Normal third ventricle			
Total cases	17	75	92
no. hyponatremia	6	18	24
% hyponatremia	35	24	26
Totals			
Total cases	38	95	133
no. hyponatremia	18	26	44
% hyponatremia	47	27	33

Intraventricular hemorrhage was very strongly related to initial enlargement of the third ventricle (21/41 versus 17/92, $p < 0.001$; Table 3).

Cerebral infarcts occurred more often in patients with initially enlarged third ventricles (18/41 = 44%) than in patients who had a normal third ventricle (28/92 = 30%). This difference did not reach statistical significance. Fatal infarcts were more frequent in patients with initial enlargement of the third ventricle (9/41 = 23%), versus 9/92 (10%) in patients who had a normal third ventricle (not statistically significant, $0.05 < p < 0.01$).

An aneurysm was demonstrated by angiography or at postmortem examination in 31 patients with hyponatremia. Of these, 13 had an aneurysm of the anterior communicating artery (42%), 11 of the carotid artery (35%), 3 of the middle cerebral artery (9%) and 4 of the posterior circulation (13%). For the 68 patients with normal sodium levels and a proven aneurysm, the distribution was similar: 26 (38%), 22 (32%), 13 (9%) and 7 (10%), respectively.

Nine patients with an enlarged third ventricle underwent ventricular drainage, six of whom had developed hyponatremia. In four of these six patients the size of the third ventricle did not change after shunting, and hyponatremia persisted. In the two other patients, both the size of the third ventricle and the sodium level returned to normal after ventricular drainage.

DISCUSSION

The risk of developing hyponatremia after SAH was found to be significantly increased in patients with enlargement of the lateral ventricles as well as of the third ventricle on the admission CT scan, and also in patients with enlargement of only the third ventricle. This suggests that the size of the third ventricle is the crucial factor in the relationship that was previously found between acute hydrocephalus and hyponatremia (134). Furthermore, the relationship between an initially enlarged third ventricle and subsequent hyponatremia remained at more marked levels of hyponatremia and continued to exist during the actual period of hyponatremia.

The pathogenesis of hyponatremia after SAH is not known. It has been suggested that the hypothalamus may be damaged by rupture of an aneurysm of the anterior circulation (22, 118) and that this damage may result in disturbances of the electrolyte balance (93). However, a difference in the distribution of aneurysms in patients with or without hyponatremia could not be demonstrated in our series.

Another possibility is that hyponatremia is caused by hypothalamic dysfunction secondary to spasm of vessels which supply the hypothalamus. Since vasospasm is often multifocal, it might - in this view - account for both hyponatremia and cerebral infarction. If this hypothesis were true, an association between the amount of cisternal blood and hyponatremia should be found, as cerebral ischemia is associated with the amount of cisternal blood (56, 65). However, after adjustment for the amount of cisternal blood, the relationship between enlargement of the third ventricle and hyponatremia remained unaltered. In contrast, the significant relationship between enlargement of the third ventricle and hyponatremia was weakened after adjustment for the amount of intraventricular blood. The direct contribution of intraventricular hemorrhage towards the development of hyponatremia is, however, small, and the main effect of intraventricular blood is that it causes enlargement of the third ventricle which then results in hyponatremia.

Now that it has been shown that enlargement of the third ventricle is an important factor in the development of hyponatremia, with some contribution of intraventricular blood, a better explanation might be that mechanical pressure on the hypothalamus from within the third ventricle is responsible for hyponatremia. This is further supported by the observation that hyponatremia persisted when ventricular drainage did not result in a decreased size of the third ventricle, whereas hyponatremia disappeared if the third ventricle did shrink. This is in agreement with an observation of Wise (147). In his report two patients developed hyponatremia after obstruction of a previously placed ventriculo-atrial shunt, and the sodium levels again became normal following revision of the shunt.

Dysfunction of the hypothalamus might cause hyponatremia in different ways. It was originally thought that hypothalamic lesions might functionally

isolate the osmoreceptors leading to an inappropriate and excessive ADH release (27). However, the recent findings of volume depletion and salt wasting in patients with hyponatremia after SAH do not support this hypothesis (88, Chapter III). An alternative explanation for salt wasting after SAH is that dysfunction of the hypothalamus has an effect on the heart resulting in the release of the atrial natriuretic factor (ANF) which in turn causes salt wasting (93). Such a course of events might be related to changes in the heart that have been described after SAH (29). This hypothesis might be tested with the recently developed assays that detect the atrial natriuretic factor in plasma. Another explanation might be that pressure on the hypothalamus by the third ventricle causes the release of natriuretic peptides that are present in the anteroventral region of the third ventricle (93).

Finally, although enlargement of the third ventricle is important in the development of hyponatremia, it is neither a necessary nor a sufficient factor, as half of the patients with hyponatremia had a normal ventricular system, and half of the patients with an expanded third ventricle had constant levels of sodium. It might be that natriuresis has causes other than hydrocephalus, and that it does not always result in hyponatremia.

Patients with SAH who develop hyponatremia are at a greater risk of cerebral infarction. This was demonstrated earlier in the same group of patients, although fluid restriction was a confounding factor (Chapter II). Since hyponatremia is caused by natriuresis and is accompanied by hypovolemia (Chapter III), fluid restriction might have aggravated a hypovolemic state resulting in ischemia. That the volume status plays a role in the development of ischemia is further supported by reports that an increase in plasma volume reverses cerebral ischemia (63).

The limits of our sample size and the contribution of other factors in the pathogenesis of cerebral ischemia may explain why a direct relationship between enlargement of the third ventricle and subsequent infarction could not be demonstrated. Nevertheless, the presence of a large third ventricle on the initial CT scan indicates that such patients are at a greater risk of developing hyponatremia and therefore need a careful control of the fluid and sodium balance to prevent cerebral ischemia.

Chapter VI

DIGOXIN-LIKE IMMUNOREACTIVE SUBSTANCE

INTRODUCTION

Hyponatremia after SAH has been attributed to the syndrome of inappropriate secretion of antidiuretic hormone (21). It has been demonstrated that hyponatremia in SAH is preceded by a negative sodium balance and that it is associated with a decrease in plasma volume (7, Chapter III). The vasopressin levels were initially high but had decreased when hyponatremia developed (Chapter III). Therefore, the older explanation for hyponatremia after SAH, cerebral salt wasting (21, 95, 144), is more plausible than the inappropriate antidiuretic hormone syndrome. What factor causes natriuresis after SAH is not known.

We investigated if an endogenous digoxin-like substance, which is known to enhance sodium excretion by inhibiting sodium transport in the kidney (24), was detectable in the plasma of patients with SAH during the first days after the hemorrhage.

PATIENTS AND METHODS

Patients

We studied twenty-five consecutive patients with signs and symptoms of SAH who showed computed tomographic evidence of blood in the basal cisterns indicating a ruptured aneurysm.

Reasons for exclusion from the series were an interval of more than 48 hours since the presenting hemorrhage, death within six days, endocrine disturbances, heart failure, renal failure, neoplasm and treatment with diuretics, steroids or digoxin. In 22 of the 25 patients an aneurysm was demonstrated by angiography or postmortem examination. In the other three patients, angiography and surgical treatment were not considered because of age (over 70) or impaired level of consciousness. However, rupture of an aneurysm in these patients was considered highly probable because of the presence of blood in the interhemispheric, suprasellar or sylvian cisterns without evidence of another cause of SAH (130, 133). All patients were under continuous observation in an intensive care unit and were studied for ten days after admission. In most patients clipping of the aneurysm was carried out on the twelfth day.

Fluid and sodium balance, and blood pressure

We obtained daily measurements of electrolytes, blood urea nitrogen, creatinine, serum osmolality and hematocrit. All patients had a minimal fluid intake of 1,500 ml per 24 hours.

The sodium intake was calculated from the sodium content of the food, which was specially prepared, and from the sodium content of the fluids intravenously administered. Sodium excretion was measured in 24-hour urine samples. Salt balance was considered negative when sodium excretion in the urine was larger than the daily sodium intake. Loss of sodium from the skin or in the feces was not included in the calculation of the sodium balance. The mean blood pressure was calculated from four blood pressures taken at 6-hour intervals at 6, 12, 18 and 24 hours. Hypertension was defined as a mean blood pressure (diastolic value + 1/3 of the pulse pressure) of 120 or more on at least one day.

R.I.A. for digoxin-immuno-activity

The plasma level of the digoxin-like factor was determined in blood, drawn in heparinized plastic tubes, which was centrifuged and stored at -70°C . The magnitude of the digoxin-like factor was determined by competitive displacement of ^{125}I digoxin from antidigoxin antibodies relative to digoxin standards. The determination of digoxin-like immunoreactive substances (DLIS) was done by means of a radioimmunoassay (RIANEN TM Digoxin, New England Nuclear, cat. no. NEA-082).

The procedure prescribed by the manufacturer in the instruction manual for this assay was followed with a few modifications. In order to increase the sensitivity we examined different combinations of volumes for standards/samples, tracer and antiserum complex. Without performing an extensive search for the lowest possible detection limit we found the following modifications in the original instruction manual suitable for our study:

The volume of standards and samples was increased from 100 to 200 μl . The volume of tracer was reduced from 500 to 200 μl .

Standards 0.00 - 0.05 - 0.10 - 0.20 - 0.30 - 0.50 - 1.00 - 2.00 and 4.00 ng digoxin/ml were prepared by dilution of a 8.00 ng/ml standard with "0" standard. This resulted in a typical standard curve with values for the normalized percent bound or %B/Bo of: 100.0 - 92.2 - 86.2 - 73.5 - 65.8 - 51.1 - 33.7 - 19.3 and 9.0%, respectively. The lower limit of sensitivity was 0.05 ng/ml.

