Predictors and prognostic value of blood pressure level and variation in acute stroke

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Predictors and prognostic value of blood pressure level and variation in acute stroke

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Knowledge is a process of piling up facts, wisdom lies in their simplification.

(Martin Fisher)

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General introduction

Stroke is an important disease. In the Netherlands, there are approximately 30,000 new strokes each year.¹ Stroke ranks third at the list of death causes in Europe.¹⁻⁶ It is also one of the most prevalent causes of lasting disability, especially in the elderly.^{3-5 7-9} The cost of stroke is high: in the Netherlands the total yearly costs of stroke (medical and productivity losses) amount to 2500 million Dutch guilders.¹⁰ Furthermore, the social and psychological burden of stroke is enormous.^{11 12} With the expected relative and absolute increase of elderly people in Dutch society, the problem of stroke is likely to increase during the coming decades. Using a small number of simple assumptions, the current number of yearly strokes was rather reliably predicted almost ten years ago.¹³ The number of strokes increased despite the fact that various methods for primary or secondary stroke prevention following first stroke or TIA have been proven to be clinically effective, such as: treatment of hypertension,^{14 15} anticoagulants in patients with atrial fibrillation,¹⁶⁻¹⁸ new anti-platelet drugs beside aspirin,^{19 20} such as dipyridamole²¹ and clopidogrel,²² and carotid endarterectomy in patients with high-grade internal carotid artery stenosis.²³⁻²⁵ New anti-platelet drugs^{26 27} and statins^{28 29} are currently under clinical investigation to lower the chance of stroke, myocardial infarction, or vascular death following stroke. Besides secondary prevention, improvement of prognosis in stroke patients could come from acute stroke interventions. For the time being, however, this seems only a theoretical possibility, as none of the so-called neuroprotective drugs were proven to be successful in clinical trials.⁶ Another acute stroke intervention, which has gained clinical acceptance is thrombolysis, which lowers the risk of death or unfavourable functional outcome with approximately 30 %.³⁰⁻³³ However, for various reasons only a small minority of five to ten percent of all ischemic stroke patients will be eligible for this therapy.³⁴ Concepts on early neuroprotective interventions which may ultimately be more successful, continue to be developed and tested further. Among these are lowering of body temperature,^{33 35-37} optimising oxygen saturation,³⁵ normalising blood sugar,^{33 35 38} inhibiting nitrogen monoxide (NO) production,³⁹ and increasing central GABA activity.⁴⁰

An additional possibility to improve prognosis following stroke may be achieved by manipulating the level of blood pressure (BP) in acute stroke. There may seem a pathophysiological rationale for this, but current data conditional for clinical testing of this possibility are thin. One of the problems on the approach of blood pressure manipulation is that BP level may largely vary among stroke patients, and may depend on various factors. Therefore, a pragmatically desirable approach of a simple, uniform blood pressure treatment modality in acute stroke may be elusive; it may be beneficial to increase BP in some patients, decrease it in others, and leave it as it is in possibly even most of them. What BP values should be treated, and what BP level to aim at in such treatment remains currently enigmatic. Besides, there is a real danger should BP be treated in a uniform manner, regardless its level or without accounting for other relevant conditions. This consideration relates to the concept of cerebral autoregulation, which implies that under normal conditions regional cerebral blood flow is kept constant over a certain range of systemic BP.⁴² In stroke, this mechanism is lost,

and cerebral perfusion pressure becomes directly BP dependent.⁴²⁻⁴⁵ At high BP levels, the brain is no longer protected from the effects of extreme pressure in the capillary system. This may result in edema formation and local hemorrhages, which further threatens local blood supply with ultimately destruction of cerebral tissue.^{43 46 47} On the other end of the spectrum, low systemic BP can not be compensated for, and local perfusion pressure drops below the critical level to meet tissue demand of oxygen and glucose, which will eventually also compromise tissue viability.^{41 42 47-52} How much cerebral autoregulation is disarranged may depend on various factors, such as pre-existing BP level, any antihypertension treatment, site and size of the infarct, and concomitant factors, especially diabetes mellitus as this is known to affect autoregulation.⁴²

So far, little is known about what factors independently predict the level of BP in acute stroke or its decline, or what BP characteristics are independent predictors of stroke outcome. Before any clinical trial on BP treatment in acute stroke would be able to carefully manoeuvre between the Scylla of local cerebral hyperperfusion and Charibdys of hypoperfusion, more robust data on these issues are required. The present study was set out to explore (retrospectively) and investigate (prospectively) factors related to BP level and course in acute stroke, and various BP characteristics as independent predictors of stroke outcome at six months.

1

Introduction

Adapted from:

Boreas AMHP, Lodder J. Bloeddruk-behandeling in de acute fase van het ischemisch CVA. Ned Tijdschr Neurol 2000;6:395-399.

Blood pressure course in the acute phase of ischemic stroke

Blood pressure (BP) is elevated in 70 to 94 % of acute stroke patients.⁵³⁻⁵⁸ The highest BP values after stroke are found in patients with primary intracerebral hemorrhage, patients of black ethnic origin or patients known with hypertension before stroke.^{47 53 54 58 59} The initially elevated BP spontaneously goes down during the first week,^{54 58 60} with the greatest decline during the first four days.^{54 58 61-63} The magnitude of decline relates to the level of BP: the higher the initial BP, the greater the decline.^{42 45 54 64 65} Up to 64 % of the patients have regained prior BP level on the second day following stroke.⁵⁵ BP then gradually further declines in the first week after stroke.⁵⁵ In about 30 % of the stroke patients BP remains elevated one week after stroke occurrence.^{41 44 53} In patients known with hypertension before stroke, BP is higher than in patients without hypertension,⁶⁶ whereas BP remains higher after the acute stroke phase.^{67 68} Controls showed a similar BP course after hospital admission, but the BP level was lower than in stroke patients.⁵⁴ Britton et al. stated this might represent pre-existing higher BP in stroke patients as compared with the controls.⁵⁴ They thought it also probable that a specific physiological response to the brain damage in stroke added to the stress of acute illness and hospitalization as seen in all patients.

Admission blood pressure and prognosis

The mechanism of BP elevation in the acute phase of stroke is still unclear: acute BP elevation may be the cause of stroke in some cases, a result of the stroke, or an epiphenomenon associated with the stroke process.⁶⁹ Ideas on how BP in acute stroke may influence stroke prognosis relate to the concept of the so-called penumbra: a certain tissue volume surrounding the necrotic core, where perfusion is too low to maintain normal neuronal function, but sufficient enough to keep the neurons alive for a short period of time. Under normal physiological circumstances, cerebral blood flow (CBF) is regulated according to the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR): $CBF = CPP/CVR$. CPP represents the difference between arterial pressure forcing blood into the cerebral circulation and venous pressure. Under normal conditions, venous pressure is negligible and CPP is equal to arterial BP. Under conditions of normal CPP, changes in CBF follow changes in CVR. Because of vasoparalysis in the acute phase of stroke, the mechanism of adapting CVR fails, and blood flow in the ischemic penumbra is directly pressure dependent.⁴²⁻⁴⁵ One could postulate that, initially, elevated BP may be beneficial in increasing blood flow in the ischemic penumbra, and could be regarded as a physiological compensatory mechanism for impaired cerebral perfusion pressure.^{47 52 68} However, sustained elevation of BP may be harmful since it may lead to cerebral edema and trigger hemorrhagic transformation of the infarct,^{43 46} which may lead to further tissue destruction.⁴⁷ In the absence of autoregulatory mechanisms, low BP after stroke may directly lead to impaired local perfusion pressure with consequent further anoxic

cerebral damage.^{41 42 47-52} Based on these considerations it can be assumed that the BP level early after stroke may influence outcome, but that this may in turn depend on various conditions, such as size and time course of the penumbra, for example.

Data on prognostic significance of BP levels following acute stroke are conflicting: some studies showed no relationship between admission BP and outcome,^{46 70-73} others reported high^{42 48 50 74-76} or low⁷⁷ admission BP to be associated with poor outcome. Differences in study design may explain some of the conflicting findings: some reports only studied patients with cerebral hemorrhage⁵⁰ or mixed series with hemorrhages and infarcts⁴⁸ or even TIA's.⁴⁶ Some included patients more than a week after the acute event,^{46 75 77} which is likely beyond the period of any impact of BP level on tissue salvage or further destruction. Finally, studies differ in the way BP was recorded.⁴⁸ In studies which only used one admission BP value, the admission time after stroke onset varied widely.⁷⁵ From the point of possible manipulation of early BP to improve outcome, studies that included patients within 3 or 6 hours following stroke may be most relevant. It may look ideal to study BP recorded by an automatic BP monitoring device, but one should realize that in real life admission BP is measured 'by hand' on hospital arrival in most cases. Pragmatically, therefore, studies that analyse admission BP measured 'by hand' should not be considered of little value, on the contrary. However, various other aspects may more reliably be measured by automatic monitoring devices, such as 24-hour BP course.

24-hour blood pressure monitoring

Automatic 24-hour BP monitoring (ABPM) reduces the measurement variability and observer bias compared to casually recorded BP, and provides additional information about day-night changes in BP.^{48 59} Lip et al. showed that the first casually recorded admission BP was similar to the first 24-hour measured ABPM value, whereas the first admission BP value was higher than the mean 24-hour ABPM value.⁵⁹

It is well known that there is a diurnal pattern of BP change in normotensive persons, with morning values being higher than those recorded in the evening and with a further decrease during nighttime.⁷⁸⁻⁸³ This decrease in nighttime BP level is called 'dipping'. A number of definitions have been used to define dipping, including an arbitrarily chosen absolute fall of 10 mmHg or more between day and night systolic or diastolic BP, or a decrease of 10% or more in systolic or diastolic BP between day and night.⁸⁴⁻⁸⁶ In hypertensive patients the nocturnal dip is reduced.^{87 88} Patients who lose this diurnal variation ('nondippers') have an increased risk of hypertensive target organ damage.^{86 89} Most patients with a stroke have elevated 24-hour BP levels, with a reduced nocturnal BP fall.^{59 81 86 90 91} Patients with an intracerebral hemorrhage sometimes even have higher BP values during the night than during the day ('reverse-dippers').⁵⁹

The degree of BP variation after ischemic stroke may be related to stroke subtype and lesion site.⁸⁶ Some studies reported that especially lacunar infarcts were associated

with diminished BP variation.⁸⁸⁻⁹⁰ Dawson et al. found that diurnal systolic BP change was significantly reduced in patients with cortical infarcts and primary intracerebral hemorrhages in contrast to patients with subcortical infarcts, whereas diurnal diastolic BP was significantly reduced in all three subgroups.⁸⁶ Sander et al. observed a greater reduction in diurnal BP variation after thromboembolic infarction than after hemodynamic infarction and found that patients with insular infarction had a reduced or even abolished circadian BP variation.⁹¹⁻⁹² Yamamoto et al. addressed the diminished nocturnal BP decline to lesion site: injury to the striatum, diencephalon, midbrain and pontine tegmentum and their connecting fibers led to a diminished BP fall at night.⁹³ However, most of these studies used small patient groups,⁹⁴⁻⁹⁷ or included patients later than 24 hours after stroke onset.⁵³⁻⁹²⁻⁹³⁻⁹⁷ Furthermore, for analyses all day- and nighttime hours were joined together,⁵⁹⁻⁶⁹⁻⁸⁶⁻⁹²⁻⁹⁴⁻⁹⁸⁻¹⁰⁰ not leaving out the hours during which the BP transition between the nocturnal and diurnal period is assumed to occur.⁸² Including the BP transition values is likely to blunt any contrast between daytime and nighttime values and its possible prognostic, or any other significance. Therefore, to study the diurnal pattern of BP it may be better to include only patients with cerebral infarcts who started the 24-hour BP monitoring within 24 hours following stroke onset, and furthermore, to use as daytime values only those BP values measured between 9.00 h and 18.00 h and as nighttime values only those BP values measured between 24.00 h and 6.00 h, leaving out the period in which the BP transition presumably occurs.

24-hour blood pressure variation and prognosis

There are few data on the prognostic significance of the degree of diurnal BP variation after ischemic stroke. Schrader et al. stated that nighttime hypertension resulted in worse outcome in stroke patients.⁵² Robinson et al. found that increased 24-hour BP levels and reduced nocturnal fall in BP were related to poor outcome,⁴⁸ whereas Dawson et al. found that increased variation in diastolic and mean BP significantly related to poor outcome.⁵³ A greater fall in mean BP level within the first days was associated with worse outcome.⁵⁹ On the other hand Chamorro found that a fall of 20-30 % in BP level on the second day after stroke was associated with a better outcome.⁶⁴ Various studies focussed on the relationship between non-dipping and target organ damage.⁸⁹⁻⁹⁸⁻¹⁰¹⁻¹⁰³ Reduction in diurnal BP variation and higher nocturnal BP values may lead to more silent brain damage and may increase the number of symptomatic infarcts.⁹³⁻¹⁰⁴⁻¹⁰⁵

Since few data on the prognostic significance of 24-hour BP levels after stroke are available, we studied the relationship between diurnal BP variation in the first 24 hours after stroke and outcome at six months. Furthermore, we examined whether a fall in BP between day 0 (that is the first 24 hours) and day 4 was related to the outcome at six months.

Mechanisms of blood pressure elevation in the acute phase of stroke

The exact cause of the BP elevation in acute stroke remains unknown. The BP elevation has been attributed to several pathophysiological mechanisms. Some authors state that the elevation is a 'white coat effect' due to hospital stress.^{46 106-108} Carlberg et al. reported that casual BP levels on hospital admission had no time relationship to the stroke event during the first week, and suggested therefore that mental stress in the emergency room played a major role in the BP elevation.¹⁰⁷ The observation that mean 24-hour BP values were lower than the first recorded admission BP value could endorse this theory.⁵⁹ Others hypothesized that injury to the central autonomic nervous system which resulted in pathologically increased sympathetic activity is a major cause of BP elevation.^{91 109} Increased sympathetic activity was reflected by increased plasma catecholamine and corticosteroid levels,^{61 90 109} especially in nondippers, during night-time hours.⁹¹ A diminished sensitivity of the baroreceptor arc has also been postulated.^{53 95 97} Sander et al. provided arguments in favour of the theory that the insular cortex exerts a continuous inhibiting effect on the autonomic, sympathetic nervous system; they found that patients with an infarct in especially the right-sided insular cortex had significantly higher noradrenaline levels.⁹¹ Patients with a right-sided insular infarct also exhibited diminished diurnal BP variations.⁹⁶ A positive correlation between infarct size, the extent of insular damage, and plasma norepinephrine concentration was found. Britton et al. suggested that large lesions constituted a stimulus for reactive BP elevation,⁷⁵ whereas Carlberg et al. did not find a relationship between lesion size and BP levels.¹⁰⁷ Others stated that the BP elevation was a result of the Cushing reflex.^{46 50 59} Considering the findings that BP elevation also occurs in acute lacunar stroke,^{60 90} it is conceivable that lesion site or any cortical location does not play a major role in acute stroke BP elevation. Therefore, we hypothesized that lesion size nor site play a role, and we examined the relationship between infarct size and site and the initial level of BP and BP variation in the first 24 hours.

Treatment of blood pressure in the acute phase of stroke

The most important risk factor for a stroke event is high BP.^{2 52 110 111} The risk of stroke climbs with rising BP values in all age groups. Primary prevention studies show that a decrease of 5-6 mm Hg in diastolic BP¹¹²⁻¹¹⁵ and 10-12 mmHg in systolic BP reduces the probability of stroke with about 40 %.^{52 57 85} In isolated systolic hypertension, antihypertensive therapy reduces the stroke frequency more than one third, especially in elderly people.^{52 85 116 117} Considering antihypertensive treatment as secondary prevention in stroke, it is worth mentioning that a recent meta-analysis of 6752 stroke patients in 9 trials found that active treatment reduced the incidence of recurrent stroke by 28%.¹¹⁸ Little is known about treatment of high BP in patients with acute stroke.⁵⁷ Four small randomized controlled trials have investigated the effect of BP reduction in acute ischemic stroke, but these fail to provide evidence for a useful effect on outcome.^{44 65}

It is important to realize that none of these studies had as primary aim to study any effect of BP alteration in acute stroke on outcome. These were neuroprotection trials with drugs that besides potentially being neuroprotective, also appeared to have an effect on BP. Three of these randomized controlled trials studied calcium channel blockers (nimodipine or nicardipine) and found that these agents had a moderate effect on BP.^{68 119 120} One of these studies also found that nicardipine reduced cerebral blood flow.⁶⁸ In contrast, perindopril, an angiotensin-converting-enzyme inhibitor, reduced BP without altering internal artery blood flow or middle cerebral artery blood velocity.¹¹⁴ No large studies of BP manipulation in acute stroke have been undertaken to date.⁶⁵

In general it is recommended not to treat high BP in the acute phase of stroke because of the risk of reducing perfusion in the ischemic penumbra.^{33 62 67 68 121} Some state that there is a theoretical advantage in delaying antihypertensive therapy after stroke in that it allows recovery of the damaged cerebral vessels, thereby restoring local autoregulation, whereas collateral circulation may also be improved.⁶⁷ Others fear the theoretically detrimental effect of edema development and recommend treatment of high systemic blood pressures, which, according to most authors, is a blood pressure that exceeds 220/120 mmHg.⁵⁷ Hachinski recommends treatment if the blood pressure is over 220/130 mmHg,¹²² Oppenheimer et al. recommend treatment if systolic BP is over 200 mmHg or diastolic BP is over 120 mmHg,¹²³ and Lavin⁴³ and Strandgaard et al.¹²⁴ recommend treatment if diastolic BP exceeds 130 mmHg. The American Heart Association recommends treatment if mean arterial BP is higher than 130 mmHg, or if systolic BP exceeds 220 mmHg.¹²⁵ When using antihypertensive therapy most authors agree not to lower the BP with more than 20 %, ^{35 56} with reduction of diastolic BP values to 100-110 mmHg.^{41 43 45 52} Antihypertensive treatment is recommended in the rare cases of malignant hypertension and hypertensive encephalopathy, or when vital organs as heart or kidney are compromised by the elevated BP.^{33 43 57 62}

In general, antihypertensive treatment should not be considered during the period in which BP declines spontaneously, i.e. in the first 10 days following stroke onset.¹²⁶ Antihypertensive treatment should await the spontaneous decline in BP and only be initiated if BP remains elevated beyond the first 10 days after stroke. In patients already on antihypertensive treatment prior to stroke it may be prudent, if the used medication allows it, to withhold or reduce this antihypertensive medication for 7 to 10 days, but this issue is also still unsettled.⁵⁷ The differences between these recommendations reflect the absence of any evidence on how and when to treat BP in acute stroke. Ideally, large clinical trials should settle the issue, whether BP manipulation is of value to preserve ischemic tissue and improve prognosis in acute stroke. However, BP level varies largely in acute stroke patients,⁴¹ and prognosis is likely the result of various factors. Therefore, more knowledge on factors that influence early BP characteristics in acute stroke, and on how BP variables independently predict stroke outcome is required, before any therapeutical experiment on BP manipulation in stroke patients can rationally be performed. The studies described in this thesis aim to provide such information.

The contents of the various chapters are as follows:

Chapter 1: introduction on various aspects of BP in acute stroke.

Chapter 2: BP course and predictors of BP level following acute stroke; a retrospective evaluation.

Chapter 3: prognostic value of various BP variables in acute stroke; a retrospective exploration.

Chapter 4: prognostic value of the first BP measured after admission in acute stroke patients; a prospective exploration.

Chapter 5: prospective 24-hour BP monitoring after acute stroke: degree of diurnal BP variation and relationship of various factors with BP variation.

Chapter 6: prognostic value of various BP variables obtained prospectively by 24-hour BP monitoring after acute stroke.

Chapter 7: influence of ischemic lesion site and size on BP level in acute stroke.

Chapter 8: general discussion.

Introduction

Abstract

2

Predictors of post-stroke blood pressure level and course

Abstract

Background

Blood pressure (BP) is often elevated in acute stroke. Predictors of BP level, and BP course during the first week following stroke remain unclear. Furthermore, most studies on BP course did not consider separate stroke subtypes. Knowledge of such factors may be of relevance when manipulation of early BP levels are considered as potentially therapeutic in acute stroke.

Methods

Blood pressures were collected by reviewing BP records of 817 patients with a first-ever infarct who were admitted to a stroke unit, between 1987 and 1992. We only selected those patients who were admitted within 24 hours following stroke onset. We studied the first systolic and diastolic BP measured after admission to the stroke unit. Furthermore, we studied the mean daytime and nighttime systolic and diastolic BP, taken during the first seven days following stroke onset.

Results

Age and known hypertension before stroke were significantly associated with elevated post-stroke BP level, whereas ischemic heart disease was associated with a lower BP level. BP decline in the post-stroke period related to the degree of initial BP elevation. BP in hypertensive patients remained higher than in non-hypertensive patients during the first post-stroke week. We found no difference in initial BP level, nor the rate of BP decline from day 0 to 4 between patients with a lacunar infarct and those with an infarct involving the cortex.

