Dissertation

Peri- and postinterventional management of stroke patients treated with mechanical thrombectomy

submitted by

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Univ.-Prof. Dipl.-Ing. Dr. Andrea Berghold

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the ***Guidelines of the Medical University of Graz on Good Scientific Practice****.*

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Disclosures

Part of this thesis has been published in the following two articles:

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Table of Contents

List of Abbreviations

ASITN - American Society of Interventional and Therapeutic Neuroradiology
ASPECTS - Alberta Stroke Programme Early CT Score
CI - Confidence interval
CS - Conscious sedation
CT - Computed tomography
DAP - Diastolic arterial pressure
GA - General anaesthesia
HbA1c - Haemoglobin A1C
ICA - Internal carotid artery
IQR - Interquartile range
LDL - Low-density lipoprotein
LVO - Large vessel occlusion
MAP - Mean arterial pressure
MCA - Middle cerebral artery
mmHg - Millimetre of mercury
MRI - Magnetic resonance imaging
NICU - Neurointensive care unit
NIHSS - National Institutes of Health Stroke Scale
OR - Odds Ratio
RCT - Randomized controlled trial
rt-PA - Recombinant tissue plasminogen activator
ROC - Receiver operating characteristic
SAP - Systolic arterial pressure
TICI - Thrombolysis In Cerebral Infarction

List of Figures

List of Tables

Abstract

Background

Mechanical thrombectomy has become the primary treatment strategy for stroke due to large vessel occlusion of the anterior cerebral circulation. However, many questions regarding the optimal peri- and postinterventional management remain unanswered.

We aimed to investigate the clinical impact of periinterventional blood pressure drops and of the duration of mechanical ventilation in stroke patients treated with mechanical thrombectomy.

Methods

We identified consecutive patients with stroke due to anterior circulation large vessel occlusion from our thrombectomy registry, in which clinical data were prospectively collected. For the investigation of periinterventional blood pressure, patients were included from January 2011 to June 2016. Periprocedural data were additionally extracted from electronic anaesthesia records, blood pressure was measured by invasive monitoring.

For the examination of ventilation time, patients in the time period between January 2011 to April 2019 were included. The duration of ventilation time was both analysed as a continuous variable and grouped into extubation within six hours ("early"), 6-24 hours ("delayed") and >24 hours ("late").

The main outcome variable in both studies was favourable functional neurological outcome, defined as modified Rankin Scale scores of 0-2 at a follow-up examination three months post-stroke.

Results

We were able to analyse 115 patients with complete electronic periinterventional vital sign recordings and found that single severe blood pressure drops were associated with unfavourable outcome. The strongest effect was seen in mean arterial pressure drops below 60 mmHg ($p=0.01$), which remained independently associated with poor functional outcome in multivariable analysis ($p<0.01$).

Regarding ventilation time, we included 441 patients with available follow-up data. Favourable outcome correlated with shorter ventilation time (Spearman's Rho=0.39, $p<0.001$). Specifically, we found that extubation within six hours was associated with favourable outcome compared to delayed extubation (6-24 hours, odds ratio 2.40, $p<0.001$). This association remained statistically significant in multivariable analysis ($p=0.01$). Patients who were extubated after more than 24 hours often had severe stroke-related complications and generally much worse outcome.

Conclusion

Both the avoidance of severe periinterventional blood pressure drops and the strategy of early extubation after mechanical thrombectomy are associated with favourable outcome after three months in stroke patients and should therefore be recommended in the peri- and postinterventional stroke management.

Zusammenfassung

Hintergrund

Die mechanische Thrombektomie hat sich in der Behandlung des akuten Schlaganfalls mit Großgefäßverschluss in der vorderen zerebralen Zirkulation bewährt, es bleiben allerdings noch viele offene Fragen hinsichtlich des optimalen peri- und postinterventionellen Managements. Wir untersuchten die klinischen Auswirkungen periinterventioneller Blutdruckabfälle und der Beatmungszeit bei SchlaganfallpatientInnen, welche mit mechanischer Thrombektomie behandelt wurden.

Methoden

Wir identifizierten konsekutive SchlaganfallpatientInnen mit Großgefäßverschluss in der vorderen Zirkulation aus unserem Thrombektomieregister, in welchem klinische Daten prospektiv gesammelt wurden. Für die Untersuchung des periinterventionellen Blutdrucks wurden PatientInnen aus dem Zeitraum von Jänner 2011 bis Juni 2016 eingeschlossen. Zusätzlich wurden periprozedurale Daten aus den elektronischen Anästhesieprotokollen und Blutdruckwerte über invasives Blutdruckmonitoring erhoben.

Hinsichtlich der Untersuchung der Beatmungszeit wurden PatientInnen im Zeitraum von Jänner 2011 bis April 2019 eingeschlossen. Die Beatmungszeit wurde sowohl als kontinuierliche Variable, als auch gruppiert in Extubation innerhalb von sechs Stunden („früh“), 6-24 Stunden („verzögert“) und nach 24 Stunden („spät“) analysiert.

In beiden Studien wurde als primäre Zielvariable guter funktioneller neurologischer Outcome als Punktewerte von 0-2 in der modifizierten Rankin-Skala im Zuge einer Follow-Up-Untersuchung drei Monate nach dem Schlaganfall definiert.

Ergebnisse

Wir konnten 115 PatientInnen mit vollständiger elektronischer Dokumentation der periinterventionellen Vitalparameter analysieren und dabei zeigen, dass bereits einzelne schwere Blutdruckabfälle mit schlechtem Outcome assoziiert waren. Den stärksten Effekt hatten Abfälle des mittleren arteriellen Drucks unter 60 mmHg ($p=0.01$), welche auch in

multivariabler Analyse unabhängig von anderen Variablen mit schlechtem funktionellem Outcome assoziiert waren (p<0.01).

In die Analyse der Beatmungszeit konnten insgesamt 441 PatientInnen mit Follow-Up-Daten eingeschlossen werden. Guter Outcome korrelierte dabei deutlich mit kürzerer Beatmungszeit (Spearman’s Rho=0.39, p<0.001). Insbesondere konnten wir zeigen, dass eine Extubation innerhalb von sechs Stunden mit besserem Outcome assoziiert war, verglichen mit verzögerter Extubation (6-24 Stunden, Odds Ratio 2.40, p<0.001). Diese Assoziation blieb auch in einer multivariablen Analyse statistisch signifikant (p=0.01). PatientInnen, welche nach mehr als 24 Stunden extubiert wurden, hatten häufig schwere schlaganfallassoziierte Komplikationen und einen deutlich schlechteren klinischen Outcome.

Schlussfolgerung

Sowohl die Vermeidung von kritischen periinterventionellen Blutdruckabfällen, als auch die frühe Extubation nach mechanischer Thrombektomie sind mit gutem Outcome nach drei Monaten assoziiert und sollten daher im peri- und postinterventionellen Schlaganfallmanagement empfohlen werden.

1 Introduction

1.1 Ischemic Stroke

Stroke is the second leading cause of death and disability-adjusted life years worldwide, with 5.5 million deaths and 116 million disability-adjusted life years lost every year as estimated in the Global Burden of Disease Study 2016.[1,2] The global lifetime risk of stroke was estimated at approximately 25% for adults from the age of 25 years onwards and slightly lower in the region of Western Europe (which includes Austria) with 22.7%.[3]

While the mortality and disability-adjusted life years attributed to stroke show a decreasing trend globally, the incidence of stroke has been decreasing less rapidly and an estimated 13.7 million strokes occurred in 2016.[4] In Austria, about 24.000 strokes were estimated to occur yearly in 2016, with 3.900 deaths and 69.000 disability-adjusted life years attributed to stroke, which is a sharp decrease compared to numbers from 1990.[4]

Ischemic stroke has been defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction, with evidence from either neuroimaging, pathological examination or alternatively clinical symptoms persisting ≥24 hours or until death, excluding other aetiologies.[5] Ischemic stroke is the most frequent manifestation of stroke, encompassing about 85% of all strokes.[4] Haemorrhagic strokes (intracerebral and subarachnoid bleeding) make up most of the remainder, while venous stroke is much rarer (<1%).[6,7]

Ischaemic stroke is a very heterogenous disease with many different aetiologies, the most important groups of which are cardioembolism (most importantly, atrial fibrillation), macroangiopathy (such as atherosclerosis-related carotid stenosis or occlusion) and cerebral small vessel disease. This differentiation is especially important for tailored secondary stroke prevention.[7] Modifiable risk factors are responsible for more than 90% of the stroke burden, the most critical of which are hypertension, poor dietary and physical activity habits, smoking, alcohol abuse, diabetes, obesity, dyslipidaemia, cardiac disease, psychosocial stress, low socioeconomic status and air pollution.[8]

In acute stroke, neuroimaging is required to differentiate between ischemic and haemorrhagic stroke. Because of fast acquisition and widespread availability, this is usually done via noncontrast CT. However, MRI has some advantages including better visualisation of early ischemia, identification of minor strokes and brainstem lesions[9], assessment of stroke age[10] and differentiation to stroke mimics, allowing for better patient selection in strokes with unknown onset[11], but takes longer to acquire, is not as universally available and has some contraindications, including metallic implants and claustrophobia.

CT angiography using iodinated contrast agents or MR angiography using time-of-flight and/or contrast-enhanced angiography is performed to identify intra- or extracranial large vessel stenoses or occlusions.[7] A large vessel occlusion (LVO), most frequently the occlusion of the middle cerebral artery (MCA), is found in 24-46% of acute stroke patients presenting to emergency departments and strongly associated with more severe strokes, worse functional outcome and higher mortality.[12,13] In patients with unknown symptom onset, CT or MRI perfusion imaging allows for identification of salvageable brain issue (penumbra).[7]

In a middle cerebral artery occlusion stroke, an average of 1.9 million neurons are estimated to get lost every minute, 120 million every hour, equivalent to an accelerated aging of 3.6 years per hour.[14] In acute ischemic stroke, it was calculated that each minute of earlier treatment with intravenous thrombolysis saves about two days of healthy life.[15] Hyperacute stroke treatment primarily aims towards restoring brain tissue perfusion, as early vessel recanalization is strongly associated with better functional outcomes and reduced mortality.[16]

Recanalization can be achieved by intravenous thrombolysis using recombinant tissue plasminogen activators (rt-PA) and/or endovascular treatment (mechanical thrombectomy).[7] Both have limitations and contraindications, it was estimated that according to current guidelines approximately 25% of all ischemic strokes would be eligible to be treated with thrombolysis and 10-12% with thrombectomy.[7]

Thrombolysis is indicated in patients with a disabling ischemic stroke presenting within 4.5 hours of symptom onset. Contraindications include multiple factors associated with an increased risk of bleeding complications.[17] The first large randomized-controlled trial supporting its use in ischemic stroke was published in 1995[18], and although initially controversial, large meta-analyses have since shown its benefit in acute stroke.[19] Unfortunately, the recanalization rate in LVO stroke through thrombolysis alone is rather low (between 20-40%) and failed recanalization is strongly associated with thrombus length and more proximal vessel occlusion.[20–23] This situation led to the need for the development of alternative treatment options for LVO stroke.

1.2 Mechanical Thrombectomy

Although in 1999 the PROACT-2 trial demonstrated improved outcomes in patients with MCA occlusion treated with intraarterial thrombolysis using prourokinase,[24] subsequent trials investigating the benefits of intraarterial thrombolysis for acute LVO stroke mostly showed neutral results.[25] In the following years, specific devices for intraarterial thrombectomy were developed, with the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) device used in the first studies. However, those first studies failed to show benefit for mechanical thrombectomy, which can be attributed to slow treatment times, issues in patient selection, insufficient experience and suboptimal thrombectomy devices.[7,25]

Stroke care was revolutionized in the years 2014-2016, when six randomized-controlled trials (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, SWIFT-PRIME and THRACE) were published, which all showed significantly improved patient outcomes in LVO stroke patients treated with mechanical thrombectomy together with intravenous thrombolysis compared to intravenous thrombolysis alone, mostly using second-generation thrombectomy devices such as the Solitaire® and Trevo® stent retrievers.[26–31] A meta-analysis of those trials showed an impressive number needed to treat for improved patient outcome of only 2.6.[32] Most patients in these trials were treated within six hours of symptom onset. Two recently published randomized-controlled trials (DAWN and DEFUSE-3) showed significant benefit of mechanical thrombectomy also in patients carefully selected by multimodal neuroimaging with time windows up to 24 hours after symptom onset (or last seen well, if the symptom onset was unknown).[33,34]

Therefore, current Austrian, European and American guidelines recommend mechanical thrombectomy in patients with large vessel occlusion stroke within six hours of symptom onset, and between 6-24 hours of symptom onset based on the inclusion criteria of the DAWN and DEFUSE-3 trials (namely, relatively small infarct cores and mismatch between either clinical symptoms or the size of hypoperfused tissue compared to the infarct core using multimodal neuroimaging).[17,35]

Many open questions regarding the indication of mechanical thrombectomy for intracranial large vessel occlusion remain, including whether patients with more distal vessel occlusions (such as M2/M3 segments), low stroke severity, with occlusion of anterior cerebral or vertebrobasilar arteries (as the randomized trials mostly investigated MCA and intracranial ICA occlusions) and in advanced treatment windows of 6-24 hours should be treated with mechanical thrombectomy.[17] In recent years, numerous new thrombectomy devices have been developed. For example, the COMPASS trial comparing direct aspiration catheters to stent retrievers showed no significant differences between both types of devices.[36]

In Europe alone, it was estimated that 27.500 mechanical thrombectomies were performed in 2016, with rapidly rising numbers worldwide.[37] In 2016, the Society of Vascular and Interventional Neurology announced their plan *"Mission Thrombectomy 2020"* to increase the yearly number of mechanical thrombectomies performed globally to 202.000 by the year 2020, although it was estimated that 1.7 million patients worldwide would be eligible to be treated with mechanical thrombectomy every year.

While intravenous thrombolysis can be performed in smaller hospitals and only needs limited medical infrastructure, mechanical thrombectomy requires complex structural and medical prerequisites including an adapted angio suite, experienced neurointerventionalists, anaesthesiologists and specifically designed pre- and postinterventional care, including a specialized (neuro-)intensive care unit or stroke unit.

Therefore, in Austria, thrombolysis is offered in numerous regional hospitals equipped with a stroke unit, while mechanical thrombectomies are usually performed only in dedicated comprehensive stroke centres. This means that patients eligible for mechanical thrombectomy are often transferred from regional hospitals to such intervention centres. A tight net of stroke units and comprehensive stroke centres offering mechanical thrombectomy has been set up in Austria in the recent years, usually with one tertiary/university hospital offering a 24/7 thrombectomy service per region (with multiple centres sharing service availability in Vienna and Upper Austria).[38] For example, the LKH-Universitätsklinikum Graz offers a 24/7 thrombectomy service for the whole region of Styria and the southern parts of Burgenland.

In LVO stroke patients, successful recanalization is one of the strongest predictors of improved outcome and reduced mortality.[39,40] However, even though high-volume thrombectomy centres achieve recanalization rates between 70-90% (higher than in the initial randomized-controlled trials, presumably because of increased treatment experience), only 40-55% of patients achieve a good functional outcome (usually defined as a score of 0-2 in the modified Rankin Scale).[41] Risk factors for bad outcome despite recanalization include high stroke severity, more proximal and larger vessel occlusion, high thrombus amount, subtotal recanalization or repeated thrombectomy attempts, high age and diabetes mellitus.[41,42]

Aside from those non-modifiable or directly intervention-related risk factors, multiple clinical factors may play a role in poor patient outcome despite technically successful recanalization through mechanical thrombectomy. Better patient outcomes are strongly related to shorter time from stroke symptom onset to recanalization.[43] Furthermore, it was shown that longer time from symptom onset was also associated with lower rates of successful recanalization using mechanical thrombectomy.[44] Multiple measures allow for reduction of time delays, including improved prehospital management, faster in-hospital patient transfers, enhanced teamwork and multidisciplinary feedback.[45]

However, aside from reducing the time from symptom onset to recanalization, multiple factors in the peri- and postinterventional treatment phase have been proposed or shown to influence long-term functional outcomes of stroke patients treated by mechanical thrombectomy. Those will be discussed in the following two sub-chapters.