For the determination of DLIS, samples were diluted 1:3 with deionized water in glass tubes and placed in a boiling water bath for 5 minutes. Subsequently the samples were analyzed as described above. According to the dilution factor, the lower limit of sensitivity rose to 0.2 ng/ml for this procedure. This method, described by Valdes et al. (127) results in the release

of the digoxin-like substance from its protein binding, thus enhancing measured immuno-activity.

In the patients with subarachnoid hemorrhage, serum samples were taken on admission (day 0) and after six days, always before plasma volume determinations. We also assayed serum samples from healthy volunteers and newborn infants (128).

Plasma volume determination

All patients underwent plasma volume determinations on admission and again on the sixth day. Plasma volume was determined by the isotope dilution technique with ^{131}I labeled to human serum albumin as described in detail in Chapter III. We expressed the results in total plasma volume and calculated the percentage of change between the two measurements. We considered only a decrease of more than 10% to be substantial.

Ventricular size, amount and site of hemorrhage

As a linear measurement of ventricular size, we used the bicaudate index, that is the width of the frontal horns at the levels of the caudate nuclei divided by the corresponding diameter of the brain. The width of the third ventricle was measured on the slice where the third ventricle had the maximal transverse diameter. The bicaudate index and width of the third ventricle were converted into a relative size by dividing the absolute values by the upper limit for age (134, Chapter V). An intraventricular hemorrhage was considered to be frank when at least one ventricle was completely filled with blood.

The amount of cisternal hemorrhage was graded separately for each of the following cisterns on a scale of 0 to 3 (0 = no blood, 1 = sedimentation of red blood cells in a cistern, 2 = cistern or fissure partly filled with blood, 3 = cistern or fissure completely filled with blood): frontal interhemispheric fissure, quadrigeminal cistern and paired suprasellar cisterns, ambient cisterns, basal sylvian fissures and lateral sylvian fissures (56, 134). The site of the hemorrhage was classified into two main groups: subarachnoid blood with the center of the hemorrhage located in the frontal interhemispheric fissure (12 patients), and subarachnoid blood with the center of blood unilaterally in suprasellar cistern, sylvian fissure or ambient cistern (13 patients) (131). The admission CT scans were graded without knowledge of the results of the digoxin immunoassay.

RESULTS

Digoxin immunoassay values

All samples measured before heating contained values below the detection limit, except for the plasma of the newborn infants, which contained a digoxin-like substance in all cases (range 0.2-0.4, mean 0.3 ng/ml). After heating, the plasma values for digoxin-like substance from 17 healthy volunteers contained no detectable digoxin in 16; in one the value was 0.2 ng/ml. In all four newborn infants digoxin-like substance was found and ranged from 0.3 to 0.8 ng/ml (mean 0.5 ng/ml). Eleven of the 25 patients with SAH had detectable digoxin-like substance on admission. The values ranged from 0.2 to 0.5 ng/ml (mean 0.4 ng/ml). On second measurement (day 6 after admission), 17 had detectable digoxin-like substance; the values ranged from 0.2 to 0.8 ng/ml (mean 0.4 ng/ml). Ten of the 25 patients with SAH had detectable levels in both samples, 8 in only one sample and in 7 patients the samples were negative on both occasions (Figure 1).

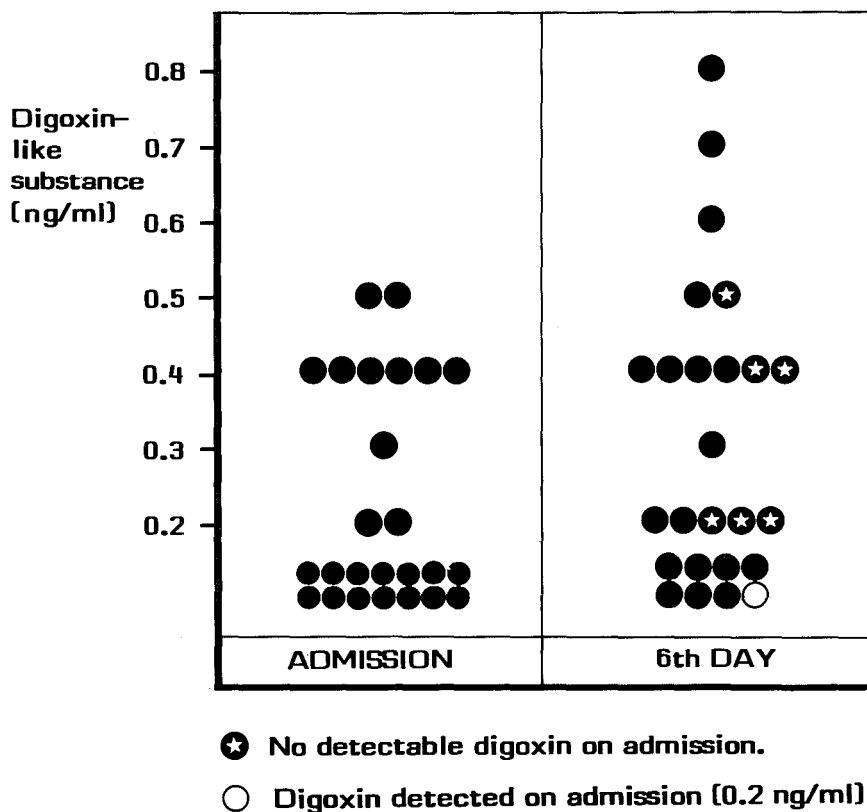


Figure 1. Digoxin-like substance values in 25 patients with a ruptured aneurysm.

Digoxin-like substance and relation with blood pressure, fluid and sodium intake

We investigated if hypertension after the hemorrhage or the intake of fluid and sodium might have caused the presence of the digoxin-like substance on the sixth day after admission. The incidence of hypertension was not significantly different between patients with detectable digoxin values (9/17 or 52%) and patients without detectable digoxin values (6/8 or 75%) ($p > 0.1$). Blood urea nitrogen and creatinine levels remained within normal limits in all patients.

Sodium intake ranged from 205 to 1355 mmol (mean 586 mmol) in digoxin-positive patients and from 135 to 850 mmol (mean 609 mmol) in digoxin-negative patients (Mann-Whitney, $p > 0.1$).

Fluid intake, cumulative over five days, ranged from 8.4 to 13.9 liters (mean 10.9) in digoxin-positive patients and from 10.6 to 15.9 liters (mean 12.0) in digoxin-negative patients, which is not significantly different (Mann-Whitney, $p > 0.1$).

Fluid balance was similar in both groups of patients. The values of the cumulative fluid balance ranged from -0.6 to 7.0 liters (mean 4.0 liters) in digoxin-positive patients and from -0.9 to 7.0 liters (mean 4.0) in patients without digoxin-like substance. No atrial arrhythmias were observed in any of the patients.

Digoxin-like substance, sodium balance and volume depletion

Given the result that the presence of a digoxin-like substance on day 6 could not be explained by differences in blood pressure or in intake of water and sodium, the next question was whether the substance itself (on day 0 or 6) may have contributed to changes in sodium balance and plasma volume. A negative cumulative sodium balance over five days was found in 14 (78%) of the 18 patients who had a detectable digoxin-like substance in one or two of the plasma samples, and in 3 of the 7 patients (43%) who had no detectable values in the two samples. This difference did not reach statistical significance (Fisher's exact test, $p_2 = 0.1$). The cumulative sodium balance values ranged from -72 mmol to -179 mmol (mean -169 mmol) in the 14 digoxin-positive patients and from +110 to -370 mmol (mean -53 mmol) in digoxin-negative patients (Mann-Whitney, $p > 0.1$).

The plasma volume decreased more than 10% in 12 of the 18 digoxin-positive patients (67%) and in 3 of the 7 digoxin-negative patients (43%), Fisher's exact test, $p > 0.1$.

Digoxin-like substance and relation with clinical and CT features

The Table shows the occurrence of unconsciousness at the time of hemorrhage, Glasgow Coma Score (120) on admission, enlargement of lateral and

Table. Clinical and CT features in 25 patients with and without digoxin-like substance following subarachnoid hemorrhage.

Clinical and CT features	No. of patients (%)			
	Digoxin-like substance (n = 18)		No digoxin-like substance (n = 7)	
Loss of consciousness at ictus	6	(33)	3	(43)
Glasgow Coma Score	< 12	2	(11)	0
	12, 13	3	(17)	0
	14	13	(72)	7 (100)
Enlarged lateral ventricles	5	(28)	0	
Enlarged third ventricle	10	(56)	2	(29)
Frank intraventricular hemorrhage	5	(28)	2	(29)
Amount of cisternal hemorrhage*	0-5	1	(6)	1 (14)
	6-10	4	(22)	4 (57)
	11-15	6	(33)	2 (29)
	16-20	4	(22)	0
	21-25	3	(17)	0
	26-30	0		0
Site of subarachnoid blood*				
center of hemorrhage in frontal interhemispheric fissure	11	(61)	1	(14)
center of hemorrhage in other cisterns or fissures	7	(39)	6	(86)

* $p < 0.02$.

third ventricles and the presence of frank intraventricular hemorrhage on the initial CT scan for patients with and without digoxin-like substance. Patients with digoxin-like substance more often had an impaired level of consciousness on admission and enlarged lateral and third ventricles on the first CT scan, but none of these differences reached statistical significance.

The amount of cisternal blood on the initial CT scan was significantly associated with the presence of digoxin-like substance (Mann-Whitney test, $p < 0.02$).