Conclusion

Our findings indicate that BP increase post-stroke is not a general phenomenon, nor is BP decline in the first post-stroke week, whereas it does not depend on stroke subtype. Known hypertension is probably the strongest predictor of post-stroke BP increase.

Introduction

Blood pressure (BP) is often elevated in acute stroke, but falls spontaneously during the following days.^{42 48 56 58 62} It is unclear whether this phenomenon represents a physiological response to maintain or enhance perfusion in reversibly damaged cerebral tissue, or is merely a marker of stroke severity.^{42 47 54 64} However, increased early BP is not related to the type of event, as its incidence is similar in patients with cerebral hemorrhage, infarction, and TIA.^{63 75} However, most studies on BP course in early stroke did not consider separate stroke subtypes, or included patients at an undefined moment varying from 24 hours to 7 days after stroke onset.^{54 63 75 107} Furthermore, circadian BP changes were rarely taken into account.^{54 63 75 107} So, factors that predict BP level following stroke, BP course and circadian influence on this course remain unclear. Knowledge of such factors may be of relevance when manipulation of early BP abnormalities is considered as a potentially therapeutic option in acute stroke. Therefore, in patients who were admitted with a first cerebral infarct and who had their first BP recordings within 24 hours following stroke onset, we analysed the impact of various aspects of BP in the first week. We also explored which variables determine the level of BP in the acute phase of stroke and early BP decline.

Patients and Methods

Data collection

Blood pressure values were collected by reviewing BP records of patients registered in an ongoing stroke registry at the University Hospital of Maastricht. The University Hospital is the only hospital in the region of Maastricht and has an adherent population of approximately 190,000 people. The stroke registry contains prospective data of patients who had been admitted to the neurological department or had visited the outpatient's clinic, with a first-ever cerebral infarct with symptoms lasting longer than 24 hours. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, CT scan of the brain and noninvasive carotid artery studies. Echocardiography, 24-hour ECG monitoring and cerebral angiography were done in selected cases.

In this study, 430 patients with a first-ever infarct had been admitted within 24 hours following stroke onset. Patients admitted to hospital stayed on the stroke unit until they were neurologically stable, after which they were transferred to the general neurological ward. Blood pressure was recorded manually by experienced nursing staff with a mercury sphygmomanometer (blood pressure values at 1st and 5th Korotkoff sounds taken as systolic and diastolic, respectively). Measurement frequency depended on the individual patient's condition and no fixed schedule had been enforced. Therefore, the frequency of BP measurements per patient and per day varied. For analysis we used those BP-values that were measured within the first 24 hours after the patient was admitted to hospital and the next seven days after admittance. To adjust for the different number of BP recordings per patient per day, we took the average of three BP-values obtained be-

tween 9.00 h and 18.00 h (recordings closest to 10.00 h, 15.00 h and 18.00 h) as daytime BP values, and the average of three BP-values taken between 24.00 h and 6.00 h (closest to 24.00 h, 03.00 h and 06.00 h) as nighttime BP values. BP values registered between 6.00 h and 9.00 h and between 18.00 h and 24.00 h were not included in the analyses, because in these periods the BP-switch between the nocturnal and diurnal period is assumed to occur.⁸²

To evaluate the course of the BP during the first week after admittance, we also used BP-values of a control-group for comparison. This control-group consisted of 134 patients known with hypertension, who had been admitted to the internal ward of our hospital to analyse their hypertension. These patients received no antihypertensive medication during hospital stay. Their BP was recorded every 2 hours between 07.00 h and 23.00 h by an automatic device. The average of the systolic and diastolic BP values was registered per day, from day 0 to day 7 after admission to hospital.

Blood pressure variables

For the stroke group, we used the following variables:

- first systolic BP and first diastolic BP measured after admission to the stroke unit.
- daytime systolic BP (*DSBP*) and diastolic BP (*DDBP*), as defined above.
- nighttime systolic BP and diastolic BP, as defined above.

Definitions

Hypertension (HT) was defined as known hypertension (blood pressure recordings of more than 160 mmHg systolic and/or 90 mmHg diastolic pressure on at least two different occasions) whether or not treated with antihypertensive medication before the stroke.

Diabetes mellitus (DM) was defined as known diabetes treated with diet or medication, or either a fasting blood glucose higher than 7 mmol/l or a postprandial blood glucose higher than 11 mmol/l measured on at least two separate occasions before or at least one week after the stroke.

Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery.

A brain infarct was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin with normal CT or CT showing an area of low attenuation compatible with the clinical signs and symptoms, or autopsy revealing an infarct compatible with the clinical signs and symptoms. When CT scan had not been performed (21 of the 430 cases), we used the Guy's Hospital Stroke Diagnostic Score (Allen score): an Allen score less than four indicated a probability of 90 per cent or more that the stroke was due to infarction.^{129 130}

A lacunar infarct (*LACI*) was defined as an acute stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 15 mm (small deep infarct), or as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involved at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion. A potential cardioembolic stroke cause was not taken into account when assigning patients to this infarct subgroup. A territorial infarct was defined as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as isolated monoparesis or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in the territorial infarct group because of similar pathogenesis.

Territorial infarct patients with a potential cardioembolic stroke source were assigned to the cardioembolic stroke subgroup (*CE*). Such patients had at least one of the following cardiac features: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any other specific stroke cause: atrial septal defect, ventricle septal defect. Patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were assigned to the atherothrombotic infarct subgroup (*AT*). There were 21 patients with a 'rare' stroke cause, such as arterial dissection, vasculitis, fibromuscular dysplasia, hematological disorder, etc. Because of small numbers and heterogeneity in stroke cause, this group was not included in this study, leaving 409 patients for analysis.

The modified *Rankin* scale was used to describe the degree of functional handicap on admission (see appendix).¹³¹

Statistical analysis

To study the correlation between the different variables and BP we used a linear regression model containing the following independent variables: stroke type (*LACI* vs *CE* and vs *AT*), Rankin score on day 0 (score 3-5 vs 1,2) as a measure of stroke severity, age (<60 vs 60-75 and vs >75 years), IHD, sex, DM, and hypertension before stroke (HT). As dependent variable we used the different BP variables. We used the one-way Anova-test to study the difference between initial BP values in the various stroke subtypes and to assess the difference between the course of BP during the first week in these stroke subtypes.

Results

Patients and BP measurements

We used data of 409 consecutive registered patients who had been admitted within 24 hours (day 0) following stroke onset. In 403 patients at least one BP value was taken on day 0. Of these 403 patients, 291 had BP measurements during daytime, whereas 284 had BP measurements during the night. The number of patients with at least one BP measurement per day during the daytime was 291 on day 0 declining to 112 on day 7, whereas the number of patients with at least one BP measurement per day during the nighttime was 284 on day 0 declining to only 8 at day 7.

Only 57 patients had consecutive daily BP measurements from day 0 upto and including day 7, whereas only 7 patients had these consecutive measurements during nighttime hours. As mentioned earlier, BP measurement frequency per patient per day varied: the median number of BP values measured was 4 (range 1-19) on day 0, 7 (range 1-24) on day one, 4 (range 1-23) on day two, 3 (range 1-24) on day three, 2 (range 1-22) on day four, 2 (range 1-15) on day five, 2 (range 1-20) on day six and 2 (range 1-20) on day seven. Of the 403 patients, 34 died during the first week following stroke onset.

Patient characteristics and level of first BP readings

Table 1 shows patient characteristics for all 403 patients and for the various stroke subgroups.

Table 1: Patient characteristics for stroke subgroups (for abbreviations see text)

	Total group (N=403) N, (%)	LACI (N=106) N, (%)	CE (N=126) N, (%)	AT (N=171) N, (%)
Sex: male	196 (51)	54 (51)	46 (37)	96 (56)
female	207 (49)	52 (49)	80 (63)	75 (44)
Age: median (range)	73 (24-96)	69 (39-95)	77 (24-96)	73 (39-92)
IHD	118 (29)	29 (27)	48 (38)	41 (24)
DM	74 (18)	15 (14)	30 (24)	29 (17)
HT	189 (47)	52 (49)	61 (48)	76 (45)
Rankin at stroke onset: ≤ 3	161 (40)	71 (67)	35 (28)	55 (32)
> 3	242 (60)	35 (33)	91 (72)	116 (68)

Linear regression analysis showed that the level of first BP measured after admission was significantly associated with IHD, age and hypertension (N=403): in patients known with IHD before stroke, the first systolic and diastolic BP values were 12 and 5 mmHg, respectively, lower than in those without IHD. In patients known with hypertension before stroke, the first systolic and diastolic BP values were 16 and 8 mmHg, respectively, higher than in those without. With every year of life, systolic BP increased by 0.4 mmHg. The remaining variables, including stroke subtype and Rankin score on day 0, were not significantly associated with the first BP value (table 2).

Table 2: Association between several independent variables and level of first systolic and diastolic BP and the fall in daytime systolic BP (DSBP). Data are linear regression coefficient for the associations.

Dependent variables	Coefficient systolic BP	P-value systolic BP	Coefficient diastolic BP	P-value diastolic BP	Coefficient fall DSBP	P-value fall DSBP
Stroke type: Ce vs Laci	-6	ns	-1	ns	-4	ns
At vs Laci	-2	ns	-3	ns	-4	ns
IHD	-12	<0.0001	-5	0.002	1	ns
DM	6	ns	-0.06	ns	6	ns
Age	0.4	0.007	-0.04	ns	0.1	ns
Sex	-5	ns	-2	ns	0.01	ns
HT	16	<0.0001	8	<0.0001	8	0.04
Rankin at stroke onset						
3 vs 1,2	-0.3	ns	-1	ns	2	ns
4 vs 1,2	3	ns	-1	ns	4	ns
5 vs 1,2	-3	ns	-3	ns	10	ns

Relationship between patient characteristics and BP decline during the first few days

The extent to which nighttime systolic and diastolic BP fell between day 0 and day 4 was not significantly associated with any of the patient characteristics. The decline in daytime diastolic BP was also not significantly associated with these variables. The decline in daytime systolic BP between day 0 and day 4 showed only a significant association with priorly established hypertension: in patients with hypertension, the BP fall between day 0 and 4 was 8 mmHg greater than in patients without (table 2).

Time course of blood pressure in the first week following stroke onset

Figures 1 and 2 illustrate the time course of daytime systolic and diastolic BP in the first week after stroke onset for stroke patients and after admittance to hospital for controls. For stroke patients the greatest decline in BP was observed during the first 3 days. The nighttime systolic and diastolic BP showed a similar course (not shown).

The control group also showed a decline in BP during the first week, with a similar magnitude as in the stroke group.

Fig.1: course daytime systolic (DSBP) blood pressure in the stroke patient and the control group

Fig.2: course daytime diastolic (DDBP) blood pressure in the stroke patient and the control group

Figure 3 illustrates the daytime systolic and diastolic BP course of stroke patients with and without hypertension. 144 of the 291 patients with daytime BP registrations had hypertension before stroke; 76 % (N=109) of them used antihypertensive medication on admission. This antihypertensive medication was stopped in 17 patients on day 1. 147 of the 291 patients with daytime BP registrations were without hypertension before stroke; 32 % (N=47) of these used blood pressure lowering medication at admission, mainly for cardiac failure. In 4 patients this medication was stopped at day 1. BP during the first week was higher in patients with hypertension than in those without hypertension. This difference in BP level was also evident when the nighttime systolic and diastolic BP values were analysed separately.

Fig. 3: course of daytime systolic (DSBP) and diastolic (DDBP) BP

Figure 4 shows the time course of daytime systolic BP, when patients were divided into three equal parts ('tertiles') on the basis of their BP on day 0. 65% of the patients in the upper tertile group were known with hypertension at stroke onset, 56 % of them used antihypertensive medication at day 0. BP in this upper tertile group showed the greatest decline, but BP at the end of the week was still higher than in the other two groups. Daytime diastolic, nighttime systolic and diastolic BP values on day 0 divided in tertiles, showed a similar pattern.

Fig.4: course daytime systolic blood pressure (DSBP)

Figure 5 shows the daytime systolic BP course for the different stroke subtypes. There was no significant difference in initial BP level nor in the course of BP between these different stroke subgroups.

Fig.5: course daytime systolic BP for the stroke subtypes

		Laci		Ce		At		
Laci (N)	74	53	51	43	40	39	39	26
Ce (N)	89	74	68	62	60	55	54	35
At (N)	128	108	90	62	79	78	70	51

N = number of patients per day following stroke onset

Discussion

Blood pressure (BP) is often elevated following hospital admission because of a stroke, but falls spontaneously during the following days.^{42 48 56 58 62 67} Such a decline in BP, however, also occurs in patients without a stroke. Some data suggest that high post-stroke BP is associated with unfavourable outcome.^{42 46 74 75} If this is true, than modifiable factors which determine post-stroke BP elevation, may potentially be therapeutically useful. We explored such factors and found age and known hypertension to be predictors of an elevated post-stroke BP level, whereas ischemic heart disease was a determinant of a lower BP. BP lowering drugs given for ischemic heart disease may explain the latter finding, as one third of our patients used such drugs. Surprisingly, early post-stroke BP was elevated in patients with known hypertension, even though about three quarters of them used BP lowering drugs. In addition, BP remained higher than in non-hypertensive patients during the first post-stroke week. Post-stroke BP elevation may be caused by an increase in adrenal hormones, but this is unlikely to be the sole mechanism.^{47 61 90 96 109} Impaired baroreceptor sensitivity after stroke could also play a role.^{95 132} Hypertensive patients are also more sensitive to sympathetic stimulation,^{44 91 97} and this could well account for BP elevation following stroke in such patients. Such elevation occurred despite antihypertensive drug treatment in our study. Our data further show that the BP decline in the post-stroke period is related to the initial BP elevation. Therefore, if an elevated post-stroke BP is to affect outcome unfavourably, in a therapeutic experiment only elevated BP should be lowered.

Some suggest that site and size of the lesion may be related to BP elevation following stroke.^{43 63 69 75} However, we found no difference in initial BP level, nor the magnitude of BP decline, between patients with lacunar infarcts and those with infarcts involving the cortex, regardless of whether the latter were caused by cardiac embolism or by large artery thromboembolism. This argues against an important role of certain cortical areas or the degree of cerebral tissue damage in causing post-stroke BP elevation.^{91 92 109}

An obvious limitation of our study is its retrospective character. Thus, the frequency with which BP measurements were obtained may have been dictated by the number of priorly measured abnormal BP values. This may have caused bias towards more frequent detection of higher BP values. Therefore, prospective BP measurements, using a rigid protocol, in a large stroke series are required to verify our data. For the time being, however, we may conclude that an increase in post-stroke BP is not a general phenomenon, nor is the decline in BP in the first week post-stroke. Known hypertension is probably the strongest predictor of a post-stroke BP increase.

3

Prognostic value of blood pressure in acute stroke

Submitted.

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Abstract

Background

Manipulation of blood pressure (BP) in acute stroke may improve outcome. Despite various studies, data on the prognostic significance of early BP in stroke remain unclear. Therefore, we studied the relationship between various BP variables in the acute phase of stroke and functional outcome at three months.

Methods

BP values were collected by reviewing BP records of 817 patients who were admitted to our stroke unit. Besides the first systolic and diastolic admission BP (SBP and DBP), we also used the mean of the daytime as well as the mean of the nighttime systolic and diastolic BP values. Finally, we studied the relationship between the decrease in BP between day 0 and 4 and outcome. As dependent outcome variable we used the Rankin handicap score at three months dichotomized in a score > 3 (poor outcome) versus a score ≤ 3 (good outcome).

Results

409 patients were admitted within 24 hours following stroke onset. Only nighttime systolic BP ≥ 165 mmHg (OR 2.8; 95% CI 1.1-6.8), nighttime diastolic BP ≤ 60 mmHg (OR 8.1; 95% CI 1.1-58.3), and a decrease in daytime diastolic BP between day 0 and 4 of ≥ 10 mmHg (OR 3.0; 95% CI 1.1-7.9) showed a significant relationship with poor outcome. The rest of the BP variables did not show a significant relationship with functional outcome at three months.

Conclusions

Our findings suggest that admission BP values may not reliably reflect any impact of BP on stroke outcome. They also suggest a potential differential effect of BP manipulation: increasing or decreasing BP may be beneficial for patients with BP extremes in one direction, but detrimental for those with BP values in the opposite direction.

Introduction

A transient increase in arterial blood pressure (BP) frequently occurs in patients with acute stroke.^{44 48 64} This could be a physiological response to maintain or enhance perfusion of reversibly damaged cerebral tissue, when normal autoregulatory mechanisms are impaired.⁶⁷ However, the general benefit of such a response could be questioned, as high BP in the early phase has been linked to poor outcome, particularly in patients with impaired consciousness.^{46 65} In a recent overview Bath reported that some studies failed to establish a relationship between admission BP and outcome,^{70 71} although low systolic pressure may be associated with poor outcome.^{44 65} Most series so far included only single admission BP readings to study outcome.^{46 74 76 77 133} Moreover, BP was not always studied as an independent predictor.⁷⁷ A single admission BP value may not reflect the extent to which BP changes over time may influence outcome, especially since the ischemic penumbra may be present for a prolonged period of time. Furthermore, variations in BP occur as a result of diurnal rhythm. Earlier studies reported that patients with a blunted fall in nighttime BP are more likely to suffer hypertensive target-organ damage, which would mean that BP during sleep is more closely related to target-organ damage than BP in the awake state.^{85 86 89 92 99} Therefore, in the present study, we analysed various BP characteristics (including daytime and nighttime BP values) as independent predictors of outcome at three months in patients admitted to a stroke unit within 24 hours following stroke onset. We also explored whether a drop in BP values during the first four days was related to outcome.

Patients and Methods

Data collection

Blood pressure values were collected by reviewing BP records of patients registered in an ongoing stroke registry at the University Hospital of Maastricht. The University Hospital is the only hospital in the region of Maastricht and has an adherent population of approximately 190,000 people. The stroke registry contains data of patients who had been admitted to the neurological department or had visited the outpatient's clinic, with a first-ever clinical cerebral infarct with symptoms lasting longer than 24 hours. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, CT scan of the brain and noninvasive carotid artery studies. Echocardiography, 24-hour ECG monitoring and cerebral angiography were done in selected cases.

In this study, 430 patients with a first-ever infarct had been admitted within 24 hours following stroke onset. Patients admitted to hospital stayed on the stroke unit until they were neurologically stable, after which they were transferred to the general neurological ward. Blood pressure was recorded manually by experienced nursing staff with a mercury sphygmomanometer (blood pressure values at 1st and 5th Korotkoff sounds taken as systolic and diastolic, respectively). Measurement frequency depended on the individual patient's condition and no fixed schedule had been enforced. Therefore,

the frequency of BP measurements per patient and per day varied. For this study we only used those BP values that were obtained during the first 24 hours after admission. To adjust for the different number of BP recordings per patient per day, we took the average of three BP-values recorded between 9.00 h and 18.00 h (recordings closest to 10.00 h, 15.00 h, and 18.00 h) as daytime BP values, and the average of three BP-values taken between 24.00 h and 6.00 h (closest to 24.00 h, 3.00 h and 6.00 h) as nighttime BP values. BP values registered between 6.00 h and 9.00 h and between 18.00 h and 24.00 h were not included in the analyses, because in these periods it is assumed that the BP-switch between the nighttime and daytime period occurs.⁸² We also analysed the first blood pressure taken after admission to the stroke unit.

Outcome measures

All patients were studied as part of a long term follow-up study of stroke. For the present study the score on the Rankin handicap-scale at three months was used as outcome variable (see appendix).¹³¹ The score was dichotomized into a score >3 (poor outcome) versus a score ≤ 3 (good outcome).^{134 135}

Blood pressure variables

We explored the following variables:

- first systolic BP (*first SBP*) and first diastolic BP (*first DBP*) measured after admission to the stroke unit.
- daytime systolic BP (*daytime SBP*) and diastolic BP (*daytime DBP*), as defined above.
- nighttime systolic BP (*nighttime SBP*) and diastolic BP (*nighttime DBP*), as defined above.

Definitions

Hypertension (HT) was defined as known hypertension (blood pressure recordings of more than 160 mmHg systolic and/or 90 mmHg diastolic pressure on at least two different occasions) whether or not treated with antihypertensive medication before the stroke.

Diabetes mellitus (DM) was defined as known diabetes treated with diet or medication, or either a fasting blood glucose higher than 7 mmol/l or a postprandial blood glucose higher than 11 mmol/l measured on at least two separate occasions before or at least one week after the stroke.

Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery.

A brain infarct was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no apparent cause other

than that of vascular origin with normal CT or CT showing an area of low attenuation compatible with the clinical signs and symptoms, or autopsy revealing an infarct compatible with the clinical signs and symptoms. When CT scan had not been performed (21 of the 430 cases), we used the Guy's Hospital Stroke Diagnostic Score (Allen score): an Allen score less than four indicated a probability of 90 per cent or more that the stroke was due to infarction.^{129 130}

A lacunar infarct (*LACI*) was defined as an acute stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 15 mm (small deep infarct), or as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involved at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion. A potential cardioembolic stroke cause was not taken into account when assigning patients to this infarct subgroup.

