Acute stroke – a dynamic process

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INTRODUCTION

Stroke is a leading cause of death and disability against which new treatment options are much needed. In order to establish new potential treatment targets, we need detailed knowledge of the natural course of the disease.

The aim of the studies on which this thesis is based was to explore the hypothesis that acute stroke is a dynamic process by investigating patients in which the acute brain damage affects not only the brain but induces a multitude of systemic changes. By serial measurements commencing so early that the patophysiological changes were not yet completed the course of temperature, blood pressure, glucose and heart rate was described. We further wanted to look into the interplay of heart and brain as well as the stress response in order to investigate their possible impact in the first hours after stroke onset.

We documented that acute stroke is a dynamic process and that stroke severity is determinant in the changes of physiological parameters. The stress response as well as cardiac changes may contribute to poor prognosis especially in severe stroke and may have a role in future therapeutic strategies. Damage to the right insula may hold a key role for the stress response and cardiac changes after stroke.

BODY TEMPERATURE (PAPER I)

A meta-analysis based on nine studies and 3,790 patients concluded that high body temperature on admission had negative prognostic impact in acute stroke (1). The latency from stroke onset to admission and body temperature measurement was, however, not included in the analysis. Consequently, body temperature was assumed to be a static parameter in acute stroke.

However, the course of body temperature in the first hours after stroke was not described before our publication (paper I).

Body temperature follows a distinctly different time course in patients with mild to moderate stroke in comparison to patients with severe stroke; in patients with severe cerebral infarctions or severe intracerebral haemorrhage body temperature increased within the first 8-10 hours. The rise in body temperature related to initial stroke severity, reached significance 4 to 6 hours after stroke onset, and was only present in patients with severe stroke. In severe cerebral infarction, the mean increase was app. 0.5 °C, in intracerebral haemorrhage, the mean increase was app. 1.0 °C. No change was observed in patients with mild to moderate cerebral infarction. In patients with mild to moderate haemorrhagic stroke, an uncertain tendency towards an increase was observed. Admission temperature correlated significantly to the latency from stroke onset.

In these early-admitted patients, on whom we based our analysis, body temperature tended to be low on admission in severe stroke before the temperature increase. After the increase, body temperatures were 0.5-1.0 °C higher than in patients with mild to moderate stroke. The univariate correlations between body temperature and outcome, and between body temperature and stroke severity, corresponded to this development: initially severe stroke and poor outcome related to low body temperature and from 8 hours after the stroke onset, severe stroke and poor outcome related to high body temperature. Body temperature was measured by a tympanic thermometer, which we have validated against rectal mercury thermometry in patients with acute stroke and found that the agreement was acceptable (2).

Castillo et al have also looked into the timing of post-stroke hyperthermia in acute stroke with the aim of investigating the timing at which a cerebral lesion may be aggravated by hyperthermia. They reported that it was only in the first 24 hours after stroke onset that body temperature measurements >37.5 °C related to large infarctions and poor outcome (3), however they did not include time points before 6 hours after stroke onset. Consequently, body temperature was not measured early enough to tell if it were the severe stroke patients who experienced an increase in body temperature.

According to our observations, the body temperature increase occurred hours after the stroke was clinically manifest; therefore we assume that the cerebral lesion causes the hyperthermia.

If hyperthermia contributes to secondary brain damage, this cannot occur within at least the first 4 to 6 hours. After this time clinically relevant damage should at least in theory be detected either as neurological deterioration or as reduced recovery.

A number of studies have looked into the natural history and the prognostic implications of body temperature and concluded that post-stroke pyrexia predicted poor outcome (4-6) even after long-term follow-up (7). According to the presented Kaplan-Meier plots, however, no excess mortality seemed to be present in the pyrexia group after the acute stroke period. In these studies (7-16) the majority of patients were admitted after the time of our reported temperature increase, thus patients with severe stroke may be expected to have high temperature already on admission.

In our study body temperature on admission within six hours of stroke onset did not independently predict outcome in patients with ACI or ICH in multivariate analysis.

We found that hyperthermia on admission was a rare finding in a patient population admitted early after stroke onset: body temperature was elevated above 37.5 °C in 3.5% of patients with cerebral infarcts and in 5% of patients with intracerebral haemorrhages. Reith et al. (11), on the contrary, found increased body temperature, >37.5 °C on admission within 6 hours of stroke onset without specifying the exact time of the recording, in 25% of a mixed stroke population.

There is no straightforward explanation of the different results. However, our repeated measurements clearly demonstrated that body temperature increases in severe stroke. Thus if the initial body temperature measurement is done 8 to 10 hours or more after stroke onset, it might lead to the impression that admission temperature determines stroke severity and not vice versa (11).

In a study on patients with supratentorial intracerebral haemorrhage, Schwartz et al observed that the body temperature increase that occurred in the first 72 hours in 91% of patients was associated with poor outcome (10). Suzuki et al presented a correlation between haematoma volume and body temperature as well as between higher body temperature and mortality in patients with ICH (8); this is in accordance with our finding that body temperature increases in patients with severe stroke and poor prognosis.

Some could not confirm the prognostic value of admission body temperature (12; 15; 16).

The maintenance of temperature homeostasis is located in the hypothalamus. Regulation of heat loss is located in the preoptic anterior hypothalamus, which functions as a thermostat. The posterior hypothalamus regulates heat-production. It has been observed that lesions of the preoptic anterior hypothalamus result in hyperther-

mia whereas lesions of the posterior hypothalamus cause hypothermia or poikilothermia (17; 18). In trauma or infection, cytokines including IL-1 and TNF-α induces inflammation and fever most likely through a direct effect on the hypothalamus (19). The mechanism of cerebral fever in brain damage has not yet been established.

In conclusion, it is well documented and in accordance with our observations that high body temperature is found in patients with severe stroke hours and days after stroke onset and that body temperature at this time relate to outcome.

In this study, we could not confirm that body temperature on admission within six hours of stroke onset related to outcome in multivariate testing. On the contrary, it appeared that low body temperature was often detected in patients with severe stroke and subsequent poor outcome. We have speculated if the reason for this could be exposure during transportation or immobilisation or both. Not until eight hours after stroke onset, did higher body temperature relate to poor outcome three months after stroke in our study. When analysing from this point in time, our results are in accordance with the studies by Castillo and Reith (3; 11).

We cannot exclude that treatment with paracetamol in patients with body temperature > 37 °C may have blunted the rise in temperature but it had no influence on the levels of admission temperatures. It is likewise possible that the treatment with paracetamol in 12 of the 35 patients with initially increased temperature may have had a beneficial effect on outcome. The temperature lowering effects of paracetamol in the temperature span relevant for acute stroke are, however, not fully convincing. Two smaller randomised trials have reported temperature decreases of 0.22 °C (20) and 0.3 °C (21), and intracerebral temperature has been found unaffected by paracetamol (22).

The results from the present study show that stroke severity determines the increase in body temperature. The fact that body temperature is an epiphenomenon to stroke severity does not exclude that it may later contribute to secondary brain damage or that hypothermia treatment may be beneficial. This has to be documented in randomised controlled studies.

BLOOD PRESSURE (PAPER II)

Elevated blood pressure is often observed on admission in patients with acute stroke, and followed by a return to normal within the first ten days after admission (23). This finding has been reported by several researchers independent of the time lapse from stroke onset to admission (24-35).

The aetiology of this increase – whether it reflects physiological parameters or mental stress – and if it is beneficial or detrimental remains undetermined.

We recorded serial blood pressure measurements in patients with symptoms of acute stroke that were admitted to hospital within six hours of stroke onset with the purpose of describing the time course of blood pressure in acute stroke.

We found that the blood pressure course depended on stroke severity in such a way that blood pressure in patients with mild to moderate stroke or TIA decreased within the first hours after admission and reached a stable level 24 hours after admission. In patients with severe stroke, a slow decline was observed.

A fall in blood pressure during the first 4 hours after admission was associated with mild stroke and favourable outcome, whereas a maintained high blood pressure was associated with severe stroke and poor outcome.

Blood pressure related to time of admission and not to time of stroke onset, a finding that is in accordance with the majority of studies, where the blood pressure decrease is reported in the hours or days after admission without regard to the latency from symptom onset to admission that differs from minutes to several days.

Some reports support our finding that the blood pressure decrease relates to the timing of the admission and not the latency from stroke onset. Carlberg et al (27) found no correlation between the latency from stroke onset and blood pressure level, and concluded that mental stress was responsible for hypertension on admission. We confirmed that observation. Broderick et al (28) obtained serial blood pressure measurements from 69 patients with a mean delay from stroke onset to first blood pressure measurement of 19 minutes; the patients were evaluated for but not included in a phase I rt-PA trial. They reported a significant decline within the first 90 minutes. Jørgensen et al (36) reported a relation between time from stroke onset to admission and blood pressure measurement, as they found that systolic blood pressure levels decreased with later admissions. They did, however, not report if there were relations between delay and stroke severity, which might have strengthened this interesting observation.