Predominance of subarachnoid blood in the interhemispheric fissure, suggesting rupture of an anterior communicating artery, was significantly associated with the presence of digoxin-like substance (Fisher exact test $p_2 = 0.02$). Angiography or autopsy was performed in 10 of the 12 patients with subarachnoid blood mainly located in the frontal interhemispheric fissure on CT, and an aneurysm of the anterior communicating artery was demonstrated in all (Figure 2). Angiography or autopsy was done in 12 of the 13

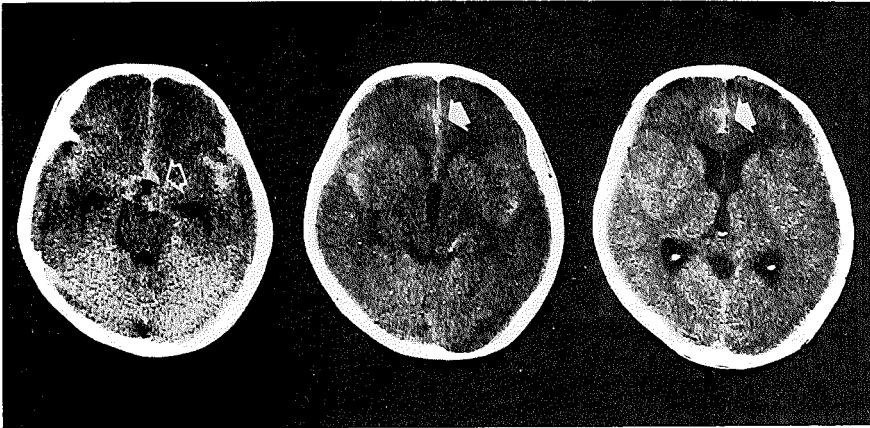


Figure 2. Computed tomogram of a patient with diffusely distributed blood with the center of the blood located in the frontal interhemispheric fissure (solid arrow), near the hypothalamus (open arrow). The digoxin values were 0.4 ng/ml on admission and 0.6 ng/ml on the 6th day.

patients with the center of the hemorrhage in other cisterns or fissures, and a differently located aneurysm was demonstrated in all (five aneurysms of the middle cerebral artery, five aneurysms of the carotid artery and two aneurysms at the basilar bifurcation).

DISCUSSION

Before the description of the syndrome of inappropriate antidiuretic hormone (SIADH) (7, 27, 61, 110), natriuresis after SAH was attributed to a putative natriuretic factor. This was termed cerebral salt wasting (21, 95, 144). Our findings demonstrate that after SAH a digoxin-like natriuretic factor circulates and that its release is related to cerebral factors such as the amount and the site of the hemorrhage. Factors which are known to be associated with the presence of this substance in plasma, such as hypertension (26), fluid and salt loading (39, 46), were similarly distributed between the groups of patients with and without digoxin-like substance, and in none of the patients renal failure (44) or atrial arrhythmias (64) could account for the reaction to digoxin antibodies. The presence of this substance was associated with extensive cisternal hemorrhage and with a distribution of blood suggesting rupture of an anterior cerebral artery aneurysm. These findings suggest that in patients with subarachnoid hemorrhage a cerebral factor is responsible for the release of a digoxin-like substance.

In patients with subarachnoid hemorrhage, digoxin-like substance could be detected only after heating of the plasma. In the control group, consisting

of healthy hospital personnel, heating of the plasma samples revealed a very low value in only one subject. The levels in patients with subarachnoid hemorrhage were in the range of the values observed in newborn infants, which suggests that these findings have pathological significance.

Digoxin-like substance appears to have natriuretic properties, as was demonstrated in salt-loaded healthy subjects and in untreated hypertensive patients (26, 39, 66, 97). Further evidence for its natriuretic activity was found in studies showing the inhibition of membrane-bound sodium-potassium ATP-ase leading in turn to inhibition of sodium reabsorption in the renal tubule (72). Our results also suggest an association between digoxin-like substance and natriuresis, but this association did not reach statistical significance. A similar association was found between digoxin-like substance and volume depletion.

Natriuresis after SAH is a clinically important phenomenon, since it is associated with volume depletion (Chapter III), which plays a role in the development of cerebral ischemia (113).

Cerebral ischemia is one of the major complications after subarachnoid hemorrhage. It is traditionally attributed to vasospasm, but not all patients with vasospasm develop ischemia (53). It might be that hypovolemia increases blood viscosity and that this, in combination with vasospasm, may lead to an impaired cerebral blood flow and cerebral ischemia. This is supported by the observation that cerebral ischemia may be successfully treated by volume expansion (23, 98, 116) and that the incidence of cerebral ischemia increases if fluid restriction is applied to correct hyponatremia (Chapter II).

We found that the presence of a digoxin-like substance was associated with an extensive subarachnoid hemorrhage and also with an aneurysm of the anterior communicating artery. In both these conditions lesions of the hypothalamus have been described (22) and it might be that hypothalamic lesions are the crucial factor in the release of digoxin-like substance. It is not unlikely that the human hypothalamus contains a digoxin-like substance, as this has been demonstrated in the ox and guinea pig (35, 51). An alternative explanation of the relation between blood in the interhemispheric fissure and the release of a digoxin-like substance involves not only the hypothalamus, but also the heart. Areas of myofibrillar degeneration in the heart have been shown in association with hypothalamic lesions after SAH (29). Therefore, a ruptured anterior aneurysm or a large hemorrhage might result in a hypothalamic lesion which would then lead to myofibrillar degeneration in the heart by which a digoxin-like substance is released.

Chapter VII

THE EFFECT OF FLUDROCORTISONE ACETATE ON PLASMA VOLUME AND NATRIURESIS

INTRODUCTION

In a previous study we demonstrated that a decrease in plasma volume of more than 10% occurs in approximately 50% of patients with aneurysmal subarachnoid hemorrhage (SAH) (Chapter III). This hypovolemia is considered harmful because it might precipitate cerebral infarction (113, Chapters II and III). The cause of the hypovolemia has been a matter of debate. Although bed-rest and daily blood sampling could lower plasma volume, these effects cannot account for the hypovolemia, because the total amount of blood withdrawn for diagnostic laboratory tests was approximately 140 ml and bed-rest does not usually decrease the plasma volume by more than 10% (45, 112). A better explanation is that volume depletion after SAH is caused by natriuresis (21, 95, Chapter III).

Hypovolemia might be treated by increasing salt intake, but this only further enhances sodium excretion (99). Therefore, it would be more appropriate to prevent volume depletion by diminishing renal sodium excretion. Fludrocortisone acetate has mineralocorticoid activity and enhances distal tubular sodium reabsorption in the kidney. In order to investigate the feasibility of this approach a pilot study was performed of the effect of fludrocortisone acetate on plasma volume, sodium balance, renin values, and on the incidence of medical complications such as hypokalemia and cardiac failure.

PATIENTS AND METHODS

Patients

We prospectively studied a consecutive series of 39 patients with signs and symptoms of subarachnoid hemorrhage and with computed tomographic evidence of blood in the basal cisterns, in the absence of lesions other than aneurysms that might cause subarachnoid hemorrhage (130, 133).

All patients were admitted within 48 hours of the initial hemorrhage. Patients with any of the following conditions were excluded: endocrine disturbances, heart failure, renal failure, neoplasm or treatment with diuretic

drugs before admission or during the study. Patients over 70 years of age were excluded, because of the risk of heart failure during the treatment protocol. None of the patients was treated with steroids or antifibrinolytic agents.

Eighteen of the 39 patients admitted to the study were excluded. The reasons for exclusion were: arteriovenous malformation (2 patients), negative angiography in 9 patients (in 5 of these 9 patients a negative angiography was predicted from CT, with a predominantly perimesencephalic hemorrhage (133)), fatal rebleed before the second plasma volume determination (3 patients), heart failure (2 patients), and incomplete sodium balance data due to urinary incontinence (2 patients).

In 19 of the remaining 21 patients an aneurysm was demonstrated. In two patients angiography was not performed, because surgical treatment was felt to be precluded by an impaired level of consciousness. However, rupture of an aneurysm was highly probable because of the presence of blood in the basal cisterns, without evidence of another lesion or subarachnoid hemorrhage of the perimesencephalic type (130, 133).

On admission eleven of the 21 patients had a maximal Glasgow Coma score of 14, eight patients had a Glasgow Coma score of 12 or 13, one had a Glasgow Coma score of 7, and one of 5.

During the study period, which lasted 12 days, all patients were under continuous observation in an intensive care unit. CT was performed on admission and was repeated if a patient's clinical condition deteriorated. We obtained daily measurements of electrolytes, blood urea nitrogen, serum osmolality and hematocrit.

The mean blood pressure was calculated from four blood pressures taken at 6-hour intervals at 6, 12, 18 and 24 hours. Hypertension was defined as an average mean blood pressure (diastolic value + 1/3 of the pulse pressure) of 120 or more on at least one day.

Hyponatremia was defined as a sodium level lower than 135 mmol/L on at least two consecutive days (Chapter II). The calculations of sodium balance and the determination of plasma volume with ^{131}I labeled to human serum albumin were performed according to previous descriptions (Chapter III). Plasma renin concentration was measured with a radioimmunoassay as described elsewhere (25).

Treatment with fludrocortisone acetate was always started within 48 hours of the hemorrhage, in a dose of 0.2 mg twice a day intravenously, in 200 ml glucose 5%. All patients had a fluid intake of at least 3,000 ml per 24 hours. Treatment was discontinued on the 12th day, at the time of operation (10 patients, usually on the 12th day) or when patients developed overt heart failure.

RESULTS

Hyponatremia and changes in plasma volume

Hyponatremia developed in four of the 21 patients, on days 2, 3, 3 and 4 after admission. In these four patients serum sodium levels dropped to 128, 131, 131 and 133 mmol per liter. The sodium values returned to normal 5, 2, 2 and 4 days later, respectively. In these patients the plasma volume decreased more than 10% in three and 8% in the fourth. Of the 17 patients in whom sodium levels remained normal, plasma volume decreased with 16% in one, decreased less than 10% in four, increased from 1 to 10% in seven, increased from 11 to 20% in two, and increased considerably in three (23%, 33% and 50%, Figure 1).

Sodium balance

The individual sodium balance charts and cumulative sodium and fluid balance data are summarized in Figures 1 and 2. A negative sodium balance preceded the development of hyponatremia in three of the four patients. In four of the 17 patients with continuously normal sodium values, the sodium balance was also negative.

