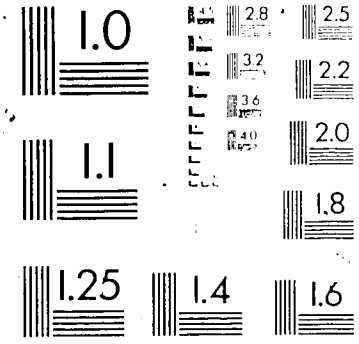

1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0

CANADIAN THESES

THÈSES CANADIENNES

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

Canada

National Library of Canada
Bibliothèque nationale du Canada

Canadian Theses Division
Division des thèses canadiennes

Ottawa, Canada
K1A 0N4

0-315-24813-0

PERMISSION TO MICROFILM — AUTORISATION DE MICROFILMER

• Please print or type — Ecrire en lettres moulées ou dactylographier

Full Name of Author — Nom complet de l'auteur

[illegible]

Date of Birth — Date de naissance	Country of Birth — Lieu de naissance
Feb 25 1952	Canada

Permanent Address — Résidence fixe

[illegible]

Title of Thesis — Titre de la thèse

[illegible]

University — Université

[illegible]

Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée

M Sc

Year this degree conferred — Année d'obtention de ce grade	Name of Supervisor — Nom du directeur de thèse
1984	Dr. S.K. Lucas

Permission is hereby granted to the NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

Date	Signature
October 9 1984	[illegible]

NL-91 (4/77)

THE UNIVERSITY OF ALBERTA

CARDIOPULMONARY EFFECTS OF NIMODIPINE AFTER SUBARACHNOID HEMORRHAGE IN MONKEYS

by

SUSAN L. NORRIS

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

FALL, 1984

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR SUSAN L. NORRIS

TITLE OF THESIS CARDIOPULMONARY EFFECTS OF NIMODIPINE AFTER SUBARACHNOID HEMORRHAGE IN MONKEYS

DEGREE FOR WHICH THESIS WAS PRESENTED MASTER OF SCIENCE

YEAR THIS DEGREE GRANTED FALL, 1984

Permission is hereby granted to THE UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(SIGNED) .....

PERMANENT ADDRESS:

.....

.....

.....

DATED .....19..

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled CARDIOPULMONARY EFFECTS OF NIMODIPINE AFTER SUBARACHNOID HEMORRHAGE IN MONKEYS submitted by SUSAN L. NORRIS in partial fulfilment of the requirements for the degree of MASTER OF SCIENCE.

.....

Supervisor

.....

.....

Date.....

Abstract

The objectives of this study were to examine the cardiopulmonary effects of subarachnoid hemorrhage, and of nimodipine used in a model of chronic cerebral vasospasm.

In the first study 29 cynomolgus monkeys had a subarachnoid clot placed via a craniectomy. Five monkeys died in the first 24 hours after clot placement. Twenty-four monkeys survived and were started on the nimodipine trial. The survivors were divided into four equal groups in a double-blind fashion, and six animals were each given nimodipine 3 mg/kg po q8h, 6 mg/kg po q8h, and 12 mg/kg po q8h. The fourth group of monkeys received a placebo, polyethylene glycol 400 0.33 ml/kg q8h. Twenty-three animals completed the 1-week course of nimodipine, with one animal dying of septicemia. Four sets of cardiopulmonary indices were measured under general anesthesia: baseline (Stage I), pre- and post-clot placement (Stage II), and after receiving nimodipine for 7 days (Stage III).

The acute cardiopulmonary effects of nimodipine were examined under general anesthesia. Oral nimodipine was given in doses of 20 mg/kg to two monkeys, 30 mg/kg to a third monkey, and 30 mg/kg to two cats. Intravenous nimodipine was administered in sequential doses of 0.012 mg/kg, 0.105 mg/kg, and 0.458 mg/kg to a monkey, and 0.010 mg/kg, 0.103 mg/kg and 0.517 mg/kg to a cat.

Using an *in vitro* model of thermodilution cardiac output, volumetrically measured flows were compared to flows

recorded by the Edwards' Cardiac Output Computer. Eighteen flows between 130 and 1035 ml/min were examined.

Stage III indices were compared to Stage I for each treatment group. All groups had a fall in heart rate. Mean arterial pressure fell in the 12 mg/kg group ($p<0.10$). Cardiac index and stroke index fell in the placebo group, and increased with increasing nimodipine dosage (not significant, $p<0.05$). Systemic vascular resistance fell significantly ($p<0.05$) in the nimodipine 6 and 12 mg/kg groups. Pulmonary vascular resistance increased ($p<0.10$) in the placebo group, and tended to fall with increasing dosage. There were no remarkable changes in pulmonary artery wedge pressure, central venous pressure, $A\text{-}aDO_2$, $a\text{-}\bar{v}O_2$ difference, and % shunt.

Cardiopulmonary indices measured before and after placement of the subarachnoid clot were compared. In the surviving monkeys heart rate increased significantly ($p<0.05$), stroke index fell ($p<0.01$), and pulmonary artery pressure, pulmonary artery wedge pressure and central venous pressure fell ($p<0.05$). In the non-survivors heart rate increased slightly (not significant), cardiac index ($p<.05$) and stroke index ($p<0.05$) fell more than in the survivors, and pulmonary artery pressure, pulmonary artery wedge pressure and central venous pressure fell (not significant). There was a significant difference between the two groups for cardiac index and stroke index.

In four control monkeys there was some degree of variability in all cardiopulmonary indices measured over a 5-hour period.

Minimal cardiovascular effects were demonstrated in monkeys given oral nimodipine up to 30 mg/kg. Intravenous nimodipine 0.458 mg/kg produced an early and transient fall in heart rate and mean arterial pressure.

Nimodipine 10 mg/kg po produced lethal cardiovascular depression in one cat. Intravenous nimodipine 0.517 mg/kg produced early and transient cardiovascular depression similar to that produced in the monkey.

The correlations between volumetrically measured flows and flows recorded by the Edwards' Cardiac Output Computer were all highly significant ($p<0.001$). The Edwards' system tended to overestimate flow, particularly at the lowest flows.

The possibility that subarachnoid hemorrhage has acute and chronic cardiopulmonary effects is relevant to the clinical and pharmacologic management of these patients. The minimal cardiopulmonary effects of oral nimodipine demonstrated in the cynomolgus monkey suggest that the dose-effect curve for nimodipine in this monkey differs from that of other species previously studied.

Acknowledgements

The author would like to acknowledge the counsel and support of Dr. E.G. King and Dr. B.K. Weir and the technical assistance of Ms. T. Gorodetsky, Dr. G. Hill, Ms. C. Krueger, Ms. M. Norris, Dr. M. Nosko, Dr. J.A. Rogers, Ms. L. Russell, Dr. B. Sykes, Mr. P. van Moll, and Mr. A. Wells.

Table of Contents

List of Tables

List of Figures

I. Introduction

Subarachnoid Hemorrhage

Subarachnoid hemorrhage is the form of intracranial hemorrhage in which bleeding occurs into the subarachnoid space. When bleeding occurs directly into the subarachnoid space it is referred to as primary subarachnoid hemorrhage. Secondary subarachnoid hemorrhage occurs when the source of the hemorrhage is outside the subarachnoid space, and blood then bursts into this space or is transferred there through CSF channels. In this second situation the primary bleed may be intracerebral, subdural, epidural, intraventricular or intraspinal.

The etiology of subarachnoid hemorrhage is diverse, as outlined in Table 1. Trauma is the most frequent cause of blood in the subarachnoid space. Pakarinen (1967) has done the most extensive population study of primary subarachnoid hemorrhage, studying the total population of Helsinki from 1954 to 1961. He found that of primary subarachnoid hemorrhages, 76% were due to ruptured aneurysms, 2% to arteriovenous malformations (AVM's), and 22% were of unknown origin. This latter group is probably due to small AVM's or aneurysms destroyed with rupture, or to arteriosclerotic arteries. The etiology is age dependent. In children AVM's are as common a cause of primary subarachnoid hemorrhage as aneurysms.

In the United States there are 11.6 cases of primary subarachnoid hemorrhage diagnosed per 100,000 population per year (Phillips et al., 1980). Pakarinen's incidence in his Finnish population was 16.8 (1967). The incidence of primary subarachnoid hemorrhage increases with age to the seventh decade. Secondary subarachnoid hemorrhage is mainly a disease of young people.

Subarachnoid hemorrhage has a high mortality. Alvord and Thorn (1977) have calculated survival for ruptured aneurysms from Pakarinen's data. These patients received the best current medical therapy of the 1960's, with no surgical intervention. Patients dying prior to hospitalization were included. They reported that if a patient is seen within 3 days of subarachnoid hemorrhage the likelihood of survival is 70% by 2 weeks, 62% by 1 month, 54% by 3 months and 45% by 2 years. Sundt and Whisnant (1978) estimated a 20% mortality from subarachnoid hemorrhage in the first day and a 50% mortality by 2 weeks if treatment was not instituted.

Sudden, unexpected death is not uncommon in patients with subarachnoid hemorrhage. Fifteen percent of patients with spontaneous subarachnoid hemorrhage die before reaching the nearest hospital (Secher-Hansen, 1964). Hamman (1934) found that 8% of all patients who died suddenly had some form of cerebral hemorrhage. Subarachnoid hemorrhage is responsible for 4.7% of all sudden deaths (Helpern and Rabson, 1945). Secher-Hansen (1964) analyzed 115 autopsy-proven cases of spontaneous subarachnoid hemorrhage

in patients who had died within 24 hours of the onset of symptoms. It was found that 75% of these patients had died instantaneously.

The morbidity of primary subarachnoid hemorrhage, irrespective of etiology, is also significant. After a 5-year follow-up 70% of patients are well, 19% are partially disabled (have a significant neurologic deficit or seizures but are able to do light work), and 11% are totally disabled (Pakarinen, 1967).

There are numerous complications of subarachnoid hemorrhage. Cerebral complications include hematomas, cerebral edema, hydrocephalus, increased intracranial pressure, rebleeding of the aneurysm, seizures, focal neurologic deficits, and cerebral vasospasm. Metabolic complications include inappropriate ADH production, and an increase in hydroxycorticosteroids. Cardiovascular and pulmonary complications are described.

Vasospasm

Vasospasm may be defined as a condition of reversible constriction of cerebral arteries. The incidence of radiographic vasospasm following aneurysmal rupture, without regard to the length of time from rupture, ranges from 21% to 62% (Kwak et al., 1979). Vasospasm can also follow trauma (Suwanwela and Suwanwela, 1972), central nervous system infections (Lyons and Leeds, 1967), intracranial surgery, or drug therapy (Sonntag and Stein, 1974).

Vasospasm is rarely detected preoperatively in patients before 2 to 3 days after subarachnoid hemorrhage. This spasm is usually maximal from day 6 to day 8 and is often gone by day 12 (Weir et al., 1978), although it can persist for 2 to 4 weeks (Drake, 1971; Maspes and Marini, 1962).

Cerebral vasospasm has great clinical significance as it is a major cause of morbidity and mortality following aneurysmal rupture (Weir, 1980). The major conducting vessels exposed to a clot become constricted, and most investigators agree that if this decrease in arterial diameter is severe it can lead to focal cerebral ischemia and infarction (Fisher et al., 1977; Crompton, 1964). Neurologic deterioration correlates directly with angiographic evidence of vasospasm (Allcock and Drake, 1965; Graf and Nibbelink, 1974). Focal neurologic deficits, as well as pathologic evidence of infarcts, usually correspond to the area of supply of the vessels in spasm (Allcock and Drake, 1965; Graf and Nibbelink, 1974; Schneck and Kricheff, 1964).

Numerous agents have been hypothesized to play a role in the origin of vasospasm including whole blood, erythrocyte breakdown products, hemoglobin, fibrin degradation products, prostaglandins, thromboxane A2, 5-hydroxytryptamine, potassium, catecholamines, histamine, vasopressin and angiotensin (Towart, 1982). There is evidence against a single causative factor (Towart, 1982). Other theories of vasospasm have been advanced including

mechanical damage leading to muscle rigor (Kapp et al., 1968), endothelial damage (Tanabe et al., 1979), or a decreased production of some vasodilator agent such as prostacyclin which is normally present (Boullin, 1980; Sasaki et al., 1981).

Modalities proposed for the management of chronic cerebral vasospasm are as diverse as the theories of its etiology. Physiologic measures such as hypercarbia (Pribram, 1965) and hypertension induced by either fluid or drugs (Giannotta et al., 1977; Kassell et al., 1982; Kosnik and Hunt, 1976) have been attempted. Parenteral treatment with direct smooth-muscle relaxants such as nitroprusside (Heros, 1976), papaverine (Kuyawa et al., 1972), or nitroglycerine (Lowe and Gilboe, 1973) tends to be complicated by systemic hypotension before any permanent relaxation of cerebral blood vessels is noted. Alpha-adrenergic blocking agents can decrease spasm when applied topically (Handa et al., 1975), however, systemic administration produces hypotension. The use of β-adrenergic drugs has provided some encouraging results (Sundt, 1975). Serotonin blocking agents have not proved useful (Moncy, 1969).

Thus at present there is no proven effective drug treatment for vasospasm. A new group of drugs has recently become the subject of intense investigation in the management of cerebral vasospasm. Calcium channel blockers, and in particular the dihydropyridine derivative nimodipine, are being studied in clinical and laboratory settings as

possible therapeutic agents for chronic cerebral vasospasm.

II. Cardiopulmonary Effects of Subarachnoid Hemorrhage

A. Cardiac Effects

Since Cushing (1901) published his observations relating changes in intracranial pressure with profound changes in cardiovascular hemodynamics, there have been a multitude of observations relating the heart and lung to central nervous system injury.

ECG Changes

The most commonly observed cardiac effects of subarachnoid hemorrhage are ECG changes. The first published association of an abnormal ECG and cerebral hemorrhage was reported by Byer et al. in 1947. A 37 year-old woman with a history of recurrent chest pain and two episodes of loss of consciousness developed a sudden left hemiparesis and had a bloody CSF tap. The ECG showed prolonged Q-T intervals and large T-waves in leads I and II. These changes disappeared after 9 days. Levine (1953) reported ECG changes simulating acute myocardial infarction in a 63-year-old woman with intracranial hemorrhage but with a normal heart at autopsy. Burch et al. (1954) provided the first extensive study of the subject when they convincingly demonstrated that cerebrovascular attacks correlated directly with changes in the ECG in 17 patients with no myocardial pathology. Abnormalities found were prolonged Q-T intervals, large amplitude T-waves and prominent U-waves. Improvement in the

ECG occurred with clinical improvement.

Large series since Byer's publication have revealed ECG abnormalities in approximately one-half of patients with subarachnoid hemorrhage where routine ECG's were performed. The variable incidences reported reflect to some extent patient selection. Sarner and Crawford (1965) reported an overall incidence of 60% in a series of patients with subarachnoid hemorrhage that included patients with heart disease. Hersch (1964) excluded patients with clinically or pathologically verified heart disease and found a 40% incidence.

Although ECG changes are most frequently observed with subarachnoid hemorrhage secondary to ruptured aneurysms, they have been observed in a variety of other acute intracranial processes including meningitis, tumors, cerebral infarcts, head trauma, and intracerebral hemorrhage, as well as in some subacute conditions such as diffuse metastatic disease.

The most common abnormalities noted in the ECG are elevation or depression of the S-T segments. However, a wide range of abnormalities have been described (Table 2).

Disorders of rhythm are less well documented than ECG changes, although numerous rhythm disturbances have been noted (Table 2). The exact incidence of serious arrhythmias in subarachnoid hemorrhage is not known as often these are transient and the patients are not carefully monitored. In experimental animals subarachnoid hemorrhage invariably

produces a rhythm disorder (Estañol et al., 1977).

The nonspecific nature of these ECG abnormalities and their resemblance to changes seen in myocardial ischemia or infarction has led to confusion in the diagnosis of cerebral pathology.

An unusual case was reported in 1959 (Beard et al.) where a patient presented with chest pain and an ECG suggestive of an acute anterior wall myocardial infarction without Q-waves. The woman was anticoagulated and discharged, but returned in 1 week with a subarachnoid hemorrhage. She died postoperatively after clipping of a right internal carotid artery aneurysm. Autopsy revealed normal coronary arteries and myocardium. Other cases are cited in the literature where the ECG abnormalities were a source of error in diagnosis (Cropp and Manning, 1960; Srivastava and Robson, 1964).

As well as making diagnosis difficult, the rhythm disturbances associated with subarachnoid hemorrhage may be life-threatening (Estañol et al., 1977; Estañol and Marin, 1975; Parizel, 1973; Smith, 1972). As previously noted sudden death is common in patients with subarachnoid hemorrhage. The mechanism of death in these patients is not entirely clear, and multiple factors are likely involved. Certainly the acute destruction and compression of vital cerebral structures is significant in some cases (Berkheiser, 1972; Dinning and Falconer, 1953). However, death can occur suddenly in the absence of progressive

neurologic lesions (Parizel, 1979) and there is often little or no evidence of focal brain damage. Cardiac arrhythmias may play a significant role in morbidity and mortality in these patients, and may explain in some patients the initial loss of consciousness that usually accompanies subarachnoid hemorrhage (Estañol and Marin, 1975).

Estañol et al. (1979) prospectively studied 15 patients with CSF and angiographic evidence of subarachnoid hemorrhage secondary to a ruptured cerebral aneurysm. The patients selected were less than 50 years old and had no history of cardiac disease or hypertension. These patients underwent cardiac monitoring for 5 days after their hemorrhage. Twenty percent of the patients had runs of ventricular tachycardia, and two of these three patients died. Sixty percent of patients had prolonged Q-T intervals, including all three patients with serious ventricular arrhythmias. The prolonged Q-T interval appears to be secondary to a non-uniformity in the rate of repolarization (Han et al., 1966), and results in an increase in duration of the vulnerable period with an increased susceptibility to the development of ventricular arrhythmias (James, 1969). Patients with this finding should be carefully monitored.

Myocardial Pathology

In an attempt to relate the cardiac abnormalities to subarachnoid hemorrhage, pathologic studies were performed. Koskelo and Punsar (1964) first reported myocardial

pathology after subarachnoid hemorrhage, describing three patients with subarachnoid hemorrhage and ischemic T-wave changes on ECG. Autopsy in each case revealed subendocardial hemorrhage and normal coronary arteries. They suggested that these ECG changes did not simulate cardiac disease, but rather were evidence of it.

In another autopsy series of 235 patients with fatal intracranial disease (Smith and Tomlinson, 1954), subendocardial hemorrhage was found in only 29 patients. This abnormality was seen most commonly in post-traumatic and postoperative tumor patients, and was not found in any of 11 patients with spontaneous subarachnoid hemorrhage.

Microscopic changes in the heart have been found in patients dying after subarachnoid hemorrhage. Hammermeister and Reichenbach (1969) reported a 49-year-old patient with a ruptured aneurysm and pulmonary edema and ECG evidence of transmural infarction. Autopsy revealed a grossly normal heart but microscopy showed multiple foci of myocytolysis resembling the "norepinephrine myocarditis" described by Szakacs and Cannon (1958). In another series (Reichenbach and Benditt, 1970) all 20 patients dying of subarachnoid hemorrhage had some degree of myocardial myofibrillar degeneration. Other pathologic changes have been described in the myocardium (Connor, 1969; Reichenbach and Benditt, 1970): collapse of reticulum, scattered areas of cell loss, cytoplasmic banding, and lipofuscin pigment deposition in the myofibrils.

Elevated serum creatine phosphokinase (CPK) levels have been found in a significant number of patients with cerebral dysfunction, head injury and encephalitis (Acheson et al., 1965; Dubo et al., 1967; Schiavone and Kaldor, 1965). In series CPK levels were elevated in 60% of patients with cerebral dysfunction of diverse etiology (Schiavone and Kaldor, 1965). Connor (1967) has shown that this CPK originates in foci of myocytolysis of the myocardium.

Hemodynamic Effects

The hemodynamic effects of subarachnoid hemorrhage are not as well studied as the ECG changes, rhythm disturbances, and myocardial pathology. There are reports in the literature relating subarachnoid hemorrhage to an increase in blood pressure (McCordock, 1923). Estañol et al. (1979) found nine of 15 patients with a subarachnoid hemorrhage had blood pressure elevations during the first 5 days after hemorrhage, with diastolic pressures between 90 and 115 mm Hg.

There is little data in the published literature relating subarachnoid hemorrhage and other hemodynamic indices. A Russian study (Galat, 1982) found that cardiac output is increased in stable patients with subarachnoid hemorrhage, whereas in very ill patients the cardiac output is decreased and is associated with an increase in systemic vascular resistance.

Etiology of Cardiac and Hemodynamic Effects

The etiology of the cardiac and hemodynamic effects of subarachnoid hemorrhage is uncertain. There are numerous theories. A number of studies point to involvement of the autonomic nervous system. Manning et al. (1937) showed that vagal stimulation in dogs produced ECG changes and myocardial damage which are blocked by atropine and accentuated by the cholinergic agent eserine. Similar observations have been made in baboons (Groover, 1965). However, alterations in sympathetic tone by stellate ganglion stimulation in dogs can produce ECG abnormalities and subendocardial hemorrhage (Klouda and Brynjolfsson, 1969). Arrhythmias produced by experimentally induced subarachnoid hemorrhage in rabbits can be blocked by propranolol (Offenhaus and Goal, 1969). Catecholamine studies also support sympathetic nervous system involvement. Systemic norepinephrine infusion can produce subendocardial hemorrhages (Szakacs and Cannon, 1958) and the injection of norepinephrine into the jugular vein of dogs produced microscopic changes in the myocardium as well as hemodynamic and ECG changes identical to those produced by subarachnoid hemorrhage in the same model (Jacob et al., 1972). Epinephrine infusion into the left coronary artery of dogs produced an increase in T-wave amplitude and S-T segment depression. After cessation of the infusion the T-waves became inverted. These changes lasted 7 to 10 days before returning to normal (Barger et al., 1961).

Greenhoot and Reichenbach (1969) hypothesized that the microscopic pathologic changes were caused by brain stem sympathetic stimulation which in turn caused intramyocardial release of catecholamines from the norepinephrine cardiac nerve network described by Norberg (1967). This is supported by McNair et al. (1970), who produced subarachnoid hemorrhage in mice and found focal myocardial necrosis in 48% of animals. With reserpine pretreatment myocardial lesions were absent in 92% of the animals.

Urine catecholamine levels have been found to be elevated in some patients with subarachnoid hemorrhage, with a significant correlation between ECG abnormalities and urinary normetanephrines and metanephrines (Cruickshank et al., 1974).