The high blood pressure on admission in patients with mild to moderate stroke may well be an impact of hospitalisation. This is illustrated by the results from the studies of Jansen et al and Semplichini et al (26; 35). Both reported a return to a level lower than the pre-stroke office blood pressure 2-3 days after admission, followed by a blood pressure 3 months after stroke onset that equalled the pre-stroke blood pressure; it seems that the patients got used to blood pressure measurements during the stay in hospital as no other explanation such as blood pressure lowering treatment was present. Semplichini et al (35) also documented two peaks in the blood pressure course: the first in the emergency room and the second when the patients reach the Neurological department: in my opinion this illustrates the effect of two admissions. Semplicini et al (35) found that the highest levels of blood pressure on admission were found in patients with lacunar stroke, defined according to the OCSP classification, corroborating earlier findings (31). As lacunar stroke in the OCSP classification (LACI) is defined based on motor and/or sensory findings only, it is reasonable that they find the same results in patients with LACI, as we did in patients with mild stroke, as they are largely the same. The authors do, however, not agree with my interpretation (37).

We do therefore believe that their data, in spite of the researchers' own different interpretations, corroborate our findings. This finding, however, led to the conclusion that blood pressure level related to stroke subtype and therefore was a physiological phenomenon and not a mental reaction to stroke and admission. In my opinion that conclusion is preconceived as stroke severity differs largely between stroke subtypes and is therefore not excluded as a causal factor (37).

That the blood pressure peak in acute stroke is only found in mild to moderate stroke and is related to the time of admission renders the hypothesis of a mental response to a very disturbing acute condition and hospital admission most likely. Patients with severe stroke often have symptoms of stroke such as impaired consciousness or neglect that are likely to blur their evaluation of their present state. Evolving brain oedema and increased intracranial pressure also cause an increase in systemic blood pressure. However, these factors are not likely to be major determinants of the systemic blood pressure in patients with acute ischaemic stroke within six hours of stroke onset. In patients with haemorragic stroke, on the contrary, increasing intracranial pressure is a likely determinant. This difference offers an explanation for our finding that high admission blood pressure in ischaemic stroke related to mild to moderate stroke and a favourable outcome, whereas in haemorrhagic stroke increasing blood pressure related to severe stroke and poor outcome.

Salivary cortisol has been positively associated with 24-hour blood pressure, which supports the theory of the stress response being a determinant of blood pressure levels in acute stroke (38).

There is not yet agreement if these blood pressure changes represent some physiological and perhaps beneficial response to stroke, or if it reflects a mental reaction to stroke and admission.

However, it would only be biologically reasonable to believe that it was a predominately physiological response if it related to the time of stroke onset, and not if it related to the time of admission.

Higher levels of blood pressure on admission are reported in patients with previous hypertension (27; 36; 39), patients with intracerebral haemorrhage (27; 30; 35; 36). We also found higher levels of blood pressure in patients with a history of hypertension, and in patients with ICH.

Jørgensen et al (36) reported that determining factors for higher blood pressure in acute stroke included a history of hypertension, intracerebral haemorrhage, and male sex, whereas ischaemic heart disease and atrial fibrillation related to a lower blood pressure level.

Another question is whether blood pressure affects the patients' recovery. We found that admission blood pressure measurements, but not any later measurements, and the size of the blood pressure decrease related to outcome in such way, that a large spontaneous decrease and a high blood pressure related to good outcome in ischaemic stroke, whereas high admission blood pressure related to poor outcome in haemorrhagic stroke. A Japanese study in patients with known pre-stroke blood pressure levels reported a correlation between the post-stroke elevation and the neurological outcome, corroborating our results (40).

Based on baseline blood pressure measurements (inclusion within 48 hours of stroke onset) from the 17,398 patients that were included in the IST trial Leonardi-Bee et al (41) concluded that both high and low blood pressure were prognostic factors for poor outcome, a U-shaped relation. The same group has later published a systematic review of 32 studies with a total of more than 10,000 patients and no time limits for the blood pressure measurements; this study supported the groups prior findings (42). The evidence of a U-shaped relation has been supported by Vemmos et al (43) and further supperted by Castillo et al (44) who even presented a relation between blood pressure and final CT infarction volume.

However, according to our findings admission blood pressure and blood pressure at the time of inclusion into a trial is not the same thing in acute stroke, as the timing of the measurements is different. In patients with mild to moderate stroke, blood pressure is most likely to have decreased before inclusion according to our observation, so that high and low blood pressure on inclusion would most likely reflect usual blood pressure levels or increased intracranial pressure (45). The relationships found by Leonardi-Bee et al appeared to be mediated in part by increased rates of early recurrence and death resulting from presumed cerebral oedema in patients with high blood pressure, and increased coronary heart disease in those with low blood pressure. This finding corroborates earlier findings regarding patients with very high blood pressure in acute stroke (46; 47).

It is hypothesised that high as well as low blood pressure affected outcome in acute stroke. High blood pressure may increase the risk of new stroke or coronary events (41) and promote cerebral oedema (32) whereas low pressure may reflect severe heart disease or cause hypo-perfusion of the ischaemic border-zone (48). Jørgensen et al (48) reported that systolic blood pressure >160 mmHg on admission reduced the risk of deteriorating stroke. They suggested the penumbra-zone could benefit from a higher systemic blood pressure. This finding that spontaneously lower blood pressure increases the risk of neurological deterioration was not reproduced in our study (paper II). Nevertheless, pharmacologically induced blood pressure reductions in the range of at least 15-20 mmHg appears to be detrimental in observational studies (29; 44; 49-52).

However, very high and very low blood pressure is not very common in acute stroke. According to the IST data (41), 81.6% of patients had systolic blood pressure >140 mmHg when they were included in the study within 48 hours of stroke onset, and had systolic blood pressure <120 mmHg 5% at the same time. In the INWEST study, 15.3% of patients had an inclusion blood pressure >190/105 (inclusion within 24 hours of stroke onset). In our study population 3.1% of patients had systolic blood pressure <120 mmHg and 13.7% >200 mmHg on admission; 24 hours after admission 7.1% had systolic blood pressure <120 mmHg and 5.4% >200 mmHg, unpublished data.

A major conclusion based on our results is that the prognostic implications of blood pressure in acute ischaemic stroke varies with the time of the measurement: relations are found between the admission blood pressure and stroke severity and outcome that are not found in later blood pressure measurements. From comparison of studies by others, there even seems to be a tendency towards a steeper blood pressure decrease when blood pressure is measured with few hour intervals in comparison to once daily measurements. This means that single admission blood pressure measurements – if the patient has not reached a stable level – are of little use both in studies of blood pressure and clinical practice.

Looking at the patient population as a whole, we found a steady state of blood pressure had been reached before 24 hours after stroke onset. This is earlier than what has been described in most studies; we believe that a possible explanation may be the comforting effect of frequent blood pressure measurements by a nurse. Early identification of patients with hypertension holds a treatment perspective as it could reduce the frequency of early stroke recurrences and myocardial infarctions and allow for systematic hypertension screening in the stroke units.

However, a number of studies have not come to the conclusion that blood pressure reduction in acute stroke is deleterious. Powers et al. lowered MAP by 15% with nicardipine or labetalol in patients with small to medium sized acute ICH and found that autoregulation of CBF was preserved with arterial blood pressure reductions in the studied range. Chamorro et al (32) found that complete recovery was facilitated in patients who received oral antihypertensives during acute stroke care. They hypothesised that the benefit could result from a reduction in brain oedema facilitating a more adequate brain perfusion.

However, stroke affects the autoregulation of cerebral blood flow and then even minor blood pressure reductions could reduce the cerebral blood flow (53).

The ACCESS study was designed to assess the safety of modest blood pressure reduction by candesartan cilexetil in the early phase of ischaemic stroke (54). A significant treatment benefit was observed even though no significant blood pressure reduction was observed in the treatment group, which might have been caused by other effects of the angiotensin type 1 receptor blockade. A new trial of candesartan in acute stroke, the Scandinavian Candesartan Acute Stroke Trial (SCAST) is currently ongoing. Simultaneously the effect of induced hypertension and antihypertensive treatment is currently tested in different trials (55; 56).

In conclusion, high blood pressure on admission in acute stroke may reflect different variables; in patients with mild to moderate stroke it most commonly reflects pre-existing hypertension and the mental response to hospital admission; in patients with severe stroke especially in ICH it may reflect severe intracranial pathology. In the vast majority of patients the spontaneous levels are probably not of any consequence to stroke recovery but blood pressure already few hours after admission may be of interest in relation to secondary prevention of stroke.

BLOOD GLUCOSE (PAPER III)

Hyperglycaemia during the first days after stroke has been related to increased morbidity and mortality and it has further been reported an independent predictor of outcome.

Hyperglycaemia may reflect a stress response to stroke or it may independently contribute to stroke outcome by inducing secondary brain damage; these two hypotheses are not mutually exclusive.

The existing literature on hyperglycaemia in acute stroke is predominately based on single blood glucose measurements that were obtained from patients admitted to hospital 12-24 hours or more after symptom onset. In most studies, the time from symptom onset to blood glucose measurement is not well defined.

If blood glucose increased after stroke onset mainly in severe stroke, late blood glucose measurements would show higher blood

glucose in patents with severe stroke who are most likely to have unfavourable outcome (57).

We studied blood glucose in 445 non-diabetic patients who were admitted with symptoms of acute stroke within six hours of stroke onset and who had two blood glucose measurements within 12 hours of stroke onset. We found that blood glucose increases in the first 12 hours after stroke onset in patients with discharge diagnoses of ACI, ICH and TIA and that the increase is greater in severe stroke. The highest median levels of blood glucose were reached in patients who died within seven days of stroke onset. The size of the increase of blood glucose within 12 hours of stroke onset did not independently affect outcome in multivariate testing. Blood glucose results both from the first and the second reading correlated with stroke severity on admission and outcome three months after stroke. This transient increase is corroborated by results from animal models (58; 59).

