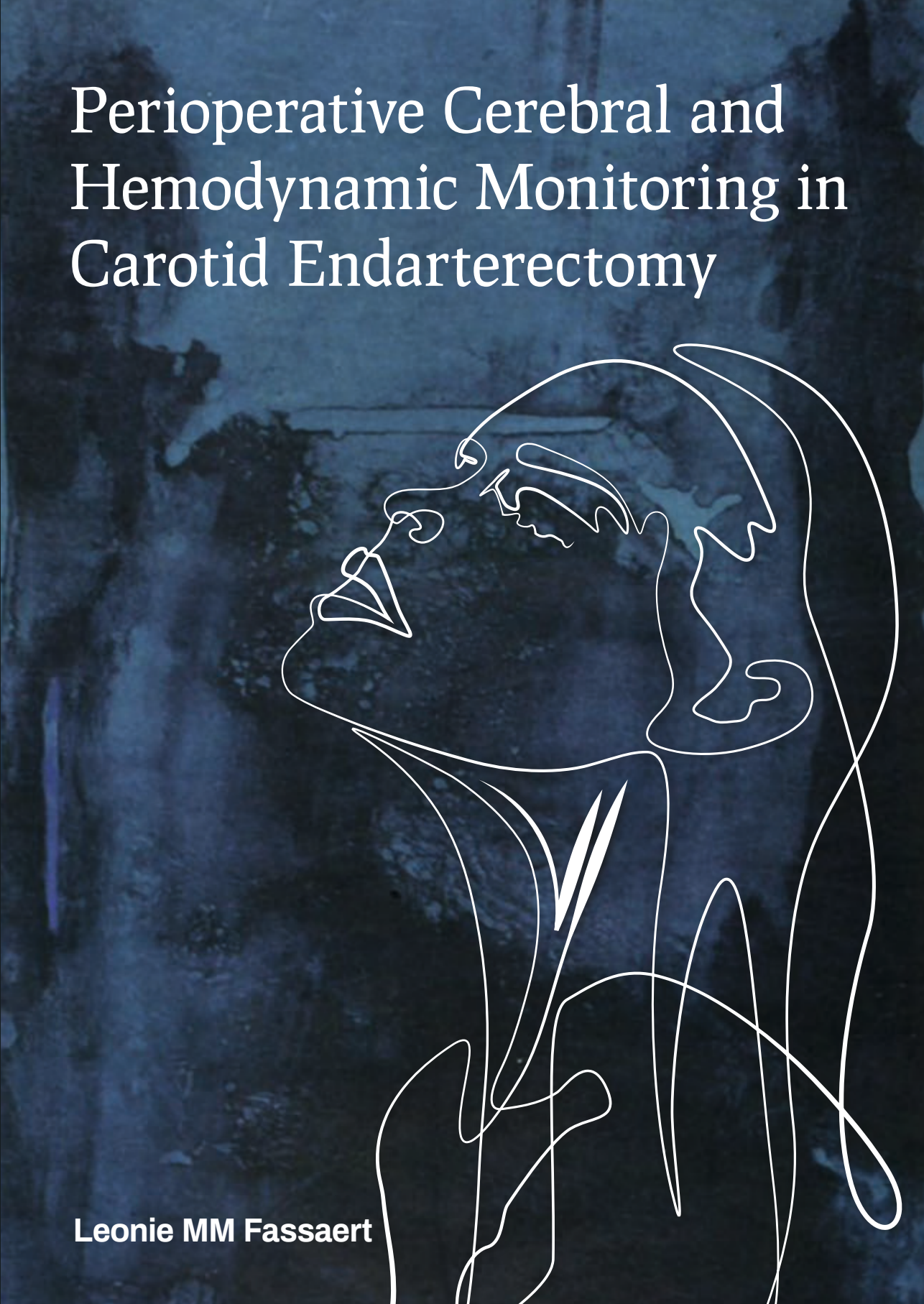
Perioperative Cerebral and Hemodynamic Monitoring in Carotid Endarterectomy



Leonie MM Fassaert

Perioperative Cerebral and Hemodynamic Monitoring in Carotid Endarterectomy

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Perioperative cerebral and hemodynamic monitoring in carotid endarterectomy
PhD thesis, Utrecht University, The Netherlands

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Perioperative Cerebral and Hemodynamic Monitoring in Carotid Endarterectomy

Cerebrale monitoring en hemodynamiek rondom carotis endarteriëctomie
(met een samenvatting in het Nederlands)

Proefschrift

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Leonie Madelein Maria Fassaert

geboren op 20 mei 1990
te ‘s-Hertogenbosch

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Prof. dr. G.J. de Borst

Copromotor:
Dr. R.V. Immink

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CHAPTER 1

General introduction and thesis outline

2.1 GENERAL INTRODUCTION

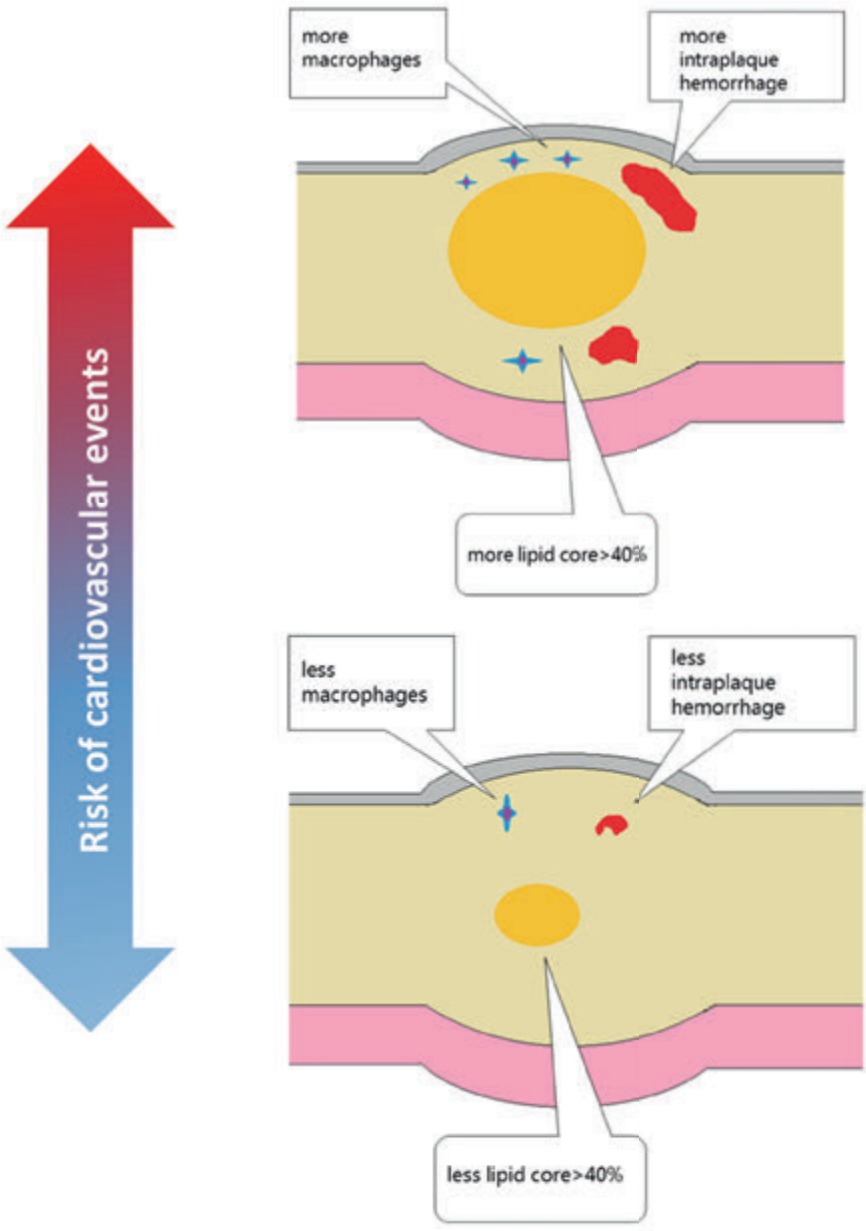
Atherosclerotic disease and carotid artery stenosis

Cardiovascular diseases (CVD), such as ischemic heart disease and stroke, account for one third of 56.9 million deaths from all causes globally in 2016.[1] Over 75% of CVD deaths occur in low- and middle-income countries and 85% of all CVD deaths are due to heart attacks and strokes.[1] Moreover, the number of deaths due to CVD increased significantly over the past ten years, due to a larger ageing population, exposure to a westernized diet and increasing rates of diabetes mellitus.[1,2] According to the World Health Organization ischemic heart disease and stroke are respectively the number one and two leading causes of mortality globally in the last 15 years.[1,3]

For the majority of CVD atherosclerosis is the underlying pathology. Atherosclerosis is a systemic lipid driven inflammatory disease of the arterial vessel wall. Early lesions of atherosclerosis consist of subendothelial accumulations of cholesterol-filled macrophages, so-called fatty streak lesions. These fatty streaks are the precursors of more advanced lesions containing smooth muscle cells and lipid-rich necrotic debris. Atherosclerotic lesions can develop into complex lesions with calcification and small vessels growing into the lesion, sometimes accompanied by intraplaque hemorrhage.[4] The presence of intraplaque hemorrhage is considered a high-risk factor for future cardiovascular events (CVE).[5] Intraplaque hemorrhage is, together with presence of a high number of macrophages, microvessels and a large lipid core, indicative for a more vulnerable plaque.[6] Vulnerable plaques are more likely to result in CVE. Increase of atherosclerotic plaque in the arterial lumen can slowly diminish proper tissue oxygenation by decreased blood flow. Acute luminal narrowing will occur after activation of blood platelets on an eroded or ruptured plaque surface and lead to newly formed thrombus. This can in its turn result in a total occlusion of more distally located vessels and consequently in sudden ischemic organ damage.[7] When cerebrally, this can be experienced as a transient ischemic attack or stroke.

Cerebral strokes can roughly be divided into ischemic strokes and hemorrhagic strokes; ischemic due to atherosclerotic disease, and hemorrhagic caused by rupture of an intracranial vessel. About 80% of all strokes are ischemic, and in one in five ischemic strokes the underlying cause is significant stenosis of the carotid artery.[8–10]

Figure 1. Risk of cardiovascular disease based on atherosclerotic plaque characteristics.



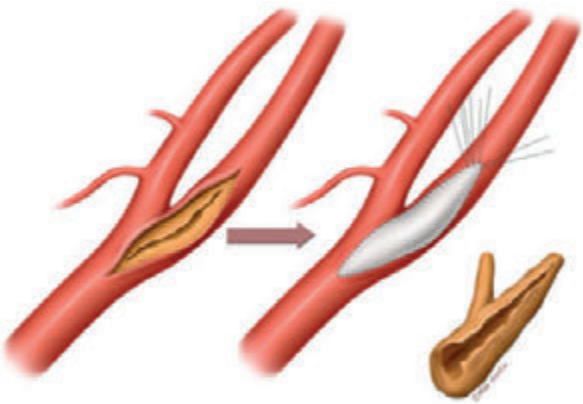
Current treatment of severe carotid artery stenosis

To prevent future neurologic events, carotid revascularization is in addition to best medical treatment, a well-studied and frequently used treatment option. Removal of the carotid plaque by carotid endarterectomy (CEA) is effective for severe symptomatic

carotid artery stenosis in reducing the risk of future stroke and stroke-related death.[11] Carotid artery stenting, although minimally invasive, is currently only performed in asymptomatic patients in clinical trials or in specific subgroups of symptomatic patients such as those at high-risk for surgery.[11]

The internal carotid arteries form together with the basilar artery and communicating arteries the circle of Willis and supply all parts of the brain of oxygenated blood. The cerebral oxygenation therefore strongly depends on adequate cerebral blood flow. During CEA, a surgical procedure of the extracranial carotid artery, the atherosclerotic plaque will be dissected from the artery wall by arteriotomy. By removing the atherosclerotic plaque of the internal carotid artery, the blood flow will be restored. Unfortunately, CEA is not without risk. Some patients will develop a stroke during or shortly after the procedure due to the procedure itself.[12] Thus, to benefit from CEA in the long term, it is critical to reducing the periprocedural risk to the bare minimum.

Figure 2. Principle of carotid endarterectomy



Current procedural monitoring

Periprocedural stroke

The mechanism of periprocedural strokes is multifactorial and comprises thromboembolic, cardio-embolic and hemodynamic events or a combination of those mechanisms.[10,13,14] A clinically relevant distinction between intraoperative stroke and postoperative stroke after a symptom-free interval can be made. Intraoperatively, the majority of strokes are the result of cerebral ischemia due to carotid clamping, embolization due to manipulation of the carotid artery or dissection of the atherosclerotic plaque and thrombosis of the artery during the closure. Changes in hemodynamics can also trigger a stroke. Intraoperative hypotension may lead to

cerebral hypoperfusion resulting in inadequate cerebral perfusion and subsequently ischemic cerebral compromise. Besides, hypoperfusion may contribute to a diminished wash-out of artery-to-artery emboli resulting in new ischemic lesions on diffusion-weighted imaging (DWI).[15–17]

The increased understanding of the mechanism underlying intraoperative strokes has led to improvements in surgical techniques, preoperative workup and use of cerebral monitoring.[11] Intraoperative monitoring modalities like electroencephalography (EEG), transcranial Doppler (TCD) and Near Infra-Red Spectroscopy (NIRS) are introduced to detect disturbances in cerebral blood flow, cerebral oxygenation, emboli detection and to assess the need for shunting during carotid cross-clamping and ensures continuous shunt function.[18–20] The use of these cerebral monitoring techniques can guide the surgeon to adjust the surgery technique or selectively shunt the carotid artery.[14,19] Although guidelines do not specifically recommend these modalities, they are frequently used in clinical practice.

Strict arterial blood pressure control is advocated to preserve adequate cerebral perfusion during CEA. Under physiological conditions, the cerebral blood flow will generally be unaffected by changes of the cerebral perfusion pressure or blood pressure with the help of cerebral autoregulation. However, in the majority of patients with severe carotid artery stenosis, both the cerebral autoregulation and baroreceptor sensitivity are impaired.[21,22] In these patients blood pressure disturbances cannot be counter-regulated by the brain vasculature, resulting in dependence of cerebral blood flow on systemic blood pressure.[10] This can be especially the case during carotid cross-clamping, when the cerebral blood flow depends on adequate collateral circulation through the Willis' circle and contralateral cerebral perfusion.[23,24] Despite the importance of adequate cerebral perfusion and knowledge that intraoperative hemodynamic disturbances have been associated with increased postoperative stroke risk, guidelines lack to recommend optimal hemodynamic thresholds intraoperatively.[10,25] Besides, the effect of intraoperative subtle blood pressure variations on periprocedural stroke is unknown. Therefore, more clarity regarding intraoperative blood pressure policies is warranted.

Strict arterial blood pressure control seems both important during CEA to preserve adequate perfusion and reduce postoperative stroke and also for CVE occurring in the years after CEA. There is mounting evidence that hypertension is associated with CVE. The risk of cardiovascular deaths increases gradually with increased systolic and diastolic blood pressure.[26] There seems to be a linear relation between high systolic blood pressure and stroke risk, in which a 10 mmHg reduction of systolic blood pressure

was associated with a one-third decrease of stroke incidence.[27,28] Also in secondary prevention increased blood pressure seems to be a risk factor for postoperative stroke/death.[29,30] Intensive blood pressure lowering is associated with a reduction of stroke and myocardial infarction.[31,32]

Despite hypertension is a clear cardiovascular risk factor, it is still unclear if hypertension is independently associated with vulnerable plaque characteristics like intraplaque hemorrhage.

Current postprocedural monitoring

The majority of postoperative strokes after CEA in symptomatic patients becoming apparent after a symptom-free interval following awakening from general anesthesia and are of hemodynamic etiology.[10,14] Postoperative hemodynamic disturbances due to impaired cerebral autoregulation and postoperative changes in cerebral hemodynamics can lead to ipsilateral cerebral hyperperfusion and subsequently cerebral hyperperfusion syndrome (CHS). CHS can occur between directly postoperatively up to 4 weeks postoperative and results in cerebral hemorrhage when left untreated.[33] Early recognition of cerebral hyperperfusion and strict blood pressure lowering therapy is highly effective in preventing CHS.[34,35]

Intraoperative TCD is considered the gold standard in identifying patients at risk of CHS by monitoring the increase of the blood flow velocity in the middle cerebral artery.[36] Additional two hours postoperative TCD measurement improved the prediction rate of CHS. Unfortunately, both TCD measurements are associated with both false positive and false negative results, which may result in overtreatment and increased hospital costs.[34,36,37] As a result, in the current guidelines there is no consensus on whether cerebral monitoring reduces 30-day death/stroke after CEA and is therefore not recommended.

Regarding postoperative hemodynamics, guidelines recommend monitoring blood pressure invasively for the first 3-6 hours, followed by hourly BP monitoring during the first 24 hours. However, no specific guidance is provided by the guidelines what postoperative accepted blood pressure thresholds or policy should be used, partly because of the difficulty to prove that specific hemodynamic monitoring policies directly affect clinical outcome.[25] As a consequence, the optimal postoperative blood pressure policy is an ongoing matter of debate in clinical practice. A suggested one fits all postoperative systolic policy for all CEA patients strikes the belief of individualized patient systolic thresholds based on the increase of cerebral blood flow measured by TCD.[38,39] To be able to reduce the postoperative stroke risk, further research on this topic is warranted.

2.2 THESIS OUTLINE

The research presented in this thesis evaluates the several aspects of periprocedural monitoring in carotid surgery. The improvements over the past years in carotid revascularization and current clinical practice were evaluated in part I. Intraoperative monitoring in the widest sense of the word are discussed in part II. In part III, various aspects of postoperative monitoring and management were evaluated to reduce the risk on perioperative neurologic complications and extend postoperative care outside of the hospital.

CHAPTERS & RESEARCH QUESTIONS

Part I – Current clinical practice

- What are the technical improvements in carotid revascularisation based on pathophysiological mechanism of stroke (chapter 2)?
- What are the current applied monitoring policies of all medical centres performing carotid endarterectomy in the Netherlands (chapter 3)?

Part II – Procedural monitoring

- What is the effect of vasopressor agents, administered to treat intraoperative hypotension, on the frontal lobe cerebral tissue oxygenation during surgery (chapter 4)?
- Is there an association between blood pressure and the presence of vulnerable plaque characteristics in the carotid atherosclerotic plaque (chapter 5)?
- What preoperative blood pressure measurements should be used to assess a definition of the 'awake baseline BP' (chapter 6)?
- Is there a relation between perioperative blood pressure and the presence of silent brain ischemia after carotid endarterectomy (chapter 7)?

Part III – Postprocedural monitoring

- Is there a role for postoperative non-invasive blood pressure monitoring over invasive blood pressure monitoring after carotid endarterectomy (chapter 8)?
- What is the predictive value of additional transcranial Doppler measurements 24 hours after surgery for the prediction of cerebral hyperperfusion syndrome (chapter 9)?
- What is the feasibly and patient experiences of daily BP-measurements at home during thirty days following hospital discharge after carotid endarterectomy (chapter 10)?
- Is there a place for a one fits all systolic blood pressure policy for postoperative blood pressure monitoring (chapter 11)?

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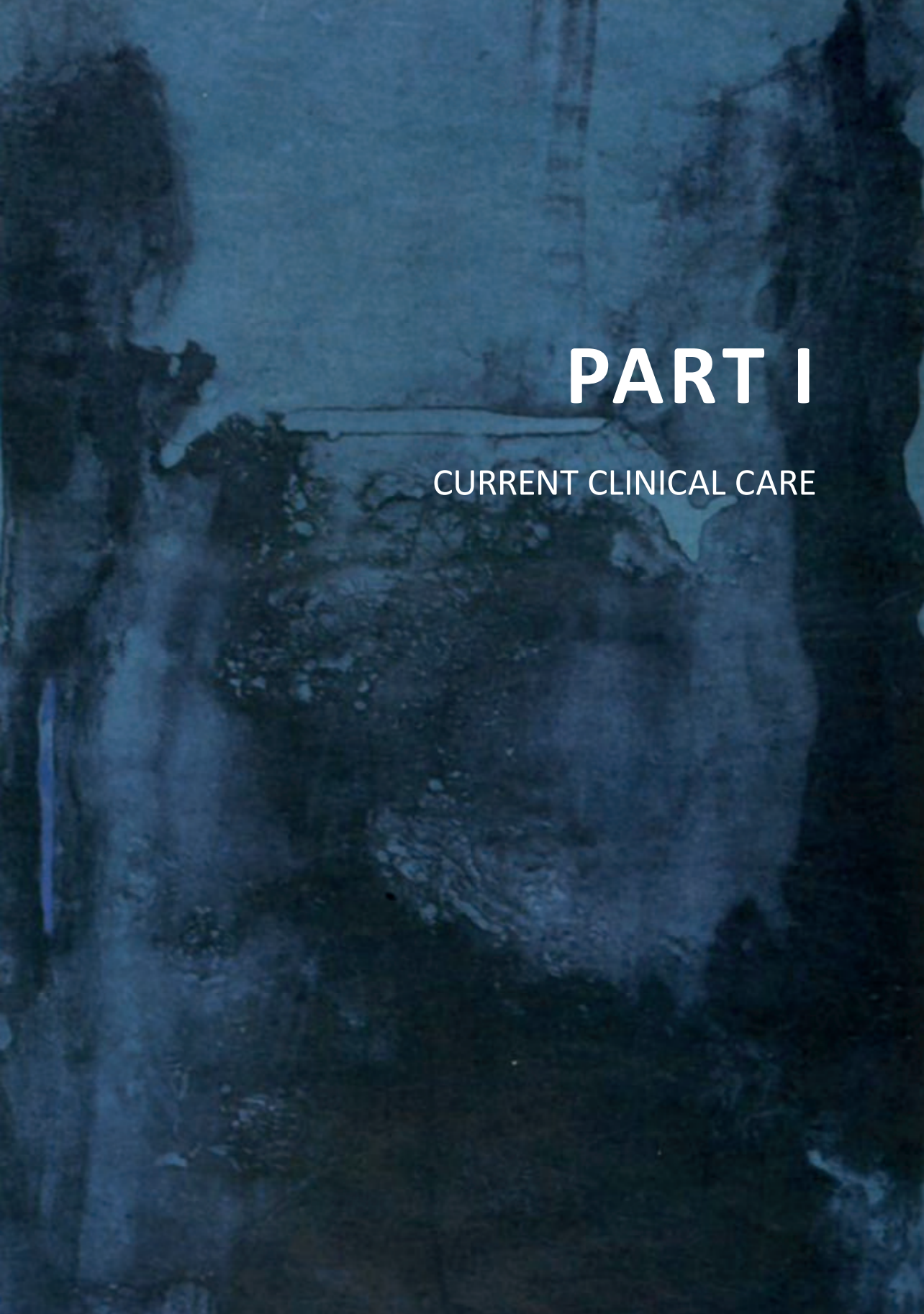

PART I

CURRENT CLINICAL CARE

CHAPTER 2

Technical improvements in carotid revascularization based on the mechanism of procedural stroke

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(Invited article)

ABSTRACT

The benefit of carotid revascularization in patients with severe carotid artery stenosis is hampered by the risk of stroke due to the intervention itself. The risk of periprocedural strokes is higher for carotid artery stenting(CAS) as compared to carotid endarterectomy(CEA). Over the past years, the pathophysiological mechanism responsible for periprocedural stroke seems to unfold step by step. Initially, all procedural strokes were thought to be the result of technical errors during surgical repair: cerebral ischemia due to clamping time of the carotid artery, cerebral embolization of atherosclerotic debris due to manipulation of the atheroma or thrombosis of the artery. Following improvements in surgical techniques, technical skills, new intraoperative monitoring technologies such as angioscopy, and the results of the first large clinical randomized controlled trials (RCT) it was believed that most periprocedural strokes were of thromboembolic nature, while a large part of these caused by technical error. Nowadays, analysis of underlying pathophysiological mechanisms of procedural stroke makes a clinically relevant distinction between intra-procedural and post-procedural strokes. Intra-procedural stroke is defined as hypoperfusion due to clamping (CEA) or dilatation (CAS) and embolization from the carotid plaque (both CEA and CAS). Post-procedural stroke can be caused by thrombo-embolization but seems to have a primarily hemodynamic origin. Besides thrombotic occlusion of the carotid artery, cerebral hyperperfusion syndrome (CHS) due to extensively increased cerebral revascularization is the most reported pathophysiological mechanism of post-procedural stroke.