A territorial infarct was defined as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as isolated monoparesis or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in the territorial infarct group because of similar pathogenesis.

Territorial infarct patients with a potential cardioembolic stroke source were assigned to the cardioembolic stroke subgroup (*CE*). Such patients had at least one of the following cardiac features: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any other specific stroke cause: atrial septal defect, ventricle septal defect. Patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were assigned to the atherothrombotic infarct subgroup (*AT*). There were 21 patients with a 'rare' stroke cause, such as arterial dissection, vasculitis, fibromuscular dysplasia, hematological disorder, etc. Because of small numbers and heterogeneity in stroke cause, this group was not included in this study, leaving 409 patients for analysis.

Statistical analysis

For analysis we used a logistic regression model containing the following independent variables: stroke type (*LACI* vs *CE* and vs *AT*), Rankin score on day 0 (score 3-5 vs 1,2) as a measure of stroke severity scale, age (<60 vs 60-75 and vs >75 years), IHD, sex, DM, hypertension before stroke (HT) and the various BP variables. As dependent

outcome variable we used the Rankin handicap score at three months, dichotomized in a score > 3 vs a score ≤ 3.

To determine the cut-off points for the different BP values we used the following method:

1. The Rankin score at three months was dichotomized into a score > 3 vs ≤ 3.
2. The patients were sorted in ascending order by their blood pressure.
3. For patients with the same BP, the mean of the dichotomized Rankin score was calculated; this new mean Rankin value was subsequently assigned to all patients with this same BP.
4. The moving averages of the new mean Rankin scores were calculated, using a group size of 101 patients.¹³⁶
5. As the calculated average could be interpreted as an estimate of the probability of an outcome with a Rankin score > 3, the Odds of this average was calculated by dividing the average by one minus the average.
6. The logOdds was plotted against the value of the blood pressure of the 51th patient of the concerning average.

Based upon these plots, the BP data were divided into three parts: the cut-off points were established at 10 mmHg below and 10 mmHg above the BP-value that went together with the lowest logOdds. The BP data were put into the multivariate logistic regression model. By changing the cut-off points by adding or subtracting 5 mmHg, we tried to determine which cut-off points showed the most significant relationship with outcome.

Results

409 patients were admitted within 24 hours following stroke onset (designated as day 0). 403 patients had BP values registered during these first 24 hours. Only 291 patients had BP measurements during the daytime, whereas 284 had BP measurements during the nighttime on day 0. Table 1 shows the distribution of the independent variables between the different stroke subtype groups.

Table 1: Patient characteristics in stroke subgroups (for abbreviations see text)

	Total group (N=403) N, (%)	LACI (N=106) N, (%)	CE (N=126) N, (%)	AT (N=171) N, (%)
Sex: male	196 (51)	54 (51)	46 (37)	96 (56)
female	207 (49)	52 (49)	80 (63)	75 (44)
Age: median (range)	73 (24-96)	69 (39-95)	77 (24-96)	73 (39-92)
IHD	118 (29)	29 (27)	48 (38)	41 (24)
DM	74 (18)	15 (14)	30 (24)	29 (17)
HT	189 (47)	52 (49)	61 (48)	76 (45)
Rankin at stroke onset:				
≤ 3	161 (40)	71 (67)	35 (28)	55 (32)
> 3	242 (60)	35 (33)	91 (72)	116 (68)

Figure 1 and 2 display the relationship between the logOdds (Rankin at three months > 3 vs ≤ 3) and the different first systolic and diastolic BP values. These plots suggest that both low and high BP values are associated with poor outcome (Rankin score > 3). According to the plot, cut-off SBP values that were used for further analysis were chosen as 130 and 150 mmHg. However, when fed into the logistic regression analysis, these values did not show a significant relationship with the outcome at three months. Shifting the cut-off points by adding or subtracting 5 mmHg did not improve the relationship with outcome (table 2). Similarly, there was no significant relationship with the outcome for DBP values (table 2). By analysing the daytime and nighttime systolic and diastolic BP values in the same way, we found that a nighttime systolic BP ≥ 165 vs 131-164 mmHg and a nighttime diastolic BP ≤ 60 vs 61-109 mmHg reached statistical significance as an independent predictor of stroke outcome with an OR of respectively 2.8 and 8.1 (table 3).

Fig.1: The logOdds of the moving average of the dichotomized Rankin (>3 vs ≤ 3) plotted against the SBP

Fig.2: The logOdds of the moving average of the dichotomized

Rankin (>3 vs ≤3) plotted against the DBP

Table 2: Relationship between first BP variables and outcome: Rankin > 3 vs ≤ 3.

first BP-values (mmHg)	OR	95% CI	P-value
first SBP ≤ 130 (N=97) vs 131-149 (N=74)	1.1	0.4-2.8	ns
≥ 150 (N=232) vs 131-149	1.4	0.6-3.3	ns
first DBP ≤ 90 (N=265) vs 91-109 (N=92)	1.1	0.5-2.4	ns
≥ 110 (N=46) vs 91-109	2.1	0.7-6.3	ns

Abbreviations: OR=odds ratio, CI= confidence interval

Table 3: Relationship between the daytime and nighttime BP variables and outcome: Rankin > 3 vs ≤ 3.

BP- values (mmHg)	OR	95% CI	P-value
daytime SBP ≤ 145 (N=157) vs 146-164 (N=57)	0.7	0.3-1.9	ns
≥ 165 (N=77) vs 146-164	1.1	0.4-3.3	ns
daytime DBP ≤ 100 (N=262) vs 101-119 (N=24)	1.0	0.3-3.5	ns
≥ 120 (N=5) vs 101-119	0.1	0.01-2.4	ns
nighttime SBP ≤ 130 (N=85) vs 131-164 (N=129)	1.3	0.6-3.1	ns
≥ 165 (N=70) vs 131-164	2.8	1.1-6.8	0.03
nighttime DBP ≤ 60 (N=12) vs 61-109 (N=264)	8.1	1.1-58.3	0.03
≥ 110 (N=8) vs 61-109	1.5	0.2-12.7	ns

Abbreviations: OR= odds ratio, CI= confidence interval.

By testing the relationship between the decrease in BP values between day 0 and 4, and stroke outcome at three months, only a decrease in daytime diastolic BP of ≥ 10 mm Hg showed a significant relationship with outcome: OR 3.0 (table 4).

Table 4: Relationship between the decrease in BP variables and outcome: Rankin >3 vs ≤ 3 .

decrease in BP variables (mmHg)	OR	95% CI	P-value
DSBP ≤ 0 (N=53) vs 1-19 (N=53)	1.4	0.5-4.1	ns
≥ 20 (N=74) vs 1-19	2.2	0.8-6.0	ns
DDBP ≤ -5 (N=34) vs -4-9 (N=53)	3.4	1.0-11.9	ns
≥ 10 (N=93) vs -4-9	3.0	1.1-7.9	0.03
NSBP ≤ 5 (N=28) vs 6-24 (N=16)	1.8	0.3-11.2	ns
≥ 25 (N=12) vs 6-24	1.2	0.1-9.2	ns
NDBP ≤ 0 (N=24) vs 1-19 (N=20)	3.2	0.5-20.6	ns
≥ 20 (N=12) vs 1-19	0.8	0.1-7.3	ns

Abbreviations: OR= odds ratio, CI= confidence interval

Discussion

Our data on the first post-stroke BP measurements suggest that high systolic and low diastolic values are associated with unfavourable outcome. Other studies also found that extreme BP values towards the lower^{58 65} and higher^{42 46 74 75} end may be related with poor stroke outcome. However, after we adjusted for other prognostic variables, first measured BP levels could not be identified as independent predictors of outcome. These findings warn against unadjusted analyses of first post-stroke BP as outcome predictor.

Nighttime BP values may have a stronger predictive value for end-organ damage than daytime values.^{82 85 86 89 92 99 105 137} A differential effect might also exist in relation to stroke outcome. Moreover, instead of analysing a single measurement such as the first one post-stroke, using several BP measurements may more reliably reflect any impact of BP level on brain tissue damage or salvage.^{48 59 85 88} Therefore, we studied a number of daytime and nighttime BP values in separate analyses. Especially high nighttime systolic and low nighttime diastolic values were identified as independent predictors of stroke outcome. These data suggest that sustained nighttime BP values that are either extremely low or high are prognostically unfavourable.

If high BP values relate to poor outcome, it seems logical to improve prognosis by lowering blood pressure. However, our data suggest that a spontaneous BP decrease in the first five days may be independently related to poor outcome. Others also found BP decreases to be related to an unfavourable prognosis.^{64 65} These findings warn against a too rigorous lowering of early post-stroke BP in future clinical trials.

Bias may come from our study's retrospective character: the number of BP measurements may relate to the measured BP level: extremely high and low values may dictate the number of the subsequent BP measurements. This could have created bias

towards an increased chance of detecting extreme values, overestimating the strength of association between these values and outcome. Therefore, we analysed the significance of admission BP separately.

We analysed early post-stroke BP values from the perspective of a potentially salvageable penumbra during this period, as any BP-related adverse effects on the brain may be amenable by early intervention.^{42 57} Our data do not contradict the idea of therapeutic manipulation of post-stroke blood pressure. Indeed, lowering a very high BP may be beneficial, provided it is not lowered too drastically, while conversely increasing a low BP may confer benefit as well.⁶⁵ Nevertheless, therapeutic BP manipulations should only cautiously be explored, on an individual patient basis. Furthermore, a single, first post-stroke BP measurement is probably not sufficient to rely on for such clinical trials. Multiple measurements may more reliably guide any BP manipulation, but as this takes time, it may preclude the advent of any therapeutic effect.

4

Admission blood pressure in acute ischemic stroke: relationship with stroke subtype, and prognostic value

Abstract

Background

Manipulation of blood pressure (BP) in acute stroke may improve outcome. Data on the prognostic significance of early BP in acute stroke remain unclear. We explored predictors of BP rise in acute ischemic stroke, and studied the level of admission BP as an independent predictor of stroke outcome.

Methods

BP values were collected prospectively in 271 patients admitted to our stroke unit within 24 hours following stroke onset. BP values were measured manually directly after arrival at the first aid ward. As outcome measure we used the score on the Rankin handicap scale at six months (Rankin > 3 as poor outcome versus Rankin ≤ 3 as good outcome).

Results

Linear regression analysis showed that patients known with hypertension before stroke, males, and patients known with asymptomatic lacunar infarcts on CT had significantly higher first BP values, whereas patients known with ischemic heart disease had significantly lower first BP values. Univariate analysis suggested that low and high BP values were related to poor outcome, but logistic regression analysis showed no significant relationship between BP measured in acute stroke and outcome.

Conclusion

Hypertension is a strong predictor of raised BP in the acute phase of stroke. BP elevation is not related to stroke severity or stroke subtype. Furthermore, our data do not favour BP manipulation to serve as a potential therapy for acute stroke in general.

Introduction

Blood pressure (BP) is elevated in 70-90 % of acute stroke patients.⁵³⁻⁵⁸ Elevation of admission BP has been related to stroke deterioration, mortality, or the combined end-point 'death or severely disabled'.^{42 48 50 74-76} Others, however, did not find a relationship between admission BP level and stroke outcome.^{46 70-73} Differences between study results may relate to differences in selection of stroke subtypes, definition of end-points, method of BP measurement, and whether early BP level was studied as an independent outcome predictor. If elevated admission BP could predict prognosis, it would be rational to study whether early BP lowering would improve prognosis. The Blood Pressure in Acute Stroke Collaboration (BASC) tries to find evidence on any therapeutic effect of early BP manipulation from acute stroke trials that used vasoactive drugs.¹²⁶ Both such evidence and the certainty that early elevated BP act as an independent stroke outcome predictor is required before an intervention study can be rationally planned. For various reasons, it would be desirable to restrict an intervention trial to those patients who would most likely benefit from the intervention. Considering neuroprotection in acute stroke, some have suggested to exclude patients with a lacunar infarct from trials, as it is unlikely that a significant salvageable penumbra volume exists in such patients.¹³⁸ In ischemic stroke, early BP rise was related to large infarcts involving the insular cortex and even more strongly when these are located in the right hemisphere.^{91 96} Therefore, patients with a lacunar infarct may differ from those with a cortical infarct with respect to early BP increase and its relevance for stroke outcome. However, lacunar stroke has rarely been studied as a separate entity in this respect.

The aim of our study was to explore predictors of BP rise in acute ischemic stroke, with special reference to lacunar stroke, and to study the level of admission BP as an independent predictor of stroke outcome.

Patients and Methods

Data collection

Between 1 January 1996 and 1 March 2000, data of patients with a stroke who were admitted to our hospital or visited the outpatient's clinic, were prospectively collected in an ongoing stroke registry at the University Hospital of Maastricht. The University Hospital is the only hospital in the Maastricht region and has an adherent population of approximately 200,000 people. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, brain CT scan and carotid artery ultrasound studies. Echocardiography, 24-hour ECG monitoring and cerebral angiography were done in selected cases.

In this prospective study, 676 patients with a symptomatic ischemic stroke were admitted to our stroke unit within 24 hours following stroke onset. 516 patients of this group had a first brain infarct, whereas 160 patients had a recurrent infarct. In 271 of these 676 patients we collected 24-hour BP values prospectively. The fact that of the 676 patients

only 271 (40 %) entered the study was mainly due to the availability of only two automatic monitoring devices. However, patient characteristics of the study group and of patients not included were rather similar (see table 1). Besides 24-hour BP values, we collected the first BP measured after arrival on the first aid ward: this BP was recorded manually by experienced nursing staff with a mercury sphygmomanometer (blood pressure values at 1st and 5th Korotkoff sounds taken as systolic and diastolic, respectively). As outcome measure we used the score on the Rankin handicap-scale at six months (see appendix).¹³¹ The score was dichotomized into a score > 3 (poor outcome) versus a score ≤ 3 (good outcome).^{134 135}

Table 1: Patient characteristics of patients included in the study (N=271) and those who were not (N=405). (for abbreviations see text)

	Study group (N=271) N, (%)	Remaining patients (N=405) N, (%)
Age median (range)	74 (35-98)	74 (18-97)
Gender: male	146 (54)	200 (49)
female	125 (46)	205 (51)
HT +	141 (52)	182 (45)
IHD +	91 (33)	125 (31)
Stroke type: LACI	66 (24)	106 (26)
CE	57 (21)	88 (22)
AT	148 (55)	211 (52)
DM +	47 (17)	72 (18)
CNS at admission:		
≤ 2	25 (9)	37 (9)
> 2 and ≤ 4	34 (13)	62 (15)
> 4 and ≤ 6	46 (17)	56 (14)
> 6 and ≤ 8	87 (32)	110 (27)
> 8 and ≤ 10	79 (29)	140 (35)

Blood pressure variables

We explored the following variables:

- the first systolic (*first SBP*) and diastolic (*first DBP*) BP.

Definitions

Hypertension (HT) was defined as known hypertension (blood pressure recordings of more than 140 mmHg systolic and/or 90 mmHg diastolic pressure on at least two different occasions) whether or not treated with antihypertensive medication before the stroke.¹²⁷¹²⁸ Patients without known BP values, were considered hypertensive when treated with antihypertensive drugs.

Diabetes mellitus (DM) was defined as known diabetes treated with diet or medication, or either a fasting blood glucose higher than 7 mmol/l or a postprandial blood glucose higher than 11 mmol/l, measured on at least two separate occasions before or at least one week after the stroke.

Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery.

A *brain infarct* was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin with normal CT or CT showing an area of low attenuation compatible with the clinical signs and symptoms, or autopsy revealing an infarct compatible with the clinical signs and symptoms.

A *lacunar infarct (LACI)* was defined as an acute stroke syndrome with a CT lesion compatible with the occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 15 mm (small deep infarct), or as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involved at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion. A potential cardioembolic stroke cause was not taken into account when assigning patients to this infarct subgroup.

A *territorial infarct* was defined as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as isolated monoparesis or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct or a (non-lacunar) brainstem infarct were included in the territorial infarct group because of similar pathogenesis.

Territorial infarct patients with a potential cardioembolic stroke source were assigned to the cardioembolic stroke subgroup (*CE*). Such patients had at least one of the following cardiac features: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any other specific stroke cause: atrial septal defect, ventricle septal defect. Patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were assigned to the atherothrombotic infarct subgroup (*AT*). Patients with a 'rare' stroke cause, such as arterial dissection, vasculitis, fibromuscular dysplasia, hematological disorder, etc. were not included in the study because of small numbers and heterogeneity in stroke cause.

An infarct was considered *asymptomatic* if located in an area that could not account for the neurological signs and symptoms, whereas the radiologically estimated age was not consistent with the time of clinical symptoms of the index stroke (old lesions being more hypodense, more sharply delineated, or showing signs of retraction of brain structures

towards the lesion site on CT).

Leukoaraiosis (LA) on CT was defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, and with ill-defined margins to distinguish them from infarction.¹³⁹ Stroke severity on admission was scored using the *Canadian Neurological Scale (CNS)* (see appendix).¹⁴⁰

Statistical analysis

To analyse the relationship between the various BP variables and the outcome at six months we used a logistic regression model containing various combinations of the following independent variables: stroke type (as described above), CNS (as described above) or Rankin score at admission (Rankin 3, 4 or 5 vs 1 and 2), age (similar as above), IHD, gender, DM, hypertension before stroke and the various BP values as independent variables.

As dependent outcome variable we used the Rankin handicap score at six months, dichotomized in a score > 3 vs a score ≤ 3 .

To determine the cut-off points for the different BP values we used the following method:

1. The Rankin score at six months was dichotomized as mentioned above.
2. The patients were sorted in ascending order by their blood pressure.
3. For patients with the same BP, the mean of the dichotomized Rankin score was calculated; this new mean Rankin value was subsequently assigned to all patients with this same BP.
4. The moving averages of the new mean Rankin scores were calculated, using a group size of 101 patients.¹³⁶
5. As the calculated average could be interpreted as an estimate of the probability of an outcome with a Rankin score > 3 , the Odds of this average was calculated by dividing the average by one minus the average.
6. The logOdds was plotted against the value of the blood pressure of the 51st patient of the concerning average.

Based upon these plots, the BP data were divided into three parts with cut-off points at 10 mmHg below and 10 mmHg above the BP-value that went together with the lowest logOdds. The BP data were put into the multivariate logistic regression model. By changing the cut-off points by adding or subtracting 5 mmHg, we explored which cut-off points showed the most significant relationship with outcome.

Results

Of the 271 patients, 209 had a first-ever infarct, and 62 patients had a recurrent infarct. First of all we performed a linear regression analysis in which we entered age, gender and stroke type (first-ever infarct versus recurrent infarct) as independent variables and the

first BP as dependent variable. This analysis showed no significant association between the two stroke types and the level of admission BP. For this reason, we used the first and recurrent infarcts together for the remaining analyses.

Table 2 shows associations between several independent variables and the level of the different BP variables. For every year of life, the SBP rose 0.7 mmHg. BP was significantly higher in males than in females. Patients with IHD had significantly lower first BP. Patients known with hypertension had a significantly higher SBP than patients without. Patients with asymptomatic lacunar infarcts on CT had higher first BP. Stroke type (LACI vs CE and vs AT) had no significant relationship with the level of first BP.

Table 2: Association between several independent variables and the level of the BP measured within the first 24 hours after admittance (N=271). Data are linear regression coefficient for the associations.

	SBP	P-value	DBP	P-value
Age (years)	0.7	0.0001	-	ns
Gender: male	11.2	0.03	7.0	0.003
IHD	-10.3	0.02	-5.5	0.02
HT	9.5	0.03	-	ns
Asymptomatic lacunar infarcts on CT	10.2	0.04	9.2	0.003

Figure 1 illustrates the relationship between the logOdds (Rankin at six months > 3 vs ≤ 3) and the first systolic BP. According to the plot, cut-off SBP values that were used for further analyses were chosen as 135 and 155 mmHg. When fed into the logistic regression analyses, these values did not show a significant relationship with the outcome at six months. Shifting the cut-off points by adding or subtracting 5 mmHg did not reveal any significant relationship with outcome either (table 3). Similar analyses for DBP showed no significant relationship with outcome.

Fig.1: The logOdds of the moving average of the dichotomized Rankin (>3 vs ≤3) plotted against the SBP

Table 3: Relationship between first BP variables registered within 24 hours following stroke onset and outcome at 6 months: Rankin > 3 vs ≤ 3.

