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Chirurgische notfallmäßige Revaskularisation eines kompletten Verschlusses der A. carotis interna im Stadium des akuten Schlaganfalls

DISSERTATION

zur Erlangung des Grades eines Doktors der Medizin
Der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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Clinic for Vascular Surgery and Kidney Transplantation
of the Heinrich-Heine-University Düsseldorf
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Emergent surgical revascularisation of the complete Internal Carotid Artery occlusion at the stage of acute stroke

A dissertation in partial fulfillment of
the requirements for the degree of
Doctor of Medicine

By

Asya Spivak-Dats

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dedicated to my parents

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List of abbreviations used in this paper

ACA	Anterior cerebral artery
CCA	Common cerebral artery
CEA	Carotid endarterectomy
CCT	Cerebral computed tomography
CTA	Computed tomographic angiography
CVB	Cerebral blood volume
DSA	Digital subtraction angiography
DWI	Diffusion weighed imaging
EEG	Electroencephalogram
HIT II	Heparin induced thrombocytopenia of type II
ICA	Internal carotid artery
ICH	Intracerebral haemorrhage
I.U	International units
i.v	Intravenous
M2	M2 segment of the middle cerebral artery
M3	M3 segment of the middle cerebral artery
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRs	Modified Rankin Stroke Scale
MTHFR	5,10-methylenetetrahydrofolate reductase gene
PCA	Posterior cerebral artery
PET	Positron emission tomography
PTT	Partial thromboplastin time
PWI	Perfusion weighed imaging
rt-PA	Recombinant tissue plasminogen activator
s.c.	Subcutaneous
TEA	Thrombendarterectomy

1. Introduction

Stroke is the leading cause of long term disability and, after coronary heart disease and lung cancer, third cause of mortality in the industrialized world[1]. It affects more than 250 000 individuals annually in Germany[2], over 700 000 in North America and 15 million worldwide[3]. Cerebral ischemia accounts for almost 85% of strokes and is in up to 60% due to atherosclerotic changes of the large muscular arteries, the so called macroangiopathy[4, 5]. Clinical observations showed that in 90% brain infarction is located in the supply area of the internal carotid artery (ICA) and in about 10-20% brain infarction is due to the occlusive carotid artery disease[6].

The clinical prognosis of the acute carotid occlusion if left untreated is poor: 2-12% patients recover completely, 40-69% patients retain neurological deficits and 16-55% will have died in the follow up[7]. The annual stroke recurrence rate varies according to different studies between 4 - 27% in symptomatic occlusions and up to 8 % in asymptomatic ICA occlusions[8, 9, 10], the five year survival rate lays at 62%, compared to the expected rate of 90% in a matched normal population[10].

These statistics justify the need for prompt treatment of the occlusive artery disease by reestablishing of the blood supply to the impaired brain region.

The importance of the neck arteries was already recognized in the ancient Greece: the word “carotid” is derived from the Greek *karoo* meaning “to stupefy”, already back then it was thought that compression of these vessels leads to deep sleep.

1. Introduction

By the 19th century association between ICA occlusion and severe ischemic stroke was an established postulation[11].

Development of new diagnostic modalities has lead to new therapeutic options in the treatment of the occlusive carotid artery disease: Egaz Moniz of Lisbon developed the technique of cerebral angiography in 1927 and in 1937 demonstrated cases of carotid occlusion angiographically[11, 12]. In the late 1940s the ultrasound energy was first applied to the human body for medical purposes and from the late sixties on for assessment of the internal carotid artery stenosis[13].

In 1946 thromboendarterectomy for restoring flow in peripheral vessels was developed and first successful carotid endarterectomy (CEA) was performed by Dr Michael De Bakey on August 7, 1953[12]. He and other vascular surgeons recognized the increased risk for recurrent ischemic events due to persistent embolic source and hemodynamic insufficiency of the occluded carotids and undertook attempts to remove vessel obstruction in the phase of the acute stroke. However, limited preoperative diagnostic options and monitoring of the early postoperative cerebral situation had led to unacceptably high postoperative mortality ranging from 16% to 50%, which was mostly due to intracranial hemorrhage[14, 15, 16]. Thus, the early carotid revascularisation was abandoned for years, the accepted policy being to delay surgery for at least four to six weeks in patients with acute stroke to possibly avoid bleeding complications.

Nowadays the possibilities to evaluate the vascular system and the brain are substantially different compared to the time of the joint study[17]. Ultrasound

technology, angiography and neuroimaging such as cerebral computed tomography (CCT) or magnetic resonance imaging (MRI) with diffusion-weighted (DWI) and perfusion-weighted imaging (PWI) allow for rapid and accurate diagnosis of extra- and intracranial vascular occlusion and its associated acute ischemic stroke. But it was not before the advent of thrombolytic therapy for acute intracranial thrombotic occlusion that surgical treatment of acute extracranial ICA occlusion was reinvented. Systemic thrombolytic therapy within 3 hours after symptoms onset has shown to be effective in reduction of neurological disorders caused by intracranial vascular occlusion[18, 19, 20]. However, when aimed at revascularisation of the atheroslerotically deformed internal carotid artery (ICA) occlusion, the systemic thrombolysis has brought poor results with recanalisation rate ranging only between 0-50% whereas morbidity and mortality rate was high with up to 50%[21, 22, 23].

In the acute ICA occlusion the neurological disorder occurs due to reduction of cerebral blood flow (CBF) which is either due to thromboembolism or from hypoperfusion of the dependent hemisphere in patients with insufficient collateral blood flow[18]. The progression to irreversible neuronal cell injury occurs at different rates in the ischemic region, primarily related to the severity of CBF decline. The affected region, also termed as infarction core, with the lowest residual CBF (<10ml/100g/min) rapidly evolves into irreversible injury, whereas brain regions with more modest CBF decline (12-25ml/100g/min) evolve more slowly and are functionally, but not irreversibly impaired. These differently affected brain regions might be represented by the different rates of oxygen extraction in positron

emission tomography studies (PET) and, more practically, by the presence of cytotoxic oedema and perfusion difference in the in the magnetic resonance imaging diffusion/perfusion mismatch studies [24, 25, 26].

Thus, the timely surgical revascularisation of acute symptomatic carotid occlusion pursues following goals:

- to quickly restore the blood supply to the functionally impaired but still viable brain tissue in hope to minimize neurological damage and improve clinical outcome,
- to remove the source of occlusion (mostly fresh thrombus on already pre-existing high grade atherosclerotic formations) before definite thrombus organisation, in order to eliminate constant embolic origin from the occluded carotid stump and
- to re-establish the blood supply to the dependent hemisphere.

2. Objectives of the study

In the acute ICA occlusion the neurological disorder is thought to be due to reduction of cerebral blood flow (CBF) which is either due to thromboembolism or due to hypoperfusion of the dependent hemisphere in patients with insufficient collateral blood flow[18]. It has been shown that progression to irreversible neuronal cell injury occurs at different rates in the ischemic region, primarily related to the severity of CBF decline. The affected regions with CBF under critical perfusion volume undergo definite neuronal cell death whereas the hypoperfused areas with limited CBF contain functionally impaired, but potentially viable brain tissue[24].

This study was underlined by the hypothesis that rapid surgical re-establishment of the cerebral blood flow in the acute stroke phase could reduce the size of the definite brain infarction and minimize the risk of recurrent embolic events from the vessel stump, thus potentially improving clinical outcome. Furthermore, it was presumed that a re-opened internal carotid artery could be beneficial for later life by minimizing further embolisation from the occluded vessel stump and ensuring adequate perfusion in patients with insufficient collateral circulation.

The retrospective analysis of the data aimed at answering following questions:

1. Can acutely occluded internal carotid arteries be reopened? Is there a time limitation for technically successful revascularisation?

2. Do patients profit clinically from this surgical procedure? Can the slogan “time is brain” also be applied to the revascularisation of acute carotid occlusion?

2. Objectives of the study

3. Is the emergent revascularisation of acute ipsilateral carotid artery occlusion safe?

4. Does success of the clinical and surgical outcome depend on time, as in medical treatment of acutely occluded middle cerebral artery (MCA) with systemic thrombolytics?

3. Study design, methods and statistical analysis

3.1 Study design

3.1.1 Primary endpoints of the study

Between November 1997 and November 2006 patients with clinical signs of stroke were routinely admitted to the emergency ward or directly to the stroke unit of the Heinrich-Heine-University Neurological Clinic in Düsseldorf. We focused on a subgroup of patients with acute ICA occlusion and ipsilateral stroke who underwent acute surgical revascularisation.

Primary efficacy endpoint of the study was:

- Proportion of good clinical outcome as defined by adjusted modified Rankin Stroke Scale at discharge

Primary safety endpoint was:

- Rate of stroke recurrence, haemorrhagic transformation or secondary intracerebral haemorrhage and any death between treatment and day 30

3.1.2 Secondary endpoints of the study

Key secondary endpoint(s) were:

- Re-opening rate of acute carotid occlusion after surgical revascularisation
- Rate of re-infarction or intracranial bleeding during hospital stay
- Clinical outcome during follow up

The patient data with acutely occluded ICA and emergent revascularisation and available neurological and surgical file records were prospectively collected but retrospectively analysed.

All available written preoperative and postoperative radiological reports, the print outs and CDs of digital subtraction angiography (DSA), magnetic resonance angiography (MRA), computed tomography angiography (CTA), CCT and MRI scans of the already selected patients were retrieved from the archive of the Institute for Radiology at the Heinrich-Heine-University, and, to ensure the certainty of the radiologic data, and were blindly re-evaluated by an experienced neuroradiologist.

3.2 Methods

3.2.1. Neurological evaluation

All patients underwent a standardized clinical neurological examination. The degree of the functional impairment was objectified by using the Barthel's index of Activities of Daily Living, the modified Rankin Stroke Scale for stroke assessment (mRs), the European Stroke scale as well as the NYH Stroke Scale. The most complete data was gathered for the modified Rankin scale for stroke assessment (mRs) and therefore only this scale was used for further analysis (Appendix 1).

3.2.2 Evaluation of the extracranial and intracranial circulation

When ipsilateral ICA occlusion was suspected by extra- and intracranial ultrasound, additional extracranial MRA and/or DSA was performed to obtain precise information of the intracranial vascular status. It should be noted that frequently there is an additional occlusion of the distal internal carotid artery, particularly in the supraclinoid segment - the result from embolisation or distal propagation of the thrombus. However, surgical revascularisation can only be achieved if the ICA occlusion is limited to its extracranial part. Therefore,

visualisation to confirm patency of the distal vessel is essential before performing surgical revascularisation[18].

3.2.3 Cerebral evaluation

All patients underwent preoperative cerebral imaging, either in form of the cerebral computed tomography (SOMATOM, Sensation Cardiac, (64)) or cerebral magnetic resonance imaging (TIM-TRIO, Siemens, 3 Tesla), combined in several cases with the so called “stroke imaging” that included T1, T2 sequences, diffusion- and perfusion studies as well as the intracranial magnetic angiography.

3.2.4 Indications for surgery

In selected cases emergent operative revascularisation of the acutely occluded ICA was performed. Based on previous studies and own experience, following criteria had to be met in order to undergo emergent revascularisation and to be enrolled in the study:

Inclusion criteria

- Time period between November 1997 and November 2006
- Admission to the emergency ward or the stroke unit of the Neurological Clinic, University-Hospital of Düsseldorf
- Time interval between the onset of symptoms and the surgery not more than 168 hours
- No signs of an intracranial haemorrhage in the preoperative radiological work-up
- Definite signs of cerebral infarction in the preoperative radiological work-up

3. Study design, methods and statistical analysis

- Cerebral infarction ipsilateral to the occlusion of the internal carotid artery, limited to less than one third of the medial cerebral artery (MCA) supply territory
- Occlusion of the internal carotid artery limited to its extracranial segment proven by magnetic resonance or digital subtraction angiography

Exclusion criteria

- Time interval between the onset of symptoms and the surgery more than 168 hours
- Signs of intracerebral haemorrhage in the preoperative radiological imaging
- No definite signs of brain tissue ischemia in the preoperative radiological work-up
- Cerebral infarction spreading to more than one third of the MCA supply territory
- Occlusion of the intracranial portion of the internal carotid artery

3.2.5 Surgical technique

If inclusion and exclusion criteria for the emergent ICA revascularisation were met, patients were immediately transferred to the operating theatre. Intraoperative neuromonitoring modalities consisted of continuous somatosensory evoked potentials registration of the N. medianus of the ipsilateral hemisphere or ipsilateral encephalographic (EEG) registration[27]. General anaesthesia was initiated and after exposure of the carotid bifurcation, 2500 I.U. heparin were administered intravenously. The common carotid artery (CCA) and the external carotid artery (ECA) were double cross-clamped. Longitudinal CCA arteriotomy

extending into the ICA was carried out[28]. Chronic atherosclerotic stenosis as underlying cause for acute occlusion was treated by thromboendarterectomy (TEA).The fresh thrombus, which was usually found above the chronic bifurcation process was either flushed out by elevating the systemic systolic pressure to at least 180 mmHg, to increase the retrograde blood flow, or in case of insufficient backflow, a 2F balloon catheter was advanced with caution towards the carotid siphon and thrombectomy was performed. Still insufficient backflow was an indication for an intraoperative arteriography. After achieving adequate backflow, the arterial incision was closed by using autogenous patch graft from the greater saphenous vein of the ankle. Restoration of ICA blood flow was controlled intraoperatively by Doppler sonography.