Multiple technical improvements have attempted to lower the risk of periprocedural stroke. The introduction of antiplatelet therapy (APT) has significantly reduced the risk of thromboembolic events in patients with carotid stenosis. Over the years, recommendations regarding APT changed. While for a long time APT was discontinued prior to surgery because of a fear of increased bleeding risk, nowadays continuation of APT during carotid intervention (aspirin monotherapy or even dual APT including clopidogrel) is found to be safe and effective. In CAS patients, dual APT up to three months' post-procedural is considered best. Stent design and cerebral protection devices (CPD) for CAS procedure are continuously under development. Trials have suggested a benefit of closed-cell stent design over open-cell stent design in order to reduce procedural stroke, while the benefit of CPD during stenting is still a matter of debate. Although CPD reduce the risk of procedural stroke, a higher number of new ischemic brain lesions detected on diffusion weighted imaging was found in patients treated with CPD. In patients undergoing CEA under general anaesthesia, adequate use of cerebral monitoring (EEG and transcranial Doppler(TCD)) has reduced the number of intraoperative stroke by detecting embolization and thereby guiding the surgeon to

adjust his technique or to selectively shunt the carotid artery. In addition, TCD is able to adequately identify and exclude patients at risk for CHS. For CAS, the additional value of periprocedural cerebral monitoring to prevent strokes needs urgent attention.

In conclusion, this review provides an overview of the pathophysiological mechanism of stroke following carotid revascularization (both CAS and CEA) and of the technical improvements that have contributed to reducing this stroke risk.

INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity worldwide. Each year over 7 million people worldwide suffer an ischemic stroke.[1] One in five ischemic strokes is caused by carotid artery stenosis > 50%.[2,3] To prevent patients with severe carotid artery stenosis from future neurologic events, carotid revascularization in addition to best medical treatment is a well-studied treatment option.

INTRODUCTION CEA

In 1953 the first and successful carotid endarterectomy (CEA) was performed by DeBakey in a symptomatic patient suffering from repeated ischemic neurological events.[4] Several years later, the first single-centre consecutive series of performed CEAs described by Browse et al. showed that this treatment appeared to be advantageous with low rates of stroke and death (2.35% and 0.47%, respectively).[5,6] These relatively small series of CEA were followed by three large randomized controlled trials in the '90s, comparing CEA with optimal medical treatment for the treatment of symptomatic carotid artery stenosis. The risk of stroke following CEA in symptomatic patients within these trials was 6-8%.[7–9] Subsequent large randomized clinical trials comparing CEA with carotid artery stenting (CAS) (SPACE-trial, ICSS-trial, EVA-3S trial) reported a procedural risk of stroke after CEA of 3-6%.[10–12] In all clinical trials a significant reduction of ipsilateral stroke and perioperative stroke or death was seen in symptomatic patients treated by CEA combined with best medical treatment as compared to best medical treatment (BMT) alone. This benefit of surgical intervention increased with a higher degree of stenosis; moderate stenosis (50-69% stenosis) led to a 5-year risk reduction of stroke or death of 7.8% and high grade stenosis (70-99%) to a risk reduction of up to 17%.[8] Based on the results of these large clinical trials, CEA has become the standard treatment for symptomatic patients with severe carotid artery stenosis. Regarding asymptomatic patients, the ACST-1 trial randomized patients with severe asymptomatic carotid artery stenosis to either CEA or indefinite referral of surgery and reported a low risk of stroke of 2.7% in the CEA-arm.[13] This suggests that CEA can be considered as treatment for severe carotid artery stenosis in asymptomatic patients as well. Currently recruiting trials will help to determine the role of revascularization in asymptomatic patients and if so, what type of revascularization (CEA or CAS) is most appropriate.[14–16]

INTRODUCTION CAS

Nearly 30 years after the first CEA was performed, carotid angioplasty (CAS) for carotid stenosis was introduced as a non-invasive alternative. The first CAS for carotid artery

stenosis performed in a human was described by Kerber et al. in 1980.[17] A consecutive series of 110 CAS procedures published by Dietrich et al. in 1996, reported a high technical success rate of 89.1%, however this was accompanied by a neurological complication rate of almost 11%.[18] Potential benefits of carotid artery stenting (CAS) were shorter intervention and admission time. Moreover, the less invasive aspect of the procedure, since no surgical intervention is required, leads to avoidance of general anaesthesia and enables continuous neurological monitoring during the procedure. Unfortunately, over the past years several large clinical trials unambiguously reported a higher risk of stroke and death within 30 days after CAS than after CEA (SPACE-trial, EVA-3S trial, ICSS-trial).[10–12] The CREST-trial (Carotid revascularization endarterectomy versus stenting trial), including both symptomatic and asymptomatic patients, was the first clinical trial that showed an advantage in favour of CAS: the risk of myocardial infarction after carotid revascularization was reduced despite the increased stroke risk of CAS.[19] In patients younger than 70 years no significant difference was found between CAS and CEA in periprocedural stroke risk, however the number of patients in this age cohort was small in all RCTs.[11] A pooled meta-analysis with data of several large clinical trials (ICSS, CREST, EVA-3S and SPACE) confirmed these findings. CAS patients older than 80 years were four times more likely to suffer a procedural death/stroke.[20] (OR 4.15, 95% CI 2.20-7.84*)*

In 2010, The Carotid Stenosis Trialists' Collaboration (CSTC) published the short-term outcomes of pooled data of three large randomized clinical trials: EVA-3S, SPACE, and ICSS. The risk of stroke or death within 120 days of the procedure for CEA was 5.8% and for CAS 8.9% (risk difference 3.2% [95% CI 1.4-4.9]).[21]

Recently published 10-year follow-up of pooled RCT data on the long-term outcomes following carotid revascularization reports a similar annual rate of ipsilateral stroke per person per year for CEA (0.6%) and CAS (0.64%). However, a higher early stroke risk associated with CAS makes that the risk of any stroke or death up to 120 days and ipsilateral stroke thereafter up to 10 years, is favourable in CEA patients. This may suggest that when early stroke risk following CAS can be reduced to the minimum with optimal periprocedural safety, CAS might become a true competitive alternative for CEA.[22]

Up to now, guidelines only recommended CAS as an alternative to CEA in patients with severe carotid artery stenosis at low-risk for complications and high-risk for surgery. However, as a result of careful patient selection, improvements in technical skills, developments in stent design (open- or closed-cell design) and use of distal and proximal emboli protection devices, the results of the aforementioned large RCTS might

be considered slightly outdated and may no longer be representative of the current status of CAS.

In conclusion, both CEA and CAS are still hampered by the risk of stroke due to the intervention itself. To benefit from carotid revascularization on the long term, stroke prevention in the early phase is critical. To be able to reduce this risk to the bare minimum, understanding the mechanism of stroke related to carotid revascularization is of utmost importance.

MECHANISM STROKE CEA

The mechanism of periprocedural stroke depends on various factors, e.g. the type of revascularization, the onset of stroke (differentiating between intraoperative versus postoperative stroke), patient selection and hospital or operator volume. Mechanisms of stroke comprise thromboembolic, cardio-embolic or hemodynamic events or a combination of these. For a long time, a large part of procedural strokes were thought to be the result of technical errors. Cerebral ischemia due to clamping time of the carotid artery was expected to be the main cause. Other causes included embolization to the brain due to manipulation of the carotid atherosclerotic atheroma or thrombosis of the artery caused by a technical error during repair. Our group previously investigated the pathogenesis of perioperative stroke and the role of cerebral monitoring in the prevention of these strokes in an attempt to achieve more information about the mechanism of intraoperative versus postoperative stroke.[23] We found a clear difference between intraoperative versus postoperative stroke: in 599 single centre CEA patients under general anaesthesia, the majority of intraoperative strokes (n=4) were of ischemic origin due to embolization that were significantly reduced over time with help of electroencephalography (EEG) and transcranial Doppler (TCD). However postoperatively, most strokes after CEA were still caused by thrombus formation and occlusion of the carotid artery and thus not prevented over time by the application of standardized intraoperative cerebral monitoring (n=16).[23] In short, introduction of standardized cerebral monitoring significantly reduced the number of intraoperative strokes but did not alter the postoperative stroke rate.[23] Within the ICSS-trial, the incidence of stroke after CEA was 3.3% and in 78% of ischemic nature.[10] Although multifactorial in origin, the majority of strokes in patients with symptomatic carotid artery stenosis within this study occurred in the postoperative phase (56%), which is in accordance with the results found within our centre. These postoperative strokes were predominantly major and most often caused by cerebral hyperperfusion.[3] Within an asymptomatic trial cohort (ACST-1) most strokes in patients undergoing CEA occurred on the day of the procedure and were caused by thrombosis or thrombotic occlusion of the ipsilateral

carotid artery, emphasizing the importance of immediate post-stroke diagnosis to allow prompt intervention of the treated carotid artery.[13]

MECHANISM STROKE CAS

The pathophysiological mechanism of periprocedural stroke after CAS was also studied within the ICSS-trial.[3] A stroke rate in the CAS-arm of 7.3% was reported (compared to 3.3% in the CEA-arm). Strokes following CAS were more likely to occur on the day of the procedure. These strokes were predominately minor and most often ischemic strokes caused by a hemodynamic mechanism, followed by a carotid-embolic cause.[3] A previous ICSS substudy found a correlation between hemodynamic depression during CAS and periprocedural ischemia.[24] The mechanism of stroke following CAS in asymptomatic patients is still unknown. Interim analyses within the ACST-2 trial, randomizing between CAS and CEA in asymptomatic patients, reported a death/stroke rate of 1% for all patients. Unfortunately, no information regarding mechanism of stroke in ACST-2 has been reported yet.[15]

In order to reduce the periprocedural risk associated with carotid revascularization to the minimum, several periprocedural technical improvements have been introduced over the past years. These aspects will be addressed in the following chapters.

TECHNICAL IMPROVEMENTS CEA

General

Surgical techniques of carotid endarterectomy have barely changed over the past years. Most adjustments to reduce the risk of periprocedural stroke have been made in the preoperative work-up, patient selection and timing of the intervention. Improvements in intra- and postoperative hemodynamic and cerebral monitoring have altered perioperative care to its current form.

Patient selection

Adequate patient selection is crucial for reducing the risk of procedural stroke. The three critical pillars in adequate patient selection are symptomatology, the degree of carotid artery stenosis and careful consideration of the best possible treatment discussed within a multidisciplinary team of radiologists, neurologists and vascular surgeons. For symptomatic patients, timing of the intervention is now the fourth critical pillar. In deciding what patients are suitable for CEA, it is of utmost importance to identify what features increase or decrease the procedural risk.[25] In addition to the grade of stenosis, age influences the periprocedural stroke risk. In general, the risk of

adverse cardiovascular events increases with age, with myocardial infarction being the main driver. Therefore, in symptomatic patients ≥ 70 years of age with moderate to severe grade of carotid stenosis, CEA is preferred over CAS. In symptomatic patients younger than 70 years CAS may be considered as an alternative to CEA if the predicted procedural death/stroke rate is <6%.[25]

Regarding the preoperative work-up, angiography of the carotid arteries was the gold standard for a long time. Angiography at that time was not without any consequences as in the Asymptomatic Carotid Atherosclerosis Study (ACAS), half of all strokes were related to angiography.[26] This finding was strengthened by Bendszus et al. reporting a 23% rate of new ischemic brain lesions detected by diffusion weighted imaging (DWI) in patients undergoing consecutive diagnostic cerebral angiographies.[27] Over the past years, invasive imaging strategies have changed to non-invasive imaging techniques. Currently duplex ultrasound combined with CT-angiography or with MR-angiography is most widely used to evaluate stenosis severity and to provide additional information on the intra- and extracranial circulation.[25] With these techniques the risk of cardiovascular complications is virtually abandoned.

Antiplatelet therapy

Optimal medical therapy for primary and secondary prevention consists of lipid lowering, adequate blood pressure regulation and antiplatelet therapy (APT). APT strategies have evolved tremendously over the last decades. As roughly 80% of all cerebral ischemic events are thought to be of thromboembolic origin, APT has gained an important role in both secondary and tertiary prevention in patients with carotid artery stenosis. For secondary prevention, the use of low-dose aspirin monotherapy reduces the risk of thromboembolic events by 23% compared to patients without any APT.[28] Also in asymptomatic patients, APT in the form of low-dose aspirin is recommended to prevent late myocardial infarction and other adverse cardiovascular events.[28] Regarding tertiary prevention, a large trial published in the late 90s reported a relative risk reduction of 37% for stroke with dual antiplatelet therapy (DAPT) consisting of aspirin combined with dipyridamole relative to aspirin monotherapy.[29] The CAPRIE-trial showed that clopidogrel monotherapy was superior over aspirin monotherapy in reducing the risk of a combined end-point consisting of stroke, myocardial infarction or any vascular death in patients with atherosclerotic vascular disease (RRR 8.7%, p=0.043**).**[25,30,31] In 2008, the PRoFESS trial revealed that clopidogrel monotherapy was superior to aspirin and dipyridamole as DAPT in the prevention of recurrent stroke in symptomatic patients.[32]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial studied the efficacy and safety of

clopidogrel plus aspirin as DAPT compared with aspirin alone in patients with a high risk for cardiovascular events. They found no significant benefit of DAPT over aspirin monotherapy. For patients with established coronary, cerebral or peripheral arterial disease there was a suggestion of benefit from clopidogrel and a suggestion of harm for asymptomatic patients with multiple risk factors.[33]

Based on the results of the PRoFESS and the CHARISMA trial and with the knowledge of CAPRIE trial, clopidogrel monotherapy is now recommended as first-choice APT for the prevention of recurrent cerebral events.[31,32] For a long time, APT therapy prior to surgery was believed to be notorious for an increased risk of bleeding. Therefore, discontinuing ATP before surgery, risking a potentially increased risk of perioperative thromboembolic complications, was widely accepted as standard of care. However, several RCTs showed the beneficial effect of continuing APT prior to surgery in reducing the risk of stroke after CEA.[31,34] Nowadays, there is sufficient evidence that the beneficial effects of perioperative APT continuation outweigh the risk of bleeding. Current guidelines recommend APT continuation both throughout the perioperative period and during long term treatment in CEA patients.[25,35] Since the introduction of direct-acting oral anticoagulants (DOACs) as novel anticoagulating agents a few years ago, no data yet have been reported on perioperative DOAC therapy for CEA or CAS yet. Postoperatively, for tertiary prevention of recurrent stroke, clopidogrel is recommended in all CEA patients.

Among patients with stable peripheral atherosclerotic vascular disease, rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes (and more bleeding events) than aspirin monotherapy. Further investigation into the beneficial effects in atherosclerotic diseases (peripheral atherosclerotic vascular disease and carotid artery disease) is expected in the near future.[36]

Regarding the efficacy of the several perioperative heparinization strategies during CEA, to our knowledge no trial has attempted to investigate the benefit of either.[31]

Timing/window of surgery

Pooled post-hoc sub-analyses within randomized data of ECST and NASCET trials learned the benefit of surgery within 2 weeks after symptom onset: the number needed to undergo surgery to prevent one ipsilateral stroke in 5 years was five for patients randomized within 2 weeks versus 125 for those randomized after more than 12 weeks.[7,8] The risk of stroke was reduced with 30% when patients were operated within 2 weeks after their last event, while surgery performed after 4 weeks or later reduced this advantageous decrease of stroke-risk by one third.[37] Based on these analyses,

the current ESVS guideline recommends to perform carotid revascularization as soon as possible, preferably within 14 days after symptom onset.[25] This recommendation needs to be put in perspective as this 14-day threshold was selected for methodological convenience rather than clinical relevance and is subgroup specific. Additionally, none of the large recent RCTs comparing CEA with CAS had a timing between index event and revascularization within these 14 days. In addition, outcomes of very early CEA (<48 hours after index event) compared to early CEA within 14 days in respect of recurrent stroke have not yet been determined. Future trials must be performed to define the optimal time window for revascularization regarding stroke prevention.[38]

Intraoperative technical improvements

Type of anaesthesia

Several studies have investigated the influence of type of anaesthetics, regional and general anaesthesia, on the risk of 30-day death/stroke. General Anaesthesia versus Local Anaesthesia Trial (GALA-trial), the largest RCT on this subject, reported no significant difference regarding perioperative death, stroke or myocardial infarction (MI) between patients undergoing CEA under local regional anaesthesia compared to CEA under general anaesthesia. Therefore, guidelines recommend that type of anaesthesia during CEA is the choice of the surgical team.[25,39]

Surgical technique

In order to reduce the risk of periprocedural stroke, surgical techniques have slightly changed over the years. Several studies showed that the type of surgical technique to dissect the carotid artery, differentiating between eversion and longitudinal arteriotomy, did not contribute to reducing intraoperative stroke in CEA patient.[40] The choice between eversion and patched endarterectomy therefore is left to the discretion of the operating surgeon.[25]

Intraoperative cerebral monitoring & hemodynamics

In contrast to the low influence of surgical techniques on perioperative stroke reduction, the positive influence of cerebral monitoring has indeed been proven. The introduction of intraoperative cerebral monitoring by EEG and TCD has significantly reduced this intraoperative stroke rate in patients undergoing CEA under general anaesthesia.[23,41,42] The use of these cerebral monitoring techniques can guide the surgeon to adjust the surgical technique or to selectively shunt the carotid artery.[23,42] Intraoperative TCD monitoring is able to detect both macro- and micro embolization during the carotid mobilization and dissection phase. In addition, TCD is able to monitor the blood flow in the ipsilateral middle cerebral artery (MCA) which ensures continuous shunt function and may detect thrombosis of the treated artery by a progressive decline of flow in de

MCA and accumulating embolization. EEG, whether or not accompanied by TCD, has been proven to be of its additional value in shunt need in patients undergoing CEA under general anesthesia.[41,43]

Careful regulation of perioperative hemodynamics is required to maintain and preserve adequate cerebral perfusion during surgery. The presence of an experienced cardio-anaesthesiologist during carotid revascularization under general anaesthesia is of major importance. In both ICSS and ACST-1-trials, increased preoperative diastolic blood pressure (BP) turned out to be a risk factor for 30-day death/stroke in symptomatic and asymptomatic patients**.**[44,45] Intraoperatively, hypotension can lead to hypoperfusion and subsequently to ischemic stroke. To minimize the risk of intraoperative stroke, arterial BP has been advised to be kept between normal and 20% above baseline.[46] Surprisingly, the definition of 'baseline' is poorly described in literature and this recommendation therefore is multiple interpretable. Several trials studied the effect of intraoperative hypotension on clinical outcome. Within the MRI substudy of the ICSS trial, no significant association was reported between hemodynamic complications and 30-day death/stroke outcome in CEA patients. In addition, the hypothesis that intraoperative hemodynamic depression during CEA impaired the washout of emboli during revascularization causing a significant increase of new ischemic brain lesions, was not observed in CEA patients.[47,48] Important limitations of these studies that need to be addressed, are the lack of information regarding the exact used thresholds to define hemodynamic depression and the duration of hemodynamic depression. Therefore, future studies regarding intraoperative hemodynamics and stroke/new ischemic brain lesions are required.

Postoperative technical improvements

Postoperative cerebral monitoring & hemodynamics

The mechanism of stroke in the postoperative phase following CEA is suggested to be of hemodynamic origin in the majority of cases, mainly as a result of postoperative hypertension. ICSS reported a significantly higher rate of postoperative hypertension in CEA patients compared to CAS (8.3% vs 1.5%, $p<0.0001$).[48] Immediate strict (invasive) blood pressure therapy directly after surgery is required in all patients.