The cumulative sodium intake over five days was higher in patients with a positive sodium balance (range 680 to 1090 mmol, mean 888 mmol) than in patients with a negative sodium balance (range 220 to 945, mean 674), but this difference did not reach statistical significance (Mann-Whitney $0.05 < p < 0.1$).

Plasma volume decreased with more than 10% in three of the seven patients with a negative sodium balance and in only one of the 14 patients with a positive sodium balance. This difference reached statistical significance only on one-sided testing, in keeping with our previous hypothesis (Fisher's exact test, $p_1 = 0.04$, $p_2 = 0.08$).

Renin values were measured in samples from 15 patients treated with fludrocortisone acetate and in stored samples from 18 previous patients not treated with fludrocortisone acetate.

Of the 15 patients from the present series, six developed a negative sodium balance; these six had renin levels ranging from 2.4 to 23.7 $\mu\text{U}/\text{ml}$ (mean 10.6 $\mu\text{U}/\text{ml}$) on admission, and from 1.5 to 34.4 $\mu\text{U}/\text{ml}$ (mean 10.4 $\mu\text{U}/\text{ml}$) on second measurement (6 days after admission). In the nine patients with a positive sodium balance the values were 0.6 to 21.2 $\mu\text{U}/\text{ml}$ (mean 8.8 $\mu\text{U}/\text{ml}$) and 1.1 to 13 $\mu\text{U}/\text{ml}$ (mean 5.9 $\mu\text{U}/\text{ml}$), respectively (figure 3).

The stored plasma samples of the 18 patients from a previous study (Chapter III) were assayed together with the samples of the 15 patients of the current study. The renin values in patients who developed a negative sodium balance ranged from 5.3 to 66.1 $\mu\text{U}/\text{ml}$ (mean 22.4 $\mu\text{U}/\text{ml}$) on admission and

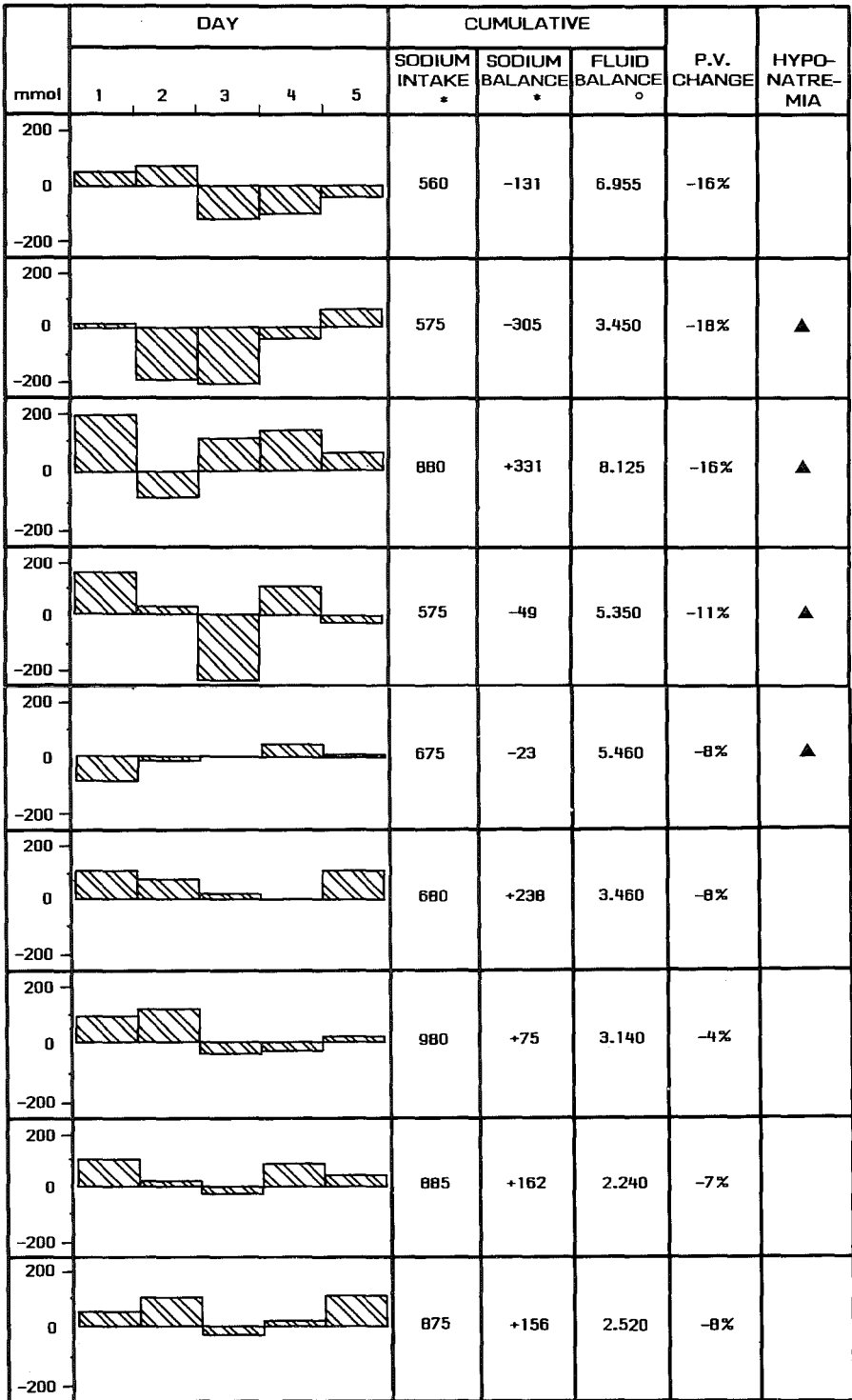


Figure 1. Sodium balance in patients with a decrease in plasma volume of more than 10% or between 0 and 10%. (stars = data expressed in mmol; circles = data expressed in liters).

mmol	DAY					CUMULATIVE			P.V. CHANGE
	1	2	3	4	5	SODIUM INTAKE *	SODIUM BALANCE *	FLUID BALANCE °	
200 0 -200		945	+378	3.650	+50%				
200 0 -200		750	+429	2.100	+1%				
200 0 -200		770	+12	8.725	+10%				
200 0 -200		1170	-134	5.445	+23%				
200 0 -200		965	+43	3.540	+1%				
200 0 -200		220	-203	4.825	+3%				

Figure 2. Sodium balance in patients with an increase in plasma volume. (stars = data expressed in mmol; circles = data expressed in liters)

mmol	DAY					CUMULATIVE			P.V. CHANGE
	1	2	3	4	5	SODIUM INTAKE [*]	SODIUM BALANCE [*]	FLUID BALANCE ^o	
200 0 -200						1090	+111	1.520	+6%
200 0 -200						970	+444	4.795	+12%
200 0 -200						825	+274	6.285	+33%
200 0 -200						945	-152	2.925	+18%
200 0 -200						930	+41	2.700	+10%
200 0 -200						900	+312	4.025	+4%

Figure 2 (continued)

increased substantially after 6 days (range 2.8 to 136.2 $\mu\text{U}/\text{ml}$, mean 49.5 $\mu\text{U}/\text{ml}$). Patients with a positive sodium balance had renin values ranging from 5.8 to 23.7 $\mu\text{U}/\text{ml}$ (mean 12.1 $\mu\text{U}/\text{ml}$) on admission and from 3.7 to 282.6 $\mu\text{U}/\text{ml}$ on second measurement.

The changes in renin values are summarized in Figure 3. A substantial increase in renin values was observed particularly in patients with a negative sodium balance who were not treated with fludrocortisone acetate. With two exceptions, the renin values showed no appreciable change in the other patients.

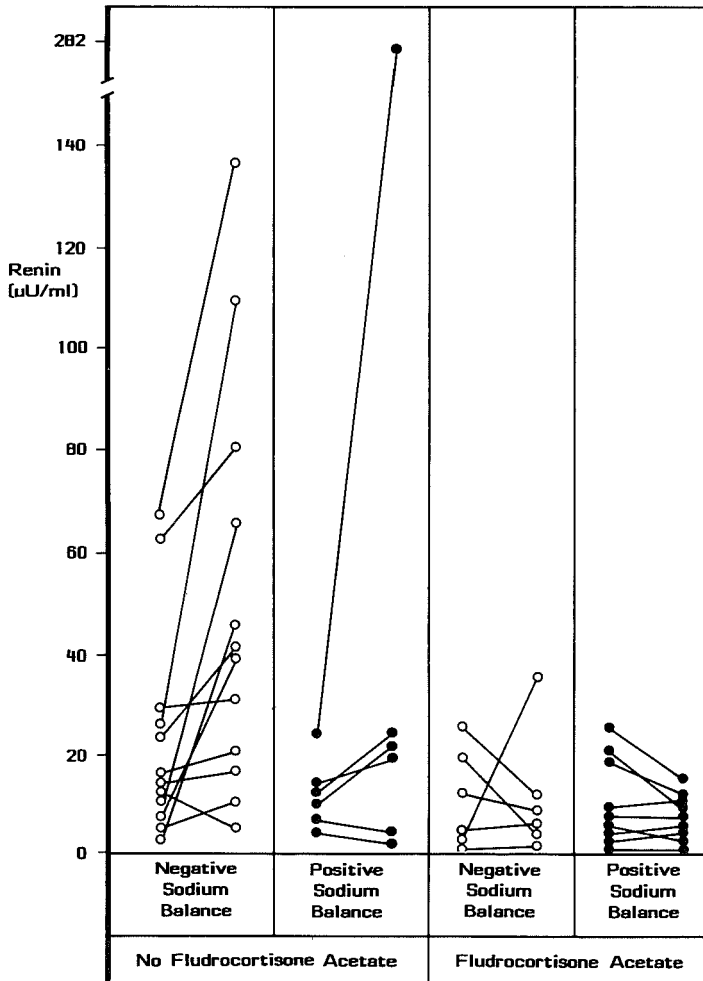


Figure 3. Plasma renin values in 15 patients with SAH treated with fludrocortisone acetate and in 18 patients without fludrocortisone acetate treatment (from a previous study (Chapter III)), related to cumulative sodium balance.