1.3 Periinterventional Management

There is an ongoing debate whether mechanical thrombectomy for LVO stroke should be performed in general anaesthesia (GA), conscious sedation (CS) or local anaesthesia. General anaesthesia with intubation offers the advantage of full patient immobilization, which might be associated with improved angiographic image quality, potentially leading to shorter procedure time, lower rates of endovascular complications and slightly higher rates of recanalization. In contrast, inducing general anaesthesia could cause a time delay to groin puncture and vessel recanalization. Furthermore, it more frequently causes blood pressure drops due to vasodilatory side effects of anaesthesia drugs and therefore has an increased necessity for vasopressors.[46,47]

Several retrospective cohort studies have shown worse outcome in patients under general anaesthesia compared to conscious sedation.[48–51] However, numerous potential biases may explain this finding. Most importantly, in a clinical setting where anaesthesiologists are able to choose between different anaesthetic techniques, patients in a worse clinical condition and with more severe strokes (therefore per se at a higher risk for worse outcomes) will more likely be treated under general anaesthesia. Although some of the retrospective cohort studies tried to correct for some of those potential biases using different statistical methods, it is likely that not all biases could be accounted for.

Since 2016, four single-centre randomized controlled trials (RCT) investigating this topic have been published (SIESTA, ANSTOKE, GOLIATH and CANVAS). All four showed no significant differences between general anaesthesia and conscious sedation on the main outcome parameters.[52–55] However, meta-analyses of their pooled data have indicated some advantages for general anaesthesia, including increased recanalization rate and improved functional outcome using the modified Rankin Scale.[56–58] Limitations of the RCTs include rather small study samples, single-centre design and rigorous focus on anaesthesia quality (potentially different to real-world treatment). Conversely, meta-analyses including both data from retrospective cohorts and RCTs mostly showed worse outcomes under general anaesthesia.[59,60] This may primarily be explained by the remarkably higher patient numbers in the retrospective cohorts.

In conclusion, while RCT generally indicated neutral results or slight advantages for general anaesthesia, observational studies have shown worse outcomes under general anaesthesia. One reason for this dissociation could be the greater challenge of blood pressure management during the induction of general anaesthesia, when hypotension may be caused by the cardio-depressive and vasodilatory side effects of most anaesthetic agents.[61] In real-world patients treated under general anaesthesia compared to those included in RCTs specifically investigating the anaesthetic management of stroke patients treated with mechanical thrombectomy, hypotensive periods are likely to occur more frequently.

Previous studies investigating periinterventional blood pressure showed diverging results. While some studies indicated worse outcomes for patients who had periprocedural blood pressure drops,[62–64] other studies did not confirm these results.[65–67] It is important to note that the definition of blood pressure drops varied between those studies. While some studies specifically investigated blood pressure drops, others analysed mean blood pressure values throughout the entire periinterventional period. Furthermore, two post-hoc analyses of randomized-controlled trials comparing general anaesthesia to conscious sedation did not show outcome differences[65,66], possibly because severe blood pressure drops occurred much less often due to the rigorous blood pressure targets and focus on anaesthesia quality.

Aside from different definitions of blood pressure drops, several of these studies investigated only systolic arterial blood pressure (SAP), which although often focussed on in clinical practise, is unlikely to be the most important blood pressure-related parameter of cerebral blood flow. The minimal threshold for adequate autoregulation of cerebral blood flow has been shown to be a mean arterial pressure ≥60 mmHg[68], which might therefore be a critical target blood pressure level, especially in the setting of a large vessel occlusion in the brain. Patients with worse collateral blood flow might be at additional risk in such a situation, but this has not been investigated in depth so far.[46]

While anaesthetic guidelines have recommended maintaining systolic periinterventional blood pressure above 140 mmHg (with no mean or diastolic values mentioned) and below 180 mmHg (and diastolic blood pressure below 105 mmHg) during mechanical thrombectomy, current stroke guidelines only state the same maximum thresholds, with no minimal blood pressure targets mentioned.[17,69]

Regarding the usage of different anaesthetic drugs for either general anaesthesia or conscious sedation, studies are scarce.[70] One single-centre retrospective study found very heterogenous anaesthetic techniques and agents used in real-world practice, with a tendency for better outcomes for patients receiving only volatile agents after induction of anaesthesia.[71]

1.4 Postinterventional Management

Postinterventional care of stroke patients treated with mechanical thrombectomy is complex and should be performed in specialized (neuro-)intensive care units or stroke units.[72] Numerous potential complications need to be monitored for after thrombectomy, including complications related to the intervention (arterial access site, vessel injury or vasospasm, contrast-related allergy or nephropathy), the stroke itself (intracerebral haemorrhage, malignant oedema, dysphagia, pneumonia, other infections), vital parameters (arrhythmias, hyper- or hypotension, hyperglycaemia, hyperthermia) and other general complications related to critically ill patients, such as stress ulcers, peripheral venous thrombosis and pressure ulcers.[73]

One of the most important early complications of ischemic stroke is secondary symptomatic intracerebral haemorrhage. A pooled meta-analysis of studies on mechanical thrombectomy showed that there was no difference in rates of either symptomatic or asymptomatic intracranial haemorrhage in patients with large vessel occlusion stroke who were treated with mechanical thrombectomy or not. The rate of symptomatic intracranial haemorrhage was found to be between 2-3%.[74]

Mechanical thrombectomy reduces brain oedema and associated intracranial mass effects[75] and therefore the risk of malignant cerebral oedema potentially leading to brain herniation, which may require decompressive hemicraniectomy. With rising numbers of mechanical thrombectomy, the number of decompressive hemicraniectomies for ischemic stroke has strongly declined within the last years.[76]

Most patients treated with mechanical thrombectomy received iodinated radiocontrast agents for CT angiography and/or CT perfusion studies before the intervention, and then further contrast agents during the catheter-based angiography. However, contrast-induced nephropathy, which was more feared traditionally, is likely very rare to negligible in stroke patients, especially when modern radiocontrast agents are used and patients get hydrated adequately.[73,77]

The arterial access site for the thrombectomy procedure (usually a femoral artery) needs to be adequately compressed after the intervention (especially as many patients previously received intravenous thrombolysis or heparin). This is commonly done with the support of closure devices. Careful surveillance for rare, but clinically relevant access-site complications such as occurrence of groin haematomas, pseudoaneurysms, dissections, limb ischemia and retroperitoneal haematomas is important in the following hours and days.[73]

As hyperglycaemia has been shown to be associated with worse outcome in stroke patients treated with mechanical thrombectomy,[78] current guidelines recommend treating hyperglycaemia, although there is currently no clinical consensus how tightly glucose levels should be controlled.[17]

Hyperthermia leads to increased cerebral metabolic demand and is related to poor outcome in stroke patients.[79] Therefore, hyperthermia should be treated with local cooling therapy and/or antipyretics, and sources of hyperthermia (such as pneumonia or urinary tract infections) should be addressed directly, e.g. with antibiotics.[73]

There is very limited data on nutrition in patients with acute stroke, but guidelines recommend initiation of an enteral diet within the first few days of admission. In patients with severe dysphagia where oral feeding is not possible, placement of a nasogastric tube is recommended in the first week post-stroke.[17]

For prevention of deep vein thrombosis, intermittent pneumatic compression in addition to routine care is recommended in immobile patients without contraindications,[17] as a large randomized-controlled trial in acute stroke patients showed significant reduction of deep vein thrombosis.[80] Furthermore, low-molecular-weight heparin in a prophylactic dose may be used to reduce the risk of deep vein thrombosis or pulmonary embolism.[81]

Regarding blood pressure after thrombectomy, one study showed that severe hypertension after mechanical thrombectomy is strongly associated with worse outcomes, although there was no difference regarding the risk of symptomatic intracranial haemorrhage.[82] On the other hand, hypotension is likely also detrimental to maintaining brain perfusion in patients post-thrombectomy, especially if complete recanalization could not be achieved.[73] Therefore, blood pressure targets post-thrombectomy might be chosen differently in patients depending on their reperfusion status (normotension in successfully recanalized patients versus permissive or even augmented hypertension in patients with partial or failed recanalization).[73]

Generally, longer ventilation time is known to increase the risk for ventilator-associated pneumonia and other complications in neurological patients.[83,84] However, rash extubation of patients after thrombectomy may also cause complications including hypertensive periods, aspiration and respiratory failure. One rather small retrospective study investigated this issue and found worse outcome in patients who were extubated after more than 24 hours, but no differences between ventilation times of less than 24 hours.[85] Another small retrospective study showed improved functional outcome in patients who were extubated directly post-procedure.[86] Currently, there are no guidelines regarding the timing of extubation after mechanical thrombectomy and data on the best point in time for extubation are still lacking.

1.5 Aims and Scope

In this doctoral thesis, I planned to address two specific open questions regarding the peri- and postinterventional management of stroke patients treated with mechanical thrombectomy.

In the first project, I explored the impact of periprocedural blood pressure during mechanical thrombectomy. Specifically, the hypothesis that critical blood pressure drops below a mean arterial pressure of 60 mmHg would be related to worse long-term functional outcomes was investigated. Furthermore, different blood pressure values (absolute and relative changes, systolic, diastolic and mean arterial pressure) and the impact of the collateral blood flow status were examined. For this purpose, consecutive patients with anterior large vessel occlusion stroke who underwent mechanical thrombectomy under general anaesthesia and had continuous invasive blood pressure monitoring were analysed.

In the second project, I investigated the clinical impact of artificial ventilation time after mechanical thrombectomy. The main hypothesis was that longer ventilation time would be associated with worse outcomes and higher rates of pneumonia. Major interest was placed on the analysis whether "early" extubation (<6 hours) after thrombectomy would have a beneficial effect on patient outcomes compared to "delayed" extubation (6-24 hours). In addition, reasons that caused delays in extubation, especially in patients with "late" extubation (>24 hours), were explored. This analysis was performed using a large cohort of consecutive patients who were treated with mechanical thrombectomy for anterior large vessel occlusion stroke.

Both projects could add important data on peri- and postinterventional management of stroke patients treated with mechanical thrombectomy, potentially influencing clinical management and fostering prospective multicentre studies. The most significant limitation of both projects is the retrospective study design, though a selection bias could be prevented by including consecutive patients over a long time period.

2 Material and Methods

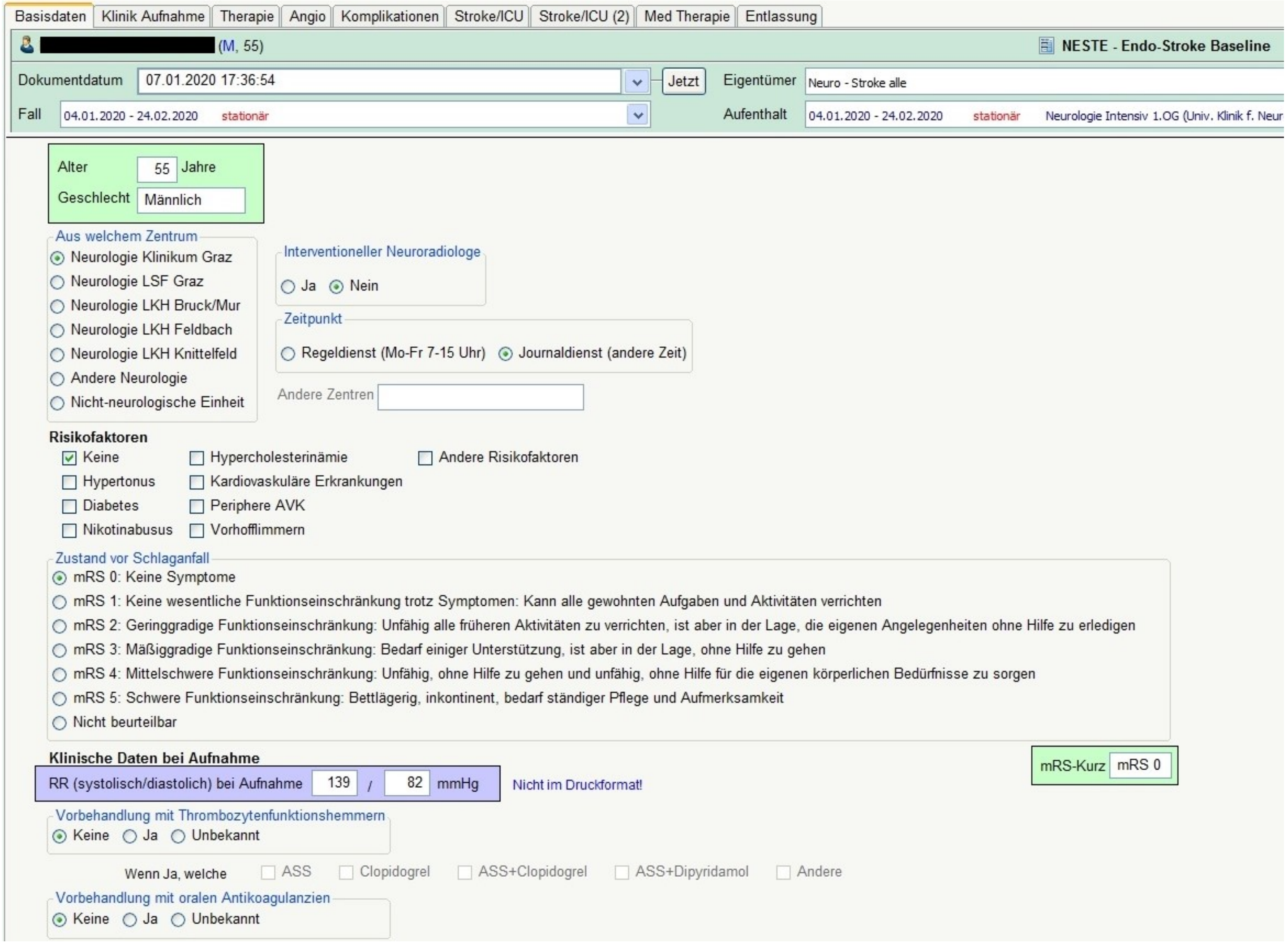
Parts of this section were similarly published in articles by Fandler-Höfler et al.[87,88]

2.1 Project 1: Periprocedural blood pressure

Study setting and participants

The Austrian Stroke Unit Registry was established in 1998.[89] Since then and now mandated by the Gesundheit Österreich GmbH, it has grown to include data on all patients treated in the 39 Austrian Stroke Units. This large registry allowed answers on a broad range of research questions, including the establishment of a predictive score for early mortality in acute ischemic stroke, the investigation of sex-related differences of acute stroke unit care and the predictive value of risk scores in minor stroke.[90–92] Clinical data are entered by the respective Stroke Units and transmitted pseudonymised to the Gesundheit Österreich GmbH, which in turn processes the data and provides detailed analyses including benchmark evaluation for the individual centres.

Mechanical thrombectomies have been performed at our centre, the LKH-Universitätsklinikum Graz, since the late 2000s, at first as an individual treatment option in selected cases. For quality control and evaluation, all patients treated with mechanical thrombectomy have been entered in a thrombectomy registry since 2011. The parameters accessed in Austrian Stroke Registry have changed over the years and started to include data on endovascular treatment in October 2013.[38] To address multiple research questions regarding mechanical thrombectomy in our centre, we improved our thrombectomy registry with support from the Institute for Medical Informatics, Statistics and Documentation. Aside from the data collected for the Austrian Stroke Registry, additional parameters were assessed and entered in the medical documentation system Archimed-RDA, developed by the Institute for Medical Informatics, Statistics and Documentation (example shown in **figure 1**).