Impaired cerebral autoregulation and post-CEA triggered changes in cerebral hemodynamics are the assumed mechanism underlying cerebral hyperperfusion syndrome (CHS). Cerebral monitoring of the cerebral blood flow measured by TCD allows for early detection of cerebral hyperperfusion. While, intraoperative TCD is still considered the gold standard in identifying patients at risk of CHS,[43,49–51] adding an extra postoperative TCD measurement two hours after surgery improved the prediction

rate of CHS.[52] Due to a high negative predictive value of 99%, this technique can accurately exclude patients who are not at risk of CHS.[49] Hence, no patients needing strict BP therapy as treatment for cerebral hyperperfusion will be left untreated. As a consequence, only a small subset of CEA patients with TCD measured hyperperfusion require immediate and strict lowering of the maximum accepted BP threshold on a high care unit.[49] Patients without TCD identified hyperperfusion can be safely discharged without strict BP lowering measures. Treatment of postoperative hypertension in this patient group can be postponed to the ward or particularly to a follow-up visit at outpatient clinic.

Some believe a one fits all postoperative systolic blood pressure policy for all CEA patients will prevent for CHS.[41] As an alternative, by means of TCD based identification of patients at risk of CHS only a selection of all CEA patients will be treated to prevent CHS.

The benefit of cerebral monitoring is still doubted by some considering it is more time-consuming and costly than beneficial.[43] Within the current guidelines, there is no consensus on whether cerebral monitoring may reduce 30-day death/stroke after CEA.[25] Regarding blood pressure treatment, no specific guidance is provided concerning baseline blood pressure nor the maximum accepted periprocedural (intra- and postoperative) blood pressure thresholds.[25]

TECHNICAL IMPROVEMENTS CAS

General

Patient selection

For CAS, the risk of procedural stroke rises with increasing age, as a consequence of increasing plaque vulnerability in elderly patients.[53] Hence, guidelines recommend CAS only for symptomatic patients older than 80 years who are at high-risk of surgery (because of previous cervical radiation therapy or clinically unfit for surgery). CAS can be considered in these patients in case of restenosis after CEA.[25] *[ESVS guidelines]* In asymptomatic patients, patients with severe carotid stenosis (70-99%) and an expected procedural risk less than 3% and low to average risk for treatment can be selected for CAS over CEA or best medical treatment.[19,25,54] Future results of the Asymptomatic Carotid Surgery Trial (ACST-2) will provide more information on most appropriate treatment of asymptomatic patients.

Antiplatelet therapy

In order to reduce the risk of thrombotic embolization causing strokes during stenting and thrombosis or occlusion of the carotid artery after stenting, the use of APT has been

shown to be advantageous. Guidelines now recommend dual APT (DAPT) throughout and for up to three months following the carotid stenting procedure.[25] The ARMYDA-9 CAROTID trial reports that a high loading dose of clopidogrel (600mg) before stenting reduces the risk for post-treatment stroke or TIA within 30 days postoperative.[55] Unfortunately, large RCTs comparing different APT strategies in CAS patients are currently lacking. Periprocedural heparinization is frequently used to reduce thrombus formation after stenting, however no recommendations have been made regarding this topic in guidelines.[31]

Timing of stenting

The safety of early revascularization with CAS in symptomatic patients is controversial. Several studies showed an increased risk in 30-day stroke rate when CAS is performed within two weeks after the index event compared to revascularization performed after ≥ 14 days. Pooled meta-analyses of symptomatic patients randomized within CREST, ICSS, EVA-3S and SPACE trial reported higher 30-day rates of any death/stroke when CAS was performed within 7 days after symptom onset compared to >7 days. The 30-day death/stroke outcomes of CAS compared to CEA were 8.4% vs 1.3% <7 days and 7.1% vs 3.6% > 7 days, respectively.[56] However, the number of patients in the very early subgroup (<7 days) were small. No other high level evidence data sets are available yet on the safety of very early revascularization after the index event.

Intra- and post-procedural technical improvements

Stent technology

Although stenting techniques and devices are under continuous development, guidelines are inconclusive regarding the optimal stent design.[25] Pooled analysis with randomized data of EVA-3S, SPACE and ICSS concluded that a closed cell stent design was less often accompanied by procedural stroke or death compared to open-cell stents. (6.0% vs 10.3%, respectively) An observational study within ACST-2 reported that the majority of surgeons and radiologists, when giving the choice, preferred to use closed-cell stents during CAS while the choice of stent or protection device was primarily based on vascular anatomy rather than plaque characteristics or patient characteristics.[14]

Cerebral protection devices

The role of cerebral protection devices (CPD) in preventing procedural stroke after stenting has shown conflicting outcomes in previous published studies. Distal occlusion devices, proximal occlusion devices and filter-type embolic CPD were introduced with the intention to prevent or reduce embolization of dislodged embolic particles into the cerebral circulation due to guide wire manipulation or angioplasty. Distal occlusion devices and filter-type embolic CPD both have to first pass the stenosis, while the use

of a proximal occlusion device does not require manipulation of the atherosclerotic stenosis itself. Regarding the blood flow, distal and proximal occlusion CPD require a flow arrest or flow reversal due to dilation of the protection balloon which will not be tolerated by all patients, depending on collateral cerebral blood flow. In filter-type CPD the antegrade blood flow will be maintained with the use of a permeable device. The benefit of reducing stroke risk by catching debris during the stenting procedure might be hampered by micro-embolization as a result of manipulation of the stenosis and deployment of the CPD itself.[57]

Various studies and meta-analyses have been conducted comparing CAS patients treated with and without CPD. The meta-analysis performed by Garg et al. indicated that CPD decreased the risk of perioperative stroke. However this might be biased since stenting techniques and risk factor management improved over time and most unprotected CAS were performed earlier.[58] A meta-analysis using RCT data concluded no significant difference in 30-day death/stroke rate based on the use of CPD (OR 0.95, 95% CI 0.38-2.41, p=0.92). Within the ICSS-trial, patients who underwent a protected CAS with CPD of the choice of the interventionalist experienced a higher risk of 30-day death/strokes rate compared to those undergoing unprotected CAS. This did not reach statistically significance (4.6% unprotected, 8.5% protected CAS, p=0.056).[59]

To develop more useful surrogate parameters to compare CAS with/without CPD use, transcranial Doppler (TCD) measured micro-embolic signals or new ischemic brain lesions detected on post-procedural diffusion-weighted imaging (DWI) must be considered in addition to death/stroke rate as clinical outcome. Where the ICSS-trial failed to prove significant disadvantages of CPD use, a substudy of ICSS reported an increased rate of new ischemic brain lesions detected on MRI-DWI after CAS compared to CEA in centres routinely using filter-type CPD than in centres performing unprotected stenting.[60] This observation corresponds with the results of two small RCTs showing higher rates of DWI lesions after the use of CPD compared to unprotected stenting. [61,62] Regarding micro-embolic signals detected by TCD, various relatively small studies report an increased detection of micro-emboli by TCD in patients undergoing filter-protected CAS compared to non-protected procedures. A possible hypothesis for this observation is that filter-type CPD subsequently disintegrated macro-emboli into smaller patent particles, which increase the number of micro-emboli.[63] Therefore, the clinical relevance of micro-emboli must be taken in perspective since the clinical outcome of death/stroke did not differ between these patients.[57,61]

In accordance with the ESVS guideline that advises to reconsider the use of CPD in CAS, we do believe that the benefit of routine CPD/filter-type protection devices during CAS must be seriously questioned.[25]

Cerebral monitoring

None of the large RCTs including CAS (EVA-3S, SPACE, ICSS) reported cerebral monitoring during CAS.[10–12] This can be contributed to the fact that CAS is performed under regional anaesthesia and thus that the patient is awake during the intervention. In contrast with CEA, EEG monitoring during CAS might be redundant since periprocedural cerebral monitoring can be relied on motor function of speech. As mentioned, TCD is able to detect both micro and macro-embolic signals and provides information on cerebral blood flow changes during balloon dilation or during the period of no flow state due to proximal or distal CPD.

CHS is also a serious and frequent complication in the very early post-procedural period in CAS patients (3.5% risk).[64] This may support the consideration to add periprocedural TCD measurements to CAS, not only to provide information on cerebral blood flow changes and embolic-signals during procedure but also to identify patients at risk of post-procedural CHS.

Since no studies have proven the additional value of TCD in reducing death/stroke as clinical outcome after CAS, TCD has not been considered mandatory for periprocedural monitoring during CAS.[63,65] Therefore, the specified use of intraprocedural or post-procedural TCD during CAS has not been recommended in guidelines (yet).[25]

Hemodynamics

Most ischemic strokes after CAS are of hemodynamic origin as a result of hypoperfusion. It is known that arterial hypotension is a frequent complication of CAS and is attributed to manipulation of baroreceptor cells in the carotid sinus and baroreceptor dysfunction due to atherosclerotic disease.[66,67] Prophylactic administration of glycopyrrolate or atropine prior to balloon angioplasty have shown to be effective in preventing stenting induced hypotension and bradycardia. Over the past years, administration of such agents have become standard treatment in CAS studies and is recommended by guidelines.[25,68,69] In a few observational studies, hemodynamic depression after CAS has been found to be associated with major adverse events like periprocedural stroke, myocardial infarction or death. [66,67,70] The ICSS-trial compared the incidence of hemodynamic complications between CAS and CEA. Periprocedural hemodynamic depression occurred significantly more often after CAS than after CEA (13.8% vs 7.2%, respectively) and led to a significant decrease of systolic BP in the first days after CAS.[47]

In addition, post-procedural hypertension is described after a period of procedural hypotension. Yet, no significant association between hemodynamic complications like hypotension and 30-day stroke, MI or death were reported.[24] Contradictory, periprocedural hemodynamic depression turned out to be associated with a three times higher number of new ischemic brain lesions on MR-DWI after CAS.[71] Despite the fact that large trials have not provided conclusive evidence on specific blood pressure regimens during CAS, guidelines advises to maintain periprocedural hemodynamic stability and to monitor hemodynamic parameters up to six hours after the procedure.[25]

BOTH CEA & CAS

Imaging (DWI lesions)

Magnetic resonance diffusion weighted imaging (DWI) can be used to detect ischemic brain lesions shortly after carotid intervention and is an increasing topic of interest.[27,72,73] Over the years, DWI is increasingly being used as a surrogate marker for stroke, since it is able to detect silent events in addition to clinically symptomatic strokes.

Trials showed an incidence up to 50% new DWI lesions in symptomatic CAS patients and 31% in asymptomatic CAS patients. The incidence of new DWI lesions after CEA was 17% in symptomatic patients and 8.6% in asymptomatic patients.[74] An MRI substudy of the ICSS-trial concluded that although the number of new DWI lesions after CAS was higher, while the lesions after CAS were smaller in size compared to the lesions found after CEA. Follow-up data (median 4.1 years) of the ICSS MRI substudy concluded that new ischemic brain lesions discovered on DWI after CAS in symptomatic patients seem to be a marker of increased risk for recurrent cerebrovascular events (Stroke or TIA). For CEA, neither the number nor the presence of DWI lesions was associated with the risk of future cerebrovascular events.[75] Of additional clinical relevance, new ischemic lesions, with or without corresponding focal deficits, may cause clinically relevant future events such as cognitive decline and dementia.[76]

Different theories regarding the aetiology of these DWI lesions exist. Periprocedurally, stent deployment or manipulation of the carotid artery during CEA potentially cause thromboembolism. Secondly, impaired cerebral perfusion in the ipsilateral hemisphere in CAS patients is thought to be responsible for a decreased wash out of micro-emboli, causing new ischemic brain lesions.[77] ICSS MRI-substudy supported this theory by reporting a 3 times higher number of new ischemic brain lesions on DWI in CAS after periprocedural hemodynamic depression.[48] Additionally, a higher incidence of new DWI lesions have been reported after the use of CPD compared to no use of CPD as well as an increased risk of new DWI-lesions in patients treated with open-cell stent design.[57] In

CEA, the mandatory use of a shunt over selective shunting led to an increased incidence of new ischemic brain lesions on DWI MRI.[27,74]

Hospital + operator volume

Last, hospital volume and operator volume have increasingly become a topic of interest. Several studies and meta-analyses published over the past years concluded that high operator and high hospital volume is associated with a decreased risk of procedural death and stroke after CEA.[78,79] This association was also found between hospital volume and CAS.[80] In addition, the annual volume of the operator did influence the 30-day death/stroke rate of CAS patients. Low annual CAS experience resulted in a significantly higher 30-day death/stroke rate compared to high volume operators (10% vs 5.1%, respectively).[81] Frequent annual CAS procedures (10-15) were advised to maintain competency, preceded by 25 CAS procedures to achieve the competency.[82]

UNRESOLVED ISSUES

Despite the extending and evolving technical improvements of carotid revascularization in order to reduce procedural induced complications, a few open ends have yet to be resolved. First, current guidelines extensively report on the risk of stroke after carotid revascularization and on how to minimize this risk by secondary and tertiary prevention which we addressed in this review.[25] Up to now, recommendations concerning the response to periprocedural stroke itself are lacking in European guidelines and local protocols. A modified Delphi consensus of iterative consultation between clinicians involved in the treatment of carotid disease worldwide is currently being applied. Recommendations regarding best treatment of in hospital stroke during or after CEA, differentiating between imaging or direct surgical re-intervention, are expected soon.

Second, adequate hemodynamics during carotid revascularization have been considered important to maintain optimal cerebral perfusion but also to avoid cerebral hyperperfusion. Intraoperative hypotension and postoperative hypertension are suggested to be harmful, although details on duration and thresholds of these definitions are lacking. Further research on this topic is needed.

Third, guidelines recommend to consider CEA in patients when the expected risk of the treatment is <6% in symptomatic patients and <3% in asymptomatic patients. These thresholds are based on results of trials performed in the 90s and 00s. As we addressed in this review, several technical developments have improved carotid revascularization and medical treatment is optimized over the past years. In respect of the CEA patient, a lower threshold for periprocedural complication rate would be more acceptable.

Last, the results of previous and future trials determine the benefit of carotid revascularization over best medical treatment for subgroup of patients (symptomatic, asymptomatic) and which treatment will be the most appropriate. However, these randomized trials are conducted under idealized and controlled conditions that might not be representative of daily clinical practice. Technical improvements in surgical technique of CAS develop faster than recruitment of a large RCT with set CAS and CEA procedures. Unlike patients recruited in RCTs comparing different treatments, the choice of treatment for patients in daily practice is not interchangeable without a suspected increase of risk. Therefore, separate large cohort studies of CAS and CEA will be necessary to study the current periprocedural stroke rate of these treatments.

CONCLUSIONS AND PERSPECTIVES

In conclusion, the increased understanding of the mechanism underlying periprocedural stroke after carotid revascularization has led to multiple technical improvements (table 1). Adequate patient selection and timing of surgery, optimization of antiplatelet therapy and cerebral monitoring, and improvement of stenting techniques seem to be paying off by decreasing death/stroke risk over the recent decades. Although both CAS and CEA seem to have similar annual rates of ipsilateral stroke, the increased procedural stroke risk after CAS causes that CEA remains preferred over CAS.[22] This emphasizes the importance of increasing periprocedural safety of CAS and its potential benefit in reducing stroke.

Further research is warranted to fully untangle all aspects of the mechanism of stroke following CAS and CEA in asymptomatic patients. Future results of the currently recruiting ACST-2 trial are expected to provide more information on asymptomatic patients and the mechanism of periprocedural stroke. Regarding future perspectives, new surrogate markers for stroke like DWI-lesions should be added as a (primary) endpoint in future trials and consensus on how to treat periprocedural stroke should be obtained. By those means, periprocedural strokes associated with carotid revascularization will hopefully belong to the past in the near future.

Table 1. Overview of mechanism of stroke and technical improvements

	Stroke mechanism	Carotid Endarterectomy (CEA)	Carotid artery stenting (CAS)
In general	n.a.	• Patient selection • Timing of surgery • Diagnostic work-up • Hospital/operator volume	• Patient selection • Timing of surgery • Diagnostic work-up • Hospital/operator volume
Intra-procedural	Thrombo-embolic	• APT: clopidogrel* • APT: continuation prior to surgery • No routinely shunt use • Cerebral monitoring (TCD/EEG)	• DAPT: aspirin+clopidogrel* • Preferably closed-cell stent design • No routinely CPD-use • Cerebral monitoring (TCD)
	Hemodynamic	• Cerebral monitoring (TCD) – *shunt/CHS* • Attending cardio-anaesthesiologist • BP monitoring	• Atropine pre-dilation • Cerebral monitoring (TCD) during dilation
Post-procedural	Thrombo-embolic	• APT continuation	• DAPT first 3 months
	Hemodynamic	• BP monitoring/therapy *(hypertension)* • Cerebral monitoring (TCD) - *CHS*	• BP monitoring/therapy *(hypotension)*

APT: antiplatelet therapy. DAPT: dual antiplatelet therapy. TCD: transcranial Doppler. EEG: electroencephalography. CHS: cerebral hyperperfusion syndrome. BP: blood pressure
** Antiplatelet therapy of first choice.*

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CHAPTER 3

Variation in perioperative cerebral and hemodynamic monitoring during carotid endarterectomy

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ABSTRACT

Objective: Hemodynamic disturbances cause half of the perioperative strokes following carotid endarterectomy (CEA). Guidelines strongly recommend strict pre- and postoperative blood pressure (BP) monitoring in CEA patients, but do not provide firm practical recommendations. Although in the Netherlands 50 centres perform CEA, no national protocol on perioperative hemodynamic and cerebral monitoring exists. To assess current monitoring policies of all Dutch CEA-centres, a national survey was conducted.

Methods*:* Between May 2017 and July 2017 all 50 Dutch CEA-centres were invited to complete a 42-question survey addressing perioperative hemodynamic and cerebral monitoring during CEA. Non-responders received a reminder after one and two months. By November 2017 the survey was completed by all centres.

Results*:* Preoperative baseline BP was based on a single bilateral BP-measurement at the outpatient-clinic in the majority of centres (n=28). In 43 centres (86%) *pre*-operative monitoring (transcranial Doppler (TCD, n=6), electroencephalography (EEG, n=11), or TCD+EEG (n=26)) was performed as a baseline reference. Intraoperatively, large diversity for type of anaesthesia (general:45 vs local (LA):5) and target systolic BP (>100mmHg – 160mmHg (n=12), based on preoperative outpatient-clinic or admission BP (n=18), other (n=20)) was reported. Intraoperative cerebral monitoring included EEG+TCD (n=28), EEG alone (n=13), clinical neurological examination with LA (n=5), near-infrared spectroscopy with stump pressure (n=1), and none due to standard shunting (n=3). Postoperatively, significant variation was reported in standard duration of admission at a recovery or high-care unit (range 3-48hours, mean:12h), maximum accepted systolic BP (range >100mmHg – 180mmHg (n=32)), postoperative cerebral monitoring (standard TCD (n=16), TCD on indication (n=5) or none (n=24)) and in timing of postoperative cerebral monitoring (range directly postoperative – 24h postoperative; median 3h).

Conclusion: In Dutch centres performing CEA the perioperative hemodynamic and cerebral monitoring policies are widely diverse and require standardization. This national audit emphasizes that a standardised and detailed (inter)national protocol on perioperative hemodynamic and cerebral monitoring during CEA is urgently needed.

INTRODUCTION

Strict perioperative arterial blood pressure (BP) control is advocated to preserve adequate cerebral perfusion during carotid endarterectomy (CEA).[1] Despite these efforts, under the currently applied protocols, hemodynamic disturbances during CEA may contribute to intraprocedural strokes and play an important role in the aetiology of postoperative strokes.[1–4] Additionally, an increased risk of perioperative cerebral events has been reported in patients with elevated preoperative BP.[5,6] Intraoperative hypoperfusion is the most frequent cause of cerebral ischemia whereas postoperative ipsilateral hyperperfusion has been correlated to cerebral hyperperfusion syndrome (CHS) resulting in cerebral haemorrhage when left untreated.[4,7,8] Theoretically, periprocedural strokes due to hemodynamic disturbances seem preventable. The subsequent question relates on optimal perioperative hemodynamic and cerebral monitoring policy to adequately identify and timely address these disturbances.

Cerebral monitoring techniques such as electroencephalography (EEG), transcranial Doppler (TCD), or Near Infra-Red Spectroscopy (NIRS) all claim to detect disturbances in cerebral blood flow in order to prevent cerebral ischemia and to assess the need for shunt placement during carotid cross-clamping under general anesthesia.[9–11] Intraoperative changes in the middle cerebral artery blood flow velocity (MCA*V*) detected by TCD however remains the gold standard for CHS risk prediction following CEA.[12,13] Postoperative TCD measurements two hours and 24 hours in addition to intraoperative TCD measurements have been shown to increase the prediction rate for CHS.[12,14]

Recent guidelines by the European Society for Vascular Surgery (ESVS) recommend preoperative antihypertensive treatment in patients with hypertension to maintain long-term BP <140/90 mmHg. Furthermore, when preoperative systolic BP exceeds 180 mmHg, it is advised to first treat hypertension before proceeding with CEA. Postoperatively, invasive BP monitoring is recommended during the first 3-6 hours at a recovery or high-care unit, followed by hourly non-invasive BP control during the first 24 hours. Unfortunately, specific recommendations regarding the intraoperative and postoperative BP thresholds, BP treatment or on the type or duration of cerebral monitoring are still lacking.[1,15]

In the Netherlands, CEA is currently performed in 50 medical centres (total of 2306 CEA-procedures in 2016, range 20-91 CEA-procedures per centre).[16] Nevertheless, a national protocol on optimal perioperative hemodynamic and cerebral monitoring does not exist. To assess the currently applied monitoring policies, we conducted a national

survey on perioperative hemodynamic and cerebral monitoring during CEA within the Netherlands.