In later unpublished analysis we found that in the 445 patients included in the blood glucose study, as well as in the total non-diabetic population, 947 patients of the 1192 patients in the acute stroke unit study population, admission blood glucose (within six hours of stroke onset) predicted three months mortality independent of pre-stroke mRS, stroke severity and age; blood glucose + 1mmol/L OR 1.1 (1.01-1.2) in the 445 patients and OR 1.2 (1.1-1.3) in the 947 patients, corroborating the general findings concerning this issue.

We believe that the blood glucose had already increased in the interval from stroke onset to hospital admission based on three observations:

1. Blood glucose level on admission with a median delay of two hours already correlated with stroke severity
2. Blood glucose (on admission) in patients who died within seven days of stroke onset was significantly higher than in surviving patients
3. Glycosylated haemoglobin or glycaemic index has not convincingly been related to stroke severity.

It has been discussed whether hyperglycaemia was present before stroke onset or only after stroke onset and studies of glycosylated haemoglobin (HbA1c) and later glycaemic index (60) has been performed. Hyperglycaemia in acute stroke might represent a diabetic state, which could be both causal for the stroke and cause further neuronal damage (61; 62). However, the correlation between HbA1c and blood glucose on admission was only present in the diabetic end of readings and no other researcher have yet reproduced a predictive value of glycosylated haemoglobin or glycaemic index in non-diabetic patients. It was concluded that the hyperglycaemia occurs after stroke onset and represent a stress response to stroke (63-70), which may well be deleterious (71).

So it remains most likely that pre stroke blood glucose in non-diabetic patients does not predict stroke prognosis. This is also reasonable in the context of our results, as they show a reaction in blood glucose occurring most likely as a result of the stroke.

O'Neill et al found that cortisol was a major determinant of blood glucose in acute stroke and that blood glucose did not predict outcome independent of cortisol levels (72), a finding that was corroborated by the results of Murros et al (73) and Tracey et al (65), while van Kooten et al reported that blood glucose did not relate to catecholamin levels (74). In our study on cortisol, we found that cortisol and blood glucose both predicted three months mortality independent of age and stroke severity (paper IV), the difference may be due to our larger sample size.

A number of variables have been related to hyperglycaemia in acute stroke. Melamed related hyperglycaemia to diabetes, stroke severity, and mortality (75). Candelise et al (76) also related blood glucose to lesion size on CT-scan, thereby relating blood glucose in acute stroke to both clinical and radiological findings. Scott et al reported that even though patients with severe stroke are most likely to have hyperglycaemia, it was almost as frequent in patients with less severe stroke (77).

Several studies including our own have shown that blood glucose on admission independently predicts functional outcome and/or mortality after stroke (48; 63; 64; 78-81). Not all have corroborated these findings (14; 82). Bruno et al (83) demonstrate an interaction between blood glucose and outcome already within three hours of stroke onset. Further, persistent hyperglycaemia in acute stroke was related to infarct expansion and poor clinical outcome; blood glucose and admission neurological deficit was just above the limit of statistical significance (84).

A systematic overview concerning the effect on outcome of hyperglycaemia in non-diabetic and diabetic patients found that hyperglycaemia, according to the definitions of the included studies, increased the risk of 30-days mortality in non-diabetic patients OR 3.0 (CI 95% 2.5-3.8), but not in diabetic patients (85). The authors did not include delay form stroke onset to blood glucose measurement and. Risk of poor functional outcome was also increased in non-diabetic patients OR 1.4 (CI 95% 1.2-1.7), but not in diabetic patients.

This difference may reflect that blood glucose control was more likely to be instituted in patients with diabetes, but another likely explanation is that high blood glucose in non-diabetic patients predominantly occurred after severe stroke.

Some concern has been raised about the statistical validity of studies basing their conclusions on multiple regression analysis. Counsel et al (86) had two objections to the publication of Weir et al (87): 1) stroke severity was assessed relatively inaccurately (by the OCSP scale) and when two variables are closely correlated – for example, stroke severity and glucose concentration – the one that is the most accurately measured (glucose concentration) will always emerge as the strongest explanatory variable in multiple regression even if it is, in fact, less important; 2) the other objection was that they could not reproduce the findings of Weir et al. in their data from the Oxfordshire Community Stroke Project.

Counsel's objections are important and may be attributed to practically all analyses including both paraclinical data and a clinical scale. The size of this problem may depend on how detailed the chosen stroke scale is, as it appears likely that a detailed stroke scale like National Institute of Health Stroke Scale (NIHSS)(88) or Scandinavian Stroke Scale (89) will depict stroke severity more accurate than e.g. Canadian Stroke Scale(90) or OSCP Scale (91) which has been used as a measure of stroke severity in some publications (87). Interventional trials may eventually close this issue, as a treatment effect of blood glucose reduction would render the notion of hyperglycaemia in acute stroke as an innocent bystander phenomenon to the stroke unlikely.

Hyperglycaemia and diabetes were reported predictors of ICH in rt-PA treated patients (92) and Els et al reported that hyperglycaemia in patients with a focal MCA ischaemia caused worse clinical outcome despite recanalisation with rt-PA (93). However, the reported levels of glucose were surprisingly high (94) in comparison to what we have found and may represent diabetic conditions. In one paper hyperglycaemia was only related to poor outcome in rt-PA treated patients that achieved reperfusion (95), suggesting that hyperglycaemia only causes infarct growth in reperfused tissue.

Parsons et al (96) investigated if acute hyperglycaemia is causally associated with worse stroke outcome or simply reflects a more severe stroke. They identified perfusion diffusion mismatch by MRI and lactate production in the brain lesion by Magnetic Resonance Spectroscopy (MRS) and compared these findings to blood glucose in patients with acute stroke. Scans were performed within 24 hours of stroke onset and on day 3. They concluded that acute hyperglycaemia increased brain lactate production and facilitated conversion of hypoperfused at-risk tissue into infarction. However, there may be some shortcomings in this study. In MRS, the voxel was placed in the ischaemic core region; however, the authors extrapolate the results to the ischaemic border zone. The authors do not relate to the time factor; it is well documented that a perfusion diffusion mismatch disappears in hours after stroke onset if reperfusion does not

occur. The scans in which mismatch was found were performed substantially earlier than those where no mismatch was found. In comparison of the two groups they reported that in the mismatch group blood glucose was independently related to outcome, final infarction volume and penumbral salvage, whereas in patients with no mismatch stroke severity appeared to be the determining factor. These two groups are not really comparable because they not only differ in mismatch but also in latency from stroke onset, which is a likely cause for the difference in mismatch. A possible explanation for the findings in the mismatch group may be that increasing blood glucose biologically reflected stroke severity but emerged as the strongest explanatory factor in regression analysis because it is measured more accurately, as suggested by Counsil.

Another point is, we know that the amount of tissue to be salvaged after stroke is reduced with time, and if we assumed that blood glucose increased after stroke onset, another possible explanation for reported inverse relation between penumbral salvage and blood glucose appears. Based on these considerations it is not possible to conclude that high blood glucose affects outcome negatively by increasing lactate production in the penumbra and thereby increasing the infarction volume. Interventional studies are likely to clarify this point, and the GIST trial (97; 98) may show if reduction of blood glucose in the acute phase of stroke is beneficial. Blood glucose reduction is, however, already recommended by some (99).

In conclusion, blood glucose increases following stroke and the size of this increase relates to stroke severity but not to stroke outcome. Blood glucose as early as three hours after stroke onset was related to stroke outcome and a relation was suggested between blood glucose and lactate production in the cerebral lesion. A possible explanation of these apparently contradictory data could be that stroke severity determines the increase in blood glucose but it is the actual level that determines an eventual effect on outcome in non-diabetic patients. Another explanation remains that the negative effect of hyperglycaemia reflects undiagnosed or latent diabetes, as up to one third of all patients with acute stroke may have diabetes (100).

SERUM-CORTISOL (PAPER IV)

Stroke is regarded as a stressful medical condition and a humeral stress response to stroke has been acknowledged since the 1950's. In patients with acute stroke high levels of cortisol was identified and higher levels were found in fatal cases than in survivors (101). This has further has been corroborated in animal models (58). Modification of the stress-response has proven beneficial in other fields of medicine. The aim of the present study was to better describe the stress response in acute stroke.

We found that s-cortisol was significantly higher in patients who died within seven days in comparison to survivors and independently predicted seven days mortality. S-cortisol related to stroke severity, as well as to final CT-lesion volume.

Freibel et al (102) reported that urinary catecholamins and plasma-cortisol levels were well correlated in acute stroke and both related to mortality and post-stroke disability in 65 patients with cerebral infarction or SAH. We found that cortisol predicted mortality; not the combined endpoint of death or dependency or neurological deterioration, independent of stroke severity, early infarction signs age and blood glucose, OR for death within seven days, s-cortisol + 100 nmol/L OR 1.9 (95% CI 1.01-3.8) (paper IV). Myers et al (103) confirmed earlier findings by reporting higher levels of catecholamins in stroke patients in comparison to controls. They later reported (104) that both catecholamins and the frequency of ECG-findings were high in patients with acute stroke in comparison to controls, but that the level of catecholamins did not relate to ECG-findings within the stroke population. We confirmed these findings in our patient population, unpublished data.