3.2.6 Postoperative treatment

All patients were monitored at the Intensive Care Unit or Intermediate Care Unit that included invasive blood pressure measurement for better control of the blood pressure fluctuations. If no complications occurred, patients were transferred back to the stroke unit 24 hours after surgery. Primary postoperative anticoagulation consisted of 10 000 I.U./24 hours intravenous low dose heparin which was then replaced by low weight subcutaneous heparin. One patient received hirudin because of the HIT II syndrome. At discharge all patients received secondary prophylaxis consisting of a thrombocyte aggregation inhibitor (aspirin, combination of aspirin and dipyridamol or clopidogrel).

3.2.7 Postoperative diagnostic work-up

The clinical neurological examination and the modified Rankin Stroke Scale were performed routinely during the postoperative hospital stay. The latest available modified Rankin Stroke Scale before the median discharge of 11 and average of 13 days was compared to its preoperative value. In case of transfer to another clinic at discharge, information on further clinical state of the patients was obtained (in form of discharge reports, faxes and telephone calls). This information was then used for determination of the 30 days mortality.

Doppler- and/or Duplex sonography of the operated vessels was performed to monitor the postoperative status. In case of clinical neurological deterioration there was always postoperative cerebral imaging performed. In particular, 23 (47%) patients were postoperative re-evaluated by CCT and 29 patients (59%) by MRI.

3.2.8 Follow-up

All surviving patients were contacted by telephone. The patients were encouraged to come to the department of Neurology for a clinical neurological check-up, Duplex examination of the neck arteries and Doppler sonography of the intracranial circulation (Elegra Sonoline, Siemens or MULTI-DOP L). Present social and medical history (information on current state of health, recurrent cerebro-vascular events, hospital stays) was taken. Current modified Rankin Stroke Scale was determined. If patients were not able to come to the clinic, general practitioners, practicing neurologists as well as hospitals and rehabilitation clinics were contacted for latest medical records such as Doppler- and Duplex

sonographic findings of the cerebral circulation, radiological reports and discharge letters. In case of death, date, place and cause of death were documented.

3.3 Statistical analysis

3.3.1 Evaluation of clinical outcome and time intervals

One goal was to evaluate the clinical outcome. The other goal was to find out whether there existed correlation between the rate of successful ICA revascularisation and the time interval between the onset of symptoms and the surgery.

For that purpose, the total time period of 168 hours from the onset of symptoms to the time of the emergent surgery hours was split into four groups:

1. group: the time from the onset of symptoms to the emergent surgery within the first 24 hours,
2. group: the time from the onset of symptoms to the emergent surgery within 48 hours,
3. group: the time from the onset of symptoms to the emergent surgery within 72 hours,
4. group: included patients that underwent emergent surgery within 73-168 hours after onset of symptoms.

The difference in the preoperative and postoperative modified Rankin Stroke Scale (mRs) was used to determine degree of clinical outcome: clinical improvement was indicated by the positive difference in the mRs by at least one point, same

outcome – by the nil difference in the mRs and clinical deterioration was indicated by the negative value of the difference in the preoperative and postoperative mRs by at least one point or by perioperative death. The difference in the preoperative and postoperative modified Rankin Stroke Scale was then mapped in the Excel Microsoft program and tendency line was integrated.

3.3.2 Statistics

The obtained personal and medical and radiological information on each patient was entered in a computerized database designed by my supervisor Barbara Theresia Weis-Müller, MD and myself. Microsoft Access program from the Microsoft package XP 2000 was used for programming this database. The collected data were then exported to the Excel program from the same Microsoft package for the statistical analysis.

Two by two contingency tables were constructed for each subgroup of patients. Fisher exact test and the chi-square test were used for the statistical analysis[29]. Fisher exact test was taken from the internet site designed by Oyvind Langsrud, the chi-square analysis was designed by the SAS program of the Statistical Analysis Systems Company.

These tests were used to test for significant difference (p value < 0.05) in following analyses:

- Dependence of the rates of successful ICA revascularisation on defined time intervals between the onset of symptoms and the surgery

3. Study design, methods and statistical analysis

- Dependence of clinical neurological outcome (including death) on the time of the emergent ICA revascularisation.

- Dependence of clinical neurological outcome on the rate of successful ICA revascularisation.

4. Patients

4.1 Number of patients, age, gender

In the study period from November 1997 to November 2006 a total of 1810 patients underwent carotid surgery for occlusive disease at the Clinic for Vascular Surgery and Kidney Transplantation at the Heinrich-Heine-University in Düsseldorf. During this time 5369 patients were examined at the stroke unit of the Neurological Clinic and 502 symptomatic patients from this patient collective were transferred to the Clinic for Vascular Surgery and Kidney Transplantation of the Heinrich-Heine-University for ICA reconstruction.

A subgroup of 49 patients underwent emergent revascularisation of the acutely occluded ICA. The study population consisted of 40 (81.6%) men and 9 (18.3%) women. The average age of the patient collective was 731+/-124.7 months (60.9 years old), the median age was 748 months (62.3 years old). The youngest patient was 382 months (31.8 years old), the oldest patient was 948 months (79 years old).

4.2 Cerebrovascular risk factors

Following risk factors relevant to the ischemic cerebro-vascular disease were identified: hypertension in 35 (71%) patients, history of smoking in 24 (49%) patients, diabetes mellitus in 11 (22%) patients, and coronary heart disease in 14 (29%) patients and hyperlipidemia in 23 (47%) patients. The risk factors are displayed below (Table 1):

Cardiovascular risk factor	n	%
Arterial hypertension	35	71
Smoking	24	49
Diabetes mellitus II	11	22
Hyperlipidemia	23	47
Coronary heart disease	14	29
Total patients	49	100

n= number of patients, % = percentage of patients

Table 1: Distribution of the cardiovascular risk factors

4.3 Preoperative clinical status

14 (28%) patients showed stable clinical preoperative status and 5 (10%) experienced clinical improvement of the initial neurological deficit. Fluctuating neurological deficits occurred in 17 (35%) patients, stroke in progression was observed in 13 (26, 5%) patients. This distribution is pictured below (Table 2):

Preoperative clinical Status	n	%
Improvement	5	10
Stable	14	28
Fluctuating	17	35
Progressing deficit	13	26
Total	49	100

n= number of patients, % = percentage of patients

Table 2: Preoperative clinical status

4.4 Neurological deficit before surgery

The extent of the neurological deficit at admission and before surgery was measured by the mRs: Three out of 49 (6%) patients had no symptoms at all (mRs – 0), 5 (10%) patients showed no significant disability despite symptoms (mRs – 1), 4 (8%) patients suffered slight disability (mRs – 2), 8 (16%) patients suffered moderate disability (mRs – 3), 18 (37%) suffered moderate severe disability (mRs – 4) and 11 (22%) patients were severely affected and were bedridden (mRs – 5).

Diagram 1 displays the preoperative modified Rankin Stroke Scale distribution.

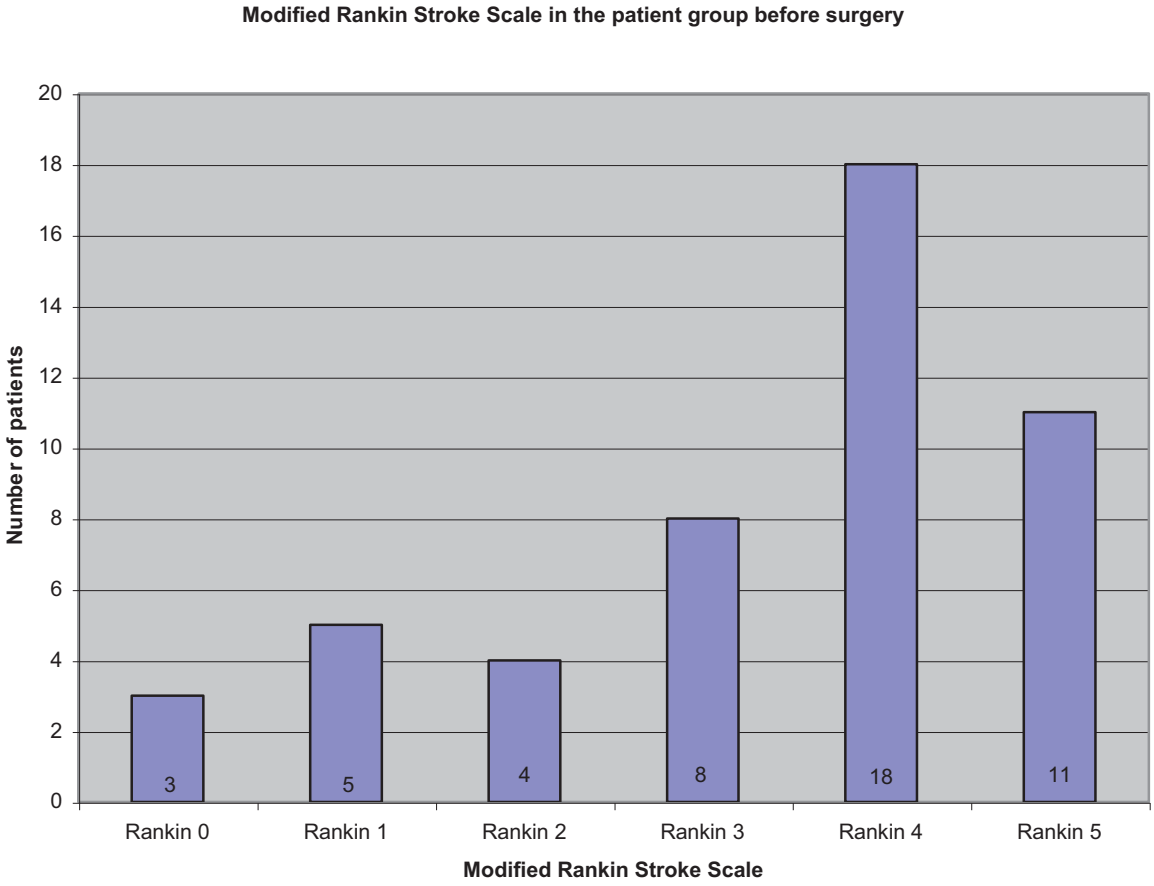

Diagram 1: Distribution of the modified Rankin Stroke Scale in the patient group before surgery

For better overview in the later sections, all patients were listed in appendix 2 with respect to the change in the postoperative clinical outcome expressed by the difference in the mRs.

4.5 Preoperative diagnostic work up

4.5.1 Neuroimaging studies

31 (63%) patients received emergent cerebral computed tomography, 39 (80%) patients underwent cerebral magnetic resonance imaging, in 37 (75%) cases there was diffusion/perfusion study performed, 25 (51%) patients were examined by both neuroimaging methods. All patients displayed signs of a fresh infarction in the ICA supply area.

4.5.2 Sonographic studies

47 of 49 (96%) patients received Doppler sonography of the extracranial vessels, for 2 (4%) patients there were no sonographic records found, however there were records of the angiographic studies: one patient underwent CTA, one other patient underwent DSA. 39 (80%) patients received additional examination of the intracranial vessels by transcranial sonography, 38 (78%) patients underwent additional Duplex sonography of the extracranial vessels. All 47 patients and the two with CTA and DSA displayed extracranial ICA occlusion.

4.5.3 Preoperative angiographic findings

If acute ICA-occlusion was suspected, additional extracranial MRA and/or DSA was performed to obtain precise information on the intracranial vascular status. Therefore, 30 (61%) patients were evaluated by means of MRA and 24 (49%)

patients by DSA alone or by both angiographical methods. In all but two angiographies acutely occluded ipsilateral ICA occlusion was suspected. In these two cases subtotal stenosis was seen in angiography, which then transformed to occlusion after the intervention.