Medical and neurological complications of treatment

In three of the original 39 patients pulmonary edema developed (8%), treated successfully by diuretics. In two patients hypoxia associated with pulmonary edema developed within six days of admission. These patients were excluded from a second plasma volume determination, because diuretic treatment was necessary. In one patient neurogenic pulmonary edema was observed on admission. Because a rapid improvement occurred within 24 hours after artificial ventilation, this patient was included as yet. However, on the 7th day of admission a relapse of pulmonary edema occurred. Plasma volume had increased with 50%.

In four of the 21 patients, hypokalemia developed (range 3.1 to 3.4 mmol/L, mean 3.3 mmol/L), but this was easily corrected by the administration of potassium chloride intravenously.

Eight of the 21 patients (38%) had a raised mean blood pressure of more than 120 mm Hg. In five of these eight patients plasma volume had increased, which occurred in a similar proportion (7 of 13) in patients with normal blood pressures. None of these eight patients developed a deterioration that could be attributed to these high blood pressures.

Eight of the 21 patients developed a clinical deterioration: six from rebleeding and two from cerebral infarction; in all episodes the diagnosis was confirmed by CT scanning. Plasma volume increased from 6 to 33% (mean 13%) in four of the six patients with a rebleed, which was not significantly different from plasma volume increase in patients without a rebleed (8 of 15 patients, range 1-50%, mean 15%).

DISCUSSION

The results of this study suggest that fludrocortisone acetate in the dosage we used, together with adequate salt intake, may limit the occurrence of hypovolemia in patients with SAH. The plasma volume decreased more than 10% in 4 of the 21 patients, against 11 of the 21 in our previous study (Chapter III). Although the two series of patients were not studied in a parallel fashion, the medical management other than treatment with fludrocortisone was the same. Comparison of the degree of plasma volume changes showed a statistically significant difference in favor of treatment with fludrocortisone (Figure 4). Moreover, in the study of Solomon et al., 44% of the patients (11/25) had a decreased blood volume (113), which is similar to our series without fludrocortisone (Chapter III). In keeping with the volume status, the cumulative sodium balance was negative in only 7 of 21 patients, against 14 of 21 in our previous study (Chapter III), and renin values were lower in patients who were treated with fludrocortisone (Figure 3).

An important question in this preliminary study was whether patients treated with fludrocortisone suffer side effects which would preclude this

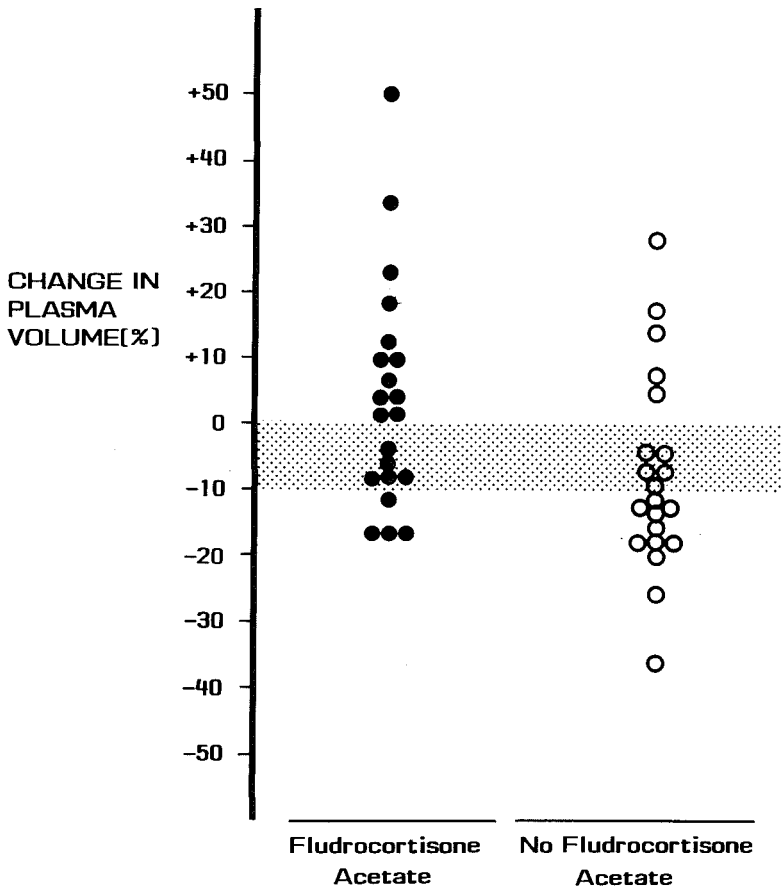


Figure 4. Plasma volume changes in 21 patients with a ruptured aneurysm treated with fludrocortisone acetate compared with patients without fludrocortisone acetate treatment from our previous study (Chapter III). (Mann-Whitney, $p < 0.04$).

treatment in SAH. In three of 39 patients (8%), signs of pulmonary edema developed, but this could be easily reversed by diuretic treatment. In one of these three patients, pulmonary edema had already been present on admission and in retrospect this patient should not have been included in the study. Low serum potassium values were observed in only four patients after the administration of fludrocortisone, but these were easily corrected. Volume expansion in patients with SAH may in theory increase blood pressure with an increased risk of rebleeding. In this small series of patients the incidences of both hypertension and rebleeding were unchanged when compared with our previous study.

Volume depletion in SAH is considered clinically important, because patients with vasospasm have a higher risk of developing cerebral ischemia if they are volume-depleted (113). This is supported by the observation that patients who developed hyponatremia and were fluid-restricted had an increased risk of cerebral ischemia (Chapter II). Moreover, several reports suggest that cerebral ischemia can be reversed by the use of volume expanders (63, 98, 116). The use of volume expanders and also of induced hypertension in patients who have developed signs of cerebral ischemia is not without risks and not easy to carry out. Kassell et al. demonstrated that such measures are accompanied in 20% of cases by side effects such as overhydration; 5% had clotting abnormalities (63). Recently, Finn et al. recommended the use of Swan Ganz catheters to control the volume status in SAH patients (33).

We think it worthwhile to try and prevent volume depletion by inhibiting excessive sodium excretion instead of treating volume depletion after signs of cerebral ischemia have already developed. That fludrocortisone can increase plasma volume by inducing sodium retention has been demonstrated in other clinical situations (19, 124). The present study suggests that fludrocortisone treatment is a relatively simple and safe method of decreasing the incidence of volume depletion and sodium loss in patients with SAH. Obviously, this has to be confirmed in a study with concurrent controls, which we have now embarked upon. Moreover, it remains to be established that these measures result in a decreased incidence of cerebral ischemia, one of the major complications after SAH (53).

GENERAL DISCUSSION

This study focuses on hyponatremia following aneurysmal subarachnoid hemorrhage. Hyponatremia is often explained by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In that case, sustained secretion of antidiuretic hormone is maintained in the face of low serum osmolality and an expanded extracellular fluid volume, which in turn causes hyponatremia and natriuresis. Recently, however, it has been questioned whether inappropriate secretion of ADH really occurs after SAH, since decreased blood volumes have been demonstrated in patients with hyponatremia, although they fulfilled the laboratory criteria for SIADH. This doubt was corroborated by our retrospective review of a consecutive series of patients, which demonstrated that hyponatremia and fluid restriction were associated with an increased risk of cerebral infarction (Chapter II).

Blood volumes in the earlier study had been measured only once, when hyponatremia had occurred. In our prospective study we could demonstrate that the plasma volume decreases in patients who develop hyponatremia by comparing two measurements, one on admission and one after five days. In addition, we measured sodium balance, body weight, and secretion of antidiuretic hormone (vasopressin) and renin. Hyponatremia was associated with a decrease in plasma volume and a decrease in body weight, and it was preceded by a negative sodium balance in all instances. Serum vasopressin levels were increased or normal on admission, but had decreased at the time of hyponatremia. Conversely, plasma renin values increased between the two measurements. An additional finding was that plasma volume considerably decreased also in some patients with normal sodium levels, usually as a result of excessive natriuresis (Chapter III).

All these findings support the concept of salt wasting and negate the syndrome of inappropriate ADH secretion. These observations confirmed experiments in monkeys, which clearly showed the development of a negative salt balance before hyponatremia occurred. In the fifties, before the SIADH had been described, hyponatremia in various neurological disorders was also attributed to cerebral salt wasting. In that concept a cerebral factor was responsible for the release of a putative natriuretic hormone. After we had demonstrated that hyponatremia after SAH is caused by excessive natriuresis, we investigated if a substance which possessed natriuretic properties could be detected in plasma of patients with SAH. At that time the so-called atrial natriuretic peptide could be detected only in tissues and not in plasma. Another natriuretic substance, the digoxin-like immunoreactive substance

could actually be measured in plasma, was identified in 61% of the patients with an aneurysmal SAH and was, although not significantly, associated with natriuresis and volume depletion (Chapter VI). In the mean time assays have been developed by which the atrial natriuretic peptide can be measured in plasma. At present we are investigating if these substances circulate after SAH.

What cerebral factor causes the release of the digoxin-like substance is uncertain. We found an association between the presence of this substance and the site of the ruptured aneurysm at the anterior communicating artery, and also between hyponatremia on the one hand and an enlarged third ventricle and intraventricular blood on the other (Chapter VI). These findings can make some sense if we assume that an enlarged third ventricle, intraventricular blood and a ruptured anterior aneurysm may all result in damage of the hypothalamus. Similarly, an extensive extravasation of blood which was also related with the presence of the digoxin-like substance, may contribute to hypothalamic damage. Hypothalamic damage may directly result in the release of a local natriuretic substance. Another possibility is that hypothalamic damage has an effect on the heart, which results in the release of these substances from the myocardium via monoamines or other humoral factors. If this last hypothesis were true, there should be an association between ECG changes or CPK levels and the presence of natriuretic substances. This is also under current investigation.