In the present study, cortisol related to blood glucose. Cortisol and blood glucose predicted three months mortality independent of each other, stroke severity, and early infarction signs.

This reproduces earlier findings in cardiovascular patients based on whom Juul Christensen and Videbæk reported a relation between stress hormones and blood glucose in the acute phase of myocardial infarction, as noradrenalin levels were elevated and closely related to blood glucose levels (105), which was confirmed by Little et al (106) who also suggested that a simultaneous increase in cortisol was present.

We also found that s-cortisol related to pulse rate, a new finding that is not surprising as the stress response is the determining factor of heart rate in the non-febrile resting person (107).

Stirling Meyer et al (108) reported that catecholamin concentrations in plasma and CSF were higher in patients with stroke in comparison to controls, higher in patients with haemorrhagic stroke, and higher in hypertensive patients than in other patients and controls. Also 24-hour blood pressure and night-time blood pressure in acute stroke have been associated with cortisol levels, suggesting that stress may be a determinant for high blood pressure in acute stroke (38).

We did not find a relation between s-cortisol and hypertension; s-cortisol did not relate to a history of hypertension or to any one blood pressure measurement from admission to three months after stroke, unpublished data.

The results from one animal model suggested that catecholamins are only affected by stroke if the insular regions are involved in the lesion (109), furthermore, insular stimulation has resulted in increasing catecholamin levels (110). We found that serum cortisol was significantly higher in patients with insular involvement and highest in patients with right insular involvement. However, insular involvement related to stroke severity, but in the 50% of patients with milder stroke cortisol was still significantly higher in patients with insular involvement. This is supported by the results from a recent study where it was reported that higher levels of noradrenalin and adrenalin was found in patients with insular stroke lesions (111). However, right insular infarction may predict three months mortality independent of cortisol and early infarction signs in multivariate logistic regression analysis (112).

Increased activity of the hypothalamic-pituitary-adrenal (HPA)-axis has been demonstrated by abnormal dexamethasone suppression test failing to suppress cortisol activity and which resulted in high post-test cortisol levels (113). Olsson et al (114) further reported that ACTH injection in stroke patients also generates an abnormally large cortisol response. Fassbender et al (115) investigated serial measurements of plasma-cortisol and ACTH in 23 patients with acute stroke. They reported increased levels of cortisol throughout the first week together with a transient increase in ACTH; this might suggest an initial stress induced activation of hypothalamus, followed by a strong cortisol-induced feedback suppression of ACTH levels. Orlandi et al (116) demonstated that levels of catecholamins in blood and urine decreases within the first seven days after stroke. Urinary free cortisol excretion within the first week after stroke has been related to poor functional outcome and limb paresis (117), which is not contradicted by our findings that cortisol relates to stroke severity and mortality.

Francheschini et al (118) investigated the circadian secretion of cortisol in acute stroke and found no significant variations in acute stroke, which was in contrast to ten days after stroke or to an age-matched control group. We could not – in our single measurements – find any relation to time of the day (unpublished data) or delay form stroke onset. Johansson et al (119) suggested that the ACTH/cortisol dissociation – that is the finding that high levels of circulating cortisol is found together with low levels of circulating ACTH in the days after acute stroke – might be explained by cytokine (TNF-α and IL-6) induction of cortisol; as they found correlations between levels of cytokines and cortisol, but not between cortisol and ACTH. Johansson et al has further reported a relation between cytokines in acute stroke and disturbances of circadian variations in acute stroke (120).

We investigated possible relations to cytokines from the IL-1/TNFα-systems and only found a correlation to the levels of IL1RA. As IL1RA is likely to reflect the magnitude of a passed IL-1-response this may reflect such relation. Another possibility is that the relation is due to common relations to stroke severity, as we have previously demonstrated in IL1RA (121).

A chance finding remains a third possibility. The correlation between cytokines and cortisol that was reported by Johansson et al (120) may be due to an interaction with stroke severity. Another problem in their suggestion is, that a cortisol response is expected within about four hours after a relevant stimulus; in contrast, an IL-6 response is not expected before at least 12-24 hours after the stimulus, the possible effects of IL-6 can therefore only be to maintain a cortisol response and not to initiate it.

Slowik et al. (122) investigated 70 patients with supratentorial ischaemic stroke admitted within 24 hours of stroke onset and 24 controls. They reported hypercortisolaemia in 35.7% of patients combined with reduced circadian variation. In contrast to other studies, they did not find cortisol levels related to blood glucose or urine-catecholamins, and suggested based on correlations between cortisol and CRP, WBC, fibrinogen, and fever that the cortisol response related to the inflammatory response rather than the stress response. Unfortunately Slowik et al did not correct for stroke severity or lesion size in their study, a factor that is most likely strongly related to the size of both the cortisol and the inflammatory response and may well determine both.

We did not find a relation between CRP and WBC and cortisol on the day of admission. CRP and WBC on day 2 correlated to cortisol on day 1, unpublished data, suggesting a slower response of CRP and WBC to stroke than cortisol, which is in accordance with the expected biological response times.

In conclusion, levels of cortisol relate to severity of neurological deficits as well as to lesion volumes in acute stroke. Cortisol predicts short-term mortality but is not an important predictor of functional outcome. Cortisol relates to insular damage, especially right insular damage, which may contribute to cerebrogenic cardiac death.

Cortisol also relates to other markers of stroke severity including body temperature and blood glucose, and cortisol and blood glucose predict outcome independent of each other. A relation between s-cortisol and the inflammatory response – other than occurring at the same time and being caused by the same event – is in my opinion doubtful, as a biologically plausible route of activation has not yet been proposed, which also accounts for the timing.

ECG-ABNORMALITIES (PAPER V)

ECG changes are frequently observed in patients with symptoms of acute stroke, however, the prevalence and the prognostic impact in patients with acute cerebral infarction and intracerebral haemorrhage is not well described (123), as concluded in a systematic review based on 29 studies including a total of 1,844 patients; the majority of whom had suffered SAH.

We described (paper V) the prevalence and the prognostic impact of common ECG-abnormalities. The study was based ECGs in 12 leads obtained on admission and the results from ECG-monitoring in the first 12-24 hours of hospital stay. The analysis included 1070 patients in whom ECG's were retrievable, and who were admitted to hospital within 6 hours of onset of stroke symptoms. Patients were included in the analysis without regard to history of cardiac disease.

ECG-abnormalities were observed in 55.3% of all patients; in 60.1% of patients with acute cerebral infarction, in 49.7% of patients with intracerebral haemorrhage, and in 44.4% of patients with TIA. This difference between diagnoses was primarily due to high frequencies of atrial fibrillation, atrio-ventricular block, ST-depression and T-wave inversion in patients with ischaemic stroke. However, rates of sinus tackycardia, ectopic beats and ST-elevation were higher in both ischaemic and haemorrhagic stroke in comparison to TIA.

ST-segment changes and/or prolonged QTc-interval were observed in 32.5% of patients with ischaemic stroke. In patients with haemorrhagic stroke, ectopic beats and sinus tachycardia were observed most frequently, and ST-segment changes and/or prolonged QTc-interval were found in 23.8% of patients. In patients with TIA ectopic beats and atrio-ventricular block were found most frequently; ST-segment changes and prolonged QTc interval were seen in 23.8% of patients.

A number of previous studies have described the prevalence of ECG abnormalities in smaller stroke patient populations recruited at various mostly not well-defined time intervals after stroke. In patients with acute cerebral infarction and to some extend intracerebral haemorrhage, the pathophysiology of the strokes often include ECG-abnormalia e.g. in atrial fibrillation. It has been concluded that the observed ECG-changes often suggest aetiology for the patient's stroke (124). However, also T-wave changes, ST-depression, and prolonged QTc were reported in patients with ACI or ICH. Prolonged QT interval and T-wave changes in a patient with SAH was first reported in 1947 (125). It was later suggested that the reported QT- prolongation in patients with stroke was most probably due to fusion of large U-waves and T-waves, so that the measured interval was actually the Q-U interval (126). In 1953 Levine et al first reported ECG-signs of myocardial infarction in a patient with SAH whose heart was later found to be normal on autopsy (127). ECG abnormalities, including atrial fibrillation, atrial flutter, sinus bradycardia and tachycardia, atrio-ventricular block, ST-segment changes, prolonged QTc interval, ectopic beats, U-wave, and ventricular tachycardia have been reported after admission with acute stroke in patients with intracerebral haemorrhage or acute cerebral infarction. Higher frequencies of ECG-abnormalities are found in patients with prior heart disease (128-133).

The reported frequencies vary largely, which may reflect that the studies were performed at various time intervals after stroke onset, and included relatively few patients. No study focusing on patients with ICH was found. Moreover, the aims of the studies varied, e.g. to compare ECG-findings to CK-MB (134), or to diagnose unsuspected ECG-changes after stroke (135; 136).

The rates of ECG-abnormalities that we found were low in comparison to some other reports (130-132; 134; 137; 138) and comparable to some (128; 129; 139). Our frequencies are comparable to those reported from a comparable acute stroke unit setting (129). A possible explanation of our lower frequencies – ECG abnormalities were observed in 55% of patients – could be that our patients were admitted and had their 12 lead ECG's recorded and ECG monitoring started within six hours of stroke onset, where effects from brain swelling are not yet fully developed, so that it is possible that the frequencies would have been higher, if the observation period had started later. Another explanation remains, that the 122 patients who were excluded from this study due to missing ECG-data constitute a selection bias as we found that they had significantly more severe strokes and poorer outcome in comparison to patients with ECG's. Age and pre-stroke handicap did not differ. However, if we assume that all 122 excluded patients had abnormal ECG's, the over all frequency of abnormal ECG's would be 60% instead of 55%. Our data should probably be looked on as minimum data.

