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Vivantes Klinikums im Friedrichshain
Akademisches Lehrkrankenhaus der Charité-Universitätsmedizin Berlin

DISSERTATION

Clinical Outcome of Patients who Underwent Extracranial-Intracranial Bypass Surgery

zur Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

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Datum der Promotion: 05.12.2014

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ABSTRACT

Background and Purpose: Ever since Yaşargil performed the first EC-IC bypass in 1967 it has been discussed whether patients profit from this procedure. Our retrospective one center study is aimed at evaluating the operation results with regard to the change of clinical symptoms. Moreover, we analyzed the change in regional CBF using perfusion SPECT with acetazolamide.

Materials and Methods: This study is from a neurosurgical center with a cerebrovascular focus (Neurosurgical Department, Vivantes Klinikum im Berlin-Friedrichshain). It is non-selective, focuses on patient-centered care and includes patients who underwent STA-MCA bypass procedures between August 2008 and June 2011. Inclusion criteria: at least one symptomatic ICA occlusion confirmed by DSA and reduced or absent rCVR on ^{99m}Tc-HMPAO –SPECT.

Results: Out of the initially 21 patients, four were excluded, since the reserve capacity was found to be normal and thus, they have not been operated on. The remaining 17 patients have been operated on, since they fulfilled all inclusion criteria. The peri-operative morbidity and mortality were 11.8% (n=two) and 0%, respectively. During follow-up (10-46 months) all bypasses remained patent. We did not detect any significant increase of local perfusion in previously poorly supplied areas in our cohort. A significant decrease of the number of patients who suffered from TIA (four patients compared to 9 patients before the surgery, $p=0.020$) or headaches (two patients compared to six patients before the surgery, $p=0.041$) was observed. Even though it was not significant ($p>0.05$), a reduction in the frequency and intensity of symptoms such as hemiparesis, aphasia and visual deficits was detectable for all patients.

Conclusion: Bypass surgery can be seen as success since significantly fewer patients suffer from TIA or headaches after the surgery compared to before. In addition a clear though not significant tendency towards the amelioration of other clinical symptoms was detected. Nevertheless, the perfusion SPECT did not show any significant increase of perfusion. All in all it seems reasonable to perform this surgery in a broader context

and we see it as a convincing opportunity which should be considered for the described group of patients.

ABSTRAKT

Hintergrund und Fragestellung: Seitdem Yaşargil 1967 die erste extrakranielle-intrakranielle Bypass Operation durchgeführt hat, wird der Vorteil dieses Eingriffes für Patienten diskutiert. Das Ziel unserer retrospektiven Studie war einerseits, die Effektivität der Operation hinsichtlich der Veränderung von klinischen Symptomen zu evaluieren. Andererseits analysierten wir den regionalen zerebralen Blutfluss unter Verwendung von Acetazolamid stimulierten Perfusions-SPECT Untersuchungen.

Methodik: Diese ein zentrische Studie wurde in der Klinik für Neurochirurgie mit zerebrovaskulärem Schwerpunkt des Vivantes Klinikums im Friedrichshain durchgeführt. Es handelt sich um eine nicht selektive Erhebung, die den Fokus auf patientenzentrierte Versorgung legt. Es erfolgte eine Analyse aller Patienten, die sich zwischen August 2008 und Juni 2011 einer extrakraniellen-intrakraniellen Bypass Operation unterzogen.
Einschlusskriterien: mindestens ein symptomatischer Verschluss der A. carotis interna mittels digitaler Subtraktionsangiographie nachgewiesen und eine eingeschränkte oder aufgehobene relative zerebrovaskuläre Reservekapazität nachgewiesen mittels ^{99m}Tc-HMPAO –SPECT.

Ergebnisse: Von den ursprünglich 21 Patienten wurden vier nicht operiert und daher ausgeschlossen, da sie keine eingeschränkte oder aufgehobene Reservekapazität zeigten. 17 Patienten erfüllten alle Einschlusskriterien und wurden operiert. Die perioperative Morbidität und Letalität beliefen sich auf 11,8% (n=zwei) bzw. 0%. Alle Bypässe waren während der Nachsorge (zehn bis 46 Monate) durchgängig. Es konnte kein signifikanter Anstieg der lokalen Perfusion in zuvor minder-durchbluteten Arealen nachgewiesen werden. Jedoch zeigte sich eine signifikante Reduktion der Anzahl der Patienten, die unter transitorisch ischämischen Attacken (postoperativ vier Patienten im Vergleich zu neun Patienten präoperativ, p=0.020) oder Kopfschmerzen (postoperativ zwei Patienten im Vergleich zu sechs Patienten präoperativ, p=0.041) litten. In allen Fällen wurde eine nicht signifikante Reduktion (p>0.05) der Symptome wie Hemiparese, Aphasie oder visuelle Defizite in Frequenz und Intensität erzielt.

Diskussion: Die Bypass-Operation kann als Erfolg gewertet werden, da sie eine signifikante Reduktion der Anzahl der Patienten, die unter transitorisch ischämischen Attacken oder Kopfschmerzen leiden, ermöglicht. Hinzu kommt, dass eine deutliche, wenn auch nicht signifikante Tendenz zur Besserung weiterer klinischer Symptome nachgewiesen werden konnte. Nichtsdestotrotz ließ sich mittels Perfusions-SPECT Untersuchung kein signifikanter Anstieg der Perfusion belegen. Zusammenfassend erachten wir es für sinnvoll, Bypass-Operationen im größeren Rahmen durchzuführen. Wir halten diese Technik für eine überzeugende Möglichkeit, die für die beschriebene Patientengruppe in Betracht gezogen werden sollte.

ABBREVIATIONS

ACA	Anterior Cerebral Artery
(r) CBF	(Regional) Cerebral Blood Flow
COSS	Carotid Occlusion Surgery Study
(r)CVR	(Relative) Cerebrovascular Reserve Capacity
DSA	Digital Subtraction Angiography
EANM	European Association of Nuclear Medicine
EC-IC bypass	Extracranial-Intracranial Bypass
ECA	External Carotid Artery
HBO_2 therapy	Hyperbaric Oxygen Therapy
(^{99m} Tc-) HMPAO	(Technetium-99m) Hexamethylpropylene Amine Oxime
ICG	Indocyanine green
ICA	Internal Carotid Artery
MCA	Middle Cerebral Artery
MMSE	Mini Mental State Examination
NR	Non-Randomized
NRS	Numeric Rating Scale
P	Prospective
PCA	Posterior Cerebral Artery
PET	Positron Emission Tomography
R	Retrospective
SPECT	Single Photon Emission Computed Tomography
SE	Standard Error
SNM	Society of Nuclear Medicine
SPM	Statistical Parametric Mapping
STA-MCA bypass	Superficial Temporal Artery to Middle Cerebral Artery Bypass
TCD	Transcranial Doppler Ultrasound Examination
TIA	Transient Ischemic Attack
UC	Uncontrolled
VOIs	Volumes of Interest

INTRODUCTION

Yaşargil first succeeded in performing an extracranial-intracranial bypass [EC-IC bypass] in a dog in 1966 (1). In 1967, Yaşargil and his group successfully implemented this technique in a human being for the first time. As a result many neurosurgical centers started to perform bypass surgery. To confirm whether bypass surgery could be a standard procedure which should be carried out in all neurosurgical departments, several attempts to verify the benefit from bypass surgery have been made. The best-known of these is the 1985 International Extracranial-Intracranial Bypass Trial which included 71 centers and did not reveal a general advantage for patients with varying degrees of ICA stenosis (2, 3, 4). Later on, this discrepancy in the severity of symptoms and grades of ICA stenosis as well as several biases due to the multicenter setting have been criticized. It was not before 1987 that it emerged that 2572 patients of the participating centers had not been randomized but excluded from the trial since they had been characterized as high risk patients and underwent bypass surgery immediately. Thus, the patients with the greatest benefit were excluded from the trial (5). Nevertheless, this technique had been excluded from clinical practice in most neurosurgical centers all over the world for several years. Taking into account that an anastomosis should in general improve the patients' symptoms via an increased blood supply, several neurosurgical centers continued to use this technique. There have been some studies suggesting a positive effect of EC-IC bypasses for a subgroup of patients. Recently, it was the multicenter Carotid Occlusion Surgery Study [COSS] that reported, on the contrary, that bypass surgery does not have any advantages over best medical care if the risk of future ischemic strokes is taken into account (6).

Aim

The first aim of our retrospective study was the evaluation of the bypass surgery itself. We hypothesized that we can achieve a favorable change in clinical symptoms and an amelioration of the perfusion situation measured via single photon emission computed tomography [SPECT].

Yet another objective was the assessment of SPECT in the clinical setting and to describe its value with regard to our secondary purpose of identifying a subgroup of patients that profits better from EC-IC bypass surgery than others.

Hence, we included a subgroup of patients suffering from atherosclerotic occlusive cerebrovascular lesions associated with hemodynamic insufficiency, which manifested in form of transient ischemic attack [TIA], reversible ischemic neurological deficits or major completed stroke. Those patients had previously been identified to have the greatest benefit from EC-IC bypass surgery (7, 8). Many of our patients initially presented with TIA of varying degrees and forms. Thus, the third aim of our study was to determine if the TIA frequency and intensity were reduced due to the bypass when the correct subgroup identification criteria were applied.