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NESTE - Endo-Stroke Baseline

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Eigentümer: Neuro - Stroke alle

Fall: 04.01.2020 - 24.02.2020 stationär

Aufenthalt: 04.01.2020 - 24.02.2020 stationär Neurologie Intensiv 1.OG (Univ. Klinik f. Neur

Alter: 55 Jahre

Geschlecht: Männlich

Aus welchem Zentrum
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- ○ Neurologie LSF Graz
- ○ Neurologie LKH Bruck/Mur
- ○ Neurologie LKH Feldbach
- ○ Neurologie LKH Knittelfeld
- ○ Andere Neurologie
- ○ Nicht-neurologische Einheit

Interventioneller Neuroradiologe
○ Ja ● Nein

Zeitpunkt
○ Regeldienst (Mo-Fr 7-15 Uhr) ● Journaldienst (andere Zeit)

Andere Zentren

Risikofaktoren

☑ Keine
☐ Hypertonus
☐ Diabetes
☐ Nikotinabusus
☐ Hypercholesterinämie
☐ Kardiovaskuläre Erkrankungen
☐ Periphere AVK
☐ Vorhofflimmern
☐ Andere Risikofaktoren

Zustand vor Schlaganfall
- ● mRS 0: Keine Symptome
- ○ mRS 1: Keine wesentliche Funktionseinschränkung trotz Symptomen: Kann alle gewohnten Aufgaben und Aktivitäten verrichten
- ○ mRS 2: Geringgradige Funktionseinschränkung: Unfähig alle früheren Aktivitäten zu verrichten, ist aber in der Lage, die eigenen Angelegenheiten ohne Hilfe zu erledigen
- ○ mRS 3: Mäßiggradige Funktionseinschränkung: Bedarf einiger Unterstützung, ist aber in der Lage, ohne Hilfe zu gehen
- ○ mRS 4: Mittelschwere Funktionseinschränkung: Unfähig, ohne Hilfe zu gehen und unfähig, ohne Hilfe für die eigenen körperlichen Bedürfnisse zu sorgen
- ○ mRS 5: Schwere Funktionseinschränkung: Bettlägerig, inkontinent, bedarf ständiger Pflege und Aufmerksamkeit
- ○ Nicht beurteilbar

mRS-Kurz: mRS 0

Klinische Daten bei Aufnahme

RR (systolisch/diastolich) bei Aufnahme 139 / 82 mmHg   Nicht im Druckformat!

Vorbehandlung mit Thrombozytenfunktionshemmern
● Keine ○ Ja ○ Unbekannt

Wenn Ja, welche ☐ ASS ☐ Clopidogrel ☐ ASS+Clopidogrel ☐ ASS+Dipyridamol ☐ Andere

Vorbehandlung mit oralen Antikoagulanzien
● Keine ○ Ja ○ Unbekannt

***Figure 1**: Medical documentation system Archimed-RDA*

For the investigation of periprocedural blood pressure during mechanical thrombectomy, we used a consecutive cohort from our thrombectomy registry, identifying all adult patients who had been treated with mechanical thrombectomy for an anterior circulation large vessel occlusion stroke (patients with occlusions of the intracranial internal carotid artery and/or middle cerebral artery in the M1 or M2 segments) between January 2011 and June 2016.

In our centre, mechanical thrombectomy is routinely performed by experienced interventional radiologists. As a primary strategy and therefore performed in the vast majority of patients, general anesthesia is induced by specialized neuroanaesthesiologists. The type and dose of anaesthetic agents were individually chosen by the treating anaesthesiologist.

In order to achieve a homogenous and well-characterized study cohort, we excluded patients from this study who were intubated prehospitally or in a transferring hospital (n=12), as in those cases we would not have detailed uniform data on blood pressure and other vital signs in the critical time period of anaesthesia induction. Patients were also excluded if they were treated in conscious sedation opposed to general anesthesia (n=6). Furthermore, we did not include patients with occlusions of the posterior (vertebrobasilar) circulation in order to increase homogeneity (as those patients may require different management and have a divergent prognosis).

In addition, we excluded all patients that did not have an electronic anaesthesia record or those with significant gaps (≥five minutes) of blood pressure and vital sign documentations (n=50). This further included patients with paper-only anaesthesia records (n=33), which are sometimes used in our centre if there are issues with the electronic documentation. As we aimed to only include exact and complete hemodynamic documentation free of potential observer bias, we had to exclude those patients. A detailed flowchart of patient selection can be found in **figure 2**.

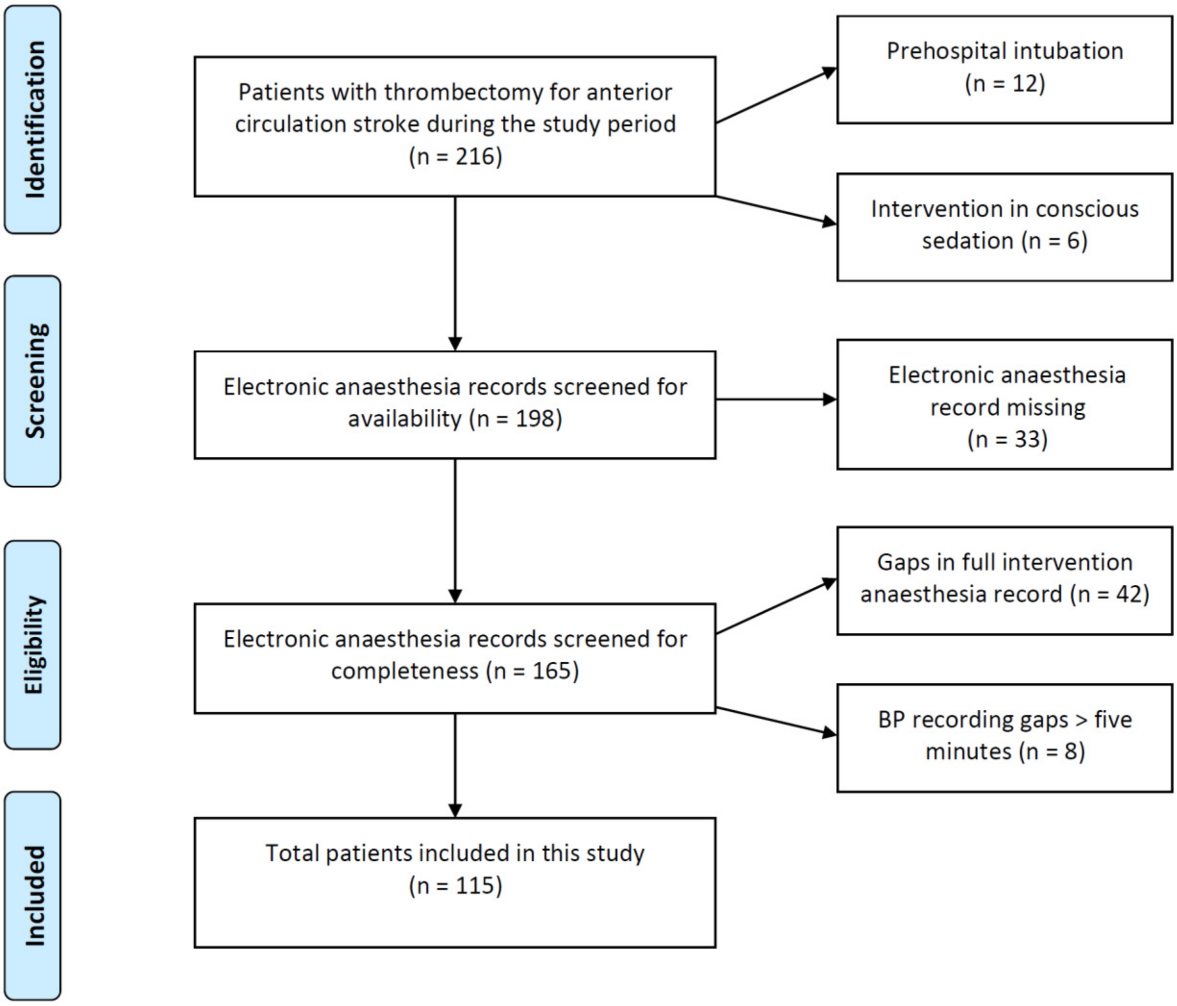

Figure 2: *Study flowchart for the investigation of periprocedural blood pressure (as published* [87]*)*

Data Assessment

In our thrombectomy registry mentioned above, we collected clinical data including demographics, clinical risk factors, stroke symptoms and severity, acute stroke treatment, and functional outcome including a follow-up examination three months post-stroke.

Using the electronic anaesthesia records, we extracted data regarding anaesthesia management and periinterventional vital signs (including heart rate, systolic, diastolic and mean arterial blood pressure and end-tidal carbon dioxide, each measured every minute, exemplarily shown in **figure 3**). Blood pressure values were measured using invasive blood pressure monitoring via peripheral arterial lines in all patients.

Additionally, experienced neuroradiologists blinded to clinical data scored the severity of ischemic changes on baseline and postinterventional CT and MRI scans according to the well-established Alberta Stroke Program Early CT Score (ASPECTS).[93] Furthermore, they classified the cerebral collateral flow on CT angiography using the TAN scale.[94]

Mechanical thrombectomy was defined as successful if a postinterventional Thrombolysis In Cerebral Infarction (TICI) scale score of 2b-3 was achieved, which is in line with most other thrombectomy studies. An example of a proximal middle cerebral artery occlusion successfully recanalized with mechanical thrombectomy is provided in **figure 4**.

We defined functional neurological outcome according to the well-established modified Rankin Scale (mRS)[95] three months post-stroke as the main outcome variable and dichotomized it to favourable (scores 0-2) or unfavourable outcome (scores 3-6). These scores were rated by experienced stroke physicians during a routine follow-up visit at our stroke outpatient clinic.

Regarding stroke risk factors, hypertension was defined as blood pressure >140/90 mmHg or previously initiated antihypertensive therapy. Dyslipidaemia was diagnosed if there was an LDL ≥100 mg/dl or a previously initiated lipid-lowering therapy such as statins. Diabetes was defined as HbA1c ≥48 mmol/mol (6.5%) or earlier diagnosis. Chronic heart disease was defined as the presence of either coronary artery disease, heart failure, cardiomyopathy or significant valve disease.

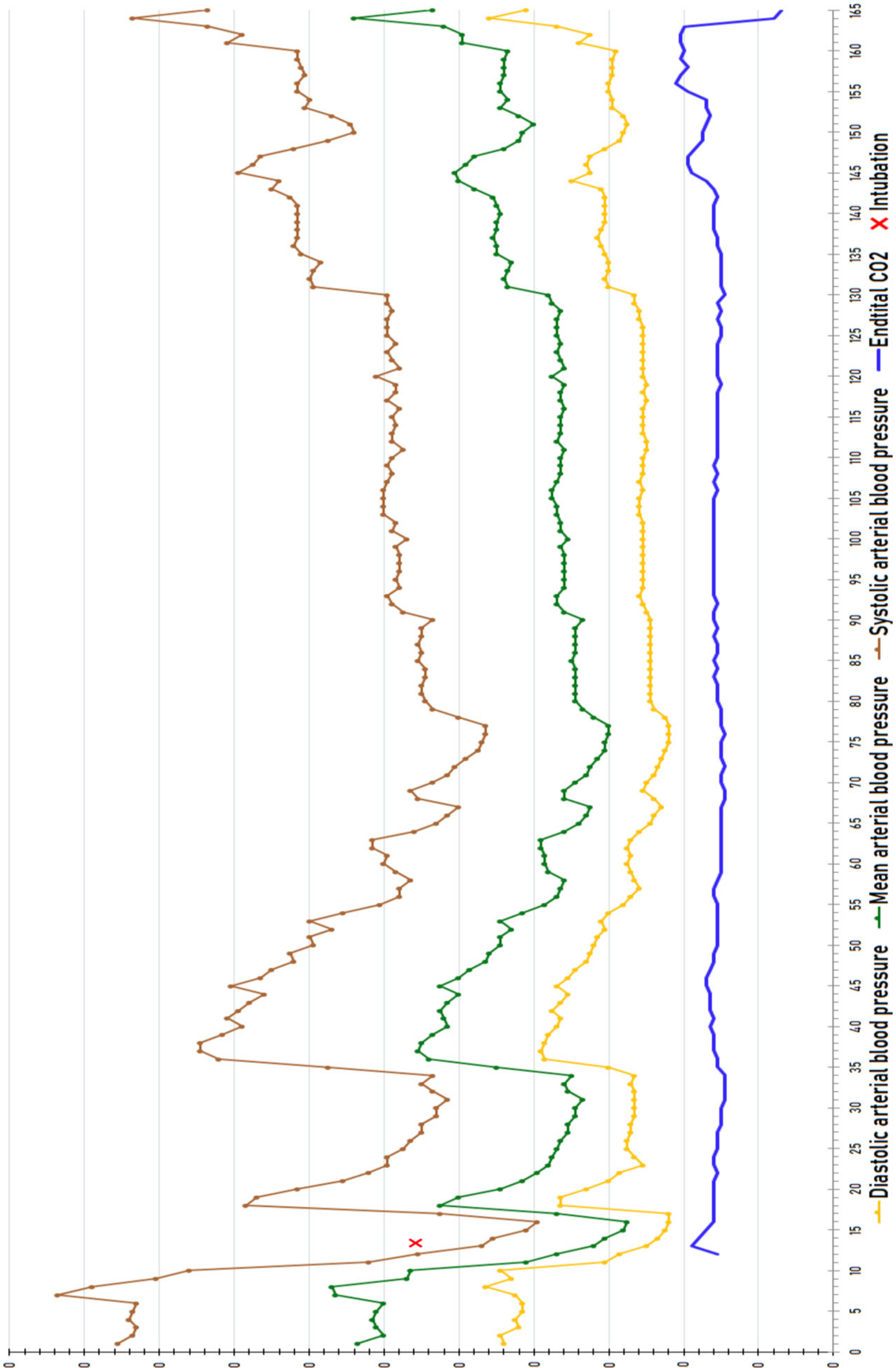

Figure 3: *Continuous electronic periinterventional blood pressure monitoring in a representative patient, showing a severe blood pressure drop after induction of anaesthesia (red cross), as published* [87]

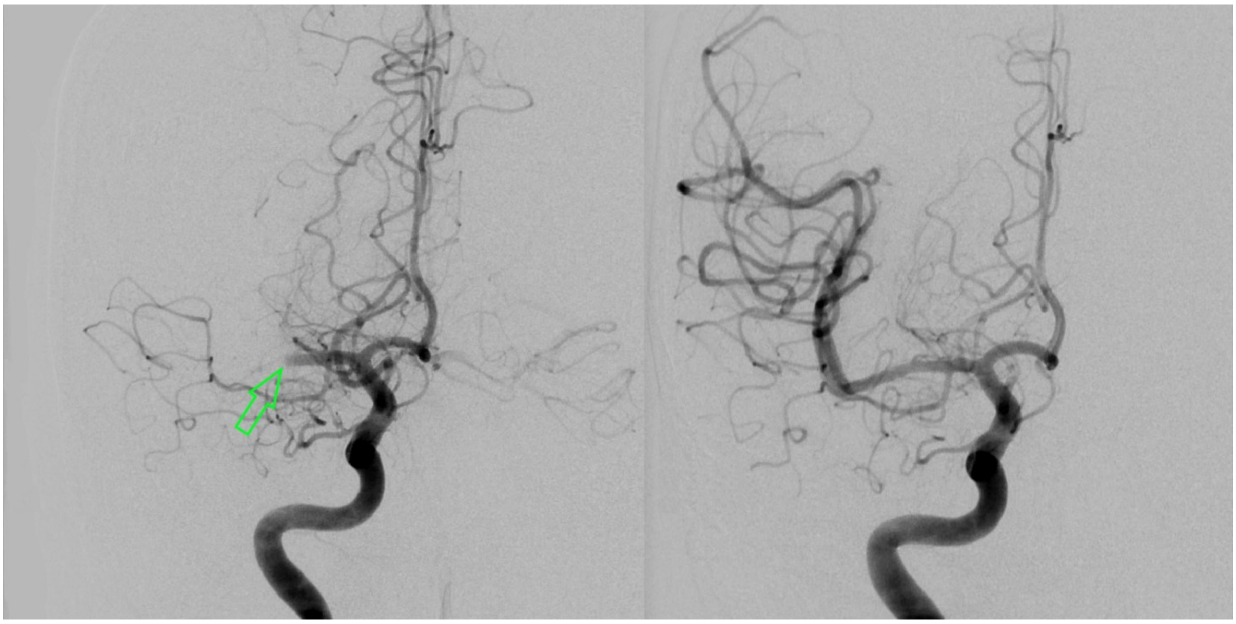

Figure 4: *Example of a proximal middle cerebral artery occlusion (green arrow), successfully recanalized by mechanical thrombectomy (left image: initial angiography depicting the arterial occlusion, right image: angiography after successful mechanical thrombectomy showing restored normal blood flow), published similarly* [96]

2.2 Project 2: Ventilation time

Study setting and participants

For this retrospective cohort study, we again used data collected in our thrombectomy registry as outlined in the previous chapter. We identified all consecutive adult patients who were treated with mechanical thrombectomy for an anterior circulation large vessel occlusion stroke (defined as occlusion of the internal carotid and/or middle cerebral artery in the M1 or M2 segments) at our centre in the time period between January 2011 and April 2019. As patients with occlusion in the posterior circulation (vertebral, basilar and posterior cerebral arteries) have different clinical characteristics, which potentially influence decisions regarding extubation and ventilation time, they were excluded from this study in order to increase homogeneity in our cohort.