There seems to be a tendency that abnormalities that result from manifest cardiac disease, e.g. atrial fibrillation or heart block, are found more often in patients with ischaemic stroke, while ST-segment changes that are likely to result from the stroke are frequent in patients with ICH.

Serial Holter ECG in the first week after stroke showed that the ECG-changes after stroke are transient; arrhythmias were seen in 70.5% of patients on admission day, in 43.2% on day 3, and in 6.5% on day 7 (116). Low frequencies of abnormalities are recorded on Holter-ECG weeks to months after stroke in patients with acute cerebral infarctions and no history of heart disease (135; 136). These findings document the high frequencies of ECG-abnormalities in acute stroke as a transient phenomenon.

Tabel V 1. Comparison of ECG abnormalities in patients with stroke and controls in literature.

Author	N stroke patients	% abn. ECG or*	N controls	% abn. ECG or*
Lavy et al (140)	200	68 %	200	29.5%
Dimant et al (134)	100	90 %	50	50 %
Norris et al (139)	312	50 %	92	22 %
Goldstein et al (137)	150	92 %	150	65 %
Myers et al (104)	100	225*	50	52*

*) Number of serious arrhythmia hours in observation period.

Another question is whether the rates of ECG abnormalities in patients with acute stroke differ from the rates of otherwise comparable patients. At least five studies have compared the rates of ECG-abnormalities in patients with stroke with a control group including surgical patients, patients with other neurological diseases than stroke, or other age and sex-matched patients (104; 134; 137; 139; 140). They all found higher frequencies of ECG-abnormalities in patients with stroke than in controls, however frequencies varied largely, Table V 1.

It has previously been reported (129) that mortality was increased in patients with ECG-abnormalities and that arrhythmias were most frequent in patients with haemorrhagic stroke and hemisphere lesions (116). The question of a relation between ECG-abnormalities and the severity of the neurological deficit has previously been addressed by Lindgren et al (131), who in a study of 24 patients found no relation between ECG findings and lesion size or outcome. We found in patients with ischaemic stroke, but not in haemorrhagic stroke, that significantly more severe deficits (lower SSS) were found in patients with atrial fibrillation, prolonged QTc, atrio-ventricular block, ST-depression, and ST-elevation than in patients without those abnormalities. Atrial fibrillation causes stroke through a cardio-embolic stroke mechanism that generates more severe strokes; it is therefore not surprising that more severe strokes are found in patients with atrial fibrillation however, ST-segment changes may result from e.g. a stress response or be cerebrogenic cardiac effects.

In patients with ischaemic stroke, ECG abnormalities predicted three months mortality: atrial fibrillation, OR 2.0 (95% CI 1.3-3.1), A-V block OR 1.9 (95% CI 1.2-3.9), ST-elevation OR 2.8 (95% CI 1.3-6.3), ST-depression OR 2.5 (95% CI 1.5-4.3), and inverted T-wave OR 2.7 (95% CI 1.6-4.6) independent of stroke severity, pre-stroke disability and age. In patients with ICH, sinus tachycardia OR 4.8 (95% CI 1.7-14.0), ST-depression OR 5.2 (CI 95% 1.1-24.9), and inverted T-wave OR 5.2 (95% CI 1.2-22.5) predicted mortality at three months, independent of pre-stroke disability, stroke severity, and age.

Our findings that ECG abnormalities relate to outcome, are in accordance with Lavy (129) and Miah (141) while Myers et al suggested that cardiac arrhythmias had little influence on subsequent recovery in patients with ACI or ICH (104). A larger number of patients should, however, render our results more robust.

The findings from a large recent study in patients with TIA (142) suggested that ECG-changes – especially atrial fibrillation – predicted and directly affected outcome. This is not surprising, as ECG-changes such as atrial fibrillation, at least high degree atrio-ventricular block, or ST-elevation are well known to affect prognosis in any patient as they represent significant cardiological conditions that call for treatment. A possible prognostic impact of an inverted T-wave is more intriguing as this does not seem to be a serious condition in itself.

ECG-changes in acute stroke may reflect the aetiology of the stroke (124) like in atrial fibrillation, reflect the general cardiac condition of the patient – like in atrio-ventricular block – which may well be a determinant for prognosis, or changes may directly result form the cerebral lesion. This may either result from global effects such as increased intracranial pressure or local effects such as lesions to the insular regions. The relation of transient changes to stroke severity supports the idea that generalised cerebral mechanisms, e.g. increased intracranial pressure, generate ECG-abnormalities after cerebral lesions in contrast to the theory that it is caused by lesions to specific structures like the insula.

Another aspect of heart function in acute stroke is the heart rate. Sinus tachycardia predicted poor outcome in patients with ischaemic and haemorrhagic stroke independent of neurological deficit.

Heart rate was significantly higher in severe stroke than in mild to moderate stroke and followed a different time course: in mild to moderate stroke, heart rate declined rapidly after admission, whereas a slow decline at a higher heart rate was observed in severe stroke. In the analysed interval from 6-14 hours after stroke onset, a risk increase of 1.2-1.3 for three months mortality with each increase in heart rate of 10 bpm. Pulse rate higher than median, 12 hours after admission predicted three months mortality OR 1.7 (95% CI 1.02-2.7) independent of age, pre-stroke mRS, stroke severity, and body temperature (measured at the same time as heart rate).

The heart rate reflects the stress response, which is a likely explanation for the observed effect as the stress-response is important in determining the heart rate in a resting person with normal body temperature (107). This interpretation is in accordance with the finding that s-cortisol correlates to heart rate and predicts three months mortality.

In conclusion, ECG-abnormalities are frequent in acute stroke and may reflect both cardiac morbidity and the stroke incident. Some ECG-abnormalities and increasing heart rate predict poor recovery.

CARDIAC TROPONIN I (PAPER VI)

Cardiac troponin I (cTnI) is a protein of the thin filament regulatory system of the contractile complex of the heart that is specific for the myocardium in contrast to cardiac troponin T (cTnT), where isoforms are detected in injured skeletal muscles (143). Cardiac TnI and cTnT are extensively used in detecting myocardial injury, as the sensitivity is superior to the sensitivity of the CK-MB test, cTnI being the most sensitive (144; 145).

The analysis of cTnI or cTnT is at the present standard in establishing the diagnosis of acute myocardial infarction, however it has also proven useful in detecting other kinds of myocardial damage, including post-mortem documentation of cardiogenic sudden death (146). Cardiac troponin I is a predictor of in-hospital clinical outcome as well as of cardiac risk in patients with unstable angina (147; 148). In congestive heart failure, troponin-levels parallel the severity of the disease (149). Cardiac troponin I predicts short-term mortality after vascular surgery (150), adult cardiac surgery (151), and minor increases in cTnI predict decreased left ventricular ejection fraction after high-dose chemotherapy (152). Cardiac troponin I elevation has been demonstrated in otherwise healthy subject following ironman triathlon competition, but in this case decreased ejection fraction documented that significant myocardial damage was present (153).

Elevation of cTnI or more frequently cTnT without a link to myocardial injury may occur in patients with severe renal dysfunction (154), however, unexplained elevations of cTnI are considered rare.

A small number of studies have dealt with cTnI or cTnT in acute stroke. This is a relevant issue because stroke has well documented cardiac consequences and relations to the less cardiospecific CK-MB enzyme have been described. ECG-abnormalities occur after stroke and may be related to increased sympathetic tone especially after right-sided insular lesions (155). If this increased sympathetic tone – or any other cerebrogenic influence on the heart – resulted in actual damage to the myocytes, increased levels of troponin would be expected. In case of a relation to sympathetic tone, a relation to stress hormones and insular, especially right insular lesions would be expected. However, the issue is rather complex in this patient population, as patients with acute stroke have a high prevalence of heart disease, like congestive heart failure that may also cause increased levels of troponin.

We investigated cTnI in a population of 172 patients with acute

stroke and detected cTnI in 35% of patients; in 16.3% of patients cTnI >0.5 *m*g, the upper normal limit of cTnI. Cardiac TnI correlated to age, pre-stroke handicap, neurological disability (SSS) from admission to three months after stroke, and outcome (mRS at three months). Cardiac TnI was significantly higher in patients who died within three months in comparison to survivors. Cardiac TnI level also predicted death or dependency three months after stroke independent of stroke severity, pre-stroke handicap, age, body temperature and pulse rate.

James et al (156) reported based on patients with acute ischaemic stroke, that cTnT >0.1 μg, which in the used method was the upper normal limit and not discriminatory of acute myocardial infarction, predicted in-patient mortality independent of relevant confounders. In our study, cTnI only related to mortality in univariate analysis; in multivariate analysis it only predicted the combined endpoint of death or dependency. Mortality was higher in the study reported by James et al, 31/181 patients died in hospital; in our study 21/172 died within three months. Patient age was in the mid 70's in both studies; James et al. did, however, not report any data concerning stroke severity and had their patients suffered more severe strokes this might be related to the differences in mortality. The lower mortality in our study may have reduced our power in detecting a relation between three months mortality and cTnI.