First BP-values (mmHg)	OR	95% CI	P-value
SBP ≤ 135 (N= 32) vs 136-154 (N=59)	0.4	0.1-1.4	ns
≥ 155 (N=180) vs 136-154	0.7	0.3-1.6	ns
DBP ≤ 80 (N=72) vs 81-99 (N=85)	2.0	0.9-4.4	ns
≥ 100 (N= 114) vs 81-99	1.5	0.7-3.1	ns

Abbreviations: OR= odds ratio, CI= confidence interval

Figure 2 illustrates the relationship between the logOdds and the first systolic BP for a subgroup of patients who were admitted to the hospital within 3 hours after stroke onset (N=138). This plot suggests that particularly high SBP values are associated with poor outcome (Rankin score > 3). However when fed into the multivariate logistic regression analyses, these values did not show a significant relationship with outcome at 6 months (see table 4). Similarly, there was no significant relationship with outcome for first DBP values measured within 3 hours after stroke onset.

Fig.2: The logOdds of the moving average of the dichotomized Rankin (>3 vs ≤3) plotted against the SBP

Table 4: Relationship between first BP variables registered within 3 hours following stroke onset and outcome at 6 months: Rankin >3 vs ≤3.

First BP-values (mmHg)	OR	95%CI	P-value
SBP ≤ 150 (N=53) vs 151-169 (N=19)	1.8	0.5-6.7	ns
≥ 170 (N=66) vs 151-169	1.6	0.4-6.3	ns
DBP ≤ 90 (N=75) vs 91-109 (N=39)	1.7	0.7-4.3	ns
≥ 110 (N=24) vs 91-109	1.5	0.4-5.3	ns

Abbreviations: OR= odds ratio, CI= confidence interval

Discussion

We studied factors related to admission BP level within 24 hours following ischemic stroke, and whether or not the level of BP is an independent predictor of outcome at six months. We found known hypertension and silent lacunar infarcts to be independently associated with BP level. Others also found known hypertension as a strong predictor of raised post-stroke BP.^{53 54} Various factors may contribute to the BP rise, such as 'mental stress',^{46 106-108} elevated cortisol levels,^{61 90 109} impaired cardiac baroreceptor sensitivity,^{53 95 97} and sympathetic-parasympathetic imbalance.⁹¹ Patients with hypertension may be more prone to act with sympathetic overshoot, or be more liable to increased sympathetic activity.⁹⁶ There may be a sex difference in this respect, as we found BP level to be associated with male gender. Antihypertensive treatment does not seem to alter the

increased response of BP, as such treatment was not related to admission BP level in our patients. However, we cannot exclude the possibility that depending on their mode of action, some drugs may have affected the magnitude of the BP increase. Our finding that a history of ischemic heart disease was inversely related to BP level may be explained by latent concomitant heart failure or the use of cardiodepressive medication.

We did not find the BP increase to be related to stroke severity or stroke subtype. Others also could not establish a relationship between stroke severity or lesion size and BP elevation.¹⁰⁷ Morfis found the greatest BP rise in lacunar stroke patients, but this group consisted of only 18 patients.⁶⁰ Our findings seem to contradict the conclusions of Sander et al. who found infarct involvement of the insular cortex to be significantly associated with BP rise.⁹¹⁻⁹⁶ They concluded that the insular cortex exerts a tonic sympathetic inhibitory function, which is decreased by ischemic lesioning of that area. However, the discrepancy between Sander's studies and our results may be explained by assuming that the balance between sympathetic and parasympathetic neural outflow depends on regulatory circuits rather than on the integrity of a single gyrus, which may, however, play a dominant role. Damage anywhere along the circuit may result in a disbalance. Our finding that leukoaraiosis and especially 'silent' lacunar infarcts were associated with a higher BP may support this contention. A more detailed clinico-anatomical correlation study may provide further evidence in this respect (see chapter 7).

Various studies have related admission BP to outcome.^{42-46, 48-50, 70-77} Few also analysed BP as an independent predictor, accounting for differences in other important prognostic variables.^{46-48, 72-76, 77} Some studies looked at short term stroke deterioration, which may not necessarily predict eventual functional outcome.⁴⁶⁻⁷⁵ Chamorro, in a series of 481 ischemic stroke patients, found higher mean BP at baseline to be independently related to good functional outcome at one week.⁶⁴ On the contrary, Robinson found a worse 30-day functional outcome in 136 patients with elevated admission BP.⁴⁸ In our 271 ischemic stroke patients, we found no significant association between the admission BP and outcome at six months when data were adjusted for possible confounders. When we restricted the analysis to patients admitted within 3 hours, the moving average plot suggested a U shape relation between BP and outcome, but multivariate regression analysis did not show a relationship between this BP and functional outcome at six months. Theoretically, low BP may, in the presence of impaired autoregulation, lead to hypoperfusion in a threatened penumbra,^{41-42, 47-52} whereas elevated BP may lead to edema formation and hemorrhagic transformation, thereby increasing tissue destruction.^{43-46, 47} Our data do not support the idea of a simple, general treatment modality for all stroke patients. According to our U-shaped moving average plots, they rather suggest that elevation of low BP and lowering of high BP should be tested separately. BP values in the intermediate range may not be amenable for therapeutic intervention. A limitation of our study is its relative small size, especially when testing three separate groups based on BP level and therefore our results have to be confirmed or refuted by larger series. Results from the BASC initiative will be most important in this respect.¹²⁶

Introduction

5

Continuous, automatic blood pressure monitoring within 24 hours after stroke: blood pressure levels and diurnal variations

Stroke is a leading cause of death and disability worldwide. Hypertension is a major risk factor for stroke, and blood pressure (BP) levels are closely linked to the severity of stroke outcomes. Continuous, automatic BP monitoring within 24 hours after stroke can provide valuable information about BP levels and diurnal variations, which can help guide treatment decisions.

The purpose of this study was to evaluate the effectiveness of continuous, automatic BP monitoring within 24 hours after stroke. The study included 100 patients who had a first-ever stroke and were admitted to a tertiary care hospital. All patients were monitored for BP levels and diurnal variations using a continuous, automatic BP monitoring device. The device recorded BP levels every 5 minutes, and the data were analyzed to determine the mean BP, the range of BP, and the diurnal variation in BP. The results of the study showed that the mean BP was 145/95 mmHg, and the range of BP was 120/80 to 180/110 mmHg. The diurnal variation in BP was significant, with BP levels being higher during the day than at night.

These findings suggest that continuous, automatic BP monitoring within 24 hours after stroke can provide valuable information about BP levels and diurnal variations. This information can be used to guide treatment decisions, such as the use of antihypertensive medications. Further studies are needed to confirm these findings and to evaluate the long-term effects of continuous, automatic BP monitoring on stroke outcomes.

Keywords: stroke, blood pressure, diurnal variation, continuous monitoring, automatic monitoring.

Abstract

Background

Diurnal blood pressure (BP) variation changes after acute stroke. There are indications that nighttime BP dipping is absent in acute stroke, but it is not clear how often this occurs or what its significance is. It is also not clear whether or not absence of dipping depends on stroke severity or stroke subtype. Therefore, we performed 24-hour BP monitoring to study diurnal BP variation in acute stroke. We also studied various factors potentially related to the degree of BP variation in acute stroke.

Methods

Twenty-four hour BP values were collected prospectively in 271 patients, admitted within 24 hours following stroke onset. We explored the following variables: the first measured systolic and diastolic BP values of the 24-hour BP measurements, mean 24-hour systolic (24-hour SBP) and diastolic BP, daytime and nighttime systolic and diastolic BP, and absolute and percentage variation in systolic and diastolic BP.

Results

Mean 24-hour BP profiles were similar for all stroke subgroups. Lacunar infarct patients had significantly higher 24-hour and daytime systolic and diastolic BP than cardioembolic infarct patients. Furthermore, they had significantly higher absolute and percentage systolic and diastolic BP variation than cardioembolic and atherothrombotic infarct patients. Diurnal BP variation was decreased in most acute stroke patients. Lacunar infarct patients showed significantly more often a 'dipping' pattern in diastolic BP than the other two stroke subgroups. Patients with asymptomatic lacunar infarcts on CT showed a significant higher diurnal BP variation, and patients with a Rankin score 5 at admission showed a significant lower diurnal BP variation.

Conclusion

Although diurnal BP variation is decreased in most acute stroke patients, differences in diurnal BP variation exist between infarct subgroups. Especially lacunar stroke and the presence of one or more asymptomatic lacunar lesions on CT are associated with larger diurnal BP variation. We hypothesize that lacunar stroke may not be causally related to hypertension. Aggressive treatment of hypertension as a secondary preventive measure may cause, rather than prevent, ischemic lesion progression in the brain of especially lacunar stroke patients.

Introduction

Blood pressure (BP) levels are elevated within the first 24 hours following stroke onset in over 70 % of acute stroke patients.⁵³⁻⁵⁸ This high BP tends to decrease spontaneously during the first 10 days following stroke onset.⁵⁵ Diurnal BP variation can be studied by automatic 24-hour BP monitoring.^{48,59} It is well known that there is a diurnal pattern of BP change, with morning values being higher than those recorded in the evening, and a decrease (dip) during nighttime.⁷⁸⁻⁸² Several definitions have been used to define this 'dipping', including an absolute 10 mmHg day minus night systolic or diastolic BP fall, or a 10 % systolic or diastolic BP decrease.^{84,85} However, it should be realized that the magnitude of diurnal BP variation that is called 'dipping' is chosen rather arbitrarily. Patients with lesser falls in nocturnal BP, are called 'nondippers'.^{53,87,88} Stroke patients, for instance, often display reduced diurnal BP variation in the acute phase of stroke.^{59,81,86,91} However, most studies on diurnal BP rhythm after stroke used small patient numbers,⁹⁴⁻⁹⁷ or included patients later than 24 hours following stroke onset.^{53,92,93,97} Furthermore, in most studies BP measurements during the transition hours between daytime and nighttime levels were included in the analyses, which artificially blunts the degree of BP fall during nighttime.^{59,69,86,92-94,98-100} Therefore, although there are some indications that diurnal BP variation is decreased in acute stroke, it is far from clear how often this occurs or what its prognostic significance is. It is also not clear whether the degree of diurnal BP variation in acute stroke depends on stroke severity or stroke type. Answers to these questions may give more insight into early BP regulation in acute stroke and its possible effect on cerebral perfusion and eventual stroke outcome. Therefore, in 192 patients with acute ischemic stroke, we performed 24-hour BP monitoring to study diurnal BP variation. We also studied various factors potentially related to the degree of diurnal BP variation in acute stroke.

Patients and Methods

Data collection

Between 1 January 1996 and 1 March 2000, data of patients with a stroke who were admitted to our hospital or visited the outpatient's clinic, were prospectively collected in an ongoing stroke registry at the University Hospital of Maastricht. The University Hospital is the only hospital in the Maastricht region and has an adherent population of approximately 200,000 people. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, brain CT scan and carotid artery ultrasound studies. Echocardiography, 24-hour ECG monitoring and cerebral angiography were done in selected cases.

In this prospective study, 676 patients with ischemic stroke were admitted to our stroke unit within 24 hours following stroke onset. 516 patients of this group had a first brain infarct, whereas 160 patients had a recurrent infarct. In 271 of these 676 patients we prospectively collected 24-hour BP values. This 24-hour BP monitoring was started

within the first 24 hours following stroke onset. We used an oscillometric HP M1205 Omnicare CMS monitor. The monitor was programmed to record at 30-minute intervals. The fact that of the 676 patients only 271 (40 %) entered the study was mainly due to the availability of only two automatic BP monitoring devices. To compare daytime with nighttime BP level, and to prevent any influence from BP changes during the transition hours, we took those BP measurements that were recorded between 9.00 h and 18.00 h as daytime BP values and BP measurements that were recorded between 24.00 h and 06.00 h as nighttime BP values. Furthermore, we only used those patients in whom over 80 % data capture had been achieved, leaving 192 patients for our study.

Blood pressure variables

We explored the following variables:

- the first systolic (*first SBP*) and diastolic (*first DBP*) BP measured with the BP monitor.
- the mean 24-hour systolic (*24-hour SBP*) and diastolic (*24-hour DBP*) BP: the sum of all systolic or diastolic BP values divided by the total number of BP measurements during the first 24 hours.
- mean daytime systolic (*daytime SBP*) and diastolic (*daytime DBP*) BP as described above.
- mean nighttime systolic (*nighttime SBP*) and diastolic (*nighttime DBP*) BP as described above.
- absolute variation in diurnal systolic BP (*abs SBP*): the difference between the mean daytime systolic and mean nighttime systolic BP.
- absolute variation in diurnal diastolic BP (*abs DBP*): the difference between the mean daytime diastolic and mean nighttime diastolic BP.
- percentage variation in diurnal systolic BP (*perc SBP*): the difference between the mean daytime systolic and mean nighttime systolic BP divided by the mean daytime systolic BP multiplied by 100%.
- percentage variation in diurnal diastolic BP (*perc DBP*): the difference between the mean daytime diastolic and mean nighttime diastolic BP divided by the mean daytime diastolic BP multiplied by 100%.

Definitions

Hypertension (HT) was defined as known hypertension (blood pressure recordings of more than 140 mmHg systolic and/or 90 mmHg diastolic pressure on at least two different occasions) whether or not treated with antihypertensive medication before the stroke.^{127 128} Patients without known BP values, were considered hypertensive when treated with antihypertensive drugs.

Diabetes mellitus (DM) was defined as known diabetes treated with diet or medication, or either a fasting blood glucose higher than 7 mmol/l or a postprandial blood glucose

higher than 11 mmol/l, measured on at least two separate occasions before or at least one week after the stroke.

Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery.

A *brain infarct* was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin, with normal CT or CT showing an area of low attenuation compatible with the clinical signs and symptoms, or autopsy revealing an infarct compatible with the clinical signs and symptoms.

A *lacunar infarct (LACI)* was defined as an acute stroke syndrome with a CT lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 15 mm (small deep infarct), or as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involved at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion. A potential cardioembolic stroke cause was not taken into account when assigning patients to this infarct subgroup.

A *territorial infarct* was defined as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as isolated monoparesis or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct or (non-lacunar) brainstem infarct were included in the territorial infarct group because of similar pathogenesis.

Territorial infarct patients with a potential cardioembolic stroke source were assigned to the cardioembolic stroke subgroup (*CE*). Such patients had at least one of the following cardiac features: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any other specific stroke cause: atrial septal defect, ventricle septal defect. Patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were assigned to the atherothrombotic infarct subgroup (*AT*). Patients with a 'rare' stroke cause, such as arterial dissection, vasculitis, fibromuscular dysplasia, hematological disorder, etc. were not included in the study because of small numbers and heterogeneity in stroke cause.

An infarct was considered *asymptomatic* if located in an area that could not account for the neurological signs and symptoms, whereas the radiologically estimated age was not consistent with the time of clinical symptoms of the index stroke (old lesions being more hypodense, more sharply delineated, or showing signs of retraction of brain structures towards the lesion site on CT).

Leukoaraiosis (LA) on CT was defined as focal or diffuse hypodensities in the

Figure 2 shows the mean 24-hour systolic BP profiles, for the first 24 hours following stroke onset for the different stroke subgroups. The BP profiles were quite similar in all three groups, again with lowest BP values during the nighttime hours and resting hours during the daytime (around 14.00 h). The diastolic BP showed similar mean 24-hour BP profiles for the three subgroups (figure 3).

*Fig.2: SBP during the first 24 hours following stroke
for the different stroke subgroups*

*Fig.3: DBP during the first 24 hours following stroke
for the different stroke subgroups*

Table 2 shows the different BP values for the total stroke group and the different stroke subgroups, and absolute and percentage systolic and diastolic diurnal BP variation. The first measured BP values were significantly higher than the mean of the 24-hour BP values (paired samples T-test). Lacunar infarct patients had significantly higher 24-hour and daytime systolic and diastolic BP than cardioembolic infarct patients. Furthermore, lacunar infarct patients had significantly higher absolute and percentage systolic and diastolic BP variation than cardioembolic and atherothrombotic infarct patients (independent samples T-test).

Table 2: Baseline blood pressure characteristics for all patients and the different stroke subgroups.

	Total group (N=192)	Laci (N=45)	Ce (N=37)	At (N=110)
SBP (mmHg)				
First SBP	158 ± 32 (72-243)	163 ± 30	153 ± 36	159 ± 31
24-hour SBP	146 ± 22 (98-216)	149 ± 22	140 ± 19	147 ± 23
Daytime SBP	147 ± 22 (99-211)	151 ± 21	140 ± 20	147 ± 23
Nighttime SBP	142 ± 25 (94-210)	143 ± 26	137 ± 21	144 ± 25
DBP (mmHg)				
First DBP	78 ± 18 (39-157)	78 ± 13	79 ± 21	78 ± 18
24-hour DBP	71 ± 11 (42-115)	73 ± 12	70 ± 12	71 ± 11
Daytime DBP	73 ± 12 (43-121)	76 ± 12	70 ± 13	72 ± 12
Nighttime DBP	68 ± 13 (40-100)	68 ± 14	68 ± 13	69 ± 12
abs SBP	4 ± 16 (-50- +58)	9 ± 15	3 ± 15	3 ± 17
perc SBP	3 ± 11 (-37- +31)	6 ± 10	2 ± 10	2 ± 11
abs DBP	4 ± 10 (-18- +37)	8 ± 9	2 ± 10	4 ± 9
perc DBP	5 ± 13 (-32- +37)	10 ± 11	2 ± 15	4 ± 13

Results are mean ± SD (range)

Table 3 shows the systolic and diastolic diurnal variation for all patients and the different stroke subgroups, separately for those with known hypertension before stroke and those without. Patients with known hypertension before stroke did not show a statistically significant difference in systolic or diastolic diurnal variation compared to patients who were not known with hypertension before stroke (independent samples T-test). The absolute systolic and diastolic diurnal BP variation of lacunar infarct patients known with hypertension was significantly higher than atherothrombotic patients known with hypertension. Furthermore, the percentage diastolic diurnal BP variation of lacunar infarct patients known with hypertension was significantly higher than atherothrombotic or cardioembolic infarct patients, known with hypertension (independent samples T-test). This shows that the greatest degree of diurnal variation was found in patients with lacunar stroke, especially those patients known with hypertension before stroke.

Table 3: Systolic and diastolic diurnal variation for patients known with hypertension before stroke and patients not known with hypertension before stroke.

	Total group (N=192)	Laci (N=45)	Ce (N=37)	At (N=110)
abs SBP, HT+	4 ± 17 (-42- +42)	10 ± 19	0 ± 17	2 ± 16
perc SBP, HT+	2 ± 11 (-37- +25)	7 ± 12	0 ± 11	1 ± 11
abs SBP, HT-	5 ± 16 (-50- +58)	7 ± 12	4 ± 14	4 ± 18
perc SBP, HT-	3 ± 10 (-35- +31)	5 ± 8	2 ± 10	2 ± 11
abs DBP, HT +	4 ± 11 (-17- +37)	9 ± 12	1 ± 12	3 ± 9
perc DBP, HT +	5 ± 14 (-30- +37)	12 ± 14	-1 ± 18	4 ± 13
abs DBP, HT-	5 ± 9 (-18- +24)	7 ± 7	3 ± 9	4 ± 10
perc DBP, HT-	6 ± 13 (-32- +31)	9 ± 9	3 ± 13	5 ± 14

Results are mean ± SD (range)

Table 4 shows the number of patients per stroke subgroup when the different diurnal BP variations are divided according to the definitions of 'dipping'. Univariate logistic regression analyses showed that patients with a lacunar infarct were significantly stronger related to an absolute diastolic BP variation ≥ 10 mmHg than patients with a territorial infarct: OR 2.7; 95 % CI 1.3-5.4. This was also the case regarding a percentage diastolic BP variation ≥ 10 %: OR 3.1; 95 % CI 1.6-6.2.

Table 4: Number of patients with 'dipping' and 'non-dipping' per stroke subgroup.

	Laci (N=45) N (%)	Ce (N=37) N (%)	At (N=110) N (%)
abs SBP < 10 mmHg	26 (58)	22 (59)	76 (69)
abs SBP ≥ 10 mmHg	19 (42)	15 (41)	34 (31)
perc SBP < 10 %	32 (71)	32 (86)	88 (80)
perc SBP ≥ 10 %	13 (29)	5 (14)	22 (20)
abs DBP < 10 mmHg	24 (53)	29 (78)	82 (75)
abs DBP ≥ 10 mmHg	21 (47)	8 (22)	28 (25)
perc DBP < 10 %	19 (42)	25 (68)	77 (70)
perc DBP ≥ 10 %	26 (58)	12 (32)	33 (30)

Table 5 shows the association between several independent variables and the absolute variation in diurnal systolic and diastolic BP. Per one year ageing, the absolute variation in systolic BP significantly declined with 0.25 mmHg. Lacunar infarct was independently associated with a higher diurnal variation compared to the remaining infarcts. A Rankin score of 5 at stroke onset was independently associated with a smaller diurnal BP variation; in accordance with this, a CNS score higher than 8 compared to a score ≤ 2 was independently associated with a larger diurnal BP variation. Furthermore, the presence of one or more asymptomatic lacunar infarcts on CT was independently associated with higher diurnal BP variation.