Furthermore, we excluded patients from this study if mechanical thrombectomy was performed under conscious sedation (n=15) or if decompressive hemicraniectomy was performed in the days following the stroke, likely influencing decisions regarding sedation and ventilation (n=4). A detailed study flow chart is shown in **figure 5**.

Data Assessment

Using the thrombectomy registry, we exported clinical data including information on patient demographics, stroke severity, acute stroke treatment and clinical course, as well as complications, risk factors and patient outcome including a follow-up examination three months post-stroke.

In addition, we retrospectively collected more detailed information regarding early stroke complications including pneumonia rate, the exact time points of extubation and clinical reasons for not extubating patients. This was done by in-depth patient chart review of medical reports, using the electronic hospital information system *MEDocs*.

Clinical stroke risk factors were defined as outlined in **chapter 2.1**. We defined pneumonia according to established clinical criteria: The presence of an infiltrate on chest X-ray, plus at least two of the following factors: fever >38.0°C, purulent secretions, leucocytosis or leucopenia.[97,98]

We defined ventilation time as the time from intubation to extubation (deliberately not including non-invasive ventilation). Ventilation was analysed both as a continuous variable, but also trichotomized according to three subgroups, as we aimed to depict common clinical scenarios:

- „Early“ extubation (within 6 hours), encompassing all patients extubated directly after mechanical thrombectomy, either within the angio suite or shortly after admission to the neurointensive care unit.
- “Delayed” extubation (6-24 hours), encompassing patients with some, but not severe delays of extubation.
- “Late extubation (>24 hours), encompassing patients who were ventilated for at least one full day after thrombectomy.

The primary outcome variable was defined as functional neurological outcome at three months post-stroke according to the modified Rankin Scale (mRS) and dichotomized into favourable (scores 0-2) opposed to unfavourable (scores 3-6) outcome. During the follow-up examination at three months, these scores were rated by experienced stroke physicians during an in-person visit at the stroke outpatient department or telephone interview, if the former was not possible.

We also investigated pneumonia rate, symptomatic intracranial haemorrhage, duration of stay in the stroke unit/neurointensive care unit, stroke severity according to the NIHSS at discharge and ordinal mRS scores at three months post-stroke as secondary outcome parameters.

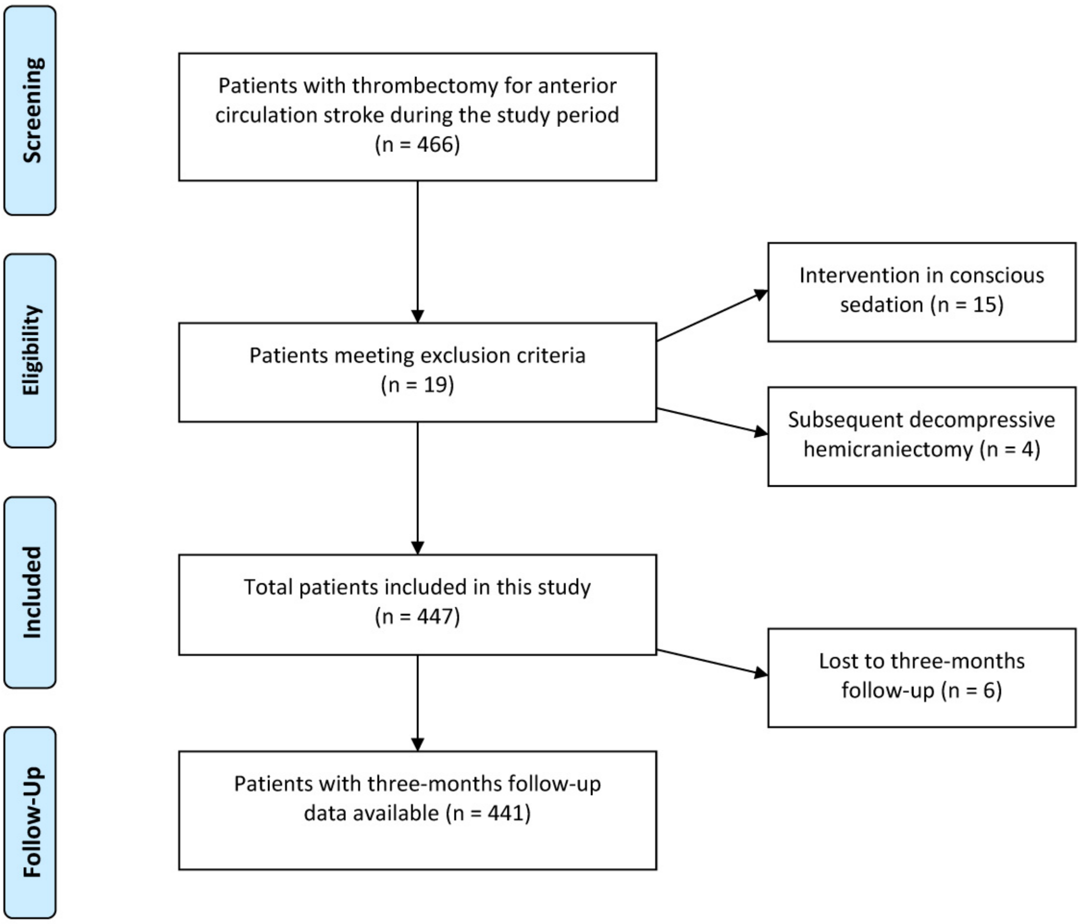

Figure 5: *Study flowchart for the investigation of ventilation time (as published* [88]*)*

2.3 Statistical analysis, data availability statement, ethical approval

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov–Smirnov test and histograms, normally distributed continuous variables were compared by the unpaired Student’s t-test, for other distributions nonparametric tests such as the Mann-Whitney U-test were used. Categorical variables were investigated using Pearson's chi-squared test.

A binary multivariable regression model for predictors of favourable outcome at three months was calculated in both projects entering all baseline variables with $p<0.10$ in the univariable analysis. Consecutively, stepwise backward elimination was performed using a threshold of $p<0.10$. In project 1, receiver operating characteristic (ROC) curves for analysis of sensitivity and specificity of blood pressure values towards patient outcome were calculated.

P-values of less than 0.05 were considered statistically significant.

Data Availability Statement

Anonymized datasets generated and/or analysed during these studies are available from the author upon reasonable request.

Ethical Approval

These studies were approved by the ethics committee of the Medical University of Graz.

3 Results

Parts of this section were similarly published in articles by Fandler-Höfler et al.[87,88]

3.1 Project 1: Periprocedural blood pressure

Study cohort characteristics

We screened 216 patients who were treated with mechanical thrombectomy for an anterior circulation large vessel occlusion stroke during the study period. A total of 101 patients had to be excluded, the final study cohort therefore consisted of 115 patients (detailed inclusion and exclusion criteria and respective numbers of excluded patients can be found in **chapter 2.1** and **figure 1**).

When comparing included and excluded patients, we found no significant differences regarding demographic data, clinical risk factors, radiological findings and intervention data including recanalization rate and time windows. However, excluded patients showed slightly higher stroke severity measured with the NIHSS (median 15 vs. 14 in included patients, detailed information is given in **table 1**).

Among included patients, the mean age was 65.3 years (range 27-85 years), 44.3% were female. The most prevalent stroke risk factors were hypertension (diagnosed in 62.6% of patients) and atrial fibrillation (41.7%). Median NIHSS at admission was 14, indicating severe strokes. The majority of patients had an occlusion in the M1-segment of the middle cerebral artery (75.7%). Pre-interventional ASPECT scores were relatively high (median 9, range 5-10), 60% of patients were also treated with intravenous thrombolysis. The median time from stroke onset to groin puncture was three hours and 20 minutes, recanalization was achieved in a median time of four hours and 20 minutes. The median anaesthesia duration per patient (patient preparation, induction of general anaesthesia, periinterventional anaesthesia until transfer of patient) was close to two hours. Successful recanalization (TICI score 2b-3) was achieved in the vast majority of patients (83.5%, **table 1**).

Table 1: Comparison of clinical and radiological data in included versus excluded patients (published in part [87])

	Study Cohort n=115	**Excluded patients** n=101	**p-value**
Clinical data			
Age (mean±SD)	65.3±13.0	66.7±13.9	0.43
Male sex	64 (55.7%)	51 (50.5%)	0.53
Hypertension	72 (62.6%)	67 (66.3%)	0.66
Dyslipidaemia	17 (14.8 %)	20 (19.8%)	0.33
Chronic heart disease	17 (14.8 %)	17 (16.8%)	0.55
Diabetes	16 (13.9%)	23 (22.8%)	0.06
Atrial fibrillation	48 (41.7%)	40 (39.6%)	0.85
Prestroke mRS (median, IQR)	0 (0)	0 (0)	0.47
Stroke of unknown symptom onset	27 (23.5%)	13 (12.9%)	0.05
NIHSS at admission (median, range)	14 (4-25)	15 (6-34)	**0.01**
Radiological findings			
MCA/M1-occlusion	87 (75.7%)	76 (75.2%)	0.95
MCA/M2-occlusion	13 (11.3%)	4 (4.0%)	0.05
Intracranial ICA occlusion	11 (9.6%)	18 (17.8%)	0.08
CTA collateral scoring (TAN, median, range)	2 (0-3)	2 (0-3)	0.16
ASPECTS pre-intervention (median, range)	9 (5-10)	9 (3-10)	0.20
Intervention			
Intravenous thrombolysis	69 (60%)	68 (67.3%)	0.43
Time to groin puncture (minutes, median, IQR)	200, 82	205, 84	0.56
Time to recanalization (minutes, median, IQR)	260, 93	271, 90	0.36
Successful recanalization (TICI score 2b-3)	96 (83.5%)	82 (81.2%)	0.43
ASPECTS 24 hours post-intervention (median, range)	5 (0-9)	5 (0-9)	0.41

Legend: ASPECTS: Alberta Stroke Program Early CT Score, CTA: Computed tomography angiography, ICA: Internal carotid artery, MCA: Middle cerebral artery, NIHSS: National Institutes of Health Stroke Severity Scale, mRS: Modified Rankin Scale, TICI: Thrombolysis In Cerebral Infarction

Clinical characteristics and outcome

At the follow-up examination three months post-stroke, slightly more than half of the patients (51.3%) had a favourable outcome (mRS 0-2), while 14 patients (12.2%) had died.

Patients with unfavourable outcome were older (mean age 68.7 vs. 62.1 years in patients with favourable outcome, p=0.001), more frequently had hypertension (76.8% vs. 49.2%, p=0.002) and diabetes (23.2% vs. 5.1%, p=0.005). They also had more severe strokes (median NIHSS 16 vs. 13, p<0.001) and worse cerebral collaterals (median TAN score 1 vs. 2, p=0.04).

No significant differences could be found regarding patient sex, location of vessel occlusion, usage of intravenous thrombolysis and procedural time windows of mechanical thrombectomy.

However, in patients with unfavourable outcome, successful recanalization was achieved less frequently (71.4% vs. 94.9%, p=0.001), mean anaesthesia duration was longer (131 vs. 108 minutes, p=0.02, likely due to more complex interventions) and postinterventional ASPECT scores were significantly lower (median 3 vs. 6, p<0.001), indicating larger final infarct sizes. Detailed information on the comparison regarding patient outcome can be found in **table 2**.

Table 2: Clinical and radiological data of the study cohort regarding three-month outcome (published in part [87])

	mRS 0-2 n=59 (51.3%)	**mRS 3-6** n=56 (48.7%)	**p-value**
Clinical data			
Age (mean±SD)	62.1±13.8	68.7±11.1	**0.001**
Male sex	31 (52.5%)	33 (58.9%)	0.49
Hypertension	29 (49.2%)	43 (76.8%)	**0.002**
Dyslipidaemia	7 (11.9%)	10 (17.9%)	0.37
Chronic heart disease	5 (8.5%)	12 (21.4%)	0.05
Diabetes	3 (5.1%)	13 (23.2%)	**0.005**
Atrial fibrillation	22 (37.3%)	26 (46.4%)	0.32
Prestroke mRS (median, IQR)	0 (0)	0 (0)	0.13
Stroke of unknown symptom onset	11 (18.6%)	16 (28.6%)	0.21
NIHSS at admission (median, range)	13 (4-22)	16 (8-25)	**<0.001**
Radiological findings			
MCA/M1-occlusion	44 (74.6%)	43 (76.8%)	0.78
MCA/M2-occlusion	7 (11.9%)	6 (10.7%)	0.85
Intracranial ICA occlusion	5 (8.5%)	6 (10.7%)	0.68
CTA collateral scoring (TAN, median, range)	2 (0-3)	1 (0-3)	**0.04**
ASPECTS pre-intervention (median, range)	9 (5-10)	9 (3-10)	0.05
Intervention			
Intravenous thrombolysis	39 (66.1%)	30 (53.6%)	0.17
Time to groin puncture (minutes, median, IQR)	203 (81)	197 (74)	0.55
Time to recanalization (minutes, median, IQR)	254 (92)	272 (77)	0.68
Anaesthesia duration (minutes, median, IQR)	108 (54)	131 (67)	**0.02**
Successful recanalization (TICI score 2b-3)	56 (94.9%)	40 (71.4%)	**0.001**
ASPECTS 24 hours post-intervention (median, range)	6 (2-9)	3 (0-8)	**<0.001**

Legend: ASPECTS: Alberta Stroke Program Early CT Score, CTA: Computed tomography angiography, ICA: Internal carotid artery, MCA: Middle cerebral artery, NIHSS: National Institutes of Health Stroke Severity Scale, mRS: Modified Rankin Scale, TICI: Thrombolysis In Cerebral Infarction

Periinterventional blood pressure

On average, preinterventional blood pressure values in our study cohort were slightly hypertensive (150/81 mmHg, mean arterial pressure 107 mmHg). We frequently identified significant periinterventional blood pressure drops. The lowest periprocedural blood pressure recorded on average were 87, 46 and 60 mmHg (systolic/diastolic/mean arterial blood pressure). This corresponded to an average blood pressure drop to about 60% of preinterventional values **(table 3)**.

There were no differences between preinterventional blood pressure values regarding three-months outcome. Average and minimal procedural blood pressure values were also not significantly different. Investigating specific blood-pressure cut-off values, we found that a periinterventional mean arterial pressure drop below 60 mmHg was associated with worse outcome at three months (Odds Ratio 2.72, 95% CI 1.26-5.85, **table 3**).