Hyponatremia following aneurysmal SAH is of clinical importance. In our retrospective study, hyponatremia developed between the second and the tenth day after the initial hemorrhage. A striking finding was that secondary deteriorations could not be attributed to hyponatremia alone, probably because hyponatremia developed gradually and serum sodium levels did not fall below 120 mmol/L. But when a clinical deterioration occurred after hyponatremia, it was invariably caused by cerebral infarction (Chapter II). In these patients fluid restriction was applied to correct low sodium levels. Since we now know that patients with hyponatremia have decreased plasma volume levels, this treatment must have aggravated a hypovolemic state. This is especially dangerous at a time when these patients are at risk of developing cerebral ischemia, the more so since evidence is accumulating that cerebral ischemia can be reversed by hypervolemia. How hypovolemia causes cerebral ischemia is unclear, but a likely explanation is that hypovolemia is associated with an increased blood viscosity, which may result in impaired cerebral perfusion. Measurement of blood viscosity and of cerebral blood flow and metabolism might elucidate this problem.

The volume status in patients with SAH is extremely important. In the maintenance of this volume status two approaches are possible. From the onset of the hemorrhage an intake of 3 to 3.5 liters fluid can be prescribed. If cerebral ischemia develops despite these measures, extra fluid albumin or dextran can be given until the central venous pressure is about 12. It has been

advised to control this extra fluid intake by Swan Ganz catheter monitoring. We have tried to prevent a negative fluid balance by the administration of extra sodium solutions or of albumin. In some of these patients the fluid balance remained negative, because the increased fluid intake was followed by a proportionally increased fluid excretion.

A second approach could be to prevent hypovolemia by inhibition of sodium excretion. In a pilot study (Chapter VII) we demonstrated that fludrocortisone in the dosage we administered is comparatively safe and that the results on plasma volume and natriuresis are encouraging. Further studies are needed to confirm these results in a comparison with concurrent controls and to demonstrate that these measures result in fewer cerebral infarcts.

Another attempt to prevent cerebral ischemia is by means of induced hypertension. The most important hazard of induced hypertension in patients with an unclipped aneurysm is rebleeding. Conversely, review of the same consecutive series of patients described in Chapter II showed that patients who presented with hypertension and were treated with antihypertensive drugs, had a significantly higher incidence of cerebral infarction (Chapter IV). Surprisingly, average blood pressures were still higher in patients treated with antihypertensive drugs, and hyponatremia occurred more often (although not significantly). The results are difficult to explain. Hypertension or antihypertensive drugs might perhaps inhibit the fibrinolytic system, but such an effect has not yet been reported. Another possibility is that hypertension is related to vasospasm, perhaps as a compensatory response. This hypothesis might be tested by investigating the relation between blood pressure and vasospasm, for instance by means of serial transcranial ultrasound techniques.

Cerebral ischemia is a devastating complication after SAH. Our studies showed that volume status and blood pressure play an important role in the development of cerebral ischemia. The task ahead is to assess the effect of optimal management of blood volume and blood pressure on rebleeding – that other great risk – and on the general outcome of patients with aneurysmal subarachnoid hemorrhage.

SUMMARY

The aim of this study was to investigate if and why patients with subarachnoid hemorrhage (SAH) and hyponatremia have a poor outcome, how hyponatremia develops and how it can be prevented.

In Chapter I the natural history and complications after SAH are discussed. Aneurysmal SAH has an incidence of between 11 and 19 per 100,000 inhabitants per year. It is a severe disorder with high mortality and morbidity. As a result of the initial bleeding about a third of the patients will die or become severely disabled. These patients are probably beyond the influence of medical or surgical treatment. However, it has been suggested that many destructive hemorrhages are preceded by minor warning bleeds and that the majority of these patients can be saved if these warning bleeds are recognized.

Half of the patients who survive the initial hemorrhage in a good clinical condition subsequently die or become incapacitated by complications that occur especially during the first weeks after the hemorrhage. In patients who are admitted, the aim of the management is to prevent these serious complications.

In part 2 of Chapter I, the neurological complications are reviewed. Rebleeding and cerebral infarction are the two major factors that influence the outcome of patients following SAH. The overall outcome of patients who rebleed is poor, as 82% will die within three months. The peak incidences of rebleeding are at the end of the second and third weeks and probably on the first day. Rebleeding can be prevented by clipping of the aneurysm. The timing of surgery, early – within 72 hours – or delayed, and the selection of patients who should be operated on are major points of controversy.

Tranexamic acid considerably decreases the risk of rebleeding, but the outcome of the patients does not improve, because of a concomitant increase in the incidence of cerebral infarcts. Therefore, antifibrinolytic treatment is not beneficial unless cerebral ischemia can be prevented.

Cerebral infarction occurs in about 27% of the patients. The ischemic lesions are multifocal, mainly in cortical areas and boundary zones. Cerebral ischemia develops gradually. Most patients have focal deficits, but a decrease in consciousness preceded this and can be the only sign. Many therapeutic measures have been tried: especially volume expansion and induced hypertension might be beneficial.

Acute hydrocephalus occurs in 20% of the patients who are admitted early after the hemorrhage, at least if there is no referral bias with the selection of patients in good clinical condition. The immediate effect of shunting on the level of consciousness is impressive, but nevertheless a larger percentage die from rebleeding and cerebral infarction. Careful techniques of drainage might improve the outcome.

The medical complications are discussed in part 3. Electrocardiographic abnormalities associated with an elevation of serum cardiac enzymes are frequently seen after SAH. Diffuse myofibrillar degeneration accounts for these ECG changes. However, of all acute cardiorespiratory complications, most are primary disorders of respiratory rhythm and not cardiac arrhythmias. Neurogenic pulmonary edema is a dramatic complication, but mortality has decreased by the introduction of positive end-expiratory pressure (PEEP).

Hypertension frequently develops in patients with SAH who did not have a previous history of hypertension. Treatment of hypertension immediately following the acute event is an important dilemma. Hypertension might increase the incidence of rebleeding or aggravate cerebral ischemia by edema formation. On the other hand, lowering the blood pressure might result in cerebral ischemia by impairing cerebral perfusion. Less common medical complications are gastrointestinal bleeding, septicemia and hyperglycemia.

In part 4, sodium homeostasis and causes of hyponatremia are reviewed. Originally hyponatremia in SAH was attributed to a putative natriuretic hormone that caused true sodium depletion. This phenomenon was termed cerebral salt wasting. After the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was defined, hyponatremia after SAH has generally been attributed to SIADH. In SIADH the osmotic receptors function inappropriately, which results in a sustained secretion of antidiuretic hormone. This leads to an increase in the extracellular volume with subsequent hyponatremia and natriuresis. To reverse this dilutional hyponatremia, fluid restriction is recommended. But fluid restriction may be harmful rather than beneficial if hyponatremia is after all associated with volume depletion, because fluid restriction may aggravate a hypovolemic state leading to hemoconcentration and changes in blood viscosity. This may be especially dangerous in patients with vasospasm who already have an impaired cerebral perfusion. If this were true, it is to be expected that patients with hyponatremia who were treated with fluid restriction were at a higher risk of developing infarcts. Therefore, we studied the relationship between hyponatremia and cerebral infarction.

The results of this study are described in Chapter II. In a series of 134 consecutive patients with SAH, 44 patients had sodium levels below 135 mmol per liter on at least two consecutive days. Hyponatremia developed between the second and the tenth day after the hemorrhage. Severe hyponatremia (sodium level of 120 to 124 mmol/L) occurred in only 6 of the 44 patients. Twenty-five of the 44 patients fulfilled the laboratory criteria of

SIADH, twelve had other conditions that might have contributed to hyponatremia (sepsis, severe vomiting, renal disease, Addison's disease and diuretics). In seven patients the cause remained unknown because of incomplete laboratory investigations. The incidence of cerebral infarction as well as mortality from cerebral infarction was found to be significantly higher in patients who developed hyponatremia. None of the episodes of clinical deterioration could be attributed to hyponatremia alone, without signs of cerebral ischemia.

Twenty-six of the 44 patients with hyponatremia had been treated with fluid restriction to correct the serum sodium levels and cerebral infarcts developed in 21. It appears that fluid restriction to correct hyponatremia is potentially dangerous in patients with SAH. This observation indirectly supported the notion that hyponatremia was caused by salt wasting.

To elucidate the cause of hyponatremia in SAH - sodium dilution or sodium depletion - a prospective study was performed on plasma volume, sodium balance and secretion of antidiuretic hormone in 21 patients with aneurysmal SAH (Chapter III). In 11 of the 21 patients, the plasma volume, measured by an isotope dilution technique, decreased more than 10%. This was accompanied by a negative sodium balance and hyponatremia in six patients, a negative sodium balance without hyponatremia in four patients, and a positive sodium balance in one patient. Together with a decrease in plasma volume, blood urea nitrogen content increased and body weight decreased. Serum vasopressin values were elevated on admission and declined in the first week in all patients, regardless of the presence of hyponatremia.

These findings are consistent with a salt wasting syndrome rather than with inappropriate secretion of antidiuretic hormone. This study confirms that patients with SAH have volume depletion and natriuresis and ought to be treated with volume expansion. Maintenance of an adequate intravascular volume is important in the management of patients with SAH. Patients with SAH are threatened by vasospasm, which may lead to cerebral ischemia. Cerebral blood flow may be further impaired in patients with volume depletion through an increased blood viscosity. The effectiveness of volume expansion in increasing cerebral perfusion may be explained by an improvement in blood viscosity or a rise in cardiac output. The importance of an adequate intravascular volume has been corroborated by reports describing improvements of clinical deficits attributed to cerebral ischemia after volume expansion.