Other possible causes of the ECG changes have been postulated: electrolyte abnormalities, alkylosis, anoxia, and enzyme abnormalities including transaminases, lactic acid, and triglycerides (Eisalo et al., 1972; Hunt et al., 1969). None of these correlated with ECG changes.

Attempts have been made to relate the site of the cerebral lesion with ECG alterations. Cropp and Manning (1960) described 29 cases of subarachnoid hemorrhage in which 15 patients had T-wave abnormalities suggestive of myocardial ischemia. Of these 15 patients, 11 had the site of bleeding in the anterior cranial fossa. The authors hypothesized that lesions of the orbital surface of the frontal lobes produced vagal stimulation.

The rostral connections for the autonomic nervous system are located in the hypothalamus and therefore the pathologic changes and functional effects of stimulation and ablation of this region have been extensively studied.

Hypothalamic stimulation in cats will produce ECG changes similar to those seen in humans with central nervous system lesions (Fuster and Weinberg, 1960; Manning and Cotton, 1962; Melville et al., 1963). These changes can be abolished by cervical spine transection, but not by bilateral vagotomy (Mauck et al., 1964). Normally these changes revert one-half minute after stimulation, but if stimulation is repeated the changes become persistent (Porter, 1962). Hall et al. (1972) demonstrated electronmicrographic changes in the myocardium of dogs within 4 hours of hypothalamic stimulation. Doshi and Neil-Dwyer (1980) demonstrated hypothalamic and myocardial lesions in 42 of 54 patients dying of subarachnoid hemorrhage. They suggested that subarachnoid hemorrhage induced spasm of the small vessels supplying the hypothalamus which led to sympathetic stimulation and increased catecholamine production. Other areas of the brain which produce ECG changes on stimulation include the midbrain reticular formation, ventral hippocampus and medial nuclei of the amygdala (Manning and Cotton, 1962; Porter et al., 1962).

The role of increased intracranial pressure (ICP) in the genesis of cardiac arrhythmias of neurogenic origin has

been a focus of research. Smith and Ray (1972) provoked cardiac arrhythmias by a rapid increase in ICP or by instantaneous release of an elevated ICP. Atropine or vagotomy prevented the arrhythmias.

In a canine model, Estañol et al. (1977) examined the relationship between subarachnoid hemorrhage, ICP, arrhythmias, and vagal and sympathetic function. The rise in ICP correlated with the onset of the arrhythmias when vagi and sympathetics were intact. All animals with intact vagi had sinus arrest or bradycardia immediately after the elevation of ICP. Ventricular arrhythmias were only seen in animals with intact cervical sympathetics, spinal cord, or both. Animals with sectioned vagi and sectioned heart sympathetic innervation and an intact spinal cord developed arrhythmias several minutes after the subarachnoid hemorrhage and increased ICP. The authors suggested that the subarachnoid hemorrhage and resultant increase in ICP somehow induced a massive sympathetic and vagal discharge. When only the spinal cord remained intact the delayed and inconsistent arrhythmias were possibly due to increased circulatory or tissue catecholamines.

The autonomic nervous system is involved in the hemodynamic responses to intracranial injury. Cushing (1901) demonstrated cardiac standstill and temporary cessation of respiration after a rapid rise of ICP in anesthetized dogs. This response could be eliminated by vagotomy. After respiration was resumed an increase in heart rate and blood

pressure was noted with rhythmic changes in the latter. Section of the spinal cord at the level of the atlas resulted in the initial vagal response with no increase in blood pressure.

In the same model described above, Estañol et al. (1977) demonstrated an elevation of blood pressure following subarachnoid hemorrhage when both vagi and heart sympathetic supply were disrupted, but an absence of blood pressure elevation when the cervical cord was sectioned. This indicated that the increase in blood pressure was mediated through the sympathetic nervous system travelling in the spinal cord.

Cardiovascular responses including vasoconstriction, augmented myocardial contraction and cardioacceleration, have been produced following stimulation of the diencephalon in vagotomized cats (Manning and Peiss, 1960).

The etiology of the effects of subarachnoid hemorrhage on the heart and systemic vascular system has yet to be determined. Both the parasympathetic and sympathetic nervous systems play a role. However, multiple factors are likely involved, with the mechanism a complex interrelationship of neural, enzymatic and cardiovascular factors.

B. Pulmonary Effects

Subarachnoid hemorrhage has effects on pulmonary function. This has been mainly studied in the context of neurogenic pulmonary edema (NPE).

The clinical picture of NPE was first described by James Hope in 1832. Since then many others have reported the rapid onset of pulmonary edema following various central nervous system insults including seizures, trauma, cerebrovascular accidents including subarachnoid hemorrhage, tumors and increased intracranial pressure (Theodore and Robin, 1976). Although the fulminant form of pulmonary edema is relatively uncommon in the clinical setting, a post-mortem study found 71% of patients with fatal subarachnoid hemorrhage had pathologic evidence of pulmonary edema (Wei 1978).

The pathogenesis of the fluid shifts in NPE is unclear. The most extensive studies concerning the early hemodynamic alterations associated with NPE were reported by the Sarnoffs (1952, 1952a). They produced pulmonary edema by injecting thrombin and fibrinogen into the cisterna magna of rabbits and dogs. The animals showed massive increases in aortic, systemic arterial, pulmonary arterial, pulmonary venous and central venous pressures with a concurrent decrease in aortic blood flow. Systemic blood volume decreased and pulmonary blood volume increased (Sarnoff and Berglund, 1952). These studies support the concept that NPE is due to an unbalancing of the Starling forces across pulmonary capillary walls. However, it is felt that conventional left ventricular failure probably does not play a role (Theodore and Robin, 1976).

Increased pulmonary capillary permeability may also be important in the pathogenesis of NPE. The edema fluid has a high protein content, and contains red blood cells (Cameron, 1949; Weisman, 1939).

Theodore and Robin (1976) synthesized the available literature into a theory for the pathogenesis of NPE: A centrally mediated, massive sympathetic discharge is the initial result of the CNS insult. This produces a transient, intense and generalized vasoconstriction with a shift of blood to the low resistance pulmonary circulation. This produces a hydrostatic effect resulting in fluid being forced into the alveoli. This pulmonary hypervolemia damages pulmonary vessels and alters pulmonary capillary permeability. The hydrostatic effect resolves, but the permeability abnormality persists.

Various sites and mechanisms have been described in attempts to link the cerebral lesions to the pulmonary disturbances. An "edemagenic centre" has been postulated by Gamble and Patton (1953). They produced acute hemorrhagic lung edema by making discrete electrolytic lesions in the preoptic region of the hypothalamus in rats. In persuing this finding they found that bilateral vagotomy preceeding production of the lesions offered no protection from edema, whereas spinal transection at C8 or bilateral splanchnic sympathectomy offered some protection (Maire and Patton, 1956, 1956a). Based on studies of irritative electrolytic lesions, Reynolds (1963) suggested that stimulation of

sympathetic pathways located in the hypothalamus was involved. Richards (1963), however, was unable to support this theory in a post-mortem study of 88 patients with pulmonary edema and intracranial disease. Consistent cerebral lesions or damage to the hypothalamus could not be demonstrated. Various pharmacologic studies suggest that NPE is mediated through the sympathetic nervous system, specifically the α-adrenergic system (Bean and Beckman, 1969; MacKay, 1950).

Minor changes in pulmonary function occuring in subarachnoid hemorrhage have not been assessed.

III. Calcium Channel Blockers

Calcium

Calcium plays an important role in the molecular mechanisms of electrical activity in all electrically excitable tissue. Local changes in the relative permeabilities of surface membranes of nerve or muscle cells generates an electrical potential difference. Subsequently, voltage gradients are established which force the movement of extracellular and intracellular ions. A local circuit current is created which spreads the impulse from active to passive regions and forms the basis of nerve impulse propagation in excitable cells.

The sequential changes in the potential difference across the cell membranes (the action potentials) vary in different tissues depending on the relative amounts of the various currents or the total number of time-dependent currents in a particular region. Although a detailed description of ionic mechanisms in different cardiac tissues and other excitable tissues is still evolving, the roles of ionic currents in different action potential phases are similar. The currents involved in generation of the Purkinje fiber action potential are well studied (Noble, 1979; McAllister, 1975). One current, mediated by sodium ions, is responsible for the rapid upstroke and fast impulse conduction in the specialized conducting system of the heart as well as in atrial and ventricular muscle. A second

current is carried by calcium ions and generates the action potential in nodal tissue, underlies slow impulse conduction in the A-V node, and maintains the plateau phase of the action potential in other parts of the heart.

Calcium also plays an important role in the contraction of cardiac and smooth muscle cells. Knowledge of the contractile mechanism and the mechanisms of uptake, storage, release, and regulation of calcium is necessary for an understanding of the effects of calcium channel blockers.

The basic contractile unit of striated muscle is the sarcomere. Long chains of sarcomeres form myofilaments, bundles of which form myofibrils. Two types of filaments are arranged in an organized latticework within the myofibrils: thick filaments and thin filaments. The thick filaments are composed mainly of the protein myosin and the thin filaments mainly of the protein actin. It is the reaction between these two filaments that is responsible for shortening of the sarcomeres producing a contraction of the muscle. Polymerized actin molecules are arranged in a double helix in the thin filament. Associated with the thin filaments is a second protein tropomysin which forms a ribbon on both sides of the actin double helix. Distributed along the thin filaments at regular intervals are the troponin complexes. These consist of three proteins: TnT, TnI which inhibits the actin-myosin interaction, and TnC which is a specialized calcium receptor.

Myosin is formed by two heavy chains and four light chains. The relatively heavy chains have a long tail and an ellipsoid 'head' which projects from the thick filament forming cross-bridges with the actin molecules.

In relaxed muscle tropomysin molecules are situated so that they block the formation of cross-bridges with the actin molecules. With the influx of calcium into the myofilament spaces calcium binds to TnC which results in the movement of tropomysin into a non-blocking position. Cross-bridges can then be formed and contraction occurs.

Two membrane systems regulate this reaction of the thick and thin filaments by controlling the amount of calcium in the myofilament space. The sarcolemma is the outer covering of the cell and forms invaginations into the interior called T-tubules. The second system, the sarcoplasmic reticulum (SR), forms a closed intracellular net of tubules surrounding the myofibrils. Mitochondria, important in providing adenosine triphosophate (ATP) for various processes, may also alter the activity of calcium in the myofilament space.

The sarcolemma functions in regulating ion fluxes important to muscle contraction and to nerve impulse initiation and propagation. Sodium and calcium concentrations are higher in blood than sarcoplasm, while potassium concentration is higher in the sarcoplasm. Sodium and potassium gradients are established by an ATP-requiring active transport process. Calcium is extruded from the cell

by several transport systems: the coupling of the increased flow of sodium down its chemical gradient to an outward flow of calcium and a Ca-ATPase that extrudes calcium from the cell.

Flows of sodium, calcium, and potassium across the sarcolemma occur through membrane channels that open or close depending on the electrical potential across the sarcolemma (Morad and Goldman, 1973; Reuter, 1970). Hormones and drugs which act on receptors in the sarcolemma can alter these channels and therefore alter the ion fluxes. Calcium can also enter cells by a passive leak.

Calcium is transported into the SR via a magnesium-dependent calcium-stimulated ATPase. The SR is probably the primary source of calcium that activates myofibrils. Calcium release from the SR is triggered by a small trans-sarcolemmal flux of calcium.

There are several important differences in the regulation of the contractile mechanism of smooth and striated muscle. In vascular smooth muscle the calcium binding protein calmodulin is involved in regulating actin-myosin interactions. The calcium-calmodulin dependent phosphorylation of the P-light chain of myosin is the key regulatory step for initiating actin-myosin interactions in smooth muscle. Troponin is not present in smooth muscle. The main source of calcium for the initiation of contractile activity in smooth muscle is extracellular in contrast to striated muscle where it is intracellular. Contraction in

cardiac muscle is associated only with cell membrane depolarization, while smooth muscle contraction can occur by a second mechanism independent of depolarization.

In vascular smooth muscle there are two separate types of calcium channels: those operated by membrane potential depolarization (PDCs) and those operated by receptor activation (ROCs). Van Breemen et al. (1979) supported this multi-channel theory by showing that verapamil can close channels sensitive to high potassium, while ROCs stimulated by noradrenalin could be kept open.

Activation of either channel, ROC or PDC, allows calcium influx as well as the release of calcium from superficially located intracellular stores. As well, ROC activation liberates bound calcium from the external surface of the membrane and depolarizes the membrane with consequent opening of PDCs.

Calcium Channel Blocking Drugs

Recent research into cellular calcium functions has led to the identification of a multitude of drugs which have calcium blocking properties. With certain defined criteria of selectivity and potency of action, a group of drugs has emerged which are termed calcium channel blockers (CCBs). This chemically heterogeneous group of drugs was first described by Fleckenstein (1977), and is subdivided into several classes. One group of compounds, including the phenothiazine antipsychotic agents, block calcium-calmodulin

activated events. The calcium blockers typified by nifedipine, verapamil, and diltiazem appear to exert their major effects by blocking cellular calcium entry at the PDC of the plasmalemma. It is this class of drugs to which nimodipine belongs and around which the remainder of this discussion will focus. Other classes of calcium blockers with specificity for other sites of action undoubtedly exist.

Little data is available which specifically defines the site of action of the CCBs. A plasmalemmal locus of action is suggested by the ineffectiveness of CCBs in skinned cardiac muscle and smooth muscle (Fleckenstein, 1971). Increased extracellular calcium reduces the inhibitory effect of CCBs in both cardiac and smooth muscle (Triggle, 1981). It is uncertain whether this represents a competitive inhibition or an allosteric interaction or some other mechanism. Further evidence that CCBs reduce calcium flux across the sarcolemma was seen in heart muscle preparations which showed a shortened plateau phase of the action potential and a depressed peak isometric twitch tension when exposed to CCBs. The reduced calcium current may decrease twitch tension either by reducing the amount of calcium-induced calcium release from SR or by reducing the amount of calcium sequestered in the SR over many beats.

As mentioned previously the two types of calcium channels can be separated pharmacologically. Firstly, calcium influx occurs in response to potassium activation

which produces depolarization and opening of PDCs, and secondly influx occurs in response to an agonist such as noradrenalin which causes calcium influx through both ROCs and PDCs (Van Breemen et al. 1982). Contractile responses induced by potassium-depolarization are uniformly sensitive to these blockers, whereas agonist-induced responses exhibit variable sensitivity. These findings tend to correspond with the degree to which the response is dependent on extracellular calcium. Potassium-induced responses are highly dependent as are many agonist responses that are sensitive to calcium blockers.

In summary, the CCBs have several common properties. They reduce the flow of calcium across the sarcolemma resulting in a shortened plateau phase of the action potential and an inhibition of the development of muscle tension. At low concentrations they uniformly inhibit PDCs and inhibit ROCs with some selectivity. Tension development due to calcium leak or the release of intracellularly stored calcium is not inhibited.

The CCBs are, however, a complex and diverse group of drugs. This diversity makes it impossible to reliably extrapolate the pharmacologic responses of one drug in one model to another drug in another model.

CCBs may have different effects in different tissue types. The basis for these differing effects may be differences in calcium-related mechanisms between tissues. Differences between calcium regulation and contractile

mechanisms of cardiac and smooth muscle have already been mentioned. Agonists, for example noradrenalin, can produce different contractile responses in various vessel types and various species. Whether this heterogeneity represents differences in receptor function or structure, transduction events, calcium channel mechanisms, or amount of available calcium for influx, is uncertain. Binding site structure may vary between tissues with the result that different CCBs may have different potencies or different effects in different tissues. For example, niludipine is several hundred times more potent in intestinal smooth muscle than in cardiac muscle (Hashimoto, 1979).

The magnitude of intracellular calcium stores varies greatly depending upon the source of the smooth muscle. For each type of vascular smooth muscle the fraction of contraction due to the influx of calcium compared to that due to intracellular calcium release can be determined. The efficacy of CCBs is related to this ratio.

The concentration of the CCB also is a factor in determining its effect. CCBs lose some of their specificity at high concentrations where these drugs can exhibit other pharmacologic properties such as ROC blocking, sodium-channel blocking, and local anesthetic properties (Jim et al., 1981; Triggle, 1981; Triggle and Swamy, 1980).

Drugs classified as CCBs have markedly different chemical stuctures and pharmacologic profiles. A unified concept of calcium channel blocking is untenable. It is

likely that CCBs act at multiple sites of calcium regulation, or they may act indirectly via modulating other surface receptors. Structurally unrelated CCBs may bind to different sites of the same channel or to distinct populations of calcium channels (Henry, 1982).

The effects of CCBs *in vivo* must be clearly distinguished from their effects *in vitro*. The *in vivo* responses represent the integrated result of direct effects of the drug on many calcium dependent processes in the body, as well as the indirect effects of the body's compensatory mechanisms. For example, the vasodilating effects of the dihydropyridines may trigger autonomic reflux adjustments such as tachycardia (Kawai et al., 1981).

CCBs are emerging as an important clinical tool in a wide variety of cardiovascular disorders. They are being examined for potential use in several cerebrovascular disorders including cerebral vasospasm and ischemic insults.

As noted above, there are numerous agents which may play a role in the genesis of chronic cerebral vasospasm following subarachnoid hemorrhage. Increase in intracellular calcium may, however, be the underlying common mechanism of the vasoconstriction (Bolton, 1979; Van Neuten and Vanhoutte, 1981). Therefore, CCBs have been investigated for use in the treatment of chronic cerebral vasospasm. Vasospasm may, of course, be more complex than transarcarcolemmal calcium influx. Varsos et al. (1983) have suggested that there may be a derangement in the underlying

contractile process as not all CCBs reverse vasospasm.

Ideally a therapeutic agent would be selective for cerebral vessels thus minimizing effects on cardiac and systemic vascular function. The potential for selectivity exists in that cerebral vessel contraction differs from that of the systemic vasculature. Cerebral vascular smooth muscle appears to be more dependent on extracellular calcium than other vascular smooth muscle and intracellular calcium pools have little significance in cerebral vessels, even in response to agonist-induced contractions (Allen et al., 1976; McCalden and Bevan, 1981; Nakayama and Kato, 1979; Pearce and Bevan, 1983; Toda, 1974).

The effects of a number of CCBs have been studied on isolated cerebral arteries. Diltiazem (Shimizu et al., 1980), flunarizine (Nakayama and Nasuya, 1980), cinnarizine (Nakayma and Nasuya, 1980), and verapamil (Hayashi and Toda, 1977; McCalden and Bevan, 1981; Shimizu et al., 1980) all dilate cerebral vessels in response to contractions induced by a variety of agonists. Nifedipine and nimodipine are the most potent agents in cerebral vessels (Edvinsson et al., 1979; Nakayama and Nasuya, 1980; Towart, 1981a; Towart and Perzborn, 1981).

In vivo, diltiazem increased cerebral blood flow (CBF) in dogs (Pearce and Bevan, 1983). Nifedipine had a similar effect in rats (Sandahl et al., 1978), and 1 mg/kg po of nifedipine increased CBF in humans (Angelino et al., 1975). In several animal models of vasospasm, CCBs have been shown

to produce cerebral vasodilation (Allen and Bahr, 1979; Tanaka et al., 1982). Nimodipine's use in the management of vasospasm will be discussed further.

IV. Nimodipine

Nimodipine (Bay e 9736) is a calcium channel blocking drug belonging to the dihydropyridine family, which also includes nifedipine and niludipine.

Nimodipine is a finely crystalline substance with a molecular weight 418.5. It melts at 125-126°C. The drug is insoluble in water but soluble in chloroform, ethyl acetate, ethanol, and polyethylene glycol. It is sensitive to alkali, but stable in neutral or acid media. Nimodipine is sensitive to light of wavelengths less that 450 nm.

Pharmacologic studies have shown that [^{14}C]-labelled nimodipine is metabolized rapidly to inactive 1,4-dihydropyridines and pyridines (Meyer et al., 1983). These metabolites are excreted in urine (20%) and feces (80%). Biotransformation products excreted in the bile are conjugated with glucuronic acid. In serum samples the active, unchanged drug is present up to 1 hour after oral administration (Meyer et al., 1983).

Nimodipine qualifies as a CCB as it has been shown to inhibit the influx of extracellular calcium in depolarized smooth muscle cells. Kazda and Towart (1982) have demonstrated dose-dependent inhibition of calcium-induced contractions of rabbit aortic strip. Potassium-induced contractions of aorta (Towart and Kazda, 1979), saphenous and basilar arteries (Towart, 1981a) are readily inhibited by nimodipine due to block of PDCs.

Nimodipine's action in the presence of agonist-induced contractions is more complex. Norepinephrine-induced contractions of aorta (Towart and Kazda, 1979) and saphenous artery (Towart, 1981) are unaffected by nimodipine. This is due to agonist-induced release of intracellular calcium by unaffected ROCs.

The cerebral vasculature has a different response to certain CCBs in the presence of agonist-induced contractions. The initial phasic component of the serotonin-induced contraction of basilar artery is little affected by nimodipine, being inhibited only at very high concentrations. However, the sustained tonic component of serotonin-induced contractions of the basilar artery is potently inhibited by nimodipine (Towart, 1981). Nimodipine also inhibits contractions of basilar arteries induced by carbocyclic thromboxane but does not inhibit this agonist in saphenous arteries (Towart and Perzborn, 1981).

There are several possible explanations for the different responses to nimodipine by the peripheral and cerebral vessels. Allen and Banghart (1979) hypothesized that the basilar artery uses primarily extracellularly bound calcium to provide agonist-induced contractions whereas the femoral artery uses intracellular calcium. Towart (1981) disagrees, having found that extracellular calcium is essential to sustained contraction in both basilar and saphenous arteries.

The possibility exists that certain agonists act on the basilar artery by depolarizing it (Towart, 1981a). This remains to be clarified.

A further possibility (Towart, 1981a) is that the ROCs of the basilar artery differ from those of the systemic vasculature, the former being sensitive to calcium antagonists such as nimodipine. This would produce a selective block of ROCs in cerebral vessels.

Research has been carried out to identify the specific binding sites for radiolabelled nimodipine. Although the localization of the specific receptors has not been demonstrated, [^{3}H]nimodipine has been shown to bind reversibly to high affinity, stereospecific binding sites in membranes prepared from brain, heart, lung and kidney cells of guinea-pigs (Harper et al., 1981).

The physiologic effects of nimodipine *in vitro* and *in vivo* have been studied over the last several years. The remainder of this discussion will summarize what is known about these effects.