METHODS

Survey

Between May 2017 and July 2017 vascular surgeons of all Dutch medical centres performing CEA were invited by email to participate in an online survey (SurveyMonkey Analyze 2017, see Supplement 1.). Non-responders received a maximum of two reminder invitations, send one and two months after initial invitation. The survey was completed by surgeons from all CEA-centres in November 2017. The survey contained 42 questions addressing type of anaesthesia, preoperative, intraoperative and postoperative hemodynamic policies and monitoring, cerebral monitoring and length of stay on a high care unit (HCU). The survey had been compiled, discussed and improved on by an expert panel consisting of vascular surgeons and a vascular medicine specialist. Questions were multiple-choice with the option to clarify the answer in a text field. In case of multiple vascular surgeons performing CEA within one centre, a consensus was obtained by the corresponding vascular surgeon on behalf of his/her colleagues to represent their centres' policy. The database of the Dutch Audit for Carotid Interventions (DACI) was used to calculate numbers of CEA procedures per centre in 2016.[16]

Definitions

CEA was performed under general or local anaesthesia, via eversion or longitudinal incision with patch or primary closure. Cerebral monitoring included EEG, TCD, NIRS, stump pressure or intraoperative neurological examination in case of local anaesthesia. Perioperative period can be divided in preoperative phase, intraoperative phase and postoperative phase. Preoperative phase is period from admission to ward to surgery. Intraoperative phase extends from moment of admission to the operating room (OR) until patient is transported to the recovery unit. Postoperative phase is defined from admission to recovery unit until hospital discharge. Based on volume, medical centres were subdivided into low volume centres (LVC): 20 – 50 CEA procedures annually and high volume centres (HVC): >50 CEA procedures annually.[16] High care unit was defined as a nursing ward with availability of continuous invasive monitoring and observation, and intravenous BP support (i.e. medium care unit, intensive care unit). Recovery unit was determined as a post-anaesthetic care unit for short-term observation directly after surgery.

Statistical analysis

Data were collected with an online survey tool, SurveyMonkey Analyze. The results were processed and analysed using IBM SPSS Statistics for Microsoft Windows version 25.0th Edition (IBM Corp., Armonk, NY, USA). Categorical data were reported as a quantity with percentages. Continuous data were reported as means with standard deviation (SD) when normally distributed and median with interquartile range (IQR) when non-normally distributed. Outcomes were reported separately presented for perioperative phase. In addition, per perioperative phase results were stratified for centre volume.

RESULTS

Participants

In total, all 50 Dutch centres performing CEA completed the survey (100% response rate), provided by either individual surgeons (n= 45) or by consensus (n=5). In 2016, 32 LVC (64%; total: 1119 CEAs, mean: 35/centre (range 20-49)) and 18 HVC (36%; total: 1187, mean: 66/centre (range 51-91)) were identified.[17] CEA was performed under general anaesthesia (GA) in 45 centres (90%), solely under local anaesthesia (LA) in one centre (2%) whereas in three centres (6%) the decision for GA versus LA was patient specific.

Blood pressure protocol

In 39 of 50 CEA-centres (78%; LVC 24 and HVC 15) a general protocol for BP regulation during CEA was available and in use. A specific protocol for CHS was available in 34 centres (68%; LVC 21 and HVC 13). Protocols concerning BP regulation specifically differentiating between the preoperative, intraoperative and postoperative phases were available in a fewer centres. Just 15 centres (30%; LVC 8 and HVC 7) reported a specific protocol concerning preoperative BP regulation, 26 centres (52%; LVC 17 and HVC 9) for intraoperative BP regulation and 40 centres (80%; LVC 25 and HVC 15) reported an active protocol specific for postoperative BP regulation.

Antihypertensive treatment

No consensus existed regarding perioperative antihypertensive drug therapy. Preoperatively, hypertension was not a contraindication for surgery in almost half of centres (n=23). If antihypertensive treatment was required, oral labetalol or beta-blockers were administered most commonly. Intraoperatively and postoperatively, intravenous labetalol was administered most frequently (Table 1). Many different specialists were responsible for BP treatment during the periprocedural phases (Table 1).

Periprocedural hemodynamics

In the majority of centres (66%; LVC 21, HVC 12), the preoperative BP-measurement was based on a single non-invasive bilateral BP-measurement at the outpatient clinic, in which the highest value was considered as the most accurate. In seventeen centres (34%; LVC 11, HVC 6) the preoperative BP was performed by a random side single BP-measurement or a standardized side single BP-measurement. Intra- and postoperatively, centres predominantly performed invasive monitoring (intraoperatively 48 centres; LVC 31, HVC 17 and postoperatively 46 centres; LVC 30, HVC 16).

There was not much similarity between centres on the level of maximum-accepted BP thresholds periprocedural, either systolic or diastolic. A broad and very heterogeneous range of applied systolic BP thresholds during the different phases were reported by all centres (Table 2). Postoperative maximum-accepted systolic BP thresholds on the ward as well as for discharge also varied extensively, ranging from < 140 mmHg to < 180 mmHg or the preoperative admission BP.

The basis upon the systolic BP thresholds are defined were highly diverse, varying from protocol-based, experienced-based, based on preoperative BP-measurement and cerebral monitoring-based to a combination of the previously mentioned (Table 2). BP thresholds for discharge were primarily based upon the level of preoperative BP (11 centres) or local protocol (20 centres).

Follow up of blood pressure

In 42 of the 50 centres (84%; LVC 29 and HVC 13), the recommended maximum accepted systolic BP for discharge was documented in the electronic patient file, in the letter of discharge to patient's general practitioner (GP) or both. Follow up on BP and BP threshold was performed in most centres by the GP (24 centres, 48%) or vascular surgeon (12 centres, 24%). A small number of centres referred this follow-up to the internal or vascular medicine specialist (4 versus 6 centres, respectively).

Cerebral monitoring

In the preoperative phase, cerebral monitoring was performed in 43 CEA-centres (86%). In the majority of these centres, the monitoring consisted of TCD combined with EEG (60%) versus TCD (14%) or EEG (26%) alone. Intraoperatively, for CEA under GA, more than half the centres used EEG combined with TCD (62%), 13 centres (29%) solely applied EEG-monitoring while one centre used NIRS combined with stump pressure (2%). In three centres no intraoperative cerebral monitoring was performed due to routine shunting of the internal carotid artery. The centres that performed CEA under LA monitored their patients by continuous awake cerebral neurological examination

(CNE). Postoperatively, approximately half of the centres did not perform cerebral monitoring (48%) or only on indication (TCD: 10%, EEG: 2%). In only 16 centres (32%), EEG and/or TCD monitoring were part of the standard postoperative care. The timing of this standardised postoperative monitoring varied from directly after surgery up to 24 hours after surgery (median: 3 hours) (Table 3, Fig. 1).

Postoperative observation

Immediately after surgery, patients were admitted to the recovery unit in 16 centres (32%; LVC 11 and HVC 5). In the majority of centres, patients were admitted to a HCU like intensive care or medium care unit as a standard procedure (60%; LVC 19 and HVC 11). The standard observation duration ranged from 3 to 48 hours (mean: standard 12h). Centres based the duration of observation on a protocol (68%; LVC 20 and HVC 14) or on patient-specific parameters (32%, LVC 12 and HVC 4) (Table 4, Fig. 2).

DISCUSSION

Perioperative hemodynamic and cerebral monitoring policies during carotid surgery vary widely. Although the majority of centres do have a written (general) protocol on BP regulation and more specifically on prevention of CHS after CEA, a highly heterogeneous approach in all phases of the in-hospital period was reported. Intraoperative and postoperative cerebral monitoring policies and applied baseline BP-measurements differed substantially. The wide variety in centre-specific policies results in fragmented care, and as a consequence seriously limits the comparability of outcome between centres.

The recent 2017 guideline on treatment of atherosclerotic carotid artery disease published by the ESVS provides several recommendations regarding periprocedural hypertension treatment and cerebral monitoring.[1] However, no specific guidance was provided regarding the determination of baseline BP, the maximum accepted periprocedural BP, nor use of cerebral monitoring to minimize the risk of complications. Level one evidence regarding these topics is lacking, most likely due to the difficulty to prove that these monitoring factors directly affect clinical outcome.[1] Still, since one out of three perioperative events in carotid surgery is attributed to hemodynamic origin and such events seem preventable, improvement in perioperative care with standardization of best practice is indicated and some form of monitoring mandatory.[4]

Although not specified by the guidelines, intraoperative arterial BP during CEA is advised to be kept between baseline and 20% above to minimise the risk for intraoperative stroke.[18] Unfortunately, the applied term ‘baseline’ is poorly defined in the literature.

Frequently, this led to the use of a baseline BP based on BP-measurement in the OR before induction of anaesthetics, which is often higher (up to 14 mmHg) compared to BP measured at the outpatient-clinic for preoperative evaluation.[19–21] Additionally, it can be challenging to achieve and maintain these BP targets intraoperatively, and the direct effects of altering or shifting these strict intraoperative BP thresholds have not yet been investigated for efficacy in preventing CHS. For postoperative BP management, a one size fits all systolic BP policy by treating >170 mmHg in patients without symptoms or >160 mmHg in patients with symptoms is often suggested to prevent postoperative complications.[22] However, this policy may cause significant overtreatment and extensive workload, but will not prevent CHS since this complication may still occur without systolic hypertension (i.e. systolic BP ≤140 mmHg).[14,23,24] As a consequence, a standard 160 mmHg maximum BP policy will still allow for severe complications of CHS to occur despite following a BP policy.

Intraoperatively, the majority of centres have implemented both EEG and TCD monitoring as standard clinical care. These cerebral monitoring methods inform the surgeon on the presence of both macro- and micro-emboli during carotid mobilization and dissection phase, guide to selectively shunt the carotid artery and ensures continuous shunt function, which is also relevant in standard shunting.

The ESVS guideline recommends to invasively monitor BP of CEA patients on an advanced care unit during the first 3-6 hours postoperatively. We observed that 60% of the centres admitted their CEA patients to a HCU for an average duration of 22 hours as part of standard postoperative care. Besides overtreatment, it seems evident that standard postoperative admission to a HCU goes hand in hand with high costs and workload.[1] Interestingly, no studies provide any insight regarding the specific interventions which are adopted during the first twenty-four hours admission to a HCU in comparison to admission to the ward/recovery unit. This makes it hard to objectify the clinical benefit of standard HCU admission. By implementing TCD monitoring to perioperative clinical care, patients at high risk of CHS can be easily identified. As a consequence, only a small subset of patients require strict and immediate BP lowering and monitoring on a HCU while the majority of operated patients can safely be discharged for further BP regulation via the nursing ward or via the outpatient clinic.[14,25] This risk based strategy will lead to a decrease in hospital costs and is more patient-friendly than standard extended strict BP monitoring by a radial artery line.

On the other hand, the need for fifty different centres performing CEA in the Netherlands containing 18 HVC and 32 LVC with a mean caseload of 46 CEAs per centre per year can be questioned. Hospital care and specific specialised treatments are increasingly

centralised, resulting in high operator and centre volume which have been associated with a decreased risk of procedural death and stroke after CEA and CAS.[26] We predict that centralization with standardized protocols for perioperative care among the country may lead to lower periprocedural complication rates.

In the end, the overall aim is to achieve best clinical care. Therefore, since 2013 it is mandatory for all Dutch centres performing carotid artery interventions to provide data that include patient characteristics and surgical treatment annually to DACI. The objective of this nationwide audit is to measure and improve the quality of care in carotid interventions and to monitor the adherence of national guidelines and clinical outcomes.[16] The wide variability of the centre-specific perioperative hemodynamic and cerebral monitoring policies has not been included in this audit and may be the cause of a distorted view of national clinical outcomes and limits the comparability. This emphasizes the need for a univocal perioperative protocol or at least include these variables in the audit.

The results of this national survey should be interpreted in light of several limitations. First, the survey used in this study was a non-validated questionnaire. Due to the lack of availability of validated questionnaires on this topic, the survey was compiled by an expert panel consisting of vascular surgeons and a vascular medicine specialist. However, as most required data focused on objective measures and not subjective interpretation we believe that our data provide a good insight in current Dutch practice. Second, in five out of fifty centres a post-hoc consensus was mandatory due to a contradiction in answers of multiple vascular surgeons within one centre. In case one surgeon per centre filled out the survey, this answer was accepted although it is likely that the same variety existed within that centre. This makes the validity of the responses by a single surgeon slightly disputable as different approaches may be applied by individual surgeons. Finally, no association was made between the used hemodynamic targets and cerebral monitoring policies and periprocedural stroke/death rate per centre. Therefore, the presented results should be interpreted as a general overview and not as individual centre results.

CONCLUSION

Applied perioperative hemodynamic and cerebral monitoring policies during carotid surgery among Dutch centres are widely diverse. In only one in every two centres a specific protocol concerning intraoperative BP regulation was available. As hemodynamic disturbances are an important cause of potentially preventable periprocedural strokes, we consider that improvements in perioperative monitoring are

required. Alignment of centre-specific policies to one detailed univocal (inter)national protocol on perioperative hemodynamic and cerebral monitoring during CEA would improve standardization of care and facilitate outcome comparisons.

Acknowledgements
We wish to greatly thank all Dutch vascular surgeons who contributed to this paper by completing the survey.

Table 1. Hemodynamic topics

	Preoperative			Intraoperative			Postoperative		
	LVC (n=32)	*HVC (n=18)*	*Total (n=50)*	*LVC (n=32)*	*HVC (n=18)*	*Total (n=50)*	*LVC (n=32)*	*HVC (n=18)*	*Total (n=50)*
Responsible for target BP									
Vascular surgeon	-	-	-	11 (34)	10 (56)	21 (42)	16 (50)	14 (78)	30 (60)
Anaesthesiologist	1 (3)	1 (6)	2 (4)	4 (13)	-	4 (8)	-	-	-
Vascular surgeon & anaesthesiologist	-	-	-	11 (34)	6 (33)	17 (34)	5 (16)	2 (12)	7 (14)
Internal medicine specialist	13 (41)	7 (39)	20 (40)	-	-	-	-	-	-
Vascular medicine specialist	7 (22)	5 (28)	12 (24)	-	-	-	-	-	-
Internal + vascular medicine specialist	5 (16)	3 (17)	8 (16)						
Intensive care specialist	-	-	-	-	-	-	3 (9)	1 (6)	4 (8)
Vascular surgeon + neurologist	-	-	-	1 (3)	1 (6)	2 (4)	-	-	-
Combination of specialists (all the above)	5 (16)*	1 (6)*	6 (12)*	3 (9)†	1 (6)†	4 (8)†	8 (25)¨	1 (6)¨	9 (18)¨
Non applicable	1 (3)	1 (6)	2 (4)	2 (6)	-	2 (4)	-	-	-
Antihypertensive agents, if required									
RAAS inhibitors	-	1 (6)	1 (2)	-	-	-	-	-	-
ACE inhibitors	1 (3)	1 (6)	2 (4)	1 (3)	-	1 (6)	-	-	-
Other beta-blockers	6 (19)	-	6 (12)	5 (16)	2 (11)	7 (14)			
Labetalol, intravenously	-	-	-	16(50)	5 (28)	21 (42)	23 (72)	12 (67)	35 (70)
Labetalol, oral	7 (22)	2 (11)	9 (18)	-	-	-	2 (6)	1 (6)	3 (6)
Clonidine, intravenously	-	-	-	-	-	-	1 (3)	-	1(2)
Nicardipine, intravenously	-	-	-	-	-	-	2 (6)	1 (5)	3 (6)
Other	5 (16)	4 (22)	9 (18)	5 (16)	4 (22)	9 (18)	4 (13)	4 (22)	8 (16)
Unknown by respondent	13 (41)	10 (56)	23 (46)	10 (31)	8 (44)	18 (36)	-	-	-

Data are expressed as quantities with (percentages). LVC represent low volume centres that perform 20-50 CEA procedures annually. HVC represent high volume centres that perform >50 CEA procedures annually. BP: blood pressure. *Combination of specialist preoperatively consisting of internal medicine specialist, neurologist, cardiologist, anaesthesiologist, vascular surgeon, vascular medicine specialist. † Combination of specialists consisting of anaesthesiologist, vascular surgeon and neurologist. ¨Combination of specialists postoperatively consisting of vascular surgeon, anaesthesiologist and intensive care specialist.

Table 2. Hemodynamic thresholds

	Preoperative	**Intraoperative**	**Postoperative**
	Total (n=50)	*Total (n=50)*	*Total (n=50)*
Maximum systolic BP threshold			
No	26 (52)	7 (14)	0 (0)
Yes	24 (48)	43 (86)	50 (100)
• 180 mmHg	8 (16)	-	1 (2)
• 170 mmHg	1 (2)	-	2 (4)
• 160 mmHg	6 (12)	2 (4)	12 (24)
• 150 mmHg	3 (6)	4 (8)	11 (22)
• 140 mmHg	1 (2)	4 (8)	4 (8)
• 130 mmHg	1 (2)	-	-
• 120 mmHg	0	1 (2)	1 (2)
• >100 mmHg	0	1 (2)	1 (2)
• BP at admission/outpatient clinic	3 (6)	18 (36)	8 (16)
• BP at admission + 10 mmHg	1 (2)	1 (2)	-
• BP at admission + 20 mmHg	-	5 (10)	-
• 20% below preoperative BP	-	1 (2)	-
• Preoperative MAP ±10	-	2 (4)	1 (2)
• Preoperative MAP 80-90	-	1 (2)	-
• <180, unless TCD >100%	-	-	2 (4)
• <160 mmHg, unless TCD >100% or high risk	-	-	3 (6)
• Dependent on TCD measure	-	-	2 (4)
• Normotensive BP	-	2 (4)	2 (4)
• missing	-	1 (2)	-
Threshold based upon:			
• Protocol		6 (12)	17 (34)
• Experienced-based		9 (18)	3 (6)
• Preoperative BP		30 (60)	7 (14)
• Experience + preoperative BP		2 (4)	3 (6)
• Experience + preoperative/intraoperative BP		1 (2)	1 (2)
• Experience + preoperative BP + postoperative PB		-	1 (2)
• Experience + protocol + preoperative BP		-	1 (2)
• Experience + protocol + intraoperative BP		-	1 (2)
• TCD pre/intra/post or combination		-	7 (14)
• TCD intraoperative & preoperative BP		-	1 (2)
• TCD postoperative & postoperative BP		-	1 (2)
• TCD postoperative & protocol		-	1 (2)
• Protocol + preoperative BP + intraoperative BP		-	1 (2)
• Protocol + intraoperative BP		-	1 (2)
• One fits all-policy			
• 160-180 mmHg		-	1 (2)
• <160 mmHg		-	1 (2)
• <150 mmHg		-	3 (6)

Data are as quantity with percentages. TCD: transcranial Doppler. BP: blood pressure. MAP: mean arterial pressure.

Table 3. Cerebral monitoring

Cerebral monitoring	Preoperative			Intraoperative			Postoperative		
	LVC (n=32)	*HVC (n=18)*	*Total (n=50)*	*LVC (n=32)*	*HVC (n=18)*	*Total (n=50)*	*LVC (n=32)*	*HVC (n=18)*	*Total (n=50)*
TCD&EEG	15 (47)	11 (61)	26 (52)	15 (47)	13 (72)	28 (56)	4 (13)	0	4 (8)
TCD	4 (13)	2 (11)	6 (12)	-	-	-	6 (19)	6 (33)	12 (24)
EEG	8 (25)	3 (17)	11 (22)	10 (31)	3 (17)	13 (26)	1 (3)	0	1 (2)
CNE	-	-	-	4 (13)	1 (6)	5 (10)	3 (9)	0	3 (6)
NIRS + stump pressure	-	-	-	1 (3)	0	1 (2)	-	-	-
TCD on indication	-	-	-	-	-	-	2 (6)	3 (17)	5 (10)
EEG on indication	-	-	-	-	-	-	0	1 (6)	1 (2)
None	5 (16)	2 (11)	7 (14)	2 (6)	1 (6)	3 (6)	16 (50)	8 (44)	24 (48)

Data are expressed as quantities with (percentages). LVC represent low volume centres that perform 20-50 CEA procedures annually. HVC represent high volume centres that perform >50 CEA procedures annually. TCD: transcranial Doppler. EEG: electroencephalography. NIRS: near-infrared spectroscopy. CNE: cerebral neurological examination.

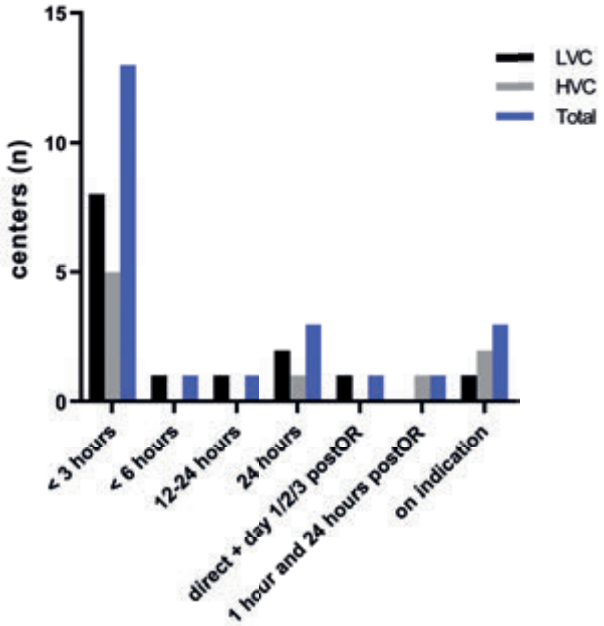
Table 4. Postoperative admission high care unit

	Postoperative		
	LVC (n=32)	*HVC (n=18)*	*Total (n=50)*
Standard admission HC unit			
• IC unit	10 (31)	6 (33)	16 (32)
• MC unit	9 (28)	5 (28)	14 (28)
• Observatory unit	11 (34)	5 (28)	16 (32)
• Other	2 (6)	2 (11)	4 (8)
Duration of observation based on:			
• Protocol, observatory unit	6 (19)	1 (6)	7 (14)
• Protocol, MC unit	6 (19)	4 (13)	10 (20)
• Protocol, IC unit	5 (16)	3 (6)	8 (16)
• Protocol, observatory + HC unit	3 (9)	6 (19)	9 (18)
• Patient specific, MC unit	5 (16)	1 (6)	6 (12)
• Patient specific, IC unit	4 (22)	3 (17)	7 (14)
• Patient specific, depending on patient's recovery	3 (17)	0	3 (6)

Data are expressed as quantities with (percentages). LVC represent low volume centres that perform 20-50 CEA procedures annually. HVC represent high volume centres that perform >50 CEA procedures annually. IC: intensive care, MC: medium care, HC: high care. Data are as quantity with percentages.