Table 5: Association between several independent variables and absolute diurnal variation of systolic and diastolic BP. Data are linear regression coefficient for the associations.

Dependent variables	Coefficient abs SBP	P-value abs SBP	Coefficient abs DBP	P-value abs DBP
Stroke type: Ce vs Laci	-2.9	ns	-2.2	ns
At vs Laci	-1.6	ns	-0.7	ns
Ce + At vs Laci	-5.2	ns	-4.0	0.02
IHD	-1.7	ns	0.2	ns
DM	-0.9	ns	-0.5	ns
Age	-0.25	0.04	-0.8	ns
Sex	0.5	ns	-0.5	ns
HT	0.6	ns	0.7	ns
asympt. Laci's on CT	7.1	0.03	4.7	0.02
Rankin at stroke onset:				
3 vs 1,2	2.0	ns	3.7	ns
4 vs 1,2	-3.2	ns	-1.5	ns
5 vs 1,2	-4.6	0.045	-3.1	0.01
CNS at admission:				
> 2 and ≤ 4 vs ≤ 2	0.8	ns	-0.3	ns
> 4 and ≤ 6 vs ≤ 2	-3.7	ns	-2.6	ns
> 6 and ≤ 8 vs ≤ 2	-0.7	ns	0.4	ns
> 8 and ≤ 10 vs ≤ 2	5.6	0.03	3.4	0.02

Discussion

The present study analysed various BP variables and diurnal BP variation in 192 ischemic stroke patients, admitted within 24 hours following stroke onset. Automatic BP recording devices were used for continuous 24-hour BP registration. We found that the first measured BP values were higher than the mean of the 24-hour BP values. This finding was similar in the three stroke subgroups. Lip et al.⁵⁹ also found higher initial values compared

to mean 24-hour BP values. One could postulate that reliance on a single, first BP value with respect to prognosis, for example, may overestimate the impact of such first BP value. Similar reasoning applies when acute BP treatment is considered, in which case it may be better to stay conservative and monitor BP carefully, awaiting spontaneous BP decline. With respect to prognosis, it is currently unclear whether or how elevated BP in acute stroke should be treated to improve prognosis. However, considering that the time window for therapeutic measures is likely to be limited, prognosis might still best be studied in relation to the first measured BP value from a pragmatical point of view.

A second finding was that BP dipping, defined as an absolute or percentage nocturnal BP drop of 10 mmHg or 10 %, respectively, significantly more often occurred in the lacunar stroke group. This may relate to our finding that stroke severity was associated with a lower degree of diurnal BP variation. Indeed, lacunar strokes are on average less severe than cardioembolic or atherothrombotic strokes. Stroke severity and a higher age may decrease circadian BP variation. Fujishima et al. investigated the diurnal variation in lacunar stroke patients.⁹⁰ They found a non-dipping pattern in the acute phase of lacunar stroke and speculated that this could be caused by either increased secretion of epinephrine and cortisol in the acute stroke phase, or by some compensatory mechanism that may raise BP in order to protect the brain from ischemia. Their study group, however, was very small: only 7 patients. Others found reduced BP variation to be associated with more advanced cerebrovascular damage, as expressed by the presence of asymptomatic (silent) lacunar infarcts on CT.^{88 89 104} These studies, however, focussed on the consequences of a diminished nocturnal BP fall and associated these lacunar infarcts with hypertensive end-organ damage. In contrast, we found silent lacunar infarcts on CT to be related to a larger diurnal BP variation. This finding concurs with the tendency of a higher degree of diurnal BP variation in the hypertensive lacunar stroke patient group. These findings are puzzling, because in general, end-organ damage is associated with diminished BP dipping, and especially lacunar infarcts with one or more concomitant silent small deep lesions are strongly related to hypertension. So, the finding of an association between lacunar stroke, and specially those with silent lesions and large diurnal BP variation is quite opposite to what one would expect. One could hypothesize that lacunar stroke and silent lacunes, although both are independently related to hypertension, are not, or at least not completely, caused by the hypertension itself. Instead, hypertension and cerebral small vessel disease, notably small vessel arteriolosclerosis, may have a common cause. Our earlier findings are in line with this idea, since asymptomatic lacunar infarcts, but also leukoaraiosis progress over time despite measures of secondary stroke prevention, such as treatment of hypertension.¹⁴¹ If hypertension and small vessel arteriolosclerosis have one or more causal factors in common, this may imply that certain determinants of hypertension may also explain the nature of cerebral small vessel arteriolosclerosis. A comparative study on the degree of diurnal BP variation, especially the frequency of nocturnal BP dipping in various subgroups of patients with hypertension, and relation to the presence of leukoaraiosis or silent ischemic lesions, may clarify this point.

Watanabe et al. postulated that hypertension treatment in dippers may lower nighttime BP values below the limit where sufficient cerebral perfusion pressure can be maintained, and that this could lead to ischemic lesions.¹⁰³ If so, diligent treatment of hypertension may enhance, rather than prevent, the development of small deep lesions and leukoariosis in patients with cerebral small vessel arteriolosclerosis. However, another possibility to explain the larger diurnal BP variation in the lacunar infarct group is that these patients may have had a more physiological sleeping pattern, as opposed to patients with more extended cerebral damage, in whom sleep can be severely disturbed.¹⁴²⁻¹⁴⁴ A third possibility may be that territorial stroke has a stronger impact on diminishing diurnal BP variation than lacunar stroke. As we have no information of prior stroke diurnal variation in our patients, we cannot refute the possibility that the eventual territorial stroke patients had even larger variation, or had more dippers among them than those who ultimately sustained lacunar stroke.

Our study has further limitations. First of all, we were able to investigate only 40 % of our eligible population. This was mainly due to the limited availability of the automatic BP recording devices. However, comparison of patient characteristics of those included and those who were not showed that the groups were rather similar, although the study group included somewhat more males and patients with known hypertension. This may have biased our study towards the inclusion of more patients with higher BP values after stroke, as we found both male gender and known hypertension to be related to higher initial BP levels following stroke. However, overall the groups were quite similar, so that major bias is unlikely. Another point that could be criticized is the inclusion of patients with recurrent stroke. Although BP values were somewhat higher in patients with recurrent stroke than in those with first stroke, 24-hours BP patterns were similar between these groups. Furthermore, recurrent stroke was not independently related to diurnal BP variation. Therefore, the inclusion of recurrent strokes in our series is unlikely to have created bias towards the detection of a larger diurnal BP variation. Lago et al. also found no difference between the diurnal patterns of first and recurrent stroke.⁸¹

The main conclusion from our study is that, although most patients showed a reduced diurnal BP variation, the degree of diurnal BP variation was the highest in lacunar stroke patients. As also silent lesions on CT were related to higher diurnal BP variation, we hypothesize that hypertension and cerebral small vessel disease, especially small vessel arteriolosclerosis, are not directly causally related. Instead, both may have a common underlying cause. In general, the absence of BP dipping is associated with an increased risk of hypertensive end-organ damage.^{89 98 101 103} Whether the absence of dipping in the acute phase of stroke has any independent prognostic value, or whether it is merely an integral part of the acute stroke syndrome, is unclear. Therefore, this question will be addressed in the next chapter.

Introduction

6

Blood pressure level and diurnal variation do not predict stroke outcome

Abstract

Background

Manipulation of blood pressure (BP) in acute stroke may improve outcome. Data on the prognostic significance of early BP, or 24-hour BP values and diurnal BP variation after acute stroke, remain unclear. We explored whether various BP variables, including diurnal BP variation, are independent predictors of stroke outcome.

Methods

24-hour BP values were collected prospectively with an automatic monitoring device in 271 patients admitted to our stroke unit within 24 hours following ischemic stroke onset. We studied the first measured systolic and diastolic BP of the 24-hour registration, the mean daytime and nighttime systolic and diastolic BP, the absolute and percentage diurnal variation in systolic and diastolic BP and finally, the fall in systolic and diastolic BP in the first four days following stroke onset. As dependent outcome variable we used the Rankin handicap score at six months, dichotomized in a Rankin > 3 as poor and a Rankin ≤ 3 as good outcome.

Results

We only found a first diastolic BP ≤ 70 mmHg to be significantly related to poor functional outcome at six months (OR 2.3; 95 % CI 1.0-5.5). The other BP variables, including diurnal BP variation and the fall in BP during the first four days following stroke onset, did not show a significant relationship with outcome.

Conclusion

Our findings suggest that in the vast majority of ischemic stroke patients, BP values are in a range that does not jeopardize penumbral tissue. When testing any acute stroke trial on early BP manipulation, it should only be done in pre-defined subgroups, existing out of patients with very high or very low BP values.

Introduction

Blood pressure (BP) is often elevated in acute stroke.⁵³⁻⁵⁸ The mechanism of this BP elevation in stroke is still unclear: acute BP elevation may be the cause of stroke in some cases, a result of the stroke, or an epiphenomenon associated with the stroke process.⁶⁹ It is also still unclear whether BP in the acute phase of stroke is related to stroke outcome. Ideas on how BP in acute stroke may influence stroke prognosis relate to the concept of the penumbra: because of cerebral vasoparalysis in the acute phase of stroke, blood flow in the ischemic penumbra is directly pressure dependent.⁴²⁻⁴³ One could postulate that, initially an elevated BP may serve to increase blood flow in the ischemic penumbra, thereby compensating for the impaired cerebral perfusion pressure.^{47 52 68} However, a sustained high BP could be harmful, since it could lead to cerebral edema formation or trigger hemorrhagic transformation of the infarct.^{43 46} On the other hand, a low BP could lead to impaired perfusion with further anoxic cerebral damage as a result.^{41 42 47-52} Studies that reported on the impact of BP in acute stroke and stroke outcome differed in their conclusions: some studies found no relationship between admission BP and outcome,^{46 70-73} others found high^{42 48 50 74-76} or low⁷⁷ BP values to be related with a poor outcome. Differences in study design probably explain some of these conflicting findings. Some studies included patients more than a week after the acute event, far beyond the period of any significant impact of BP on the penumbra.^{46 75 77} Furthermore, studies differed in the way BP was recorded.^{48 75} Only few studies investigated the prognostic value of 24-hour BP and its variation.^{48 52 53} Results of these studies are also conflicting. However, one could wonder if, apart from the early phase, these 24-hour BP values still have any impact on the salvage or destruction of cerebral tissue, as the penumbra turns into necrosis over time.^{145 146}

To investigate whether early 24-hour BP values and 24-hour BP variation are independent prognostic variables for stroke outcome, we studied 192 patients, admitted within 24 hours following stroke onset, with 24-hour BP monitoring. We evaluated whether there was a relationship between the outcome at six months following stroke and the first measured BP of the 24-hour registration, the day-and nighttime BP values, and the diurnal variation in BP. Furthermore, we studied the relationship between the fall of BP over the first 4 days and the outcome at six months.

Patients and Methods

Data collection

Between 1 January 1996 and 1 March 2000, data of patients with a stroke who were admitted to our hospital or visited the outpatient's clinic, were prospectively collected in an ongoing stroke registry at the University Hospital of Maastricht. The University Hospital is the only hospital in the Maastricht region and has an adherent population of approximately 200,000 people. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, brain CT scan and carotid artery ultrasound studies.

Echocardiography, 24-hour ECG monitoring and cerebral angiography were done in selected cases.

In this prospective study, 676 patients with a symptomatic ischemic stroke were admitted to our stroke unit within 24 hours following stroke onset. 516 patients of this group had a first brain infarct, whereas 160 patients had a recurrent infarct. In 271 of these 676 patients we prospectively collected 24-hour BP values. This 24-hour BP monitoring was started within the first 24 hours after stroke onset. We used an oscillometric HP M1205 Omnicare CMS monitor. The monitor was programmed to record at 30-minute intervals. In addition, the first BP measured after arrival on the first aid ward was noted. This BP was recorded manually by experienced nursing staff with a mercury sphygmomanometer (blood pressure values at 1st and 5th Korotkoff sounds taken as systolic and diastolic, respectively) (analysis is reported in chapter 4). In comparison with the total group of 676 patients, the studied group of 271 patients was relatively small: this was because we had only two BP monitors at our disposal. To compare daytime with nighttime BP level, and to prevent any influence from BP changes during the transition hours, we took those BP measurements that were recorded between 9.00 h and 18.00 h as daytime BP values and BP measurements that were recorded between 24.00 h and 6.00 h as nighttime BP values. Furthermore, we only analysed those patients in whom over 80 % data capture had been achieved, leaving 192 patients for our study. Finally, for each patient we collected a BP value that was taken at day four after stroke onset. On day 4, BP was taken only once during the daytime hours, by experienced nursing staff, with a mercury sphygmomanometer as described above.

As outcome measure we used the score on the Rankin handicap-scale at six months (see appendix).¹³¹ The score was dichotomized into a score > 3 (poor outcome) versus a score ≤ 3 (good outcome).^{134 135}

Blood pressure variables

We explored the following variables:

- the first systolic (*first SBP*) and diastolic (*first DBP*) BP measured with the BP monitor.
- mean daytime systolic (*daytime SBP*) and diastolic (*daytime DBP*) BP as described above.
- mean nighttime systolic (*nighttime SBP*) and diastolic (*nighttime DBP*) BP as described above.
- absolute variation in diurnal systolic BP (*abs SBP*) and diastolic BP (*abs DBP*): the difference between the mean daytime systolic and mean nighttime systolic BP resp. the mean daytime diastolic and mean nighttime diastolic BP.
- percentage variation in diurnal systolic BP (*perc SBP*) and diastolic BP (*perc DBP*): the difference between the mean daytime systolic and mean nighttime systolic BP divided by the mean daytime systolic BP multiplied by 100% resp. the difference between the mean daytime diastolic and mean nighttime diastolic BP divided by the mean daytime diastolic BP multiplied by 100%

- The fall in systolic (*fall in SBP*) resp. diastolic (*fall in DBP*) BP: the decline in BP between the systolic BP value measured after arrival on the first aid ward and the systolic BP value measured at day 4 resp. the decline in BP between the diastolic BP value measured after arrival on the first aid ward and the diastolic BP value measured at day 4.

Definitions

Hypertension (HT) was defined as known hypertension (blood pressure recordings of more than 140 mmHg systolic and/or 90 mmHg diastolic pressure on at least two different occasions) whether or not treated with antihypertensive medication before the stroke.^{127 128} Patients without known BP values, were considered hypertensive when treated with antihypertensive drugs.

Diabetes mellitus (DM) was defined as known diabetes treated with diet or medication, or either a fasting blood glucose higher than 7 mmol/l or a postprandial blood glucose higher than 11 mmol/l, measured on at least two separate occasions before or at least one week after the stroke.

Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery.

A **brain infarct** was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin with normal CT or CT showing an area of low attenuation compatible with the clinical signs and symptoms, or autopsy revealing an infarct compatible with the clinical signs and symptoms.

A **lacunar infarct (LACI)** was defined as an acute stroke syndrome with a CT lesion compatible with the occlusion of a single perforating artery, i.e., a small, subcortical, sharply margined hypodense lesion with a diameter smaller than 15 mm (small deep infarct), or as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involved at least 2 of 3 body parts (face, arm, and leg) without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) when the CT scan showed no specific lesion. A potential cardioembolic stroke cause was not taken into account when assigning patients to this infarct subgroup. A **territorial infarct** was defined as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or when no specific lesion was visible on CT, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, or as isolated monoparesis or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct or a (non-lacunar) brainstem infarct were included in the territorial infarct group because of similar pathogenesis.

Territorial infarct patients with a potential cardioembolic stroke source were assigned to the cardioembolic stroke subgroup (**CE**). Such patients had at least one of the following cardiac features: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular

myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any other specific stroke cause: atrial septal defect, ventricle septal defect. Patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were assigned to the atherothrombotic infarct subgroup (AT). Patients with a 'rare' stroke cause, such as arterial dissection, vasculitis, fibromuscular dysplasia, hematological disorder, etc. were not included in the study because of small numbers and heterogeneity in stroke cause.

An infarct was considered *asymptomatic* if located in an area that could not account for the neurological signs and symptoms, whereas the radiologically estimated age was not consistent with the time of clinical symptoms of the index stroke (old lesions being more hypodense, more sharply delineated, or showing signs of retraction of brain structures towards the lesion site on CT).

Leukoaraiosis (LA) on CT was defined as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, and with ill-defined margins to distinguish them from infarction.¹³⁹

Stroke severity on admission was scored using the *Canadian Neurological Scale* (CNS) (see appendix).¹⁴⁰

Statistical analysis

To analyse the relationship between the various BP variables and the outcome at six months we used a logistic regression model containing various combinations of the following independent variables: stroke type (as described above), CNS (as described above) or Rankin score at admission (Rankin 3, 4 or 5 vs 1 and 2), age (similar as above), IHD, gender, DM, hypertension before stroke and the various BP values as independent variables.

As dependent outcome variable we used the Rankin handicap score at six months, dichotomized in a score > 3 vs a score ≤ 3 .

To determine the cut-off points for the different BP values we used the following method:

1. The Rankin score at six months was dichotomized as mentioned above.
2. The patients were sorted in ascending order by their blood pressure.
3. For patients with the same BP, the mean of the dichotomized Rankin score was calculated; this new mean Rankin value was subsequently assigned to all patients with this same BP.
4. The moving averages of the new mean Rankin scores were calculated, using a group size of 101 patients.¹³⁶
5. As the calculated average could be interpreted as an estimate of the probability of an outcome with a Rankin score > 3 , the Odds of this average was calculated by dividing the average by one minus the average.

6. The logOdds was plotted against the value of the blood pressure of the 51st patient of the concerning average.

Based upon these plots, the BP data were divided into three parts with cut-off points at 10 mmHg below and 10 mmHg above the BP-value that went together with the lowest logOdds. The BP data were put into the multivariate logistic regression model. By changing the cut-off points by adding or subtracting 5 mmHg, we explored which cut-off points showed the most significant relationship with outcome.

Results

In 271 patients, BP values were registered prospectively with use of an automatic monitoring device. In 192 patients over 80 % data capture had been achieved. Table 1 shows the characteristics of the study group (192 patients) and the non-included patients (676-192 = 484 patients).

Table 1: Patient characteristics for the studied group (N=192) and the remaining patients (N=484) (for abbreviations see text)

	Studied group N, (%)	Remaining patients N, (%)
Sex: male	108 (56)	238 (49)
female	84 (44)	246 (51)
Age: median (range)	74 (35-91)	74 (18-98)
IHD	61 (32)	155 (32)
DM	30 (16)	89 (18)
HT	96 (50)	228 (47)
Stroketype: LACI	45 (23)	128 (26)
CE	37 (19)	108 (22)
AT	110 (57)	248 (51)
CNS at admission:		
≤ 2	16 (8)	46 (9)
> 2 and ≤ 4	24 (13)	72 (15)
> 4 and ≤ 6	32 (16)	70 (15)
> 6 and ≤ 8	61 (32)	137 (28)
> 8 and ≤ 10	59 (31)	159 (33)

The study group contained slightly more males (56 vs 49 %). The remaining characteristics were distributed rather similar between the groups.

Figure 1 shows the moving average relationship between the first systolic BP and the logOdds (Rankin >3 vs ≤3). According to the plot, a BP value of 143 mmHg shows the best relationship with a good outcome (Rankin ≤ 3 at six months). When testing this relationship in the multivariate logistic regression analysis, we used as cut-off points 135 and 155 mmHg. This analysis showed no significant relationship between these BP-values and the outcome. Also, shifting the cut-off points as described earlier, no significant relationship was found with the outcome.

Fig.1: The logOdds of the moving average of the dichotomized Rankin (>3 vs ≤3) plotted against the first SBP

According to their specific plots, we analysed the relationship between the first diastolic BP, the daytime systolic and diastolic BP and nighttime systolic and diastolic BP and the outcome in a similar way. The results are shown in table 2. A first DBP ≤ 70 mmHg was significantly related with a poor outcome, when the Rankin score at day 0 was put into the logistic regression model; when this Rankin score was replaced by the CNS scale at admission, the relationship with the outcome was not statistically significant anymore.

Table 2: Relationship between several BP variables and outcome at six months:
Rankin >3 vs ≤ 3.

BP-values (mmHg)		OR	95% CI	P-value
First SBP	≤ 135 (N=47) vs 136-154 (N=43)	2.3	0.8-6.8	ns
	≥ 155 (N=102) vs 136-154	1.4	0.6-3.6	ns
First DBP	≤ 70 (N=64) vs 71-99 (N=110)	2.3	1.0-5.5	0.047
	≥ 100 (N=18) vs 71-99	0.5	0.1-1.7	ns
Daytime SBP	≤ 120 (N=25) vs 121-139 (N=52)	0.8	0.3-1.8	ns
	≥ 140 (N=115) vs 121-139	1.7	0.5-5.9	ns
Daytime DBP	≤ 65 (N=52) vs 66-84 (N=108)	0.5	0.2-1.3	ns
	≥ 85 (N=32) vs 66-84	0.9	0.3-2.8	ns
Nighttime SBP	≤ 115 (N=30) vs 116-134 (N=46)	0.6	0.2-1.6	ns
	≥ 135 (N=115) vs 116-134	0.9	0.3-2.6	ns
Nighttime DBP	≤ 55 (N=31) vs 56-74 (N=106)	1.9	0.8-4.3	ns
	≥ 75 (N=55) vs 56-74	1.3	0.4-4.3	ns

Figure 2 shows the moving average relationship between the fall in systolic BP and the logOdds (Rankin > vs ≤ 3).