The systemic vasodilating effects of nimodipine have been demonstrated in dogs, as femoral blood flow increases after sublingual administration of the drug. Mesenteric and renal blood flow were unaffected (Kazda et al., 1979).

Nimodipine has a negative inotropic and chronotropic action in isolated heart preparations (Thomas et al., 1983). Noradrenalin-induced reflex bradycardia is nearly abolished by nimodipine in a dose of 30 µg/kg iv in dogs (Taylor and

Kowalski, 1983). Infusions of nimodipine (0.1 to 1.0 μg/kg/min iv for 20 minutes) inhibit tachycardia evoked by acetylcholine in α-chloralose anesthetized dogs pretreated with propranolol (Taylor and Kowalski, 1982).

Oral nimodipine in a dose of 3.16 mg/kg produced a slight decrease in blood pressure in conscious squirrel monkeys (personal communication, Dr. R. Battye, 1983). Ten mg/kg produced a fall in mean blood pressure of 50 mm Hg. The half-life of this fall was 140 minutes. Heart rate was not changed substantially. Nimodipine in a dose of up to 1 mg/kg po in cats produced an increase in cardiac output that was dose dependent (Kazda et al., 1979). There was no change in blood pressure.

Nimodipine has a preferential action on cerebral vessels (Towart, 1981). Not all CCBs show this preference, however the 1,4-dihydropyridines, and particularly nimodipine, have a special affinity for the ROCs in cerebral vessels (Kazda and Towart, 1982). The effect of nimodipine on cerebral blood flow has been extensively studied. Nimodipine dilates cerebral vessels (Auer et al., 1982, 1983; Kazda et al., 1982; Tanaka et al., 1980) and increases cerebral blood flow after intraarterial, intravenous, oral and sublingual administration in a number of species (mice, rats, rabbits, cats, dogs, and primates) (Auer, 1981; Harper et al., 1981; Hoffmeister et al., 1979; Kazda et al., 1982). Both small and large cerebral arteries are affected. The effective dose range is 0.001 to 0.1 mg/kg iv, and 0.01 to

2.0 mg/kg po.

Resistance to flow decreases in both the brain and femoral arterial beds, however, cerebral vascular resistance is reduced more markedly than femoral resistance. Nimodipine's effect on cerebral vascular resistance is dose-dependent, that on femoral resistance is not (Kazda et al., 1982). In these acute experiments mean arterial blood pressure was not significantly decreased after intraarterial injection of 0.01 mg/kg in dogs, although heart rate increased significantly. Intravenous infusions of 0.0032 mg/kg/min in cats produced an average fall in blood pressure of 30%.

As well as dilating normal cerebral blood vessels, nimodipine also dilates pathologically contracted blood vessels. Ischemia produces vascular changes that limit the potential for recovery of the ischemic brain (Olsson and Hossman, 1971). In cats subjected to 7 minutes of global cerebral ischemia, impaired reperfusion of the brain is completely prevented by administration of 1.0 mg/kg of nimodipine orally when given immediately before the ischemic episode. The post-ischemic mortality was reduced from 90% to 10% (Kazda et al., 1979). The theory for nimodipine's beneficial action in the ischemic model is that nimodipine inhibits the transmembrane calcium influx that is caused by ischemia-induced increased extracellular potassium with resultant depolarization (Kazda et al., 1982; Towart et al., 1982).

Thromboxane A2, formed by platelets, brain tissue and cerebral vessels (Hagen et al., 1979) is increased during cerebral ischemia (Gaudet and Levine, 1979). It is a potent vasoconstrictor and may be involved in the pathology of cerebral disorders (Boullin, 1980; Ellis et al., 1977). Nimodipine selectively inhibits contractions induced by carbocyclic thromboxane A2 (a stable analogue) in cerebral vessels (Towart and Perzborn, 1981).

Ott and Lechner (1980) demonstrated that oral nimodipine causes redistribution of blood flow in an infarcted hemisphere, with flow increasing in ischemic areas and decreasing in hyperemic areas without affecting hemispheric blood flow. This may be the mechanism of the myocardial protective effects of nimodipine (Gross et al., 1980; Poole-Wilson, 1980; Weishaar et al., 1979). However, Harris et al. (1982) suggested the possibility of some detrimental effects of this drug. With intracarotid infusion of nimodipine in primates they found that nimodipine did not increase blood flow in a closed skull preparation, and that cerebrovascular responses to alterations in arterial Pco_2 and hemorrhagic hypotension were reduced. The critical level of blood flow at which edema formation began and ion homeostasis was disturbed was increased.

Studies indicate that nimodipine may effect pathologic spasm of cerebral vessels. Tanaka et al. (1982) induced vasospasm in cats by autologous clot placement in the cisterna magna. Administration of nimodipine 0.1 mg/kg iv 30

minutes after the subarachnoid hemorrhage resulted in complete disappearance of the spasm. The dilatory response was most marked in the smaller arteries (≤100 μm).

Nimodipine is being investigated in a number of clinical settings. The area of most intense research relates to the management of cerebral vasospasm. Auer et al. (1982) found that topical intracisternal administration of nimodipine reversed intraoperative vascular spasm and decreased postoperative symptomatic vasospasm.

Allen et al. (1983) provided strong evidence of decreased neurologic deficits and decreased mortality after prophylactic administration of oral nimodipine was commenced within 96 hours of a subarachnoid hemorrhage. Another study involving 10 patients with acute ischemic stroke showed that nimodipine produced an increase in hemispheric blood flow in all patients (Gelmers, 1982).

V. Objectives

Subarachnoid hemorrhage is associated with a significant morbidity and mortality. Two complications of subarachnoid hemorrhage have been outlined. Certain aspects of the cardiopulmonary effects of subarachnoid hemorrhage are well described: ECG changes, enzyme changes, pathologic changes in the myocardium, and neurogenic pulmonary edema in its fulminant form. However, a number of questions remain unanswered. Both acute and chronic hemodynamic changes are not well studied. The effects of subarachnoid hemorrhage on pulmonary function when pathologic or clinical evidence of pulmonary edema is not present have not been studied.

Nimodipine may prove useful in the prophylaxis and management of cerebral vasospasm after subarachnoid hemorrhage. Both acute and chronic *in vivo* studies of the cardiovascular effects of the drug are limited. The chronic cardiovascular effects of nimodipine administration in a model of subarachnoid hemorrhage have not been studied. In view of the potential for subarachnoid hemorrhage to cause deleterious cardiac effects, it is imperative that the cardiac and hemodynamic effects of chronic administration of nimodipine be well understood.

The objectives of this study were to examine, in a primate model of subarachnoid hemorrhage, the following questions:

1. What are the effects of subarachnoid hemorrhage on cardiovascular and pulmonary function?

2. What are the effects of nimodipine, administered in the management of subarachnoid hemorrhage, on cardiovascular and pulmonary function?
3. What are the acute effects of nimodipine on cardiovascular function?

VI. Methods

A. Cardiopulmonary Effects of Nimodipine After Subarachnoid Hemorrhage in Monkeys

Twenty-nine female cynomolgus monkeys *Macaca fascicularis* (Charles River Research Corporation, Port Washington, New York) with an average weight of 3.3 kg (range 2.8 to 4.2 kg) were used in the study. All animals were observed for at least 1 week between receipt of the animal and experimentation in order to permit recovery from transport. The monkeys all appeared grossly healthy, active, and well nourished. They were kept singly in primate cages, and were fed High Protein Monkey Chow (#5045, Ralston Purina Co., St. Louis, Missouri) and fresh fruit.

Each of the 24 monkeys who started the nimodipine trial underwent three stages of experimentation, termed Stage I, Stage II, and Stage III. Stage I involved baseline measurements. Stage II involved the placement of a subarachnoid clot, and occurred any number of days after Stage I. Following Stage II nimodipine was administered for 7 days, then Stage III measurements were taken and the animal was sacrificed.

The anesthetic and operative procedures were identical for Stages I and III. The animals were sedated with ketamine hydrochloride 6 to 10 mg/kg im, and intravenous access established. The monkey's weight and head-anus height were obtained. Intubation was performed using a 4.5 or 5.0 mm

endotracheal tube (Portex Inc., Scarborough, Ontario). Ventilation was commenced with a small animal volume-cycled respirator (model 665, Harvard Apparatus, Inc., Dover Road, Millis, Massachusetts) at a rate of 26 to 30 per minute, an inspiratory/expiratory ratio of 0.6, and a tidal volume of 13 to 18 ml/kg adjusted to maintain an arterial Pco_2 of approximately 40 mm Hg. Inhaled gases were a 2:1 $N_2O:O_2$ mixture. Gallamine 2 mg/kg iv was given approximately every 45 minutes as required to achieve adequate muscle relaxation. Procaine penicillin 100,000 IU/kg im was given at the time of induction.

Using sterile technique a femoral cutdown was performed and the artery and vein isolated using a low-power operating microscope (CM-III Microscope, Mentor Division, Codman and Shurtleff, Inc., Randolph, Massachusetts). A No. 5-Fr sigmoid-tipped, polyethylene catheter was inserted into the femoral artery and under fluoroscopic control was placed in the innominate artery for cerebral angiography and cerebral blood flow determinations. Arterial blood pressure was recorded at frequent intervals with a transducer (Stratham P23dB pressure transducer, Stratham Instrument Co., Oxnard, California) connected to a recorder (Dynograph Recorder R 611, Beckman Instruments, Inc., Schiller Park, Illinois).

A No. 5-Fr Swan–Ganz catheter (model 93-132-5F, Edwards Laboratories, Santa Ana, California) was inserted into the femoral vein, and under fluoroscopic visualization was floated into either of the pulmonary arteries with 0.2 to

0.3 ml of air in the catheter's balloon. Pressures of the distal and proximal port of the Swan-Ganz catheter were recorded on the Beckman recorder via a Stratham transducer. The arterial and venous lines were flushed at intervals with 0.5 ml of heparinized saline (10 IU/ml) to prevent clotting.

Body temperature was maintained close to 37°C using a heating pad, and temperature was monitored with a rectal thermometer (Tele-Thermometer, Yellow Springs Instrument Co., Yellow Springs, Ohio).

Airway pressures were measured with a transducer (Stratham PM5 pressure transducer, Stratham Instrument Co., Oxnard, California) connected via a needle to the endotracheal tube, and a continuous pressure tracing obtained.

In 13 animals, during one of the three stages, either a No. 8-Fr foley catheter or No. 160 polyethylene tubing was inserted into the bladder and urine outputs and urine sodium concentrations were measured.

Following the procedure paralysis was reversed with prostigmine 0.07 mg/kg iv and atropine 0.02 mg/kg iv. The animals were ventilated for several minutes with 100% O_2, suctioned, and when the gag reflex returned the monkeys were extubated.

The anesthetic technique of Stage II differs in one respect from Stages I and III. Sodium pentobarbital 26 mg/kg iv was used as the inducing agent instead of ketamine hydrochloride. It had been previously found that the

barbiturate improved survival from the craniectomy (personnal communication, Dr. F. Espinosa, 1983). The barbiturate, however, affects cerebral blood flow and could therefore not be used in Stages I and III.

The subarachnoid hemorrhage was placed by Dr. M. G. Nosko. Using sterile technique a right frontotemporal craniectomy was performed. Dura was incised and opened and the temporal lobe was retracted posteriorly. The distal internal carotid artery, the A1 segment of the anterior communicating artery, the posterior communicating artery, and the proximal middle cerebral artery were identified and the arachnoid dissected away. A 6- to 7-ml autologous clot was then packed around the exposed vessels. The dura was closed with 6-0 silk to effect a water-tight seal. The scalp incision was closed in layers with 2-0 silk and 3-0 dermalon.

After clot placement the animal was kept in her cage overnight, and the following morning started on the nimodipine trial.

Twenty-four monkeys were started on the nimodipine study. These 24 animals were randomly placed into four equal groups by a pharmacist (Faculty of Pharmacy, University of Alberta) not otherwise connected with the study. The treatment groups were nimodipine 3 mg/kg q8h po, 6 mg/kg po q8h and 12 mg/kg po q8h. The fourth group received a placebo of polyethylene glycol 400 0.33 ml/kg q8h.

In addition to the 24 monkeys who started the nimodipine series, five additional animals underwent Stages I and II, but died in the first 24 hours following placement of the subarachnoid clot.

The nimodipine (Miles Laboratories, Inc., New Haven Conneticut) was prepared by the pharmacist by dissolving the drug in polyethylene glycol 400 in concentrations of 9, 18, and 36 mg/ml in order that each animal would receive 0.33 ml/kg of solution q8h. Drug preparation was carried out under gold light (F 1518-GO gold, Westinghouse Electric Corp., Pittsburgh, Pennsylvania), and the drug protected in amber bottles. Drugs were refrigerated at 5°C until just prior to use.

The nimodipine was administered every 8 hours via nasogastric tube after the animal had been sedated with ketamine hydrochloride 6 to 10 mg/kg im. The animals were kept in a room with gold lights in order to protect the nimodipine from light induced decay during administration. Seven days after commencing nimodipine treatment, and 2 to 3 hours after the last dose, the animals were brought to the laboratory for Stage III.

Each of Stages I, II, and III involved obtaining an identical set of cardiopulmonary indices. In Stages I and III these were obtained immediately after establishment of arterial access, and prior to angiography and measurement of cerebral blood flow performed by Dr. M. G. Nosko. In Stage II measurements were taken prior to the craniectomy, then

repeated 30 to 60 minutes after placement of the subarachnoid clot.

The cardiopulmonary indices recorded were heart rate, mean arterial blood pressure, pulmonary artery pressure, pulmonary artery wedge pressure, central venous pressure, cardiac output, arterial Po_2, Pco_2 and pH, mixed venous Po_2, Pco_2 and pH, fractional concentration of inspired O_2 (FiO_2), and hemoglobin. The derived cardiopulmonary indices examined were stroke index, systemic and pulmonary vascular resistance, arterial mixed veinous oxygen difference ($a-\bar{v}O_2$ dif.), alveolar arterial oxygen difference ($A-aDO_2$, and % shunt.

All of the hemodynamic indices were measured three times and the mean value determined. All pressure measurements were recorded at end expiration as indicated by the airway pressure tracing. Arterial and pulmonary artery pressures were always recorded with sharply defined pressure waves and the ports were flushed to achieve good tracings. Pulmonary artery wedge pressure was obtained by inflating the balloon of the Swan-Ganz catheter with 0.2 to 0.3 ml of air as required to obtain a wedged tracing.

Cardiac outputs were obtained by the thermodilution technique with an Edwards' Cardiac Output Computer (model 9520A, American Edwards Laboratories, Santa Ana, California). In this series of experiments 3 ml of 5% dextrose in water at 0°C was injected rapidly by hand into the proximal port. Thermodilution curves were recorded for

the last four monkeys of the series. Three cardiac output determinations were made, followed by a fourth if the values varied widely. There was a 1.5 to 2 minute pause between each injection. The catheter was not pre-cooled. All injections were made at the end of expiration.

Body surface area was calculated based on a formula for rhesus monkeys (Liu and Higbee, 1976):

$$BSA(cm^2) = W^{0.6046}(kg) \times L^{0.1802}(cm, \text{ head to anus}) \times 514$$

Arterial and mixed venous gases from the pulmonary artery were always obtained simultaneously. Po_2, Pco_2 and pH measurements were obtained from an IL Micro 13 pH/Blood Gas Analyzer (Instrumentation Laboratory Inc., Lexington, Massachusetts). Barometric pressure was recorded daily, and dry barometric pressure used in the calculation of the partial pressure of inspired oxygen (PiO_2). The FiO_2 was recorded in the input line of the ventilator (Oxygen Analyzer Model E2, Beckman Instruments, Inc., Schiller Park, Illinois). The partial pressure of alveolar oxygen (PAO_2) was calculated using a respiratory coefficient of 1. Arterial and mixed venous oxygen saturation were calculated using the following formula for the cynomolgus monkey (Novy et al., 1969):

$$\log Po_2 = 5.0198 - 0.4741\ pH + 0.3389 \log \frac{S}{100-S}$$

Arterial and venous oxygen contents were calculated using 1.34 ml O_2/gm hemoglobin. Hemoglobin was determined using a hemoglobinometer (Coulter Electronics, Inc., Hialeh, Florida).

The effects of anesthesia on the cardiopulmonary indices were examined in four control animals to observe variability over the time course of a 5-hour anesthetic. Two monkeys were initially sedated with ketamine hydrochloride 6 to 10 mg/kg im as in Stages I and II, and then were subject to half-hourly measurement of cardiac and pulmonary indices using the same anesthetic and operative techniques described above. Cardiac outputs were determined using 1 ml iced 5% dextrose in water. Fluids were given to flush lines (1 ml normal saline with heparin prior to measurements), to replace blood losses (for hemoglobin and blood gases), and with cardiac output determinations. Two additional monkeys were subject to a similar control experiment with sodium pentobarbital 26 mg/kg iv given as the inducing agent.

Data Analysis

Data analysis was performed using a program written by Dr. G. Hill, Department of Community Medicine, University of Alberta. The difference for each measured index between Stage III and Stage I for each monkey was calculated. After the treatment code had been broken the animals were separated into the four treatment groups. For each group a mean and standard error of the mean was calculated for each

cardiopulmonary index. The paired Student's t-test was used to determine significance of changes in the placebo group. The Student's t-test was used to compare each of the treatment groups to the placebo group. The standard deviation of each nimodipine treatment group was assumed to be the same as the placebo group. An analysis of variance was performed on the four groups for each measured index. Coefficients of correlation and linear regression lines were calculated for drug dosage versus cardiac index, stroke index, mean arterial pressure and pulmonary and systemic vascular resistances.

For Stage the difference between the pre-clot and post-clot measurements was calculated for the monkeys who survived the subarachnoid hemorrhage, and for the five monkeys who died in the first 24 hours after clot placement. The mean and standard error of the mean was calculated for each measured index for each of the survivor and non-survivor groups. The paired Student's t-test was used to determine the significance of these changes. Student's t-test was also applied to detect significant differences between the survivor and non-survivor groups.

Statistical significance was assessed as $p \leq 0.05$, unless otherwise indicated.

B. Acute Effects of Nimodipine

To determine the acute effects of nimodipine, 20 mg/kg po was given to two monkeys and 30 mg/kg to a third. The monkeys underwent the same anesthetic, operative and measurement techniques as previously described, using ketamine hydrochloride for induction. One ml 5% dextrose in water was used for each cardiac output determination. After baseline measurements were made nimodipine was administered via nasogastric tube in a solution of polyethylene glycol 400 of volume 0.5 ml/kg.

Hemodynamic parameters (heart rate, mean arterial pressure, cardiac index, stroke index, pulmonary artery pressure, pulmonary artery wedge pressure, central venous pressure, systemic vascular resistance and pulmonary vascular resistance) were then measured every 15 minutes for 3.5 to 4.5 hours.

An identical experimental protocol was followed using one cat, with nimodipine 10 mg/kg po administered in polyethylene glycol 400, 0.5 ml/kg.

A control experiment was performed with 0.5 ml/kg polyethylene glycol 400 given via nasogastric tube to a monkey. Hemodynamic indices were measured for 3.5 hours.

Intravenous nimodipine was administered to one cat and one monkey. For each animal three sequential doses were given each as a bolus over 30 to 60 seconds. For the cat the initial dose of nimodipine was 0.010 mg/kg, followed 70 minutes later by 0.103 mg/kg, followed 65 minutes later by

0.517 mg/kg. For the monkey the doses were 0.012 mg/kg, followed 85 minutes later by 0.105 mg/kg, followed 70 minutes later by 0.458 mg/kg. The nimodipine was dissolved in 95% ethanol for intravenous administration as the viscous polyethylene glycol 400 could not be accurately administered in small volumes. The volumes of alcohol injected into the cat were 0.03 ml, 0.3 ml, 1.5 ml for the 0.010 mg/kg, 0.103 mg/kg, and 0.517 mg/kg doses respectively. The ethanol volumes for the monkey were 0.1 ml, 0.9 ml and 0.45 ml for the 0.012 mg/kg, 0.105 mg/kg, and 0.458 mg/kg doses respectively. Heart rate and mean arterial pressure were recorded every minute for the first 15 minutes after bolus injection, after which measurements, including cardiac output, were made every 2 to 5 minutes.

C. Cardiac Output Determinations *In Vitro*

In order to evaluate the accuracy and reproducibility of cardiac output measurements in low flow states using the thermodilution technique and Edwards' Cardiac Output Computer, an *in vitro* model was devised. This was based on the model of Moodie et al. (1978), with some modifications (Fig. 1).

A water bath (Haake 4-1 water bath, Berlin, Germany) was maintained at approximately 40°C. One-quarter-inch tygon tubing (U.S. Stoneware Co., Akron, Ohio) was coiled into the water bath, with one end connected to a Travenol roller-type blood pump (Sarns Inc., Ann Arbor, Michigan) and then to a

2-l beaker filled with tap water. The other end of the tubing from the water bath was placed into a 25-ml Erlenmeyer flask and submerged in the beaker. The beaker was placed on a stir plate (model 120MR Stir Plate, Fischer Scientific Ltd., Edmonton, Alberta) with a small magnetic stir bar in the bottom of the Erlenmeyer flask. A No. 5-Fr Swan-Ganz catheter was placed into the tubing such that the proximal port emptied into the Erlenmeyer flask. Thirty cm of catheter were submerged in the beaker. A thermister probe (Bailey Type T thermocouple and temperature recorder model BAT-12, Bailey Instuments, Saddlebrook, New Jersey) was placed into the beaker, and the temperature maintained at 37°C ± 0.1°C. The perfusion pump was regulated to 18 different flows between 130 ml/min and 1035 ml/min. Flows were measured volumetrically four times, and the mean flow calculated.

For each of the 18 different flows a series of three cardiac output determinations was made for each of four different injectate volumes (1,2,3, and 5 ml) at two different temperatures (iced and room temperature 5% dextrose in water). Thermodilution curves were obtained with each injection.

For each different injectate volume and temperature the volumetrically measured flows were compared to the mean of the three cardiac output determinations from the Edwards' computer. Comparison was made with regression analysis, and correlation coeffecients were determined.

VII. Results

A. Chronic Effects of Nimodipine after Subarachnoid Hemorrhage in Monkeys

Control

Figures 2 to 5 illustrate the changes in cardiac and pulmonary indices over the course of a 5-hour anesthetic in two monkeys with ketamine hydrochloride 6 to 10 mg/kg im used for induction.