Apart from the ipsilateral ICA occlusion angiography demonstrated ICA chronic contralateral occlusion in 10 (20%) patients. The studies of intracranial vessels showed patent ipsilateral middle cerebral artery (MCA) in 40 (82%) patients, in one case (2%) there was stenosis of the ipsilateral MCA, in 8 (16%) further cases there was no information obtained. The contralateral MCA was patent in 44 (90%) cases, in 5 (10%) cases there no information was obtained.

The distribution of all performed preoperative examinations can be seen below (Diagram 2).

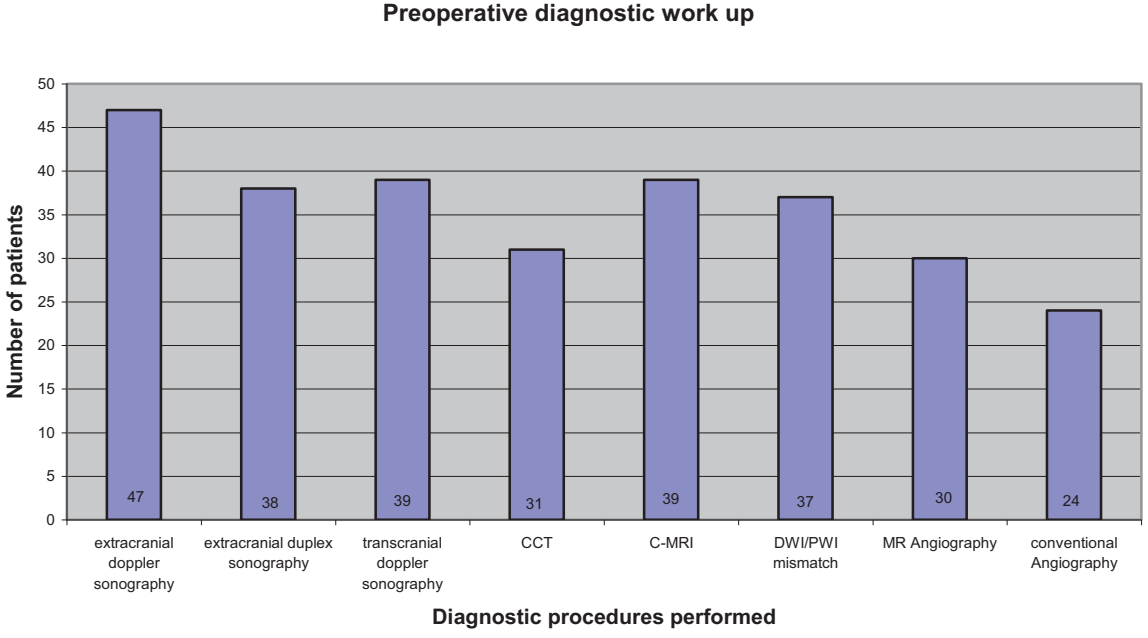

Diagram 2: Preoperative diagnostic work up

4.6 Preoperative treatment

In most cases patients received a combination of anticoagulative medication which consisted of tirofiban, i.v. or s.c. heparin, i.v. hirudin or oral aspirin.

7of 49 patients suffered severe neurological deficits and, being admitted within the 3 hour interval after the onset of symptoms, were treated with the systemic thrombolytic therapy (recombinant tissue plasminogen activator (rt-PA): one patient received the standard 0.9 mg/kg rt-PA treatment and the other 6 patients were treated with combination of rt-PA (20 mg) and tirofiban (usually 0.4 ml/h). 5 of 49 patients were treated with tirofiban and i.v. heparin.

A total of 29 of 49 patients received PTT adapted intravenous heparinisation with 10 000 - 25 000 IE, 2 patients were treated with weight adjusted fractioned low molecular weight enoxaparin subcutaneously, one patient received 50 mg /24h refludan intravenously due to the HIT II syndrome, one other patient received 100 mg aspirin orally. In 6 (12%) cases there was no information available on the preoperative treatment.

4.7 Time interval between the onset of symptoms and surgery

The patients underwent emergent reconstruction of the acute ICA occlusion at mean duration of 42.5 (4 - 165) hours after symptoms onset.

In 19 (39%) cases the surgery was performed within the first 24 hours after the onset of symptoms, in 15 (31%) cases between 25 and 48 hours after the onset of symptoms, in 6 (12%) cases between 49 and 72 hours and in 9 (18%) cases between 73 and 168 hours after the onset of symptoms.

The distribution of the time interval between the onset of symptoms and the surgery is displayed below (Diagram 3).

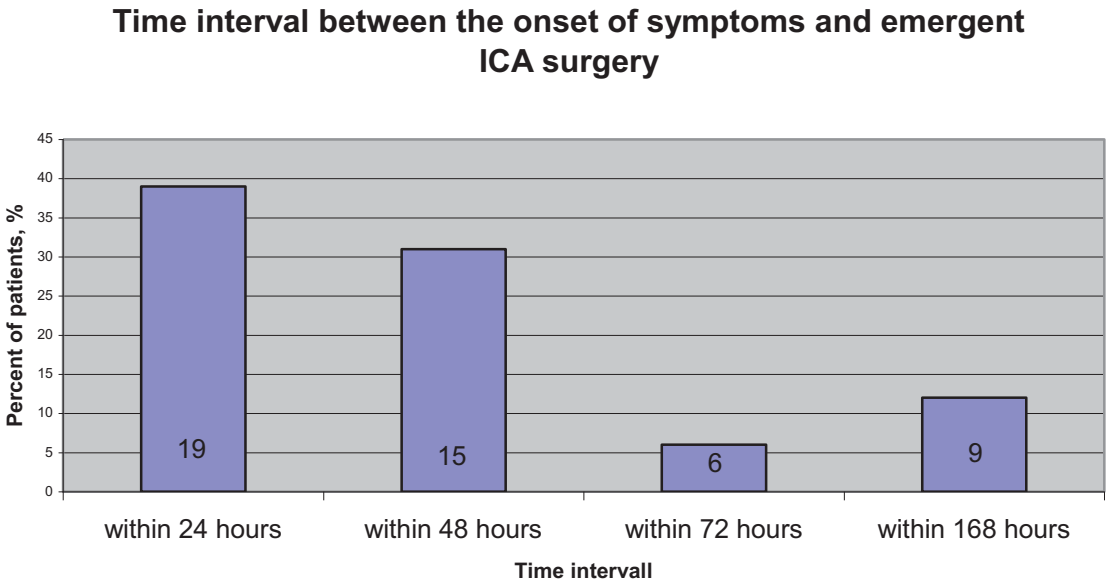

Diagram 3: Time interval between the onset of symptoms and surgery

5. Results

5.1 Intraoperative findings and surgical procedure

5.1.1 Intraoperative macroscopic findings

The nature of the ICA occlusion was determined by the intraoperative observation of the vessel wall consistency and the age of the thrombus.

In 33 (67%) cases the ICA occlusion was caused by a fresh local thrombus on the basis of high grade atherosclerosis of the carotid bifurcation.

Four (8%) of the 49 ICA occlusions were defined as embolic due to fluctuating embolus and underlying cardiac atrial fibrillation. In two of these probably embolic cases there were little or no atherosclerotic vessel changes observed: one occlusion was of older nature and could not be removed, the other one could be removed by thrombectomy. In two other cases additional low grade atherosclerosis was evident and was removed by thromboendarterectomy.

One (2%) ICA occlusion was caused by a fresh local thrombosis with no atherosclerotic vessel changes which was later found to be due to prothrombotic state.

In two other (4%) cases the ICA occlusion was caused by dissection: in one case there were atherosclerotic vessel changes evident, in the other case no atherosclerotic wall changes were observed.

In four (8%) cases the thrombus had either already propagated towards the intracranial ICA or intracranial ICA occlusion had originally been the cause of stroke.

In the remaining five (10%) patients the ICA occlusion was either chronic and the ICA already underwent fibrotic transformation or the thrombus was of older nature (Table 3).

Intraoperative findings	Number of patients	Percent %
Fresh local thrombus and atherosclerotic high grade stenosis	33	67
Embolus	4	8
Dissection	2	4
Local thrombosis without atherosclerosis	1	2
Intracranial occlusion	4	8
Old occlusion	5	10

Table 3: Intraoperative macroscopic findings

5.1.2 Choice of surgical procedure

Different surgical techniques were performed during the emergent ICA revascularisation. In 43 (88%) cases thrombectomy was performed, as described above. In the remaining 6 (12%) cases thrombectomy was not technically possible

due to an older occlusion in 5 (10%) and an intracranial occlusion in one (2%) patient.

Following thrombectomy conventional carotid endarterectomy (CEA) was carried out in 36 (73%) cases to treat the underlying atherosclerotic stenosis of the carotid bulb. In 33 (67%) cases widening of the ICA was performed by using venous patch, usually taken from the greater saphenous vein of the ipsilateral ankle. In 21 (43%) cases additional shortening of the ICA was necessary. Two (4%) additional patients underwent thrombectomy followed by thromboendarterectomy in eversion technique.

One (2%) patient without underlying atherosclerosis underwent thrombectomy of the occluding embolus without endarterectomy.

Two (4%) patients were treated for acute ICA dissection. One (2%) patient underwent resection of the diseased ICA segment. The ICA was replaced by an interposition graft from the greater saphenous vein, taken from the groin. In another (2%) case the dissecting membrane was limited to the carotid bulb. The carotid bifurcation was treated by removing the dissecting membrane together with the thrombus by Forgarty manoeuvre followed by standard CEA technique.

Due to high grade stenosis of the contralateral side simultaneous recanalisation of the contralateral ICA was performed in 3 of the 49 (6%) cases.

Successful initial surgical recanalisation of the ICA was accomplished in 40 (82%) cases and it was not successful in 9 (18%) cases.

5.2 Postoperative Doppler/Duplex assessment of the extracranial circulation

All surviving patients with successful ICA recanalisation were postoperatively examined by Doppler/Duplex sonography. At discharge, in 38 of the 40 (95%) initially successfully recanalised ICA there was good postoperative ICA result.

During the postoperative hospital stay there were two (4%) cases of re-occlusion the initially reopened ICA. In one other case the postoperative Duplex sonography could not be evaluated due to postoperative neck swelling, angiographically, however, good flow in the operated ACI was detected, as well as in the sonographic follow-up three years later.

The two (4%) cases of the postoperative ICA occlusion:

one young patient (patient 21, appendix 2) with the initial local thrombotic ICA occlusion experienced an asymptomatic postoperative CCA, ICA and ECA re-occlusion, most probably due to the increased thrombophilic state (heterozytous for Factor V Mutation, homozygotous for methylenetetrahydrofolate reductase (MTHFR) and recent consumption of anabolics), as was found out in the postoperative diagnostics. He did not wish additional diagnostics or therapy (angiography, surgery or phenprocoumon treatment) and left the clinic at his own will with 2° prophylactics consisting of clopidogrel. No information could be obtained on further clinical development of this patient. One other patient (patient 8, appendix 2) suffered ICA re-occlusion with consequent clinical deterioration

(mRs preoperatively – 4, postoperatively – 5). During surgery there was an extensive thrombectomy and thromboendarterectomy of the ICA and CCA performed and backflow, although weak, was initially achieved. The pertubation index of the perfused ICA showed sufficient laminar flow, however with increased resistance. Continuous postoperative intravenous anticoagulation with heparin followed. In the consequent MRI with intracranial angiography there was detectable increase of the pre-existing left-sided embolic infarction in the ACA and MCA territory. The operated left ICA could not be identified in angiography or Duplex sonography, the left MCA showed occlusion of the M2/M3 segment. In this case the ICA re-occlusion was most likely due to the initially increased vessel resistance in presence of distally located stenosis which could not be accessed surgically. This resulted in subsequent hypoperfusion and formation of stagnation thrombus which then embolised in the left MCA. Due to intensive rehabilitation moderate clinical improvement was achieved after 30 days (mRs – 4).

5.3 Analysis if the rate of the successful ICA recanalisation depended on the time interval between onset of symptoms and surgery.

Table 4 displays the rate of successful ICA revascularisation in the preset time intervals from onset of symptoms to the emergent ICA surgery, calculated by the chi-square test. The analysis showed tendency towards lower successful revascularisation rate if revascularisation was performed later than 72 hours after onset of neurological symptoms compared to earlier intervals but the difference was not statistically significant.