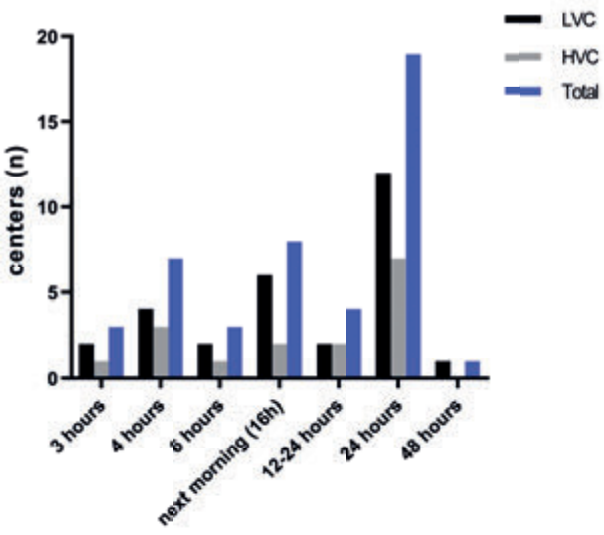
FIGURES

Figure 1. Timing of cerebral monitoring postoperative



LVC represent low volume centres that perform 20-50 CEA procedures annually. HVC represent high volume centres that perform >50 CEA procedures annually**.** postOR: post -surgery

Figure 2. Duration of postoperative admission at observational ward



LVC represent low volume centres that perform 20-50 CEA procedures annually. HVC represent high volume centres that perform >50 CEA procedures annually**.**

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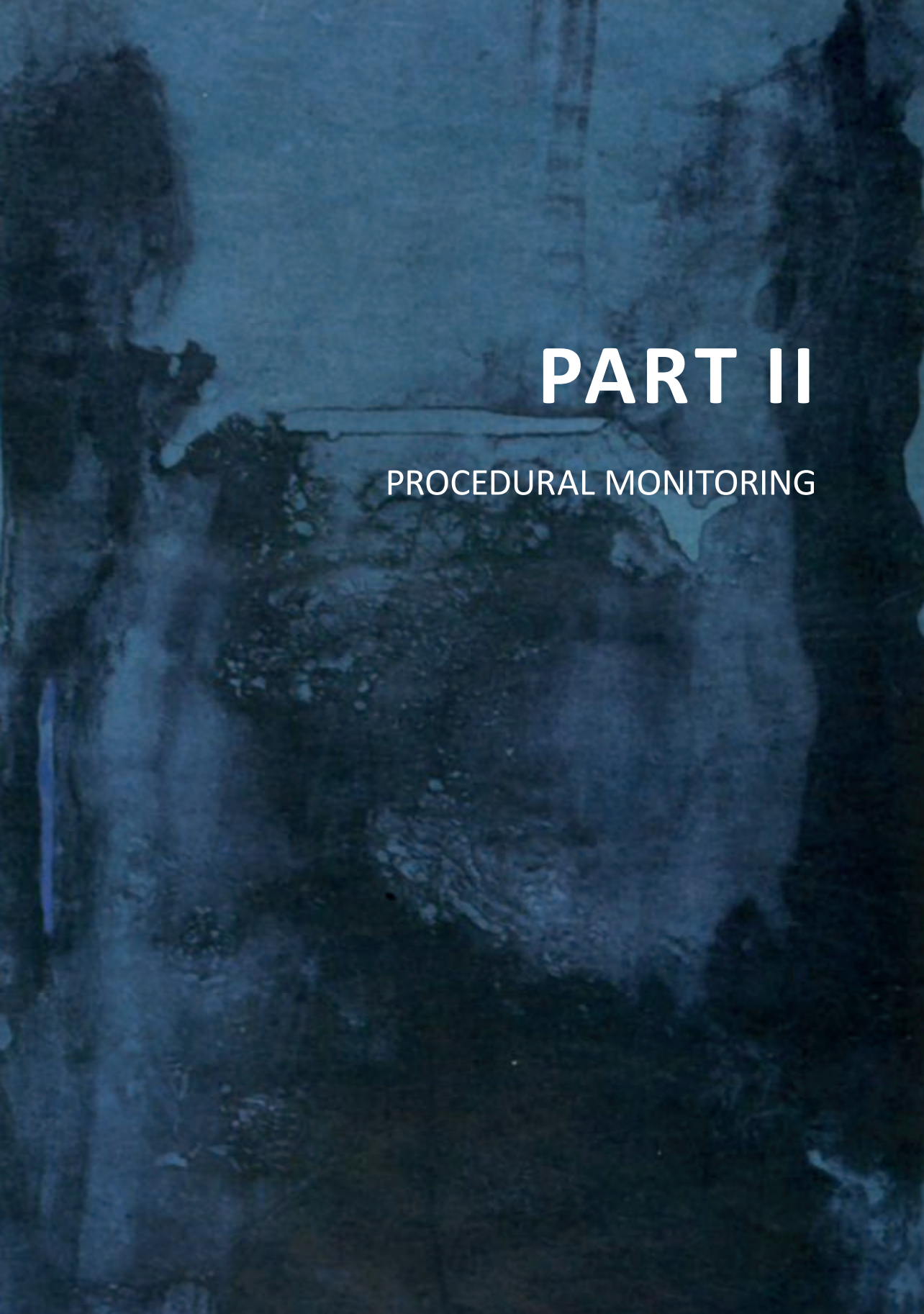

PART II

PROCEDURAL MONITORING

CHAPTER 4

Effect of phenylephrine and ephedrine on cerebral (tissue) oxygen saturation during Carotid Endarterectomy (PEPPER): A randomized controlled trial

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ABSTRACT

Background: Short-acting vasopressor agents like phenylephrine or ephedrine can be used during carotid endarterectomy (CEA) to achieve adequate blood pressure (BP) to prevent periprocedural stroke by preserving the cerebral perfusion. Previous studies in healthy subjects showed that these vasopressors also affected the frontal lobe cerebral tissue oxygenation (rSO_2) with a decrease after administration of phenylephrine. This decrease is unwarranted in patients with jeopardized cerebral perfusion, like CEA patients. The study aimed to evaluate the impact of both phenylephrine and ephedrine on the rSO_2 during CEA.

Methods: In this double-blinded randomized controlled trial, 29 patients with symptomatic carotid artery stenosis underwent CEA under volatile general anesthesia in a tertiary referral medical center. Patients were preoperative allocated randomly (1:1) for receiving either phenylephrine (50µg; N=14) or ephedrine (5mg; N=15) in case intraoperative hypotension occurred, defined as a decreased mean arterial pressure (MAP) ³20% compared to (awake) baseline. Intraoperative MAP was measured by an intra-arterial cannula placed in the radial artery. After administration, the MAP, cardiac output (CO), heart rate (HR), stroke volume and rSO_2 both ipsilateral and contralateral were measured. The timeframe for data analysis was 120 s before, until 600 s after administration.

Results: Both phenylephrine (70±9 to 101±22mmHg; p<0.001; mean±SD) and ephedrine (75±11mmHg to 122±22mmHg; p<0.001) adequately restored MAP. After administration, HR did not change significantly over time and CO increased 19% for both phenylephrine and ephedrine. rSO_2 ipsilateral and contralateral did not change significantly after administration at 300 and 600 s for either phenylephrine or ephedrine (phenylephrine: 73%,73%,73% and 73%,73%,74%. Ephedrine: 72%,73%,73% and 75%,74%,74%).

Conclusions: Within this randomized prospective study, MAP correction by either phenylephrine or ephedrine showed to be equally effective in maintaining rSO_2 in patients who underwent CEA.

Clinical trial registration: ClincalTrials.gov, NCT01451294

INTRODUCTION

In most patients scheduled for carotid endarterectomy (CEA), both baroreflex sensitivity (BRS) and cerebral autoregulation (CA) are impaired.[1,2] This results in blood pressure (BP) fluctuations that cannot be counter-regulated by the brain vasculature.[3] Therefore, during a CEA procedure systemic hemodynamics should be optimized. A rule of thumb is to keep the mean arterial pressure (MAP) between preoperative awake values upwards to 20% above baseline.[4,5] However, it can be challenging to achieve this targeted BP level intraoperatively due to induction medication and anaesthetics.[1] Thus, short-acting vasopressors like phenylephrine or a combined vasopressor and positive inotropic agent like ephedrine, are administered in relatively large quantities. Despite that both vasopressor agents effectively elevate MAP, there is mounting evidence that frontal lobe cerebral tissue oxygenation (rSO_2), measured by near-infrared spectroscopy (NIRS) decreases during the administration of phenylephrine while it remains unaffected during ephedrine use.[6,7]

The mechanism behind this observation remains unclear. In patients with intact CA, decrease in rSO_2 after phenylephrine was associated with concordant changes in cardiac output (CO), whereas rSO_2 remained unchanged when CO remained constant after treatment with ephedrine.[6] This observation confirms that changes in CO, even independently from arterial pressure, affect cerebral haemodynamics.[8,9] In both healthy and acute stroke patients, CO seemed to contribute to the regulation of the cerebral blood flow. Also, cerebral arteries are abundantly innervated by sympathetic fibres.[10] The decrease in rSO_2 after phenylephrine could be explained by a direct α_1-receptor-mediated cerebral vasoconstriction. In this respect, this would confirm a possible blood-brain barrier permeability for α_1-receptors-agonists and the presence of α-receptors in the smooth muscle layer of the cerebral vessels and microcirculation.[11,12]

In a small exploratory case series, addressing the cerebral hemodynamics of both vasopressors agents during CEA, a detrimental effect of phenylephrine consisting of a decrease of rSO_2 after administration in CEA-patients has been described.[13] Therefore, the present blinded randomized controlled study aimed to evaluate the previous observation of rSO_2 remaining unaffected after ephedrine and declining after phenylephrine when administrated for the treatment of a hypotensive period perioperative in patients undergoing CEA.

MATERIALS AND METHODS

Subjects

Ethical approval for this study (NL37658.041.11) was provided by the Medical Research Ethics Committee of University Medical Center Utrecht, Utrecht, The Netherlands (Chairperson Dr. W.A. Groenewegen) on 30 July 2012. Following approval, informed consent was obtained from 42 patients undergoing CEA between October 2012 and September 2013 at a tertiary referral vascular center, the University Medical Center Utrecht. The protocol of our randomized study was registered (Clinicaltrials.gov:NCT01451294) and has been published previously.[14] In short, patients with asymptomatic stenosis (>70%) or symptomatic stenosis (>50%) of the carotid artery scheduled for CEA were eligible for inclusion. Indications for carotid revascularization were discussed in a multidisciplinary team consisting of neurologists, radiologists and vascular surgeons. Exclusion criteria were: intraoperative decrease in MAP (expressed in mmHg) of less than 20% compared to baseline, arrhythmia or hypersensitivity to either ephedrine or phenylephrine.[14]

Carotid Endarterectomy

All patients were operated under volatile general anesthesia (GA) and received standard monitoring (non-invasive arterial BP with an upper arm cuff, electrocardiogram, pulse oximetry, end-tidal carbon dioxide, and temperature). Prior to anesthetic induction, an intra-arterial cannula (20 G) was placed in the radial artery to monitor invasive continuous beat-to-beat blood pressure (ABP). Electroencephalography (EEG, Micromed Inc., Treviso, Italy) electrodes continuously registered during surgery to monitor cerebral function state and detecting signs of cerebral ischemia. Detailed information on volatile general anesthesia and the surgical procedure are described previously in the protocol.[14] Intra-operatively, all patients received intravenous low dose norepinephrine as part of standard care.

Study design

The study aimed to investigate the impact of ephedrine and phenylephrine on frontal cerebral lobe oxygenation when administrated for correction of intraoperative hypotension in patients undergoing CEA. Secondary outcome measures of neurological or hemodynamic compromise in the postoperative phase were not analyzed in this study. Patients were allocated randomly (1:1) by computer-generated randomization for receiving either phenylephrine or ephedrine when intraoperative hypotension occurred before carotid cross-clamping. Relative intraoperative hypotension requiring intervention was defined as a decrease in MAP of ≥20% compared to awake baseline MAP. (Figure 1) The baseline MAP was the measured non-invasive BP on

the upper arm, ipsilateral to the operation site, on the ward one day before surgery. When intraoperative hypotension occurred despite low dose intravenous support of norepinephrine (hypotensive episode had to occur before cross-clamping when attending in the study), the attending anesthesiologist, blinded for the study medication, administered 1 ml from a prepared 10 ml unlabeled syringe containing either PE (50 $\mu g \cdot ml^{-1}$) or ephedrine (5 $mg \cdot ml^{-1}$). This syringe was prepared by a co-worker not involved in the study. The chosen dose of both vasopressors was based on the relative potency ratio for PE:E of 80:1.[15] The chosen timeframe for data analysis was 120 seconds before, until 600 seconds after administration.

If a patient did not respond within five minutes after the first bolus, a second bolus of the same vasopressor was given. If so, the timeframe around the second bolus was used for the data analysis. When hypotension persisted, the patient was classified as non-responder and rescue medication, as preferred by the attending anesthesiologist, was administered. Non-responders were not used for data analysis.

Intraoperative measurements

Details on intraoperative monitoring are as described in the protocol.[14] Therefore, briefly described below.

Hemodynamic

The radial ABP curve, sampled with 100Hz, was derived from the Data Ohmeda S/5™ monitoring system (GE Healthcare, Waukesha, Wisconsin, USA) and stored for offline analysis. MAP was measured as the mean integral over one heartbeat. Using the model flow method CO, SV, HR, and TPR were determined by BeatFast (TNO TPD Biomedical Instrumentation, Amsterdam, The Netherlands). Heart rate (HR) was determined as the inverse of the inter-beat-interval and expressed in beats per minute (bpm). Stroke volume (SV) was calculated from the ABP waveform incorporating age, sex, height and weight of the patients.[16] [16,17][17] The cardiac output (CO) was calculated as the product of SV and HR. The systemic vascular resistance (SVR) was the ratio of MAP and CO.

Near-infrared spectroscopy (NIRS)

Two NIRS optodes (Invos 3100; Somanetics Corporation, Troy, MI, USA) were placed bilaterally on the forehead to measure rSO_2 previous to induction. These optodes allowed continued monitoring of the rSO_2 by emitting two wavelengths of near-infrared light (730 and 805nm) from two separate (3 and 4cm) diode sources to a receiver.[18] NIRS output was sampled at 0.16Hz.

Data analysis

The offline radial ABP curve of each patient was synchronized with the rSO_2 signal, using time-markers, which were applied intraoperatively. Moment of administration was marked. The timeframes (-120 to 600 seconds) for data analysis of both curves were retrieved. The beat-to-beat data was averaged over 360 slots of 2 seconds. By polynomial interpolation, the rSO_2 signals were divided into 72 slots of 10 seconds.

Statistical analysis

Sample size calculation was based on a retrospective pilot study.[13] This retrospective pilot study showed a decrease in rSO_2 of -1.5% (±2) per 10 mmHg increase after administration of phenylephrine.[14] Based on this calculation, 14 patients in each group were needed to detect a significant decrease in rSO_2 after administration of phenylephrine (α level 0.05 and probability power 0.9). Patients who did not receive vasopressor agents intraoperative or failure of rSO_2 measurements occurred during surgery for reasons unrelated to the surgical procedure were replaced according to protocol.[14]

All analyses are performed according to the intention-to-treat principle. Results are means±SD for normally distributed data and median(range) for data not normally distributed. Changes in CO, SV and SVR are presented as percentage change from baseline. Delta (Δ) of rSO_2, MAP, HR and CO were calculated at different time points, namely the moment of maximum increase in BP, 5 minutes and 10 minutes after administration. Wilcoxon Signed Ranks Test determined multiple pairwise comparisons. Student's paired t-test was used to evaluate changes between condition, a confidence level of less than 5% (0.05) was considered significant. To compare ΔrSO_2 between PE and E, student's t-test is used, and Wilcoxon Signed Ranks Test or Mann Whitney U. Use of pacemaker and beta-blockers were taken into account and described separately. The statistical analysis was performed using Statistical Package for Social Sciences version 22.0 (SPSS Inc. Chicago, Il, USA).

RESULTS

Patient characteristics

Written informed consent was obtained from 42 patients. NIRS technical failure occurred before randomization in two cases, and 11 patients were excluded after randomization. (Figure 1) Baseline characteristics of the excluded patients did not significantly differ from the included patients. A total of 29 patients (19 male) with symptomatic carotid artery stenosis, were enrolled for the final data analysis. (Table 1) Except for history of peripheral vascular disease (PVD), the two groups were similar to each other in

perspective of baseline characteristics. Preoperative MAP was higher in the ephedrine group. In accordance with the protocol,[14] all patients had a decrease in MAP of ≥ 20%. Ephedrine was administered to 15 patients, 14 patients received phenylephrine.

Ephedrine

Awake MAP in the patients receiving ephedrine was 107±12 mmHg. A single bolus was administered in 13 subjects and a second bolus in 2 subjects. This led to restoration of MAP to 122±22 mmHg. Both ipsilateral and contralateral rSO_2 did not change significantly over time, showing a maximum decrease after administration of -2.3% and -2.5% and a maximum increase of 3.1% and 2.5%, respectively. Highest CO monitored after ephedrine administration was 118±10% compared to baseline (p<0.01). This rise in CO did not influence ipsilateral rSO_2 (p=0.107). No non-responders were reported. (Table 2 and figure 2-3)

Two patients had a pacemaker that was switched to a fixed rate of respectively 60 and 70 min^{-1}. Three patients used β-blockers. At the moment of administration, there was no difference (p=0.77) in HR (59 min^{-1} vs 61 min^{-1}) and rSO_2 both ipsilaterally and contralaterally (68±9% vs 74±8% ipsilateral, 69±11% vs 76±10% contralateral) between patients with and without β-blockers. MAP was lower at the administration of ephedrine in patients without β-blockers(p=0.311, 74 mmHg vs 80 mmHg). Additional, same applied for ipsilateral and contralateral rSO_2 measurements over time and β-blocker use.

Phenylephrine

Awake MAP in the patients receiving phenylephrine was 97±12 mmHg. A single bolus of PE was administered in 12 subjects, a second bolus in 2 subjects. MAP at the moment of administration was 70±9 mmHg. This led to restoration of MAP to 101±22 mmHg (p=0.01). The highest CO monitored after phenylephrine administration was 117±19% (p=0.01). This increase in CO resulted in an insignificant change in ipsilateral and contralateral measured rSO_2 with a maximum decrease of ipsilateral rSO_2 of -2.3% and a maximum increase of 2.8%, contralateral rSO_2 -1.8% and 2.6%, respectively. HR changed significantly from 58±14 to 64±17 min^{-1} at highest CO. (p=0.019) No non-responders were reported. (Table 2 and figure 2-3)

Six patients used β-blockers before surgery. On the moment of administration, HR was significantly lower in the patients with β-blockers versus patient without β-blockers, 49 versus 64 min^{-1} (p=0.028). The highest CO measured after administration was 109±8% for the patients using β-blockers and 125±23% for patients not using β-blockers (p=0.156). HR did not change significantly over time in patients with β-blockers and patients without β-blockers usage (β-blockers at 300sec, 600sec; p=0.257 and p=0.167

respectively. Without β-blockers at 300sec,600sec; *p*=0.233 and *p*=0.326 respectively). Of ipsilateral and contralateral rSO_2 measured over time, no difference was observed for β-blockers use. Restoration MAP was lower in the patients using β-blockers. (87±12 mmHg vs 111±22 mmHg, *p*=0.039). Four patients in the phenylephrine-arm had a history PVD. In these patients, rSO_2 ipsilateral was significantly lower at administration (67±4% vs 75±7%), minimum (64±4% vs 73±7%) and maximum (70±5% vs 78±6%) measured rSO_2 after administration compared to patients without PVD. However, the absolute change of ipsilateral measured rSO_2 did not differ between groups over time. MAP and contralateral measured rSO_2 did not differ for patients with or without PVD.

Differences between Ephedrine and Phenylephrine

Effects on systemic and cerebral hemodynamic parameters were compared between the two treatment arms. The maximum increase of MAP after administration was significantly higher in the ephedrine group (p=0.016). Changes in HR and CO after administration did not differ significantly between groups. After adjustment of preoperative beta-blocker medication use, the results did not change and no significant interaction was found. Besides, changes in rSO_2 both ipsilateral and contralateral did not show any significant differences over time after administration between the ephedrine and phenylephrine group. (Table 3-5 and figure 2,3)

DISCUSSION

Both ephedrine and phenylephrine single dose administration for correcting intraoperative hypotension during CEA showed to be effective in restoring MAP and are equally effective in preserving the cerebral oxygenation (rSO_2) measured by NIRS. Based on the results of rSO_2 changes and cardiac output (CO), no preference can be expressed in favor of one of the investigated vasopressor agents. In this randomized controlled setting, our results do not confirm the findings of different clinical reports, which described a negative impact of administration of phenylephrine on rSO_2.[6–8,19,20]

Phenylephrine, as a pure α_1-adrenergic receptor agonist, solely increases peripheral total resistance, devoid of direct effects on cardiac contractility.[21] By stretching the arterial baroreceptors, an increase of MAP results in a baroreflex leading to a decrease of sympathetic activity on the peripheral blood vessels and the heart. This results in bradycardia and a decrease of CO.[7,22] It is remarkable that in the current study this suspected decrease in HR and CO, as a reflex to the increase in MAP, did not occur after administration of phenylephrine. These findings are confirmed by a recent study showing that baroreflex sensitivity (BRS) is absent during general anesthesia with sevoflurane. This explains the nonappearance a suspected BRS mediated decrease in

HR.[23] No difference was seen in CO after administration between groups. This can be explained by the ambiguous influence of phenylephrine on cerebral hemodynamics. In healthy subjects, phenylephrine administration led to a decrease in rSO_2.[6] While SV was not influenced, HR was lowered following phenylephrine administration resulting in a decrease in CO and restraining of cerebral oxygenation.[6] Others endorse the suggestion that administration of PE increases the arterial pressure, but lowers the rSO_2, as a consequence of the decrease in CO.[7,8,24] Conversely, the impact of a bolus of phenylephrine on CO is also related to the preload dependence of the heart. In preload-dependent patients, no effect of phenylephrine on CO will be expected.[24,25] Also, the patient population in the present study was vascular compromised, with a high possibility of systemic atherosclerotic vascular disease. This might suggest a different response in CO to phenylephrine in comparison with a healthy patient population.[26]

The earlier described decrease in rSO_2 after administration of phenylephrine, primarily measured in healthy non-cardiovascular patients, is more difficult to explain. We are aware of the fact that phenylephrine does not cross the blood-brain barrier. However, the influence of sympathetic activity on the cerebral blood flow is a matter of ongoing debate. Several studies showed the presence of α-receptors in the smooth muscle layer of the cerebral vessels and possible blood-brain permeability for α-receptors-agonists. In healthy subjects a change in rSO_2 determined with NIRS was inversely related to changes in MAP and cerebral blood flow. A reduction of cerebral perfusion has been observed despite an increase of the MAP.[27] This underpins the theory of cerebral vasoconstriction due to an α_1-effect of phenylephrine after all.[11,12] Further studies need to be addressed to determine the underlying mechanism behind this theory and to investigate the effect of catecholamines after a period of cerebral ischemia.