In addition, we aimed not only to evaluate and improve the indication for the bypass but also to scrutinize the bypass technique itself by applying different investigation techniques which are discussed later on. The maintenance of this technique is particularly important because it can be used for a great variety of indications including e.g. tumor or aneurysm surgery.

PATIENTS

Overview

The neurosurgical department of the Vivantes Klinikum im Friedrichshain, Berlin provides care to an estimated 600,000 to 700,000 people. Between August 2008 and June 2011, a total of 21 patients presented at our hospital with a pattern of various forms of neurological deficits and internal carotid artery [ICA] occlusion confirmed by digital subtraction angiography [DSA]. We suspected a reduced or missing relative cerebrovascular reserve capacity [rCVR] and baseline and acetazolamide-stimulated technetium-99m hexamethylpropylene amine oxime [^{99m}Tc-HMPAO] SPECT was performed for all 21 patients. For an overview of the apparatus investigation techniques applied, see *Table 1 Overview of Applied Apparatus Investigation Techniques*.

Inclusion Criteria

We only included those patients who were expected to be compliant during the time of follow-up especially with regard to the DSA six month after the procedure.

The criteria for the inclusion of patients in this study were:

1) The patient had to present with at least one symptom of occlusion of the ICA such as various degrees of hemiparesis, hypesthesia, aphasia and retinal ischemia.

2) DSA, performed under standard conditions, was used for pre-surgical confirmation of the carotid artery stenosis of 70% or more of the vessel diameter measured according to the European guidelines.

3) This symptomatic cerebral ischemia, including TIA and all other clinical and radiological features of hypoperfusion, in general had to date back by at least six weeks before the surgery. We ensured that there was no disturbed blood brain barrier in or around the hypodense area in the CT. Hypodensity in CT was seen as a sign of ischemia. One emergency bypass was indicated for the therapy of an acute in-stent stenosis with progressing aggravation of symptoms (for details see illustrative cases).

4) A reduced or absent rCVR was measured by ^{99m}Tc-HMPAO-SPECT with baseline and acetazolamide-stimulated imaging.

5) An appropriate donor artery (one branch of STA) in the external carotid artery [ECA] circulation needed to be identified.

Type of In-vestigation	Technical Features	Type of Assessment	Objective	Further
DSA	Siemens Artis zee systems; isoosmolar contrast material Ultravist®	Transfemoral catheterisation using 5F, VERT PERFORMA® catheters (100 cm, .038”, 1050 psi); DSA ICA and ECA on both sides	Selective four-vessel angiography to determine uni- or bilateral ICA occlusion and to identify appropriate donor artery (caliber > 1mm) in ECA circulation	Gold standard for diagnosis of intracranial stenosis; pre-op and six months post-op
^{99m}Tc-HMPAO-SPECT	Matrix 128 x 128; slice thickness 3.5 mm; two-head SPECT camera; Neurolite® and Neurospect® as perfusion tracer	Screen native and acetazolamide (1000 mg i.v.) stimulated	Measure regional CBF and CVR	Ischemia defined as lower accumulation with regard to surrounding tissue
Intra-op TCD	16 MHz micro-doppler pulsed wave	Sterile probe is placed at corresponding location of vessels	Control of blood circulation and possible leakages	
Intra-op ICG Angiography	Infrared angiography using i.v. ICG-pulsion®, invisible light with 800 nm is sent to brain’s surface from surgical microscope	I.v. injection of 0.5 ml (≙ 2.5 mg) ICG, resulting florescence can be detected by the camera in the surgical microscope 25-45 sec p.i.	Control of blood circulation and possible leakages	Penetration depth of about 2 mm
Native and Angiographic Cerebral CT	Helical 64-slice CT	Patient is placed in supine position, images are gained	Identification of ischemic area and description with regard to reason for ischemia	Ischemia defined as hypodense lesion compared to normal brain tissue

Table 1: **Overview of Applied Apparatus Investigation Techniques**

The table gives an overview of all apparatus investigation techniques that were applied during the different steps from first diagnosis to final follow-up.

Abbreviations: cerebral blood flow [CBF], cerebrovascular reserve capacity [CVR], digital subtraction angiography [DSA], external carotid artery [ECA], hyperbaric oxygen therapy [HBO_2 therapy], indocyanine green [ICG], internal carotid artery [ICA], technetium-99m hexamethylpropylene amine oxime [^{99m}Tc-HMPAO] single photon emission computed tomography [SPECT], transcranial doppler ultrasound examination [TCD]

Exclusion Criteria

1) No patient was excluded due to unfavorable outcome or unwillingness to participate.
2) Patients who presented with a symptomatic ICA occlusion which was proved using DSA but who had a normal rCVR were excluded and did not undergo bypass surgery. This reduced the number by four.

Follow-up

Clinical follow-up took place 3, 6 and 12 months after surgery and involved a history and physical examination at each visit. DSA was performed after six months. Baseline and acetazolamide-stimulated ^{99m}Tc-HMPAO-SPECT was repeated once. Transcranial Doppler ultrasound examination [TCD] was performed several times. The final follow-up took place between 10 and 46 months after the surgery. It included two-step measurement of blood pressure, fundoscopy, a questionnaire including recording of current medication and monitoring of risk factors (for detailed information on topics assessed see *Table 2 Characteristics of Patients* and *Figure 1 Comparison of Items Assessed in Questionnaire*, an overview of the medications is shown in *Table 3 Overview of Medications*) as well as mini mental state examination [MMSE] as one of the most accepted tests internationally for assessing cognitive deficits.

Item	Classification	Numbers
Gender	male	15
	female	2
Age (years)		47 – 74
Obesity (body mass index > 30 kg/m²)	yes	3
	no	11
	no data	3
Smoking	yes	6
	no	2
	former	8
	no data	1
Alcohol (> 24 g/d, i.e. more than 2 drinks/d) #	yes	5
	no	6
	former	5
	no data	1
Blood pressure > 140/90 mmHg	yes	16
	no	1
Diabetes mellitus type II	yes	5
	no	12
Hypercholesterolemia	yes	12
	no	4
	no data	1
Peripheral arterial occlusive disease	yes	7
	no	8
	no data	2
Coronary artery disease	yes	5
	no	11
	no data	1

Table 2: **Characteristics of Patients**

Data concerning several items was collected for each patient.

Over the past years, numerous studies and meta-analyses revealed that moderate alcohol consumption of not more than two drinks per day (≤ 24 g/d) decreases the relative risk of ischemic stroke. This finding can be expressed by a J-shaped curve for the association between alcohol consumption and relative risk of stroke (9, 10).

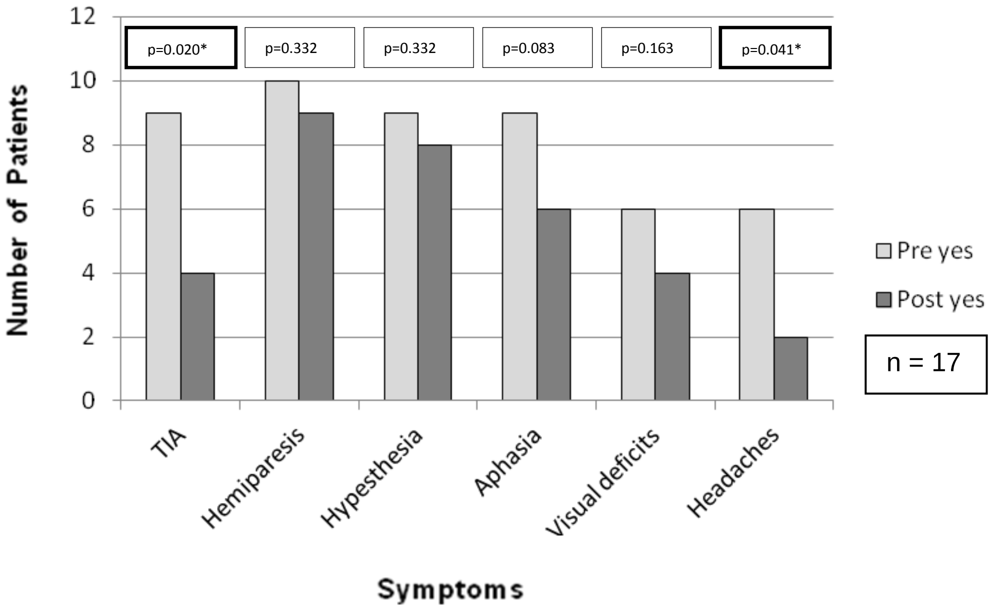


Figure 1: **Comparison of Items Assessed in Questionnaire**
During the final follow-up, patients were asked whether they experienced certain symptoms. The figure shows that fewer patients reported the assessed symptoms post-operatively when compared to pre-operatively. A student's t-test for paired variables was performed and the corresponding p-values are given. As indicated by *, a significant reduction in the number of patients suffering from TIA and headaches was achieved through the surgery.