Time Interval	Surgery n	p.o. ICA reopened n	p.o. ICA occluded n	Success %	*p*
< 24 hours	19	16	3	84%	n.s.
25 h to 48 h	15	13	2	87%	
49h to 72 h	6	4	2	67%	
73 h to 168h	9	5	4	56%	
Total	49	38	11	77%	

Time interval is from onset of neurological symptoms to surgery,
p.o. means postoperative, ICA means Internal Carotid Artery, h means hours,
p was analysed with chi-square test

Table 4: Rate of successful revascularisation in different time intervals from onset of symptoms to the emergent ICA surgery

5.4 Postoperative clinical reassessment

For better overview, all patients were listed in appendix 2 with respect to the change in the postoperative clinical outcome expressed by the change in the mRs: the first 12 patients suffered deterioration or death and therefore in the column “Difference in the preop. to postop. mRs” are designated with a negative value, patients 13-26 remained stable with no change in the preoperative clinical status (nil mRs difference), and patients 27-49 experienced partial or complete neurological recovery (positive value in the mRs difference).

The postoperative clinical reassessment took place immediately after surgery, during further treatment on the stroke unit and prior to discharge. Median hospital stay lay at 11 days, average hospital stay lay at 13 days. Following tendencies were observed:

In total, 23 out 49 (47%) patients improved clinically by at least one point in the mRs, 14 (28%) patients remained stable, 6 (12%) patients deteriorated by at least

one point in the mRs and 6 (12%) patients died within 30 days of the emergent revascularisation.

In the successfully revascularised population, which at discharge consisted of 38 patients, 21 (55%) patients improved postoperatively by at least one point in the mRs, whereas 10 (26%) patients remained at the same clinical level, 3 (7.8%) patients deteriorated and 4 (10.5%) patients died.

In the subgroup of 11 out of 49 patients, where revascularisation was not achieved (in 9 cases the initial surgical recanalisation attempt failed, in 2 cases there was postoperative ICA re-occlusion of the initially recanalised ICA), there were 2 (18%) cases of clinical improvement, 4 (36%) cases of clinical stability, 3 (27%) cases of clinical deterioration and 2 (18%) deaths (Table 5).

Patients subgroup	Number of patients	Improved	Stable	Worse	Death
ICA reopened	38	21 (55%)	10 (26%)	3 (8%)	4 (11%)
ICA not reopened	11	2 (18%)	4 (36%)	3 (27%)	2 (18%)
Total	49	23 (47%)	14 (28%)	6 (12%)	6 (12%)

Improvement or deterioration means change by at least one point in modified Rankin Stroke Scale

Table 5: Postoperative clinical status in the revascularised and non-revascularised subgroups

5.4.1 Clinical improvement

23 of 49 (47%) patients showed clinical improvement by at least one point in the mRs. Of these, 14 patients improved by one point in the mRs, 6 patients by two points and three patients improved by three points in the mRs. In two of the 23 cases neurological improvement occurred despite failure to revascularise the occluded ICA: in one case the ICA occlusion was of older nature (this patient showed clinical improvement from four to three points in the mRs), in the other case there was the ICA occlusion was intracranial. This patient showed significant clinical improvement by three Rankin scale points (mRs of four prior to surgery and mRs of one at discharge).

5.4.2 No change in the postoperative neurological status

14 out of 49 (29%) patients did not show signs of any clinical change in the postoperative neurological status: 3 patients remained severely disabled with score of five in the mRs as before surgery, 3 patients showed unchanged moderately severe disability with mRs of four, 2 patients remained stable with mRs of three, one patient remained stable with mRs of two, 3 patients were not significantly disabled (unchanged mRs of one) and 3 patients showed no symptoms at all (unchanged mRs of zero). In four of the 14 cases the clinical status remained the same despite failure of the initial ICA revascularisation.

5.4.3 Clinical deterioration

6 of 49 (12%) patients suffered clinical deterioration after surgery: one patient suffered clinical deterioration by 5 points in the mRs, one patient by 3 points, one patient by 2 points and three patients showed deterioration by one point in the mRs.

In three of these cases the operated ICA remained open, in two cases the operated ICA remained occluded and in one case the initially re-canalised ICA re-occluded postoperatively.

Detailed information on each of the deteriorated patients is comprised in appendix 2.

Patient 1: suffered acute progressing left stroke due to the left ICA occlusion. The emergent ICA revascularisation was successful, however extreme clinical deterioration (mRs at admission –0, postoperatively – 5) followed due to embolisation from the operated region in the ipsilateral MCA resulting in new infarction. The revascularised ICA remained patent.

Patient 4: suffered acute ipsilateral stroke due to the right ICA occlusion. The emergent ICA revascularisation was successful. Postoperatively this patient suffered new subcortical contralateral infarction that led to acute clinical deterioration (mRs before surgery –1, 10 days after surgery – 4). It was assumed that the new infarction resulted from the hypercoagulative state due to sepsis of unknown origin. The right ICA patency persisted.

Patient 6: suffered acute progressing left sided stroke due to the left ICA occlusion. Revascularisation of the ICA was not achieved due to the intracranial ICA occlusion. In the postoperative course there was further clinical deterioration observed (mRs at admission – 3, after surgery – 5) due to haemorrhagic transformation with mass effect of the initial infarction and evolution of new embolic infarctions. Emergent trepanation was performed to release the increased intracranial pressure. The left ICA remained occluded.

Patient 7: suffered embolic left ICA occlusion with ipsilateral MCA infarction due to atrial fibrillation, which intraoperatively was found to be of older nature and could not be revascularised. Due to evolution of new embolic infarction in the ACA and MCA supply areas, emboli most likely being from the thrombus stump, there was clinical deterioration of the initial clinical status from four to five in the mRs during the postoperative course.

Patient 8: suffered acute ipsilateral stroke due to the left ICA occlusion. The emergent ICA revascularisation was initially successful, although only insufficient flow in the left ICA due to increased distal vessel resistance was achieved. In this case the ICA re-occlusion was most likely due to the initially increased vessel resistance in presence of distally located stenosis which could not be accessed surgically. This resulted in subsequent hypoperfusion and formation of stagnation thrombus which then embolised in the left second and third MCA segments and led to development of new embolic infarctions with subsequent clinical deterioration from four to five points in the mRs.

Patient 10: suffered acute ipsilateral stroke due to the right ICA occlusion. The emergent ICA revascularisation achieved vessel patency. Postoperatively it came to a slight leak from the patch region which required surgical revision. During further postoperative course there was clinical deterioration observed (mRs prior to surgery – 2, afterwards –3), which resulted from secondary ICH with ventricle involvement into the infracted region. Also, there were signs of beginning resorption of a subarachnoidal bleeding. There was no further clinical deterioration

observed, so that neurosurgical intervention was not required. The right ICA patency persisted.

5.4.4 30 days mortality

6 (12%) patients died within 30 days of the surgical treatment of the acute ICA occlusion. Prior to surgery, these six patients had following ranges of clinical impairment: one patient had mRs of 2, the second patient mRs of three, the third patient was moderately to severely impaired with the mRs of four, the remaining 3 patients were severely impaired with mRs of five and had an impaired level of consciousness.

In 4 of these six cases it was possible to re-open the occluded ICA, in 2 cases (both patients had mRs of five and had an impaired level of consciousness) no ICA recanalisation was achieved. The detailed account on the preoperative and postoperative course of these six patients is included in appendix 2.

Causes of death in these 6 patients were:

Patient 2: was slightly impaired at admission (mRs of 2), the ICA revascularisation was successful and was followed by good clinical recovery (postoperative mRs of 1). Unfortunately this patient suffered traumatic massive subdural hematoma due to an occipital collision with a wall and died due to cerebral impingement on the 18th day after the emergent successful CEA.

Patients 12 and 3: These patients (4%) died due to secondary intracerebral bleeding: patient 12 was already severely clinically impaired upon admission (mRs

of 5) and underwent the i.v. rt-PA lysis prior to surgery. This patient developed secondary haemorrhage into the infarction site and died on the second postoperative day. It is open to speculate whether the bleeding was due to the thrombolytic therapy or due to the reperfusion trauma or combination of both.
Patient 3 was moderately impaired at admission (mRs of 3) but developed malign MCA infarction with secondary haemorrhage and died on the 24th day due to cerebral impingement. In both cases the operated ICA remained patent postoperatively.

Patient 5: showed initial clinical improvement at discharge (mRs of 4 preoperatively and mRs of 3 postoperatively), however developed deep venous thrombosis during rehabilitation and died due to fulminant lung embolism on the 17th postoperative day. The operated ICA remained open.

Patient 9: was severely affected with impaired level of consciousness in the preoperative clinical assessment (mRs of 5). Further clinical deterioration followed, although in the postoperative neuroimaging neither infarct enlargement nor new infarctions or bleeding were observed. This patient died due to cardiovascular failure on the 15th postoperative day. The ICA occlusion was of older nature and could not be removed.

Patient 11: was severely affected with impaired level of consciousness in the preoperative clinical assessment (mRs of 5). Further clinical deterioration and death on the 7th postoperative day were due to enlargement of the initial ipsilateral

infarction and development of new embolic contralateral infarctions. Due to intracranial obstruction, the ICA patency could not be achieved.

5.5 Analysis if rate of clinical improvement or rate of deterioration or death depended on the time of the emergent ICA revascularisation

It was attempted to find out if a certain "cut-off" time existed for the emergent surgery to have significant benefit.

5.5.1 Rate of clinical improvement

Table 6 displays the rate of the clinical improvement divided into defined time intervals, in which the emergent revascularisation took place. The chi-square test was used for this calculation. The rate of the clinical improvement showed continuous decline with increase of the time interval at onset of symptoms to the emergent surgery. Emergent revascularisation on the same day (within the first 24 hours after onset of symptoms) brought clinical improvement in 68% of cases, whereas the rate of success in terms of clinical improvement within the following 24 hours fell to 47%, and within the third day (time interval within 72 hours after onset of symptoms) showed further decline to 33%. Only one out of nine patients (11%) profited clinically if the emergent surgery was performed within 4^{th} to 7^{th} day after onset of symptoms.

Time Interval	Surgery n	Improved n	Stable deteriorated Dead n	Improve-ment %	*p*
< 24 hours	19	13	6	68	<0,05
25 to 48 h	15	7	8	47	
49 to 72 h	6	2	4	33	
73 to 168	9	1	8	11	

Time interval is from onset of neurological symptoms to surgery, n means number of patients, h means hours, p was analysed with chi-square test

Table 6: Rate of postoperative clinical improvement at defined time intervals

The Fisher exact test was used in the following three calculations to also test if the rate of the clinical improvement depended on the time of revascularisation (Tables 7-9). The rate of the postoperative clinical improvement following surgery within the first day after onset of symptoms was compared to that within the following 2nd-7th day, then the rate of the clinical improvement within 2 days (within the first 48 hours) after onset of symptoms was compared to that within the following 3rd-7th day, and the rate of the clinical improvement within the third day (within 72 hours after onset of symptoms) was compared to that within 4th-7th day.

Time Interval	Surgery n	Improved n	Stable Deteriorated Dead n	Improve-ment %	*p*
< 24 hours	19	13	6	68	<0.05
25 to 168 h	30	10	20	30	
Total	49	23	26	47	

h means hours, n means number of patients, p was analysed with Fisher exact test

Table 7: Rate of clinical improvement after emergent ICA revascularisation: Surgery within 24 hours after onset of symptoms compared to surgery within 25 to 168 hours

Time Interval	Surgery n	Improved n	Stable Deteriorated Dead n	Improve-ment %	*p*
< 48 hours	34	20	14	59	<0.05
49 to 168 h	15	3	12	20	
Total	49	23	26	47	

h means hours, n means number of patients, p was analysed with Fisher exact test

Table 8: Rate of clinical improvement after emergent ICA revascularisation: Surgery within 48 hours after onset of symptoms compared to surgery within 49 to 168 hours

Time Interval	Surgery n	Improved n	Stable Deteriorated Dead n	Improve-ment %	*p*
< 72 hours	40	22	18	55	<0.05
73 to 168 h	9	1	8	11	
Total	49	23	26	47	

h means hours, n means number of patients, p was analysed with Fisher exact test

Table 9: Rate of clinical improvement after emergent ICA revascularisation: Surgery within 72 hours after onset of symptoms compared to surgery within 73 to 168 hours

The Fisher exact test and the chi-square test showed that the clinical outcome depended on the time interval between onset of symptoms and that shorter revascularisation times were associated with better clinical outcome.

5.5.2 Rate of postoperative clinical deterioration or death

Table 10 displays the rate of the postoperative deterioration or death in the defined time intervals, in which the emergent revascularisation took place. The chi-square test was used for this calculation.