Stenosis of the carotid artery, due to its predominantly location in the proximal internal carotid and carotid bifurcation, can reduce the sensibility of the carotid sinus and consequently may impair the BRS.[1,28] Abnormal HR responses are described to various tests, as the Valsalva manoeuvre or postural test, in patients with a stenosis of the carotid.[29] Since the patients in this study have severe carotid artery stenosis, there is a high chance an impaired BRS will accompany this. We, therefore, hypothesize that patients with carotid stenosis and an impaired BRS respond differently to the administration of phenylephrine: after an increase of MAP, HR is not lowered and subsequently, CO does not decrease. (Figure 3) Although 43% of the patients in the PE group used preoperative β-blockers, no significant increase in HR after administration was measured.

Administration of ephedrine causes a release of norepinephrine, hereby stimulating α- and β-adrenergic receptors. This results in an elevation of MAP, HR and CO.[6] Ephedrine is effective in raising MAP in different scenarios, varying from volatile general intravenous anesthesia to spinal anesthesia. Ephedrine is not associated with a decrease of rSO_2 after administration.[7,8]

Pennekamp et al. described in 2012 a decrease of rSO_2 after administration of phenylephrine for treatment of hypotension in patients with carotid artery stenosis undergoing CEA.[13] Unlike these results, in this randomized controlled trial no decrease in rSO_2 was found after administration of phenylephrine in a similar, although larger patient population. Although a significant difference in rSO_2 was found in a small patient population that might suggest a powerful effect of phenylephrine on rSO_2, this decrease was noticed in only four CEA-patients. The small patient population (ephedrine n=7 and phenylephrine n=4) in the study of Pennekamp might have contributed to a distorted view, especially since patients were retrospectively included and not randomized to a treatment arm. This makes considerations of anesthesiologists to administer either phenylephrine or ephedrine for hypotension treatment not transparent. Therefore, we cannot rule out that the decision might be influenced by patient characteristics leading to confounding by indication. Second, the retrospective study of Pennekamp was used for power analyses calculation of this randomized controlled trial. Taken the above into consideration, this might have given an underestimation of the sample size and consequently our results.[13] A similar randomized controlled study to ours found a higher restoration of ipsilateral and contralateral rSO_2 after administration of ephedrine compared to phenylephrine and therefore recommends to prefer ephedrine. However, in our study, no significant difference was found in a decrease of rSO_2 after administration between both vasopressor agents.[30]

Limitations

In our study, the administrated dose of 50µg of phenylephrine was less compared to other studies, which used 80-200µg.[6–8] Nevertheless, the increase of MAP (70 to 87 mmHg after 5 minutes) in our study is comparable to other studies in which a larger bolus of 80µg was administrated and reported an increase of MAP from 73 to 86 mmHg or from 72 to 87 mmHg.[8,24]

Secondly, we used sevoflurane or isoflurane for maintenance of anesthesia, in contrast to other studies, who used propofol.[6,8] Due to the suppressive effect of propofol on the EEG monitoring, both sevoflurane or isoflurane are used regularly during CEA when EEG is monitored intra-operatively to decide whether a shunt is used or not.[31] Sevoflurane impairs cerebral autoregulation in high burst-suppression doses and has a vasodilatory

effect on the cerebral arteries.[32] It might have blunted the decrease in rSO_2 after a bolus of phenylephrine. Although a minimum alveolar concentration (MAC) of 0.5–1 was administered, which is beneath burst-suppression levels, little is known about the influence of sevoflurane on the already impaired CA. It is suggested that normal dose of sevoflurane does not affect an already impaired cerebral autoregulation.[23] Of note, within the current study we did not determine individual CA.

Thirdly, we used NIRS as cerebral perfusion monitoring for data analysis. A few reports have demonstrated that the NIRS signal is influenced significantly by extracranial contamination. Oxy-hemoglobin signals were affected by changes in skin blood flow during infusion of norepinephrine, hyperventilation, whole-body heating, injections of ephedrine and local extracranial hypoxia through a circumferential pneumatic head cuff.[33–35] The clinical implication of this extracranial contamination is uncertain. Several studies consider NIRS as complementing monitoring, to TCD and EEG, for detecting cerebral ischemia.[18] [18] Cerebral desaturation as detected by NIRS may be associated with adverse neurological outcomes and prolonged hospital stay.[36]

Fourth, all patients in both treatment arms received intravenous low dose norepinephrine at the moment of administration of the study medication conform standard anesthesiology care during carotid endarterectomy in our hospital. The effect of a single dose of phenylephrine and ephedrine for restoring of MAP after a period of hypotension on rSO_2 during CEA was determined. The period of hypotension of interest occurred under intravenous administration of norepinephrine. Vasopressor agents in both study arms were additional to intravenous peripheral low dose norepinephrine to restore MAP. In our belief, this reflects reality concerning the treatment of intraoperative hypotension during CEA. Additional, average given intravenous doses of norepinephrine in both study arms were similar. Therefore, the possible influence of norepinephrine on the results is suspected equally for both study arms. However, a pharmacological effect of both norepinephrine and volatile general anesthesia (sevoflurane or isoflurane) in combination with administration of either phenylephrine or ephedrine on the results cannot be excluded. Therefore, the results of this study cannot be directly extrapolated to the awake patient undergoing carotid endarterectomy.

Fifth, gold standard for determination of CBF is invasively and time consuming. A minimal-invasive alternative is determination of CBF by TCD. Unfortunately, TCD measurements were excluded from analyses due to a lot of missing data and therefore not reliable and useable for this study. Therefore, we were not able to determine the percentage changes in the flow in the middle cerebral artery per patient.

Finally, intraoperative hypotension in this study was defined as a decrease ≥20% to the awake baseline mean arterial pressure (MAP). The decrease of MAP at the moment of administration of vasopressor agents was in both groups ≥ 20% compared to awake MAP one day before surgery, which is according to protocol.[14] This used baseline BP was based on a single BP measurement and might not reflect patients' BP at home due to anxiety-induced stress of being in the hospital facing surgery. However, it is difficult to define a realistic baseline BP measurement which makes a ≥20% decrease of MAP intraoperative unclear. The previous study concluded that an optimal reference value or baseline BP for research purposes should be based on a preoperative 24h measurement at home. [37,38]

CONCLUSION

In the present randomized controlled study on intraoperative hypotension control, we did not find a different effect between phenylephrine and ephedrine on frontal cerebral lobe oxygenation in patients undergoing carotid endarterectomy. Both vasopressor agents maintained rSO_2. Based on our observations we cannot advise prioritizing the use of one of the agents above the other during CEA.

Acknowledgements
The Invos Cerebral Oximeter (Somanetics Corporation, Troy, MI, USA) was provided for the duration of the study by Covidien Nederland B.V., Zaltbommel, The Netherlands.

Table 1. Baseline characteristics

	Ephedrine (n=15)	Phenylephrine (n=14)
Age, years	72±8	71±9
Gender, male	7 (47%)	12 (86%)
BMI, kg·m^{-2}	27±5	27±4
DMII	4 (27%)	7 (50%)
Hypertension	10 (67%)	11 (79%)
Hypercholesterolemia	3 (20%)	8 (57%)
CAD	2 (13%)	5 (36%)
PVD	-	4 (29%)
AF	2 (13%)	1 (7%)
Pacemaker	2 (13%)	-
Smoking	6 (40%)	8 (57%)
• **Current**	5 (33%)	6 (43%)
• **Past**		
Alcohol	6 (40%)	9 (64%)
Pre-operative ß-blocker	3 (20%)	6 (43%)
Statin use	11 (73%)	13 (93%)
Operation-side (right)	5 (33%)	6 (43%)
Symptomatic, yes	15 (100%)	14 (100%)
Degree of ipsilateral stenosis	2 (13%)	5 (36%)
• **>95%**	13 (87%)	7 (50%)
• **70-95%**	-	2 (14%)
• **50-70%**		
Degree of contralateral stenosis	-	-
• **Occlusion**	-	1 (7%)
• **70 – 99%**	15 (100%)	13 (93%)
• **<70% or N.A.**		
Shunt use	2 (13%)	2 (14%)
NE infusion, µg·kg^{-1}·min^{-1}	0.05±0.03	0.05±0.03
Isoflurane, n (%)	6 (40%)	5 (36%)
Isoflurane dose, %	0.61% (IQR 0.20)	0.79% (IQR 0.53)
Isoflurane MAC-value	0.51 (IQR 0.17)	0.68 (IQR 0.45)
Sevoflurane, n (%)	9 (60%)	9 (64%)
Sevoflurane dose, %	1.65%(IQR 0.62)	1.46% (IQR 0.75)
Sevoflurane MAC-value	0.66 (IQR 0.25)	0.58 (IQR 0.30)
Non-responders	-	-
Preoperative systole, mmHg	154±13	142±19
preoperative diastole, mmHg	83±14	75±12
Preoperative MAP, mmHg	107±12	97±12

BMI: body mass index; DMII: Diabetes Mellitus type II; CAD: coronary artery disease; PVD: peripheral vascular disease; NE infusion: intravenous norepinephrine infusion rate at moment of administration of the study medication; MAP: mean arterial pressure. Values are shown as mean (±SD) or number of patients (%). MAC-value: minimum alveolar concentration. IQR: inter quartile range.

Table 2. Systemic and cerebral haemodynamics.

	Baseline	Drug Administration	300sec post	600sec post	Highest MAP	Highest CO	Lowest rSO_2
Ephedrine (n=15)							
MAP (mmHg)	80±14	75±11	94 ±17*	99±23*	122±22*	95±21	98±21
CO (%)	100±5	99±4	99±14	98±10	93±19	118±10^{+}	95±11
HR (min^{-1})	61±8	61±8	62±10	63±9	68±11*	69±10*	60±9
SV (%)	101±3	100±4	98±9	96±10	85±17*	102±12	97±9
SVR (%)	101±8	96±5	122±24†	128±32†	177±85*	103±9	132±38
rSO_2 (%) ipsi	73±9	72±9	73±8	73±7	73±8	74±8	70±8*
rSO_2 (%) contra	75±11	75±10	74±10	74±10	74±9	75±10	71±10*
Phenylephrine (n=14)							
MAP (mmHg)	76±13	70±9	87±13*	84±14*	101±22*	83±13	76±13
CO (%)	101±4	98±6	99±9	93±11	96±9	117±19	95±14
HR (min^{-1})	57±11	58±14	58±14	55±9	59±13	64±17†	56±13
SV (%)	101±5	100±7	99±10	96±9	92±10+	102±11	95±14
SVR (%)	104±7	96±10	123±19*	125±27†	140±24*	101±18	113±22
rSO_2 (%) ipsi	74±7	73±7	73±8	73±8	73±7	74±7	71±7*
rSO_2 (%) contra	74±8	73±8	73±8	74±8	72±9	74±9	72±8†

Systematic and cerebral haemodynamic variables in 120 seconds before administration (baseline), on the moment of administration (drug injection), at 300sec and 600sec after administration, during the highest mean arterial pressure (MAP), during the highest cardiac output (CO) and during the lowest frontal cerebral lobe oxygenation (rSO_2). HR: heart rate, SV: stroke volume, SVR: systemic vascular resistance. Data presented as mean ±SD. *p-value <0.001, †p-value <0.05 compared to administration.

Table 3. Cerebral oxygenation (rSO_2) over time between Ephedrine-group and Phenylephrine-group

	Ephedrine (n=15)	Phenylephrine (n=14)	*p*-value
Cerebral perfusion: ipsilateral to surgery			
rSO_2 at baseline,%	73±9	74±7	0.734
rSO_2 at administration,%	72±9	73±7	0.848
Lowest rSO_2,%	70±8	71±7	0.839
Highest rSO_2,%	76±7	76±7	0.912
Mean rSO_2 after administration,%	73±7	73±7	0.928
Restoring effect rSO_2 %%	100±3	99±4	0.302
Cerebral perfusion: contralateral to surgery			
rSO_2 at baseline,%	75±11	74±8	0.759
rSO_2 at administration,%	75±10	73±8	0.651
Lowest rSO_2,%	72±10	71±8	0.797
Highest rSO_2,%	77±9	76±9	0.674
Mean rSO_2 after administration,%	74±9	73±8	0.762
Restoring effect rSO_2 %%	100±3	99±2	0.875

MAP: mean arterial blood pressure. rSO_2: cerebral tissue perfusion. *P*-value was considered significant <0.05. Data in mean (standard deviation). Mann-Whitney U test was used to calculate the *p*-value for non-parametric variables. Restoring effect of rSO_2 was calculated by dividing 'mean rSO_2 after administration' by 'rSO_2 at baseline' *100.

Table 4. Absolute change after administration in systemic and cerebral haemodynamics

	Ephedrine (n=15)	Phenylephrine (n=14)	*p*-value
ΔMAP (mmHg)			
120sec	23±13	13±14	0.057
maximum	44±18	27±15	0.011
ΔrSO_2 ipsilateral (%)			
120sec	-.63±.9	0.04±1.9	0.239
Lowest	-2.3±1.5	-2.3±1.7	0.978
Highest	3.1±2.5	2.8±1.8	0.739
At highest MAP	-.4±1.9	0.7±2.3	0.657
ΔrSO_2 contralateral (%)			
120sec	-.9±2.2	-.04±1.3	0.227
Lowest	-2.5±2.2	-1.8±1.6	0.327
Highest	2.5±2.1	2.6±1.9	0.813
At highest MAP	.9±2.3	1.1±2.5	0.818
ΔHR (min^{-1})			
120sec	1±4	-2±6	0.069
Lowest	-9±7	-10±9	0.710
Highest	18±13	12±10	0.205
ΔCO (%)			
120sec	-2±7	-1±16	0.814
Lowest	-23±22	-22±14	0.819
Highest	19±9	20±18	0.874

MAP: mean arterial blood pressure. rSO_2: cerebral tissue perfusion. HR: heart rate. CO: cardiac output. *P*-value was considered significant <0.05. Data in mean (standard deviation). Mann-Whitney U test was used to calculate the *p*-value for non-parametric variables. Data analysed from moment of administration to 600 seconds after administration. Independent samples t-test.

Table 5. Relative change after administration in systematic and cerebral haemodynamics

	Ephedrine (n=15)	Phenylephrine (n=14)	*p*-value
ΔMAP (mmHg), %			
120sec	31±18	19±18	0.081
maximum	60±27	35±26	0.018
ΔHR(min^{-1}), %			
120sec	2±12	-3±9	0.211
Lowest	-4±11	-15±-14	0.013
Highest	13±25	22±20	0.318
ΔCO, %			
120sec	-2±7.5	-1±17	0.821
Lowest	-9±10	-8±9	0.756
Highest	8±7	5±8	0.379

MAP: mean arterial blood pressure. rSO_2: cerebral tissue perfusion. HR: heart rate. CO: cardiac output. *P*-value was considered significant <0.05. Data in mean (standard deviation). Mann-Whitney U test was used to calculate the *p*-value for non-parametric variables. Data analysed from moment of administration to 600 seconds after administration.

FIGURES LEGENDS

Figure 1. Flowchart of study.

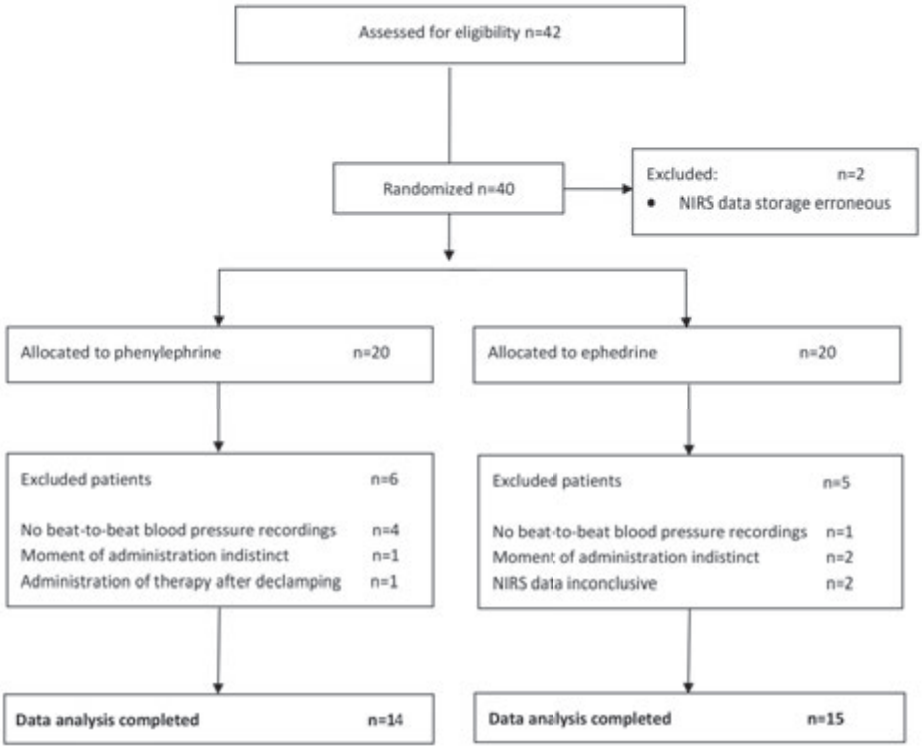


Figure 2. Percentile changes in mean arterial blood pressure (MAP) (A-B) and rSO_2 ipsilateral (%) (C-D) individually and mean for both Ephedrine and Phenylephrine over time (sec). Data in mean.

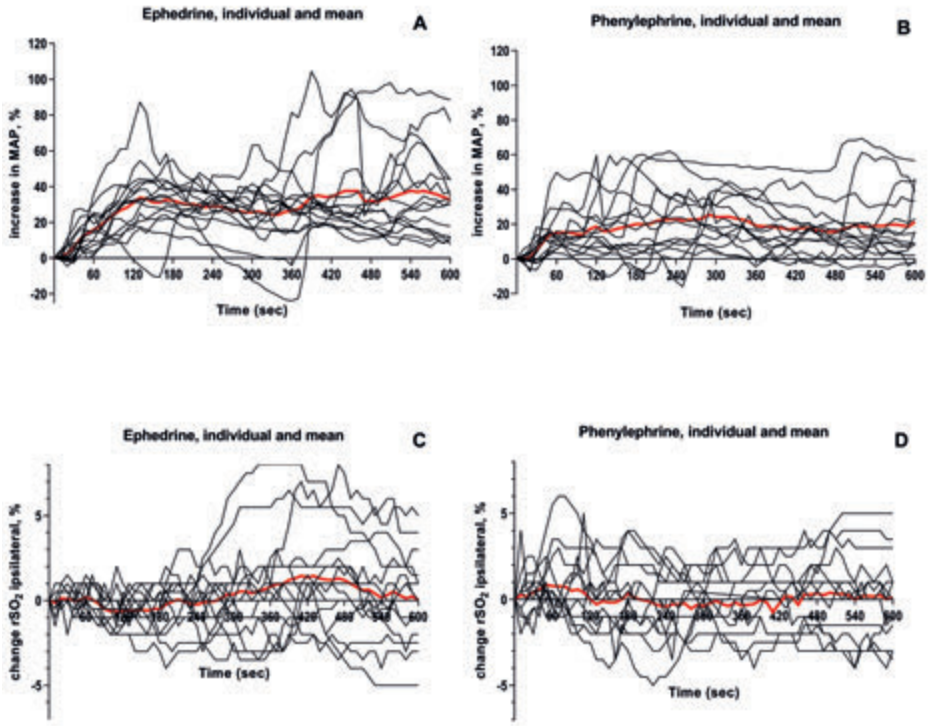
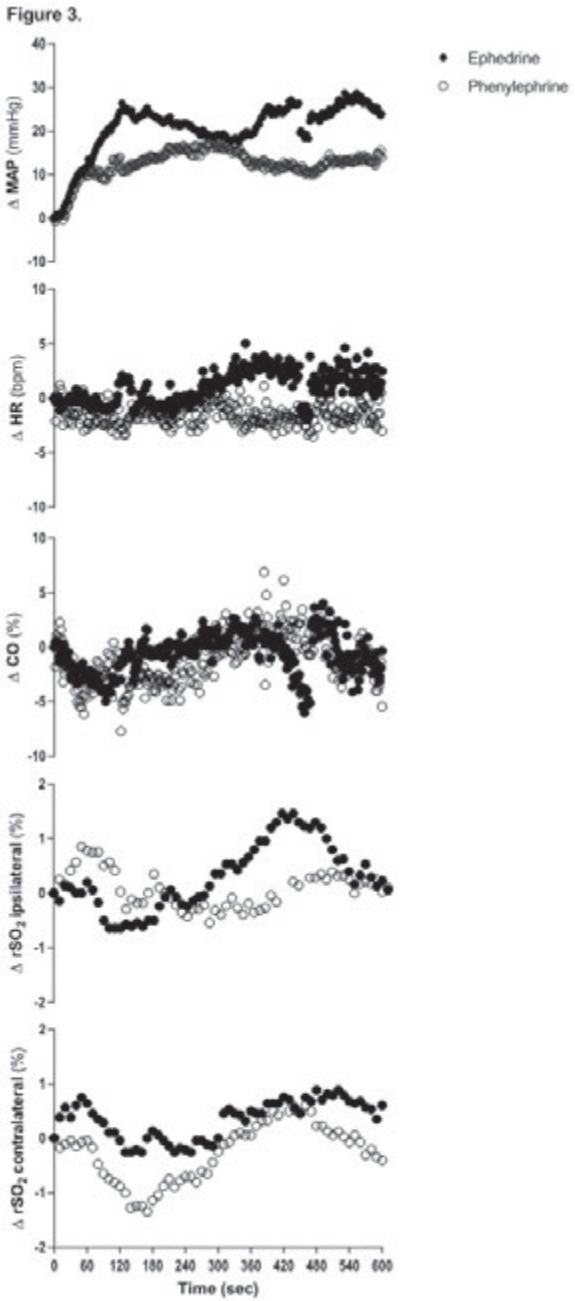


Figure 3. Changes in mean arterial blood pressure (MAP) (A), heart rate (HR) (B), percentile change in cardiac output (CO) (C) and frontal cerebral lobe oxygenation ipsilateral (D) and contralateral (E) during intravenously administration of ephedrine (filled circles) and phenylephrine (open circles) over time. Data in mean.