Abbreviations: transient ischemic attack [TIA]

Type / Class of Medication	Number of Patients Taking it
Anti-platelet agents ASS	15
Clopidogrel	3
Microsomal triglyceride transfer protein inhibitors (Statins)	12
Antiarrhythmic agents (Beta-blockers)	8
Antihypertensive agents (ACE-inhibitors)	9

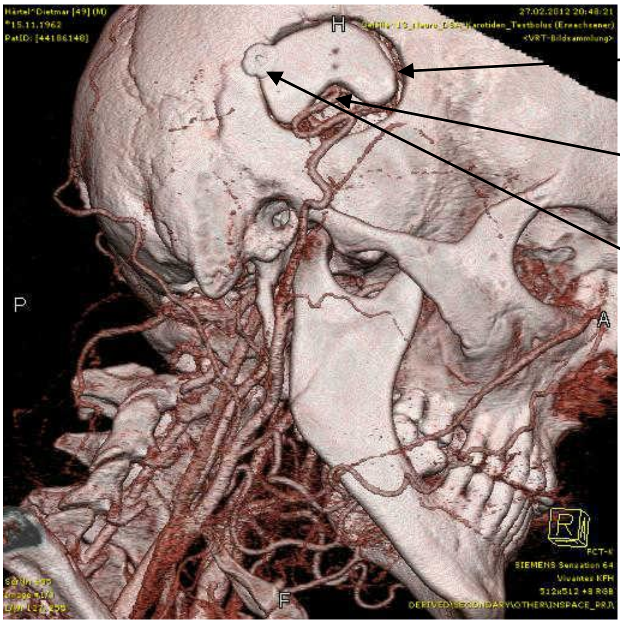
Table 3: Overview of Medications
These are the most frequently taken medications. The other medications not named include diuretics (loop diuretics), anticonvulsive agents (glutamate decarboxylase activators), anti-diabetics (biguanides, insulin) and gastric acid blockers (proton pump inhibitors).

METHODS

Cerebrovascular Surgery

The surgery was performed in the way it was by Yaşargil in 1967:

The patients are placed in a supine position with the head turned to the appropriate side in a Mayfield clamp®. After opening the scalp in a semi-circle and flapping all structures up to the aponeurotic galea, the STA is displayed and evaluated with regard to patency, pulse and diameter using a ZEISS Pentero® microscope. The chosen STA branch is prepared and flushed with a heparinized saline solution. Temporary Aesculap Yaşargil FT252T Clips® with a closing force of 20 g are applied at both sides. Then the temporal muscle is separated in a T-shaped way and craniotomy is performed. After opening the dura the sylvian fissure is displayed and the most prominent infrasylvic branch of the MCA is identified and prepared over a distance of at least 8 – 10 mm. It is selectively clipped, this time using Biemer vessel clips with a closing force of the jaws between 0.20 – 0.30 N, and flushed with a heparinized saline solution. The EC-IC bypass is assembled as an end-to-side anastomosis using 10.0 or 11.0 nylon monofilament sutures (Ethilon® or 10/0 DR-5 and 11/0 DR-4 by SERAG WIESSNER). Single interrupted sutures are applied starting with two corner joints and then suturing the posterior and the anterior rim of the orifice in the order mentioned. To ensure that the posterior wall of the vessel is not sutured to the anterior vessel wall, a 6.0 monofilament suture can be temporarily placed in the MCA branch while the sutures are applied. The cortical branch is opened and retrograde flow evaluated and any eventual leakage is arrested by placing additional suture lines. Afterwards all remaining clips are removed. In case of further leakage, temporary Aesculap Yaşargil FT252T Clips® and methoxy cellulose (Tabotamp Fibrillar®) can be applied until the leakage subsides. A well working bypass is determined either via intraoperative sonography control using a sterile 16 MHz micro Doppler ultrasound or via indocyanine green [ICG] angiography. After that the dura is adapted and methoxy cellulose (Tabotamp Fibrillar®) is applied. The bone is replaced with the exception of a part with a diameter of 2 cm to give the anastomosis enough room and the temporal muscle is attached to the subcutaneous galea in order to avoid liquor fistulas and the skin is closed as usual. A reconstructed angiographic image of EC-IC bypass showing craniotomy is shown in *Figure 2 Reconstructed Angiographic Image After Bypass Surgery*.



<u>Figure 2:</u> Reconstructed Angiographic Image After Bypass Surgery
We see a lateral view of the head and neck. It is a post-operative reconstructed angiographic image. The extracranial-intracranial bypass is shown and craniotomy with remodelled bone piece, fixed with a titanium clamp can also be seen.

^{99m} Tc-HMPAO –SPECT Imaging

All images were obtained and processed according to the guidelines of the European Association of Nuclear Medicine [EANM] and the Society of Nuclear Medicine [SNM] (11,12). Two SPECT images were acquired in each patient on two separate days (not more than three days apart) each before and again after surgery. After a rest period of 20 minutes with eyes closed, 493-566 MBq (mean 522 MBq) ^{99m} Tc-HMPAO were injected. Image acquisition started 30 min after intravenous administration of the tracer. In order to determine the rCVR, patients were given 1g of acetazolamide as continuous intravenous infusion over a period of 20 min, with blood pressure and pulse frequency being monitored during the stimulated second imaging. 15 min later, ^{99m} Tc-HMPAO was injected and 30 min after injection, SPECT was performed in a manner similar to baseline imaging.

SPECT imaging was performed using a dual-head system (Multispect® 2, Siemens Medical Systems) equipped with low-energy, high-resolution collimators. Static images were acquired in a step-and-shoot mode with 120 projection angles over 360° using an individually minimized radius of rotation. Matrix size was 128x128. The energy window (20%) was centered on 159 keV. The resulting scanning time was 20 min. Transversal, coronal and sagittal slices (thickness 3.5 mm) were reconstructed by filtered back projection using a Butterworth filter (cut-off frequency 0.38 Nyquist, order 6). First order attenuation correction was applied using the method of Chang (13). The reconstructed in-plane image resolution was 13 mm full width at half maximum (FWHM).

Method for Calculation of rCVR Using the Baseline and Acetazolamide-stimulated SPECT Images

rCVR was calculated using a fully automatic MATLAB program called HMPAO Tool developed by R. Buchert.

Stereotactic Normalization

First, the acetazolamide-stimulated SPECT image was co-registered to the baseline SPECT image using the Co-register tool of the Statistical Parametric Mapping [SPM] software package (14). The 'co-register only' option was used in order to avoid additional smoothing of the SPECT image by interpolation during reslicing. Then the baseline image was stereotacticly normalized to the SPM perfusion template using SPM's Normalize tool. Warping for elastic transformation was turned on (4x4x4 basis functions, 12 iterations). The transformation for stereotactic normalization of the baseline image was applied also to the co-registered acetazolamide-stimulated SPECT image.

Calculation of rCVR

Brain perfusion SPECT provides only relative measures of regional cerebral blood flow. Therefore, the CVR could not be estimated quantitatively form the SPECT images. Instead, estimates of the rCVR were obtained voxel-by-voxel using the following formula:

$$\mathrm{rCVR}\,[\%] = 100 * \frac{\mathrm{s} * \mathrm{diamox} - \mathrm{baseline}}{\mathrm{baseline}}\,.$$

The scale s refers to an individual factor which normalizes rCVR to a mean of 50% over the whole cortex. The rCVR in the ACA, MCA and PCA territory was obtained by averaging the rCVR over all voxels within the corresponding volumes of interest [VOIs] described in the next subsection.

VOIs

Three-dimensional VOIs of the brain territory supplied by the ACA, MCA, and PCA were obtained by combining all corresponding level 3 VOIs for the respective territory from the SPM VOItool utility (15). The resulting VOIs are shown in *Figure 3 Template for the Volumes of Interest*.

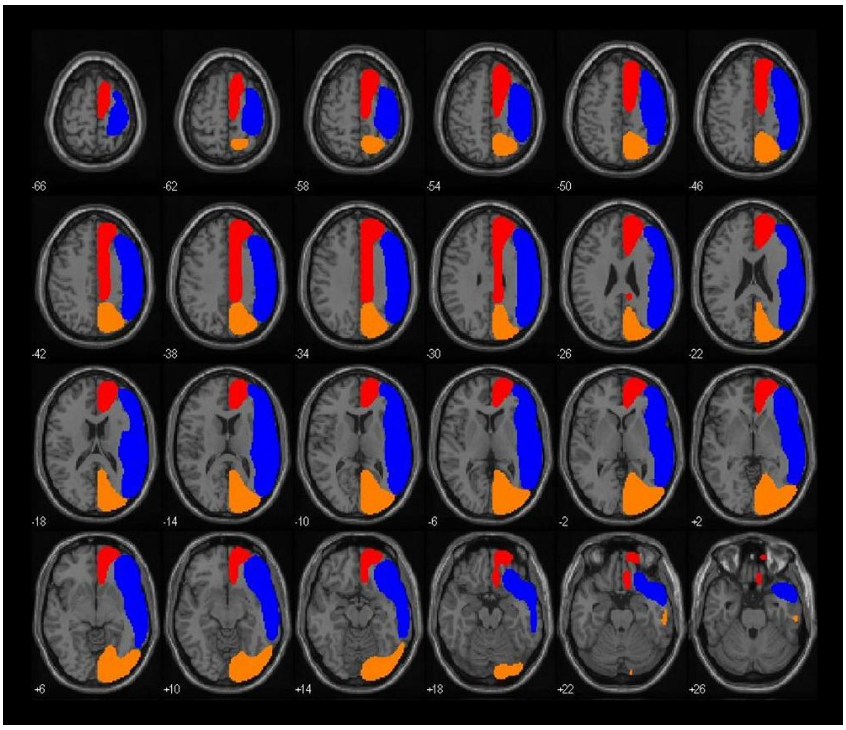


Figure 3: Template for the Volumes of Interest

Shown are axial MRI views of the brain (single subject MRI provided by Statistical Parametric Mapping). In each slice the areas suspected to be supplied by the anterior (red), middle (blue) or posterior (yellow) cerebral artery, respectively, are marked. They are used as templates to create the three-dimensional volumes of interest of the corresponding brain territory.