Heart rate remained relatively constant for the first 3 hours, then showed some variability in both animals (Fig. 2a). Mean arterial pressure remained steady in one animal, but in the second animal there was a fall in pressure after 2 hours (Fig. 2b). Cardiac output, systemic vascular resistance and pulmonary vascular resistance showed variability over the course of the anesthetic in both animals (Figs. 2c, 3a and 3b). Stroke volume changed little (Fig. 3c). Pulmonary artery pressure, pulmonary artery wedge pressure, and central venous pressure all fluctuated (Figs. 4a, 4b, and 4c). The pulmonary indices of $A\text{-}aDO_2$ and % shunt showed parallel but random changes with time (Figs. 5a and 5c). The $a\text{-}\bar{v}O_2$ difference remained at baseline level (Fig. 5b).

Urine output was approximately 1 ml/kg/hr for both animals during the course of the anesthetic. Urine sodium concentration measured in one monkey was 23 meq/l at the end

of the anesthetic.

Experimental

Twenty-three of the 24 monkeys assigned to a treatment group survived to Stage III. One animal in the placebo group died on the fourth day after craniectomy from septicemia following a wound infection. The changes in cardiopulmonary indices between Stages I and III for each of the three treatment groups and the placebo group are shown in Figures 6 to 14 and Table 3. All treatment groups showed a decrease in heart rate, however none was significant when compared to the placebo group (Fig. 6). The placebo group had a fall in mean arterial pressure of 7 mm Hg which was not statistically significant (Fig. 7). Blood pressure fell in the higher dosage treatment groups. The nimodipine 12 mg/kg group had a fall in mean arterial pressure of 39 mm Hg ($p<0.10$ when compared to the placebo group). Cardiac index was decreased 0.89 l/min/m^2 in the placebo group, however this change was not significant (Fig. 8). There was significant positive correlation betweeen nimodipine dosage and cardiac index ($r=0.977$, $p<0.05$). The cardiac index of the 12 mg/kg treatment group was increased compared to the placebo group ($p<0.10$). The changes in stroke index paralleled those of cardiac index, increasing with increasing nimodipine dosage (Fig. 9) ($r=0.995$, $p<0.01$). The stroke index was decreased 3.7 ml/beat/m^2 in the placebo group compared to an increase of 3.5 ml/beat/m^2 in the

nimodipine 12 mg/kg group. There was a significant difference between these two groups ($p<0.05$). An analysis of variance showed a significant difference between treatment groups for stroke index ($p<0.05$). There were no remarkable changes in central venous pressure. Systemic vascular resistance was increased in the placebo and nimodipine 3 mg/kg groups, and tended to fall with increasing nimodipine dosages ($r=-0.943$, $p<0.10$) (Fig. 10). The systemic vascular resistance decreased in the 6 and 12 mg/kg groups by 2694 and 4950 dyne sec cm^{-5}, respectively, and both of these groups differed significantly from the placebo group ($p<0.05$). An analysis of variance confirmed a significant difference between treatment groups ($p<0.05$). Pulmonary artery pressure increased with increasing nimodipine dosage, however none differed significantly from the placebo group (Fig. 11). There were no significant changes in pulmonary artery wedge pressure. Pulmonary vascular resistance was increased by 433 dyne sec cm^{-5} in the placebo group ($p<0.10$). Pulmonary vascular resistance tended to fall with increasing dosage (not significant).

There were no remarkable changes in $A\text{-}aDO_2$, % shunt and $a\text{-}\bar{v}O_2$ difference between the placebo and treatment groups (Figs. 13 and 14). There was a significant fall in hemoglobin in the placebo group ($p<0.05$), however the differences between each treatment group and the placebo group were not significant.

The two urine sodium concentrations measured in Stage I were 34.6 and 41.0 meq/l. Urine output was greater that 50 ml in total in three Stage I animals in whom it was measured. This massive diuresis is attributed to the injection of iothalamate meglumine for cerebral angiography. This was part of a separate study, and was performed after cardiopulmonary measurements were obtained.

B. Acute Effects of Subarachnoid Hemorrhage in Monkeys

Control

Two monkeys underwent control procedures with cardiopulmonary indices monitored over a 5-hour anesthetic with sodium pentobarbital 26 mg/kg iv used for induction. The changes in indices with time are shown in Figures 15, 16 and 17.

Heart rate increased in both control animals (Fig. 15a). Mean arterial pressure remained steady in one animal, and increased approximately 20 mm Hg in the second (Fig. 15b). Cardiac ouput increased with time (Fig. 15c), while systemic vascular resistance decreased (Fig. 16a). Pulmonary vascular resistance remained steady in one monkey, but showed marked variability in the second (Fig. 16b). Stroke volume, pulmonary artery pressure and pulmonary artery wedge pressure also fluctuated randomly (Figs. 16c, 17a and 17b). Central venous pressure remained relatively constant (Fig. 17c).

The pulmonary indices of $A\text{-}aDO_2$, $a\text{-}\bar{v}O_2$ difference and % shunt showed some variability (Figs. 18a, 18b and 18c).

Experimental

Cardiopulmonary indices measured before and 30 to 60 minutes after clot placement are shown in Table 4. The monkeys are divided into two groups: the survivors (n=23) who completed the nimodipine trial, and the non-survivors (n=5) who died in the first 24 hours after craniectomy. The one monkey who developed a wound infection is not included in this study. Heart rate increased significantly by a mean of 16 beats/min in the monkeys surviving craniectomy ($p<0.05$), while in the non-survivor group heart rate did not change significantly. Mean arterial pressure changed little in either group. Cardiac index increased slightly in the survivors, but fell significantly ($p<0.05$) in the non-survivors by a mean of 0.68 $l/min/m^2$. There was a significant difference in cardiac index between the two groups ($p<0.01$). Stroke index fell significantly in both survivors and non-survivors ($p<0.01$), with a mean decrease of 2.3 and 4.0 $ml/beat/m^2$ respectively. There was a significant difference between the two groups ($p<0.05$). Pulmonary artery pressure fell in both groups, with a very significant fall of 3.8 mm Hg in the survivor group ($p<0.001$). Pulmonary artery wedge pressure also fell significantly in the survivors, with a mean fall of 3.5 mm Hg ($p<0.001$). Central venous pressure fell in both groups,

significantly in the survivors ($p<0.05$). Systemic and pulmonary vascular resistances increased minimally in both groups.

The $A\text{-}aDO_2$ increased slightly in both groups. The $a\text{-}\bar{v}O_2$ difference increased significantly in both groups ($p<0.01$), with a mean increase of 1.0 volume % in the survivors and 1.7 volume % in the non-survivors. The % shunt fell in both groups, although the differences were not significant. Hemoglobin fell 0.8 gm/dl in the survivors (significant with $p<0.01$) and 1.1 gm/dl in the non-survivors (not significant), however there was no statistically significant difference between the two groups.

In five survivors urine sodiums were determined at the end of the craniectomy, and they ranged between 20 and 49 meq/l. In nine survivors in whom urine outputs were measured, they ranged between 2 and 7 ml/kg over the course of the 2- to 3-hour craniectomy. In the one non-survivor who was catheterized the total urine output was 4 ml/kg, and the urine sodium was 49 meq/l after clot placement.

C. Acute Effects of Nimodipine in Monkeys

Oral

1. Control

Polyethylene glycol 400 was administered in a volume of 0.5 ml/kg to one monkey and hemodynamic indices monitored

over a 5-hour period (Figs. 19, 20 and 21). Heart rate and cardiac output showed variability, with other indices remaining relatively constant.

2. Experimental

Heart rate gradually increased with nimodipine 30 mg/kg while remaining quite stable after 20 mg/kg (Fig. 22). Mean arterial pressure fell 10 to 20 mm Hg at both drug doses after 30 to 60 minutes, then exhibited variability about the baseline for the remainder of the anesthetic (Fig. 23). Cardiac index was increased between 30 and 90 minutes in two animals, one who had received nimodipine 20 mg/kg, the other 30 mg/kg (Fig. 24). The third animal showed a gradual decline in cardiac index over the course of the experiment. Central venous pressure varied only 2 to 3 mm Hg (Fig. 25). Systemic vascular resistance fell with the rise in cardiac index in two animals (Fig. 26), with no marked change in the third monkey. Stroke index increased in one monkey who received nimodipine 20 mg/kg, however stroke index fell gradually in the other two animals (Fig. 27). Pulmonary artery pressure and pulmonary artery wedge pressure fluctuated randomly over a range of 6 mm Hg (Figs. 28 and 29). Pulmonary vascular resistance also varied randomly (Fig. 30).

Intravenous

The effects of intravenous nimodipine 0.012 mg/kg, 0.105 mg/kg and 0.458 mg/kg are shown in Figures 31 to 34. Heart rate falls with the two higher drug doses 1 to 2 minutes after administration, returning to baseline with the 0.105 mg/kg dose, but remaining depressed with 0.458 mg/kg (Fig. 31). Mean arterial pressure also fell early and transiently with all three doses (Fig. 32). There was much scatter of data for cardiac output, making interpretation difficult (Fig. 33). Systemic vascular resistance measurements were likewise widely scattered (Fig. 34). Central venous pressure, pulmonary artery pressure, and pulmonary artery wedge pressure varied only 3 to 4 mm Hg over the course of the experiment.

D. Acute Effects of Nimodipine in Cats

Oral

Marked cardiovascular changes were exhibited in a cat given nimodipine 10 mg/kg dissolved in polyethylene glycol 400, 0.5 ml/kg (Figs. 35 to 38). Heart rate and mean arterial pressure fell significantly 10 minutes after administration of the drug (Figs. 35 and 36). Cardiac output remained at baseline levels for 1.5 hours, then began to decline (Fig. 37). Systemic vascular resistance fell markedly 5 minutes after nimodipine was given (Fig. 38). The cat died 5.5 hours after nimodipine administration, despite

fluid rescusitation and ventilatory support.

Intravenous

Nimodipine was administered intravenously at three different doses to a cat, producing a marked fall in heart rate and mean arterial pressure 1 minute after administration of 0.103 mg/kg and 0.517 mg/kg (Figs. 39 and 40). Baseline values were not reestablished after 0.517 mg/kg. Cardiac output remained steady at both lower doses (Fig. 41), but was not recorded at the highest dose due to technical problems. This animal survived the experiment.

E. *In Vitro* model of Thermodilution Cardiac Output

Table 5 shows the regression lines and correlation coefficients for each of the eight different injectates studied. All have correlation coefficients which are highly significant ($p<0.001$). The regression lines are plotted for 1 ml iced injectate (Fig. 43) and 3 ml iced injectate (Fig. 44).

VIII. Discussion

A. Chronic Effects of Nimodipine after Subarachnoid Hemorrhage in Monkeys

It is apparent on reviewing the two control monkeys who received ketamine for induction that there are fluctuations in cardiopulmonary indices over the course of anesthesia. This variability contributed to the large standard error of the mean for each measured index. There are a number of factors which may be contributing to this variability.

Physiologic differences could exist between animals such that some monkeys respond and compensate differently than others to the insults of anesthesia and surgery. The animals differ in age, a factor that is impossible to evaluate in these wild monkeys. Although all animals appear grossly healthy, a complete assessment is not done. The animals could have pulmonary, cardiac, renal or metabolic conditions that would influence the cardiopulmonary indices measured.

The pharmacologic responses of each animal to the drugs administered are undoubtedly different. Although the nitrous oxide is a myocardial depressant and increases sympathetic activity it is given at a constant dose throughout the procedure. A single dose of ketamine hydrochloride is given 45 minutes or more before the first measurements are taken, and should not influence cardiopulmonary indices. Gallamine, however, is given at varying intervals as required to

maintain adequate muscle relaxation. This drug has an inhibitory effect on the cardiac vagus nerve, and can produce sinus tachycardia and occasionally hypertension in man.

Fluid balance over the course of the anesthetic will influence measured indices. However, the evaluation of fluid losses is difficult. Although the determinations of urine sodium and urine output would suggest that none of the monkeys had a markedly depleted intravascular volume, in the absence of well-defined normal values for this species definite conclusions can not be reached. Ventilation on a non-humidified ventilator for several hours contributes to an indeterminate, but significant fluid loss.

The methods of measuring cardiopulmonary indices also introduce variability. Pulmonary artery pressure varies with position of the tip of the Swan-Ganz catheter in the pulmonary artery. A more proximally placed catheter records a higher mean pressure than a catheter more distally placed, despite a good pressure tracing in both positions. There are problems inherent in using the thermodilution technique to measure cardiac outputs in small animals. This will be discussed further (see page 70).

The changes in cardiopulmonary indices between Stages I and III for the placebo group of monkeys suggest that cardiac and hemodynamic alterations are occurring 7 days after placement of a subarachnoid clot. Heart rate, mean arterial pressure, cardiac index and stroke index were all

decreased, although none of these changes achieved statistical significance in this small group. Arrhythmias, ECG changes (Weintraub and McHenry, 1974) and increases in serum levels of myocardial enzymes (Connor, 1977) have been described in grade I or II patients with subarachnoid hemorrhage, however there is no published evidence that these patients have significant hemodynamic alterations. In the moribund patient hemodynamic instability has been demonstrated (Galat, 1982).

The data collected are insufficient to conclude what factors may be responsible for these changes, particularly the fall in stroke index. With no change in pulmonary artery wedge pressure preload is not likely to be involved. Systemic vascular resistance does increase, perhaps increasing the peripheral component of afterload. This latter change might reflect a persistance of the autonomic overactivity described early after subarachnoid hemorrhage (Doshi and Neil-Dwyer, 1977; Estañol et al., 1977). However, heart rate and cardiac output would also be expected to increase. Perhaps pathologic changes in the myocardium seen after subarachnoid hemorrhage lead to alterations in myocardial contractility and nodal tissue that have functional significance.

The increase in pulmonary vascular resistance may represent the increase in pulmonary blood volume that Sarnoff and Berglund (1952) demonstrated in their model of NPE.

Nimodipine has hemodynamic effects in this model. The drug has a systemic vasodilating effect at the 6 and 12 mg/kg dosages, with a resultant fall in mean arterial pressure. Despite this effect the heart rate falls in the highest dosage group, and although not a significant effect, it may indicate a negative chronotropic effect of the drug. This effect may be due to pathologic changes in the myocardium, or it may reflect nimodipine's inhibition of the baroreceptor reflex. Nimodipine does not produce the reflex tachycardia seen with nifedipine after administration of a vasodepressor (Taylor and Kowalski, 1982). With the decrease in systemic vascular resistance the cardiac output and stroke volume increase due to decreased afterload.

B. Acute Effects of Subarachnoid Hemorrhage

Subarachnoid hemorrhage has an acute depressant effect on hemodynamic indices in monkeys who die after placement of a subarachnoid clot. The cardiac index and stroke index fell significantly in these animals, although they maintained a relatively normal heart rate and mean arterial pressure with a slightly increased systemic vascular resistance. The significant increase in $a-\bar{v}O_2$ difference reflects the fall in cardiac output.

The monkeys who survive clot placement also have a depressed stroke index but they appear able to compensate for this by increasing their heart rate to maintain a relatively normal mean arterial pressure and cardiac index.

The acute depressant effects of subarachnoid hemorrhage on hemodynamic and cardiac indices have not been well studied. The autonomic nervous system is implicated in the ECG changes and myocardial pathology seen after subarachnoid hemorrhage, but precise mechanisms remain undefined. Whatever depressant factor is acting to decrease stroke index in these animals has more of an effect on the non-survivors. It appears that in the survivors the sympathetic nervous system functions to produce a compensatory tachycardia while compensation does not occur to the same degree in the non-survivors.

The significant fall in pulmonary artery pressure, pulmonary artery wedge pressure and central venous pressure in survivors was compared to a minimal fall of these pressures in the non-survivor group. The cause of these differences is unclear. In five survivors who had sequential urine sodium concentrations measured during the craniectomy, none was less than 20 meq/l. Urine output was adequate in all animals in whom it was measured. Thus by these latter two measurements none of the monkeys in the survivor group had a markedly depleted circulating blood volume, although normal values for this monkey species are not published. However, perhaps the circulating blood volume is less in the survivor group. Hemoglobin did fall significantly in the survivors, however there was not a significant difference from the fall in the non-survivors. Also this hemoglobin determination more likely reflects hemodilution from fluid

administration than acute blood loss. The increase in pulmonary blood volume described by Sarnoff and Berglund (1952) in NPE may be occurring in the animals who die, with resultant higher pulmonary vascular pressures than those of the survivors.

The pathologic changes in the myocardium after subarachnoid hemorrhage may perhaps affect myocardial contractility. The survivors' myocardial contractility may have been less affected than contractility in the animals who died, thus tending to accentuate the fall in pulmonary artery pressure, pulmonary artery wedge pressure, and central venous pressure in survivors. Alterations in afterload are unlikely to account for the pressure differences as there was not a significant change in systemic vascular resistance between the two groups.

Although it is unclear why some animals had a lower pulmonary artery pressure, pulmonary artery wedge pressure and central venous pressure, it is apparent that these factors tend to favor survival. Perhaps the survivors' ICP is lower secondary to a fall in circulating blood volume and a resultant decrease in cerebral blood flow.

Sodium pentobarbital was used as the inducing agent for the craniectomy. As barbiturates are known to decrease cardiac output and mean arterial pressure, they may be expected to depress hemodynamic indices over the 2 to 3 hours required for the craniectomy. As shown in the barbiturate control animals (Figs. 15, 16 and 17) mean

arterial pressure remained constant over the time period measured, but heart rate and cardiac output increased. The effect on cardiac output will oppose, and thus tend to minimize, the depressant effects of clot placement. However, it may be anticipated that the rise in heart rate over the course of the procedure contributed to the significant increase noted postoperatively in the survivors. Nonetheless, the survivors' heart rate increased significantly, while the non-survivors' did not.

C. Acute Effects of Nimodipine

The hemodynamic effects of nimodipine in the cynomolgus monkey in doses up to 30 mg/kg po are much less marked than those demonstrated in the cat given 10 mg/kg po. The monkey demonstrated only a slight decrease in systemic vascular resistance at 30 to 60 minutes, accompanied by a fall in mean arterial pressure and an increase in cardiac output. The cat had profound hemodynamic changes and did not survive the experiment. Other investigators have produced marked changes in hemodynamic indices in cats, dogs and squirrel monkeys (personal communication, Dr. R. Battye, 1984) at a nimodipine dose of 10 mg/kg po.

A proton nuclear magnetic resonance spectrum was performed on the drug used in these experiments, confirming that the drug was nimodipine. Studies were performed by pharmacologists to confirm *in vitro* activity of the drug by demonstrating that the nimodipine at 10^{-6} mol/l produced

vasodilation of dog middle cerebral arteries contracted by 5-hydroxytryptamine, noradrenalin, and potassium chloride.

Thus the nimodipine used in this study was chemically equivalent to that used by other investigators. However, the dose-effect curve for nimodipine in the cynomolgus monkey clearly differs markedly from that in other species studied.

In order to further define the difference in bioavailability nimodipine was given intravenously to a monkey and a cat. The cardiovascular depressant effects demonstrated were similar in both animals, and resemble those described in other species by other investigators (personal communication, Dr. R. Battye).

Ethanol was used as the solvent for intravenous injection in differing volumes for each dose in each animal. This introduced some variability for which no control was performed.

Nimodipine is thus much less potent when administered orally to the cynomolgus monkey than to other species and via other routes of administration. This would indicate that the difference in bioavailability lies in dissimilar absorption, first pass metabolism, or distribution of the drug.

Data in this study do not differentiate between these three possibilities. Although serum levels were performed at Stage III in the first series, the measuring technique (high-pressure liquid chromatography) was not sufficiently accurate or precise to be useful.

Additional work needs to be carried out to characterize the dose-effect curve of nimodipine in the cynomolgus monkey. Techniques need to be improved for the measurement of serum levels on small samples. Metabolism and protein binding of the drug should be studied. A study is underway examining the *in vitro* response of cynomolgus monkey cerebral arteries to various smooth muscle contractile agents in the presence of nimodipine.

D. Thermodilution Cardiac Output

The thermodilution technique is a very accurate and reliable method of determining cardiac output when compared to the dye dilution (Ganz et al., 1971; Weisel et al , 1975) and Fick methods (Hodges et al., 1975; Wyse et al., 1975) in the adult patient. There are a number of assumptions made when using the thermodilution technique. Four are particularly relevant to this model. Firstly, no cold solution can be lost between measurement of injectate temperature and emergence of the injectate from the proximal port. Some warming is inevitable, and therefore a set of correction factors have been determined for different injectate volumes and temperatures. The second assumption is that complete mixing of the cold solution and blood occurs before reaching the thermister. Thirdly, the injectate must not be lost into the blood vessel walls between the proximal port and the thermister. Fourthly, the injected volume must not affect flow. In a low flow state, as found in a

pediatric patient or in the cynomolgus monkey, these assumptions are particularly important.

A number of investigators have examined thermodilution cardiac output in the pediatric patient. Freed and Keane (1978) found a good correlation (r=0.91) between output measured by thermodilution and by the Fick technique at flows between 1.5 l/min and 3.0 l/min. Their regression line was y = 1.10x - 0.2 l/min where y equals cardiac output by thermodilution and x equals cardiac output by the Fick technique. Other investigators have found similar degrees of accuracy (Lawrie et al., 1975; Moodie et al., 1978). Thermodilution cardiac output may, however, progressively overestimate cardiac output in the lower output range. Runciman et al. (1981) suggest that this is due to the loss of indicator that occurs between its emergence from the Swan-Ganz catheter and its detection in the pulmonary artery, as in the lower flow states there would be more time for equilibration with surrounding tissues. Since the proximal port is located in the inferior vena cava in the monkey, this may be important (Rovek, 1974), although Hosie (1962) found that important heat loss does not take place in the walls of large vessels.

Few studies have been performed where the actual flow in the system has been measured directly (Kohanna and Cunningham, 1977; Vliers et al., 1973). Moodie et al. (1978) developed an *in vitro* model and compared flow measured volumetrically with that recorded by several different

computer systems at flows less than 2.5 l/min. They found the Edwards' computer to be inaccurate at flows less than 2 l/min, and that the thermodilution output curves were not reproducible.

There are problems with the model of Moodie et al. The thermodilution curve illustrated for a flow of 330 ml/min has a very irregular shape. Using a model identical to Moodie's, I also obtained irregular curves at low flow rates. This is likely due to incomplete mixing of cold solution which is injected into a 100-ml round flask.

Several modifications were therefore made to Moodie's model. A 25-ml Erlenmeyer flask was used as the mixing chamber to simulate more closely the size of the right heart of an animal with a cardiac output less than 1 l/min. A stir bar and plate were used to ensure complete mixing in the flask. Smooth thermodilution curves were obtained at all flow rates with this modified model, therefore complete mixing was probably occurring.