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CHAPTER 5

Preoperative Hypertension is Associated with Atherosclerotic Intraplaque Hemorrhage in Patients Undergoing Carotid Endarterectomy

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ABSTRACT

Objectives: Both hypertension and atherosclerotic plaque characteristics such as intraplaque hemorrhage (IPH) are associated with cardiovascular events (CVE). It is unknown if hypertension is associated with IPH. Therefore, we studied if hypertension is associated with unstable atherosclerotic plaque characteristics in patients undergoing carotid endarterectomy (CEA).

Methods: Prospectively collected data of CEA-patients (2002-2014) were retrospectively analyzed. Blood pressure(BP) was mean of 3 preoperative measurements. Preoperative hypertension was defined as systolic BP^{3}160mmHg. Post-CEA, carotid atherosclerotic plaques were analyzed for presence of calcifications, collagen, smooth muscle cells, macrophages, lipid core, IPH and microvessel density. Associations between BP (systolic and diastolic), patient characteristics and carotid plaque characteristics were assessed with univariate and multivariate analyses with correction for potential confounders. Results were replicated in a cohort of patients that underwent Iliofemoral endarterectomy.

Results: Within CEA-patients (n=1684), 708 (42%) patients had preoperative hypertension. Increased systolic BP was associated with the presence of plaque calcifications (adjusted OR1.11[95%CI1.01-1.22], p=0.03), macrophages (adjusted OR1.12[1.04-1.21], p<0.01), lipid core>10% of plaque area (adjusted OR1.15[1.05-1.25], p<0.01), IPH (adjusted OR1.12[1.03-1.21], p=0.01) and microvessels (adjusted beta 0.04[0.00-0.08], p=0.03). Increased diastolic BP was associated with macrophages (adjusted OR1.36[1.17-1.58], p<0.01), lipid core (adjusted OR1.29[1.10-1.53], p<0.01) and IPH (adjusted OR1.25[1.07-1.46], p<0.01) but not with microvessels nor plaque calcifications. Replication in an iliofemoral-cohort(n=657) showed that increased diastolic BP was associated with the presence of macrophages (adjusted OR1.78[1.13-2.91], p=0.01), lipid core (adjusted OR1.45[1.06-1.98], p=0.02) and IPH (adjusted OR1.48[1.14-1.93], p<0.01).

Conclusion: Preoperative hypertension in severely atherosclerotic patients is associated with the presence of carotid plaque macrophages, lipid core and IPH. IPH, as a plaque marker for CVE, is associated with increased systolic and diastolic BP in both CEA and iliofemoral population.

INTRODUCTION

Hypertension is one of the most common risk factors that affects 20-30% of the world population.[1] Hypertension is associated with cardiovascular events (CVE) such as myocardial infarction and stroke that have atherosclerosis as their underlying pathology.

In primary prevention, intensive blood pressure (BP) lowering in high-risk patients strongly reduces myocardial infarction and stroke.[2] Studies found a linear relation between high systolic BP levels and stroke risk, in which each 10mmHg reduction in systolic BP was associated with a one-third decrease of stroke incidence.[3,4] The risk of cardiovascular death increased gradually with increased systolic and diastolic BP levels.[5] Also in secondary prevention, BP lowering is associated with a reduction in stroke.[6]

CVE such as myocardial infarction and stroke mostly occur due to underlying atherosclerosis with activation of platelets on a ruptured or an eroded plaque surface. The association between BP and CVE is well established, but the association between BP and plaque progression is much less investigated. Lowering of systolic BP is associated with attenuation of coronary plaque progression while lowering of the diastolic BP is correlated with lower coronary plaque volume.[7–9] Increased BP was also associated with progression of carotid intima media thickness.[10] This shows that BP is associated with both plaque volume and plaque progression. However, no clear reversible process has been described.

On coronary plaque characteristics, a study demonstrated in a cross-sectional study design, that increased diastolic BP was correlated with higher plaque volumes, more fibrous and more calcified plaques measured by CTA.[9] No correlation between systolic BP and plaque volume or more fibrous and calcified plaques was found. These patients were well-controlled with systolic BP ranging from 95-154 mmHg. Two follow-up studies revealed that increased baseline systolic BP and diastolic BP were associated with an increase in atheroma volume of the coronary plaque after 1 or 2 years assessed with intravascular ultrasound.[7,11] It is unknown, however, if high BP is associated with IntraPlaque Hemorrhage (IPH) in coronary plaques.

Patients with carotid artery stenosis have an increased risk of CVE and death. Removal of the carotid plaque by carotid endarterectomy (CEA) is effective for severe symptomatic carotid artery stenosis in reducing the risk of future stroke and stroke-related death.[12,13] A possible association between BP and carotid atherosclerotic plaque characteristics such as IPH has not been studied despite that carotid plaque IPH is associated with

CVE.[14] For this, we hypothesize that pre-operative hypertension is associated with vulnerable plaque characteristics such as IPH in carotid plaques.

In this study, we investigated the association of pre-operative systolic and diastolic BP, on histological carotid plaque characteristics including IPH in patients undergoing CEA. As atherosclerosis is considered a systemic disease, we replicated the results of this CEA cohort in a separate cohort of patients with peripheral artery disease undergoing iliofemoral endarterectomy (IFE).

PATIENTS AND METHODS

This study was conducted in accordance with the declaration of Helsinki. Ethical approval for this study (TME/C01.18) was provided by the Medical Research Ethics Committee United (MEC-U) of St. Antonius Hospital Nieuwegein, The Netherlands on April 10, 2002.

Patient population

All patients in this study were included in the Athero-Express Biobank (AE biobank). The study protocol has been published before.[15] In short, the AE biobank is a large ongoing prospective biobank study executed in two tertiary referral hospitals in The Netherlands, namely the St. Antonius Hospital in Nieuwegein and the University Medical Center in Utrecht. This biobank collects carotid atherosclerotic plaques and preoperative blood specimens of patients undergoing carotid and/or iliofemoral endarterectomy (IFE). All consecutive patients undergoing CEA or IFE were eligible for this study. Patients were recruited on ward during admission the day prior to surgery. Written and oral information concerning participation was provided, and informed consent was signed. The indication for CEA for asymptomatic patients was based on the recommendations published by the Asymptomatic Carotid Surgery Trial (ACST) and for symptomatic patients the indication was based on recommendations based on the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[12,13,16]. Plaque removal was conducted by experienced vascular surgeons in accordance with local and international guidelines. Patients were followed for three years post-surgery for the occurrence cardiovascular events by annual standardized questionnaires and by checking medical files. In case further information was required to define whether a cardiovascular event has occurred, the general practitioner was consulted. From the included patients, 2029 out of 2341 (87%) had available follow-up data. Reasons for loss to follow-up included no response to follow-up questionnaires, referral to another hospital, unknown contact details because patients moved away or switch to different general practitioner of any reason.

Inclusion & exclusion criteria

For the present study, patients undergoing CEA or IFE between 2002 to 2014 with available plaque histology and preoperative BP measurements were included. Clinical data were extracted from patient files and collected through standardized questionnaires. Biochemical data were obtained preoperatively as part of the standard preoperative work-up, either during the visit to the outpatient clinic or on the ward. The mean of three pre-operative BP measurements was used for analyses. Patients were excluded in case no preoperative BP or histologic plaque assessment were available. Patients operated for restenosis of the carotid or iliofemoral arteries were excluded for analysis.

Sample collection

The sample collection protocol of the Athero-Express biobank had been described earlier.[17] To summarize: preoperatively a blood sample was collected and stored at -80 degrees. Routine laboratory measurements of total cholesterol, triglycerides, HDL, LDL and creatinine were assessed. The atherosclerotic plaque was processed immediately after surgery and divided into segments of 5-mm thickness. The section with the largest plaque burden was defined as the culprit lesion and was subjected to immunohistochemical staining. Segments were fixated in 4% formaldehyde, decalcified for one week in ethylenediaminetetraacetic acid (to soften the calcification in the plaque for handling purposes without fully dissolving it) and embedded in paraffin. This 5mm-segment of the culprit was cut into 5hm slices for histological analysis.

Histological assessment

Histological slides were assessed by a previously validated protocol.[15] In short, plaque specimens were stained to examine the plaque characteristics as following: CD68 for macrophages, α-actin to identify smooth muscle cells, Picro-sirius Red (PSR) for collagen, hematoxylin eosin for general overview including calcifications, hematoxylin eosin and PSR for lipid core and CD34 for microvessels. Hematoxylin and eosin staining and fibrin by Mallory's phosphotungstic acid hematoxylin staining were used to identify the presence of luminal thrombi and intraplaque hemorrhage (IPH). Semi-quantitative scoring at 40× magnification was performed for the amount of collagen, calcification, macrophage infiltration and smooth muscle cell content and was scored as (1) no or minor staining along part of the luminal border of the plaque or (2) moderate or heavy staining along the entire luminal border or evident parts within the lesion. IPH was defined as the composite of a luminal thrombi or intraplaque hemorrhages, hematoxylin-eosin and fibrin, assessed by Mallory's phosphotungstic acid hematoxylin staining. The presence of either luminal thrombosis, intraplaque hemorrhage or both was considered as positive plaque thrombosis. IPH is scored as present or absent.

Polarized light was used to assess the area of the lipid core of the plaque, expressed as a percentage of the total plaque area. In addition, macrophages and smooth muscle cells were quantified as the percentage of plaque area with the use of computerized analyses using AnalySIS 3.2 software (Soft Imaging Systems GmbH, Münster, Germany). Microvessels were counted in 3 hotspots of the plaque and subsequently averaged per slide. All histologic slides were assessed by two independent dedicated experts, who were blinded for patient characteristics and outcomes. Good inter-observer and intra-observer similarities have been confirmed previously (K 0.6-0.9).[18]

Study endpoints

The primary endpoint of this study was to determine the relation between preoperative BP and the atherosclerotic plaque characteristics. Preoperative BP was defined as BP measured on the outpatient clinic or ward before surgery. BP measurements used in this study were the mean of three available preoperative BP measurements. Preoperative hypertension was defined as systolic BP ³ 160 mmHg. Secondary, in order to obtain more information about the role of preoperative BP on the atherosclerotic plaque, results of the CEA-cohort were validated in an iliofemoral cohort. The secondary endpoint of this study was to determine the association of preoperative BP and secondary composite CVE during the three years after surgery. A composite endpoint of CVE included stroke, myocardial infarction, peripheral events or any cardiovascular death.

Statistical analyses

To evaluate whether an increased preoperative BP was associated with the presence of vulnerable atherosclerotic plaque characteristics, we analyzed our data for systolic and diastolic BP separately. Systolic and diastolic BP measurements were analyzed as a continuous variable, by steps of 20 mmHg Data was inspected for missing data. Baseline characteristics of patients with preoperative measured hypertension (systolic BP ≥160mmHg) were compared to those with normotensive preoperative BP measurement (systolic BP<160 mmHg). The chi-square test was used for categorical variables and an independent T-test or Mann-Whitney U test for continuous variables, as appropriate. Linear regression and logistic regression analysis were performed to investigate the correlation between plaque characteristics and BP, as appropriate. Non-normally distributed quantitative histological parameters, including macrophages, smooth muscle cells (SMC) and microvessels, required logarithmic transformation before entering into linear regression models. To adjust for potential confounders, multivariate logistic regression analysis and linear regression analysis was performed. Baseline characteristics that showed an association of p<0.20 with BP levels as well as with the plaque characteristic of interest were considered as potential confounders for multivariate analyses. (Supplemental Table 1,2) Since previous studies showed

time-dependent trends in plaque characteristics and simultaneously improvement in risk factor management, year of inclusion was not included as a confounder because lowering of BP is suggested to be an underlying etiological factor. (Table 1) Based on literature, symptoms status was added to the model.[17,19]

Results of multivariate logistic regression analyses of CEA-cohort will be compared to results of an iliofemoral cohort. Sub-analysis was performed to assess the relation between BP and secondary events within three years post-procedural. Cox-regression analysis was used. Values with a $p < 0.05$ were considered statistically significant. SPSS version 24.0 (SPSS Inc, Chicago, Illinois) was used for all statistical analyses.

RESULTS

Patient population

A total of 2383 patients who underwent carotid endarterectomy (CEA) and 720 patients who underwent femoral iliac endarterectomy (IFE) were included. After exclusion of patients with missing preoperative BP measurements or missing plaque histology, and restenotic lesions, 1684 CEA-patients and 657 IFE-patients were included in the analysis. 26 CEA-patients (1.5%) were also included in IFE-cohort. (See flowchart; Figure I)

CEA-cohort

Of the CEA-cohort, the majority of patients were male (68%) with a median age of 70 years (62-76, interquartile range, IQR). At the moment of inclusion, diabetes mellitus was reported in 23% of the patients, smoking in 35% and preoperative hypertension in 42%. In 87% of the patients, the carotid artery stenosis was symptomatic; these symptoms were mostly transient ischemic attacks (43%). The median timing between index event and surgery was 30 days [IQR61]. Patients with preoperative systolic hypertension were significantly older, were less often diabetic or had a history of coronary artery disease, had decreased kidney function and a more severe stenosis degree. Moreover, these patients had higher total cholesterol levels, higher LDL levels and less often used statins. Patients with preoperative systolic hypertension were operated more often in the earlier years (2002-2005) than in the later years (2010-2015). Remarkably, 80% of the patients with preoperative systolic hypertension used antihypertensive medications, for preoperative diastolic hypertension this was 75%. (Table 1)

Univariate logistic regression analyses showed a positive association between systolic BP (per 20 mmHg) and the presence of calcification, macrophage content, lipid core, IPH and the number of microvessels in the atherosclerotic plaque.

After adjustment for potential confounders, the association between increased systolic BP and macrophages (OR 1.12, 95%CI 1.04-1.21, $p < 0.01$), the presence of lipid core ≥ 10% and ≥ 40% (OR 1.15, 95%CI 1.05-1.25, $p < 0.01$ and OR 1.13, 95% CI 1.03-1.23, $p=0.01$, for 10% and 40%, respectively), calcification (OR 1.11, 95% CI 1.01-1.22, $p = 0.03$), IPH (OR 1.18, 95% CI 1.03-1.21, $p = 0.01$) and number of microvessels (OR 0.04, 95% CI 0.00 – 0.08, $p = 0.03$) remained statistically significant. (Table 2)

In addition, for diastolic BP (per 20 mmHg) univariate analysis showed that the presence of more macrophages (OR 1.36, 95%CI 1.17-1.58, $p < 0.01$), a lipid core ≥10% and ≥40% (OR1.29, 95%CI 1.10-1.53, $p < 0.01$ and OR1.25, 95%CI1.05-1.49, $p = 0.01$ for 10% and 40%, respectively) and IPH (OR1.25, 95%CI 1.07-1.45, $p < 0.01$) were associated. After adjustment for potential confounders, these vulnerable plaque characteristics retained a strong association with high diastolic BP. (Table 2)

Iliofemoral cohort

Replication of results in 657 iliofemoral patients showed similar trends in baseline characteristics and BP levels. (Supplemental Table 5,6) Univariate and multivariate analyses revealed no significant associations between systolic BP levels and vulnerable plaque characteristics. Regarding diastolic BP, increased diastolic BP showed a strong association with the presence of IPH (OR1.37, 95%CI 1.07-1.76, $p = 0.01$). (Table 3) After adjustment for potential confounders, diastolic BP remained associated with IPH (OR1.48, 95% CI 1.14-1.93, $p <0.01$). Also, increased diastolic BP levels were positively correlated with an increased number of macrophages and the presence of a lipid core >10% (OR 1.78, 95%CI 1.13 – 2.91, $p = 0.01$ and OR 1.45, 95% CI 1.06-1.98, $p=0.02$, respectively). (Table 3)

Secondary events

Three-year follow-up data of secondary composite CVE were available in 2029 patients of the total cohort of CEA (n=1448) and IFE (n=581). Secondary CVE within three years' post-procedural occurred in 669 patients (370 CVE in CEA cohort and 299 CVE in IFE cohort). Secondary CVE analyses corrected for cardiovascular risk factors showed a gradually increased risk for the composite endpoint with systolic BP (adjusted HR per 20mmHg increase 1.06, 95% CI 1.00-1.13), $p= 0.04$, but not for diastolic BP (adjusted HR per 20 mmHg 1.05, 95% CI 0.93-1.17), $p = 0.43$.

DISCUSSION

The current study investigated the association between BP and carotid atherosclerotic plaque characteristics. Our results show that both increased systolic and diastolic BP

levels were gradually associated with a more vulnerable plaque phenotype in patients with severe carotid artery stenosis undergoing CEA. Increased systolic BP and diastolic BP levels correlated with more macrophages, IPH and a larger lipid core. Similar trends were seen in the iliofemoral replication cohort as increased diastolic BP was associated with the presence of macrophages, IPH and a large lipid core.

Up to now, the relation between BP and carotid plaque characteristics has been unknown. Previous studies have mainly focused on carotid intima media thickness as determined by ultrasound. The only previous study that reported on histological carotid plaque characteristics in relation with BP was performed in a small asymptomatic hypertensive CEA cohort with specific patients that had a morning BP surge (defined as an increase of SBP ≥ 50 mmHg and/or DBP ≥22 mmHg in the early morning) versus those without. Patients with a morning BP surge showed more unstable plaques with more inflammation compared with those without a morning BP surge.[20] In contradiction to this previous study, our two cohorts are large with mainly symptomatic patients that are both hypertensive and non-hypertensive.

Although performed in a different study population and usage of different methods for plaque characterization, our results are in line with previous studies on the association of hypertension and coronary plaque characteristics. Increase in baseline BP was associated with coronary plaque atheroma (determined by intravascular ultrasound) which matches our association of high BP and a large lipid core in the carotid plaque. Intravascular ultrasound, however, does not allow detection of macrophages and IPH.

We replicated our findings in a cohort of patients undergoing IFE. Carotid and femoral plaques have been described to have different morphology.[21] While carotid plaques show more atheromatous plaques with larger lipid cores and more macrophages and T-cells and with more metalloproteinase MMP9 than the femoral plaques[21–23], femoral plaques have more stable fibrocalcified lesions with a lower concentration of cholesterol and a higher concentration of calcium.[21,22] Next to the vascular bed, this is probably due to the timing of surgery. In symptomatic patients undergoing carotid revascularization, treatment is performed preferably within the first two weeks after index event. In contrast, in patients with intermittent claudication complaints surgery is often preceded by exercise training resulting in delayed iliofemoral surgery.[24] Despite these intrinsic differences between carotid and femoral plaque morphology, we found that systolic and diastolic BP were in both cohorts associated with IPH, underlining the systemic importance of BP on IPH.

IPH in coronary plaques has been described to contain glycophorin A and iron from erythrocytes.[25] High levels of glycophorin A and iron have been associated with a large lipid core and high influx of macrophages suggesting that IPH represent a potent atherogenic stimulus.[25] In our carotid plaques, IPH is increased with high BP together with an increased lipid core and macrophage accumulation that might point to IPH increase as a result of high BP. In accordance, IPH in carotid plaques was associated with accelerated plaque progression and increased lipid core.[26]

Leakage of plaque microvessel endothelium has been held responsible for IPH in advanced human coronary atherosclerosis.[27] We only found an association of systolic BP and plaque microvessels in the CEA cohort and not in the iliofemoral cohort. One could hypothesize that increased BP could accelerate erythrocyte leakage from microvessels or cause rupture of these immature microvessels due to direct mechanic forces, both resulting in plaque instability with subsequent CVE.

Next to the association of high BP with vulnerable plaque characteristics, we found that patients despite treatment have residual hypertension, with respectively 86% and 82% of CEA and IFE patients having a systolic BP ≥160 mmHg while treated with antihypertensive medication. This could be either due to non-compliance of medications or unclose monitoring of the BP lowering effect by physicians. Surprisingly, diabetes and coronary artery disease were more frequently reported in patients with systolic BP ≤160mmHg. This is probably induced by selection bias since patients with a history of diabetes or coronary artery disease will be subjected to more stringent secondary preventive strategies and therefore more often screened for hypertension and subsequently treated with antihypertensive medications.