Time Interval	**Surgery n**	**improved stable n**	**deteriorated dead n**	**Risk %**	***p***
< 24 hours	19	17	2	11%	<0,05
25 to 48 h	15	8	7	47%	
49 to 72 h	6	6	0	0%	
73 to 168 h	9	6	3	33%	

Time interval is from onset of neurological symptoms to surgery, h means hours, n means number of patients, p was analysed with chi-square test

Table 10: Rate of clinical deterioration or death after surgery at defined time intervals

In the following calculations using the Fisher exact test it was also tested if the risk to suffer postoperative deterioration or death depended on the time of the emergent revascularisation (Tables 11-13). The rate of the postoperative clinical deterioration or death within the first day after onset of symptoms (within the first 24 hours) was compared to that within the following 2^{nd}-7^{th} day, then the rate of the clinical deterioration or death within 2 days after onset of symptoms (within the first 48 hours) was compared to that within the following 3^{rd}-7^{th} day, and the rate of the

clinical deterioration or death within the third day (within 72 hours after onset of symptoms) was compared to that within 4^{th}-7^{th} day.

Time Interval	Surgery n	Improved or stable n	Deteriorated or dead n	Deterioration or death %	*p*
< 24 hours	19	17	2	11	
25 to 168 h	30	20	10	33	n.s.
Total	49	37	12	25	

h means hours, n means number of patients, p was analysed with Fisher exact test, n.s. means not significant

Table 11: Rate of clinical deterioration or death after emergent revascularisation: Surgery within 24 hours after onset of symptoms compared to surgery within 25 to 168 hours

Time Interval	Surgery n	Improved or stable n	Deteriorated or Dead n	Deterioration or death %	*p*
< 48 hours	34	25	9	27	
49 to 168 h	15	12	3	20	n.s.
Total	49	37	12	25	

h means hours, n means number of patients, p was analysed with Fisher exact test, n.s. means not significant

Table 12: Rate of clinical deterioration or death after emergent revascularisation: Surgery within 48 hours after onset of symptoms compared to surgery within 49 to 168 hours

Time Interval	Surgery n	Improved Or stable n	Deteriorated or dead n	Deterioration or death %	*p*
< 72 hours	40	31	9	23	
73 to168 h	9	6	3	34	n.s.
Total	49	37	12	25	

h means hours, n means number of patients, n.s. means not significant, p was analysed with Fisher exact test

Table 13: Rate of clinical deterioration or death after emergent revascularisation: Surgery within 72 hours after onset of symptoms compared to surgery within 73 to 168 hours

The results of the chi-square test showed that the rate of clinical deterioration or death after the emergent CEA significantly differed from time interval to time interval, but there was no tendency that longer time intervals were worse than short time intervals. The Fisher exact test did not confirm this significance.

5.5.3 Plot of the "cut-off" time at which the rate of clinical deterioration or death predominated over the rate of clinical improvement

The difference in the preoperative to postoperative mRs was mapped below to find out if there existed a "cut-off" time, at which the rate of clinical deterioration or death predominated over the rate of clinical improvement (Diagram 4). The positive values indicate clinical improvement, the negative values stand for deterioration in clinical status or death. The patients that died during the postoperative period are marked in red.

This diagram shows that 22 out of 40 patients revascularised during the first 72 hours improved. Only one out of 9 Patients improved after 72 hours revascularisation interval. The rate of deterioration and death seemed not to depend on the time of the emergent revascularisation.

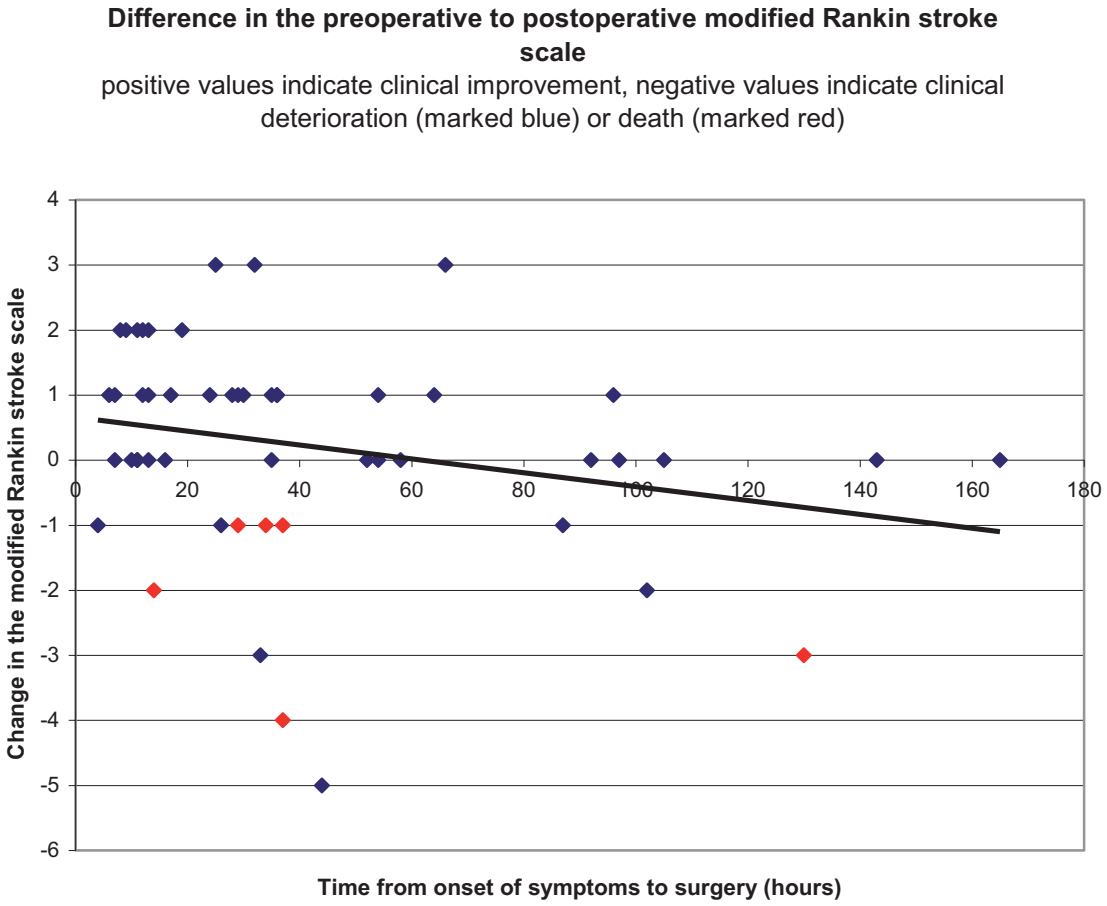

Diagram 4: Difference in the preoperative to postoperative modified Rankin stroke scale

5.6 Analysis if the rate of clinical improvement or clinical deterioration or death depended on the rate of successful ICA revascularisation

The following calculation was performed by using the chi-square test to test if the postoperative clinical changes (improvement and deterioration) depended on the rate of the successful ICA revascularisation (Table 14). The analysis showed that rate of clinical improvement in the revascularised subgroup predominated over the rate of clinical improvement in the non-revascularised group, whereas in the non-revascularised group it was the rate of clinical deterioration or death that prevailed.

p.o. clinical outcome	Surgery n	ICA p.o. re-opened n	ICA p.o. occluded n	ICA Reopened %	*p*
Improved	23	21	2	91%	<0,05
Stable	14	10	4	71%	
Deteriorated or dead	12	7	5	58%	
Total	49	38	11	78%	

p.o. means postoperative, n means number of patients
p was analysed with the chi-square test

Table 14: Postoperative clinical outcome in relation to the rate of successful ICA revascularisation

The Fisher exact test was also applied to calculate if changes in clinical outcome by at least one point in the mRs depended on the success of the surgery (Table 15). This analysis did not include the subgroup of 14 stable patients since the difference between the preoperative and the postoperative mRs was zero. The calculation also showed that revascularised patients improved significantly more often, while non-revascularised patients tended to suffer clinical deterioration more often than the revascularised subgroup.

	Surgery n	ICA p.o. re-opened n	ICA p.o. occluded n	ICA p.o. reopened %	*p*
Improved	23	21	2	91%	<0,05
Deteriorated or dead	12	7	5	58%	
Total	35	28	7	80%	

ICA means internal carotid artery, n means number of patients
p was analysed with Fisher exact test

Table 15: Rate of postoperative clinical improvement or deterioration or death in relation to the rate of successful ICA revascularisation

5.7 Postoperative intracranial status

Postoperative cerebral imaging was performed in 40 (82%) cases, in 12 (24%) cases due to clinical deterioration or death and in the remaining 28 (57%) cases to reassess the intracranial status for possible intracranial haemorrhage (ICH) or new infarcts. 9 (18%) patients showed complete neurological recovery and were discharged without further cerebral imaging. In all, there were 23 CCT and 30 MRI scans performed.

In total, 21 of 49 patients developed new perioperative/postoperative cerebral events detected by neuroimaging. Of those 7 improved in clinical outcome by at least one point in mRs (patients 27, 28, 30, 34, 35, 42, 44), 4 remained stable (patients 13, 17, 18, 22), 6 deteriorated (patients 1, 4, 6, 7, 8, 10) and 4 died (patients 3, 5, 11, 12). In the latter section all perioperative/postoperative cerebral events are mentioned in detail. As some patients simultaneously suffered several different complications, these events cannot be added.

5.7.1 Intracranial haemorrhage and haemorrhagic transformation

5.7.1.1 Intracranial haemorrhage

4 of 49 patients (8%) developed secondary intracranial haemorrhage (ICH): 1 patient improved clinically (patient 42), 1 patient deteriorated (patient 10) and two patients died (patients 3, 12). In 2 of these cases the emergent ICA revascularisation was preceded by the i.v. rt-PA lysis (patients 10, 12).

Patient 42 developed bleeding in the basal ganglia in the pre-existing MCA infarction with a slight shift of the midline. Despite the ICH this patient remained asymptomatic and even showed signs of improvement from mRs of four

preoperatively to two postoperatively. No neurosurgical intervention was necessary.

Patient 3 deteriorated clinically on the fifth postoperative day after initial improvement due to edematous enlargement of the initial infarction. Two days later there followed further deterioration, which was caused by the haemorrhage into the infarcted region. This patient died on the 24th postoperative day due to malign mass lesion with axial impingement.

In two cases i.v. lysis therapy preceded the emergent ICA revascularisation: patient 10 showed slight clinical deterioration from two to three in the mRs score during the postoperative course. This was caused by haemorrhage into the initial MCA infarction with beginning involvement of the lateral ventricle and signs of subarachnoidal bleeding. Since the ICH already showed signs of resorption and the patient remained stable, no neurosurgical intervention was necessary.
Patient 12 was already unconscious at admission. On the preoperative CCT scan there were signs of beginning infarct demarcation in the thalamus region. Being admitted within the three hour therapeutic time gap, this patient was treated with the i.v. rt-PA lysis. On the second postoperative day this patient developed signs of brainstem impingement and died due to profuse ICH into the infarcted region.

5.7.1.2 Haemorrhagic transformation
In 6 of 49 cases (12%) haemorrhagic transformation of the pre-existing infarction took place:

Two patients improved clinically by at least one point in the mRs (patients 30, 44), two patients stayed stable (patients 13, 22) while two patients deteriorated (patient 4, 6).

Clinical outcome of these patients:

Two patients improved clinically by at least one point in the mRs.

Two patients stayed asymptomatic and had no changes in the postoperative mRs.

Two patients deteriorated: patient 6 with non-recanalised intracranial ICA occlusion, enlargement of the initial infarction with haemorrhagic transformation and new ipsilateral infarctions deteriorated from three to five points in the mRs, patient 4 with successfully recanalised ICA also developed enlargement of the initial infarction with haemorrhagic transformation as well as new infarctions and suffered clinical deterioration from one to four points in the mRs.

5.7.2 Stroke recurrence

New ipsilateral infarctions developed in 8 of 49 patients (16%): 3 patients improved in the neurological status by at least one point in the mRs (patients 34, 35, 44), 4 patients deteriorated clinically (patients 4, 6, 7, 8) and 1 patient died (patient 3).

In seven cases the new ipsilateral infarctions were thought to be embolic in nature.

Clinical outcome of these patients:

3 patients remained clinically asymptomatic and improved in the neurological status by at least one point in the mRs,

5 patients deteriorated clinically or died (4 deteriorated, 1 died).

Perioperative history of these patients (also detailed account in appendix 2):

Patient 3 was moderately impaired at admission (mRs of 3) but developed malign MCA infarction with secondary haemorrhage. Also, there were signs of new embolic ipsilateral infarctions. This patient died on the 24th day due to cerebral impingement caused by the haemorrhagic mass lesion. The operated ICA remained open.