Hyperbaric Oxygen Therapy [HBO$_2$ Therapy]

The therapy takes place on 10 successive days and is conducted according to the TS240/90 (*therapy scheme* at an absolute pressure of *240 kPa* at a depth of 14 m with *90 min* of O_2 breathing) scheme of the Deutsche Gesellschaft für Tauch- und Überdruckmedizin (GTÜM, German society for diving and hyperbaric medicine). After entering the pressure chamber compression is achieved by raising the pressure at a

rate of 0.1 bar / min. After the required 2.4 bar end pressure is reached, the patients start to breathe 100% oxygen for 90 min with 10 min breaks every 30 min during which they breathe normal ambient air. Decompression is as well effected at a rate of 0.1 bar / min. Thus, the whole application lasts 138 min.
With regard to the hyperbaric pressure, there are several contraindications that need to be ruled out. This includes severe asthma, COPD, emphysema or any other pulmonary deregulation, because the hyperbaric pressure has an immense influence on the lung volume; untreated high blood pressure or any severe cardiac disease (e.g. NYHA 3 and 4); known epilepsy because HBO_2 therapy decreases the convulsive threshold. Therefore, all patients had their blood pressure, pulmonary function, resting ECG and chest X-ray taken to ensure that they were eligible for HBO_2 therapy in case of necessity.

RESULTS

Patients and Follow-up

17 patients (15 males and two females) aged 47 – 74 years (mean 60.1 years) fulfilled the inclusion criteria for this study.

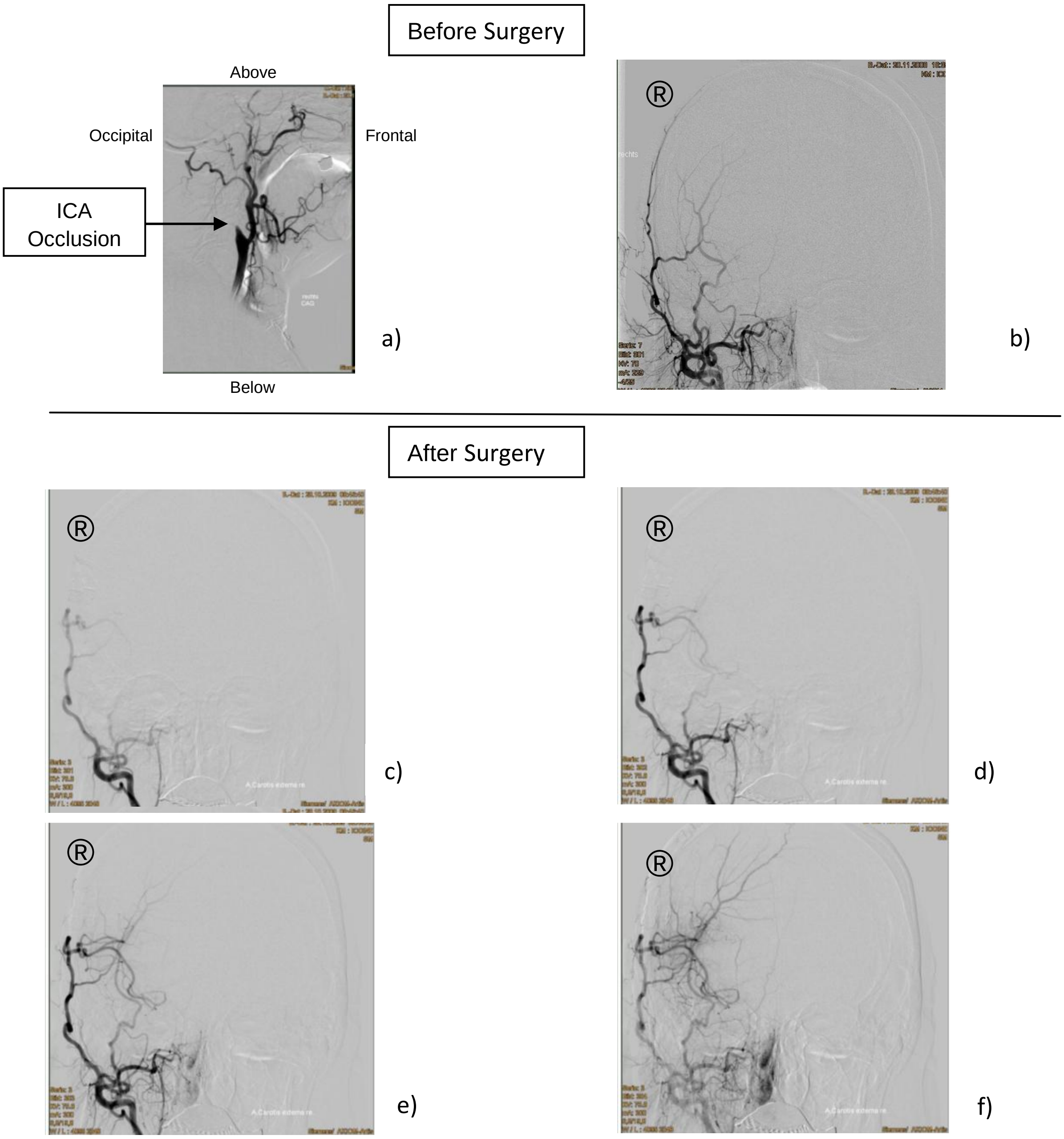
Post-operative DSA was performed for all of the 17 patients included at six months after surgery and showed that all bypasses remained patent at that time (for angiographic images see *Figure 4 Exemplary Angiographic Image of Right-Sided EC-IC Bypass*).

The final follow-up (between 10 and 46 months after surgery), including history and physical examination, TCD, two-step measurement of blood pressure and fundoscopy as well as a questionnaire and MMSE, was carried out for 13 patients. The reasons why the remaining four patients were lost to final follow-up are as follows: One patient is a patient from abroad who is in frequent contact with our clinic but who did not come to our clinic for that final visit. Another patient has been diagnosed with metastasized esophageal cancer after bypass surgery and is undergoing treatment for this cancer. Since he feels fine with regard to prior neurological symptoms, he decided not to participate in our investigation. The other two patients are completely lost to follow-up after their final visits after 12 months and no evidence on their health state is available neither from their general care practitioner nor from other medical departments.

Clinical Outcome

The peri-operative mortality and morbidity, respectively, were zero and two patients, including one patient with an impaired state of health and one patient who suffered a second stroke with severe hemiparesis after acetazolamide injection for the follow-up scan. When we performed the acetazolamide scan pre-operatively that patient instantly started to show symptoms of aggravated hemiparesis. Therefore, we discontinued the acetazolamide injection and took this as a sign of absent rCVR. Post-operatively, we had expected this problem to be resolved which it was apparently not and thus, we had to cancel the scan again.

A total of three patients developed vertigo of unknown origin several months after the surgery without the cause being found. Only in one of these patients TIA-related vertigo had been reported prior to surgery.



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<u>Figure 4</u>: Exemplary Angiographic Image of Right-Sided EC-IC Bypass

The contrast material is injected into the common carotid artery and digital subtraction angiography is performed. An occlusion of the internal carotid artery immediately after the bifurcation can be seen as well as the filling of the external carotid artery. Images a) and b) show the perfusion situation before the surgery. Head and neck can be seen in image a) which is a lateral view showing the occluded internal carotid artery. Image b) is an anterior-posterior view showing the external carotid artery circulation without filling of the internal carotid artery territory.

Images c) (early phase) through f) (late phase) are anterior-posterior views taken after the bypass was performed. They prove a well working superficial temporal artery to middle cerebral artery bypass. The middle cerebral artery is filled through the superficial temporal artery.

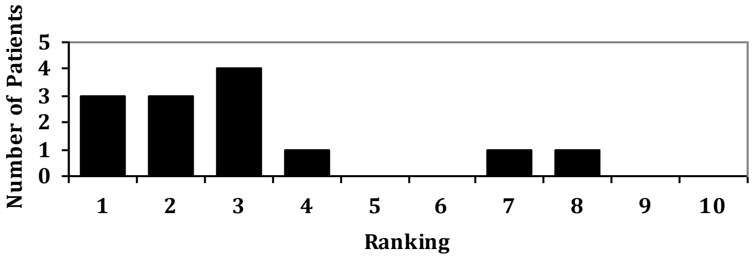
Only one patient suffered from a single episode of newly developed epilepsy (grand mal) 10 months after surgery whereas the other patient who was diagnosed with epilepsy in 1997 is medically adjusted with Gabapentin.

Further TIA were experienced by four patients. Since 9 patients reported them pre-operatively, it is a statistically significant decrease (p=0.020). If those events occurred they were only initially after surgery (one patient) or fewer and less intense than before the surgery (two patients). One patient who did not experience TIA pre-operatively but instant stroke started having TIA post-operatively.

Six patients described having headaches before surgery (numeric rating scale [NRS] between seven and 10) which were resolved in four patients and reduced in two patient (NRS three) after surgery, this equals a statistically significant decrease of the occurrence with a p-value of 0.041.

Symptoms such as hemiparesis (n=9), hypesthesia (n=eight), motor and sensory aphasia (n=six) and visual deficits (n=four) were reported only slightly less frequently after surgery compared to before the bypass was performed (p-values between 0.083 and 0.332, for detailed information see *Figure 1 Comparison of Items Assessed in Questionnaire*) but all of our patients reported that they were considerably less intense than before the surgery.