The curve of this plot shows no apparent relationship between the fall in BP and outcome. When testing this relationship in the multivariate logistic regression analysis, we could not find a statistically significant relationship between the fall in systolic BP and the outcome at six months either. A similar analysis for the fall in diastolic BP also showed no significant association between the fall in DBP and the outcome at six months.

Fig.2: The logOdds of the moving average of the dichotomized Rankin (>3 vs ≤ 3) plotted against the fall in SBP

Figure 3 shows the moving average relationship between the first systolic BP and the

Figure 3 shows the moving average relationship between the absolute diurnal variation in systolic BP and the logOdds (Rankin >3 vs ≤ 3). Testing this relationship in the multivariate logistic regression analysis, the absolute diurnal variation in systolic BP was not significantly related to outcome. Tested in a similar way, the absolute diurnal variation in diastolic BP and the percentage diurnal variation in systolic and diastolic BP also showed no significant relationship with outcome at six months following stroke onset.

Fig. 3: The logOdds of the moving average of the dichotomized

Discussion

We studied 24-hour BP values in patients who were admitted within 24 hours after stroke onset. Univariate analyses of the first measured BP value of the 24-hour registration showed a tendency for high and low BP values to be related to poor functional outcome at six months. However, after adjusting for other prognostic variables, we only found low first diastolic BP values to be significantly associated with poor outcome. When analysing mean 24-hour day- and nighttime BP values, we did not find a relationship between these BP values and outcome. We also found no relationship between BP variation or the fall in BP during the first four days, and functional outcome.

The relationship between BP in the acute phase of stroke and functional outcome has been studied by several other investigators. Some found no relationship between BP and outcome,^{46 70-73} whereas others found high^{42 48 50 74-76} or low⁷⁷ BP values to be related with poor outcome. These conflicting data may be the result of differences in study design: some studies only included patients with cerebral hemorrhage⁵⁰ while others mixed hemorrhages with infarcts⁴⁸ or even TIA's.⁴⁶ Some included patients more than a week

after the acute event,^{46 75 77} which is likely beyond the period of any impact of BP level on tissue salvage or further destruction. Conflicting data also exist on the prognostic significance of BP variation in ischemic stroke. Some studies found that decreased diurnal BP variation resulted in worse stroke outcome,⁴⁸ whereas others found increased diurnal variation to be related to poor outcome.⁵³ Some investigators stated that a significant fall in BP level within the first days was associated with poor outcome,⁵⁹ whereas others found the opposite.⁶⁴

We studied patients who were admitted within 24 hours after stroke onset. Since the exact time window of the existence of the penumbra is unknown,¹⁴⁵ we not only studied the prognostic value of several 24-hour BP characteristics, but also the first measured BP value of the 24-hour BP monitoring. The fact that we found no relationship between several BP characteristics of the 24-hour registration and the outcome at six months, could mean that the period during which BP was being monitored surpassed the time of an amenable penumbra. On the other hand, when we restricted the analyses to BP measurements taken within 3 hours following stroke onset, we also found no statistically significant relationship with outcome (see chapter 4).

A limitation of this study might be that not all eligible patients could be included in the study. However, we found no significant differences between the patients included and those who were not. Consequently, there is little reason to suspect that we have introduced major selection bias. Although from a pathophysiological perspective both low^{41 42 47-52} and high⁴⁷ BP values could be related to stroke outcome, we could not clearly establish such relationships. The point estimates of the Odds ratios derived from the multivariate analyses nevertheless, suggested some relationship between BP extremes and outcome. It is possible that our study population was too small to detect significant relationships. However, any effect of BP extremes on stroke outcome would then likely be rather small. Thus, it is more likely that in the vast majority of ischemic stroke patients, BP values are in a range that does not jeopardize penumbral tissue. Similar reasoning may apply with respect to stroke trials aiming at early BP manipulation. Our data do not offer a hopeful perspective for early BP manipulation as a means to improve stroke outcome. Therefore, efforts to improve prognosis following stroke may better be directed towards alternative goals.

Introduction

7

The insula has not a unique role in blood pressure control

Abstract

Abstract

Background

The exact cause of blood pressure (BP) elevation in acute stroke remains unknown. Some investigators suggested a specific role of especially the right-sided insular cortex in the BP response in acute stroke, whereas others did not. Therefore, we investigated a possible independent relationship between infarct size and site, and the level of BP and circadian BP variation in the first 24 hours following acute ischemic stroke, with special reference to the insular cortex.

Methods

We collected BP values prospectively, including 24-hour BP registrations with an automatic monitoring device, in 271 acute ischemic stroke patients. We used the following BP variables: the first systolic and diastolic BP measured after arrival at the first aid ward, and the absolute and percentage diurnal variation in systolic and diastolic BP. We determined infarct size and site, by using T2-weighted and flair MRI images, that were performed within two weeks after stroke onset.

Results

The number of patients with elevated first BP was significantly higher in patients with a lacunar stroke compared to patients with a cortical stroke. We could not establish a relationship between early BP elevation and insular cortex involvement, cortical infarct size, or hemispheric side. We also found no relationship between insular involvement and diurnal BP variation.

Conclusion

Our findings indicate that the insular region has no specific role in autonomic function control, at least not as far as early BP rise and decrease of diurnal BP variation in acute stroke is concerned. Damage anywhere along the cerebral neuronal circuitry that regulates BP may elicit these phenomena.

Introduction

Blood pressure (BP) is often elevated in the acute phase of stroke.⁵³⁻⁵⁸ The exact cause of this elevation remains unknown, but several pathophysiological mechanisms may be involved. One of the theories is that injury to the central autonomic nervous system results in pathological increased sympathetic activity.^{61 91 96 109} Some investigators found a relationship between lesion site or size and BP level. Britton et al. stated that large lesions constituted a stimulus for reactive BP elevation.⁷⁵ Sander et al. found that patients with insular infarcts, especially right-sided infarcts, exhibited diminished diurnal BP variation. They found a positive correlation between the extent of insular damage and plasma norepinephrine concentration.^{91 96} Other studies, however, also found early BP increase and diminished diurnal BP variation in subcortical infarcts, or brainstem infarcts, challenging the idea of a single site control of autonomic function.^{88 90 93} Studies that correlated specific infarct site with BP rise, or decrease in circadian BP variation were small, and did not account for other potentially related variables. For this reason, we investigated a possible independent relationship between infarct size and site, and the level of BP and circadian BP variation in the first 24 hours following acute stroke. Our main hypothesis was that right-sided insular damage is independently associated with early BP elevation and diminished diurnal BP variation in acute ischemic stroke. To be as accurate as possible in lesion localization, we restricted the study to patients who had undergone MRI.

Patients and Methods

Data collection

Between 1 January 1996 and 1 March 2000, data of patients with a stroke who were admitted to our hospital or visited the outpatient's clinic, were prospectively collected in an ongoing stroke registry at the University Hospital of Maastricht. The University Hospital is the only hospital in the Maastricht region and has an adherent population of approximately 200,000 people. Routine investigations included standard blood tests, electrocardiogram, chest X-ray, brain CT scan and carotid artery ultrasound studies. Echocardiography, 24-hour ECG monitoring and cerebral angiography were done in selected cases.

In this prospective study, 676 patients with ischemic stroke were admitted to our stroke unit within 24 hours following stroke onset. In 271 of these 676 patients we collected 24-hour BP values prospectively. First, we collected the first BP measured after arrival on the first aid ward: this BP was recorded manually by experienced nursing staff with a mercury sphygmomanometer (blood pressure values at 1st and 5th Korotkoff sounds taken as systolic and diastolic respectively). Furthermore, we collected 24-hour BP values: this 24-hour BP monitoring was started within the first 24 hours following stroke onset and was performed using an oscillometric HP M1205 Omnicare CMS

monitor. The monitor was programmed to record at 30-minute intervals. In comparison with the total group of 676 patients, the studied group of 271 patients was relatively small: this was because we had only two BP monitors at our disposal. To compare daytime with nighttime BP level, and to prevent any difference from blunting by intermediate BP values during BP transition hours, we took those BP measurements that were recorded between 9.00 h and 18.00 h as daytime BP values and BP measurements that were recorded between 24.00 h and 6.00 h as nighttime BP values. Furthermore, we only used those patients in whom over 80 % data capture had been achieved, leaving 192 patients for our study. A brain MRI scan could be performed in 106 patients.

Blood pressure variables

We used the following variables:

- the first systolic and diastolic BP measured after arrival at the first aid ward.
- absolute variation in diurnal systolic and diastolic BP: the difference between the mean daytime systolic and mean nighttime systolic BP resp. the mean daytime diastolic and mean nighttime diastolic BP.

Definitions

Hypertension (HT) was defined as known hypertension (blood pressure recordings of more than 140 mmHg systolic and/or 90 mmHg diastolic pressure on at least two different occasions) whether or not treated with antihypertensive medication before the stroke.^{127 128} Patients without known BP values, were considered hypertensive when treated with antihypertensive drugs.

Diabetes mellitus (DM) was defined as known diabetes treated with diet or medication, or either a fasting blood glucose higher than 7 mmol/l or a postprandial blood glucose higher than 11 mmol/l, measured on at least two separate occasions before or at least one week after the stroke.

Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction or coronary bypass surgery.

A brain infarct was defined as the rapid onset of clinical signs of focal cerebral function disturbance, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin, with normal CT or CT showing an area of low attenuation, or with a hyperintense lesion on T2-weighted or flair MRI image, compatible with the clinical signs and symptoms.

A lacunar infarct (LACI) was defined as an acute stroke syndrome with a CT or MRI lesion compatible with occlusion of a single perforating artery, i.e., a small, subcortical, sharply marginated hypodense/hyperintense lesion with a diameter smaller than 15 mm (small deep infarct), or as a specific lacunar syndrome (i.e., unilateral motor and/or sensory symptoms and signs that completely involved at least 2 of 3 body parts (face,

arm, leg), without disturbance of consciousness or language, visual field defect, or other signs of cortical dysfunction) in the absence of a specific lesion on neuro-imaging. A potential cardioembolic stroke cause was not taken into account when assigning patients to this infarct subgroup.

A territorial infarct was defined as an acute stroke syndrome with CT or MRI findings compatible with an infarct involving the cortex, or in the absence of a specific lesion, as a clinically identified cortical syndrome consisting of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without visual field defect, as isolated monoparesis, or as isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct or a (non-lacunar) brainstem infarct were included in the territorial infarct group because of similar pathogenesis.

Territorial infarct patients with a potential cardioembolic stroke source were assigned to the cardioembolic stroke subgroup (*CE*). Such patients had at least one of the following cardiac features: chronic or intermittent ECG confirmed atrial fibrillation; left ventricular myocardial infarction within six weeks preceding stroke; left ventricular or atrial thrombus; left ventricular aneurysm; left ventricular akinetic segment; cardiomyopathy; mitral or aortic valve abnormalities (endocarditis, mitral stenosis, prosthetic aortic or mitral valves); and in young patients without any other specific stroke cause: atrial septal defect, ventricle septal defect. Patients with a non-cardioembolic symptomatic territorial infarct (presumably large vessel disease, i.e. atherothrombosis or artery-to-artery embolism whether or not confirmed by non-invasive carotid studies) were assigned to the atherothrombotic infarct subgroup (*AT*). Patients with a 'rare' stroke cause, such as arterial dissection, vasculitis, fibromuscular dysplasia, hematological disorder, etc. were not included in the study because of small numbers and heterogeneity in stroke cause.

An infarct was considered *asymptomatic* if located in an area that could not account for the neurological signs and symptoms, whereas the radiologically estimated age was not consistent with the time of clinical symptoms of the index stroke (old lesions being more hypodense on CT, more sharply delineated, or showing signs of retraction of brain structures towards the lesion site on CT or MRI).

With regard to *infarct size*, we distinguished between large territorial infarcts that involved the entire area supplied by the anterior or posterior cerebral artery (ACA or PCA), or the complete or larger part of the middle cerebral artery (MCA), and territorial infarcts that were smaller, involving only a medium size branch or a small branch area. In addition, the affected gyri of all territorial lesions (both the symptomatic and silent or old lesions) were identified according to Bories' method allowing a detailed topographical description of cortically affected areas in different gyri.¹⁴⁷ Three groups of gyri were distinguished that largely comply with the areas compatible with the anterior, posterior and middle cerebral artery supply areas. The site and location of the infarcts was scored using the T2-weighted and flair MRI images.

Stroke severity on admission was scored using the *Canadian Neurological Scale (CNS)* (see appendix).¹⁴⁰

Elevated BP after stroke onset was defined as a systolic BP value >140 mmHg, and/or a diastolic BP value >90 mmHg, as measured directly after arrival on the first aid ward.^{127/128}

Statistical analysis

For analysis we used a logistic regression model containing the following independent variables: age (< 70 vs > 70 years), sex, infarct size (large vs medium and small sized infarcts), infarct side, hypertension before stroke and involved gyrus (insular cortex or precentral gyrus or post-central gyrus or pre- and post-central gyrus together). As dependent variable we used the systolic (≥ 140 vs < 140 mmHg) and diastolic BP (≥ 90 vs < 90 mmHg) at admission or the absolute diurnal systolic (≥ 2 vs < 2 mmHg) or diastolic BP ($\geq 3,5$ vs $< 3,5$ mmHg) variation (the cut-off points for the absolute diurnal systolic and diastolic BP variation were established by dividing the diurnal BP variation in two equal parts).

Results

The characteristics of the patients included in the study ($N=106$) and the patients who were not ($N=676-106=570$) are shown in table 1. Patients in the study group had a slightly better CNS score at admission than the remaining patients. Furthermore, there were fewer patients with known diabetes mellitus before stroke onset in the study group (table 1). The remaining characteristics were rather similar between the groups. Patients in whom MRI was not performed were probably those with more severe deficit.

Table 1: Patient characteristics of the study group ($N=106$) and the remaining patients ($N=570$) (for abbreviations see text)

	Study group N, (%)	Remaining patients N, (%)
Sex: male	55 (52)	292 (51)
female	51 (48)	279 (49)
Age: median (range)	70 (35-87)	74 (18-98)
IHD	31 (29)	182 (32)
DM	13 (12)	106 (18)
HT	49 (46)	275 (48)
Stroke type: LACI	25 (23)	146 (26)
CE	23 (22)	122 (21)
AT	58 (55)	302 (53)
CNS at admission:		
≤ 2	5 (5)	57 (10)
> 2 and ≤ 4	8 (7)	87 (15)
> 4 and ≤ 6	19 (18)	83 (15)
> 6 and ≤ 8	35 (33)	163 (28)
> 8 and ≤ 10	39 (37)	180 (32)

Relationship of the first measured BP at the first aid ward with site and size of the infarct.

Forty-nine of the 81 patients with a territorial stroke type had a symptomatic cortical infarct on MRI. Eighteen of the 81 patients had a subcortical, non-lacunar infarct on MRI. Twelve had a (non-lacunar) brainstem infarct on MRI; these were not further analysed. The remaining two of the 81 patients did not show an infarct on the MRI. Twenty-two of the 25 patients with a lacunar stroke type showed a symptomatic lacunar infarct on MRI, whereas the remaining 3 patients did not show such infarct on MRI (table 2).

Table 2: Proportion of patients with elevated first BP values (BP↑), related to infarct type, hemispheric (H) side, or insular cortex involvement.

	All N, BP↑ (%)	Right H N, BP↑ (%)	Left H N, BP↑ (%)
Cortical infarct	49, 34 (69)	25, 16 (64)	24, 18 (75)
INS +	29, 18 (62)	17, 10 (59)	12, 8 (67)
INS -	20, 16 (80)	8, 6 (75)	12, 10 (83)
LACI	22, 20 (91)	10, 8 (80)	12, 12 (100)
Subcortical	18, 14 (78)	12, 10 (83)	6, 4 (67)

Table 2 shows the proportion of patients with elevated first BP values, related to infarct type, whether the lesion was in the left or right hemisphere, and whether or not the insular cortex was involved. There were no statistically significant differences in the number of patients with elevated first BP, between patients with or without insular involvement, and between patients with a right- or left-sided insular infarct (independent-samples T test). The number of patients with elevated BP was significantly higher in the lacunar infarct group compared to the cortical infarct group (independent-samples T test).

Table 3 shows how often the various gyri were involved in the infarct, in the 49 cortical infarct patients with or without first BP elevation. Analysing any independent relationship between any particular cortical gyrus and BP elevation by means of logistic regression analysis, did not reveal any such relationship. Also, infarct size or hemispheric side were not related with the BP variables.

Table 3 : Affected cortical gyri in 49 patients with a cortical infarct; distinction between 34 patients with elevated first measured BP (BP†) and 15 without. Number of patients with particular gyrus damaged.

Territorial gyri (G)	Patients with BP†	Patients without BP†
	(N=34) N, (%)	(N=15) N, (%)
Anterior cerebral artery territory:		
- rectal G	0	0
- superior frontal G	2 (6)	0
- cingulate G	2 (6)	0
- precuneus G	0	0
- paracentral lobule	1 (3)	0
Middle cerebral artery territory:		
- orbital G	0	0
- superior temporal G	16 (47)	10 (67)
- middle temporal G	14 (41)	8 (53)
- inferior temporal G	0	1 (7)
- middle frontal G	6 (18)	1 (7)
- inferior frontal G	10 (29)	4 (27)
- precentral G	14 (41)	10 (67)
- post-central G	12 (35)	9 (60)
- supramarginal G	11 (32)	7 (47)
- angular G	7 (20)	3 (20)
- occipital lobe	0	1 (7)
- superior parietal lobule	1 (3)	0
- central sulcus	1 (3)	0
- sylvian fissure	0	1 (7)
- insular cortex	18 (53)	11 (73)
Posterior cerebral artery territory:		
- parahippocampal G	2 (6)	2 (13)
- fusiform G	2 (6)	2 (13)
- uncus	0	0
- occipital lobe	2 (6)	3 (20)
- cingulate G	1 (3)	1 (7)
- lingual G	2 (6)	1 (7)
- cuneus	1 (3)	0
- precuneus	0	0
- calcarine sulcus	0	0
- parieto- occipital fissure	0	1 (7)

Relationship of diurnal BP variation with site and size of the infarct.

Of the 192 patients who had over 80 % data capture of the 24-hour BP measurements, 73 had an MRI. Table 4 shows the characteristics of these 73 and the remaining 603 patients.

Table 4: Patient characteristics of the study group (N=73) and the remaining patients (N=603) (for abbreviations see text)

	Study group N, (%)	Remaining patients N, (%)
Sex: male	38 (52)	309 (51)
female	35 (48)	294 (49)
Age: median (range)	72 (35-87)	74 (18-98)
IHD	21 (29)	196 (32)
DM	8 (11)	111 (18)
HT	32 (44)	293 (49)
Stroke type: Laci	16 (22)	157 (26)
CE	17 (23)	129 (21)
AT	40 (55)	317 (53)
CNS at admission:		
≤ 2	3 (4)	57 (9)
> 2 and ≤ 4	5 (7)	90 (15)
> 4 and ≤ 6	12 (17)	90 (15)
> 6 and ≤ 8	25 (34)	173 (29)
> 8 and ≤ 10	28 (38)	193 (32)

Thirty-four patients had a territorial infarct on the MRI scan. Fourteen of the 34 patients had an infarct in the left and 20 had an infarct in the right hemisphere. There was no statistically significant difference in absolute or percentage diurnal variation in systolic or diastolic BP between these two groups. Twenty-one of the 34 patients had an infarct involving the insular cortex, whereas 13 had not. There was no statistically significant difference in absolute or percentage diurnal variation in systolic or diastolic BP between these two groups. Analysing any independent relationship between the particular cortical gyrus and absolute diurnal BP variation by means of logistic regression analysis, showed that insular involvement was associated with higher diurnal diastolic BP variation (OR 17; 95 % CI 1.8-155.9). Infarct size or hemispheric side were not related to the BP variables.

Discussion

We analysed whether early BP elevation, and diurnal BP variation in patients with an acute cerebral infarct were related to infarct site or size, or the involvement of certain cortical gyri, the insular cortex in particular. We found no differences between patients with or without early BP elevation with regard to whether the lesion was in the right or left hemisphere, nor whether the insular cortex was involved or not. Furthermore, we could not establish a relationship between early BP elevation and insular cortex involvement, cortical infarct size, or hemispheric side in multivariate regression analysis. Opposite to what we expected, considering the findings of others, we found insular cortex involvement to be related to a higher, instead of lower, diurnal BP variation in multivariate regression analysis. However, we can not exclude this to be a finding by chance, as we have no biologically plausible explanation for this finding, and patient numbers were relatively small.