Patient 4: developed postoperative infection with sepsis. Despite thorough search for the infection site, no such was found. Due to clinical deterioration intracranial imaging was performed and showed new ipsilateral infarction. The working hypothesis at the time of hospitalisation was that the procoagulative septic state had led to the local intracranial thrombosis. During the ICA reconstructive surgery the fresh thrombus was completely removed, however due to increased turbulence measurement after suturing, the ICA was re-opened and scanned for possible thrombi, although none were found. The pertubation index was then normal. The reinfarction, however, could as well have been caused by the microemboli from the operated site. The new infarct had led to the deterioration of the clinical status from one to four points in the mRs.

Patient 6: arterio-arterial embolism from the fresh intracranial non-revascularised occlusion led to the new anterior infarction. The edema of the original MCA infarction progressed to mass lesion so that trepanation had to be performed. This patient deteriorated clinically by two points from three to five in the mRs.

Patient 7: arterio-arterial embolism from an older non-revascularised extracranial ICA was thought to be the cause of the new symptomatic multiple ipsilateral

infarctions in the MCA territory. This patient suffered further clinical deterioration by one point from four to five in the mRs.

Patient 8: arterio-arterial embolism in the MCA 2/3 segment led to new ipsilateral symptomatic infarctions in this patient. In this case the intraoperative intracranial thrombectomy only achieved insufficient back flow. Most likely there was an inaccessible distal stenosis since the intraoperative resistance at the end of the surgery index was increased and the backflow after thrombectomy was lower than in the normal vessel. In the postoperative course this distal ICA stenosis most probably thrombosed due to hypoperfusion and propagated proximally, causing re-occlusion of the operated ICA and embolised distally, occluding the MCA segments. The clinical status deteriorated by one point in the mRs from four to five. Due to poor clinical status there was no attempt to revascularise the re-occluded ICA.

Patient 34: asymptomatic new ipsilateral infarcts in the postoperative CCT were small and disperse and therefore attributed to cardiac embolism in the patient with cardiac arrhythmia and coronary heart disease. However, arterio-arterial embolism from the re-opened ICA is also thinkable, especially since the new infarcts appeared only ipsilaterally. The operated ICA remained open, the postoperative mRs improved from one to zero.

Patient 35: in this case the new ipsilateral infarction was not described in the radiological report but was noted by the consulting neuroradiologist in the retrospective analysis of the postoperative intracranial imaging and was embolic in

its morphology. This patient improved clinically from 5 to 4 points in the mRs at discharge and at follow up was not functionally impaired. The revascularised ICA remained open postoperatively, there was no cardiac arrhythmia documented.

Patient 44: arterio-arterial embolism was thought to be the cause of the new asymptomatic ipsilateral anterior infarct and watershed infarct in the patient who underwent uncomplicated carotid thrombectomy followed by CEA, shortening and patch implantation. The operated ICA remained open, the postoperative mRs improved from four to two.

5.7.3 Enlargement of the initial infarction volume

There was an increase in size in 16 of 49 of initial infarctions (33%) (Patients 1, 3, 4, 5, 6, 7, 8, 11, 17, 18, 22, 27, 28, 34, 35, 44):

Clinical outcome of these patients:

5 improved clinically by at least one point in mRs (patients 27, 28, 34, 35, 44)

3 remained clinically stable without change in Rankin evaluation (patients 17, 18, 22)

5 patients deteriorated clinically by at least one point in mRs (patients1, 4, 6, 7, 8)

3 patients died (patients 3, 5, 11).

5.8 Follow-up

5.8.1 Survival and death

The follow-up contains information on all 43 patients that survived the postoperative period. The average observation period was 40.1 months (deviation from the average 18.9 months at min. 1 month, max. 114 months); the median

duration of the follow up lay at 35 months. 33 surviving patients and 10 deaths were documented at follow-up.

10 of 43 (23%) patients died by the time of follow-up after an average duration of 25.1 months (min1.1 month, max 60 months, deviation from the average 15.9 months), median time comprised 23 months.

Two patients died due to embolic contralateral or bihemispheric strokes:
One of these patients (patient 7) had already suffered embolic ICA occlusion due to cardiac arrhythmia that was found to be of older nature and could not be revascularised. 22 months after surgery this patient developed new bihemispheric strokes and died. The other patient (patient 40) received phenprocoumon therapy due to cardiac arrhythmia and suffered lethal contralateral hemorrhagic stroke 10 months after the successful ICA recanalisation. The operated ICA remained patent.

Five patients died of stroke–unrelated causes:
The first patient (patient 24) died due to myocardial infarction 24.5 months after the successful ICA recanalisation. There was no information obtained on the status of the operated ICA.
The second patient (patient 34) died during cardiac bypass surgery 40 months after the emergent successful ICA recanalisation. Sonography prior to the cardiac surgery showed patency of the operated ICA.

The third patient (patient 22) died due to cardio-pulmonary failure in the rehabilitation clinic 1.5 months following the successful emergent ICA surgery, there was no information on the status of the recanalised ICA.

The fourth and the fifth patient both died due to bronchial carcinoma: one patient (patient 15) died 1.1 month after the unsuccessful emergent ICA surgery (an older ICA occlusion), the other patient (patient 33) died 29 months after the successful emergent ICA surgery, the operated ICA remained patent.

In three cases the cause of death remained unknown (patients 6, 25, 47): two patients with non-recanalised ICAs were found dead in their wheel chairs in nursing homes - patient 25 died 60 months after the emergent ICA surgery, patient 6 - 12 months after the surgery. The third patient (patient 47) died of unknown cause 51 months after the successful emergent surgery. There was no information on the status of the revascularised ICA.

5.8.2 Sonographic findings

Of the 33 surviving patients 22 (67%) patients underwent Doppler or Duplex sonography of the extracranial portion of the carotid arteries during the follow up period, the average interval from the time of discharge to the sonography at follow-up being 31.2 months (min. 2 months, max. 106 months, deviation from the average 18.9 months), the median duration - 27 months.

In 11/33 (33%) cases there was no information on the vessel status. However it was already known that in 3 of the 11 cases (8, 21, 49) the symptomatic ICA was occluded at discharge.

Of the 22 patients that underwent sonographic control of the supraaortal vessels at follow up following information was obtained:

One patient (patient 49) had an old occlusion that could not be revascularised during the emergent revascularisation surgery.

Of the 21 patients with the initial recanalisation of the ICA, one patient (patient 16) suffered an asymptomatic re-occlusion during the follow up period, the contralateral ICA remained patent. 20 of the initially revascularised ICAs were patent at follow up. Two of the 21 patients suffered an asymptomatic re-stenosis. The first patient (patient 43) developed an asymptomatic 80% stenosis of the operated ICA and underwent successful stent implantation; the stented ICA was patent at subsequent sonographic controls. The second patient (patient 32) developed an asymptomatic 80% stenosis of the operated ICA and 50-60% stenosis of the contralateral ICA. This patient did not receive any treatment.

One of the 21 patients (patient 30) suffered an asymptomatic occlusion of the contralateral ICA; the operated ICA was patent at follow up.

5.8.3 Clinical outcome

The information on the functional status of the 43 patients that survived the postoperative period was obtained through standard clinical neurological examination by me in 8 (19%) cases, in 3 (7%) cases information on whether the patients still lived was obtained through city halls, in 16 (37%) cases the information on the functional status was obtained by phone contacts with patients,

their families and family physicians, in 16 (37%) cases the information on medical and social status was obtained through written reports from hospitals and nursing homes.

22 (67%) of the 33 surviving patients showed further clinical improvement as compared to the postoperative clinical status:
13 patients by 1 point in the mRs,
5 patients by 2 points in the mRs,
3 patients by 3 points in the mRs,
1 patient by 4 points in the mRs.

5 patients remained the same in their functional status (nil difference in the mRs).

One of the 33 surviving patients (patient 31) suffered clinical deterioration due to a new contralateral infarction with a change of –2 in the mRs.

In 5 cases there was no information obtained on the latest clinical status.

6. Discussion

Following the concept of “time is brain” and inspired by the positive long term results of the systemic thrombolysis in recanalisation of acute MCA occlusion[18], we wanted to find out if revascularisation of the acute total ICA occlusion also could bring clinical benefit for acute stroke patients. Moreover, it was attempted to find out if there was a time limit for surgical success of the revascularisation of the total ICA occlusion and a time limit, at which the risk of the acute intervention predominated over the possible clinical benefit.

Emergent revascularisation of acute ICA occlusion might have immediate and long term benefit for the hemispheric perfusion. In the acute phase of stroke it is thought to minimize the extent of the infarction by timely restoring the blood flow to the “tissue at risk” and lessen the risk of arterio-arterial embolisation from the fresh occlusion. While asymptomatic ICA occlusion has a low stroke risk of 0-8%, the symptomatic ICA occlusion carries stroke recurrence of up to 27%[9]. Hence, over the long term, removing the acute carotid occlusion could reduce stroke recurrence by eliminating the constant embolic source and improving intracranial perfusion in patients with insufficient collaterals.

Grubb et al. found that increased oxygen extraction measured with positron emission tomography scan helped to delineate a subgroup of patients at risk for cerebral hemodynamic failure due to chronic cerebral hypoperfusion. Their data showed 26.5% incidence of ipsilateral neurologic events in this patient group, thus defining a subgroup that would benefit from revascularisation[30]. The necessity of restoring the ipsilateral cerebral blood flow is also emphasized by the fact that in

every 5th patient in our study a contralateral ICA occlusion was observed in the preoperative diagnostic work up[18].

Since acute extracranial carotid occlusion usually develops due to pre-existing severe atherosclerosis, removal of the appositional thrombus and endarterectomy have to be performed simultaneously in order to restore cerebral perfusion[18]. A prerequisite for successful surgery is the limitation of the ICA thrombosis to its extracranial portion, because only then can the thrombus be retrieved either by sufficient backflow or by a balloon catheter. Therefore, preoperative angiography is crucial in the diagnostic work up as it provides information on the location of the ICA occlusion and confirms patency of the distal ICA. Besides, preoperative angiography is necessary when the ICA occlusion is suspected to have developed from the distal propagation of the intracranial ICA stenosis towards its extracranial bifurcation. In such cases surgery cannot succeed[18]. Intracranial ICA occlusions also pose problems for other types of recanalisation therapy: the participating study groups in the MERCI trial were able to achieve distal ICA revascularisation in only 53-63% with 39% good clinical outcome and 30% 90 days mortality[31,32]. Rt-PA therapy alone also showed unsatisfactory results: Linfante et al (2002) tried to revascularise 18 extracranial ICA occlusions with intracranial propagation with i.v. rt-PA thrombolysis within 3 hours of symptoms onset and observed recanalisation rate of only 31%[33]. The most optimal therapy for the operatively inaccessible intracranial ICA occlusions may be the combination of mechanical and chemical lysis as shown by the RECANALISE study[34]. In our patient collective, four patients suffered distal ICA occlusion that turned out to be inoperable. In two of these cases (patients 6, 25) the preoperative DSA showed

stop of the contrast medium at the skull base. In the other two cases (patients 12, 29) the thrombus had already propagated distally and could not be retrieved.

Also, success of the surgery depends on the duration of the occlusion. Fresh thrombus that forms in the first days of an arterial occlusion is still soft, but by the end of the first week undergoes hyalinisation and retraction, increasing its density and adherence to the vessel wall[35]. Although the time interval from onset of symptoms to recanalisation surgery in our study was limited to one week, in five cases revascularisation failed due to presence of old thrombotic tissue. Interestingly, the revascularisation times varied from 4, 13, 37, 66 to105 hours (patients 4, 29, 2, 9, 49, 23), implying that the occlusions might have well been there before onset of acute symptoms and caused stroke by embolisation from the distal end of the old thrombus stump. Despite ongoing improvements in the angiographic and sonographic imaging, it is still difficult to predict the exact age of the occlusion.

We observed that the rate of successful ICA revascularisation showed continuous decline with prolonged revascularisation times, however, due to the small patient numbers, was not statistically significant. Results of the study groups that examined relationship between surgical outcome of acute carotid recanalisation and time interval from symptoms onset and surgery correlate with our findings. According to Kasper et al., the main advantage of the early carotid revascularisation is to facilitate thrombus removal since thrombus does not have time to organize and irreversibly adhere to the vessel wall. In his study the ICA revascularisation within 8 days (average time 39 hours) after onset of symptoms

was achieved in 24/29 (83%) occlusions [36]. Berthet et al successfully recanalised all 12 ICA occlusions within 6 hours of symptoms onset[9]. An interval of 24 hours between symptoms onset and carotid artery repair in 21 cases also led to 100% patency, which still persisted at follow up 55 months later, as reported by Gay et al[37]; however in this study only 3 patients suffered symptoms due to complete ICA occlusion, whereas severe ICA atherosclerosis caused symptoms in the other 18 cases. Interestingly, Hafner and Tew also achieved 68% patency in 47 operated patients, although the time between onset of symptoms and surgery was one week and the revascularisation rate dropped to 50% if occlusion was operated one month after onset of symptoms[38]. Paty et al., reported technical feasibility in only 30/87 (34%) cases if emergent CEA was performed within 2 weeks after onset of symptoms whereas in 65% ICA revascularisation failed[39]. In our study, by the end of the first week the rate of successful revascularisation already dropped to 50%.