Using this *in vitro* model, the Edwards' computer is a reasonably accurate and precise means of determining cardiac output at flows less than 1 l/min. The coefficients of correlation between measured flows and flows recorded by the Edwards' computer were highly significant for all injectate volumes and temperatures. The slopes of the regression lines were greater than 1 (with the exception of 5 ml iced injectate), and the y-intercepts were greater than 0, so that cardiac outputs were overestimated. The percent error

is large (up to 50%) at the lowest flows, however with so little data scatter about the regression lines, this system can certainly be considered a very precise means of determining cardiac output and of following changes in output.

This *in vitro* model is not entirely analagous to the *in vivo* situation. The specific gravity and specific heat of water used as the flow medium are slightly different from that of blood. The heat capacity of the tygon tubing may differ from that of blood vessels. Backflow of injectate may occur in this model, particularly with larger injectate volumes and lower flows. No backflow was detected by observing the injection of a red dye, however even a small amount of injectate loss leads to a significant overestimation of cardiac output. Backflow may also occur *in vivo* in low flow states.

Thermodilution curves were recorded for the last four monkeys of the subarachnoid hemorrhage study. It became apparent that with injected volumes of 3 ml at 0°C some of the curves were exceeding the limits of sensitivity of the thermister in the Swan-Ganz catheter (2.6°C). When this limit is exceeded the area under the curve above this level will not be integrated, and as a result cardiac outputs are overestimated.

The flow below which this error occurred is approximatly .75 l/min. It was not possible to determine this critical flow in the *in vitro* model as the

thermodilution curves had a different shape *in vitro*: they rose much more slowly due to mixing in the larger caliber tygon tubing. Rapid injection of 3 ml of iced 5% dextrose in water into the very small vessels of the monkey produces a curve with a very rapid upstroke.

After this problem was discovered 1-ml volumes were subsequently injected for all of the acute experiments. This overestimation of cardiac outputs in the lower flows tended to minimize changes in cardiac output and overestimate changes in systemic and pulmonary vascular resistance calculated between Stages I and III, and between measurements before and after clot placement.

An additional problem with injection of a 3 ml volume is that it may affect flow considering that the stroke volume is only 3 to 4 ml/beat.

IX. Conclusions

Subarachnoid hemorrhage caused significant acute cardiopulmonary effects. While both monkeys surviving and dying after clot placement had evidence of cardiovascular depression, the effects in the survivors were less marked. The survivors were able to normalize cardiac output by increasing heart rate.

Subarachnoid hemorrhage had a tendency to depress cardiovascular function 1 week after clot placement, although the effects did not reach statistical significance.

Chronic nimodipine administration after subarachnoid hemorrhage decreased mean arterial pressure and systemic vascular resistance and increased cardiac output, with dosage correlating with effect.

Oral nimodipine had minimal acute cardiopulmonary effects in the monkey when compared to those demonstrated in the cat and in other species described in the literature. Intravenous nimodipine had cardiopulmonary effects that were similar in both the monkey and the cat. The dose-effect curve for the cynomolgus monkey differs from that of other species studied.

Thermodilution cardiac output, examined *in vitro*, was a reasonably accurate and precise means of measuring cardiac output in low flow states with a tendency to overestimate cardiac output.

Table 1

The Etiology of Subarachnoid Hemorrhage

Primary Subarachnoid Hemorrhage
- Aneurysms
- AVM's
- Unknown

Secondary Subarachnoid Hemorrhage
- Trauma
- Tumors
- Hypertension
- Hemorrhagic disorders
- Cerebral infarction
- Infection
- Intracranial venous thrombosis
- Systemic vascular disease
- Spinal cord abnormalities

Table 2

ECG Changes in Subarachnoid Hemorrhage
(Smith, 1972)

General ECG Changes in Subarachnoid Hemorrhage

1. Prolonged Q-Tc or Q-U intervals
2. Elevated or depressed S-T segments
3. Deeply inverted or tall upright T-waves
4. Large U-waves (positive or negative)
5. Q-waves in both limb and precordial leads
6. Bifid or notched T-waves

Changes in Cardiac Rhythm in Subarachnoid Hemorrhage

1. Sinus bradycardia
2. Wandering atrial pacemaker
3. Paroxysmal atrial tachycardia
4. Atrial fibrillation
5. 2:1 A-V block
6. A-V dissociation
7. Nodal bradycardia
8. Premature ventricular contractions

Table 3

Descriptive Statistics: Stage III minus Stage I

Nimodipine	0	3	6	12
Wt	-0.2±0.1	-0.1±0.1	-0.2±0.1	+0.1±0.1
Temp	-0.38±0.24	-0.34±0.37	0.00±0.40	-0.26±0.25
HR	-10±6	-4±11	-3±9	-25±14
MAP	-7±8	+6±10	-24±9	-39±12
CI	-0.89±0.44	-0.57±0.28	-0.12±0.33	+0.21±0.33
Si	-3.7±2.1	-2.6±0.9	-0.3±1.8	+3.5±2.0
SWI	-.031±.027	-.002 ±.003	-.006±.002	-.007±.004
SVR	+2663±1791	+2396±374	-2694±1420	-4950±1704
PAP	-1.2±2.6	+0.2±2.0	0±1.6	+4.0±1.9
PAWP	-1.2±1.3	+0.5±0.8	+0.2±1.1	+2.2±1.6
CVP	+0.2±0.9	+1.2±1.1	+2.5±1.2	+0.7±0.8
PVR	+433±184	+171±183	+30±67	+136±103
A-$\bar{a}DO_2$	+4±17	+17±8	-2±5	-10±17
a-$\bar{v}O_2$dif	+0.4±0.5	+0.5±0.3	-0.2±0.3	-0.4±0.4
Shunt	-1.0±3.4	-0.5±1.7	-0.4±0.9	-4.0±6.1
Hb	-2.4±0.9	-3.0±0.8	-3.0±1.0	-1.5±1.0

Nimodipine=Nimodipine (mg/kg po q8h); Wt=Weight (kg); Temp=Temperature (°C); HR=Heart Rate (beats/min); MAP=Mean Arterial Pressure (mm Hg); CI=Cardiac Index ($l/min/m^2$); SI=Stroke Index ($ml/beat/m^2$); SWI=Stroke Work Index (gm $m/beat/m^2$); SVR=Systemic Vascular Resistance (dyne sec cm^{-5}); PAP=Pulmonary Artery Pressure (mm Hg); PAWP=Pulmonary Artery Wedge Pressure (mm Hg); CVP=Central Venous Pressure (mm Hg); PVR=Pulmonary Vascular Resistance (dyne sec cm^{-5}); a-$\bar{v}O_2$dif=a-$\bar{v}O_2$ difference (vol %); Shunt=% Shunt; Hg=Hemoglobin (gm/dl)

Values are mean ± standard error of the mean.

Table 4. Descriptive statistics: pre- and post-clot.

Temp=Temperature (°C); HR=Heart Rate (beats/min); MAP=Mean Arterial Pressure (mm Hg); CI=Cardiac Index (l/min/m²); SI=Stroke Index (ml/beat/m²); SWI=Stroke Work Index (gm m/beat/m²); SVR=Systemic Vascular Resistance (dyne sec cm^{-5}); PAP=Pulmonary Artery Pressure (mm Hg); PAWP=Pulmonary Artery Wedge Pressure (mm Hg); CVP=Central Venous Pressure (mm Hg); PVR=Pulmonary Vascular Resistance (dyne sec cm^{-5}); $\bar{v}O_2$dif=a-$\bar{v}O_2$ difference (vol %) Shunt=% Shunt; Hemoglobin(gm/dl)

Values are mean ± standard error of the mean.

(*)Significant values (post-clot minus pre-clot, $p<0.05$).

	Survivors n=23		Non-survivors n=5	
	Pre-clot	Post-clot	Pre-clot	Post-clot
HR	*$1.83\times10^{2} \pm 4\times10^{0}$	$1.99\times10^{2} \pm 7\times10^{0}$	$1.86\times10^{2} \pm 5\times10^{0}$	$1.95\times10^{2} \pm 8\times10^{0}$
MAP	$8.3\times10^{1} \pm 2\times10^{0}$	$8.3\times10^{1} \pm 4\times10^{0}$	$7.8\times10^{1} \pm 6\times10^{0}$	$6.9\times10^{1} \pm 3\times10^{0}$
CI	$2.84\times10^{0} \pm 1.2\times10^{-1}$	$2.68\times10^{0} \pm 6.8\times10^{-1}$	*$2.85\times10^{0} \pm 2.7\times10^{-1}$	$2.18\times10^{0} \pm 1.1\times10^{-1}$
SI	*$1.59\times10^{-2} \pm 5\times10^{-4}$	$1.36\times10^{-2} \pm 6\times10^{-4}$	*$1.54\times10^{-2} \pm 1.4\times10^{-3}$	$1.14\times10^{-2} \pm 1.0\times10^{-3}$
SVR	$1.091\times10^{4} \pm 7.3\times10^{2}$	$1.224\times10^{4} \pm 6.4\times10^{2}$	$1.031\times10^{4} \pm 1.29\times10^{3}$	$1.178\times10^{4} \pm 1.22\times10^{3}$
PAP	*$1.09\times10^{1} \pm 7\times10^{-1}$	$7.1\times10^{0} \pm 6\times10^{-1}$	$9.4\times10^{0} \pm 1.0\times10^{0}$	$6.6\times10^{0} \pm 1.3\times10^{0}$
PAWP	*$2.9\times10^{0} \pm 5\times10^{-1}$	$6\times10^{-1} \pm 3\times10^{-1}$	$4\times10^{-1} \pm 7\times10^{-1}$	$2\times10^{-1} \pm 8\times10^{-1}$
CVP	*$2.3\times10^{0} \pm 5\times10^{-1}$	$1.0\times10^{0} \pm 5\times10^{-1}$	$2.0\times10^{0} \pm 4\times10^{-1}$	$8\times10^{-1} \pm 1.1\times10^{0}$
PVR	$1.13\times10^{3} \pm 1.4\times10^{2}$	$1.18\times10^{3} \pm 7.8\times10^{1}$	$1.14\times10^{3} \pm 5.6\times10^{1}$	$1.08\times10^{3} \pm 2.2\times10^{2}$
$A\text{-}aDO_2$	$3.43\times10^{1} \pm 4.1\times10^{0}$	$3.69\times10^{1} \pm 2.4\times10^{0}$	$4.37\times10^{1} \pm 1.12\times10^{1}$	$3.98\times10^{1} \pm 8.1\times$
$a\text{-}\bar{v}O_2$ dif.	*$2.8\times10^{0} \pm 1\times10^{-1}$	$3.8\times10^{0} \pm 1\times10^{-1}$	*$2.3\times10^{0} \pm 1\times10^{-1}$	$4.0\times10^{0} \pm 2\times10$
Shunt	$5.9\times10^{0} \pm 7\times10^{-1}$	$5.6\times10^{0} \pm 1.4\times$	$6.9\times10^{0} \pm 2.6\times10^{0}$	$3.6\times10^{0} \pm 6\times10^{-1}$
Hb	*$9.7\times10^{0} \pm 3\times10^{-1}$	$8.9\times10^{0} \pm 2\times10$	$8.3\times10^{0} \pm 9\times10^{-1}$	$7.2\times10^{0} \pm 6\times10^{-1}$

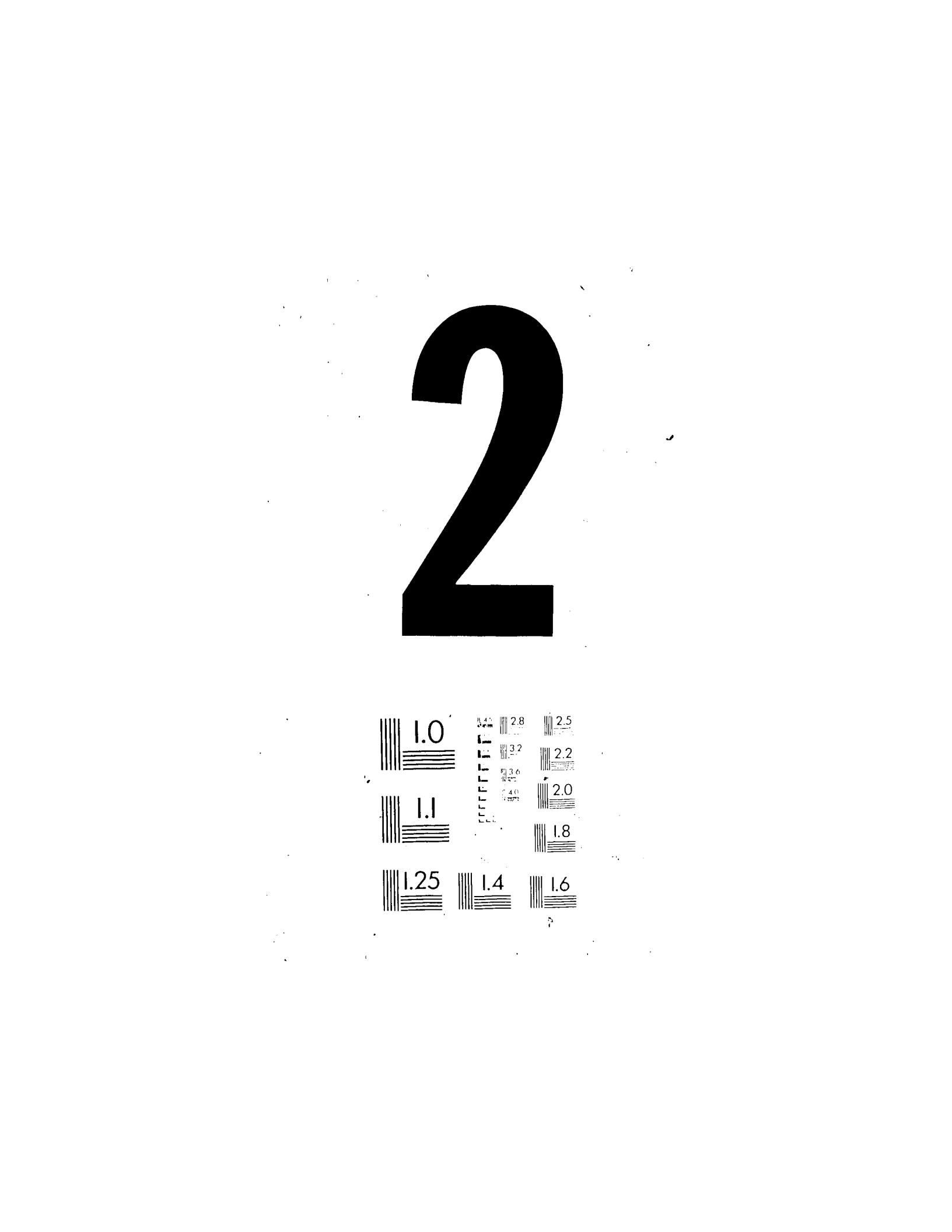

2
1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0

Table 5

Thermodilution Cardiac Output Versus Measured Flow

		r
1 ml ice	y = 1.25x + 10.64	.988
1 ml RT	y = 1.02x + 42.39	.983
2 ml ice	y = 1.15x + 12.52	.998
2 ml RT	y = 1.10x + 15.04	.973
3 ml ice	y = 1.11x + 22.34	.998
3 ml RT	y = 1.14x + 7.21	.970
5 ml ice	y = 0.97x + 107.2	.983
5 ml RT	y = 1.08x + 39.6	.954

RT = Room Temperature
y = Thermodilution Cardiac Output
x = Measured Flow

Figure 1. *In vitro* model of thermodilution cardiac output.

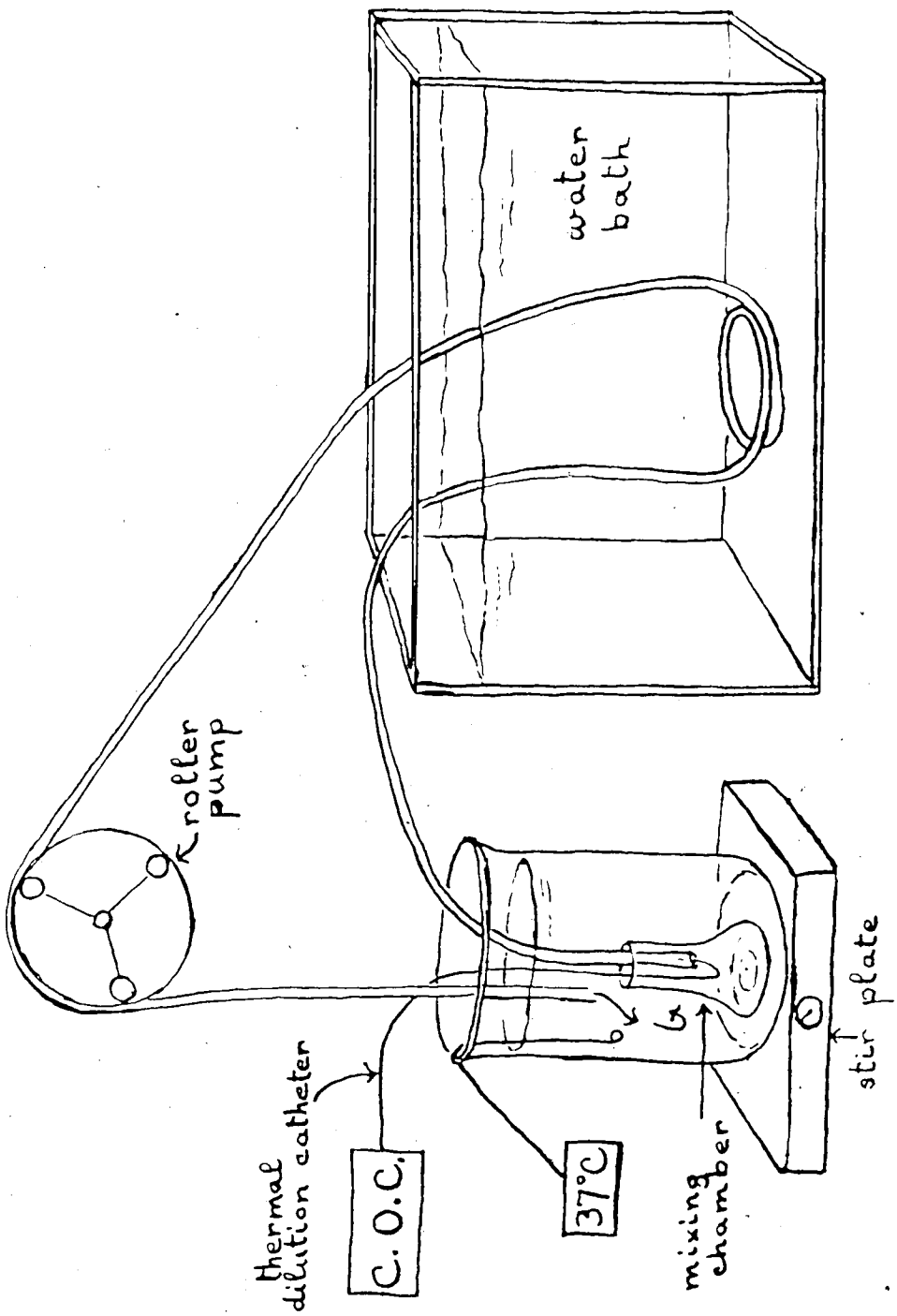

water bath
roller pump
thermal dilution catheter
C.O.C.
37°C
mixing chamber
stir plate

Figure 2. The effects of anesthesia on heart rate, mean arterial pressure and cardiac output. Ketamine hydrochloride was used for induction. Time 0 is the time of endotracheal intubation.

○ First monkey

△ Second monkey

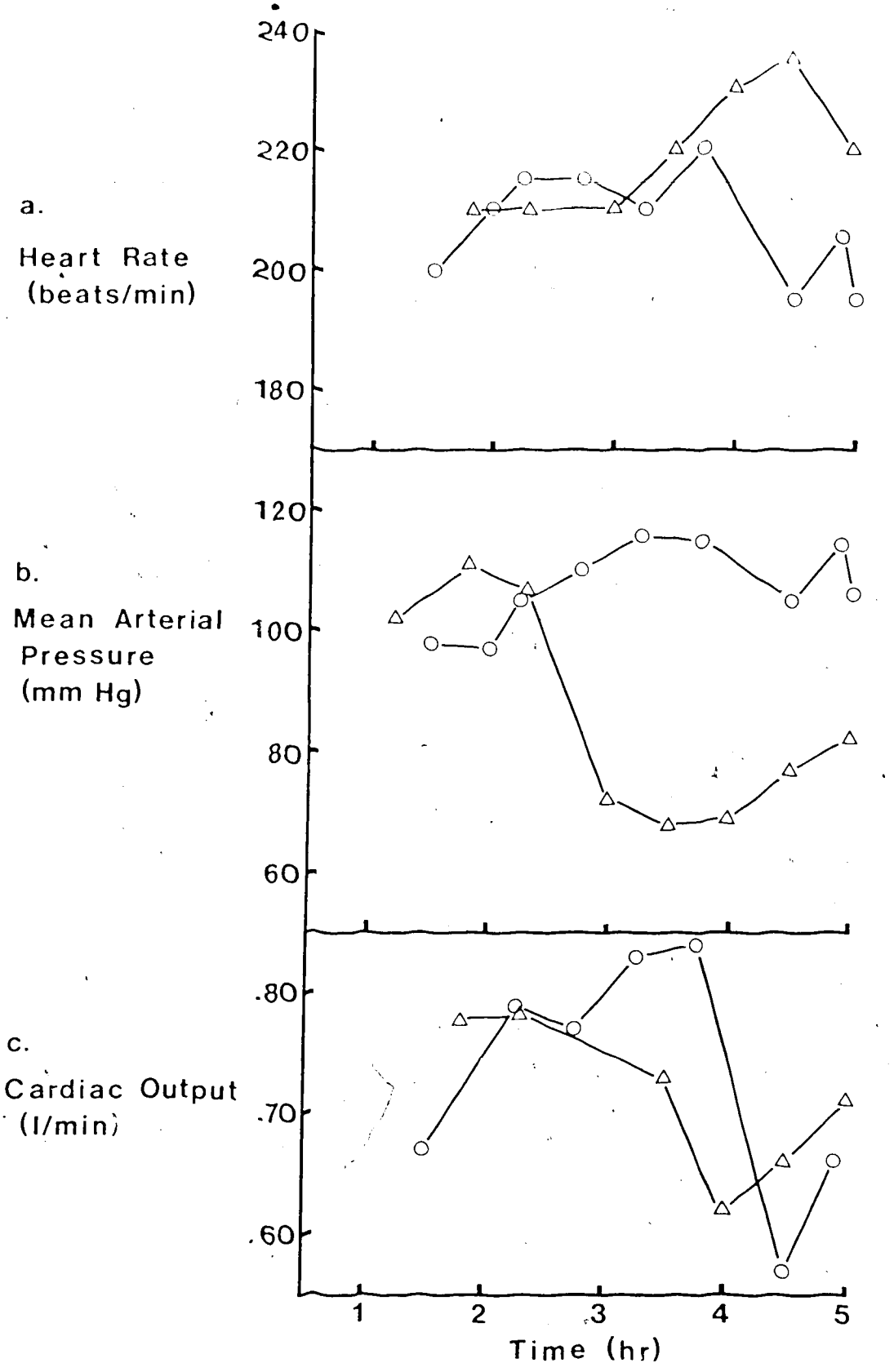

a.
Heart Rate
(beats/min)
240
220
200
180
b.
Mean Arterial
Pressure
(mm Hg)
120
100
80
60
c.
Cardiac Output
(l/min)
.80
.70
.60
1
2
3
4
5
Time (hr)

Figure 3. The effects of anesthesia on systemic vascular resistance, pulmonary vascular resistance and stroke volume. Ketamine hydrochloride was used for induction. Time 0 is the time of endotracheal intubation.