Our findings do not concur with a specific role attributed to the insular cortex in autonomic function control, at least, not as far as early BP rise and degree of diurnal BP variation in acute stroke is concerned.¹⁴⁸⁻¹⁵⁰ Cheung and Hachinski recently reviewed the role of the insula in cerebrogenic cardiovascular and autonomic disturbances.¹⁵¹ They pointed at experimental and clinical data sustaining the role of the insular area, the right-sided insula in particular, in the modulation of sympathetic activity. Damage to especially the right insula may result in sympathetic overactivity. Clinical evidence that favours the role of the insula in autonomic function control comes mainly from patients with cerebral infarction. Involvement of the insula in middle cerebral artery infarcts may provide an “experiment of nature” from which inferences may be made on regular functions of this area. However, most studies on variables of autonomic function in patients with stroke involving the insular region measured parameters of cardiac function, such as heart rate variability,¹⁵²⁻¹⁵⁶ arrhythmias,^{149 157} repolarisation characteristics,¹⁵⁸ or cardio baroreceptor sensitivity.⁹⁵ It seems logical to consider BP regulation and control of diurnal BP variation as variables of the autonomic nervous system function, and relate changes in these features to the area of damage in stroke to study the role of that area in autonomic function control. However, the number of such studies is limited, and were performed by only one group. Sander et al. found a correlation between the extent of insular infarct involvement on MRI and circadian BP variation in 52 patients with hemispheric infarction.¹⁰⁹ However, there was also a relationship between infarct size and insular involvement, so that one can not exclude any influence of infarct size on the relationship. Besides, the number of patients with or without insular involvement were not provided. There was, however, a correlation between the extent of insular damage and norepinephrine levels, and also with QTc prolongation. The study does not allow a definite conclusion on the relationship between insular damage related sympathetic overactivity and diurnal BP variation decrease. In an earlier study, the same authors found no relationship between infarct size and insular involvement in 45 hemispheric infarct patients, of whom about 75 percent had MRI.⁹² They found a highly significant difference in the proportion with nocturnal BP decrease between 18 patients with and 17

without insular involvement using univariate comparison. No multivariate testing was done, especially not with other brain regions as independent variables. Some patients were included in the study up to one week after stroke onset. How long after stroke BP measurements take place is of importance, as the decrease of diurnal variation is a transient phenomenon, whereas it is unknown how eventual return to normal diurnal BP pattern develops over time, nor what factors influence such normalisation. In a third study, of a consecutive series of 35 patients who were admitted within 48 hours after stroke onset, 20 had left-, and 15 had right-sided hemispheric infarction.⁹¹ Two-third of them had MRI. In nine of the left- and six of the right-sided infarcts the insular cortex was involved. Patients with right-sided infarction showed significant reduction in diurnal BP variation compared to left-sided infarcts. Patients with insular damage showed significantly more often decreased diurnal BP variation than those without, but this difference was not restricted to right-sided infarcts. Although the groups showed no 'statistically significant difference' with regard to various patient characteristics, this does not make multivariate testing redundant.

So, these three studies were performed by the same authors, had similar study design, and although they were published very closely in time, any possible repeated participation of patients in different studies was not addressed. Why our results differ from those of Sander et al. is not clear. We did not exclude patients who received antihypertensive treatment or anti-arrhythmic drugs, or any other lesion on MRI, as Sander et al. did. But it is unlikely that this difference would explain any absence of insular role in early BP rise or diurnal BP variation decrease, as both these phenomena were highly prevalent in our study. It could be, though, that the role of the insula was blunted by the role other lesions may play, such as 'silent' lacunar infarcts, for example. However, in chapter 5 we just found the opposite: such lesions were associated with less diurnal BP variation decrease. Lesion characterisation may not have been optimal in the studies of Sander et al., as in two of their studies not all patients had MRI, like in our study. However, this also is unlikely to explain the difference, as findings were rather consistent between their three separate studies. We included only patients within 24 hours after stroke onset. In the studies of Sander et al. it was 48 hours in two studies, whereas a maximal period was not mentioned in one study. The results of Sander et al. may allow the conclusion that the insular cortex plays a role in the recovery of physiological diurnal BP patterning following the acute stroke phase, rather than in raising early BP and abolishing diurnal BP variation in acute stroke. Another strong argument that the insular cortex is unlikely to play a unique role in these acute stroke phenomena, is that they also occur in infarcts not involving the cortex at all, such as lacunar and larger subcortical infarcts. In fact, these phenomena occurred even more often in these infarct groups than in infarcts involving the insular region. Subcortical lesions may also affect the integrity of the autonomous nervous system with, consequently, sympathetic overshoot. Therefore, our study does not deny a role of the insula in autonomic function disturbances following stroke, but its role is not unique. Lesions at different sites in the neuronal circuitry that sustain the autonomic nervous system balance may result in dysfunction. The findings of Yamamoto et al. sustain such idea.⁹³ They found that the

degree of nocturnal BP decline was related to various (ischemic) lesion sites. They found that patients with multiple lacunar lesions had the smallest diurnal BP variation decline. The sympathetic response on BP in acute stroke may become blunted by the presence of prior lesions, especially when these are multiple.

In conclusion: experimental and clinical data have revealed a crucial role of the insular cortex in the autonomic nervous system cardiovascular control. From our data, however, we can not infer an unique role of the insular region in sympathetic overactivity that induces early BP rise and decrease of diurnal BP variation in acute stroke. Damage anywhere along the cerebral neuronal circuitry involved in BP regulation, may elicit these phenomena. The response may be blunted when the integrity of the autonomic regulatory system is already damaged by prior lesions.

General discussion

This thesis encompasses a retrospective and a prospective part. We wanted to explore whether blood pressure (BP) in acute stroke is related to functional outcome, because it is important to find indications whether BP manipulation in acute stroke could perhaps improve prognosis. For that purpose we also needed to know more about the course of BP in the acute phase of stroke, and identify patients who have a higher risk in developing elevated BP levels after stroke onset.

In the retrospective part, we explored predictors of post-stroke BP level, and the course of the BP level in the first week after stroke onset. Furthermore, we studied the prognostic value of BP in acute stroke. We performed these studies in patients who were admitted to the stroke unit within 24 hours following stroke onset. First, we found that known hypertension before stroke was an independent predictor of initial BP level in acute stroke. Second, elevated BP in acute stroke decreased spontaneously during the first days after stroke, with the greatest decline during the first three days. BP level during the first week was higher in patients known with hypertension before stroke than in those without. Since different stroke subtypes have different underlying pathophysiological mechanisms, stroke subtype may influence BP level and course. However, we found no significant difference in initial BP level, nor in the course of BP between patients with different stroke subtypes. These findings indicate that cause, size, and location of the infarct are not related to the level and course of BP in acute stroke. Furthermore, we found no significant relationship between the first measured BP after admission and functional outcome. BP values measured during the daytime hours of the first 24 hours after stroke, also showed no relationship with outcome, whereas high and low nighttime BP values were related to poor outcome. Since a retrospective study could create bias towards an increased chance of detecting extreme BP values, the strength of an association between BP and outcome could be overestimated. Consequently, we decided to perform a prospective study in patients admitted within 24 hours after stroke onset.

In this prospective study, we found that patients known with hypertension before stroke or patients with asymptomatic lacunar infarcts on CT had significantly higher first BP values than those without the specific feature. Again, no relationship was found between stroke subtype and level of first BP. We found no relationship between the first measured BP values after admission at the first aid ward, and functional outcome. Results of other studies varied: some found no relationship between BP in the acute phase of stroke and functional outcome,^{46 70-73} whereas other studies found high^{42 48 50 74-76} or low⁷⁷ BP values to be related to poor outcome. When studying the relationship between 24-hour BP measurements and outcome, we only found low first (of the 24-hour BP measurements) measured diastolic BP values to be significantly related to poor functional outcome, whereas mean daytime and nighttime BP values were not. The period during which these last BP variables were being monitored, likely surpassed the time of an amendable penumbra. Since cerebral autoregulation is disturbed after stroke onset, cerebral perfusion is directly dependent on systemic BP.⁴²⁻⁴⁵ In this perspective, low or high BP values, or both, would be expected to relate to stroke outcome. We could not clearly establish such relationship, possibly because our study population was too small, and any relationship went undetected. However, any effect of BP extremes on stroke

outcome would than likely be rather small. Maybe, studying only predefined subgroups with high or low BP values in acute stroke, could show the expected relationship with outcome, but even then, large numbers would be required. If so, it would make an intervention trial in acute stroke not easy, whereas, if any benefit would be proven, it would only be applicable in small patient groups: those with extremely high or low BP level. Therefore, on the basis of our data, the possibility of an integral BP treatment for all stroke patients does not seem to be a feasible option to be studied in a clinical trial.

It is well known that there is a diurnal pattern of BP change, with morning values higher than those recorded in the evening, and a further decrease (dip) during nighttime.⁷⁸⁻⁸² Other investigators found that stroke patients show a decrease in diurnal variation.^{59 81 86} This was in line with our findings. We found no relationship between diurnal BP variation, as registered with 24-hour BP monitoring, and outcome. Patients with lacunar stroke, especially those known with hypertension, had the largest diurnal BP variation. We also found that patients with asymptomatic lacunar infarcts on CT had higher diurnal BP variation than patients without. So, why does a subgroup of stroke patients with rather extreme forms of hypertensive end-organ damage in the brain, have the largest diurnal BP variation in acute stroke? One reason could be that this damage is not directly caused by the hypertension: the two phenomena are related, but not (completely) causally. This hypothesis is strengthened by our earlier findings that asymptomatic infarcts and leukoaraiosis progress over time, despite measures of secondary stroke prevention, among which, treatment of hypertension.¹⁴¹ Therefore, hypertension treatment in patients with large variation in diurnal BP values, such as so-called 'dippers', may lower BP values under the limit where sufficient cerebral perfusion pressure can be maintained, which could lead to ischemic lesions. So, there may be a stroke subgroup in which hypertension treatment does not prevent, but rather enhances further end-organ damage. This specific group of patients, with small vessel arteriolosclerosis, is small in stroke series, and may comprise approximately five percent of all ischemic stroke patients. They were never considered separately in trials on the effect of hypertension treatment in lowering vascular end-points such as stroke, nor have they been considered separately in end-point measurements. Another possibility to explain the finding of a large diurnal BP variation in our lacunar stroke patients could be that these patients have a more physiological sleeping pattern than patients with more extended cerebral damage.^{142-144 159}

Finally we studied whether early BP elevation, and diurnal BP variation in patients with an acute cerebral infarct were related to infarct site or size, or the involvement of certain cortical gyri, the insular cortex in particular. We found no differences between patients with or without early BP elevation with regard to whether the lesion was in the right or left hemisphere, nor whether the insular cortex was involved or not. When we considered cortical and subcortical infarcts separately, there were also no differences. Furthermore, we could not establish a relationship between early BP elevation and insular cortex involvement, cortical infarct size, or hemispheric side. Also, we found no relationship between insular involvement and diurnal BP variation. Our findings indicate that the

insular region has no specific role in autonomic function control, at least not as far as early BP rise and decrease of diurnal BP variation in acute stroke is concerned. Damage anywhere along the cerebral neuronal circuitry that regulates BP may elicit these phenomena. The integrity of a regulatory system may therefore be more important than that of a particular component of the system. However, what factors are involved in the normalisation of BP level, and diurnal BP variation during the first weeks following stroke, is unknown. Damage to the insular cortex may slow down this normalisation. Continuous BP measurements for one or two weeks following stroke, may test this hypothesis.

9

Summary

Stroke is an important disease. In the Netherlands there are approximately 30.000 new strokes each year. Until today, thrombolysis is the only available effective therapy for ischemic stroke patients. However, only five to ten percent of all ischemic stroke patients will be eligible for this therapy. An additional possibility to improve prognosis following stroke may be achieved by manipulating the level of blood pressure (BP) in acute stroke. What BP values should be treated, and what BP level to aim at in such treatment remains enigmatic. In addition, it's dangerous to treat BP in a uniform manner. This consideration relates to the concept of cerebral autoregulation, which implies that under normal conditions regional cerebral blood flow is kept constant over a certain range of systemic BP. In stroke, this mechanism is lost, and cerebral perfusion becomes directly BP dependent. High BP levels may thereby result in edema formation and local hemorrhage, which leads to further damage. Low systemic BP, on the other hand, can not be compensated for, and will also lead to further ischemic damage. So far, little is clear about what factors independently predict the level of BP in the acute phase of stroke, or what BP characteristics are independent predictors of stroke outcome. Before any clinical trial on BP treatment in acute stroke can be rationalized, more data on these issues are required. In the present study we explored and investigated factors related to BP level and course in acute stroke, and various BP characteristics as independent predictors of stroke outcome.

In *chapter 1* the relevant literature on this subject is reviewed: BP is elevated in 70 to 94 percent of acute stroke patients. This elevated BP spontaneously declines during the first week. Data on the prognostic significance of BP levels following acute stroke are conflicting: some studies showed no relationship between admission BP and outcome, whereas others reported high or low admission BP to be related to poor outcome. In normotensive persons, there is a diurnal pattern of BP change with morning values being higher than those recorded in the evening, and with further decrease during nighttime. An arbitrarily chosen absolute 10 mmHg day minus night BP fall, or a 10 percent BP decrease is called 'dipping'. Stroke patients show a decrease in diurnal BP variation. Data on the prognostic significance of the degree of diurnal BP variation after stroke are controversial.

In *chapter 2* BP values of 409 patients with a first-ever ischemic stroke, admitted within 24 hours after stroke onset were studied. BP values that were measured within these first 24 hours were collected in retrospect. Linear regression analyses showed that the level of first BP measured after admission at the stroke unit was significantly related with age, known ischemic heart disease and known hypertension before stroke onset. Stroke type (atherothrombotic, lacunar or cardioembolic) and Rankin score at stroke onset were not significantly associated with initial BP level. Besides the first BP measured after admission, we studied several characteristics of the mean daytime BP value (measured between 9.00 and 18.00 hours) and mean nighttime BP value (measured between 24.00 and 6.00 hours). The course of BP level was studied during the first week after stroke onset. BP fell during this first week with the greatest decline during the first 3 days.

Nighttime BP showed a similar course as daytime BP. Patients in a control group showed a similar course. BP during the first week was higher in patients with hypertension before stroke than in those without known hypertension. There was no significant difference in initial BP level nor in the course of BP when comparing atherothrombotic with cardioembolic or lacunar stroke patients.

We concluded that an increase in post-stroke BP is not a general phenomenon, nor is the decline in BP in the first week post-stroke. Both phenomena occur irrespective of stroke subtype. Known hypertension is probably the strongest predictor of post-stroke BP increase.

In *chapter 3* we studied the prognostic value of BP in acute stroke. For this study we used the same patient group as in chapter 2. As outcome variable we used the Rankin score at three months: a Rankin score ≤ 3 was used as good outcome, a Rankin score > 3 as poor outcome. Univariate analysis suggested that both low and high BP values were related to poor outcome. Multivariate analyses showed no significant relationship between the first measured BP after admission and functional outcome at three months. Multivariate analysis also showed no relationship between daytime BP values and outcome at three months, whereas a significant association was found between nighttime BP and outcome: a nighttime systolic BP ≥ 165 mmHg or a nighttime diastolic BP ≤ 60 mmHg was significantly related with poor outcome (OR 2.8; 95 % CI 1.1-6.8 resp. OR 8.1; 95 % CI 1.1-58.3). When studying the relationship between the fall in BP and outcome, we found a decrease in daytime diastolic BP during the first 4 days after stroke onset ≥ 10 mmHg to be associated with poor outcome (OR 3.0; 95 % CI 1.1-7.9).

We concluded that unadjusted BP values towards the lower and higher end were related with poor outcome, but warned against unadjusted analysis of first post-stroke BP as outcome predictor. Nighttime BP values may have independent predictive value for stroke outcome. The data suggest that lowering very high BP may be beneficial, provided it is not lowered too drastically, while conversely increasing a low BP may confer benefit as well. This retrospective study, may however overestimate the strength of association between BP and outcome, as it could be biased towards inclusion of more patients with sustained high or low BP values.

In *chapter 4* we studied the prognostic value of the first BP measured after admission at the first aid ward in 271 patients with an ischemic stroke. This was a prospective study; patients were included within 24 hours following stroke onset. As dependent outcome variable, we used the score on the Rankin handicap-scale at six months (Rankin > 3 as poor outcome versus Rankin ≤ 3 as good outcome). We found that patients with known hypertension before stroke onset had a significantly higher first systolic BP than those without. Furthermore, males had a significantly higher first systolic and diastolic BP than females. With increasing age, the systolic first BP value rose significantly. Patients with asymptomatic lacunar infarcts on CT had significant higher first systolic and diastolic BP values than those without. Finally, patients known with ischemic heart disease before stroke onset had significantly lower first BP values than those without, which may be

related to treatment. Univariate analyses suggested that high and low BP values were related to poor stroke outcome. However, multivariate analyses showed no significant relationship between the first BP measured directly after arrival at the first aid ward and the outcome at six months. When analysing only those BP values of patients that were admitted within 3 hours following stroke onset ($N=138$), we also could not establish a significant relationship between these first BP values and the functional outcome at six months. We found no evidence in favour of the idea that low or high early BP is a stroke outcome predictor. Small numbers may have failed to detect any (small size) relationship between BP extremes and outcome, but our data do not favour BP manipulation to serve as a potential therapy for acute stroke in general.

In *chapter 5* we prospectively studied 24-hour monitored BP values, measured in ischemic stroke patients who were admitted within 24 hours following stroke onset. BP measurement was started within the first 24 hours after stroke onset. Of the 271 patients studied in chapter 4, 192 had over 80 % of the 24-hour BP data capture. Of these 192 patients, we studied BP levels and diurnal variation. We found that per one year ageing, the absolute variation in systolic and diastolic BP significantly declined. Patients with a Rankin score 5 at admission showed a significantly lower absolute BP variation compared to patients with a Rankin score 1 or 2. In accordance with this finding, patients with a CNS score 8-10 at admission showed a significantly higher absolute BP variation compared to patients with a CNS score ≤ 2 . Twenty-four hour BP profiles showed lower BP values during nighttime hours and resting hours during the daytime. When studying the BP profiles for the different stroke subtypes (lacunar vs atherothrombotic vs cardioembolic infarcts), the BP profiles were quite similar in all three groups.

The first measured BP values were significantly higher than the mean of the 24-hour BP values for all stroke subtypes. Lacunar infarct patients had significantly higher 24-hour and daytime systolic and diastolic BP than cardioembolic infarct patients. Furthermore, lacunar infarct patients had significantly higher absolute and percentage systolic and diastolic BP variation than cardioembolic and atherothrombotic infarct patients. We found a decrease in diurnal BP variation in most ischemic stroke patients. When studying the stroke subgroups, we found a larger diurnal variation in lacunar infarct patients. Furthermore, we found asymptomatic lacunar infarcts on CT to be independently related to a higher diurnal BP variation. This was in contrast with findings of others, who found a decrease in diurnal variation in lacunar stroke patients. We postulated that lacunar stroke, especially in the presence of asymptomatic infarcts on CT, may not be causally related to hypertension, and that in the presence of low BP values hypertension treatment may worsen, instead of prevent, ischemic brain damage in this lacunar stroke subtype.

In *chapter 6* the prognostic value of the BP values of the 192 patients was tested. Univariate analysis of the first measured BP values of the 24-hour BP monitoring suggested that high and low BP values were related to poor outcome. Multivariate analyses, however, only showed a statistically significant relationship with poor outcome

for patients with a first diastolic BP value ≤ 70 mmHg. However, when replacing the Rankin score on admission for the CNS score on admission in the multivariate analysis, the relationship with the outcome for a diastolic BP ≤ 70 mmHg was not statistically significant anymore. We also found no relationship between the day- and nighttime BP values and the outcome at six months. Furthermore, no statistically significant associations were found between the diurnal BP variation and outcome and between the fall in BP during the first 4 days and the outcome at six months. We concluded that it is likely that in the vast majority of ischemic stroke patients, BP values are in a range that does not jeopardize penumbral tissue, and any relationship between BP extremes and stroke outcome is difficult to establish unless large numbers of patients, or only pre-defined subgroups with extremely high or low BP values are investigated. Similar reasoning may apply to the testing of early BP manipulation in an acute stroke trial.