Another method of preventing the development of cerebral ischemia might be to increase blood pressure. This has been suggested by investigators who used induced hypertension in patients with symptomatic vasospasm and in this way produced relief of ischemic symptoms. This might mean that high

blood pressure after SAH prevents cerebral ischemia and therefore ought not to be treated with antihypertensives. On the other hand, if high blood pressure is not lowered after the initial bleeding, this might result in an increased incidence of rebleeding.

We investigated in a consecutive series of 134 patients with aneurysmal subarachnoid hemorrhage if institution of antihypertensive treatment was related to the incidence of cerebral ischemia and rebleeding. The aim of hypertensive treatment was to reduce the diastolic blood pressure to levels below 110 mm Hg. There was no difference in outcome between patients with and without antihypertensive drugs.

Rebleeding was less frequent in patients with antihypertensive treatment (12/80 patients (15%), versus 18/54 patients (33%) without antihypertensive treatment ($p = 0.012$)). Nevertheless, patients with antihypertensive treatment had, on average, still higher blood pressures than untreated patients.

Conversely, infarction occurred more often in patients with antihypertensive treatment (32/80 patients (40%) versus 14/54 (26%) without antihypertensives ($p = 0.03$)). This relationship was partly explained by co-existing hyponatremia.

Our results suggest that hypertension immediately after SAH may be a compensatory phenomenon and can be left untreated, since the prevention of rebleeding is offset by an increased risk of cerebral infarction.

Acute hydrocephalus, detected by measuring the width of the lateral ventricles on the admission CT, was found to be associated with the development of hyponatremia. A possible explanation was that enlargement of the third ventricle might interfere with hypothalamic function, which in turn might cause hyponatremia. This possibility was explored in the study described in Chapter V. We investigated if the development of hyponatremia was related to enlargement of the third ventricle on the admission CT scan, in a consecutive series of 133 patients who were seen within 72 hours of aneurysmal hemorrhage. Hyponatremia occurred significantly more often in patients with initial enlargement of the third and lateral ventricles than in patients with a normal ventricular system (12/26 versus 22/29, $p = 0.05$) and also in patients with enlargement of the third ventricle only (8/15, $p = 0.03$). The relationship between initial enlargement of the third ventricle and hyponatremia remained after adjustment for the amount of cisternal blood or for mild degrees of hyponatremia, but not entirely after adjustment for the amount of intraventricular blood. During the actual period of hyponatremia, the association with the size of the third ventricle persisted. After ventricular drainage, the sodium levels returned to normal in two patients in whom the size of the third ventricle decreased, and not in four patients with persistent enlargement of the third ventricle.

These results suggest that the size of the third ventricle is an important factor in the relationship between acute hydrocephalus and hyponatremia, possibly mediated by pressure on the hypothalamus.

Chapter VI describes the study in which it was investigated if a natriuretic factor circulates after SAH. Digoxin-like substances have been found to possess natriuretic properties by inhibiting sodium transport in the kidney and enhancing sodium excretion. This substance can be demonstrated by a radioimmunoassay.

After heating the plasma samples, an endogenous substance cross-reacting with antibodies to digoxin was identified in 18 of 25 patients with SAH. The presence of this substance was significantly associated with an extensive hemorrhage and with a distribution of blood suggesting a ruptured anterior cerebral artery aneurysm, and could not be explained by other factors which are known to be associated with the presence of this substance in plasma, such as hypertension or fluid and salt loading. A negative sodium balance and volume depletion occurred more often in patients with a positive test for digoxin, but this relationship did not reach statistical significance. The conclusion is that a digoxin-like natriuretic substance is released in response to a subarachnoid hemorrhage, probably by hypothalamic damage.

In the last chapter (VII) the results with fludrocortisone acetate treatment are presented. Fludrocortisone acetate has a mineralocorticoid action and enhances sodium absorption in the kidney. In a consecutive series of 39 patients with CT evidence of subarachnoid hemorrhage, fludrocortisone acetate treatment was started on admission. In 28 patients an aneurysm was proved or probable, and in 21 of these the effect of fludrocortisone acetate on sodium balance and plasma volume could be studied. The plasma volume decreased more than 10% in four of the 21 patients, decreased less than 10% in five, and increased in 12 patients. The cumulative sodium balance measured over five days was negative in seven of the 21 patients, including three of the four patients with a substantial decrease in plasma volume. Plasma renin values were measured in 15 patients and were less high than in 18 previous patients not treated with fludrocortisone acetate, regardless of the presence of a negative sodium balance. Permanent side effects did not occur. In three of the 39 patients signs of pulmonary edema developed, and low serum potassium values were observed in four of the 21 patients. In comparison with previous studies, these findings suggest that fludrocortisone acetate is a comparatively safe and effective method of decreasing the incidence of volume depletion and negative sodium balance.



SAMENVATTING

In dit proefschrift werd onderzocht waardoor patiënten met een subarachnoïdale bloeding (SAB) die tevens een hyponatriëmie ontwikkelden een slechte afloop hadden. Verder werden de oorzaken van een hyponatriëmie onderzocht en werd nagegaan hoe een hyponatriëmie kon worden voorkomen.

In het eerste hoofdstuk worden het natuurlijk beloop en de complicaties van een SAB beschreven. De incidentie van een SAB door een gebarsten aneurysma ligt tussen de 11 en 19 per 100.000 inwoners per jaar. Het is een ernstige aandoening met een hoge mortaliteit en morbiditeit. Ongeveer een derde van de patiënten overlijdt of wordt ernstig geïnvalideerd als direct gevolg van de bloeding. Deze groep patiënten heeft waarschijnlijk geen baat meer bij behandeling. Wel wordt verondersteld dat vele van deze ernstige en massale bloedingen worden voorafgegaan door kleine "waarschuwingsbloedingen". Daarom is het mogelijk dat een groot gedeelte van deze patiënten gered kan worden door deze waarschuwingsbloedingen tijdig te herkennen.

De helft van de patiënten die in een goede klinische toestand wordt opgenomen overlijdt of raakt ernstig gehandicapt door complicaties, die met name in de eerste weken na de bloeding optreden. De behandeling is er dus op gericht deze ernstige complicaties te voorkomen.

De neurologische complicaties worden in het tweede gedeelte van hoofdstuk I besproken. De afloop na een SAB wordt in belangrijke mate beïnvloed door twee factoren, de recidiefbloeding en het herseninfarct. De afloop van de patiënten die een recidiefbloeding krijgen is slecht, aangezien 85% binnen drie maanden overlijdt. De frequentie van de recidiefbloeding is het hoogst aan het einde van de tweede en derde week na opname en mogelijk zelfs op de eerste dag van de bloeding. Afklemmen van het aneurysma voorkomt het recidief. Er bestaan verschillende meningen over het tijdstip van operatie - binnen drie dagen of op een later tijdstip - en over welke patiënten wel dan wel niet moeten worden geopereerd.

Behandeling met antifibrinolytica (tranexaminezuur) doet de kans op een recidiefbloeding aanzienlijk verminderen, maar de uiteindelijke afloop verbetert niet, door een gelijktijdige toename van het aantal herseninfarcten. Dus is antifibrinolytische therapie niet zinvol, tenzij hersenischemie kan worden voorkomen.

Bij ongeveer 27% van de patiënten ontstaat er hersenischemie. Deze ischemie ontwikkelt zich geleidelijk en treedt met name op in de corticale en

waterscheidingsgebieden. Meestal krijgen de patiënten focale uitvalverschijnselen, maar een daling van het bewustzijn kan eraan voorafgaan. Soms is dit het enige verschijnsel. Van de vele therapeutische maatregelen die zijn geprobeerd, lijken volume-expansie en bloeddrukverhoging een gunstig effect te hebben.

Bij patiënten die vroeg na de bloeding worden opgenomen treedt in 20% een acute hydrocephalus op. Het bewustzijnsniveau verbetert indrukwekkend na een liquor-afleidende ingreep, maar desondanks overlijdt een hoog percentage aan recidiefbloedingen en herseninfarcten. Mogelijk kan de afloop verbeterd worden door meer voorzichtige drainagetechnieken.

De interne complicaties worden beschreven in het 3e gedeelte. Na subarachnoïdale bloedingen worden vaak ECG-afwijkingen en een verhoging van de hartenzymen in het bloed waargenomen. Dit is het gevolg van een diffuse myofibrillaire degeneratie. Maar desondanks zijn ademhalingsstoornissen veel frequenter dan hartritme stoornissen. Een bekende en dramatische complicatie is het neurogene longoedeem, maar gelukkig is de mortaliteit van deze complicatie gedaald door de invoering van positieve-druk-beademing (PEEP).

Hypertensie is vaak aanwezig bij patiënten met een subarachnoïdale bloeding, ook bij die patiënten die geen hypertensie in de voorgeschiedenis hebben. De behandeling van hypertensie direct na de bloeding vormt een belangrijk dilemma. Hypertensie kan de recidiefkans vergroten en hersenischemie bevorderen door de vorming van oedeem. Anderzijds kan verlagen van de bloeddruk leiden tot hersenischemie door verslechtering van de cerebrale perfusie. Minder voorkomende complicaties zijn gastro-intestinale bloedingen, sepsis en hyperglykemie.

In het vierde gedeelte van hoofdstuk I worden de zouthuishouding en de oorzaken van een hyponatriëmie besproken. Oorspronkelijk werd hyponatriëmie na een subarachnoïdale bloeding geweten aan zoutverlies door een natriuretisch hormoon, het cerebrale zoutverlies-syndroom. Later werd het beschouwd als een uiting van een "inappropriate antidiuretisch hormoonsecretie syndroom" (SIADH). Bij een SIADH werken de osmoreceptoren verhoudingsgewijs te sterk, hetgeen leidt tot een blijvend toegenomen uitscheiding van het antidiuretisch hormoon. Vervolgens leidt dit weer tot een toename van de extracellulaire ruimte, hyponatriëmie en toegenomen zoutuitscheiding in de urine. Vochtbeperking wordt dus toegepast om deze verdunnings-hyponatriëmie te bestrijden. Vochtbeperking kan schadelijk zijn als hyponatriëmie samengaat met een verlaagd intravasculair volume, omdat vochtbeperking dan kan leiden tot hemoconcentratie en veranderingen in de viscositeit van het bloed. Met name is dit gevaarlijk bij patiënten met vaatspasme en een daardoor al beperkte cerebrale perfusie. Het is te verwachten dat als hyponatriëmie samengaat met een laag plasmavolume, patiënten met een hyponatriëmie en vochtbeperking een hogere kans op herseninfarcten hebben. Vandaar dat we de relatie tussen hyponatriëmie en herseninfarcten onderzochten.