When using ROC curves to find the best cut-off value of blood pressure drops regarding functional outcome, we found that mean arterial pressure drops showed a stronger prediction for unfavourable outcome compared to systolic or diastolic pressure drops. Furthermore, absolute blood pressure values had stronger associations compared to blood pressure values relative to preinterventional levels. By conducting ROC curve analysis, we confirmed that the strongest predictive blood pressure-related value for unfavourable outcome was a mean arterial pressure below 59.5 mmHg (sensitivity 0.60, specificity 0.63, Youden's Index 0.23, positive predictive value 0.60, negative predictive value 0.63, **figure 6**).

We also performed an ordinal shift analysis of mRS values at three months and could clearly confirm worse outcomes for patients with mean arterial pressure drops below 60 mmHg ($p<0.01$, **figure 7**). When comparing patients with and without such blood pressure drops, we found no differences either in demographic, clinical or radiological variables between those groups, making significant confounders among the investigated parameters unlikely (**table 4**).

Table 3: Blood pressure values and drops in relation to three-months outcome (published in part [87])

	Study cohort n=115	**mRS 0-2** n=59 (51.3%)	**mRS 3-6** n=56 (48.7%)	**p-value**
Preinterventional blood pressure				
Preinterventional SAP (mmHg, mean±SD)	150±26	149±26	152±27	0.54
Preinterventional MAP (mmHg, mean±SD)	107±20	106±20	107±21	0.73
Preinterventional DAP (mmHg, mean±SD)	81±15	80±14	81±16	0.75
Average periinterventional blood pressure				
Average SAP (mmHg, mean±SD)	123±17	124±17	123±17	0.60
Average MAP (mmHg, mean±SD)	80±14	82±12	79±16	0.17
Average DAP (mmHg, mean±SD)	60±9	61±10	59±9	0.16
Minimal periinterventional blood pressure				
Minimal SAP (mmHg, mean±SD)	87±20	89±22	86±19	0.39
Minimal MAP (mmHg, mean±SD)	60±12	62±12	58±12	0.13
Minimal DAP (mmHg, mean±SD)	46±9	48±10	45±8	0.10
Lowest blood pressure relative to preinterventional values				
Lowest relative SAP (mean±SD)	60±16%	58±16%	61±16%	0.32
Lowest relative MAP (mean±SD)	58±15%	56±15%	60±15%	0.16
Lowest relative DAP (mean±SD)	59±15%	57±15%	61±15%	0.22
Severe single blood pressure drops				
SAP ever below 120 mmHg	112 (97.4%)	57 (96.6%)	55 (98.2%)	0.59
SAP ever below 100 mmHg	94 (81.7%)	46 (78.0%)	48 (85.7%)	0.28
SAP ever below 80 mmHg	55 (47.8%)	25 (42.4%)	30 (53.6%)	0.23
MAP ever below 80 mmHg	109 (94.8%)	55 (93.2%)	54 (96.4%)	0.44
MAP ever below 60 mmHg	66 (57.4%)	27 (45.8%)	39 (69.6%)	**0.01**
MAP ever below 50 mmHg	39 (33.9%)	17 (28.8%)	22 (39.3%)	0.24

Legend: DAP: diastolic blood pressure, MAP: mean arterial pressure, SAP: systolic blood pressure

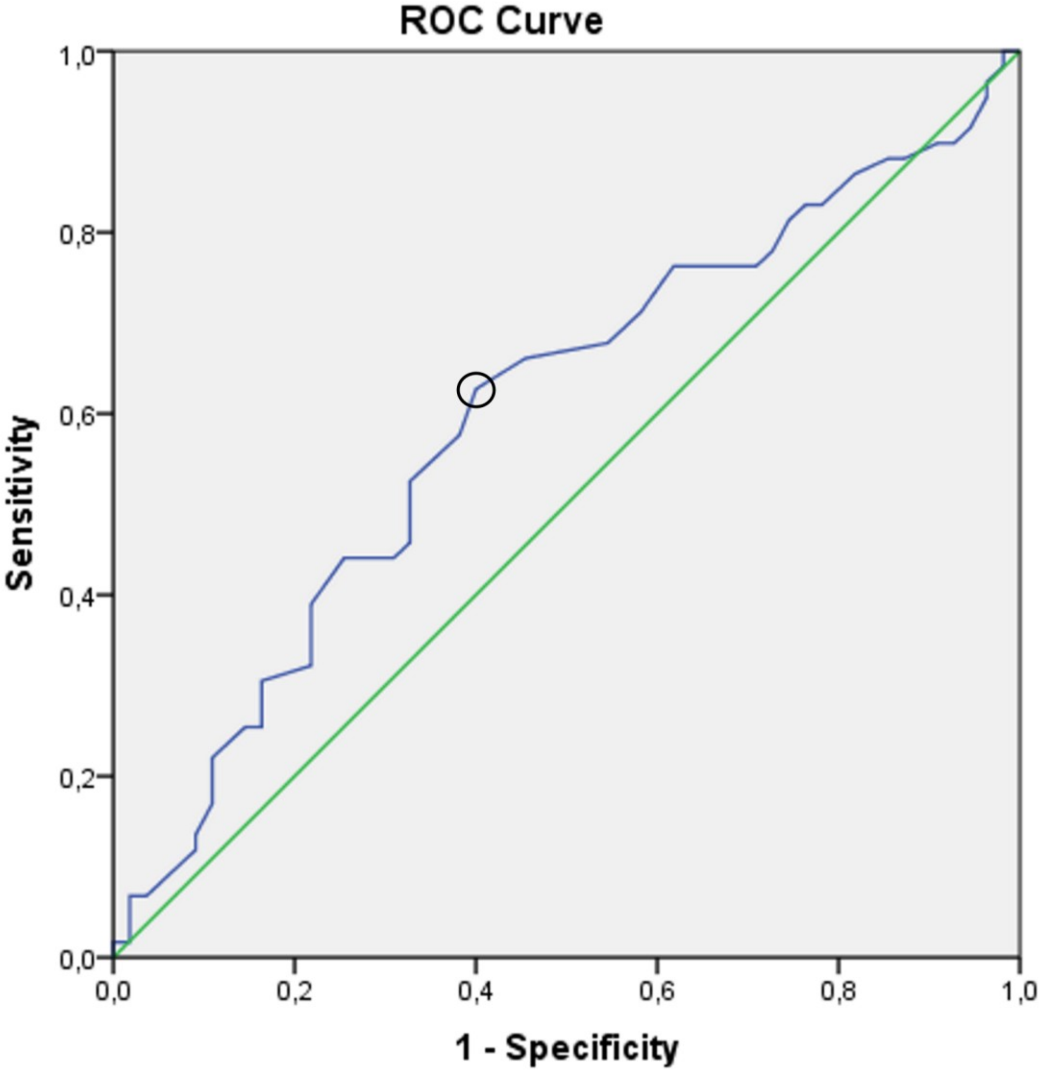

Figure 6: *ROC (Receiver operating characteristic) curve for minimal periinterventional mean arterial blood pressure compared to unfavorable patient outcome at three months, as published.*[87] *The highest Youden's Index is reached at 59.5 mmHg (black circle; Sensitivity 0.63, Specificity 0.60).*

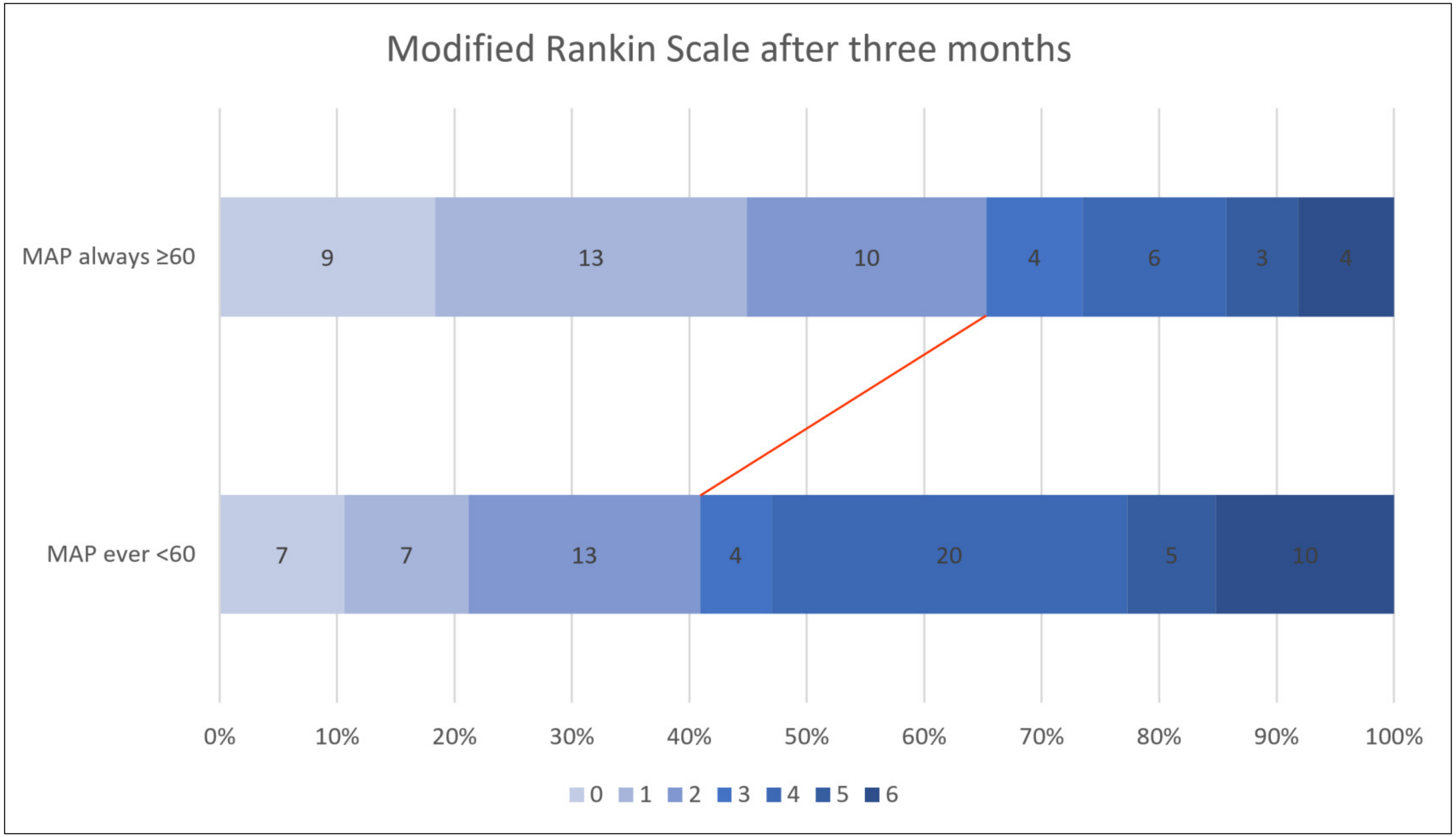

Figure 7: *Modified Rankin Scale scores at three months of patients without and with periinterventional MAP drops below 60 mmHg, the red line shows worse functional outcome (scores of 3-6) in patients with such drops (p<0.01), similarly published* [87]

Table 4: Comparison of patients with and without periinterventional MAP drops <60 mmHg (similarly published [87])

	MAP<60 mmHg n=66 (57.4%)	**MAP≥60 mmHg** n=49 (42.6%)	**p-value**
Clinical data			
Age (mean±SD)	66.3±12.6	64.0±13.5	0.36
Male sex	37 (56.1%)	27 (55.1%)	0.92
Hypertension	45 (68.2%)	27 (55.1%)	0.15
Dyslipidaemia	13 (19.7%)	4 (8.2%)	0.09
Chronic heart disease	8 (12.1%)	9 (18.4%)	0.35
Diabetes	10 (15.2%)	6 (12.2%)	0.66
Atrial fibrillation	26 (39.4%)	22 (44.9%)	0.55
Stroke of unknown symptom onset	16 (24.2%)	11 (22.4%)	0.82
NIHSS at admission (median, range)	14 (4-25)	15 (5-23)	0.82
Radiological findings			
MCA/M1-occlusion	49 (74.2%)	38 (77.6%)	0.68
MCA/M2-occlusion	6 (9.1%)	7 (14.3%)	0.38
Intracranial ICA occlusion	7 (10.6%)	4 (8.2%)	0.66
CTA collateral scoring (TAN, median, range)	2 (0-3)	2 (0-3)	0.26
ASPECTS pre-intervention (median, range)	9 (5-10)	9 (3-10)	0.45
Intervention			
Intravenous thrombolysis	36 (54.5%)	33 (67.3%)	0.17
Time to groin puncture (minutes, median, IQR)	208, 85	196, 85	0.19
Time to recanalization (minutes, median, IQR)	265, 81	245, 91	0.32
Anaesthesia duration (minutes, median, IQR)	120, 58	106, 57	0.12
Successful recanalization (TICI score 2b-3)	54 (81.8%)	41 (83.7%)	0.86
Post-intervention			
mRS 3 months post-stroke (median, range)	4 (0-6)	2 (0-6)	**<0.01**
Mortality at 3 months post-stroke	10 (15.2%)	4 (8.2%)	0.26
Periinterventional blood pressure			
Preinterventional SAP (mean±SD)	150.4±28.7	154.1±26.1	0.49
Preinterventional MAP (mean±SD)	105.5±21.9	109.6±16.2	0.30
Preinterventional DAP (mean±SD)	80.4±16.6	81.4±13.2	0.73
Minimal SAP (mean±SD)	77.9±20.0	100.0±12.5	**<0.001**
Minimal MAP (mean±SD)	53.6±10.4	68.9±7.6	**<0.001**
Minimal DAP (mean±SD)	42.1±7.7	51.6±7.8	**<0.001**
Average SAP (mean±SD)	118.2±17.0	130.6±15.0	**<0.001**
Average MAP (mean±SD)	76.3±10.8	86.0±15.8	**<0.001**
Average DAP (mean±SD)	56.5±8.6	65.0±7.9	**<0.001**

Legend: ASPECTS: Alberta Stroke Program Early CT Score, CTA: Computed tomography angiography, DAP: Diastolic blood pressure, ICA: Internal carotid artery, IQR: Interquartile range, MAP: Mean arterial pressure, MCA: Middle cerebral artery, NIHSS: National Institutes of Health Stroke Severity Scale, mRS: Modified Rankin Scale, SAP: Systolic arterial pressure, TICI: Thrombolysis In Cerebral Infarction

Collateral status, length of hypotensive periods

When investigating the influence of the collateral blood flow status, we found that in patients with poor collaterals (45.2% of the study cohort with TAN scale score of 0-1), periinterventional mean arterial pressure drops below 60 mmHg had a much more pronounced effect on unfavourable three-month outcome (Odds Ratio 4.29, 95% CI 1.12-16.39, p=0.03) compared to those patients with good collateral status (TAN scale score 2-3, Odds Ratio 1.88, 95% CI 0.61-5.81, p=0.28).

Regarding the duration of blood pressure drops, we found that in the 66 patients who had a mean arterial pressure drop below 60 mmHg, the drop had lasted for a mean of 8 minutes (interquartile range 2-15 minutes). We could not confirm an association between the length of hypotensive periods and functional outcome at three months post-stroke (either when calculating the length as a continuous variable or dichotomizing to different periods such as five, ten or ≥15 minutes).

Multivariable analysis

We calculated a multivariable logistic regression model for unfavourable outcome at three months post-stroke (defined as mRS values of 3-6) as the target variable, including all variables with a p-value of <0.1 in univariable analysis. The model showed that mean arterial pressure drops below 60 mmHg remained an independent predictor for unfavourable functional outcome (Odds Ratio 6.17, 95% CI 1.57-24.36, p<0.01), other predictive variables were age, diabetes, chronic heart disease, higher NIHSS at admission, lower preinterventional ASPECTS and unsuccessful recanalization (**table 5).**

When using backwards stepwise elimination modelling, diabetes was no longer a predictive variable for unfavourable outcome, mean arterial pressure drops below 60 mmHg remained as such (Odds Ratio 3.4, 95% CI 1.15-10.1, p=0.02) alongside the other variables stated above **(table 6)**.