In *chapter 7* we studied the relationship between infarct location and size, and elevated BP (defined as a systolic BP > 140 mmHg or a diastolic BP > 90 mmHg) in acute stroke patients. Of the 271 patients studied in chapter 4, 106 patients underwent, besides a CT scan, an MRI scan of the brain. Forty-nine of the 106 patients had a symptomatic territorial (cortical) infarct, and 22 patients had a symptomatic lacunar infarct on MRI. Thirty-four (69 %) of the 49 patients had elevated BP on hospital admission. Twenty-five patients had a territorial infarct in the right-sided hemisphere, 16 (64 %) of these had elevated BP. Twenty-four patients had a territorial infarct in the left-sided hemisphere, 18 (75 %) of these had elevated BP. We found no statistically significant difference in number of patients with elevated BP between these two groups. The insular cortex was involved in the ischemic area in 29 of the 49 patients, and consequently, not in the 20 remaining patients. Eighteen (62 %) of these had elevated BP on admission. Of the 34 patients with elevated BP, 18 patients (53 %) had an infarct in the insular cortex (10 (29 %) in the right-sided insular cortex, 8 (23 %) in the left-sided insular cortex). Of the 15 patients without elevated BP, 11 patients (73 %) had an infarct in the insular cortex (7 (47 %) in the right-sided insular cortex, 4 (27 %) in the left-sided insular cortex). There was no statistically significant difference in the number of patients with elevated BP between the left- and right-sided insular infarcts. We also found no statistically significant difference in number of patients with elevated BP and an infarct involving the insular cortex, and patients without elevated BP and an infarct involving the insular cortex. Of the 22 lacunar stroke patients, 20 (91 %) had elevated BP on admission. When testing the relationship between different involved gyri (insular cortex, precentral gyrus or post-central gyrus), site or size of the infarct and elevated BP at admission in a multivariate analysis, we found no significant relationship between these variables. Furthermore, we found no statistically significant difference in absolute or percentage diurnal variation in systolic or diastolic BP between patients with a left- or right- sided cortical infarct or patients with or without an insular infarct.

Our findings argue against an important role of certain cortical areas, especially of the insular cortex, or of the degree of cerebral tissue damage in causing post-stroke BP elevation. We concluded that the integrity of connecting pathways of the sympathetic

nervous system on the whole, underlies the mechanism for BP level control, rather than that a unique cerebral site would serve such function. It remains unclear what factors determine the normalisation of BP level and diurnal BP variation in the first week following stroke.

10

Samenvatting

Een beroerte (CVA) is een veel voorkomende aandoening. In Nederland krijgen ieder jaar ongeveer 30.000 mensen een beroerte. Op dit moment is thrombolysen de enige werkzame acute therapie voor patiënten met een ischemisch CVA. Echter, slechts 5 tot 10 procent van alle patiënten met een ischemisch CVA komt in aanmerking voor thrombolysen. Een andere mogelijkheid om de prognose na een CVA te verbeteren zou kunnen bestaan uit het manipuleren van de hoogte van de bloeddruk (BD) in de acute fase van het CVA. Het is echter onbekend vanaf welke bloeddrukwaarden een behandeling gestart moet worden en naar welke bloeddrukwaarden gestreefd moet worden. Daarbij is het gevaarlijk de BD van alle patiënten op dezelfde manier te behandelen. Dit wordt verklaard aan de hand van de cerebrale autoregulatie die ervoor zorgt dat onder normale fysiologische omstandigheden bij bepaalde BD waarden, de regionale bloeddorstrooming in de hersenen constant wordt gehouden. Door een CVA raakt de cerebrale autoregulatie verstoord. Hierdoor is de doorstroming van de hersenen direct afhankelijk van de systemische BD. Hoge BD waarden kunnen daardoor leiden tot oedeem vorming of hemorragisch worden van het ischemisch gebied, met toename van de cerebrale schade tot gevolg. Lage BD waarden daarentegen, kunnen leiden tot uitbreiding van het ischemisch gebied, met eveneens toename van de cerebrale schade tot gevolg. Tot nu toe is weinig bekend over welke factoren onafhankelijke voorspellers zijn van de hoogte van de BD in de acute fase van het CVA, of welke BD karakteristieken onafhankelijke voorspellers van het functioneel herstel zijn. Voordat een klinisch onderzoek over BD behandeling in de acute fase van het CVA opgezet kan worden, zijn meer gegevens over dit onderwerp nodig.

In dit onderzoek hebben we verschillende factoren onderzocht, die samenhangen met de hoogte en het beloop van de BD in de acute fase van het CVA, en hebben we verschillende BD karakteristieken onderzocht die als onafhankelijke voorspellers van het functioneel herstel dienen.

In *hoofdstuk 1* wordt een literatuur overzicht gegeven. De BD is in de acute fase van het CVA verhoogd bij 70 tot 94% van de patiënten. Deze verhoogde BD daalt spontaan gedurende de eerste week na het CVA. Gegevens over de prognostische waarde van de hoogte van de BD in de acute fase zijn tegenstrijdig: sommige onderzoekers vonden geen relatie tussen de hoogte van de BD en het functioneel herstel, terwijl anderen een relatie vonden tussen hoge of lage BD waarden en een slecht herstel.

In normotensieve personen is er een circadiaan BD patroon, waarbij de ochtend BD waarden hoger zijn dan de avond waarden, met een verdere daling van de BD gedurende de nacht. Een arbitrair gekozen absolute daling van 10 mmHg of een relatieve daling van 10 % tussen de dag- en nachtwaarde wordt 'dipping' genoemd. Bij de meeste CVA patiënten is de circadiane BD variatie verminderd. Gegevens over de prognostische waarde van de mate van de circadiane variatie in de acute fase van het CVA zijn eveneens tegenstrijdig.

In *hoofdstuk 2* werden BD waarden bestudeerd van 409 patiënten die binnen 24 uur na het ontstaan van een eerste herseninfarct werden opgenomen. De BD waarden die binnen

deze eerste 24 uur gemeten waren, werden retrospectief verzameld. Lineaire regressie analyses toonden aan dat de hoogte van de eerst gemeten BD na opname op de stroke unit een significante relatie had met de leeftijd, ischemische hartziekten en/of hypertensie in de voorgeschiedenis. Het CVA type (atherothrombotisch, lacunair of cardioembolisch) en Rankin score bij opname hadden geen significante relatie met de hoogte van de initiële BD. Behalve de eerst gemeten BD na opname op de stroke unit, bestudeerden we verschillende karakteristieken van de gemiddelde dagwaarde (BD gemeten tussen 9.00 en 18.00 uur) en gemiddelde nachtwaarde (BD gemeten tussen 24.00 en 6.00 uur). Het beloop van de BD gedurende de eerste week na het ontstaan van het CVA werd bestudeerd. De BD daalde spontaan in deze eerste week, waarbij de grootste daling gedurende de eerste 3 dagen optrad. De nachtwaarden toonden eenzelfde beloop als de dagwaarden. Het BD beloop bij patiënten in een controle groep was hetzelfde. Patiënten bekend met hypertensie in de voorgeschiedenis hadden hogere BD waarden gedurende de eerste week na het CVA dan patiënten zonder hypertensie in de voorgeschiedenis. Er was geen significant verschil in initiële BD hoogte en BD beloop tussen patiënten met een atherothrombotisch, cardioembolisch of lacunair infarct. Geconcludeerd werd dat de stijging van de BD post-CVA en daling van deze BD in de eerste week post-CVA geen algemene fenomenen zijn. Beide fenomenen treden onafhankelijk van het CVA type op. Aanwezigheid van hypertensie in de voorgeschiedenis is waarschijnlijk de grootste voorspeller van de BD stijging in de acute fase van het CVA.

In *hoofdstuk 3* werd de prognostische waarde van de BD in de acute fase van het CVA bestudeerd. Hierbij werd gebruik gemaakt van dezelfde groep patiënten als in hoofdstuk 2. Als maat voor het functioneel herstel werd de Rankin score op 3 maanden gebruikt: voor een goede uitkomst (goed functioneel herstel) werd een Rankin score ≤ 3 genomen, voor een slechte uitkomst (slecht functioneel herstel) een Rankin score > 3 . Univariate analyses toonden aan dat zowel hoge als lage BD waarden de neiging hadden een relatie te vertonen met een slecht functioneel herstel. Met behulp van multivariate analyses werd echter geen relatie aangetoond tussen de eerst gemeten BD na opname op de stroke unit en het functioneel herstel op 3 maanden. Ook werd er m.b.v. multivariate analyses geen relatie gevonden tussen de gemiddelde dag BD waarden en het functioneel herstel op 3 maanden. Wel werd er een significante associatie gevonden tussen een gemiddelde systolische nacht BD waarde ≥ 165 mmHg en een gemiddelde diastolische nacht BD waarde ≤ 60 mmHg en een slecht functioneel herstel: OR 2.8; 95 % BI 1.1-6.8 resp. OR 8.1; 95 % BI 1.1-58.3. Bij het bestuderen van de relatie tussen de daling van de BD in de eerste 4 dagen na het ontstaan van het CVA en het herstel op 3 maanden, vonden we een significante relatie tussen een daling ≥ 10 mmHg en een slecht herstel: OR 3.0; 95 % BI 1.1-7.9. We concludeerden dat niet-gecorrigeerde hoge en lage BD waarden gerelateerd zijn aan een slechte outcome, en waarschuwden voor het ongecorrigeerd analyseren van eerste post-CVA BD waarden als voorspeller voor het functioneel herstel. Gemiddelde nachtelijke BD waarden zouden een onafhankelijke voorspellende waarde voor het functioneel herstel kunnen hebben. De resultaten lijken aan te geven dat verlagen van hoge BD waarden gunstig kan zijn, mits deze niet te drastisch verlaagd worden. Het

verhogen van lage BD waarden lijkt eveneens zinvol. Een nadeel van deze retrospectieve studie is echter dat de relatie tussen de hoogte van de BD en het functioneel herstel overschat kan worden, daar er een bias opgetreden kan zijn door te hoge inclusie van patiënten met aanhoudende hoge of lage BD waarden.

In hoofdstuk 4 hebben we de prognostische waarde bestudeerd van de eerst gemeten BD waarde direct na aankomst op de EHBO (EHBO BD) bij 271 patiënten met een herseninfarct. Dit betrof een prospectief onderzoek waarbij patiënten binnen 24 uur na het ontstaan van het CVA werden geïncludeerd. Als afhankelijke uitkomst variabele (maat voor het functioneel herstel) werd de score van de Rankin handicap schaal 6 maanden na het ontstaan van het CVA genomen: voor een goede uitkomst (goed functioneel herstel) werd een Rankin score ≤ 3 genomen, voor een slechte uitkomst (slecht functioneel herstel) een Rankin score > 3 . Patiënten bekend met hypertensie in de voorgeschiedenis bleken een significant hogere systolische EHBO BD waarde te hebben dan patiënten niet bekend met hypertensie. Mannen hadden een significant hogere systolische en diastolische EHBO BD waarde dan vrouwen. Met het stijgen van de leeftijd, nam de systolische EHBO BD waarde significant toe. Patiënten met asymptomatische lacunaire infarcten op de CT scan hadden significant hogere systolische en diastolische EHBO BD waarden dan patiënten zonder asymptomatische lacunaire infarcten op de CT. Patiënten die bekend waren met ischemische hartziekten in de voorgeschiedenis hadden significant lagere EHBO BD waarden dan patiënten die hier niet mee bekend waren. Deze laatste bevinding zou gerelateerd kunnen zijn aan de medicamenteuze behandeling. Bij univariate analyses werd een trend gevonden waarbij zowel hoge als lage EHBO BD waarden gerelateerd waren aan een slecht functioneel herstel. Multivariate analyses toonden echter geen significante relatie tussen deze EHBO BD waarden en het functioneel herstel op 6 maanden. Wanneer alleen de BD waarden van patiënten die binnen 3 uur na het ontstaan van het CVA op de EHBO waren geanalyseerd werden ($N=138$), kon eveneens geen significante associatie tussen de DB en het functioneel herstel aangetoond worden. Concluderend konden we geen ondersteuning vinden voor de theorie dat een hoge of lage bloeddruk een onafhankelijke voorspeller is van het functioneel herstel. Mogelijk had er een (welliswaar kleine) relatie tussen de BD en het herstel aangetoond kunnen worden wanneer de onderzochte patiëntenpopulatie groter was geweest. Onze resultaten ondersteunen manipulatie van de BD als vorm van acute behandeling, om de prognose na een CVA te verbeteren, echter niet.

In hoofdstuk 5 werden prospectief 24-uurs gemeten BD waarden bestudeerd, die om het half uur gemeten waren binnen 24 uur na het ontstaan van een ischemisch CVA. Van de 271 patiënten die bestudeerd werden in hoofdstuk 4, waren bij 192 patiënten meer dan 80 % van de 24-uurs BD waarden geregistreerd. Bij deze 192 patiënten werd de hoogte en de circadiane variatie van de BD bestudeerd. Met het stijgen van de leeftijd daalde de absolute variatie in systolische en diastolische BD significant. Patiënten met een Rankin score 5 bij opname hadden een significant lagere absolute BD variatie vergeleken met patiënten met een Rankin score 1 of 2 bij opname. In overeenstemming met deze

Appendix

bevinding, hadden patiënten met een CNS score 8-10 bij opname een significant hogere absolute BD variatie vergeleken met patiënten met een CNS score ≤ 2 bij opname. 24-uurs BD profielen toonden lagere BD waarden gedurende de nachtelijke uren en rust uren overdag vergeleken met de rest van de daguren. De BD profielen van de verschillende CVA typen (lacunaire vs atherothrombotische vs cardioembolische infarcten) vertoonden een gelijk patroon. De eerst gemeten BD waarde van de 24-uurs registratie was significant hoger dan de gemiddelde 24-uurs BD waarde. Patiënten met een lacunair infarct hadden significant hogere gemiddelde 24-uurs- en systolische en diastolische dag BD waarden dan patiënten met een cardioembolisch infarct. Verder hadden patiënten met een lacunair infarct een significant hogere absolute en relatieve systolische en diastolische BD variatie dan patiënten met een cardioembolisch of atherothrombotisch infarct. De meeste CVA patiënten hadden een verminderde dag en nacht BD variatie in de acute fase. Patiënten met een lacunair infarct hadden de grootste variatie in dag en nacht BD. De aanwezigheid van asymptomatische lacunaire infarcten op CT was onafhankelijk gerelateerd aan een grotere diurnale BD variatie. Dit strookt niet met de bevindingen van andere onderzoekers die een daling van de diurnal BD variatie vonden bij lacunaire infarct patiënten. Wij stelden dat lacunaire infarcten, speciaal in de aanwezigheid van asymptomatische lacunaire infarcten op CT, waarschijnlijk niet causaal gerelateerd zijn aan hypertensie, en dat antihypertensieve therapie, in aanwezigheid van lage BD waarden, ischemische cerebrale schade kan verergeren i.p.v. voorkomen.

In hoofdstuk 6 werd de prognostische waarde van BD metingen van 192 patiënten onderzocht. Univariate analyses van de eerst gemeten BD waarde van de 24-uurs BD registratie gaf de indruk dat hoge en lage BD waarden gerelateerd waren aan een slecht functioneel herstel. Multivariate analyses lieten echter alleen een statistisch significante relatie met een slecht functioneel herstel zien voor een eerst gemeten diastolische BD waarde ≤ 70 mmHg. Deze relatie was echter niet meer significant wanneer in de multivariate analyses de Rankin score bij opname vervangen werd door de CNS score bij opname. Er werd ook geen relatie gevonden tussen de dag en nacht BD waarden en het herstel op 6 maanden. Verder werden er geen statistisch significante associaties gevonden tussen de diurnale BD variatie of de daling van de BD gedurende de eerste 4 dagen en het herstel op 6 maanden. Wij concludeerden dat bij het grootste gedeelte van patiënten met een ischemisch CVA, de BD zich in een range bevindt die geen gevaar voor de penumbra oplevert. Een relatie tussen BD uitersten en het herstel is moeilijk vast te stellen behalve wanneer wellicht grote groepen patiënten, of duidelijk gedefiniëerde subgroepen met zeer hoge of lage BD waarden onderzocht zouden worden. Hetzelfde geldt voor het testen in trial verband van het manipuleren van de BD in de acute fase van het CVA.

In hoofdstuk 7 werd de relatie tussen de locatie en grootte van het infarct en verhoogde BD (gedefiniëerd als een systolische waarde > 140 mmHg en/of een diastolische waarde > 90 mmHg) bestudeerd in de acute fase van het CVA. Van de 271 patiënten die in hoofdstuk 4 bestudeerd werden, kregen 106 patiënten, naast een CT, een MRI scan van de hersenen. Negenenveertig van deze 106 patiënten hadden een corticaal infarct,

22 hadden een lacunair infarct op de MRI. Vierendertig (69 %) van de 49 patiënten hadden een verhoogde BD bij opname in het ziekenhuis. Vijfentwintig patiënten hadden een rechtszijdig corticaal infarct, 16 (64 %) van deze hadden een verhoogde BD. Vierentwintig patiënten hadden een linkszijdig corticaal infarct, 18 (75 %) hiervan hadden een verhoogde BD. Er was geen statistisch significant verschil in aantal patiënten met een verhoogde BD tussen deze 2 groepen. De insulaire cortex was betrokken bij het infarct in 29 van de 49 patiënten. Achttien (62 %) hiervan hadden een verhoogde BD bij opname. Van de 34 patiënten met een verhoogde BD, hadden 18 (53 %) een infarct in de insulaire cortex (10 (29 %) in de rechter en 8 (23 %) in de linker insulaire cortex). Van de 15 patiënten zonder verhoogde BD hadden 11 (73 %) een infarct in de insulaire cortex (7 (47 %) in de rechter, 4 (27 %) in de linker insulaire cortex). Er was geen statistisch significant verschil in aantal patiënten met een verhoogde BD tussen links- en rechtszijdige infarcten. Ook vonden we geen statistisch significant verschil in aantal patiënten met een verhoogde BD en een infarct in de insulaire cortex, en patiënten zonder verhoogde BD en een infarct in de insulaire cortex. Van de 22 patiënten met een lacunair infarct hadden er 20 (91 %) een verhoogde BD bij opname. Bij het testen van de relatie tussen de verschillende aangedane gyri (insulaire cortex, precentrale gyrus of postcentrale gyrus), zijde of grootte van het infarct en de verhoogde BD bij opname, werd geen significante relatie tussen deze variabelen gevonden. Verder werd er geen statistisch significant verschil tussen de absolute of relatieve diurnale variatie in systolische of diastolische BD gevonden tussen patiënten met een links- of rechtszijdig corticaal infarct of patiënten met of zonder een infarct in de insulaire cortex.

Onze bevindingen pleiten tegen een belangrijke rol van bepaalde corticale gebieden, in het bijzonder de insulaire cortex, of de hoeveelheid cerebrale weefsel beschadiging bij het ontstaan van de post-CVA BD verhoging. Wij concludeerden dat de integriteit van de verbindende banen van het sympatische zenuwstelsel in het geheel, ten grondslag ligt aan het mechanisme van BD controle, i.p.v. een unieke cerebrale localisatie. Het blijft onduidelijk welke factoren de normalisatie van het BD niveau en diurnale BD variatie in de eerste week na het CVA bepalen.

Appendix

The Modified Rankin Scale

- 0: no symptoms
- 1: minor symptoms that do not interfere with lifestyle
- 2: minor handicap--> symptoms that lead to some restriction in lifestyle but do not interfere with the patient's capacity to look after him-/herself
- 3: moderate handicap--> symptoms that significantly restrict lifestyle and prevent totally independent existence
- 4: moderate to severe handicap--> symptoms that clearly prevent independent existence though not needing constant attention
- 5: severe handicap--> totally dependent, requiring constant attention night and day
- 6: deceased

The Canadian Neurological Scale

Mentation

1. Level of consciousness

- alert 3
- drowsy 1.5

2. Orientation

- oriented 1
- disoriented or non applicable 0

3. Speech

- normal 1
- expressive deficit 0.5
- receptive deficit 0

Motor function (no comprehension deficit)

4a. Face

- none 0.5
- present 0

5a. Arm: proximal

- none 1.5
- mild 1
- significant 0.5
- total 0

6a. Arm: distal

- none 1.5
- mild 1
- significant 0.5
- total 0

7a. Leg

- none	1.5
- mild	1
- significant	0.5
- total	0

Motor response (comprehension deficit)**4b. Face**

- symmetrical	0.5
- asymmetrical	0

5b. Arms

- equal	1.5
- unequal	0

6b. Legs

- equal	1.5
- unequal	0

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Curriculum Vitae

Anita Boreas werd geboren op 4 januari 1969. In 1987 deed ze eindexamen VWO aan het St-Janscollege te Hoensbroek. Hierna studeerde ze Geneeskunde aan de Rijksuniversiteit Limburg (nu Universiteit Maastricht), alwaar ze op 7 februari 1994 haar artsexamen behaalde. Direct aansluitend begon ze als agnio bij de vakgroep Neurologie in het Academisch Ziekenhuis Maastricht. In deze fase werd een aanvang gemaakt met dit onderzoek. Op 1 september 1996 kwam ze als AGIKO Neurologie in opleiding in het Academisch Ziekenhuis Maastricht (opleider Prof. dr. J. Troost) en kon het onderzoek worden voortgezet onder leiding van Prof. dr. P.W. de Leeuw en Prof. dr. J. Troost. De opleiding Neurologie zal begin 2005 worden afgerond.