On an analogue scale patients ranked their overall satisfaction with the outcome between one and eight (one = completely satisfied, 10 = totally unsatisfied). The reasons for low satisfaction were newly developed vertigo after surgery and a second stroke caused by the follow-up acetazolamide scan. This indicates that bypass surgery offers a means of improving the quality of life. An overview of the subjective ranking is shown in *Figure 5 Subjective Ranking Scale for Overall Satisfaction*.



<u>Figure 5:</u> Subjective Ranking Scale for Overall Satisfaction

Patients were asked to rank their personal satisfaction on this subjective scale during the final follow-up. They were asked to consider the development of pre-operatively experienced symptoms, the surgery and hospital care itself and their satisfaction with regard to their current mental and physical health. In this ranking, one represents total satisfaction and 10 stands for complete dissatisfaction.

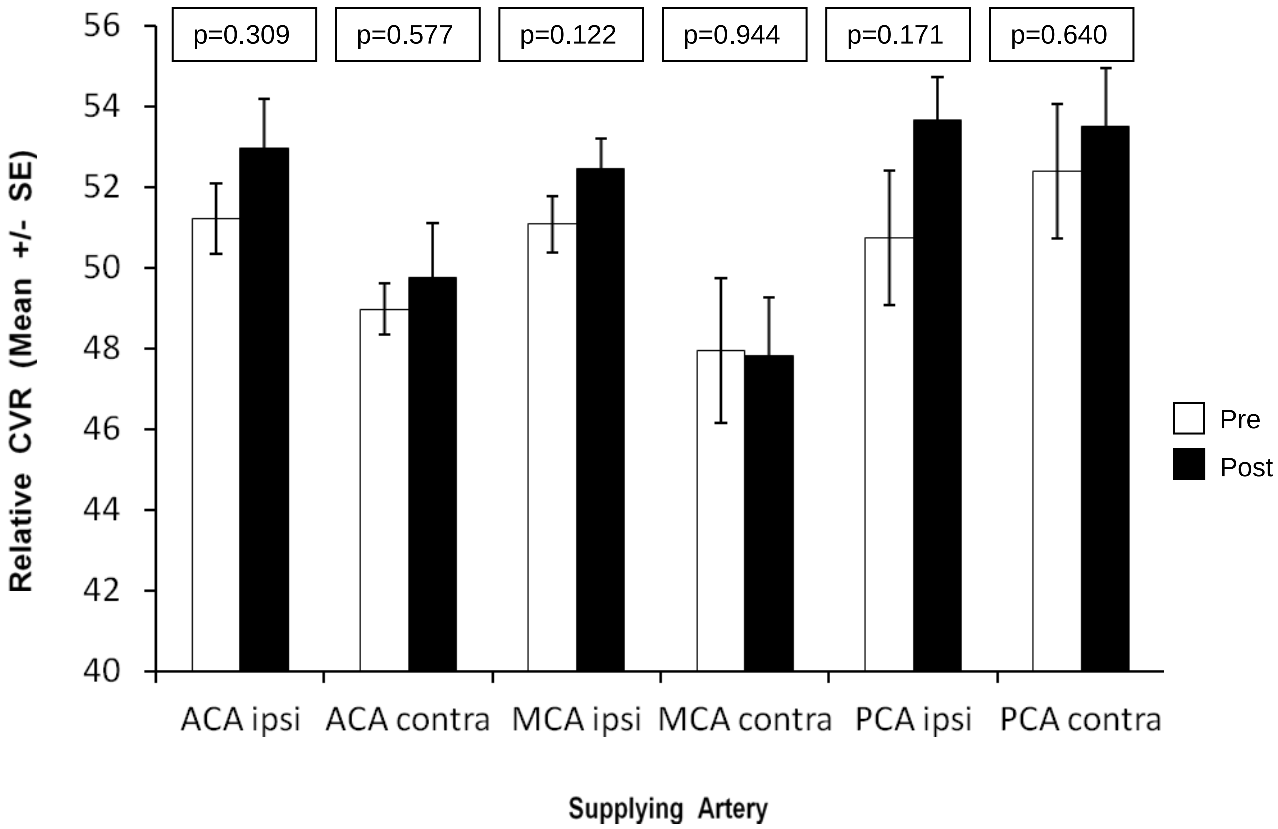
^{99m}Tc-HMPAO –SPECT Imaging and Statistic Analysis Thereof

Figure 6 Relative CVR for Different Brain Territories gives an overview of the rCVR before and after surgery for the three-dimensional VOIs of the brain territory supplied by the ACA, MCA, and PCA as well as the standard error [SE]. The p-values given in the graph were calculated using the student’s t-test for paired variables. It reveals that the rCVR does not differ significantly in any of the VOIs when comparing the pre- with the post-surgical perfusion situation.

DSA and HBO_2 Therapy

A patency rate of 100% was proved again via duplex sonography during the final follow-up and the flow velocity in the anastomosis ranged from 30 cm/s to 100 cm/s and was found at a depth between 20 to 40 mm. In all cases the flow was detected introversively without any turbulent flows.

Even though all anastomoses remained patent at all times during follow-up, three patients did not show an instant benefit initially after bypass surgery. Therefore, they were offered HBO_2 therapy which showed a good effect.



<u>Figure 6:</u> Relative CVR for Different Brain Territories

The described fully automatic MATLAB program called HMPAO Tool was used to calculate the relative CVR for each of the six corresponding brain territories, with ipsilateral and contralateral referring to the side of bypass.

Subsequently a student's t-test for paired variables was performed in order to identify any potentially significant difference between the pre- and post-operative perfusion situation. Thus, the calculated p-values are given which show no significant difference in any territory when comparing the pre-operative with the post-operative values of relative CVR.

Abbreviations: anterior cerebral artery [ACA], cerebrovascular reserve capacity [CVR], contralateral [contra], ipsilateral [ipsi], hexamethylpropylene amine oxime [HMPAO], middle cerebral artery [MCA], posterior cerebral artery [PCA], standard error [SE]

Illustrative Cases

We applied the aforementioned inclusion criteria to all our patients (irrespective of the acute bypass) and thus, the same investigation techniques were used for all of them. Nevertheless, the clinical course including symptoms and their severity at initial presentation, exact results of investigations and postsurgical outcome varies between our patients. Therefore, the following cases are meant to give a rough idea of our patient cohort by illustrating different courses.

E.H., Male, 74 Years at Surgery, Born 05/04/34

This patient presented with a history of four years of dizziness. Six times he reported situations that have been characterized as TIA later on and preceded as follows: Patient was lying and became light-headed. He felt extremely weak and this was accompanied by nausea and vomiting as well as unconsciousness. He also reported a transient amaurosis fugax on the left side and a motor aphasia. With regard to patient's age it is understandable that these situations decreased the quality of life since the TIA were followed by several hours of extreme weakness even though no motor or sensory deficits have been reported.

Angiography revealed an occlusion of the left MCA M1 segment and no filling of the anterior communicating artery was detectable. Thus, a functional ICA occlusion was assumed. The baseline SPECT showed significant right parietal and left parietooccipital perfusion deficits. With acetazolamide there was only a right-sided amelioration of the global cerebral perfusion and partly a decrease of left-sided cerebral perfusion was detected. We therefore decided to perform EC-IC bypass surgery on the left side. The surgery was essentially uncomplicated even though we could only identify a very small infrasylvic MCA branch. Duplex sonography confirmed a patent anastomosis two weeks after surgery. Angiography was performed three and eight month after surgery and revealed a regular perfusion of the anastomosis. Acetazolamide scans which were performed three and 10 months after surgery confirmed an amelioration of cerebral perfusion as well as an increase in left-sided rCVR.

After surgery the patient twice (28 and 35 months after surgery) described similar situations of vertigo but they were less intense and without any accompanying symptoms. Neurological examinations were unable to detect any pathological diagnostic findings. This and a well functioning bypass as confirmed by duplex sonography showed that the patient did not suffer from TIA again. To exclude other causes, peripheral vestibulopathy was ruled out by vestibulogram.

Overall, the patient is subjectively very satisfied and has a good outcome from a neurosurgical point of view 35 months after surgery.

D.G., Male, 55 Years at Surgery, Born 04/06/53

Severe generalized atherosclerosis was the diagnosis of this patient. First, he presented without a hemodynamically relevant stenosis on the left (four vessel angiography September 2007); successful thrombo-endarterectomy on the right side and crossover bypass of iliac arteries. Numerous episodes of several hours including aphasia, visual deficits and nystagmus without motor or sensory deficits were characterized as TIA and diagnosed to be caused by an occlusion of left ICA (CT eight months after initial DSA). The ^{99m}Tc-HMPAO-SPECT performed one month later in the course confirmed the perfusion deficits and a decreased rCVR on the left and right sides which is attributed to crossed diaschisis. Bypass surgery took place one week later and the follow-up baseline and acetazolamide ^{99m}Tc-HMPAO-SPECT scans seven months after surgery showed an increase and homogenization in the perfusion of previously poorly supplied areas on both sides and only a slight perfusion impairment remains which is less intense and affects a smaller area than before. The patient does not suffer from any symptoms any more.

On the whole, the outcome can be characterized as good also with regard to the satisfaction of the patient. He was last seen 46 months after surgery and showed no neurological deficits.