Modern diagnostics such as ultrasound sonography, angiographic studies and neuroimaging help in selection of patients, who could profit from the early ICA revascularisation. The currently existing concept of diffusion – perfusion mismatch in the MRI stroke imaging serves as surrogate marker for the functionally impaired brain tissue, providing means of early stroke identification as well as monitoring success and failure of the early therapy [25, 26, 40]. Krishnamurthy S. et al., described two cases of decrease in the initial diffusion –perfusion mismatch in MRI following early carotid endarterectomy after ischemic stroke, both cases associated with good clinical outcome[41]. Neumann-Hafelin et al., found that severe atherosclerotic ICA disease is associated with larger initial DWI/PWI mismatch than patients without ICA stenosis[42]. They also showed that 80% of patients with MRI

performed within 24 hours after onset of stroke symptoms displayed pathological perfusion time to peak delays (TTP – marker for PWI>DWI mismatch). Control imaging one week later revealed an increase in the final infarction volume in 75% patients in which perfusion time delay, compared to the unaffected hemisphere, was more than 6 seconds[43]. Although the size of DWI-PWI mismatch was not calculated for every patient, a DWI detectable stroke and a notable PWI deficit in the MRI was one of the most important selection criteria for this study.

23 patients out of 49 patients in our total revascularisation collective showed clinical improvement during hospital stay, almost one third patients (14 patients) stayed clinically stable, but 6 patients (12%) deteriorated and another 6 patients (12%) died within 30 days after emergent ICA revascularisation. As part of the inclusion criteria, the time limit for the revascularisation of the acute ICA occlusion was set at one week after onset of neurological symptoms. In the statistical analysis the clinical outcome of revascularisation within the first three days was analysed separately for day one, two and three and then compared to the clinical outcome of revascularisation at day four to seven. The analysis showed that the rate of postoperative neurological clinical improvement indeed depended on the time of the emergent revascularisation: the rate of postoperative neurological clinical improvement declined with increasing time interval from onset of neurological symptoms to the emergent surgery from 68% at day one to 33% at day three and surgery within 4-7th day was only associated with 11% clinical improvement (Table 9). Moreover, patients in the revascularised group improved clinically by at least one point in the mRs significantly more often than the non-revascularised patients. On the contrary, the non-revascularised patients suffered

clinical deterioration or death significantly more than the patients in the revascularised group. The rate of clinical improvement seemed to predominate over the rate of clinical deterioration or death within the first three days of onset of neurological symptoms to the emergent ICA revascularisation, whereas afterward the rate of clinical deterioration or death prevailed (Diagram 4).

The natural course of acute ICA occlusion is quite unclear. Several studies tried to find predictors for clinical recovery and good clinical outcome after medical treatment of stroke[44, 45, 46]. Clinical recovery was observed frequently after stroke[47,48] but none of the studies looked after the course of stroke caused by carotid artery disease or –occlusion in detail.

In our study, the early ICA revascularisation led to 46% postoperative clinical improvement in the 49 patients and persisted at 50% in the 33 surviving patients at follow up.

Various studies on clinical outcome of the emergent CEA demonstrated similarly to our observations that shorter revascularisation times can be associated with better clinical outcome: 24 hours interval from onset of symptoms to emergent carotid repair in the study by Gay et al., was associated with 57% postoperative clinical improvement[37]. However, in his study only 3 patients suffered total ICA occlusion, the rest of the acute symptoms were caused by severe ICA stenosis. Weis-Müller et al., (2007) reported 59% postoperative clinical improvement if emergent CEA due to acute ICA occlusion was performed within 36 hours after onset of symptoms[49]. Kasper et al., observed 48% improvement in the

postoperative outcome in the 29 patients that underwent emergent CEA within 8 days after total ICA occlusion[36]. In the studies with even shorter revascularisation intervals the positive clinical outcome was accordingly higher: Berthet et al., achieved 92% postoperative clinical improvement in 12 patients if emergent CEA for total ICA thrombosis was performed within 6 hours after symptoms onset[9]. Hafner and Tew described three cases of drastic clinical improvement in a series of 47 patients who underwent emergent CEA due to total ICA occlusion within only two hours of symptoms onset[38]. This rapid surgical revascularisation and the good outcome as described by Behret and Hafner and Tew can be compared to the setting of the systemic rt-PA thrombolysis[19, 50].

However, the logistics in the acute setting do not always allow such prompt handling. In the present study only one patient underwent surgery at such short time period (4 hours) and still this suffered further deterioration due new arterio-arterial embolic infarctions from an old, non-revascularised ICA occlusion.

While almost half of the patients improved clinically by at least one point in the mRs, twelve percent of our patients suffered clinical deterioration and another twelve percent died of postoperative complications (sections 5.4.3, 5.4.4). In the analysis whether the risk of clinical deterioration or death depended on the time of the emergent revascularisation, we observed tendency towards poorer clinical outcome if revascularisation was performed later than three days after onset of symptoms, but this observation was not statistically significant (Diagram 4, Tables 13-16). More likely it is the combination of preoperative clinical status, angiographic and neuroimaging aspects that influence the postoperative clinical

course. We primarily excluded patients with signs of haemorrhage in the preoperative neuroimaging, but DWI definite infarction less than 1/3 of the MCA territory was one of the main inclusion criteria. In 16 cases these preoperative infarcts evolved further, of which 6 became symptomatic with 2 cases of lethal outcome. New infarcts were detected in 8 cases: in 5 cases the re-infarctions were accompanied by neurological symptoms and in one case resulted in lethal outcome. The predominating mechanism being was thought to be an arterio-arterial embolism, which most likely occurred during surgery or postoperatively despite consequent anticoagulation.

In the literature review there were no studies found that performed emergent CEA for acute occlusion on patients with definite stroke exclusively, on the contrary, for many study groups it was often the exclusion criterion. Compared to the stroke recurrence in the natural course of the symptomatic occlusion, the re-infarction rate of 16% in the present study was considerably higher: the German Stroke Study reported 7.4 % recurrence within three days of acute symptomatic ICA occlusion[51], similar observations were made by Flaherty et al who documented 8% new strokes at thirty days in same study setting[52]. It appears that despite consequent postoperative anticoagulation the rate of recurrent embolisation from the freshly re-opened ICA is two times higher than in the natural course of acutely occluded carotid artery.

Acute carotid surgery was abandoned for years because of the risk of postoperative intracranial haemorrhage[18]. However, intracranial haemorrhage is commonly observed in the natural course of ischemic stroke with up to 40.6% at

30 days[53]. Henderson et al., examined mechanisms of ICH after carotid endarterectomy and observed doubled cerebral blood flow in patients with ICH as compared to the control group, despite lack of typical hyperperfusion symptoms in most cases[54]. Piepgras et al., proposed that chronic hemispheric hypoperfusion due to the ICA stenosis and poor collateralisation leads to impaired autoregulation which cannot be tolerated once the blood flow ipsilaterally is restored[55].

Following the example of others, we subdivided the secondary intracerebral bleeding as parenchymal haematoma or haemorrhagic infarction. Haemorrhagic infarction is petechiae or confluent haemorrhage in the area of ischemic injury; parenchymal haematoma is homogenous bleeding with circumscript clot formation and mass effect[56]. Presence of multiple cardio-vascular risk factors, advanced age, extensive cerebral microangiopathy, initial infarction size[57] and usage of antiplatelet drugs other than aspirin might have influenced development of the ICH in acute ischemic stroke[58], whereas thrombolytics or anticoagulants tended to cause massive haematoma but had less effect on haemorrhagic transformation of ischemic infarct[53].

Since DWI detectable stroke was prerequisite for the study, all 49 patients already carried a higher risk of developing a secondary haemorrhage but only four (8%) patients suffered a parenchymal haematoma after successful ICA recanalisation (section 5.7.1) and haemorrhagic transformation of the infarct without lethality was observed in six cases. Two of the patients with secondary haemorrhage died. In the available literature on emergent CEA and development on the secondary intracerebral haemorrhage, the ICH rate ranged from 0-4%[9, 36, 37, 59], but it has to

be noted that TIA patients composed the overwhelming majority of the patient collectives, whereas only in the study by Aleksic et al., 2/3 of patients displayed definite infarction in the preoperative neuroimaging[59].

Other types of acute recanalisation therapies are associated with the risk for developing secondary intracranial haemorrhage that is comparable to the risk in our study: the i.v. rt-PA lysis was associated with slightly lower secondary ICH rate of 5,2-6,4%[19, 20, 60], although the NINDS study model could predict symptomatic haemorrhage with only 57% accuracy, whereas the secondary ICH rate after endovascular interventions ranged from 2% to 14% [61, 62, 63].

It is of practice to exclude patients with profound neurological deficits from emergent ICA revascularisation for the fear of lethal outcome [9, 36]. On the contrary, we included severely disabled patients and patients with altered level of consciousness in order to evaluate the possible operative and postoperative risks. All three patients with already preoperatively impaired level of consciousness suffered lethal outcome (it is likely that the extent of the preoperative infarct in these patients already surpassed the “allowed 1/3”, but was not demarcated in the preoperative neuroimaging), two of these three patients developed secondary intracranial haemorrhage (section 5.7.1). Bone et al., also included patients with disturbed level of consciousness in their study on emergent CEA for acute ICA occlusion and found a 10 times higher mortality rate as compared to the conservative group[9]. Other study groups reported similar results: Eckstein et al., evaluated emergent CEA in 16 acute symptomatic severely disabled patients and found 56.3% improvement whereas 43.7% suffered clinical deterioration or

death[64]. Meyer et al., of Mayo Clinic investigated clinical outcome in 34 patients with angiographically proven ICA occlusion and acute profound neurological deficit and observed 67.6 % improvement in clinical outcome and 32.6% deterioration or death[7]. Our results and the results of the above mentioned studies show approximately 60% clinical improvement in patients with severe neurological disabilities, thus supporting the rationale for emergent surgery on carefully selected patients.

The risk to die after the first - ever stroke of any cause lays at 19%, as investigated in the Oxfordshire Community Stroke Project [65], whereas the natural course of the acute carotid occlusion is associated with16 - 55% death rate[7]: 7-30% die within the first 30 days of acute ICA occlusion, the 90 days mortality lies at 21.2%, while after one year 21-45% will have died[46, 47, 66]. In our study the total death rate lay at 12%. As discussed earlier, the six cases of postoperative clinical deterioration were all due to neurologic causes, whereas from the total six cases of postoperative deaths three cases were of neurologic origin (patients 7, 8, 9 in appendix 2) and the other three deaths were not directly related to stroke (patients 10, 11, 12 in appendix 2). While not significant, prolonged revascularisation times tended to result in poorer clinical outcome (Tables 13-16, Diagram 4). On the contrary, the rate of clinical deterioration or death showed significant dependency on the rate of surgical success of the emergent revascularisation (Table 15): patients in whom the revascularisation attempt failed were at higher risk of suffering postoperative deterioration or death.

This observation reinforces the importance of precise preoperative diagnostics, to improve identification of patients that could profit from the emergent surgery.

7. Summary

*Objective of the stud*y: to find out if stroke patients profited from the emergent surgical revascularisation of the acutely occluded internal carotid artery, to find out if surgical success depended on the time of the revascularisation and to evaluate the risks associated with this procedure. Therefore, all acute stroke patients that were admitted to the Stroke Unit of the Heinrich-Heine-University Neurological Clinic and then operated at the Clinic for Vascular Surgery and Kidney Transplantation in the time from November 1999 to November 2006 were prospectively collected and retrospectively analysed.

Patients and methods: 49 patients (40 males and 9 females) with average age of 60.9+/-10,4 years (the youngest patient was 31.8 years old, the oldest patient was 79 years old) with definite infarction signs in the cerebral imaging and extracranial ICA occlusion in sonographic and in angiographic studies underwent emergent ICA revascularisation within 168 hours of stroke onset. At admission 20 (41%) presented with none to moderate neurological deficits of 0-3 in the functional modified Rankin Stroke Scale (mRs) and 29 (59%) had suffered profound neurological deficits of 4-5 in the mRs.