- First monkey

Δ Second monkey

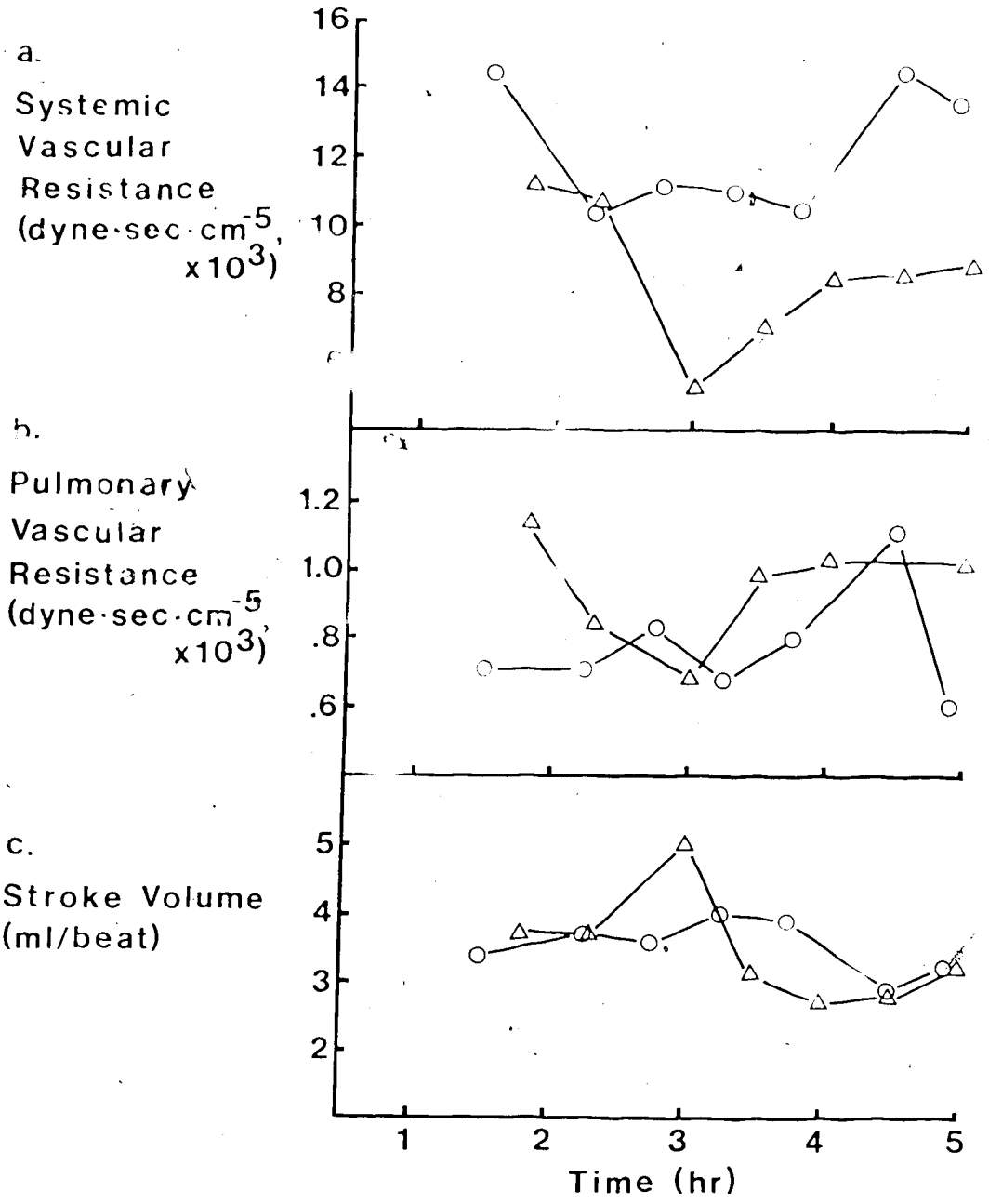

a.
Systemic
Vascular
Resistance
(dyne·sec·cm^{-5},
x10^3)
16
14
12
10
8
b.
Pulmonary
Vascular
Resistance
(dyne·sec·cm^{-5}
x10^3)
1.2
1.0
.8
.6
c.
Stroke Volume
(ml/beat)
5
4
3
2
1
2
3
4
5
Time (hr)

Figure 4. The effects of anesthesia on pulmonary artery pressure, pulmonary artery wedge pressure and central venous pressure. Ketamine hydrochloride was used for induction. Time 0 is the time of endotracheal intubation.

< First monkey

Δ Second monkey

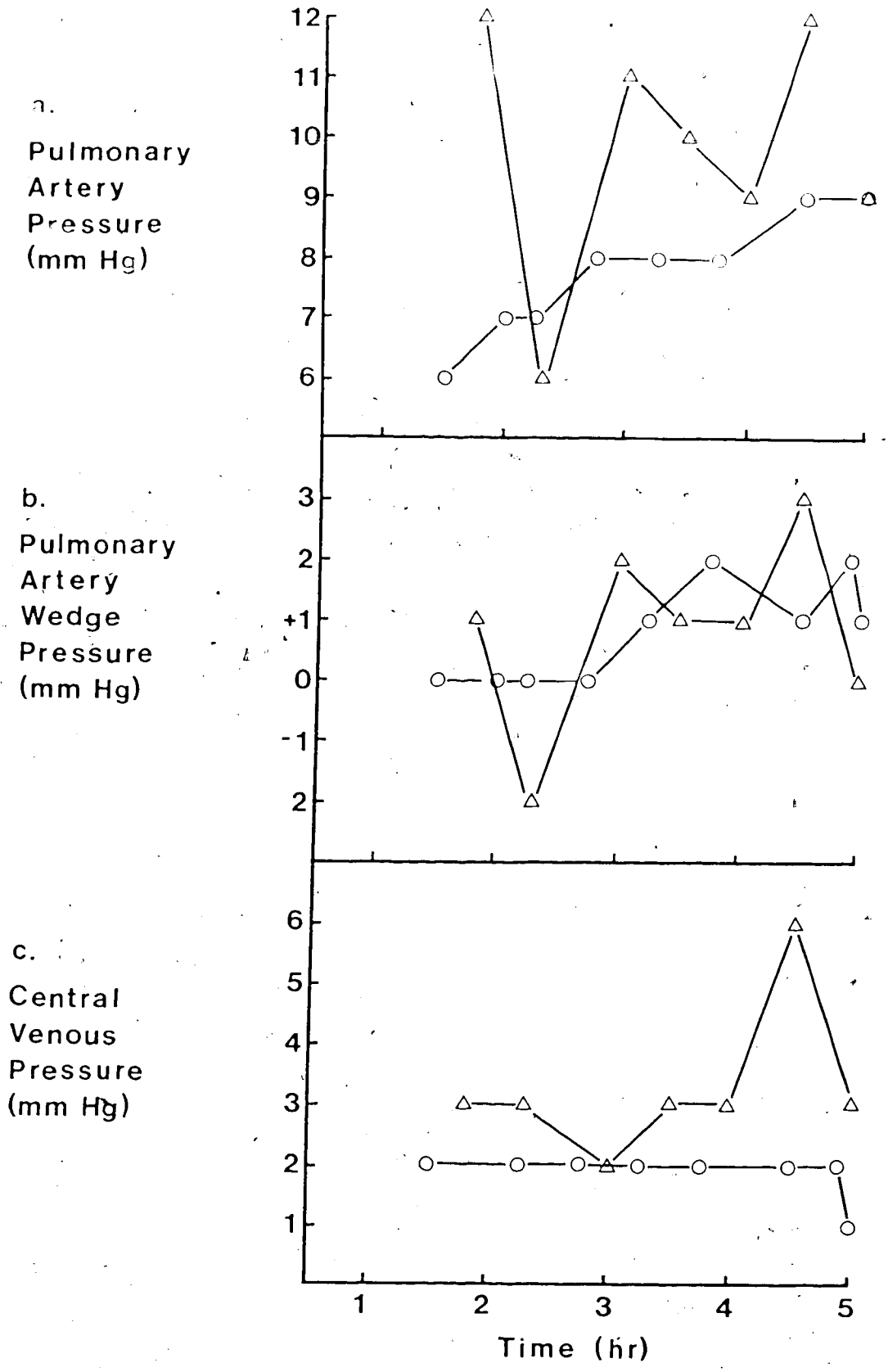

a.
Pulmonary
Artery
Pressure
(mm Hg)
12
11
10
9
8
7
6
b.
Pulmonary
Artery
Wedge
Pressure
(mm Hg)
3
2
+1
0
-1
2
c.
Central
Venous
Pressure
(mm Hg)
6
5
4
3
2
1
1
2
3
4
5
Time (hr)

Figure 5. The effects of anesthesia on $A-aDO_2$, $a-\bar{v}O_2$ difference and % shunt. Ketamine hydrochloride was used for induction. Time 0 is the time of endotracheal intubation.

○ First monkey

△ Second monkey

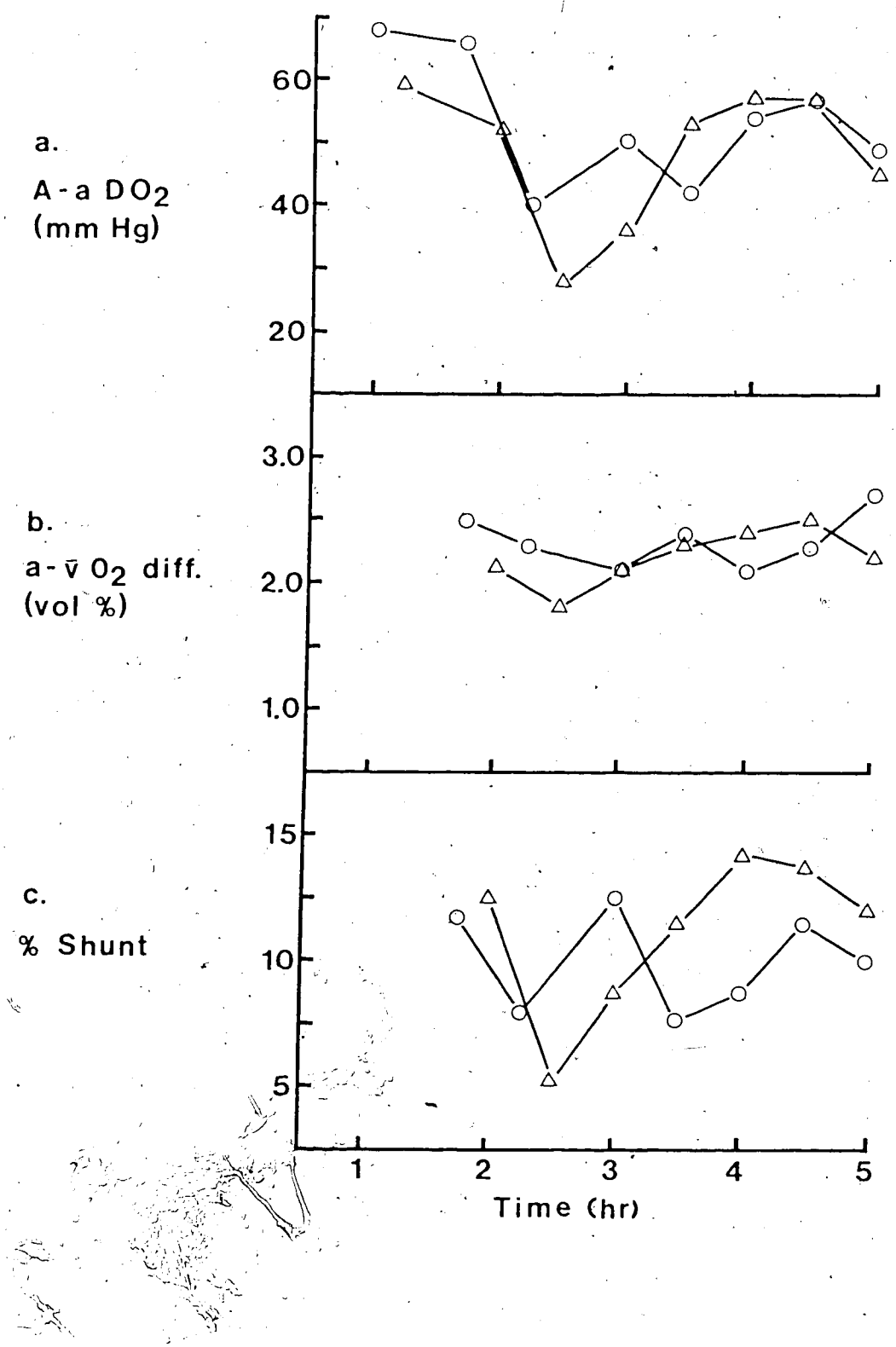

a.
A-a DO_2
(mm Hg)
60
40
20
b.
a-$\bar{v}$ O_2 diff.
(vol %)
3.0
2.0
1.0
c.
% Shunt
15
10
5
1
2
3
4
5
Time (hr)

Figure 6. Differences in heart rate between Stage III and Stage I for various nimodipine dosages. Values shown are means (Stage III minus Stage I) ± standard error of the mean.

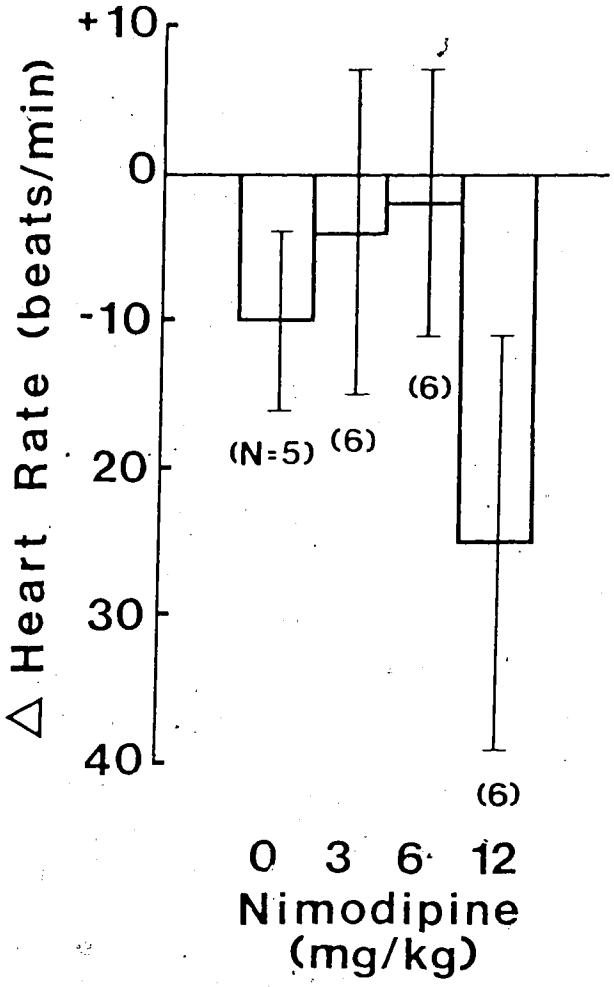
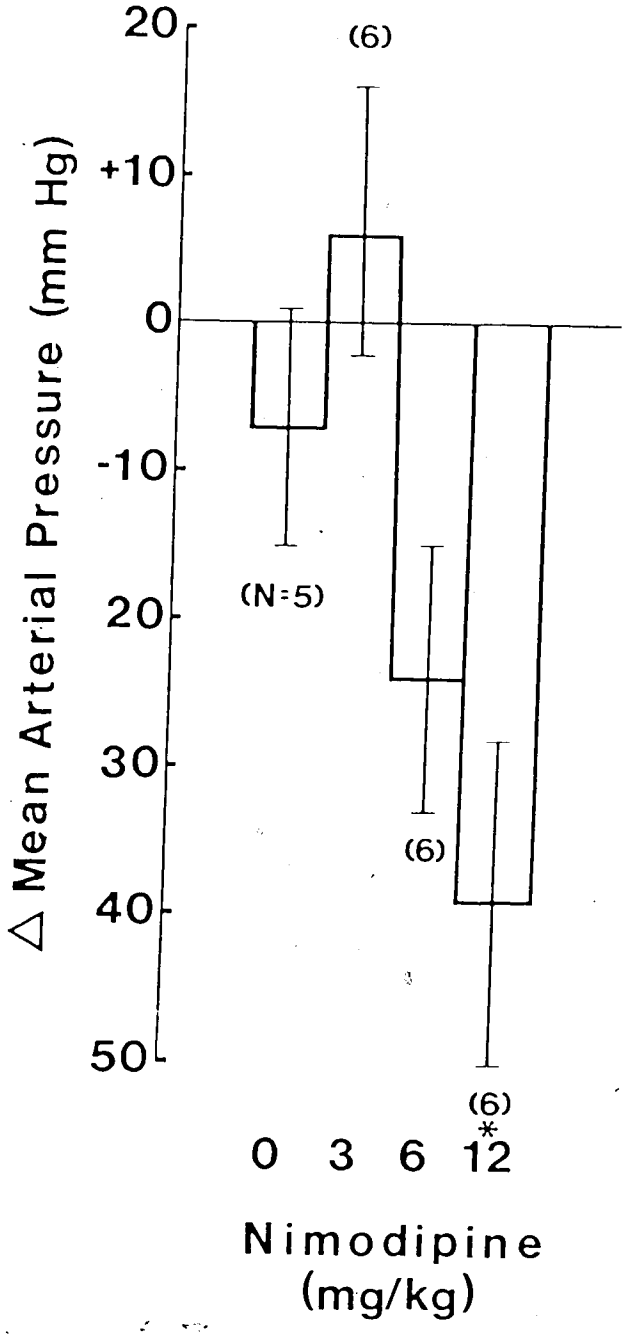

+10
0
-10
20
30
40
Δ Heart Rate (beats/min)
(N=5)
(6)
(6)
(6)
0 3 6 12
Nimodipine
(mg/kg)

Figure 7. Differences in mean arterial pressure between Stage III and Stage I for various nimodipine dosages. Values shown are means (Stage III minus Stage I) ± standard error of the mean. (*) Differs significantly from placebo group ($p<0.10$).


20
+10
0
-10
20
30
40
50
Δ Mean Arterial Pressure (mm Hg)
(6)
(N=5)
(6)
(6)
*
0 3 6 12
Nimodipine
(mg/kg)

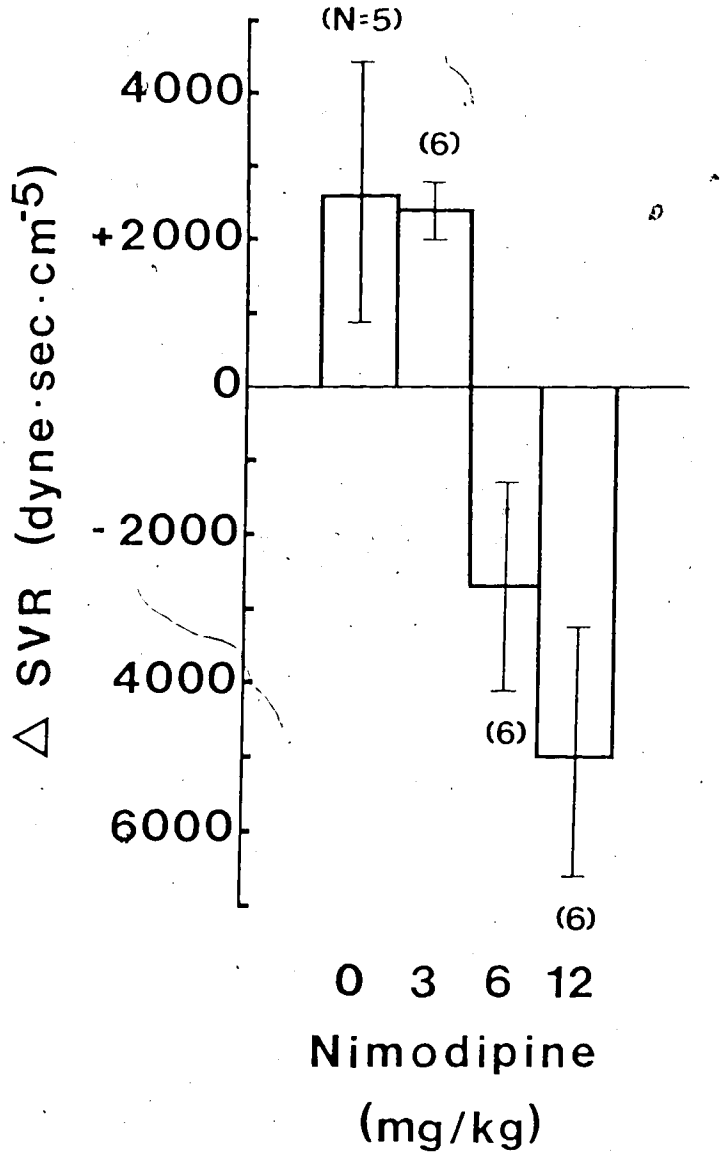

(N=5)
(6)
(6)
(6)
4000
+2000
0
-2000
4000
6000
Δ SVR (dyne·sec·cm-5)
0 3 6 12
Nimodipine
(mg/kg)

Figure 11. Differences in pulmonary artery pressure (PAP) between Stage III and Stage I for various nimodipine dosages. Values shown are means (Stage III minus Stage I) ± standard error of the mean.

Figure 13. Differences in A-aDO$_2$ between Stage III and Stage I for various nimodipine dosages. Values shown are means (Stage III minus Stage I) ± standard error of the mean.