Table 5: Binary multivariable logistic regression analysis regarding poor outcome (similarly published [87])

Test variable	Odds Ratio	95% Confidence Interval	p-value
Clinical data			
Age*	1.07	1.01-1.13	**0.03**
Hypertension	1.02	0.25-4.26	0.98
Diabetes	16.3	1.17-225.9	**0.04**
Chronic heart disease	9.29	1.31-65.96	**0.03**
NIHSS at admission*	1.27	1.07-1.49	**<0.01**
Radiological findings and intervention			
ASPECTS pre-intervention*	0.55	0.34-0.90	**0.02**
CTA collateral scoring (TAN)*	1.25	0.52-3.01	0.61
Duration of anaesthesia	0.99	0.98-1.01	0.41
Unsuccessful recanalization (TICI 0-2a)	23.2	2.17-247.9	**<0.01**
Periinterventional blood pressure drop			
MAP ever below 60 mmHg	6.17	1.57-24.36	**<0.01**

*Legend: ASPECTS: Alberta Stroke Program Early CT Score, MAP: Mean arterial pressure, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Severity Scale, TICI: Thrombolysis In Cerebral Infarction score, *per year/minute/point on respective scale*

Table 6: Binary multivariable logistic regression analysis regarding poor outcome using backwards stepwise elimination

Test variable	Odds Ratio	95% Confidence Interval	p-value
Clinical data			
Age*	1.05	1.01-1.10	**0.02**
Diabetes	4.7	0.73-30.3	0.10
Chronic heart disease	6.05	1.31-27.9	**0.02**
NIHSS at admission*	1.28	1.13-1.46	**<0.01**
Radiological findings and intervention			
ASPECTS pre-intervention*	0.68	0.49-0.94	**0.02**
Unsuccessful recanalization (TICI 0-2a)	9.42	1.46-60.7	**0.02**
Periinterventional blood pressure drop			
MAP ever below 60 mmHg	3.4	1.15-10.1	**0.02**

*Legend: ASPECTS: Alberta Stroke Program Early CT Score, MAP: Mean arterial pressure, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Severity Scale, TICI: Thrombolysis In Cerebral Infarction score, *per year/minute/point on respective scale*

3.2 Project 2: Ventilation time

Study cohort characteristics

We were able to include 447 patients in this study (mean age 69±13 years, 50.1% female), in 441 of which we had follow-up outcome data at three months post-stroke available. Hypertension was the most prevalent stroke risk factor (prevalent in 69.6% of patients), followed by atrial fibrillation (41.3%). The median NIHSS was 15 (interquartile range 11-18), two thirds of the patients (65.3%) had an occlusion of the M1 segment of the middle cerebral artery. The median time between onset of stroke symptoms to groin puncture was 200 minutes, 20.4% of patients had a stroke of unknown onset **(table 7)**.

58.6% of patients were also treated with intravenous thrombolysis, successful recanalization (TICI score 2b-3) was achieved by mechanical thrombectomy in 88.5% of patients after a mean 260 minutes from stroke onset. Periinterventional dissections were rare (2.7%).

Patient outcome

188 patients (42.6%) reached a favourable outcome (mRS 0-2) at the follow-up examination three months post-stroke. Among clinical risk factors, arterial hypertension, chronic heart disease, diabetes and atrial fibrillation were significantly associated with unfavourable outcome at three months. Other factors related to unfavourable outcome were higher age, higher pre-stroke mRS, higher NIHSS at admission and unsuccessful recanalization (**table 7**).

Ventilation time

The median ventilation time in our study cohort was three hours (with a range from 1-530 hours). 256 patients (58.0%) were extubated within six hours (“early extubation”). Another 121 (27.4%) had a delayed extubation (6-24 hours), while 65 patients (14.5%) were extubated after 24 hours (“late extubation”).

There was a positive correlation between lower duration of mechanical ventilation and better functional outcome at three months post-stroke, measured with the modified Rankin Scale (Spearman's Rho=0.39, $p<0.001$). Inversely analysed, patients with favourable outcome at three months had significantly lower median ventilation times (2 hours, IQR 1-6 compared to 11 hours, IQR 2-24 in patients with unfavourable outcome). Among patients with favourable outcome, early extubation was much more frequent, while delayed and especially late extubations were more common in patients with unfavourable outcome (**table 7**).

Table 7: Clinical data and timing of extubation in the study cohort and regarding three-month outcome (similarly published [88])

	Study Cohort n=441	**mRS 0-2** n=188 (42.6%)	**mRS 3-6** n=253 (57.4%)	**p-value**
Clinical data				
Age (years, mean±SD)	69.1±13.3	64.3±13.4	72.4±12.2	**<0.001**
Male sex	220 (49.9%)	96 (51.0%)	124 (49.0%)	0.67
Arterial hypertension	307 (69.6%)	106 (56.4%)	201 (79.4%)	**<0.001**
Dyslipidaemia	98 (20.7 %)	39 (20.7%)	59 (23.3%)	0.52
Chronic heart disease	84 (19.0 %)	26 (13.8%)	58 (22.9%)	**0.02**
Diabetes mellitus	73 (16.6%)	19 (10.1%)	54 (21.3%)	**0.002**
Atrial fibrillation	182 (41.3%)	60 (31.9%)	122 (48.2%)	**0.001**
Stroke of unknown symptom onset	90 (20.4%)	35 (18.6%)	55 (21.7%)	0.42
Pre-stroke mRS (median, IQR)	0 (0-0)	0 (0-0)	0 (0-0)	**<0.001**
NIHSS at admission (median, IQR)	15 (11-18)	13 (9-16)	16 (13-19)	**<0.001**
MCA/M1-occlusion	288 (65.3%)	122 (64.9%)	166 (65.6%)	0.88
MCA/M2-occlusion	59 (13.4%)	32 (17.0%)	27 (10.7%)	0.06
Intracranial ICA occlusion	93 (21.1%)	31 (16.5%)	62 (24.5%)	0.05
Acute stroke treatment				
Intravenous thrombolysis	258 (58.6%)	118 (62.8%)	140 (55.6%)	0.13
Symptom onset to groin puncture (minutes, median, IQR)	200 (160-247)	200 (158-244)	200 (160-252)	0.61
Symptom onset to recanalization (minutes, median, IQR)	260 (215-310)	250 (204-303)	266 (225-315)	0.42
Successful recanalization (TICI score 2b-3)	385 (88.5%)	181 (97.3%)	204 (81.9%)	**<0.001**
Periinterventional dissection	12 (2.7%)	8 (4.3%)	4 (1.6%)	0.09
Timing of extubation				
Time to extubation (hours, median, range)	3 (1-530)	2 (1-115)	11 (1-530)	**<0.001**
Early extubation (within 6 hours)	256 (58.0%)	142 (75.5%)	114 (45.1%)	**<0.001**
Delayed extubation (6-24 hours)	121 (27.4%)	41 (21.8%)	80 (31.6%)	**<0.001**
Late extubation (>24 hours)	64 (14.5%)	5 (2.7%)	59 (23.3%)	**<0.001**

Legend: ICA: Internal carotid artery, IQR: Interquartile range, MCA: Middle cerebral artery, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, TICI: Thrombolysis In Cerebral Infarction

Comparison between early, delayed, and late extubation

When comparing patients with early (≤6 hours) and delayed extubation (6-24 hours), there was no difference in demographics or clinical risk factors. However, patients with early extubation had strokes with unknown symptom onset more frequently (24.8% vs. 15.3%, p=0.04), and patients with delayed extubation had slightly higher NIHSS scores at admission (median 15 vs. 14, p<0.001). There were no differences regarding acute stroke treatment-related prognostic factors (treatment times, use of thrombolysis, rates of successful recanalization and periinterventional dissection, **table 8**). In direct comparison, early extubation was associated with favourable three-months outcome (Odds Ratio 2.40, 95% CI 1.53-3.76, p<0.001).

Patients with late extubation (>24 hours) showed no differences regarding age or sex, but more frequently had chronic heart disease (30.8% vs. 17.5%, p=0.01) and showed significantly higher NIHSS scores at admission (median 17 vs. 14, p<0.001) compared to patients with extubation within 24 hours. Those with late extubation were also treated with intravenous thrombolysis more frequently (70.8% vs. 56.2%, p=0.03) and had lower rates of successful recanalization by mechanical thrombectomy (76.6% vs. 90.5%, p=0.001). Favourable outcome was rare in this subgroup of patients (only 7.8% reached mRS scores of 0-2 after three months, **table 8**) and 90-day mortality was high (54.7%).

In ordinal mRS shift analysis, early extubation was associated with significantly better outcomes than both delayed and late extubation (p<0.001, **figure 8)**.

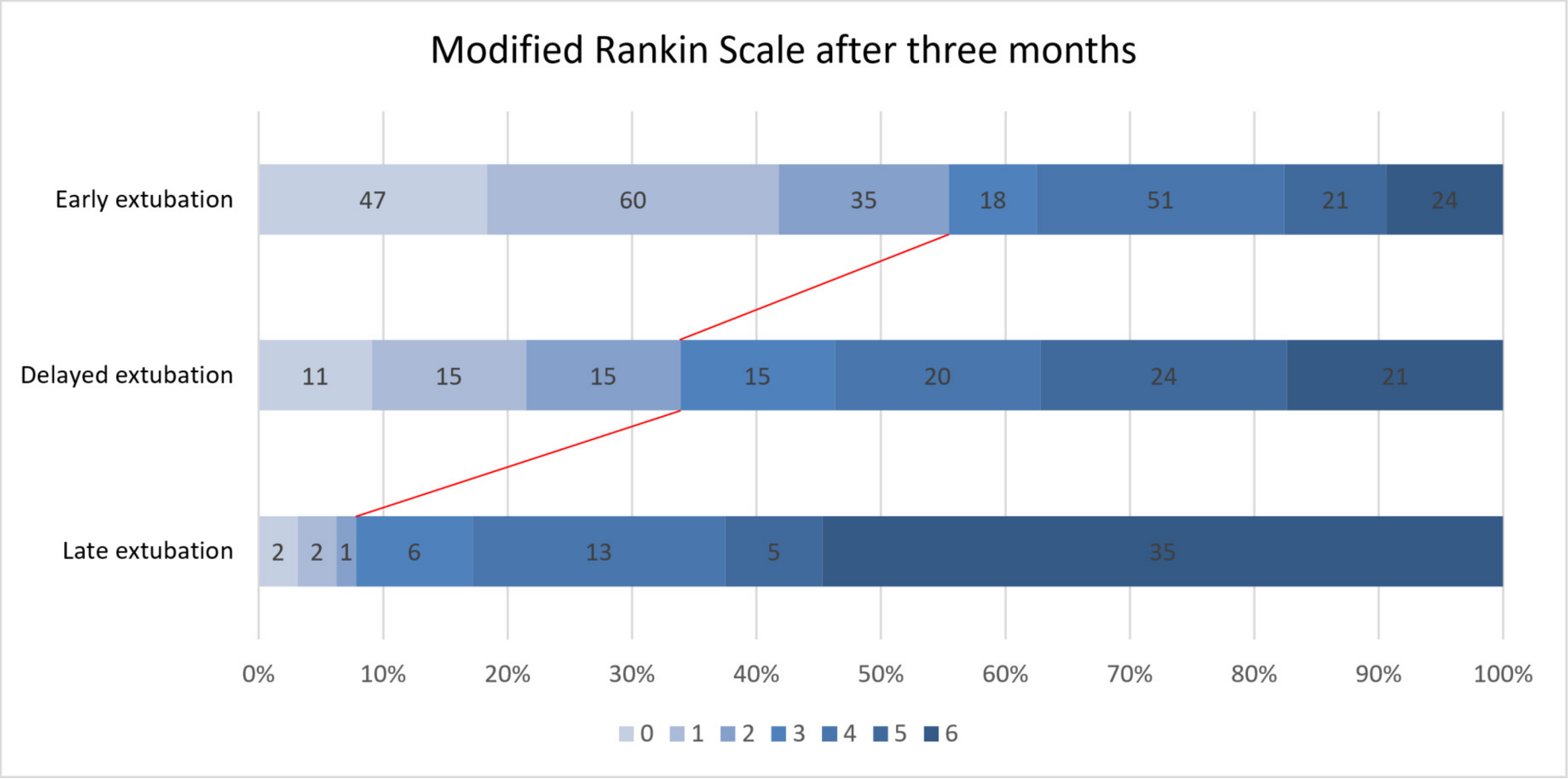

Figure 8: *Modified Rankin Scale scores at three months of patients with early (≤6 hours), delayed (6-24 hours) and late extubation (>24 hours), the red line indicates differences in proportions of patients with favourable outcome (scores of 0-2).*

Secondary outcome variables

The rate of early pneumonia within the neurointensive care unit/stroke unit stay was 15.8%. Longer ventilation time was strongly associated with a higher occurrence of early pneumonia; the median ventilation time was 15 hours in patients with pneumonia, while only three hours in those without ($p<0.001$). Patients with early extubation had the lowest pneumonia rates and significantly less compared to those with delayed extubation (9.6% vs. 20.6%, Odds Ratio 0.41, 95% CI 0.21-0.79, $p=0.007$). Similarly, patients with late extubation showed even higher rates of pneumonia (27.7%, Odds Ratio 2.49, 95% CI 1.76-4.69 compared to patients extubated within 24 hours, $p=0.004$, **table 8**).

Patients with late extubation had symptomatic intracranial haemorrhage more frequently (9.2% vs. 2.4%, $p=0.004$) and longer stays within the neurointensive care unit/stroke unit (median 6 vs. 3 days, $p<0.001$). Between patients with early and delayed extubation, there were no differences regarding those two outcome parameters. However, median NIHSS at discharge from neurointensive care unit/stroke unit was lowest in patients with early extubation (median 5, compared to 10 in patients with delayed extubation and 18 in those with late extubation), detailed information can be found in **table 8**.