The clinical outcome postoperatively and at median follow up of 35 months was measured by the difference in the mRs and the surgical outcome was evaluated by sonographic findings of the operated ICA status. Chi-square test and the exact Fisher test analysed dependence of clinical outcome on the time of revascularisation, dependence of surgical revascularisation success on the time of

revascularisation and dependence of clinical outcome on surgical success of revascularisation.

Results: perioperative clinical neurological improvement could be achieved in 47% of the patients after emergent surgery. Postoperative clinical improvement was significantly associated with early revascularisation and with surgical success of ICA revascularisation. The surgical re-opening rate of ICA occlusion was 78% and did not depend on the time of the surgery. Rate of postoperative clinical deterioration of 12% and 30 days mortality of 12% did not seem to depend on time. The total 30 days mortality was 12%, stroke related 30 days mortality was 6%. A total of 21 patients (43%) suffered peri-/postoperative intracranial complications including haemorrhagic transformation, enlargement of the pre-existing infarction, secondary haemorrhage and/or stroke recurrence.

Conclusion: emergent revascularisation of acute ICA occlusion should be performed in the first 72 hours of stroke onset because in this time period the clinical benefit for acute stroke patients seems to be at its most, whereas longer time intervals hardly bring any profit. The possibility of revascularisation of acute total ICA occlusion, the risk of postoperative clinical deterioration and death depend on the correct diagnosis and indication for the acute ICA revascularisation rather than on the time of the surgery. Therefore, precise preoperative diagnostic work up is essential for correct identification of patients who can profit from the emergent ICA revascularisation.

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11. Appendix

Appendix 1: (taken from the internet page of the Internet Stroke Centre, Stroke scales and clinical assessment tools): modified Rankin Stroke Scale

0 - No symptoms at all

1 - No significant disability despite symptoms; able to carry out all usual duties and activities

2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 - Moderate disability; requiring some help, but able to walk without assistance

4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 - Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 - Dead.

Appendix 2: Perioperative information on the 49 operated patients

Patient number	Time interval from onset of stroke symptoms to emergent ICA surgery, hours	Preop.mRs	Postop.mRs	Difference in the preop.to postop. mRs	mRs at follow up
1	44	0	5	-5	4
2	37	2	6	-4	
3	130	3	6	-3	
4	33	1	4	-3	2
5	14	4	6	-2	
6	102	3	5	-2	6
7	4	4	5	-1	6
8	87	4	5	-1	4
9	37	5	6	-1	
10	26	2	3	-1	
11	29	5	6	-1	
12	34	5	6	-1	
13	92	3	3	0	3
14	16	4	4	0	2
15	13	3	3	0	6
16	52	2	2	0	0
17	11	5	5	0	5
18	54	5	5	0	2
19	11	1	1	0	0
20	35	1	1	0	0
21	58	0	0	0	
22	7	5	5	0	6
23	105	4	4	0	3
24	97	1	1	0	6
25	165	4	4	0	6
26	143	0	0	0	0
27	6	4	3	1	2
28	12	2	1	1	
29	13	4	3	1	2
30	30	4	3	1	1
31	7	4	3	1	5
32	28	4	3	1	0
33	24	4	3	1	6
34	54	1	0	1	6
35	64	5	4	1	0
36	36	4	3	1	1
37	17	5	4	1	3
38	36	3	2	1	2
39	29	5	4	1	1
40	96	4	3	1	6
41	12	3	1	2	0
42	19	4	2	2	1
43	13	3	1	2	0
44	8	4	2	2	1
45	11	3	1	2	0
46	9	5	3	2	
47	25	4	1	3	6
48	32	5	2	3	1
49	66	4	1	3	1

11. Appendix

The postoperative course on the patients with postoperative clinical stability (13-26) or improvement (27-49) was not accounted for, for the patients with postoperative clinical deterioration or death (1-12) there follows a detailed account on their perioperative clinical course.

Patient 1 (49 years): suffered progressing left stroke due to the left ICA occlusion. In the preoperative work up (MRI angiography) detection of the M1 perfusion was missing, other MCA branches were patent despite reduced flow. The conventional angiography depicted sufficient collateral circulation, multiple DWI lesions were observed in the MRI scans. The emergent ICA revascularisation performed in 44 hours achieved patency of the left ICA. However there followed an extreme clinical deterioration (mRs at admission –0, postoperative – 5) due to embolisation in the MCA the operated region with resulting new left sided infarction.

Patient 2 (79 years): suffered an ipsilateral MCA infarction due to the right ICA occlusion. The preoperative angiography ensured sufficient collateralisation of the MCA over A. opthalmica and leptomeningeal vessels. The emergent revascularisation, performed within 37 hours after the onset of symptoms, was successful, the ICA was patent; the initial neurological deficit (mRs –2) improved. During further postoperative course the patient suffered a traumatic subdural mass haematoma due to an occipital collision with a wall. This condition required an emergent evacuation of the haematoma. Despite successful trepanation the patient died on the 18th postoperative day due to increase of the intracerebral pressure.

Patient 3 (74 years): suffered an ipsilateral territorial proximal MCA infarction due to the occlusion of the right ICA. In the medical previous history there was notion of the old left ACI occlusion. Sufficient collateralisation of the right hemisphere was ensured in the preoperative angiography. The emergent revascularisation, performed in 130 hours after the onset of symptoms, was successful and this patient initially showed signs of clinical improvement. On the 5th postoperative day, however, clinical deterioration was observed (initial mRs - 3, postoperative - 5), which was due to a beginning mass lesion as detected by the emergent postoperative imaging. Also, there were signs of new embolic ipsilateral infarctions. The right ICA and MCA showed patency, however there were irregularities of the wall vessel observed, from which consequently emboli arouse. On the seventh postoperative day there was further clinical deterioration due to secondary haemorrhage into the infarct region which promoted further development of the cerebral edema and an increase of the intracranial pressure. This patient died of cerebral impingement on the 24th postoperative day.

Patient 4 (59 years): suffered an ipsilateral stroke due to the right ICA occlusion. On admission there was a slight neurological deficit (mRs – 1). The preoperative work up ensured the MCA patency on the right. The emergent ICA followed 33 hours after the onset of symptoms, the revascularisation was successful; the fresh thrombus was removed completely. In the postoperative course this patient developed systemic infection with unknown infection site; additionally there was a small haematoma in the operated region. On the 10th postoperative day the patient developed acute clinical deterioration with left sided hemiplegia, in the emergent work up (CCT) showed new subcortical infarction on the left which was thought to

be due to haemostasis, triggered by the systemic infection. This resulted in an increase of the mRs by three points (from one to four), despite consequent postoperative ASA treatment. The right ICA patency persisted.

Patient 5 (54 years): suffered an ipsilateral MCA infarction due to the occlusion of the left ICA followed by a successful vessel recanalisation in 14 hours after the onset of symptoms. In the perioperative course there was initial improvement of the clinical status by one point according to the mRs (initially- 4, postoperatively - 3). Upon further reconvalescence in the rehab this patient developed deep venous thrombosis which then embolised into the lung. The patient died of pulmonary embolism on the 17th postoperative day.

Patient 6 (44 years): suffered progressing left sided stroke due to the left ICA occlusion. The preoperative angiography showed extracranial ICA occlusion on the left, sufficient collateral circulation in form of cross filling from the right hemisphere, however there was a stop of the contrast medium progression at the skull base, so that initially there was speculation about an ICA dissection or ICA pseudoocclusion. The emergent surgery, which followed 102 hours after the onset of symptoms, could rule out both differentials, still there was no patency of the ICA achieved. The intraoperative angiography showed an intracranial ICA occlusion. In the postoperative course there was observed further clinical deterioration (initial mRs at admission – 3, after surgery – 5) with evolution of new embolic infarctions with mass effect, followed by an emergent, successful trepanation. The new infarctions showed signs of haemorrhagic transformation, the clinical status remained stable.

Patient 7 (76 years): suffered an ipsilateral MCA infarction due to the occlusion of the left ICA due to atrial fibrillation. In the preoperative diagnostic work up there was sufficient collateralisation of the MCA. The emergent CEA was performed in 4 hours after onset of symptoms. The occlusion showed to be an older organized thrombus that did not allow recanalisation. During postoperative course there was clinical deterioration observed (initial mRs - 3, postoperatively- 5) due to evolution of new embolic infarction in the ACA and MCA supply areas.

Patient 8 (48 years): suffered an acute ipsilateral stroke due to the left ICA occlusion. In the preoperative work up diagnosis of a severe right ICA stenosis, the angiography showed insufficient collateralisation over vertebro-basilar and leptomeningeal vessels. The emergent ICA revascularisation in 87 hours after the onset of symptoms was initially successful; still there was only an insufficient flow in the left ICA due to the increased vessel resistance. In the postoperative course there clinical deterioration was observed (mRs prior to surgery – 4, afterwards – 5). There was ICA re-occlusion diagnosed in the Duplex sonography, the MRI scan depicted new embolic, infarctions in the MCA territory due to embolic occlusion of the M2/3 MCA segment, in the TOF angiography missing ICA and MCA on the left. The ICA re-occlusion was due to hypoperfusion that resulted from the initially increased vessel resistance, most likely due to distally located thrombus.

Patient 9 (68 years): One month prior to the present admission the patient suffered a left hemispheric stroke due to the left ICA occlusion. To ensure cerebral perfusion because of insufficient intracerebral collateral circulation, an

elective CEA of the right ICA for 80% stenosis was planned. During this elective hospital stay the patient suddenly developed signs of acute severe left-hemispheric infarction with alteration of consciousness (mRs - 5). The emergent MRI scan showed infarction of the left proximal MCA zone, the MCA itself was patent. The infarction was most likely caused by an arterio-arterial embolisation into the MCA, which was already spontaneously recanalised by the time of the cerebral imaging. There followed i.v. treatment with tirofiban, the rt-PA lysis could not be given because of the prior stroke. There followed an attempt to revascularise the left ICA revascularisation (in 37 hours after the onset of symptoms) but no patency could be achieved as the thrombus was of older nature. During further postoperative course, this patient developed aspiration pneumonia and atrial fibrillation and died of cardiopulmonary failure on the 15th postoperative day.

Patient 10 (48 years): suffered an ipsilateral stroke due to the right ICA occlusion. Following the emergent i.v. thrombolysis the MCA on the right showed to be patent. The emergent ICA revascularisation in 26 hours achieved vessel patency. On the first postoperative day the patient suffered bleeding in the operated region: the operative revision showed a small leak from the patch. In the further postoperative course there was clinical deterioration observed (mRs prior to surgery – 2, afterwards –3). The postoperative cerebral computed tomography showed signs of secondary bleeding in the infracted region with ventricle involvement, also there were signs of beginning resorption of a subarachnoidal bleeding. There was no further clinical deterioration, so that neurosurgical intervention was not required.

Patient 11 (69 years): suffered an acute ipsilateral stroke due to the left ICA occlusion. The previous medical history documented profuse atherosclerosis with peripheral arterial disease and extracranial atherosclerosis. 2 weeks prior to this acute stroke this patient underwent elective right CEA. In the past there were multiple episodes of transient speech disorders, the left ICA however did not show significant pathological findings. At admission this patient presented severe neurological deficit with impaired level of consciousness (mRs of five). There was no information obtained on the preoperative intracranial status (patency of the MCA, collateral supply). The emergent recanalisation of the left ICA followed 29 hours after the onset of symptoms. Despite retraction of the fresh, probably cardio-embolic thrombus from the extracranial ICA portion there was no ICA patency achieved. The postoperative angiography showed complete siphon occlusion. Possible pathophysiological mechanisms were thought to be the distal propagation of the thrombus or occlusion of the already existing siphon process apart from the occlusion of the extracranial ICA segment (this could explain previous multiple left sided TIAs). The postoperative CCT displayed evolution of the left MCA infarction as well as presence of new, embolic contralateral infarctions. The clinical status deteriorated further and this patient died on the 7th postoperative day of cardiopulmonary failure.

Patient 12 (57 years): this patient was initially scheduled for an elective left CEA due to 80-90% ICA stenosis. The past medical history documented profuse extracranial atheroslerosis with moderate right ICA stenosis, occlusion of the brachiocephalic trunk, aneurysm of the infrarenal aorta and coronary heart

disease. The reduced left MCA flow was ensured by the transcranial sonography. The patient was then found unconscious on the ward (mRs of five), in the emergent CCT there was demarcation of the left basal ganglia infarction. This patient was treated with i.v. rt-PA thrombolysis, followed by successful emergent ICA revascularisation in 34 hours after the onset of symptoms. On the 2nd postoperative day this patient suffered lethal intracranial mass haemorrhage into the infarction.