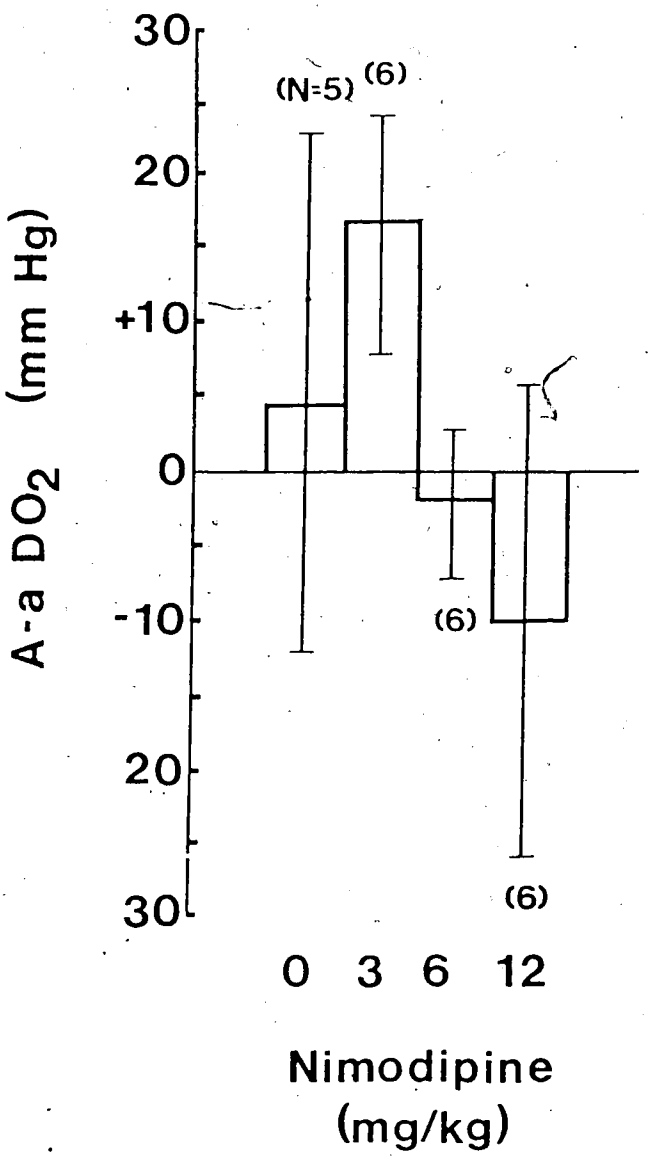

30
20
+10
0
-10
20
30
A-a DO_2 (mm Hg)
(N=5)
(6)
(6)
(6)
0 3 6 12
Nimodipine
(mg/kg)

Figure 20. The effects of polyethylene glycol 400 0.5 ml/kg on systemic vascular resistance, pulmonary vascular resistance and stroke volume. (↑) Indicates the time the polyethylene glycol was given.

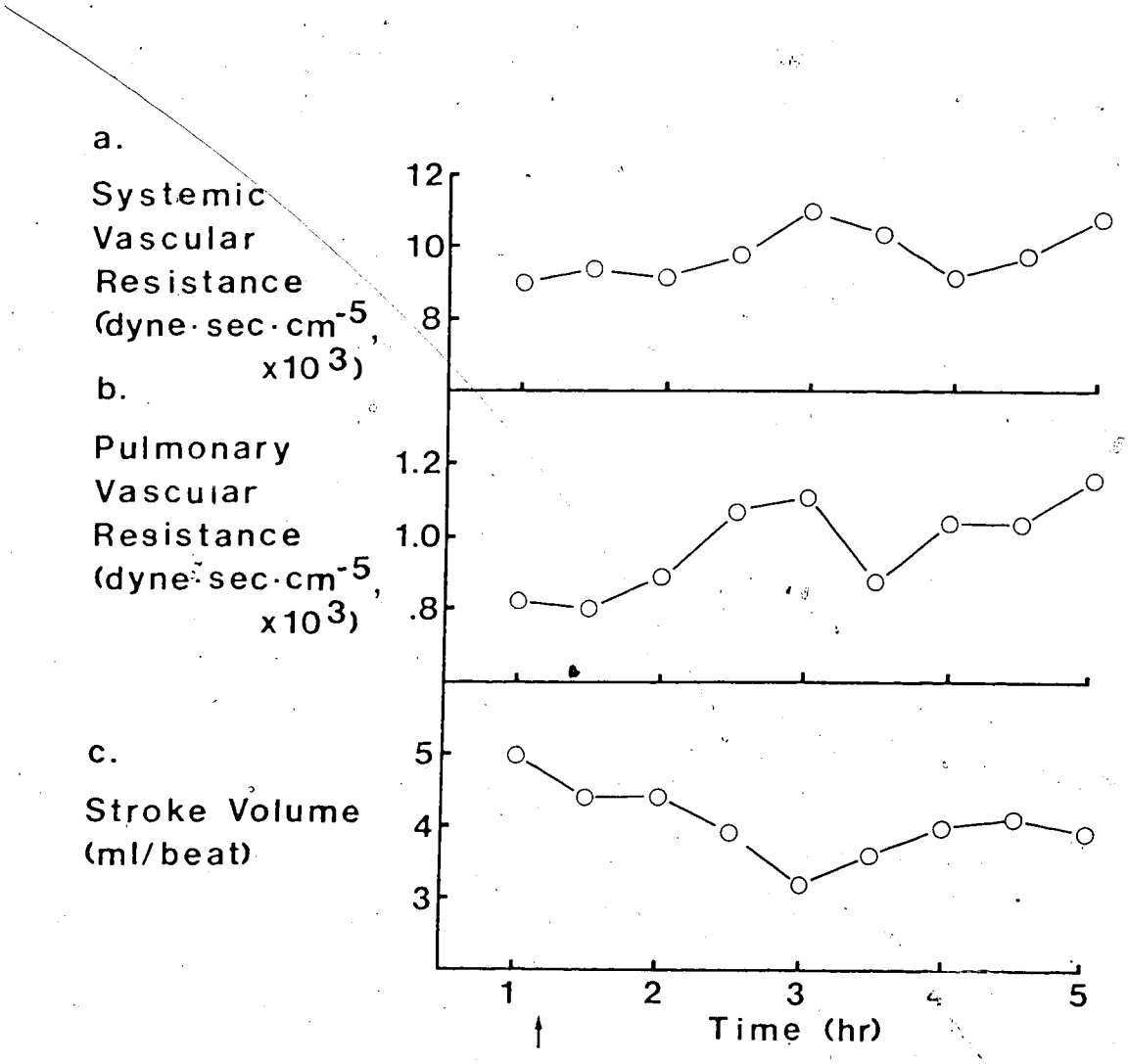

a.
Systemic Vascular Resistance (dyne·sec·cm^{-5}, x10^3)
12
10
8
b.
Pulmonary Vascular Resistance (dyne·sec·cm^{-5}, x10^3)
1.2
1.0
.8
c.
Stroke Volume (ml/beat)
5
4
3
1
2
3
5
Time (hr)

Figure 27. The effects of oral nimodipine on stroke index in monkeys. Time 0 is the time of nimodipine administration.

Nimodipine 20 mg/kg Δ,○
Nimodipine 30 mg/kg □

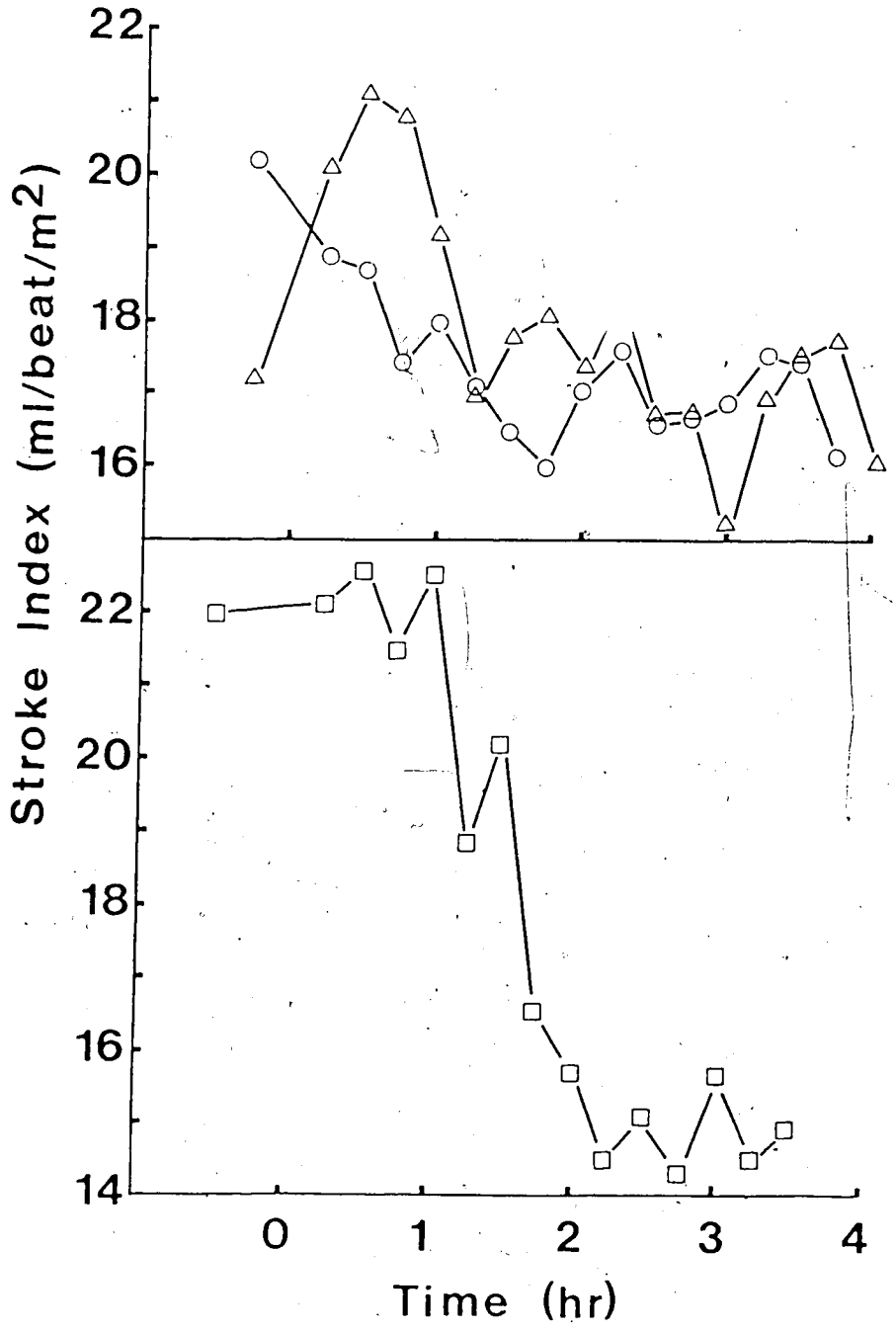

Stroke Index (ml/beat/m2)
22
20
18
16
22
20
18
16
14
0
1
2
3
4
Time (hr)

Figure 28. The effects of oral nimodipine on pulmonary artery pressure in monkeys. Time 0 is the time of nimodipine administration.

Nimodipine 20 mg/kg Δ,○
Nimodipine 30 mg/kg □

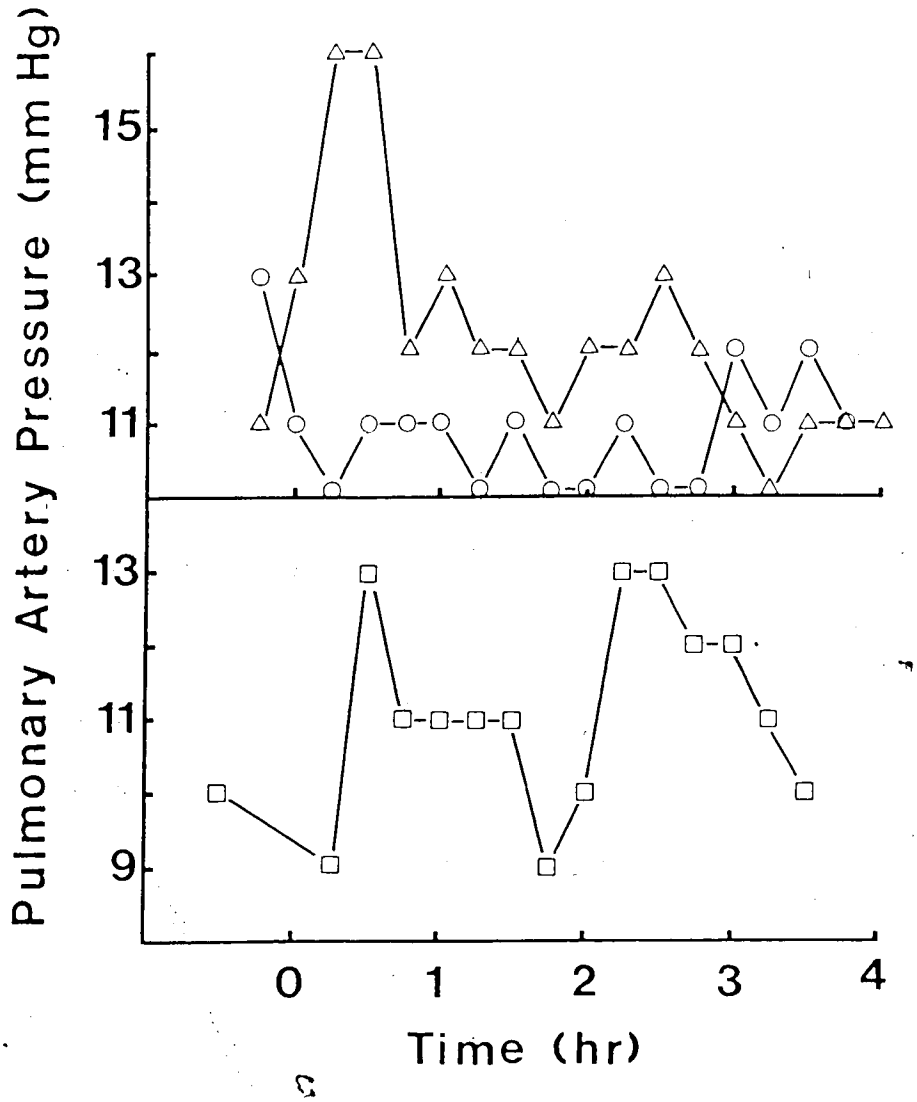
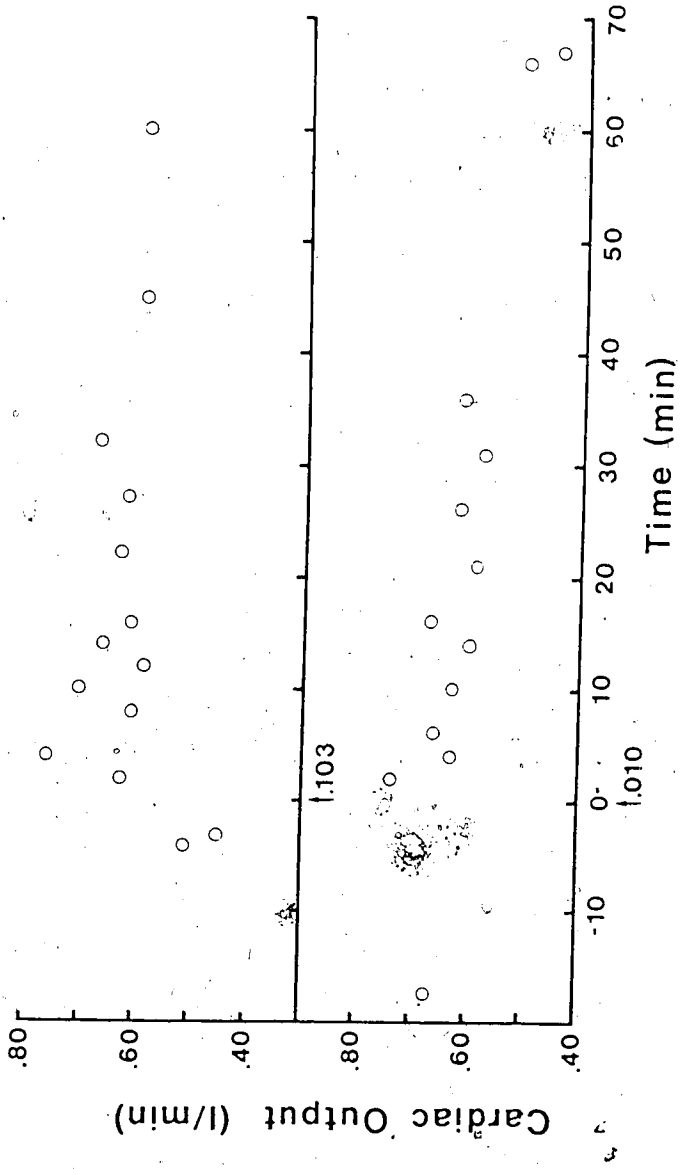

Pulmonary Artery Pressure (mm Hg)
15
13
11
13
11
9
0
1
2
3
4
Time (hr)

Figure 34. The effects of intravenous nimodipine on systemic vascular resistance in a monkey. (↑) Indicates the time of nimodipine administration in doses of 0.012 mg/kg, 0.105 mg/kg, and 0.458 mg/kg.

Systemic Vascular Resistance (dyn·sec·cm^{-5} x10^3)
8
7
6
5
4
8
7
6
5
1.458
1.105
1.012
-10
0
10
20
30
40
50
60
70
80
90
Time (min)

Figure 41. The effects of intravenous nimodipine on cardiac output in a cat. (↑) Indicates the time ot nimodipine administration in doses of 0.010 mg/kg and 0.103 mg/kg.


Cardiac Output (l/min)
.80
.60
.40
.80
.60
.40
1.103
1.010
-10
0
10
20
30
40
50
60
70
Time (min)

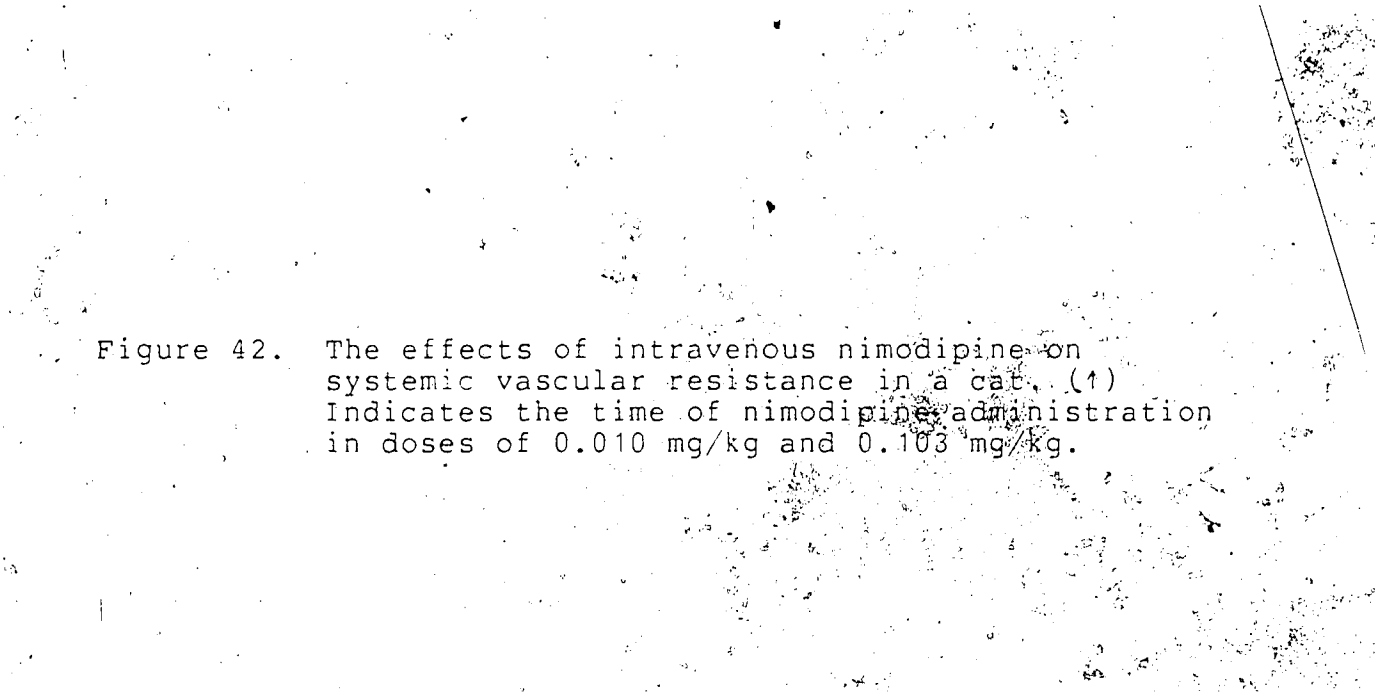
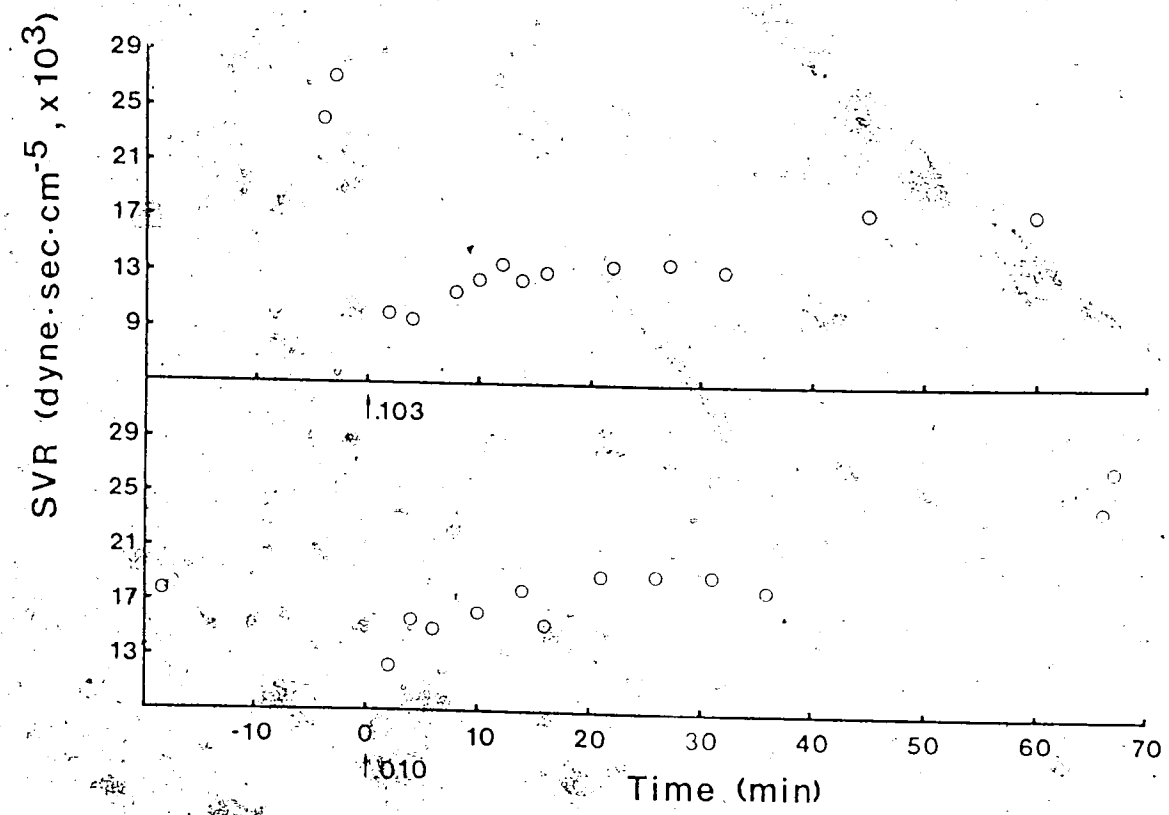


Figure 42. The effects of intravenous nimodipine on systemic vascular resistance in a cat. (1) Indicates the time of nimodipine administration in doses of 0.010 mg/kg and 0.103 mg/kg.