Table 8: Clinical and outcome-related differences between patients with early, delayed, or late extubation (similarly published [88])

	Early extubation (≤6 hours) n=258 (57.7%)	**Delayed extubation (6-24 hours)** n=124 (27.7%)	**p-value**	**Late extubation (>24 hours)** n=65 (14.5%)	**p-value***
Clinical data					
Age (years, mean±SD)	68.6±13.3	70.8±13.2	0.15	67.6±13.4	0.34
Male sex	132 (51.2%)	67 (54.0%)	0.34	35 (53.8%)	0.52
Arterial hypertension	172 (66.7%)	92 (74.2%)	0.14	49 (75.4%)	0.31
Dyslipidaemia	59 (22.9%)	32 (25.8%)	0.53	8 (12.3%)	**0.04**
Chronic heart disease	42 (16.3%)	25 (20.2%)	0.35	20 (30.8%)	**0.01**
Diabetes mellitus	37 (14.3%)	21 (16.9%)	0.51	16 (24.6%)	0.06
Atrial fibrillation	99 (38.4%)	59 (47.6%)	0.09	27 (41.5%)	0.98
Stroke of unknown symptom onset	64 (24.8%)	19 (15.3%)	**0.04**	8 (12.3%)	0.08
Pre-stroke mRS (median, IQR)	0 (0-0)	0 (0-0)	0.12	0 (0-1)	**0.02**
NIHSS at admission (median, IQR)	14 (10-17)	15 (13-18)	**<0.001**	17 (14-19)	**<0.001**
MCA/M1-occlusion	172 (66.7%)	80 (64.5%)	0.68	41 (63.1%)	0.65
MCA/M2-occlusion	37 (14.3%)	18 (14.5%)	0.96	4 (6.2%)	0.07
Intracranial ICA occlusion	49 (19.0%)	25 (20.2%)	0.79	20 (30.8%)	**0.04**
Admission outside core working hours	111 (43.0%)	102 (82.3%)	**<0.001**	43 (66.2%)	0.12
Intervention					
Intravenous thrombolysis	147 (57.2%)	67 (54.0%)	0.56	46 (70.8%)	**0.03**
Time to groin puncture (minutes, median, IQR)	195 (154-245)	210 (169-250)	0.16	204 (160-254)	0.78
Time to recanalization (minutes, median, IQR)	250 (204-306)	279 (233-324)	0.06	277 (222-302)	0.94
Successful recanalization (TICI score 2b-3)	235 (92.5%)	106 (86.2%)	0.05	49 (76.6%)	**0.001**
Periinterventional dissection	10 (3.9%)	2 (1.6%)	0.24	0 (0%)	0.15
Outcome parameters					
Pneumonia rate within NICU/Stroke Unit	20 (9.6%)	22 (20.6%)	**0.007**	18 (27.7%)	**0.004**
Symptomatic intracranial haemorrhage	7 (2.7%)	2 (1.6%)	0.51	6 (9.2%)	**0.004**
Duration of stay in the NICU/Stroke Unit (days, median, IQR)	3 (2-6)	4 (2-5)	0.86	6 (2-11)	**<0.001**
NIHSS at discharge from NICU/Stroke Unit (median, IQR)	5 (2-12)	10 (5-18)	**<0.001**	18 (10-22)	**<0.001**
mRS three months post-stroke# (median, IQR)	2 (1-4)	4 (2-5)	**<0.001**	6 (4-6)	**<0.001**
Favourable outcome at three months (mRS 0-2)	142 (55.5%)	41 (33.9%)	**<0.001**	5 (7.8%)	**<0.001**

*Legend: ICA: Internal carotid artery, IQR: interquartile range, MCA: Middle cerebral artery, NICU: Neurointensive care unit, NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin Scale, TICI: Thrombolysis In Cerebral Infarction, *calculated between patients with late extubation vs. early or delayed extubation, #six patients were lost to follow-up*

Multivariable analysis

We calculated a multivariable logistic regression model to further investigate the effect of early vs. delayed extubation towards favourable outcome at three months post-stroke as the target variable, entering all baseline variables with a p-value of <0.1 in univariable analysis **(table 7)**. The model showed that early extubation remained a significant predictor of favourable outcome after three months (OR 1.93, 95% CI 1.14-3.27, p=0.01), alongside successful recanalization (OR 6.11, 95% CI 2.07-18.0, p=0.001), lower age (OR 0.96 per year, 95% CI 0.94-0.98), lower NIHSS scores at admission (OR 0.91 per point, 95% CI 0.86-0.96, p<0.001) and lower pre-strokes mRS scores (OR 0.70 per point, 95% CI 0.50-0.99, p=0.04, **table 9**).

When using stepwise elimination, the model remained essentially unchanged with early extubation, successful recanalization, lower age, NIHSS at admission and mRS pre-stroke predicting favourable three-months outcome **(table 10)**.

Table 9: Binary multivariable logistic regression analysis regarding favorable outcome in patients who were extubated within 24 hours

Test variable	Odds Ratio	95% Confidence Interval	p-value
Clinical data and intervention			
Age (per year)	0.96	0.94-0.98	**<0.001**
Pre-stroke mRS (per point)	0.70	0.50-0.99	**0.04**
Hypertension	0.68	0.38-1.21	0.19
Diabetes	0.60	0.29-1.23	0.16
Atrial fibrillation	0.78	0.47-1.30	0.34
Chronic heart disease	0.75	0.39-1.47	0.41
NIHSS at admission (per point)	0.91	0.86-0.96	**<0.001**
MCA/M2-occlusion	1.14	0.56-2.31	0.73
Intracranial ICA occlusion	0.73	0.39-1.37	0.37
Periinterventional management			
Successful recanalization (TICI 2b-3 vs. 0-2a)	6.11	2.07-18.0	**0.001**
Early extubation (within six hours vs. 6-24 hours)	1.93	1.14-3.27	**0.01**

Legend: ICA: Internal carotid artery, MCA: Middle cerebral artery, mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Severity Scale, TICI: Thrombolysis In Cerebral Infarction score

Table 10: Binary multivariable logistic regression analysis regarding favorable outcome in patients who were extubated within 24 hours using backwards stepwise regression (similarly published [88])

Test variable	Odds Ratio	95% Confidence Interval	p-value
Clinical data and intervention			
Age (per year)	0.95	0.93-0.97	**<0.001**
Pre-stroke mRS (per point)	0.66	0.47-0.93	**0.02**
NIHSS at admission (per point)	0.90	0.86-0.95	**<0.001**
Peri-interventional management			
Successful recanalization (TICI 2b-3 vs. 0-2a)	6.97	2.38-20.4	**<0.001**
Early extubation (within six hours vs. 6-24 hours)	1.93	1.15-3.24	**0.01**

Legend: mRS: Modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, TICI: Thrombolysis In Cerebral Infarction score

Reasons for delayed and late extubation

When investigating the clinical reasons for longer ventilation, we found that in the group of 65 patients with late extubation (>24 hours), the most important reasons for prolonged ventilation were brain oedema (44.6%) and insufficient alertness for other reasons (26.1%). Other reasons included respiratory insufficiency (15.9%), status epilepticus (4.6%) and oropharyngeal bleeding (3.1%, multiple reasons possible, **figure 9**). 16.9% of patients with late extubation did not have a documented medical reason for late extubation, all of those patients were extubated within 24-48 hours.

In the 121 patients with delayed extubation (6-24 hours), none of the patients had failed a wake-up trial. We found that delayed extubation was strongly associated with patient admission outside of core working hours. While 86.8% of patients were extubated early within core working hours, only 52.1% had an early extubation outside of core working hours (Odds Ratio 6.06 for early extubation within core working hours, 95% CI 3.59-10.22, p<0.001).

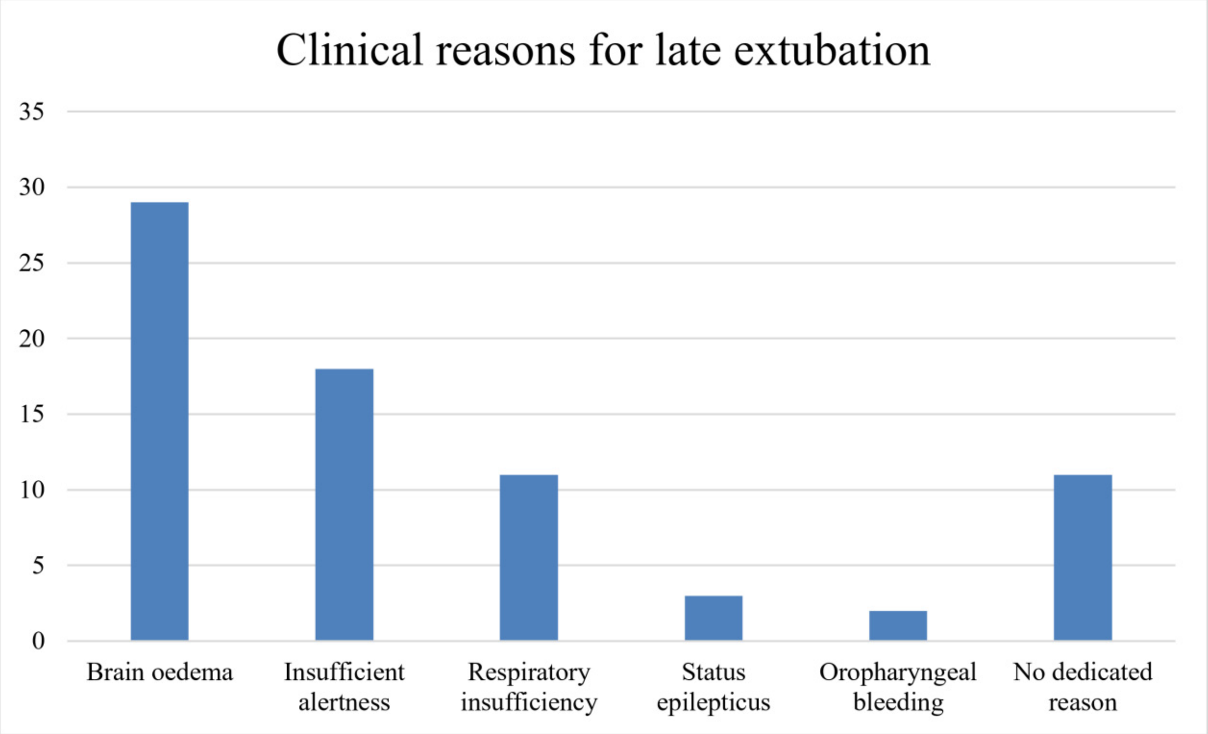

Figure 9: *Clinical reasons for late extubation (n=65)*

4 Discussion

4.1 Periprocedural blood pressure

In this cohort study, we were able to show that single mean arterial pressure drops below 60 mmHg during mechanical thrombectomy under general anaesthesia were associated with unfavourable functional outcome three months post-stroke. This association was independent of potential confounding factors and remained statistically significant in a multivariable model. As there are still many unclarities about the ideal periinterventional management during mechanical thrombectomy, this study adds a number of points to the current evidence.

In our study, we primarily focussed on single periinterventional blood pressure drops, opposed to average blood pressure values throughout the whole intervention. This is a significant methodological difference in the comparison to some of the previous studies on the influence of periinterventional blood pressure. Our results echo a Swedish study that found that severe blood pressure drops and not mean blood pressure levels were predictive of poor outcome.[62] We also analysed average periinterventional blood pressure values in our study cohort and did not find any association with patient outcome. A US study of a thrombectomy cohort managed in conscious sedation found both average blood pressure and single blood pressure drops to be associated with poor outcome.[64] Conversely, two post-hoc studies of trials comparing general anaesthesia and conscious sedation did not find any association of neither average nor single blood pressure drops with patient outcome. However, this could be explained by much more rigorous and prospectively defined blood pressure management.[65,66] In line with this, both studies report significantly higher average periinterventional blood pressure levels and less severe blood pressure drops than those found in either our or the previously discussed Swedish study.[62]

Our results point towards a higher relevance of absolute blood pressure values, compared to relative changes of pre-interventional blood pressure levels. While cerebral autoregulation is able to provide adequate blood flow to the brain between mean arterial pressures of 60-150 mmHg in physiological conditions,[68] it might be significantly impaired in acute stroke, mostly due to maximal dilatation of arterioles in the context of ischemia.[99,100] We found that mean arterial pressure drops below 60 mmHg had the strongest effect on unfavourable outcome, a point usually seen as the lower end of the autoregulatory capacity of the brain even in physiological conditions, where cerebral blood flow becomes directly dependent on mean arterial pressure. However, aside from pathological impairment of cerebral autoregulation, the individual autoregulatory curve of patients may also be shifted towards the right, particularly in patients with pre-existing severe arterial hypertension.[101] However, we did not find a difference concerning the effect of blood pressure drops in patients with or without previously known arterial hypertension in our cohort, but inter-individual differences might be difficult to distinguish and our study was not designed to investigate cerebral autoregulation in particular. Although impairment of cerebral autoregulation may vary between different cerebral pathologies,[101] our results correspond to earlier studies that showed that single systolic arterial pressure drops below 90 mmHg (approximately equivalent to a mean arterial pressure of 60) in patients with traumatic brain injury were also associated with worse patient outcome.[102]

A pivotal finding of our study is that mean arterial pressure drops showed stronger associations with outcome than systolic or diastolic changes. Currently, guidelines on the anaesthesiologic management of patients with endovascular treatment for acute ischemic stroke only point towards systolic and diastolic blood pressure targets, mean arterial pressure levels are not mentioned.[69] However, mean arterial pressure is the most significant blood pressure parameter regarding cerebral blood flow from a physiological and pathophysiological point of view.[100,103] Regarding the clinical management of patients with decreased mean arterial pressure, it is important to note that the component of diastolic pressure has more impact than systolic pressure. This means that elevation of diastolic pressure is likely to be both the easier and more effective method of increasing mean arterial pressure, which could be achieved particularly via intravenous administration of fluids in many cases. However, this intervention takes some time in most situations, which is a critical factor in the setting of anaesthesia induction within the angio suite, where time should not be wasted unless absolutely unavoidable. Too fast infusion of a large volume of fluids can cause significant side effects such as fluid overload and cardiac decompensation, especially in patients with renal or heart failure. However, it would be easily feasible to start early infusions of intravenous fluids within the emergency department before and during transfer to the angio suite, which would be especially important in patients with hypovolaemia.

Very recently, three new studies were published on the topic of periinterventional blood pressure management during mechanical thrombectomy. An US cohort study of 390 patients investigated the influence of periprocedural blood pressure not only on clinical outcome, but also on infarct growth and final infarct volume. Similar to the results of our study, this study found that while average blood pressure values throughout the intervention were not associated with patient outcome, significant blood pressure drops were predictive of worse outcome, greater infarct growth and final infarct volume. This study adds an important pathophysiological dimension not investigated by other studies before, showing that significant periprocedural hypotensive periods are not only associated with worse outcome, but also with larger infarct sizes (which are most likely responsible for the former).[104]

Furthermore, a systematic review on studies investigating periinterventional blood pressure was recently published. Although it was limited by varying definitions and reporting of blood pressure parameters as well as differing blood pressure monitoring, management and outcome parameters of included studies (as repeatedly discussed through this dissertation), it found that variously defined blood pressure drops were associated with poorer outcome in multivariable analyses.[105] Very recently, a pooled analysis of patient data from the three main randomized-controlled trials comparing general anaesthesia with conscious sedation in mechanical thrombectomy (SIESTA, ANSTROKE and GOLIATH, total n=365) found that critical thresholds of blood pressure drops that predicted poor outcome were a mean arterial pressure below 70 mmHg for more than ten minutes, or a mean arterial pressure below 90 mmHg for more than 45 minutes.[106] Those results, quite similar to those of our study, are particularly impactful as those three randomized-controlled trials have put a strong focus on anaesthetic quality and blood pressure management, and while analyses of the individual trials had not shown any effects of blood pressure drops on outcome,[65,66] the combined analysis was able to do so. This is most reasonably explained by an increased statistical power. Importantly, both recent studies used mean arterial pressure as the main blood pressure variable, also supporting our study's findings, as discussed above.

Most previous studies on periinterventional blood pressure during mechanical thrombectomy did not assess the pre-interventional collateral circulation of the brain. A post-hoc analysis of the GOLIATH trial found that low mean arterial pressure was a predictor of worse collaterals, which was measured using a modified ASITN (American Society of Interventional and

Therapeutic Neuroradiology) scale on conventional angiography before any thrombectomy attempts.[107] In other words, hypotension shortly after induction of anaesthesia (which is both when severe blood pressure drops occur most frequently, and when the first angiography is performed) was directly associated with worse collateral status. Furthermore, the study showed that larger doses of vasopressors used during mechanical thrombectomy were associated with higher volumes of infarct growth.[107] Again, large doses of vasopressors needed periprocedurally indicate that those patients had more severe blood pressure drops. In our study, we assessed pre-interventional collateral status using the TAN scale assessed by CT angiography just before mechanical thrombectomy. This means that periprocedural blood pressure values could not have influenced the collateral status as assessed in our study. However, we found that patients with worse pre-interventional collateral blood flow were even more prone to worse outcome when having severe blood pressure drops. This is an important observation and corresponds to pathophysiological considerations that patients with unfavourable collaterals are particularly vulnerable to decreases of cerebral perfusion pressure, which is especially deleterious in patients with a large vessel occlusion.[108]

The effect of mean arterial pressure drops below 60 mmHg on unfavourable outcome was quite pronounced in our study cohort, and remained significant in multivariable analysis besides well-established prognostic factors. Notably, there were no differences between patients with or without such blood pressure drops regarding demographic, clinical or treatment-related baseline factors. Therefore, our study implicates that critical blood pressure drops, especially below a mean arterial pressure of 60 mmHg, must be avoided during the periinterventional treatment of acute stroke patients. Although it could be assumed that longer durations of such severe hypotensive periods would cause more impact on brain tissue perfusion and therefore patient outcome (as shown in the previously discussed pooled data of the randomized-controlled trials on the method of anaesthesia[106]), we could not find such an effect. However, many hypotensive periods were rather short in our study and our study may have lacked statistical power to find statistically significant effects of their length on outcome. At the same time, it is noteworthy that the number of critical blood pressure drops was quite high in our study cohort, although both the severity and the frequency were very similar to the previously discussed retrospective Swedish study.[62] While blood pressure drops occurred less often in the randomized-controlled trials on periprocedural anaesthesia,[65,66] our data are more likely to represent a “real-world” scenario, compared to management of well-selected patients in the setting of randomized-controlled trials.