J.G., Male, 68 Years at Surgery, Born 06/20/41

After a technically unsuccessful desobliteration and thrombo-endarterectomy on the right side, this patient was transferred to our clinic. Both ICA were found to be stenosed filiformely between the bifurcation and the cranial basis and ^{99m}Tc-HMPAO-SPECT showed a large-area perfusion deficit. He underwent a percutaneous transluminal angioplasty in combination with a stent on the stenosed right vertebral artery because it

was angiographically determined that the right MCA was supplied by collateral circulation via the posterior communicating artery. The EC-IC bypass, which had been initially planned, was not performed because angiography and ^{99m}Tc-HMPAO-SPECT did not show the requisite indication criteria.
In May 2009, the patient suffered a stroke with a territorial infarct lesion in the area of the right MCA with a left-sided atonic hemiparesis. Angiography also showed a completely occluded left ICA and a relapsing stenosis of the right vertebral artery which was resolved by balloon percutaneous transluminal angioplasty. This time, ^{99m}Tc-HMPAO-SPECT showed a decrease of rCVR on both sides. Since the patient had already suffered a nearly complete right-sided MCA infarction, we confirmed the indication for performing a left-sided EC-IC bypass operation as a prophylactic measure against contralateral cerebral infarction due to the DSA-confirmed occlusion of the left ICA mentioned above. With intensive physical therapy the left-sided hemiparesis was slightly improved. The patient’s overall physical strength was enhanced and he is now able to perform most everyday activities without major limitations.

If only the outcome with regard to the prophylactic bypass were taken into account, it should be described as good. But we need to consider the fact that the patient had already suffered a right-sided MCA infarction resulting in a hemiparesis of the left side. Since no major improvement of this could be achieved with physiotherapy, the patient has a fair overall outcome 13 months after surgery. He is satisfied with his everyday performance.

R.S., Female, 58 Years at Surgery, Born 02/22/55

Primarily this patient presented with a giant ICA aneurysm (19 mm x 12 mm) in a supra-ophthalmic location. This was initially coiled and the rest-perfusion was treated with a flow diverter (SILK-Stent, 3.5 mm x 20 mm). She experienced an acute in-stent stenosis 13 hours after the stent implantation with the symptoms being complete aphasia and hemiplegia. In addition, she proved to be almost non-responsive to clopidogrel. We therefore decided that the indication for an acute bypass operation was given. Today, the aphasia is completely resolved and she regained most of her motor skills. A slight visual deficit remains (due to the location of the treated aneurysm). She scored 29/30 points in the MMSE.

The patient herself is perfectly satisfied with the outcome of the bypass surgery which corresponds to our investigation results which can be described as good from a neurosurgical point of view. 19 months after surgery only a slight visual and motor deficit remains.

DISCUSSION

Inconsistency in Literature

After Yaşargil had introduced EC-IC bypass surgery in 1967 it had been frequently performed. Just as the practice of myocardial revascularization, so it seemed to be self-evident that EC-IC bypass surgery would ameliorate the cerebral perfusion situation by increasing the blood supply to previously poorly supplied areas. Unlike today, previously presentation of TIA or minor completed stroke(s) and stenosis / occlusion of the MCA or ICA confirmed by angiography were basically the only criteria for performing EC-IC bypass surgery. No further investigation techniques aimed at defining a certain subgroup of patients who might show a greater benefit from the procedure than other patients were used. In 1985, EC-IC bypass surgery came under criticism with the publication of the results of the International Extracranial-Intracranial Bypass Trial. It included 1377 patients form 71 participating centers who presented with recent strokes, retinal ischemia or TIA with confirmed stenosis or occlusion of the ipsilateral ICA or MCA. Out of these 1377 patients, 714 were randomized to best medical care alone and 663 additionally received a superficial temporal artery to middle cerebral artery bypasses [STA-MCA bypasses]. Even though a patency rate of 96% was achieved, this study failed to confirm any advantage of the EC-IC bypass over best medical care in preventing further cerebral ischemia but on the contrary showed an increased risk for non-fatal and fatal stroke for the patients who had received the bypass. In addition, they were unable to identify a subgroup of patients with a certain angiographic lesion that had a significantly better outcome with regard to symptom-free survival (2). Because even though they found subgroups that showed an advantage of bypass surgery over best medical care, these were too small to be statistically significant.
The main points to be criticized are the discrepancy in the severity of symptoms and grades of ICA stenosis and occlusion and thus, a wide range of indications. Likewise, there have been several biases due to the multicenter setting. Moreover, patients characterized as high risk patients underwent surgery immediately and have not been included in the trial. Thus, the EC-IC Bypass Study Group probably excluded those patients from the trial that would have proven a benefit from bypass surgery (5).

Ever since that time authors have tried to either confirm the results of the International Bypass Trial or to ascertain a method of identifying a subgroup of patients which shows a benefit from EC-IC bypass surgery. Until today various groups report different results either in favor of or against the surgery. This might, on the one hand, be attributed to the fact that diverse criteria are used to define the indication for bypass surgery and on the other hand divergent tests are used to asses these criteria.

In this context our investigation can be seen as a kind of evaluation study for quality management. We are not attempting to give a global definitive answer to this delicate question. But since all our patients improved after the operation and most of them did not experience any further symptoms, we consider it to be necessary to determine the reason why we achieved better results than most of the multicenter studies.

As described above, we defined a reduced or absent rCVR as confirmed by SPECT as one major criterion for a patient being eligible for the EC-IC bypass procedure.
In this context we need to discuss the Carotid COSS which was published in 2011. It failed to prove any benefit from bypass surgery over medical therapy in the prevention of stroke with an ipsilateral stroke risk of 14.4% in the surgical group and 2.0% in the non-surgical group at 30 days and 21.0% and 22.7% respectively, at two years. They used PET to identify patients with hemodynamic cerebral ischemia using an oxygen ejection fraction ratio of 1.130 as cut-off (6). The use of oxygen ejection fraction to identify the subgroup of patients is one of the main differences compared to our investigation. Employing the rCVR instead of the oxygen ejection fraction as part of our inclusion criteria might have resulted in a different subgroup of patients compared to both the COSS in particular but also other studies. With regard to our results in the subgroup of patients with reduced or absent rCVR measured via acetazolamide SPECT, the presumption seems likely that our subgroup identification is more beneficial with regard to clinical aspects. In addition, the stroke rates of the COSS do not differ essentially from those in the 1985 Bypass Trial and might therefore indicate that the COSS likewise failed to identify the correct subgroup of patients with the greatest benefit from EC-IC bypass surgery (16).
This is also one of the main points of criticism, because in the COSS semi-quantitative OEF ratio was used which is not equivalent to quantitative OEF and thus, results in the identification of an altered group of patients. Besides, the cut-off for oxygen ejection fraction was determined to be 1.160 in the original study design published by the

authors in 2003 but was lowered to 1.130 in order to increase the number of patients includable in the study. Possibly this is another detriment (17, 18). Additionally, they did not refer to patients who were refractory to medical treatment and who may have profited from bypass surgery.

Table 4 Overview of the Literature About EC-IC Bypass and the Role of CBF and CVR shows an overview of four papers dealing with single-center studies published between 1991 and 2011. They discuss the usability and advantages of EC-IC bypass surgery likewise we did in our investigation, i.e. they used altered cerebral blood flow [CBF] and rCVR as criterion for the identification of patients to whom they offered bypass surgery and they confirmed the efficacy of the procedure with post-operative baseline and acetazolamide-stimulated SPECT. Additionally, they evaluated the risk of the procedure with regard to mortality and procedure-related morbidity, on the one hand, and the benefit with regard to prevention of further cerebral ischemia, stroke risk and improvement of symptoms, on the other. Overall, all of them come to the same conclusion as we do i.e. that a subgroup of patients with reduced or absent rCVR profits from EC-IC bypass. The reason that all of us equally found a reduction of symptoms and the prevention or reduction of further cerebrovascular events as well as an increase of rCVR in previously poorly supplied areas may be attributed to several factors. On the one hand, the use of SPECT imaging and the determination of reduced or absent rCVR as major inclusion criterion proves valuable. On the other hand, several biases which occur in large multicenter studies are prevented in smaller investigations. Therefore, even though they are minor in terms of the number of included patients, they are closer to clinical routine and thus, they better depict the actual situation clinicians have to face in deciding on the correct treatment for patients suffering from symptomatic ICA occlusion.