We also looked into the causes of death in patients stratified according to cTnI levels, but did not find any convincing differences. James et al reported cTnT >0.1 μg in 17% of patients; these patients were older than those with lower levels of cTnT. This is in accordance with our finding. James et al. assumed that the basis for the troponin increase was sympatico-adrenal activation caused by the stroke and that this cardiac stress was also responsible for the subsequent impact on mortality, our finding of a correlation between levels of s-cortisol and cTnI supports this assumtion. Di Angelantonio et al have recently confirmed cTnI as an independent prognostic predictor in acute stroke based on 330 patients (157).

In a study published after ours based on serial measurements of cTnI and cTnT in 174 patients, Etgen et al reports low frequencies of increased cTnI and cTnT. Their population is younger than ours or that of James' et al but there is no straightforward explanation to their differing results (158). Troøyen et al investigated cTnI in acute stroke (159). They found that patients with cTnI in levels that are regarded as diagnostic for acute MI were functionally more impaired at discharge; this is in accordance with our findings. Troøyen et al did not reproduce James findings concerning mortality. They reported a tendency towards older patients, with prior stoke or TIA, a history of heart disease and more severe strokes in the population with increased cTnI. We could not reproduce that prior stroke/TIA or heart disease significantly related to cTnI levels, the latter probably due to sample size, as it is well documented that some heart conditions do relate to cTnI levels. A Spanish study, where only the abstract was published in English, reported that cTnI and cTnT correlated with mortality in 42 patients with acute cerebrovascular disease (160). This is in accordance with the findings of James et al as well as our findings.

Ay et al. (161) reported that cTnT in comparison to CK-MB did not increase after stroke, and concluded that the previously reported CK or CK-MB increases (104) following stroke were not of cardiac origin. Butcher et al (162) responded in a letter that overwhelming evidence supports the existence of cardiac disturbances after stroke and suggested that in future studies the relations of troponin to insular lesions and stress hormones should be investigated.

We did not find a relation between cTnI levels and insular lesion or cTnI levels and side of insular lesions. Contrary to expectations (unpublished data) cTnI levels were significantly higher in patients with left-sided stroke in comparison to right-sided. This is not readily explained and is most likely a chance finding but does hold the implication that the right insular cortex is not a major determinant for cTnI levels.

The serum level of the stress hormone cortisol did, however, correlate with cTnI levels. In an attempt to further generate hypotheses concerning the mechanisms that causes troponin to be detected in acute stroke we investigated its relation to plasma-cytokines.

TNF-α enhances myocardial cell damage in septic shock, myocardial infarction and heart failure (163) and might do so also in acute stroke, which causes an inflammatory response that has been suggested to include a rise in TNF-α concentration (121). Stroke induced inflammation with rise in TNF-α could represent a second pathway of the induction of myocardial cell damage. In a multivariate logistic regression analysis, we found that TNF-α and cortisol predicted detection of cTnI independent of age and stroke severity (SSS), TNF-α $_{+ 100 \text{ pg/mL}}$ OR 1.4 (CI 95% 1.1-2.0), cortisol $_{+ 100 \text{ nmol/L}}$ OR 1.1 (CI 95% 1.01-1.2). This finding generated the hypothesis that cardiac cell damage in acute stroke is not only enhanced by the stress response to acute stroke but also by the inflammatory response.

The presence of ECG-abnormalities was not significantly related to cTnI; according to our findings, paper VII, ECG-abnormalities relate to insular damage.

In conclusion, troponin may be detected in about 35% of patients in an acute stroke population, and in 15-20% it exceeds the upper normal limit. Higher levels are found in old patients, in patients with pre-stroke handicap, in patients with severe stroke, and in patients with a poor prognosis. Elevated troponin predicted poor prognosis independent of possible confounders in at least three separate studies. Troponin levels are not closely related to insular lesions or to ECG-abnormalities but are predicted by s-cortisol and p-TNF-α, a finding that suggests that the cardiac sequels of stroke may not only be induced by insular lesions and stress hormones but also by an inflammatory mechanism.

INSULAR DAMAGE (PAPER VII)

Anatomically, the insula forms a belt of tissue between limbic and heteromodal regions and is recognizable on routine 1.5 T MRI (164). Functionally, it serves a transitional role, merging cognitive, emotional, visceral and somatosensory input.

Functional anatomical studies using PET have demonstrated that the anterior cortex has emotional functions while the posterior part deals with ascending visceral symptoms (165). Insular seizures have been documented by ictal EEG-recording, the ictal sequence consists of sensation of laryngeal constriction, unpleasant cutaneous paraestesia, and dysartric speech followed by complex partial seizures or focal motor convulsions (166).

The primary gustatory cortex has been located to the insula (167; 168), and altered food preference has been described after stroke in this area (169). Anterior insular lesions may cause dysphagia (170).

Bilateral insular lesion may cause total auditory agnosia (171); Sounds activate the insulae, which are active in the temporal processing and phonological processing of sounds as well as the visual-auditory integration and the multisensory modality integration (172), and a right insular lesion may lead to neglect in stroke (173).

Apraxia of speech has been attributed to anterior insular lesions based on the lesion overlap approach (174). However, a recent study based on MRI and clinical findings in acute stroke suggested that apraxia of speech was associated with lesions or low blood flow in the left posterior inferior frontal gyrus (175). Progressive non-fluent aphasia has been associated with hypometabolism centered on the left anterior insula in a PET-based study (176).

It has been suggested that right insular lesions in stroke causes feelings of impaired energy (177). A bilateral volume reduction in insular gray matter is reported specific to first episode patients with schizophrenia in comparison to patients with affective psychosis and controls (178).

Five main groups of clinical presentation of posterior stroke have been suggested: Somatosensory deficits – which may present as a psudothalamic syndrome – gustatory deficits, and gait instability with a tendency to fall without nystagmus, neuropsychological dis-

order including dysphasia (in left lesions), and cardiovascular episodes in right anterior insular stroke (179)

Experimental stroke models have suggested that anterior insular damage causes activation of the sympatico-adrenal system resulting from decreased inhibitory insular activity, which was also reflected by increased levels of catecholamins (109), which have been observed in patients with acute stroke (103). Heart rate frequency changes and blood pressure changes are well documented following insular stimulation or lesions in animal models (180) and conduction changes have been evoked in the rat by phasic stimulation at the time of the R-wave (181). Some studies have suggested lateralisation in ECG-abnormalities after acute stroke (182-184) with right hemisphere lesions tending to associate with ECG-abnormalities.

The relations of insular damage to ECG-changes and outcome in stroke patients were the subject of a study (paper VII) including 179 patients with acute stroke within 24 hours of study inclusion. We based diagnosis of insular damage on CT-scan on admission and on day 5-7 and detected insular involvement in 43 patients (24%). A lesion in the left insula was detected in 25 patients and a lesion in the right insula in 17 patients.

Right insular involvement independently predicted three months mortality in a multivariate logistic regression model also including stroke severity, CT lesion volume on day 5-8, and age; OR 6.2 (95% CI 1.5-25.2). Left insular involvement, or insular involvement without regard to laterality did not predict outcome. The causes of death in patients with right insular involvement did not seem to differ from that of other patients. Stroke sequels was the most common cause of death in this stroke population and it is possible that the actual event leading directly to death may have been a fatal arrhythmia as these patients were obviously not ECG-monitored at the time of their death. Stroke sequels have previously been reported as the leading cause of death after stroke (185). Another study which was prospective and based on autopsy in 42% of patients, showed cardiac death as second to stroke sequels as cause of death after the first week (186). The difficulty of obtaining post-mortem examinations hampers the possibility of obtaining precise information on the cause of death, and autopsy was only performed in one patient in our patient population.

A limited number of reports on cardiovascular disturbances after insular damage in human stroke were retrieved. Sander et al reported arrhythmias in 55.6% of patients with stroke and insular lesions in comparison to 23.5% of patients with other stroke localisations (187). Colivicchi et al corroborated our findings by demonstrating a higher frequency of arrhythmias by Holter monitoring in 103 patients with stroke (188). Sander et al did not mention the frequency of insular damage in their study published in 1995 (189), Tokgözoglu et al (190) reported that lesions involving left or right MCA-insula were observed in 48/62 patients with an ischaemic MCA-stroke >3 cm. Eckhardt el al (191) reported insular involvement in 11/40 patients with ischaemic or haemorrhagic stroke. Fink et al recently reported insular lesions in 48% of their MRI-scanned patient population with non-lacunar MCA-territory infarcts (192). Our frequencies are lower than those reported by Tokgözoglu and Fink; however, their patient population had more severe strokes based on their inclusion procedures; while our frequency is in line with what was reported by Eckardt and Sander. The finding of more left than right lesions in our study is most likely a chance finding that would not have occurred in a larger patient population.

We found ECG-abnormalities differently distributed in patients with and without insular involvement and based on the side (right or left) of the insular involvement. Sinus tachycardia HR>120, and ST-elevation were significantly more frequent in patients with insular involvement also when correcting for CT-lesion volume, which is relevant because insular damage tend to occur in patients with more severe stroke (paper IV)).

Atrial fibrillation, atrio-ventricular block, ectopic beats, and inverted T-wave were significantly more frequent in patients with right insular involvement in comparison to left insular involvement. The finding that sinus tachycardia relate to insular involvement is in accordance with results from animal studies (110; 193), however, this is generally accompanied by increasing blood pressure in animals, in contrast to our findings, where insular involvement did not affect blood pressure levels. Repolarisation changes in relation to insular damage are not well described in stroke. Fink et al reported significantly more new arrhythmias in patients with insular stroke than in patients without insular involvement (192). Two smaller studies (189; 191) suggested a relation between insular involvement and increasing occurrence of prolonged QTc, which we, however, could not confirm.