SVR (dyne·sec·cm^{-5}, x10^3)
29
25
21
17
13
9
1.103
29
25
21
17
13
1.010
-10
0
10
20
30
40
50
60
70
Time (min)

Helpern M, Rabson SM. 1945. Sudden and unexpected natural death – general considerations and statistics. NY. State J. Med. 45:1197-1201.

Henry PD. 1982. Comparative cardiac pharmacology of calcium blockers. In: Flaim SF, Zelis R, eds. Calcium blockers: Mechanisms of action and clinical applications. Urban and Schwarzenberg, Baltimore-Munich.

Heros RC, Zervas NT, Negoro M. 1976. Cerebral vasospasm. Surg. Neurol. 5:354-362.

Hersch C. 1964. Electrocardiographic ch subarachnoid hemorrhage, meningitis, and intrac ace-occupying lesions. Br. Heart J. 26:785-793.

Hodges M, Downs JB, Mitchell LA. 1975. Thermodilution and Fick cardiac index determinations following cardiac surgery. Crit. Care Med. 3:182-186.

Hoffmeister F, Kazda S, Krause HP. 1979. Influence of nimodipine (Bay e 9736) on the postischeamic changes of brain function. Acta Neurol. Scand. 60(suppl 72):358-359.

Hope J. 1832. In: A treatise on the diseases of the heart and great vessels. p. 246. William Kidd, London.

Hosie KF. 19[illegible]. Thermal dilution techniques. Circ. Res. 10:491-[illegible]

Hunt D, M[illegible] Zapf B. 1969. Electrocardiographic and serum e[illegible]changes in subarachnoid hemorrhage. Am. Heart J. [illegible]479-488.

Jacob WA, Van Bogaert A, De Groodt-Lasseel MHA. 1972. Myocardial ultrastructure and haemodynamic reactions during experimental subarachnoid haemorrhage. J. Mol. and Cell. Cardiol. 4:287-298.

James TN. 1969. QT prolongation and sudden death. Mod. Concepts Cardiovasc. Dis. 38:35-37.

Jim K, Harris A, Rosenberger LB, Triggle DJ. 1981. Stereoselective and nonstereoselective effects of D600 (methoxyverapamil) in smooth muscle preparations. Eur. J. Pharmacol. 76:67-72.

Kapp J, Mahaley MS, Odom GL. 1968. Cerebral arterial spasm. Part 2: Experimental evaluation of mechanical and humoral factors in pathogenesis. J. Neurosurg. 29:339-349.

Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP. 1982. Treatment of ischeamic d its from vasospasm with intravascular volume exp and induced arterial hypertension. Neurosurg 11:337-343.

Kawai C, Konishi T, Matsuyama E, Okazaki H. 1981. Comparative effects of three calcium antagonists, diltiazem, verapamil, and nifedipine, on sinoatrial and atrioventricular nodes: experimental and clinical studies. Circulation 63:1035-1042.

Kazda S, Garthoff B, Krause HP, Schlossman K. 1982. Cerebrovascular effects of calcium antagonist dihydropyridine derivative nimodipine in animal experiments. Arzneimittelforsch. 32:331-338.

Kazda S, Hoffmeister B, Garthoff B, Towart R. 1979. Prevention of the postischaemic impaired reperfusion of the brain by nimodipine (Bay e 9736). Acta Neurol. Scand. 60(Suppl. 72):302-305.

Kazda S, Towart R. 1982. Nimodipine: a new calcium antagonistic drug with a preferential cerebrovascular action. Acta Neurochir. (Wein) 63:259-265.

Klouda MA, Brynjolfsson G. 1969. Cardiotoxic effect of electrical stimulation of stellate ganglia. Ann. NY. Acad. Sci. 156:271-280.

Kohanna FH, Cunningham JN Jr. 1977. Monitoring of cardiac output by thermodilution after open-heart surgery. J. Thorac. Cardiovasc. Surg. 73:431-457.

Koskelo P, Punsar S. 1964. Subendocardial hemorrhage and ECG changes in intracranial bleeding. Br. Med. J. 5396:1479-1480.

Kosnik EJ, Hunt WE. 1976. Postoperative hypertension in the management of patients with intracranial aneusysms. J. Neurosurg. 45:148-154.

Kuwayama A, Zervas NT, Shintani A, Pickren K. 1972. Papaverine hydrochloride and experimental hemorrhagic cerebral arterial spasm. Stroke 3:27-33.

Kwak R, Niizuma H, Ohi T, Suzuki J. 1979. Angiographic study of cerebral vasospasm following rupture of intracranial aneurysms. I. Time of appearance. Surg. Neurol. 11:257-262.

Lawrie GM, Stacey RB, Wright DS. 1975. The perioperative measurement of cardiac output in infancy by the thermodilution technique. Anaesth. and Intensive Care. 3:317-320.

Levine HD. 1953. No specificity of the electrocardiogram associated with coronary artery disease. Am. J. Med. 15:344-355.

Liu CT, Higbee, GA. 1976. Determination of body surface area in the rhesus monkey. J. Appl. Physiol. 40:101-104.

Locksley HB. 1969. Natural history of subarachnoid hemorrhage, intracranial aneurysms, and arteriovenous malformations: based on 6368 cases in the cooperative study. Parts 1 and 2. In: Sahs AS, Perret GE, Locksley HB, eds. Intracranial aneurysms and subarachnoid hemorrhage. pp. 37-108. JB Lippincott Co., Philadelphia.

Lowe RF, Gilboe DD. 1973. Canine cerebrovascular response to nitroglycerine, acetylcholine, 5 hydroxytryptamine and angiotensin. Am. J. Physiol. 225:1333-1338.

Lyons EL, Leeds NE. 1967. The angiographic demonstration of arterial vascular disease in purulent meningitis. Radiology 88:935-938.

MacKay EM. 1950. Experimental pulmonary edema. IV. Pulmonary edema accompanying trauma to the brain. Proc. Soc. Exp. Biol. 74:695-701.

Maire FW, Patton HD. 1956. Neural structures involved in the genesis of 'preoptic pulmonary edema', gastric erosions and behavior changes. Am. J. Physiol. 184:345-350.

Maire FW, Patton HD. 1956a. Role of splanchnic nerve and the adrenal medulla in the genesis of 'preoptic pulmonary edema'. Am J. Physiol. 184:351-355.

Manning JW, Cotton deV M. 1962. Mechanism of cardiac arrhythmias induced by diencephalic stimulation. Am. J. Physiol. 203:1120-1124.

Manning GW, Hall GE, Banting FG. 1937. Vagal stimulation and the production of myocardial damage. Can. Med. Assoc. J. 37:314-318.

Manning JW, Peiss CN. 1960. Cardiovascular responses to electrical stimulation in the diencephalon. Am. J. Physiol. 198:366-370.

Maspes P. Marini G. 1962. Intracranial arterial spasm related to supraclinoid ruptured aneurysms. Acta Neurochir. (Wein) 10:630-638.

Mauck HP, Hockman CH, Hoff EC. 1964. ECG changes after cerebral stimulation. 1. Anomalous atrioventricular excitation elicited by electrical stimulation of the

mesencephalic reticular formation. Am. Heart J. 68:98-101.

McAllister RE, Noble D, Tsien RW. 1975. Reconstruction of the electrical activity of cardiac Purkinje fibres. J. Physiol. 251:1-59.

McCalden TA, Bevan JA. 1981. Sources of activator calcium in rabbit basilar artery. Am. J. Physiol. 241:H129-H133.

McCordock H[illegible]23. A case of intracranial aneurysm with fatal rupture. Bull. Buffalo gen. Hosp. 1:87.

McNair JL, Clower BR, Sanford RA. 1970. The effect of reserpine pretreatment on myocardial damage associated with simulated intracranial hemorrhage in mice. Eur. J. Pharmacol. 9:1-6.

Melville KI, Blum B, Shister HE, Silver MD. 1963. Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation. Am. J. Cardiol. 12:781-791.

Meyer H, Wehinger E, Bossert F, Scherling D. 1983. Nimodipine: synthesis and metabolic pathway. Arzneimittelforsch. 33:106-112.

Moncy E. 1969. Evaluation of topical methysergide on experimental cerebral vasospasm. Texas Med. 65:74-77.

Moodie DS, Feldt RH, Kaye MP, Strelow DA, Van Der Hagen LJ. 1978. Measurement of cardiac output by thermodilution: Development of accurate measurements at flows applicable to the pediatric patient. J. Surgical Res. 25:305-311.

Morad M, Goldman Y. 1973. Excitation-contraction coupling in heart muscle, membrane control of development of tension. Progr. Biophys. Mol. Biol. 27:259-313.

Nakayama K, Kato H. 1979. Different calcium dependency of contractile responses of cerebral artery to quick stretch and electrical stimuli. Acta Neurol. Scand. 60(Suppl. 72):508-509.

Nakayama K, Nasuya Y. 1980. Selective abolition of Ca-dependent responses of smooth and cardiac muscles by flunarizine. Japan J. Pharmacol. 30:731-742.

Noble D. 1979. In: The initiation of the heartbeat. Oxford, London.

Norberg KA. 1967. Transmitter histochemistry of the sympathetic adrenergic nervous system. Brain Res. 5:125-170.

Novy MJ, Parer JT, Behrman RE. 1969. Equations and nomograms for blood-oxygen dissociation curves in adult and fetal macaques. J. Appl. Physiol. 26:339-345.

Offenhaus L, van Goal J. 1969. Electrocardiographic changes and tissue catecholamines in experimental subarachnoid haemorrhage. Cardiovasc. Res. 3:433-440.

Olsson Y, Hossmann K-A. 1971. The effect of intravascular saline perfusion on the sequelae of transient cerebral ischemia. Acta Neuropath. 17:68-79.

Ott E, Lechner H. 1980. The influence of nimodipine on cerebral blood flow in patients with subacute cerebral infarction. (Abstract). In: Betz E, Grote, Heuser D, Wallenweber R, eds. Pathophysiology and pharmacotherapy of cerebrovascular disorders. Satellite symposium of the XXVIII International Congress of Physiological Sciences.

Pakarinen S. 1967. Incidence, aetiology, and prognosis of primary subarachnoid haemorrhage. Acta Neurol. Scand. 43(Suppl 29):1-127.

Parizel G. 1973. Life-threatening arrhythmias in subarachnoid hemorrhage. Angiology 24:17-21.

Parizel G. 1979. On the mechanism of sudden death with subarachnoid hemorrhage. J. Neurol. 220:71-76.

Pavek K. 1974. Studies on the thermodilution technique for determination of cardiac output. Acta Univers. Upsal.

Pearce WJ, Bevan JA. 1983. The cerebrovascular selectivity of diltiazem. In: Programme, Annual Meeting of the American Association of Neurological Surgeons. pp. 60-61. Washington.

Phillips LH II, Whisnant JP, O'Fallon WM, Sundt TM Jr. 1980. The unchanging pattern of subarachnoid hemorrhage in a community. Neurology 30:1034-1040.

Poole-Wilson P. 1980. Entry of Ca^{++} into the ischaemic myocardium. In; Richardson RG, ed. Ca^{++}-antagonism. Abbott Laboratories Ltd., London.

Porter RW, Kamikawa K, Greenhoot J. 1962. Persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain. Am. Heart J. 64:815-819.

Pribram HRW. 1965. Intracranial aneurysms and subarachnoid hemorrhage. In: Fields WS, Sahs AL, eds. pp. 184-215. C.C. Thomas, Springfield Ill.

Reichenbach DD, Benditt EP. 1970. Catecholamines and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeneration. Human Path. 1:125-150.

Reuter H. 1970. Divalent cations as charge carriers in excitable membranes. Progr. Biophys. Mol. Biol. 22:1-43.

Reynolds RW. 1963. Pulmonary edema as a consequence of hypothalamic lesions in rats. Science 141:930-932.

Richards P. 1963. Pulmonary oedema and intracranial lesions. Br. Med. J. 5349:83-86.

Runciman WB, Ilsey AH, Roberts JG. 1981. Thermodilution cardiac output – a systematic error. Anaes. Intensive Care. 9:135-139.

Sandahl B, Andersson KE, Aronsen KF, Ulmsten U. 1978. Effect of the calcium antagonist nifedipine on uterine blood flow in non-treated and oestradiol-treated rats. Gynecol. Obstet. Invest. 9.233-243.

Sarner M, Crawford MD. 1965. Ruptured intracranial aneurysm. Lancet 2:1251-1254.

Sarnoff SJ, Berglund E. 1952. Neurohemodynamics of pulmonary edema. IV. Effect of systemic vasoconstriction and subsequent vasodilation on flow and pressures in systemic and pulmonary vascular beds. Am. J. Physiol. 170:588-600.

Sarnoff SJ, Sarnoff LC. 1952. Neurohemodynamics of pulmonary edema. II. The role of sympathetic pathways in the elevation of pulmonary and systemic vascular pressures following the intracisternal injection of fibrin. Circulation. 6:51-62.

Sarnoff SJ, Sarnoff LC. 1952a. Neurohemodynamics of pulmonary edema. I. Autonomic influence on pulmonary vascular pressures and the acute pulmonary edema state. Dis. Chest 22:685-698.

Sasaki T, Asano T, Sano K, Murota S. 1981. Evaluation of prostacyclin biosynthetic activity in canine basilar artery following subarachnoid hemorrhage. J. Cereb. Blood Flow Metab. 1:560-561

Schiavone DJ, Kaldor J. 1965. Creatine phophokinase levels and cerebral disease. Med J. Aust. 2:790-792.

Schneck SA, Kricheff II. 1964. Intracranial aneurysm rupture, vasospasm and infarction. Arch. Neurol. 11:668-680.

Secher-Hansen E. 1964. Subarachnoidal haemorrhage and sudden unexpected death. Acta Neurol. Scand. 40:115-130. Stroke 3:27-33.

Shimizu K, Ohta T, Toda N. 1980. Evidence for greater susceptibility of isolated dog cerebral arteries to Ca antagonists than peripheral arteries. Stroke 11:261-266.

Smith M. 1972. Ventricular bigeminy and quadrigeminy occurring in a case of subarachnoid hemorrhage. J. Electrocardiol. 5:78-85.

Smith M, Ray CI. 1972. Cardiac arrythmias, increased intracranial pressure, and the autonomic nervous system. Chest 61:125-133.

Smith RP, Tomlinson BE. 1954. Subendocardial haemorrhages associated with intracranial lesions. J. Path. 68:327-334.

Sonntag VKH, Stein BM. 1974. Arteriopathic complications during treatment of subarachnoid hemorrhage with epsilon-aminocaproic acid. J. Neurosurg. 40:480-485.

Srivastava SC, Robson AO. 1964. Electrocardiographic abnormalities associated with subarachnoid haemorrhage. Lancet 2:431-433.

Sundt TM Jr. 1975. Management of ischemic complications after subarachnoid hemorrhage. J. Neurosurg. 43:418-425.

Sundt TM Jr., Whisnant JP. 1978. Subarachnoid hemorrhage from intracranial aneurysms. Surgical management and natural history of disease. N. Engl. J. Med. 299:116-122.

Suwanwela C, Suwanwela N. 1972. Intracranial arterial narrowing and spasm in acute head injury. J. Neurosurg. 36:314-323.

Szakacs JE, Cannon A. 1958. L-norepinephrine myocarditis. Am. J. Clin. Path. 30:423-438.

Tanabe Y, Sakata K, Yamada H. 1978. Cerebral vasospasm and ultrastructural changes in cerebral arterial wall. An experimental study. J. Neurosurg. 49:229-238.

Tanaka K, Gotoh F, Muramatsu Y. 1980. Effects of nimodipine (Bay e 9736) on cerebral circulation in cats. Arzneimittelforsch. 30:1494-1497.

Tanaka K, Gotoh F, Muramatsu F, Fukachi Y, Suzuki N, Okasu H, Kobari M. 1982. Effect of nimodipine, a calcium

antagonist, on cerebral vasospasm after subarachnoid hemorrhage in cats. Arzneimittelforsch. 32:1529-1534.

Taylor DC, Kowalski TE. 1982. Effects of Ca++ entry blockers on mediated heart rate responses elicited by baroreceptor reflex activation. Fed. Proc. 41:1588.

Taylor DC, Kowalski TE. 1983. Effects of nimodipine, verapamil, and diltiazem on baroreceptor reflex induced bradycardia in dogs. In: Merrill GF, Weiss HR, eds. Ca++ entry blockers, adenosine, and neurohumors. pp. 137-153. Urban and Schwarzenberg, Munich-Baltimore.

Theodore J, Robin ED. 1976. Speculations on NPE. Am. Resp. Dis. 113:405-411.

Thomas G, Schramm M, Franckowiak G. 1983. Dihydropyridines that exert positive inotropic effects in isolated cardiac muscle: evidence for Ca channel modulation. Pharmacologist 25:206-210.

Toda N. 1974. Responsiveness to potassium and calcium ions of isolated cerebral arteries. Am. J. Physiol. 227:1206-1211.

Towart R. 1981. Predilective relaxation by the calcium antagonist nimodipine (Bay e 9736) of isolated cerebral blood vessels, contracted with autologous blood. Br. J. Pharmacol. 74:268P-269P.

Towart R. 1981a. The selective inhibition of serotonin-induced contractions of rabbit cerebral vascular smooth muscle by calcium-antagonist dihydropyridines. Circ. Res. 48:650-657.

Towart R. 1982. The pathophysiology of cerebral vasospasm, and pharmacological approaches to its management. Acta Neurochir. (Wein) 63:253-258.

Towart R, Kazda S. 1979. The cellular mechanism of action of nimodipine (Bay e 9736), a new calcium antagonist. Br. J. Pharmacol. 67:409P-410P.

Towart R, Perzborn E. 1981. Nimodipine inhibits carbocyclic thromboxane induced contractions of cerebral arteries. Eur. J. Pharmacol. 69:213-215.

Towart R, Wehinger E, Meyer H, Kazda S. 1982. The effects of nimodipine, its optical isomers and metabolites on isolated vascular smooth muscle. Arzneimittelforsch. 32:338-346.

Triggle DJ. 1981. Calcium antagonists: some basic chemical and pharmacological aspects. In: Weiss GB, ed. New

perspectives on calcium antagonists. 1-18. American Physiological Society, Bethesda.

Triggle DJ, Swamy VC. 1980. Pharmacology of agents that affect calcium: agonists and antagonists. Chest 78(Suppl.):174-179.

Van Breemen C, Aaronson PI, Cauvin CA, Loutzenhiser RD, Mangel AW, Saida K. 1982. The calcium cycle in arterial smooth muscle. In: Flaim SF, Zelis R, eds. Calcium Blockers. Urban and Schwarzenberg, Munich-Baltimore.

Van Breemen C, Aaronson PI, Loutzenhiser R. 1979. Na-Ca interactions in mammalian smooth muscle. Pharmacol. Revs. 30:167-210.

Van Neuten JM, Vanhoutte PM. 1981. Calcium entry blockers, and vasospasm. In: Vanhoutte PM, Leusen I, eds. Vasodilation. pp. 459-483. Raven Press, NY.

Varsos VG, Liszczak TM, Han DH, Kistler JP, Vielma J, Black PM, Heros RC, Zervas T. 1983. Delayed cerebral vasospasm is not reversible by aminophylline, nifedipine, or papaverine in a "two-hemorrhage" canine model. J. Neurosurg. 58:11-17.

Vliers ACAP, Oeseberg B, Visser KR, Zijlstra WG. 1973. Choice of detection site for the determination of cardiac output by thermal dilution: The injection-thermister-catheter. Cardiovasc. Res. 7:133-138.

Weintraub BM, McHenry LC Jr. 1974. Cardiac abnormalities in subarachnoid hemorrhage: a resumé. Stroke 5:384-391.

Weir BK. 1978. Pulmonary edema following fatal aneurysm rupture. J. Neurosurg 49:502-507.

Weir BK. 1979. Medical aspects of the preoperative management of aneurysms: a review. Can. J. Neurol. Sci. 6:441-450.

Weir BK. 1980. The effect of vasospasm on morbidity and mortality after subarachnoid hemorrhage from ruptured aneurysm. In: RH Wilkins, ed. Cerebral arterial spasm. Williams and Wilkins, Baltimore.

Weir BK, Grace M, Hansen J, Rothberg C. 1978. Time course of vasospasm in man. J. Neurosurg. 48:173-178.

Weisel RD, Berger RL, Hechtman HB. 1975. Measurement of cardiac output by thermodilution. N. Engl. J. Med. 292:682-684.

Weishaar R, Ashikawa K, Bing RJ. 1979. Effect of diltazem, a calcium antagonist, on myocardial ischemia. Am. J. Cardiol. 43:1137-1143.

Weisman I. 1939. Edema and congestion of the lungs resulting from intracranial hemorrhage. Surgery 6:717-729.

Wyse SD, Pfitzner J, Rees A, Lincoln JCR, Branthwaite MA. 1975. Measurement of cardiac output by thermal dilution in infants and children. Thorax 30:262-265.