These findings may provide a possible explanation of the different performance of general anaesthesia compared to conscious sedation for mechanical thrombectomy between randomized-controlled trials and retrospective observational studies. It is more difficult to prevent significant hypotensive periods in general anaesthesia due to the necessity of higher doses of anaesthetic drugs with vasodilatory and cardio-depressive side effects in comparison to conscious sedation, which is particularly relevant during anaesthesia induction, where most of the critical blood pressure drops in our study occurred. This has been investigated both in prospective and retrospective studies investigating differences between general anaesthesia and conscious sedation, with more blood pressure drops occurring in patients treated under general anaesthesia.[106] Furthermore, hypotensive periods will likely occur more frequently in "real-life" settings such as our study cohort and other retrospective cohort studies compared to prospective studies specifically investigating anaesthesia management of mechanical thrombectomy. This could likely at least be a partial explanation why observational and retrospective studies have shown worse outcomes under general anaesthesia,[48–51] while meta-analyses of the randomized-controlled trials have indicated some possible advantages for general anaesthesia.[56–58]

It is largely unknown whether blood pressure targets should be different for patients treated under general anaesthesia or conscious sedation. Even though studies investigating blood pressure in patients under conscious sedation have yielded some different results compared to studies of patients under general anaesthesia, [64] many other study parameters were also different (e.g. definition of blood pressure drops, method of blood pressure monitoring, patient management, outcome parameters), therefore making it impossible to robustly determine the role of anaesthetic management. In this context, one previous study has indicated that even different types of anaesthetic drugs used may affect clinical outcome aside from blood pressure parameters.[71] Anesthesia type and periprocedural blood pressure may therefore not represent the only anesthesia-related factors relevant to patient outcome.

Several strengths of our study should be noted. Importantly, all patients were monitored using invasive blood pressure measurement, allowing for precise recordings of blood pressure and reducing artefacts associated with non-invasive sphygmomanometry. Blood pressure values were recorded at least every minute compared to every five minutes in most other studies. This means that we were able to identify occurrences and severity of blood pressure drops with much higher sensitivity, as some blood pressure drops may only be short and therefore not recognized in their severity (or not at all) when using a recording interval of every five minutes. This likely explains why our study identified even more critical blood pressure drops (below a mean arterial pressure of 60 mmHg) compared to most other studies, which mostly found higher cut-offs (such as an mean arterial pressure of 70 mmHg) associated with poor patient outcome.[106]

Another strength of our study is that we stringently excluded all patients without consistent electronic anaesthesia records or with any recording gaps, which indicates that the data quality of the core variable of study (blood pressure) can be assumed to be very good. On the other hand, this led to a rather high number of patients having to be excluded from this study. Therefore, we investigated potential differences between included and excluded patients in order to rule out potential selection biases. Notably, both groups showed almost no significant differences. The only difference was that patients excluded from the study had significantly higher NIHSS values at admission. This can reasonably be explained by the exclusion of patients that had been intubated prehospitally, as intubated patients usually have very high NIHSS values, which led to the overall difference in groups.

Furthermore, it is important to note that clinical parameters were recorded prospectively in our study as part of an ongoing thrombectomy register. Additionally, highly relevant radiological parameters such as collateral status and ASPECTS were available, allowing the comprehensive investigation of important outcome-related factors frequently missing in other studies, such as collateral circulation.

We also have to acknowledge important limitations. The retrospective analysis of this study comes with known drawbacks, although it limits potential observer effects, particularly regarding blood pressure. The rigorous inclusion criteria of our study led to a reduction in study size, limiting the statistical power. The deliberate uniformity of the study cohort also means that the generalizability of our finding to other settings (e.g. conscious sedation) is limited. In addition, we did not investigate the effect of different anaesthetic drugs, their doses and the usage of vasopressors on periinterventional blood pressure and patient outcome. We also did not analyse pre- and postinterventional blood pressure in detail.

The results of our study need to be considered in light of these strengths and limitations. Important open questions include clearer definitions of critical blood pressure cut-off values (and their duration), the influence of anaesthetic drugs and the differences between general anaesthesia and conscious sedation in “real-world” settings.

Larger, multi-centre studies involving patients treated with different anaesthetic forms, focussing not only on the differences between general anaesthesia and conscious sedation but including more detailed questions regarding periprocedural blood pressure and anesthetic techniques are required to answer those questions.

4.2 Ventilation time

In this cohort study of consecutive patients treated with mechanical thrombectomy for anterior circulation large vessel occlusion under general anaesthesia, we found that extubation delays after the procedure were associated with unfavourable functional outcome three months post-stroke. While we expected that patients with late extubation (>24 hours) would have worse clinical outcome, the most important finding of our study was that even within ventilation times below 24 hours, early extubation (within six hours) predicted favourable prognosis independent of other clinical variables.

Research on postinterventional critical care management of stroke patients treated with mechanical thrombectomy is scarce. In the single previous study investigating similar research questions compared to our study, the clinical impact of ventilation time after mechanical thrombectomy was investigated in 103 stroke patients. This German study found that patients who were ventilated for more than 24 hours had worse outcomes at three months and higher rates of pneumonia, but there was no such effect observed between the 58 patients who were intubated for a time period of less than 24 hours.[85] However, this study had several weaknesses, including the rather small sample size, retrospective data collection and missing information on reasons for prolonged ventilation. The median ventilation time was quite long with 18.5 hours, especially when compared to our study cohort with just three hours. A second small study did not investigate postinterventional management specifically, but aimed to identify risk factors for bad outcome in patients who were treated with mechanical thrombectomy under general anaesthesia. It found that patients extubated immediately after mechanical thrombectomy had better three-month outcomes.[86]

In our study, we found a strong dose-dependent effect of ventilation time on patient outcome. Most importantly, early extubation after mechanical thrombectomy was clearly associated with improved patient outcome. This novel and clinically relevant finding should influence the postinterventional management of patients treated with mechanical thrombectomy under general anaesthesia. It supports the practise of extubating stroke patients immediately after mechanical thrombectomy, either within the angio suite or shortly after admission at the intensive care unit, whenever safely possible.

Longer ventilation time could influence patient outcome for numerous reasons. One of the most important complications of ventilation in the setting of intensive care units is ventilator-associated pneumonia, the occurrence of which is strongly associated with the duration of ventilation.[109] This is in line with our results, which showed that patients with longer ventilation time had pneumonia during the stroke unit/neurointensive care unit stay more frequently. We specifically analysed pneumonia occurrence during that initial stay (and not the remaining hospital stay thereafter), as we aimed to assess pneumonia as a complication of mechanical ventilation, rather than stroke-associated pneumonia, which occurs at different time points during and after the hospital stay. In acute stroke patients, pneumonia is known to be associated with higher mortality, worse functional outcome and longer hospital stays.[110] One of the reasons for this is fever caused by pneumonia, which independently predicts worse outcome, as it can lead to elevated levels of free radicals in the brain tissue, breakdown of the blood-brain barrier, increased ischemia zones and brain oedema.[111]

Furthermore, delayed extubation means that anaesthetic and/or sedative drugs need to be administrated for longer periods. Most sedative drugs cause vasodilation and are cardio-depressive, therefore potentially resulting in hypotension, negatively affecting cerebral blood flow in the critical postinterventional period of reperfusion, which may lead to increased ischaemia and larger final infarct size. That again requires vasopressors to be given for longer periods and/or in higher doses, which might in turn impede cerebral blood flow.

In addition, ventilated patients in intensive care units often have hyperoxemia, which is generally associated with higher mortality in general intensive care unit cohorts,[112] but could specifically contribute to secondary brain injury in stroke patients.[113] This distinct point has been confirmed in a previous retrospective multicentre cohort study of ventilated stroke patients, which showed that hyperoxia was independently associated with higher in-hospital mortality.[114]

Other drawbacks of prolonged mechanical ventilation include the impracticality of early rehabilitative measures including mobilization in intubated patients. Early mobilization is recommended in stroke patients and has been shown to reduce the rate of stroke-associated pneumonia.[115] Furthermore, aetiological stroke work-up is also usually delayed in ventilated stroke patients, which may lead to increased rates of early recurrent cerebrovascular events, as potentially treatable sources may not have been identified early on.

When interpreting our work, one important confounding factor needs to be considered. Generally, physicians may be more reluctant to extubate patients in the postinterventional setting if they are in a worse overall state, including a perilous pre-interventional state, more severe strokes, failed recanalization, significant cardiopulmonary comorbidities or other markers of an expected critical disease course. We were able to confirm this in patients with late extubation (>24 hours), where we found different medical reasons, especially brain oedema, insufficient alertness and other neurological or respiratory stroke complications as important factors why earlier extubation attempts either failed or were not even attempted. Accordingly, these patients had much poorer outcome and a high mortality rate. The worse outcome can be primarily attributed to those clinical factors associated with a more critical disease course.

However, these factors did generally not apply to patients extubated within 24 hours. It is important to note that none of the patients with delayed extubation (6-24 hours) had failed an earlier wake-up trial and were still extubated on the same day, as it is usually common clinical practice to wait one day after a failed wake-up trial (to allow for recovery and potentially for diagnostic examinations, such as electroencephalography or brain CT). Conversely, we found a significant predictor of delayed extubation: Admission outside of core working hours. In this setting, there are generally fewer physicians available and fewer medical interventions are performed. For a critical care physician who admits a post-interventional stroke patient in their intensive care unit during the evening or night-time, it is often easier to continue with sedation and mechanical ventilation and delegate the extubation to the core managing team on the next morning, as numerous complications can occur during an extubation attempt and especially neurocritical care patients have a high rate of failed extubations (e.g. requiring re-intubation, which again is associated with serious complications).[116,117]

In this context, an analysis of a large US intensive care cohort using data from 2000-2009 showed that patients in intensive care units extubated during night-time had higher hospital mortality.[118] Conversely, numerous smaller cohort studies did not find worse outcomes of patients with night-time extubations, but associations with a shorter duration of mechanical ventilation and hospital stay.[119,120] In any way, it is important to note that not only medical considerations played a role in decisions regarding the timing of extubation after mechanical thrombectomy in our study cohort (and likely also elsewhere).

When comparing patients with early and delayed extubation, we found two other notable differences: Firstly, patients with early extubation had a stroke with unknown onset more frequently. Most of these strokes are wake-up-strokes, and the patients typically present to hospitals in the morning, which leads to high rates of admission during core work hours (and therefore higher rates of early extubation in our study cohort). Secondly, we found that patients with early extubation had slightly lower NIHSS scores at admission compared to patients with delayed extubation. However, after adjusting for this relevant factor in multivariable analysis, early extubation remained an independent prognostic factor for functional outcome three months post-stroke. Other than that, no differences between patients with early and delayed extubation regarding demographics, clinical risk factors and periinterventional factors including complications (such as periprocedural dissections or symptomatic intracranial haemorrhage) could be found.

Our study features several strengths: The large cohort of consecutive stroke patients allowed for reasonable statistical power, and the high follow-up rate reduced the risk of numerous biases. The detailed documentation of reasons for prolonged ventilation enabled us to investigate clinical factors influencing decisions regarding extubation.

However, a number of limitations also need to be considered. The retrospective setting of the study, as already discussed above, it the most important limitation in the interpretation of the results of our study. Although data were collected prospectively and we tried to exclude confounding factors as well as possible, different clinical reasons beside investigated variables may have played a role in decisions regarding the extubation of patients. Therefore, even though our study showed a strong association between early extubation and favourable outcome at three months, this study cannot prove causality due to the retrospective design.

Aside from this, we did not have detailed and uniform data regarding pre- und postinterventional imaging (e.g. to assess infarct size, infarct growth and intracranial haemorrhage systematically) and pre- and postinterventional blood pressure data available. Analyses of these factors would be important to further investigate postinterventional management of stroke patients treated with mechanical thrombectomy. Furthermore, our findings should not be translated to patients with vertebrobasilar artery occlusion treated with mechanical thrombectomy, which purposely we did not include in this study. Brainstem infarcts often affect numerous functional pathways responsible for swallowing, respiration and cough reflexes, and therefore negatively influence airway control and respiration.

In conclusion, we found that early extubation (within six hours) in patients treated with mechanical thrombectomy for anterior circulation large vessel occlusion independently predicted favourable outcome at three months compared to patients with delayed extubation (6-24 hours), and patients with late extubation (>24 hours) had particularly bad functional outcome. This is clinically relevant for the postinterventional management of stroke patients with anterior circulation large vessel occlusions, and indicates that extubation after mechanical thrombectomy should be performed as early as safely possible. However, due to the retrospective study design, our main findings should be considered as hypothesis-generating and need to be confirmed in prospective studies.

4.3 Conclusions and outlook

Our research adds several important points to the peri- and postintervention management of stroke patients treated with mechanical thrombectomy.

In our first project, we found that critical blood pressure drops during mechanical thrombectomy under general anaesthesia were associated with unfavourable long-term outcome. While the role of hypotension during mechanical thrombectomy was controversially discussed in earlier publications, recent publications have broadly found similar results as we did. This points towards an important reason why general anaesthesia for mechanical thrombectomy was often associated with worse outcome in retrospective and observational studies. However, as randomized-controlled trials on anaesthesia management have shown that such blood pressure drops can be avoided or at least reduced when more focus is put on anaesthesia quality and blood pressure management, this quality improvement could also be delivered to real-world patients.

Another possible disadvantage of general anaesthesia is the necessity of post-interventional management of a sedated, intubated and mechanically ventilated patient. In our second project, we were able to show that early extubation of stroke patients after mechanical thrombectomy (for anterior circulation large vessel occlusion) is strongly associated with better outcome compared to prolonged ventilation time. This aspect of the post-interventional management of stroke patients was under-investigated until now, and our results should influence the decision to extubate those patients early whenever safely possible.

However, it has to be recognized that general anaesthesia also has some advantages compared to conscious sedation – including lower periinterventional complications and potentially higher recanalization rates. If it is possible to mitigate the discussed drawbacks of general anaesthesia, such as the avoidance of critical periprocedural blood pressure drops and prolonged ventilation, advantages of general anaesthesia could be even more pronounced.

Of course, numerous open questions regarding the peri- and postinterventional management of stroke patients treated with mechanical thrombectomy remain. To further investigate differences between general anaesthesia and conscious sedation during mechanical thrombectomy, a multicentre randomized-controlled trial is currently recruiting patients.[121]

Moreover, the influence of anaesthetic drugs and their doses during both general anaesthesia and conscious sedation needs to be determined. Another important topic with open questions is the ideal post-interventional blood pressure management.[122] Furthermore, neuroprotective agents and the mitigation of potential reperfusion injury are hot topics in the pre-, peri- and postinterventional management of stroke patients with large vessel occlusion, with numerous compounds currently studied. Unfortunately, no agent was yet found to positively influence patient outcome in a large randomized-controlled trial.[123]

In conclusion, with swiftly rising numbers of mechanical thrombectomies performed in stroke patients worldwide, many aspects regarding the peri- and postinterventional management of these patients have risen. While many of these questions remain unanswered, we were able to show that the avoidance of critical blood pressure drops during and early extubation after mechanical thrombectomy are associated with favourable patient outcome, which indicates that these management strategies should be implemented in routine clinical care whenever individually possible.

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