12-lead ECGs were performed within six hours of stroke onset and ECG-monitoring was done in the first 12-24 hours in our patients, which is earlier than in other reports, and we speculate if our lower frequencies may be that the QTc interval increased gradually in the first hours after stroke, meaning that we recorded the ECG-s too early to register a change. Another possible explanation of this controversy may be that the occurrence of prolonged QTc relates to stroke severity, and stroke severity relate to insular stroke (192; 194) this may lead to the conclusion that prolonged QTc relates to insular infarction if not correcting for stroke severity. Our finding that ST-elevation related to insular involvement is in accordance with a study based on 118 patients with SAH that reported higher frequencies of ECG-abnormalities including ST-segment changes in patients with blood in the sylvian fissure – especially the right sylvian fissure (195). Oppenheimer et al (196) have demonstrated laterality in the effects of stimulation of the human insular cortex. In four patients undergoing surgery for intractable epileptic seizures the right and left insular cortices were stimulated electrically. Stimulation of the left insula caused decreasing heart rate and reduction of blood pressure while stimulation of the right insula caused increasing heart rate and blood pressure; no ECG-abnormalities were observed. This study strongly support laterality in human insular function but does not directly predict the effects of insular stroke, as the effects of electrical stimulation and cell death are not likely to be the same. Laterality in the cardiological consequences of insular stroke has previously been reported. Tokgözoglu et al (190) reported a decreased heart rate variability – a predictor of lethal arrhythmias – in patients with insular stroke, especially right insular stroke. Hirashima et al. (195) reported higher frequencies of ECG-abnormalities in patients with SAH and blood in the right sylvian fissure in comparison to other locations. Fink et al reported higher rates of arrhythmias in left insular stroke than in right insular stroke, contrary to other reports (192).

We were to my knowledge the first to demonstrate higher proportions of several ECG-abnormalities in strokes of other types than SAH related to the right insula. This finding supports the notion of specific cortical lesions being involved in the generation of ECG-abnormalities after stroke and may have clinical implications as the results suggested that these may relate to stroke outcome. We also found that ST-depression, ST-elevation and sinus tachycardia were more frequent in right insular lesions without reaching statistical significance. It would appear likely that such relation existed and that all ST-segment changes and not just some related to lesion side, and in that case the study was underpowered to detect such difference.

Insular cortical ischaemia – without regard to lesion side – has been associated with stress hyperglycaemia in an MRI-based study on 31 patients, which was published after the acceptance of our study (197). This supports the hypothesis that the effects of insular damage occur in an indirect manner by cortico-adrenal activation. We could, however, not reproduce their finding that blood glucose are higher in patients with insular lesions (198) in our larger patient population.

Insular infarctions have also been related to cerebrogenic sudden death (199), which is assumed to be an “electrical accident” caused

by fatal cardiac arrhythmias. Sudden death is generally defined as an unexpected death in a patient that had been regarded as stable until less than an hour before death. Some of the ECG-changes that have been related to a higher risk of sudden death are QTc prolongation and frequent ectopic beats. Tokgözoglu et al (190) reported seven cases of sudden death within the hospitalisation period, of whom five had right insular infarction in a population of 62 patients. No deaths were unexpected in our study population and the causes of death within three months of stroke onset did not differ according to presence and laterality of insular lesions. There is no straight-forward explanation of this discrepancy; however, whether a death is expected or not does in the end depend on the personal opinion of attending doctors, and it is possible that some general differences exist concerning this issue between Danish and Turkish doctors.

In conclusion, insular involvement in acute stroke is a frequent finding. Insular lesions relate to the presence of ECG-abnormalities, especially right insular lesions, which also predict three months mortality.

C-REACTIVE PROTEIN AND WHITE BLOOD CELL COUNT (PAPER VIII)

C-reactive protein (CRP) and white blood cell count (WBC) have been linked to risk of stroke and stroke outcome. It remains, however, unclear if these relations are primarily due to factors present prior to stroke e.g. smoking, atherosclerosis, or metabolic syndrome (200-207), by the stroke lesion itself (208; 209), by complicating infections (202; 210), or by a combination of these factors. It has even been suggested that the effect of antiplatelet therapy was based on the anti-inflammatory effects (211; 212). CRP may reflect atherosclerotic vascular changes (201) and may actively contribute to further damage by induction of PAI-1 (213), or other pathways.

We hypothesised that if levels of CRP and WBC related to the stroke lesion itself, levels would increase shortly after stroke onset and higher levels of CRP and WBC would be expected after severe than after mild to moderate stroke.

The results confirmed our hypothesis by showing that CRP and WBC levels related to the latency from stroke onset to blood sampling and that this relation depended on stroke severity. The levels of CRP increased within 24 hours of stroke onset and the levels of WBC within nine hours of stroke onset in severe stroke in our study.

Relations between the size of the inflammatory response and stroke severity have previously been suggested. Lower Barthel Index on admission in patients with high CRP has been reported (214) and a relation between CRP and CTC infarction volume has been suggested (215; 216). This is supported by the finding of an association between haematoma volume and leukocytosis (217). Our results are contradicted by Anuk et al, who found that CRP < 24 hours after stroke onset did not correlate to stroke severity on admission but correlated well to functional 8-12 months after stroke (218).

As to the timing of an increase in CRP, Winbeck et al. (214) reported that CRP did not predict outcome before 12 hours after stroke onset which in my opinion suggests a change within this period and CRP may double in eight hours (219). Our findings have been corroborated by a later study that demonstrated that increasing inflammatory parameters correlated to CTC volume as well as to stroke severity, and that successful thrombolysis alters the inflammatory response (220).

Emsley et al. reported increasing values of CRP and WBC the morning after admission in comparison to admission within 12 hours of stroke onset in 36 patients with acute stroke as well as in comparison to controls (221).

We assume that the CRP and WBC increases represent an inflammatory response to acute stroke that matches the stimulus; in this case stroke severity, and that the acute inflammatory response in acute stroke therefore are likely to be an epiphenomenon to acute stroke, which may well contribute to stroke morbidity.

It has been suggested that CRP predicted outcome in acute stroke.

We found in multivariate analysis that CRP related to 1-year mortality, but not to seven days or three months mortality. WBC did not predict mortality in multivariate analysis. This corroborates the results from other studies; Muir et al (222) reported that CRP measured within 72 hours of stroke onset independently predicted long term survival with an excess cardiac mortality. Di Napoli et al added that CRP predicted death from any cause or new cerebrovascular or cardiovascular events and that high CRP at discharge predicted poor outcome (211; 215; 223).

However, in my opinion, a discharge CRP measurement may be such strong predictor of outcome because it not only reflects vascular risk factors but also stroke morbidity including concomitant infections, and it does therefore probably not guide the attending doctor in choosing a treatment strategy. Winbeck et al and Eikelboom et al have further confirmed CRP as a prognostic predictor in acute stroke (214; 224). Some did not find any relation between CRP and outcome (225).

One study later study has suggested a relation between WBC and outcome in multivariate analysis . However, they adjusted for various risk factors but did not include e.g. stroke severity in the model. CRP and WBC in acute stroke does not only reflect the stroke incident but the CRP and WBC on the day of a stroke incident, which – as well as any other day in the patients life – appears to reflect the patient's vascular risk (226-230). We found that CRP levels related to a history of diabetes and a history of claudication, and that WBC levels related to smoking status, thus corroborating previous findings (202; 227; 228). We could not reproduce a relation to coronary heart disease, which may be due to lack of sensitivity of our analytical method as it was not performed as a hs-CRP (high sensitivity), and changes relevant to coronary heart disease may be below the detection limit of the method (231).

Beamer et al suggested that a chronic up-regulation of acute phase-reactants was present in stroke survivors, as a prolonged elevation was observed (232). Based on data from the Framingham Study, Rost et al (207) reported that CRP predicted ischemic stroke and TIA in the elderly. Chung et al (229) reported that CRP was elevated in patients with atrial fibrillation, a finding which could be reproduced in our patient population, unpublished data. However, in our patients, both CRP and WBC were significantly higher in patients with abnormal ECG than in patients with normal ECG, unpublished data, rather suggesting a relation to cardiac status and risk, than to atrial fibrillation in specific. Interestingly, Aronow et al recently reported that higher WBC predicted a higher rate of microembolic signals on TCD during carotid stenting. This indicates a relation between systemic inflammation and embolisation (233).

Another aspect is infections prior to stroke, which are bound to affect levels of CRP and WBC. Recent infection is also a risk factor of stroke (202; 234-242). We observed higher levels of CRP and WBC in patients with recent infections, which is in accordance with previous findings (243).

In conclusion, CRP and WBC increase in the first hours after severe stroke. CRP reflects risk factors of vascular disease and independently predicts long-term mortality and risk of vascular incidents.

CRP in the very first hours after stroke onset is most likely to reflect risk factors, as an increase due to stroke is seen 12-24 hours after stroke onset, and a discharge CRP will also reflect concomitant infections.

CRP, preferably hs-CRP measurements, may contribute to risk factor modification in patients with stroke, as high CRP levels indicate the presence of vascular risk factors. WBC relates to smoking, but is otherwise less strongly related to risk factors of stroke, and does not independently predict outcome after stroke.