De resultaten hiervan worden beschreven in hoofdstuk II. In een groep van 134 opeenvolgende patiënten met een SAB hadden 44 patiënten serumnatriumwaarden onder de 135 mmol per liter gedurende ten minste twee opeenvolgende dagen. Hyponatriëmie ontwikkelde zich tussen de 2e en de 10e dag na de bloeding. Ernstige hyponatriëmie (natriumwaarden van 120 tot 124 mmol/L) werd bij slechts 6 van deze 44 patiënten waargenomen. Vijfentwintig van de 44 patiënten voldeden aan de laboratoriumcriteria voor SIADH. Bij 12 waren er andere omstandigheden die hyponatriëmie konden veroorzaken (sepsis, veel braken, nierziekte, ziekte van Addison en diuretica). Bij 7 patiënten bleef de oorzaak onbekend door onvolledige laboratoriumgegevens. Het vóórkomen van de herseninfarcten, vaak met letale afloop, was significant hoger bij patiënten die een hyponatriëmie ontwikkelden. De klinische achteruitgang kon niet aan de hyponatriëmie worden toegeschreven, maar bleek enkele dagen later te berusten op een zich ontwikkeld herseninfarct.

Zesentwintig van de 44 patiënten met een hyponatriëmie werden behandeld met vochtbeperking, en bij 21 ontstonden er herseninfarcten. Het lijkt dat de correctie van hyponatriëmie door het geven van vochtbeperking gevaarlijk is bij patiënten met een SAB. Daarnaast ondersteunt dit de veronderstelling dat hyponatriëmie door zoutverlies wordt veroorzaakt.

Het onderzoek in hoofdstuk III gaat na of hyponatriëmie na een subarachnoïdale bloeding veroorzaakt wordt door een verdunningshyponatriëmie of door een primair zoutverlies. Bij 21 patiënten met een subarachnoïdale bloeding door een gebarsten intracranieel aneurysma werd een prospectieve studie verricht naar veranderingen in het plasmavolume, de zoutbalans en naar de secretie van het antidiuretisch hormoon (vasopressine). Bij 11 van de 21 patiënten daalde het plasmavolume, gemeten met een isotoop-verdunningstechniek, met meer dan 10%. Dit ging gepaard met een negatieve zoutbalans en hyponatriëmie bij zes patiënten, een negatieve zoutbalans zonder hyponatriëmie bij vier, en een positieve zoutbalans bij één patiënt. Tevens steeg het ureumgehalte in het bloed en daalde het lichaamsgewicht. De vasopressinewaarden in het serum waren verhoogd bij opneming en daalden bij alle patiënten in de eerste week, ongeacht de aanwezigheid van hyponatriëmie.

Deze bevindingen wijzen erop dat er sprake is van een zoutverliesyndroom en niet van een SIADH. Deze studie toonde aan dat patiënten met een SAB dus een volumedepletie en natriurese hebben en met volume-expansie behoren te worden behandeld. Het instandhouden van een adequaat intravasculair volume is belangrijk bij de behandeling van patiënten met een SAB. Patiënten met een SAB worden bedreigd door vaatspasme wat tot hersenischemie kan leiden als de cerebrale bloeddoorstroming verder verslechtert door volumedepletie. De doeltreffendheid van volume-expansie bij het vergroten van de cerebrale perfusie kan dan

verklaard worden door een verhoging van de viscositeit van het bloed of door een stijging van het hartminutenvolume, hetgeen nog waarschijnlijker wordt door onderzoeken die verbetering van uitvalverschijnselen ten gevolge van hersenischemie lieten zien tijdens volume-expansie.

Het verhogen van de bloeddruk is een andere manier om hersenischemie te voorkomen, wat door verschillende onderzoekers werd aangetoond. Dit kan betekenen dat hoge bloeddruk na een SAB hersenischemie voorkomt en dus niet met antihypertensiva moet worden behandeld. Echter, als een hoge bloeddruk wordt geaccepteerd kan dit een verhoogde recidiefkans tot gevolg hebben.

We onderzochten of behandeling van een hoge bloeddruk verband hield met het voorkomen van herseninfarcten en recidiefbloedingen (hoofdstuk IV). Het doel was de diastolische bloeddruk te verlagen tot onder 110 mm Hg. De uiteindelijke afloop bij patiënten met en zonder antihypertensiva bleek niet verschillend te zijn. Recidiefbloedingen kwamen minder vaak voor bij patiënten na een antihypertensieve behandeling dan bij patiënten zonder antihypertensiva (12 van 80 patiënten (15%) versus 18/54 (33%) ($p=0.012$)). Patiënten met antihypertensieve behandeling hadden gemiddeld toch nog een hogere bloeddruk dan onbehandelde patiënten. Daarentegen kwamen herseninfarcten vaker voor bij patiënten met antihypertensieve behandeling (32/80 (40%) versus 14/54 (26%) ($p=0.03$)). Deze associatie kon maar ten dele verklaard worden door een gelijktijdig aanwezige hyponatriëmie. De conclusie luidt dat hypertensie na een SAB een compensatoir mechanisme is en niet moet worden behandeld, aangezien preventie van recidiefbloedingen door een toegenomen frequentie van herseninfarcten wordt tenietgedaan.

Hyponatriëmie was gecorreleerd met de aanwezigheid van een acute hydrocephalus op de CT-scan bij opneming. Dit kon mogelijk verklaard worden door een vergroting van de derde ventrikel. Druk op de hypothalamus zou dan vervolgens kunnen leiden tot hyponatriëmie. Dit werd onderzocht in een studie beschreven in hoofdstuk V. Hyponatriëmie kwam significant vaker voor bij patiënten met een vergroting van de derde ventrikel en de zijventrikels dan bij patiënten met een normaal ventrikelsysteem, maar ook bij patiënten met vergroting van alleen de derde ventrikel. Deze correlatie bleef bestaan na correctie voor de hoeveelheid subarachnoïdaal bloed, maar niet geheel na correctie voor de hoeveelheid intraventriculair bloed. Echter, de bijdrage van intraventriculair bloed is klein en het belangrijkste effect van intraventriculair bloed is dat het een vergroting van de derde ventrikel veroorzaakt, gevolgd door een hyponatriëmie.

Welke cerebrale factor hyponatriëmie veroorzaakt is onbekend, maar deze resultaten wijzen erop dat uitzetting van de derde ventrikel een belangrijke factor is, mogelijk door druk op de hypothalamus en daardoor vrijkomen van een natriuretische factor.

Of een dergelijke factor aanwezig is bij een SAB werd onderzocht in een studie beschreven in hoofdstuk VI. Digoxine-achtige substanties blijken natriuretische eigenschappen te hebben doordat ze het natriumtransport in de nier tegengaan. Een dergelijke substantie kan worden aangetoond door een radioimmunoassay.

Bij 18 van 25 patiënten met een SAB kon na verhitten van het plasma een endogene substantie worden aangetoond die reageerde met antilichamen tegen digoxine. De aanwezigheid van deze substantie was significant gerelateerd aan de ernst van de bloeding en aan een verdeling van het bloed op de CT-scan passend bij een gebarsten aneurysma van de arteria cerebri communicans anterior. Er was geen relatie met andere factoren zoals hypertensie of vocht- en zoutbelasting. De aanwezigheid van deze digoxine-achtige substantie kwam vaker voor bij patiënten met een negatieve zoutbalans en een daling van het plasmavolume; het verschil was echter niet statistisch significant. De conclusie is dat een op digoxine gelijkende substantie vrijkomt na een subarachnoïdale bloeding, mogelijk door beschadiging van de hypothalamus.

De behandeling met fludrocortisonacetaat wordt beschreven in het laatste hoofdstuk (VII). Doordat fludrocortisonacetaat mineralocorticoïde eigenschappen heeft vergroot deze stof de natriumabsorptie in de nier. In een proefonderzoek naar het effect van fludrocortisonacetaat op de zoutbalans en het plasmavolume bij 21 patiënten met een SAB, daalde het plasmavolume maar bij slechts vier patiënten (19%) meer dan 10%. Een negatieve zoutbalans werd bij zeven van de 21 patiënten (33%) gevonden. Deze waarden werden vergeleken met de resultaten uit hoofdstuk III, waarbij 52% van de patiënten een daling van het plasmavolume van meer dan 10% toonde en 67% van de patiënten een negatieve zoutbalans had. Hieruit kan met enig voorbehoud worden geconcludeerd dat fludrocortisonacetaat een effect heeft op het plasmavolume en de zoutuitscheiding. Bovendien waren in het plasma de reninwaarden bij de behandelde patiënten lager dan bij de onbehandelde patiënten met een negatieve zoutbalans uit hoofdstuk III. Complicaties, zoals hypokaliëmie en longoedeem door overvulling waren weinig frequent en makkelijk behandelbaar. Hieruit kan worden geconcludeerd dat fludrocortisonacetaat een nuttige en vooral veilige manier is om daling van het plasmavolume en waarschijnlijk het ontstaan van een negatieve zoutbalans bij SAB te voorkomen.

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SCIENTIFIC PAPERS ON SAH

by the SAH Study Group

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De schrijver van dit proefschrift werd op 28 augustus 1954 te Leiden geboren. In 1973 deed hij eindexamen HBS-B te Dongen.

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