Author, Year and Type	Title	Main Question	Inclusion Criteria, No. of Patients	Methods	Morbidity / Mortality & Success Rate	Conclusions
Muroi C, 2011 R, UC, NR	EC-IC bypass in atherosclerotic cerebrovascular disease: report of a single centre experience (19)	Is bypass surgery effective for reducing the stroke risk of hemodynamically impaired patients?	Atherosclerotic occlusive cerebrovascular lesions with hemodynamic compromise, n = 72	$H_2{}^{15}O$ PET or ^{99m}Tc-HMPAO SPECT with acetazolamide to evaluate CBF	Stroke recurred in ten patients, improved cerebral hemodynamics in 81% of revascularised hemispheres	Effective for selected patients for prevention of further cerebral ischemia - annual stroke risk 5% vs.15%
Ishikawa T 1995 P/R, UC, NR	Cerebral hemodynamics and long term prognosis after EC-IC bypass surgery (20)	Correlation of pre- and postsurgical cerebral hemodynamics with long term prognosis	Reduced cerebrovascular reserve due to steno-occlusive cerebrovascular disease, n = 28	Measurement of CBF and CVR with native and acetazolamide activated ^{133}Xe-SPECT	Four patients experienced subsequent ischemic strokes - all four had reduced mCBF compared to patients without stroke	CBF was unchanged and CVR was improved after EC-IC bypass surgery
Schmiedek P 1994 P/R, UC, NR	Improvement of cerebrovascular reserve capacity by EC-IC arterial bypass surgery in patients with ICA occlusion and hemodynamic cerebral ischemia (21)	Does EC-IC bypass constitute appropriate therapy for a subgroup of patients with recurrent focal cerebral ischemia?	Recurring episodes of focal cerebral ischemia due to unilateral ICA occlusion, n = 28	CVR was studied using ^{133}Xe-SPECT with acetazolamide	Three patients died after massive infarction, one suffered post-operative stroke, uneventful follow-up in all other patients	CBF remained essentially unchanged but CVR showed significant improvement
Yamashita T 1991 R, UC, NR	The effect of EC-IC bypass surgery on resting cerebral blood flow and cerebrovascular reserve capacity studied with stable ^{133}Xe-CT and acetazolamide test (22)	Is ^{133}Xe-CT with acetazolamide a useful and simple method for evaluating cerebral hemodynamics?	Minor stroke or TIA, angiographically shown occlusive lesions of the major arterial trunk, n = 15	CBF and CVR were measured using stable ^{133}Xe-CT and acetazolamide SPECT	Three patients showed increase in CBF, all patients showed increase in CVR	Bypass only increases CBF in some patients but CVR was increased in all, ^{133}Xe-CT with acetazolamide is useful for evaluation

<u>Table 4:</u> Overview of the Literature About EC-IC Bypass Surgery and the Role of CBF and CVR

One center studies investigating standard-flow direct EC-IC bypass and value of CBF / CVR measured with native and acetazolamide-stimulated perfusion SPECT imaging

Abbreviations: mean/relative cerebral blood flow [m/r CBF], cerebrovascular reserve capacity [CVR], extracranial-intracranial bypass [EC-IC bypass], internal carotid artery [ICA], non-randomized [NR], prospective [P], positron emission tomography [PET], retrospective [R], single photon emission computed tomography [SPECT], transient ischemic attack [TIA], uncontrolled [UC]

Evaluation of our Results With Regard to Discussed Literature

Persistence or Recurrence of Symptoms

The finding that symptoms such as hemiparesis, hypesthesia, speech problems (motor and sensory aphasia) and visual deficits were still reported by our patients after bypass had been performed is due to the fact that most patients (15 out of 17) had suffered a complete stroke. The symptoms only experienced during the occurrence of TIA were no longer reported by the patients who stopped having TIA and were reported to be less intense by the patients who suffered further TIA.

Nevertheless, the impact of EC-IC bypass surgery lies not only in the prevention of further cerebrovascular events but we also proved that it can bring about an improvement of impaired neurological functions.

Interpretation of the SPECT Results

We hypothesized that using a decreased CVR which is confirmed via baseline and acetazolamide-stimulated SPECT can identify a subgroup of patients who profit more from EC-IC bypass surgery than other patients. Furthermore, we expected to find a significant increase of blood flow in previously poorly supplied areas. We investigated the CVR by using the three-dimensional VOIs of the brain territory supplied by the ACA, MCA, and PCA. However, this approach did not lead to the expected finding. We did not discover any significant change when comparing the pre-operative SPECT data set with the post-operative ones. Thus, we conclude that even though the assumption in general seemed to be reasonable, a certain part of our modus operandi seems unsuitable. Therefore, we started to analyze what needs to be done differently in order to possibly achieve other results. First of all, we took a holistic view of our performance starting with our hypothesis itself and ending with the application of the described VOIs.

Hypoxic damage of brain tissue is caused by decreased oxygen supply. Apart from the cases where this is caused by an altered respiratory function, a decreased blood flow is the reason for this. Consequently, using a method to measure this decrease seems like a convincing opportunity. Our approach considered not only the blood flow at rest but also under stress. Hence, this enabled us to identify patients at risk for suffering from another stroke or various symptoms of impaired blood flow.

The pre-operative SPECT results exactly map the regions of decreased or absent CVR as well as the surrounding penumbra in contrast to the remaining brain tissue. Since we expected to increase the blood flow via EC-IC bypass we also expected to observe an increase in CVR as well as an ameliorated perfusion situation in these regions when comparing the pre- with the post-operative SPECT images. To confirm this we used the described fully automatic MATLAB program HMPAO Tool and applied the illustrated three-dimensional VOIs of the brain territory supplied by the right or left ACA, MCA, and PCA. Contrary to our anticipations using these calculations and performing a t-test for paired variables did not provide the expected significance when comparing the pre- and post-operative values.

Other authors have reported various uses for SPECT. This includes CVR measurement via SPECT to predict the outcome of patients with subacute infarction without surgical intervention (23). It was also described that SPECT can be used to identify regions of hypo- and hyperperfusion in patients with moyamoya disease (24). In addition, it was stated that SPECT might be a helpful tool to identify patients at risk for complications after carotid endarterectomy (25).

Nevertheless, overall it needs to be recognized that SPECT in general may have many advantages but it did not prove valuable in our setting. On the one hand the baseline SPECT gives us a general idea of the perfusion situation and it may enable us to identify a subgroup of patients at risk of further cerebrovascular events. But on the other hand it has its limits because it is a semiquantitative examination which is therefore unable to quantify the absolute rCBF because it has no input function. It only allows a one-off rather than a dynamic measurement. Hypothesis: SPECT may not be able to deliver absolute perfusion values for the defined cerebral areas. Thus, it will be an advantage to use a perfusion PET e.g. with ^{15}O H_2O, ^{15}O butyrate, ^{18}F-FDG-PET or ^{62}Cu ATSM. Perfusion PET would then allow an absolute quantification of rCBF instead of CVR (26-28). This modality is also used for assessment of other vascular and non-vascular cerebral diseases and pre- and post-operative comparison e.g. before and after carotid artery stenting (29, 30).

Comparable to the guidelines for brain perfusion SPECT, the EANM and the SNM publish guidelines for the acquisition and processing of perfusion PET (31, 32). Nevertheless, more research is needed in order to fully establish the potential of perfusion PET for ischemic diagnostics. This was also reported by T Jones and EA Rabiner who analyzed the past and the future of brain PET in their review article (33). The problem is that perfusion PET is difficult to realize in a general clinical setting since

it requires high technical and procedural standards. Moreover, the personnel effort is immense and the technique is invasive because it includes frequent arterial blood sampling.
Another possibility was presented by JC Park and his colleagues who investigated the value of perfusion CT with simultaneous angiography compared to conventional DSA and acetazolamide-stimulated SPECT. They found their combination a valuable substitute during the follow-up after bypass surgery (34). Since this approach is less invasive and more feasible with regard to general clinical practice it seems to be a further opportunity for future investigation.
Additional possibilities include fMRI and 320-detecor row CT. The latter also offers a quantitative measurement which is comparably accurate but less invasive than PET (35, 36). Nevertheless, more research is needed in this field since hitherto mostly single center experiences but no large international trials have been reported.

Risk Factors for Vascular Diseases

Several well-known risk factors for vascular diseases were found to be positive for the majority of our patients. Most of them stated to be present (six) or former smokers (eight) with a history between 10 and 78 pack years. This was not an exclusion criterion as it has been in other studies and even though we highlighted the risks of smoking for the patients, we did not force them to cease smoking.
Atherosclerotic disease was observed in seven patients whereas neither deep vein thrombosis nor pulmonary embolism could be detected and thus, supports the idea of patients often having a generalized vascular involvement. In addition, three patients were found to have angina pectoris or coronary artery disease.

Even though only three patients were obese with respect to the definition of adipositas (BMI > 30 kg/m²), the average BMI was relatively high with 27.9 kg/m² (22 – 37 kg/m²). In general, this is seen as a risk factor for various diseases. Lately some authors described that an increased BMI might decrease the risk of in-hospital-mortality. Hutagalung and his group analyzed the data of 9,935 adult patients from all medical fields who had stayed in the ICU of their department for anesthesiology and intensive care at the university of Jena, Germany with regard to BMI and mortality. They discovered that patients who were overweight (25-29.9 kg/m²) or obese (30-39.9 kg/m²) had a decreased risk of death in the first 60 days in hospital. On the other hand, being very obese (≥40 kg/m²)) increased the risk of death. This was particularly true for the 1262 patients who had undergone a neurosurgical procedure. The divergent risk of mortality was evaluated in comparison to normal weight patients (18.5-24.9 kg/m²) as the reference group (37).

Medical Regimen

Since the highest risk of recurrence after TIA or stroke is immediately after the first event, it is especially important during those days to offer an adequate antiplatelet therapy because the risks of intracranial hemorrhage are outweighed by the risk of further infarction (38-40). Therefore, all our patients were heparinized during the peri-operative period and started to receive dual antiplatelet therapy including ASS100 and clopidogrel at the sixth post-operative day instead. Clopidogrel was discontinued after an average of six weeks and ASS100 will be continued unless contra-indications occur. Since hypercholesterolemia poses a threat for atherosclerotic disease, not only the patients with detected hypercholesterolemia but all patients were treated with statins in order to prevent the development of hypercholesterolemia.