APPENDIX I

STUDY POPULATIONS

The papers in this dissertation were based on the following two study populations.

The Bispebjerg Acute Stroke Unit Population

This database population included all patients that were admitted within six hours of symptom onset to the acute stroke unit 'Interventionsafsnittet', Bispebjerg Hospital, from 1 February 1998 to 21 October 2000, and who were discharged with a diagnose of acute cerebral infarction (ACI), intracerebral haemorrhage (ICH) or transient ischaemic attack (TIA). In total data from 1192 patients were recorded in the database. Of these patients 760 (63.8%) were diagnosed with ACI, 185 (15.5%) were diagnosed with ICH, and 247 (20.7%) with TIA at discharge. Diagnoses were in all cases based on clinical findings and CT-scan. Patient history, stroke scale, outcome scale, and vital values were registered on a structured patient file by attending doctors and nurses and the number of missing values were reduced by HC, who continuously monitored and filled out missing values in the structured patient files. Patient history including risk factors of stroke, Table A1, as well as pre-stroke handicap was recorded based on information from patients and/or relatives and/or admitting doctor and/or existing hospital files.

Handicap was assessed by the modified Rankin Scale (mRS) (244), the mRS rates handicap on a scale from 0-6 points, where 0 points represents good health with no symptoms and 6 death. Scandinavian Stroke Scale Score (SSS) (89) was used to asses neurological deficit. The SSS rates from 0-58 points, where 58 points represent no deficits in the recorded items. SSS was rated on admission, on day two, on day four, on day seven or until discharge. Nurses recorded motor function and speech every two hours in the first 24 hours after admission and every four hours in the next 48 hours. Blood pressure (systolic and diastolic), pulse rate and body temperature were recorded every two hours in the first 24 hours, every four hours in the next 48 hours, on day four, and on day seven. Blood glucose, C-reactive protein, white blood cell counts were also recorded. ECG in 12 leads was recorded on admission, and ECG surveillance was done for at least the first 12 hours after admission.

The patients were divided into groups based on stroke severity on admission. SSS ≤ 25 was selected as a cut-off point as patients below this score are all non-ambulant with other severe deficits. We termed this group 'severe strokes' and patients with SSS > 25 'mild to moderate strokes'. This dichotomisation was based on clinical grounds, and was used in most papers; a dichotomisation based on a median was used in one instance on statistical grounds (paper IV).

Deteriorating stroke was defined as a drop in SSS of at least 2 points lasting at least four hours and occurring within 72 hours after stroke onset. There is no generally accepted definition of deteriorating stroke (245).

Follow-up was performed three months and one year after stroke onset. In app. 80% of patients' three months follow-up was done by telephone interview by trained research nurse, and app. 20% of patients were seen in the out patients' department. Modified Rankin Scale was recorded in all patients as well as in deceased patients time and cause of death. In patients that were seen in out-patients' department, SSS and blood pressure were also recorded. 121 patients were lost to follow up at three months but information concerning whether they were alive or dead were achieved in all patients.

A second follow-up telephone interview was performed one year after admission, where modified Rankin Scale and cause of death were recorded. 171 were lost to follow up one year after stroke, but information regarding death was achieved in all patients.

These structured patient files were collected in all patients, and from this a database was created.

Table A1. Recorded risk factors of stroke.

Prior stroke	Diabetes mellitus
Prior TIA	Claudicatio
Atrial fibrillation	Recent infection
Arterial hypertension	Alcohol intake
Congestive heart failure	Smoking
Acute myocardial infarction	p-homocystein cholesterol

Table A2. Patients characteristics of 1193 patients with acute cerebrovascular disease included in the Intervetiondatabase.

	ACI	TIA	ICH
N =1192	759	248	185
Age, years	76 (67-82)	70 (58-79)	74 (62-81)
% Male sex	52	51	52
History of arterial hypertension (%)	36	36	37
SSS on admission	38 (22-48)	55 (49-58)	22 (8-34)
SSS on admission ≤ 25 (%)	30	3	56
7 days fatality rate (%)	7	0	31
3 months fatality rate (%)	18	5	43

SSS: Scandinavian Stroke Scale; ACI Cerebral Infarction; TIA: Transient Ischaemic Attack. Values are stated as per cent or as median values with 25 and 75% quartiles.

The general characteristics of the 1192 patients are presented in Table A2.

Registertilsynet, and later Datatilsynet approved the database. The Scientific-Ethical Committees of Copenhagen and Frederiksberg were informed of the study, and found that the study was not within the coverage of the Scientific-Ethical Committees, but had no objections to it or its conduct.

Substudy population

A prospective trial was run in the acute stroke unit of Bispebjerg Hospital from 16 February 1999 and until the unit was shut down 27 October 2000. From 27 October 2000-28 February 2001 patients were recruited from the Neurological Admission Department in Bispebjerg Hospital serving a population of 130,000, admitting patients referred from General Practitioners in the district and from the emergency room.

Patients of at least 18 years of age with clinical symptoms of stroke were included within 24 hours after stroke onset after informed consent. Patients with other acute life-threatening diseases, pregnant women and not evaluable patients – e.g. due to severe dementia – were excluded from the study.

Except during investigator's holidays etc. admitted patients fulfilling the inclusion criteria to the substudy were included consecutively if informed consent was obtained from patient or proxy. The study was approved by the scientific-ethics committee of Copenhagen, file no. (KF) 01-358/98.

A total of 184 patients were included in this substudy, however, one patient withdrew consent and four patients received another final diagnose than acute stroke (epileptic seizures, primary or secondary cerebral neoplasm). These patients were not included in the analyses. Two patients were lost in follow-up but at three months information as to whether alive or dead was achieved in these two patients. Consequently, the analyses are based upon 179 patients: 162 of whom suffered cerebral infarctions and 17 intracerebral haemorrhages.

Data from patients in the substudy population who were admitted before 21 October 2000 are included in both Bispebjerg Acute Stroke Unit Population and the Substudy population; this was considered an acceptable procedure as the two groups are analysed in different papers and therefore not compared to each other, and the investigated issues complement each other.

Data was recorded as described for the Bispebjerg Acute Stroke Unit Population, and besides this population was investigated further by collection of blood samples solely for research purpose on inclusion and three months after stroke onset, and by an additional CT-scan that was performed on day 5-8.

Two prior publications concerning cytokines and cytokine receptors (121) and deteriorating stroke (246) that formed my Ph.D. thesis have been based on this population.

SUMMARY

After arrival to hospital, changes in many physiological and biochemical variables have been observed following acute stroke. These

variables include body temperature, blood pressure, blood glucose, C-reactive protein, white blood cell counts, corticosteroids, cardiac enzymes, and ECG. These relate to outcome, and causality has been assumed for some of these variables, based on observational findings and animal models.

Most observational studies in acute stroke are based on patients admitted to hospital with some delay from stroke onset, and in a number of studies the latency from stroke onset to admission was not well defined.

These variables may be more or less static in acute stroke and changes within the first hours and days after symptom onset would in that case be negligible. This hypothesis has, however not yet been tested.

Another possibility remains that these changes evolve in the first hours after stroke onset as a result of the stroke lesion and possibly contribute to secondary brain damage.

The aim of the studies on which this thesis was based was to include this time factor in the analyses by studying a stroke population that was admitted to hospital within six hours of stroke onset, by use of serial measurements within the first hours, and by including the time factor in the analyses. We further looked into the interplay of heart and brain as well as the stress response in order to investigate their possible impact in the first hours after stroke onset.

We found that stroke severity determines an increase in body temperature, C-reactive protein, and white blood cell count in the first hours after stroke. The blood pressure course related to the time of admission and a steep decrease was observed in mild to moderate stroke. Heart rate decreased in patients with mild to moderate stroke, but remained high in patients with severe stroke and predicted outcome. Blood glucose increased and the size of the increase related to stroke severity. The cortisol response related to stroke severity, and predicted outcome independently, and related to blood glucose, heart rate, a number of ECG-abnormalities, and to insular damage. ECG-abnormalities relate to insular damage, especially damage to the right insula, and may predict prognosis. Damage to the right insula predicts mortality. Troponin I predicted outcome.

We documented that acute stroke is a dynamic process and that stroke severity is a determinant in the changes of physiological parameters. The stress response as well as cardiac changes may contribute further to poor prognosis especially in severe stroke. Damage to the right insula may have a key role for the stress response and the cardiac changes after stroke.

ABBREVIATIONS

ACI	Acute cerebral infarction
ACTH	Adrenocorticotropic hormone
App.	approximately
CI	Confidence intervals
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computer-assisted tomography
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECG	Electrocardiography
HR	Heart rate
ICH	Intracerebral haemorrhage
IL-1β	Interleukine 1β
IL-10	Interleukine 10
IL-1RA	Interleukine 1 receptor antagonist
IL-6	Interleukin-6
MAP	Mean arterial pressure (MAP = DBP + 1/3 (SBP – DBP)
MCA	Middle cerebral artery
MI	Myocardial infarction
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
OCSP	Oxfordshire Community Stroke Project Classification
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
QTc	Corrected Q-T interval
SBP	Systolic blood pressure
SSS	Scandinavian Stroke Scale
TCD	Transcranial doppler
TIA	Transient ischaemic attack
TNF-α	Tumor necrosis factor-α
TNF-R1	Tumor necrosis factor receptor 1
TNF-R1	Tumor necrosis factor receptor 2
WBC	White Blood Cell

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