HBO_2 Therapy

EC-IC bypass surgery is aimed at increasing the oxygen supply via an increased blood supply. Likewise HBO_2 therapy is a means of enhancing the oxygen concentration in the brain. When the necessity of defining a subgroup of patients who might profit better from EC-IC bypass surgery than others started in the 1970s, reactivity to HBO_2 was one possibility which was tested whether it fulfills this task. It was e.g. Holbach and colleagues who found it helpful to distinguish between reversible and irreversible changes in brain tissue after stroke. According to them, HBO_2 on the one hand improves neurological deficits in patients with reversible changes and on the other hand they found that patients who improved after HBO_2 therapy improved even more after subsequent EC-IC bypass surgery. Thus, they suggested reactivity to HBO_2 therapy as a possibility of identifying the right subgroup for surgery (41, 42). In addition, Milovanova and his group found that HBO_2 can stimulate vasculogenesis by activating an autocrine loop via the induction of oxidative stress. This increases the levels of thioredoxin-1 (Trx1), Trx reductase, hypoxia-inducible factors (HIF) 1, 2 and 3 and VEGF as well as stromal cell derived factor 1. Therefore, HBO_2 was found to trigger the growth and differentiation of vasculogenic stem cells and mobilize them from the bone marrow (43). Even though we did not use HBO_2 reactivity to distinguish between reversible and irreversible brain damage, we offered it to three patients. As mentioned before they did not show an instant benefit initially after bypass surgery but the HBO_2 therapy resulted in the desired effect of improvement of impaired neurological functions. According to this as well as the results of other investigators we recommend evaluating the possibility of HBO_2 therapy before performing the surgery.

Technical Assessment of Bypass

Duplex sonography proved to be valuable for the evaluation of bypass patency. On the one hand, it is easily accessible and, on the other hand, it provides information about the intensity of the flow, the flow direction and potential turbulences. Nevertheless, we are unable to state exactly what the varying flow intensities predict, since we did not find any divergences in the outcome of patients with a flow velocity of 30 cm/s or 100 cm/s. The same was reported by Nakamizo and his group who evaluated the value of superficial temporal artery duplex ultrasonography in predicting rCVR non-invasively (44). Thus, its sole value is the confirmation of patency and the detection of an introversive non-turbulent flow.

Since fundoscopy offers a means of directly assessing the intracranial arteries, it was performed for all patients during follow-up. As a matter of fact, it did not give any evidence of the perfusion situation of the brain and can therefore be excluded from the instruments of defining the surgical outcome.

Further Vascular Diseases for Which EC-IC Bypass can be Helpful

The EC-IC bypass is not only a surgical technique that needs to be preserved for the treatment of patients with symptomatic ICA occlusion but there are several other possible indications. These indications include emergency bypasses indicated by aggravation of symptoms (e.g. acute in-stent stenosis) and the surgical treatment of giant aneurysms or tumors such as meningeomas.

Limitations

As mentioned before, this is a non-randomized investigation without a control group and it was not blinded. This is because we do not intend to give a final answer to the discussion about the benefit of bypass surgery in general. In fact, we mainly aim at pointing out the advantages of our setting especially with regard to the identification of the appropriate patients.

Although we only included a small number of patients, the influence of bias was minimized by several different factors including the fact that all operations have been performed by the same surgeon. This is an advantage because it helps to ensure that all bypasses are performed with the same standard. In the setting of the COSS they provided videotaped instructions for all neurosurgeons who failed to prove a patency rate of at least 80% in their previous 10 EC-IC bypass operations. Now it is questionable whether this effectively guarantees the same level of bypass quality. We might state that this causes differences in the outcome we did not have to face and the quality of the performance of the surgeon is definitely a major impact factor. Furthermore, the entire ^{99m}Tc-HMPAO-SPECT tests have been read by two neuroradiologists. Therefore, the same standards were used for the evaluation of CBF and rCVR. The same is true for angiography which was performed by the same two neuroradiologists for all patients pre- as well as post-operatively.

Overall, we believe that rCVR represents a helpful criterion and a major factor for the evaluation of the eligibility of patients for bypass surgery. Above all, the baseline and acetazolamide-stimulated nuclear medicine imaging is a helpful tool to identify patients with an altered perfusion situation who are believed to be at risk for further cerebrovascular events even though we could not test this hypothesis in the retrospective setting of our study. Nevertheless, using the resulting values of the same pre-defined templates for VOIs does not lead to a statistically significant increase of perfusion when comparing the pre- with the post-operative perfusion situation. Hence, according to our data we can conclude that our approach in general to defining the subgroup of patients that will profit best from EC-IC bypass surgery seems promising. Similar experiences were made by others who reported SPECT and PET to be comparably helpful for identifying candidates for surgery (45, 46). But the perfusion

SPECT is not able to predict the clinical outcome which was determined immediately after surgery and during follow-up. Thus, performing a similar study using perfusion PET might be of interest. The main difficulty to overcome before it can be applied in clinical routine will be that perfusion PET is very demanding in the performance. A non-university hospital will not be able to provide all technical equipment including but not limited to a blood counter and a cyclotron which is essential for the necessary on-site production of ^{15}O.

A limitation of the presented retrospective setting is the obstacle that the follow-ups took place at different times after surgery. This includes e.g. the baseline and acetazolamide scans which were performed on the same day for some patients and on different days for other patients (up to three days' difference). Also the last follow-up including neurological examination, a questionnaire, MMSE, assessment of blood pressure, fundoscopy and duplex-sonography took place at different points in time after the surgery (between 10 and 46 months). This might in part be the reason for the discrepancies between the results.

Furthermore, this investigation includes only standard-flow direct bypasses using a branch (mostly the frontal) of the STA as donor vessel. Even though e.g. encephalomyosynangiosis or high flow bypasses using radial artery grafts were used as alternative in rare cases, those patients are not included in this analysis, since we wanted to examine EC-IC bypass surgery in general and not different treatment possibilities in particular.

In addition, our study is only aimed at determining the relevance of EC-IC bypass for patients presenting with cerebral ischemia. We never performed the procedure for patients suffering from possible other indications including (giant) aneurysms or tumors who have been previously described to profit from bypass surgery (47).

Open Questions

Further clarification is needed with regard to the inclusion criteria. There are studies indicating that bypass surgery should only be considered if maximum medical treatment has failed (48). This was not considered in our study and the question of whether the risk of further TIA and strokes caused by prolonged medical therapy is outbalanced by the possible risk of procedure-related morbidity needs to be resolved.

In contrast to other studies we included patients with unilateral as well as bilateral ICA occlusion and did not find any difference in the outcome in terms of radiological and clinical findings (7). Future studies also need to answer the question whether patients who have bilateral ICA stenosis but only a slightly reduced rCVR might also profit from bypass surgery to prevent ischemic events in the case that collateralization from the posterior circulation becomes insufficient.

Conclusion

EC-IC bypass surgery is a successful and promising technique which can improve the cerebrovascular supply of ischemic brain regions and lead to an amelioration of neurological deficits. Based on our assumption an estimated eight out of 1,000,000 people could profit from this technique per year through a reduction of the mortality (evidence level III). Furthermore, the evaluation for bypass surgery in a prospective multicenter setting (e.g. COSS study) is controversial and an individual decision seems to be a reasonable solution. Therefore, we recommend to reserve the bypass technique for selected patients with symptomatic ICA occlusion. ^{99m}Tc-HMPAO SPECT might be useful for the selection of surgical candidates but it is not sensitive enough to predict the outcome after revascularization.

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EIDESSTATTLICHE VERSICHERUNG

Ich, Carina Bittermann, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: *Clinical Outcome of Patients who Underwent Extracranial-Intracranial Bypass Surgery* selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM und werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.

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<u>Anteilserklärung an etwaigen erfolgten Publikationen</u>

Zum Zeitpunkt der Einreichung dieser Dissertationsschrift lag keine auf dieser Dissertation beruhende Publikation vor.

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CURRICULUM VITAE

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LIST OF PUBLICATIONS

1. Shapiro M, **Bittermann C**, Flores RM. Anomalous pulmonary vein drainage is not a contraindication for VATS lobectomy. Thorac Cardiovasc Surg 2013; epub 2013: ISSN 0171-6425.

ACKNOWLEDGMENTS

Writing a dissertation is an ongoing journey and the task of successfully receiving the degree can only be accomplished with the help of many who support you in different ways.

This is the time to show my sincere gratitude to these helping hands that supported me on my way.

First of all, I would like to thank Prof. Dr. Dag Moskopp for accepting me as a MD student at his clinic, for his wisdom, his valuable advice and his excellent guidance throughout my work.

In addition, I am deeply grateful to PD Dr. Michail Plotkin for being my adviser, for all the constructive support he provided including but by far not limited to the analysis of the SPECT data, for his patience and for his helpful recommendations.

To Dr. Ralph Buchert I owe my earnest gratitude for abandoning his MATLAB program HMPAO Tool as well as for his help with the evaluation of the SPECT data. Additionally, I am thankful for the support his technicians at the department for nuclear medicine at the Charité Universitätsmedizin Berlin provided.

Besides I also thank Michaela Großmann and the whole team of the department of nuclear medicine at the Vivantes-Klinikum im Friedrichshain for providing the SPECT data which was acquired and is stored at the Vivantes-Klinikum im Friedrichshain.

Special thanks go to my parents for the continuous help and unlimited support during my studies and while I was writing my thesis. Thank you for always believing in me and for backing me all the way. I would not be where I am today without what you did for me all of my life.