Residual hypertension in our cohorts together with the association of high BP with more macrophages, lipid core and IPH as markers of the rupture-prone plaque and IPH as plaque marker associated with CVE strongly indicates that intensive BP monitoring and intensive anti-hypertensive therapy is needed for these severely atherosclerotic patients.[14,28]

Limitations

Some limitations should be addressed. First, BP measurements used in the current study are in-hospital preoperative measurements that were assessed on the nursing ward conform preoperative work-up. Stress-induced factors or white coat hypertension can influence these in-hospital BP measurements. To diminish the effect of these factors, the used BP measurements are the mean of three preoperative BP measurements measured on the ward on separate moments in time. These blood

pressure measurements are conform BP measurements used in large clinical trials for management of arterial hypertension and most feasible in clinical practice.[29,30] Second, although we found in both carotid and iliofemoral cohort a correlation between vulnerable plaque characteristics and increased BP, no causal relation can be proven due to the cross-sectional study design. Future prospective trials should be addressed to investigate the causality of intensive BP treatment on atherosclerotic plaque characteristics. Third, as patients undergoing carotid artery stenting (CAS) were not included in these analyses, results cannot be extrapolated for CAS-patients. Finally, one out of five patients undergoing CEA have systolic BP inter-arm difference of >15 mmHg.[31] Nurses and healthcare takers in our hospitals are instructed to measure BP of patients undergoing CEA bilaterally, in which the side of the highest BP will be used for future BP measurements. However, there is no data available whether the mean of BP is solely based on single BP measurements of the highest arm. This might have influenced our results.[31,32]

CONCLUSION

In conclusion, increased systolic and diastolic BP levels are associated with more carotid plaque macrophages, lipid core and IPH in patients undergoing CEA. Replication in a separate iliofemoral cohort confirmed these associations.

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TABLES

Table 1. Patient characteristics CEA and IFE cohort

Patient characteristics	CEA (n=1684)	IFE (n=657)
Systolic BP, mmHg, mean[SD]	155 [26]	148 [23]
Diastolic BP, mmHg, mean[SD]	82 [13]	78 [13]
Sex, male(%)	1153 (69)	484 (74)
Age, years mean[SD]	69 [9]	67 [9]
BMI, mean[IQR]	26 [4]	26 [4]
Current smoker, n(%)	581 (35)	267 (41)
Alcohol use >10 units per week, n(%)	416 (25)	228 (35)
Diabetes Mellitus, n (%)	392 (23)	202 (31)
Renal function, eGFR in ml/min/1.73m2 median[IQR]	72 [27]	76 [27]
History of CAD, n(%)	519 (31)	286 (44)
Treated hypertension, n(%)	1297 (77)	553 (84)
PAOD, yes, n(%)	361 (21)	-
Clinical presentation		
• Asymptomatic, n(%)	223 (13)	-
• Ocular, n(%)	268 (16)	-
• TIA, n(%)	722 (43)	-
• Stroke, n(%)	464 (28)	-
Fontaine Classification		
• Fontaine IIb	-	308 (47)
• Fontaine III	-	156 (24)
• Fontaine IV	-	109 (17)
Stenosis ipsilateral		
• 50-70%, n(%)	118 (7)	51 (8)
• 70-99, n(%)	1528 (91)	458 (70)
Stenosis contralateral		
• 0-49%, n(%)	834 (50)	98 (15)
• >50%, n(%)	696 (41)	167 (25)
Year of surgery		
• 2002-2003, n(%)	248 (15)	39 (6)
• 2004-2005, n(%)	355 (21)	124 (19)
• 2006-2007, n(%)	285 (17)	121 (18)
• 2008-2009, n(%)	195 (12)	114 (17)
• 2010-2011, n(%)	314 (19)	164 (25)
• 2012-2013, n(%)	211 (13)	95 (15)
• 2014, n(%)	76 (4.5)	-
Triglycerides in mg/dL, median[IQR)	1.5 [1.0]	1.7 [1.2]
Total cholesterol in mg/dL, median[IQR]	4.4 [1.7]	4.4 [1.5]
HDL in mg/dL, median[IQR]	1.1 [0.4]	1.1 [0.4]
LDL in mg/dL, median[IQR]	2.4 [1.3]	2.4 [1.2]
Statin use, yes n(%)	1295 (77)	493 (75)
Antiplatelet use, n(%)	1491 (89)	548 (83)
Anti-coagulant use, n(%)	199 (12)	115 (18)

Diuretic use, n(%)	590 (35)	300 (46)
RAAS medication use, n(%)	854 (51)	417 (64)
B-blocker use, n(%)	738 (44)	301 (46)

Stenosis ipsilateral and stenosis contralateral refer to either carotid artery or iliofemoral artery. Degree of stenosis of the carotid artery was determined by the NASCET criteria. Baseline characteristics stratified for systolic and diastolic hypertension of CEA-cohort and IFE-cohort are presented in Supplemental Data.

Table 2 CEA plaque characteristics & systolic and diastolic BP

Systolic BP (per 20 mmHg)				
Semi-quantitative plaque characteristics	**Odds ratio unadjusted [95%CI]**	***p*-value univariate**	**Odds ratio adjusted [95%CI]**	***p*-value multivariate**
Moderate/heavy calcification	1.10[1.02-1.19]	**0.01**	1.11[1.01-1.22]	**0.03**[a]
Moderate/heavy collagen	1.00[0.91-1.10]	0.97	1.01[0.92-1.11]	0.83[b]
Moderate/heavy SMC	1.00[0.92-1.08]	0.90	0.95[0.86-1.04]	0.26[c]
Moderate/heavy macrophages	1.10[1.02-1.19]	**0.01**	1.12[1.04-1.21]	**<0.01**[d]
Presence of lipid core 10%	1.14[1.05-1.25]	**<0.01**	1.15[1.05-1.25]	**<0.01**[e]
Presence of lipid core 40%	1.12[1.03-1.21]	**0.01**	1.13[1.03-1.23]	**0.01**[f]
Presence of IPH	1.10[1.02-1.19]	**0.02**	1.12[1.03-1.21]	**0.01**[g]
Continuous plaque characteristics	**Beta unadjusted [95%CI]**	***p*-value univariate**	**Beta adjusted [95%CI]**	***p*-value adjusted [95%CI]**
Mean number of micro vessels per hotspot	0.04[0.01-0.07]	**0.01**	0.04[0.00-0.08]	**0.03**[h]
Diastolic BP (per 20 mmHg)				
Semi-quantitative plaque characteristics	**Odds ratio unadjusted [95%CI]**	***p*-value univariate**	**Odds ratio adjusted [95%CI]**	***p*-value multivariate**
Moderate/heavy calcification	1.05[0.91-1.21]	0.54	1.08[0.90-1.28]	0.41[i]
Moderate/heavy collagen	0.88[0.74-1.05]	0.14	0.91[0.76-1.09]	0.32[j]
Moderate/heavy SMC	0.97[0.83-1.13]	0.69	0.84[0.69-1.01]	0.06[k]
Moderate/heavy macrophages	1.32[1.14-1.52]	**<0.01**	1.36[1.17-1.58]	**<0.01**[l]
Presence of lipid core 10%	1.30[1.11-1.53]	**<0.01**	1.29[1.10-1.53]	**<0.01**[m]
Presence of lipid core 40%	1.22[1.04-1.44]	**0.01**	1.25[1.05-1.49]	**0.01**[n]
Presence of IPH	1.22[1.05-1.41]	**0.01**	1.25[1.07-1.46]	**<0.01**[o]
Continuous plaque characteristics	**Beta unadjusted [95%CI]**	***p*-value univariate**	**Beta adjusted [95%CI]**	***p*-value adjusted [95%CI]**
Mean number of micro vessels per hotspot	0.04[-0.02-0.11]	0.15	0.022[-0.51-0.10]	0.55[p]

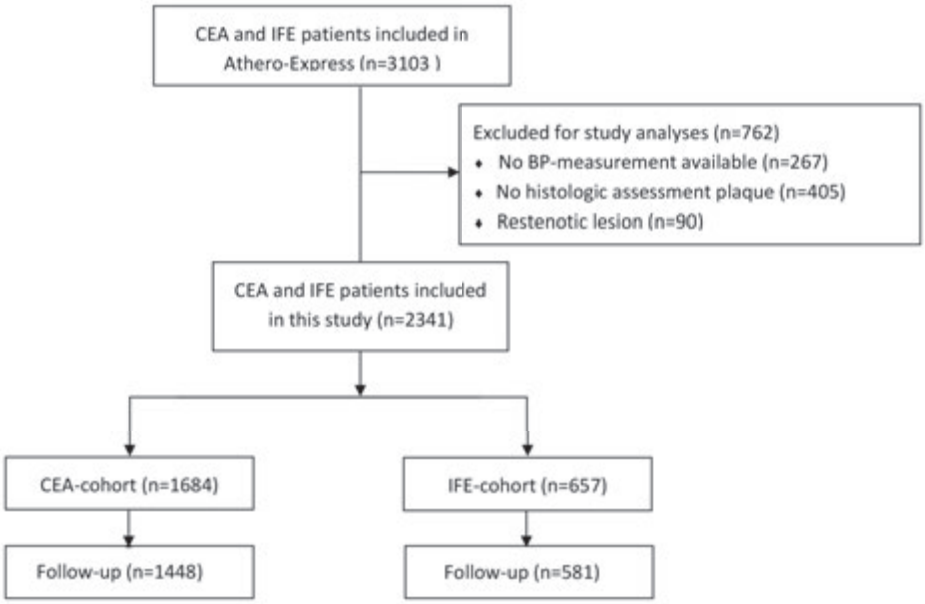
BP: blood pressure. SMC: smooth muscle cells. IPH: intraplaque hemorrhage Bold values were considered statistically significant; p<0.05. [a] corrected for age, eGFR, CAD, ipsilateral stenosis, clinical presentation, total cholesterol, gender, HDL. [b] corrected for ipsilateral stenosis, statins, clinical presentation. [C] corrected for age, clinical presentation, total cholesterol, LDL, Gender, eGFR. [D] corrected for clinical presentation, statins, gender. [e] corrected for age, diabetes, CAD, statins, gender and clinical presentation. [f] corrected for age, ipsilateral stenosis, statins, gender, clinical presentation. [g] corrected for CAD, statins, gender, clinical presentation. [h] corrected for age, diabetes, ipsilateral stenosis, clinical presentation and triglycerides. [I] corrected for age, CAD, ipsilateral stenosis, clinical presentation, total cholesterol, PAOD. [J] corrected for ipsilateral stenosis, statins, clinical presentation, PAOD. [k] corrected for age, clinical presentation, total cholesterol, LDL. [l] corrected for clinical presentation, statins, anti-coagulant use. [m] corrected for age, diabetes, CAD, statins, clinical presentation. [n] corrected for age, ipsilateral stenosis, statins, PAOD, BMI, clinical presentation. [o] corrected for CAD, statins, BMI, clinical presentation. [p] corrected for age, diabetes, ipsilateral stenosis, clinical presentation, triglycerides, BMI.

Table 3. Patient characteristics iliofemoral-cohort and systolic BP

Systolic BP (per 20 mmHg)				
Semi-quantitative plaque characteristics	**Odds ratio unadjusted [95%CI]**	***p*-value univariate**	**Odds ratio adjusted [95%CI]**	***p*-value multivariate***
Moderate/heavy calcification	1.01[0.88-1.15]	0.92	1.00[0.88-1.15]	0.95[a]
Moderate/heavy collagen	0.97[0.81-1.16]	0.72	1.03[0.86-1.24]	0.73[b]
Moderate/heavy SMC	0.95[0.83-1.10]	0.52	1.00[0.86-1.16]	0.99[c]
Moderate/heavy macrophages	0.97[0.81-1.16]	0.75	1.03[0.81-1.32]	0.79[d]
Presence of lipid core, 10 %	1.13[0.97-1.33]	0.12	1.14[0.97-1.34]	0.11[e]
Presence of lipid core, 40%	1.13[0.74-1.71]	0.57	1.10[0.74-1.36]	0.63[f]
Presence of IPH	1.05[0.92-1.19]	0.48	1.21[1.00-1.47]	0.05[g]
Continuous plaque characteristics	**Beta unadjusted [95%CI]**	***p*-value univariate**	**Beta adjusted [95%CI]**	***p*-value adjusted [95%CI]**
Mean number of micro vessels per hotspot	-0.03[-0.12-0.07]	0.61	0.39[-0.23-0.09]	-0.07[h]
Diastolic BP (per 20 mmHg)				
Semi-quantitative plaque characteristics	**Odds ratio unadjusted [95%CI]**	***p*-value univariate**	**Odds ratio adjusted [95%CI]**	***p*-value multivariate***
Moderate/heavy calcification	0.94[0.73-1.20]	0.61	1.01[0.78-1.30]	0.96[i]
Moderate/heavy collagen	0.94[0.67-1.32]	0.72	0.90[0.63-1.29]	0.57[j]
Moderate/heavy SMC	0.88[0.67-1.17]	0.38	0.79[0.59-1.05]	0.11[k]
Moderate/heavy macrophages	1.38[0.98-1.93]	0.06	1.78[1.13-2.91]	**0.01**[l]
Presence of lipid core>10%	1.30[0.96-1.76]	0.09	1.45[1.06-1.98]	**0.02**[m]
Presence of lipid core>40%	1.43[0.65-3.13]	0.38	1.55[0.71-3.42]	0.27[n]
Presence of IPH	1.37[1.07-1.76]	**0.01**	1.48[1.14-1.93]	**<0.01**[o]
Continuous plaque characteristics	**Beta unadjusted [95%CI]**	***p*-value univariate**	**Beta adjusted [95%CI]**	***p*-value adjusted [95%CI]**
Mean number of micro vessels per hotspot	0.02[-0.16-0.20]	0.82	0.08[-0.23-0.39]	0.60[p]

BP: blood pressure. SMC: smooth muscle cells. IPH: intraplaque hemorrhage. Bold values were considered statistically significant; p<0.05. *[a] corrected for age, eGFR, smoking, CAD. [b] corrected for age, anti-coagulants use, CAD. [c] corrected for age, antiplatelet use, anti-coagulant use, smoking. [d] corrected for HDL, smoking, CAD. [e] corrected for age, smoking, antiplatelet. [f] corrected for age, smoking, statins. [g] corrected for anti-coagulant use, amputation, CAD, triglycerides. [h] corrected for HDL, statins, smoking, triglycerides. [i] corrected for age, CAD. [j] corrected for age, anti-coagulant use, CAD. [k] corrected for age, anti-coagulant use. [l] corrected for HDL, LDL, CAD. [m] corrected for eGFR, age. [n] corrected for age, statins. [o] corrected for anti-coagulant use, amputation, CAD, eGFR. [p] corrected for HDL, LDL, eGFR, total cholesterol, statins.* **(supplement Table 2.)**

Figure 1. Flowchart of included patients in study



CEA: carotid endarterectomy, IFE: iliofemoral endarterectomy, BP: blood pressure.

Figure 2. Histologic panel of symptomatic and asymptomatic patients stratified for blood pressure

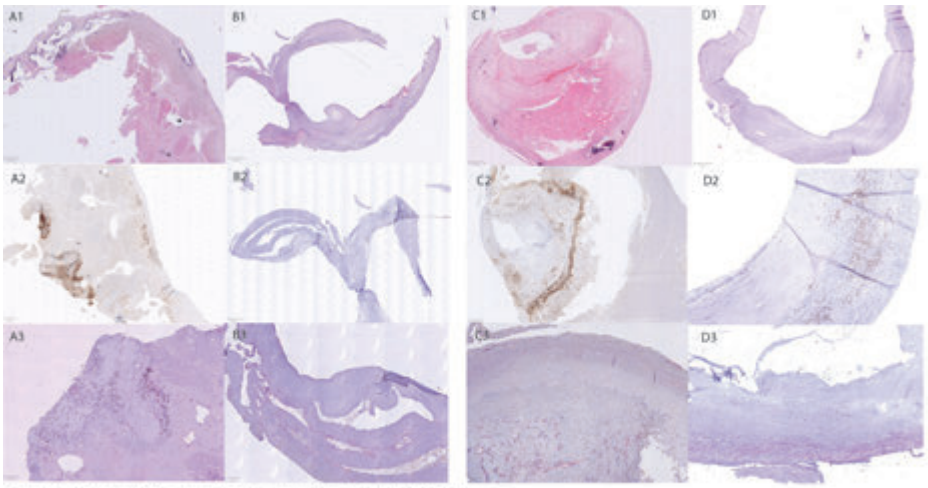


Figure 2. Histologic panel of symptomatic and asymptomatic patients stratified for blood pressure
(A) Symptomatic patient with high blood pressure. (A1) HE staining. (A2) CD68 staining. (A3) CD34 staining. (B) Symptomatic patient with normal blood pressure. (B1) HE staining. (B2) CD68 staining. (B3) CD34 staining. (C) Asymptomatic patients with high blood pressure. (C1) HE staining. (C2) CD68 staining. (C3) CD34 staining. (D) Asymtomatic patient with normal blood pressure. (D1) HE staining. (D2) CD68 staining. (D3) CD34 staining.

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SUPPLEMENTARY MATERIAL

Appendix I. CEA-cohort: confounders used for correction per plaque characteristic
Appendix II. Iliofemoral-cohot: confounders used for correction per plaque chacateristic
Appendix III. CEA-cohort: patient characteristics and systolic BP
Appendix IV. CEA-cohort: patient characteristics and diastolic BP
Appendix V. Iliofemoral-cohort: patient characteristics and systolic BP
Appendix VI. Iliofemoral-cohort: patient characteristics and diastolic BP
Appendix VII. CEA-cohort: plaque distribution
Appendix VIII. Iliofemoral-cohort: plaque distribution

Supplementary material is omitted due to space limitation, and can be found at the journal website.

CHAPTER 6

Defining the awake baseline blood pressure in patients undergoing carotid endarterectomy

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Submitted

ABSTRACT

Objective: To minimize the incidence of intraoperative stroke following carotid endarterectomy (CEA) under general anaesthesia, blood pressure (BP) is suggested to be maintained between 'awake baseline' BP and 20% above. However, there is neither a widely accepted protocol nor a definition to determine this awake BP. In this study, we analysed the BP during hospital admission in the days before CEA and propose a definition of how to determine awake BP.

Methods: Of 1180 CEA-patients, all non-invasive BP-measurements were retrospectively analysed. BP was measured during preoperative outpatient screening (POS), the last three days before surgery at the ward and in the operating room (OR) directly before anaesthesia. Primary outcome was the comparability of all these preoperative BP measurements. Secondary outcome was the comparability of preoperative BP measurements stratified for postoperative stroke within 30 days.

Results: POS BP [148±22/80±12mmHg (MAP 103±14mmHg)] and the BP measured on the ward 3,2,1 days before surgery and on the day of surgery [146±25/77±13 (MAP 100±15)], [142±23/76±13 (MAP 98±15)], [145±23/76±12 (MAP 99±14)] and [144±22/75±12mmHg (MAP 98±14)] were comparable (all p=NS). BP in the OR directly before anaesthesia was higher, [163±27/88±15mmHg (MAP 117±18mmHg)] (p<0.01 vs all other preoperative moments). In 772 patients (65%) pre-induction BP was ^{3}10mmHg higher compared to preoperative BP measured on the ward or POS. In 496 patients (42%) this difference was ^{3}20mmHg. The average difference between pre-induction BP and all preoperative BP-moments was 17±26/10±15mmHg (MAP 16±18, $p<0.001$). A significant higher pre-induction systolic BP and MAP was observed in patients with a 30-day stroke compared to patients without (p=.034 and p=.042). Preoperative BP measurements did not differ significantly between groups.

Conclusion: Awake BP should be determined by averaging available BP-values collected preoperatively on the ward and POS. BP measured in the OR directly before induction of anaesthesia is significantly higher compared to any other preoperative BP-measurement and should not be used.

INTRODUCTION

The benefit of carotid revascularization is hampered by the risk of periprocedural stroke due to the intervention itself. Although both intra-procedural and post-procedural strokes are multifactorial in origin, hemodynamic disturbances are an essential mechanism for the development of periprocedural stroke following carotid endarterectomy (CEA).[1,2]

In patients with a severe carotid artery stenosis, ipsilateral cerebral blood flow during carotid cross-clamping mainly depends on adequate collateral circulation through the Willis' circle.[3] Therefore, strict arterial blood pressure (BP) control has been recommended to preserve adequate cerebral perfusion during CEA. However, there is a precarious balance in BP control during surgery since intraoperative hypotension may lead to cerebral hypoperfusion resulting in inadequate cerebral perfusion and ischemic cerebral compromise while hypertension, on the other hand, may lead to cerebral hyperperfusion and - ultimately - cerebral haemorrhage.[1,2,4] Further, intraoperative hemodynamic disturbances have been associated with increased postoperative stroke risk.[1] To avoid these complications and to preserve and maintain adequate cerebral perfusion during surgery, it is suggested to keep the intraoperative arterial BP between 'the awake baseline BP' and 20% above.[7] In 2014, Heyer et al. found significantly fewer patients developed early cognitive dysfunction with MAP ≥20% above baseline during cross-clamp than those managed <20% above, showing the importance of this boundary.[5] Unfortunately, recommendations in current guidelines regarding BP thresholds are lacking.[6]

The applied term 'awake baseline BP' however is rarely and differently defined ranging from BP in the outpatient clinic to BP before induction in the operating room while the patient is still awake.[7–10] It is currently unknown what the variance of several preoperative BP measurements is over time in patients undergoing CEA.

In this study, we analysed the comparability of the preoperative BP before CEA to propose a uniform and standardized definition to assess the 'awake baseline BP' reliably.

MATERIALS AND METHODS

Study population and design

This study was designed as a retrospective cohort study of prospectively collected data of all patients who underwent CEA in the University Medical Centre Utrecht (UMC Utrecht), the Netherlands (a tertiary vascular referral centre) in the period between

2003 to 2017. First, all CEA patients were identified using the Utrecht Patient Oriented Database (UPOD). UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the UMC Utrecht. UPOD data acquisition and management was in accordance with current regulations concerning privacy and ethics. The structure and content of UPOD have been described in more detail elsewhere.[11] Second, of these patients, all non-invasive oscillometric BP measurements obtained preoperatively on the ward in rest on the day of surgery up to three days before surgery and on the outpatient preoperative evaluation clinic (POS) were collected from UPOD. All BP measurements on ward or POS were obtained by several automated non-invasive BP devices. On the POS, the blood pressure was measured on both arms in rest in the sitting position by a doctor or specialized nurse after the history is taken. Periprocedural BP measurements measured in the operating room (OR), non-invasively as well as invasively, were obtained by Datex-Ohmeda S/5 anaesthesia monitor (GE, Healthcare, Waukesha, WI) and Arbocath 20 G (Hospira, Lake Forest, IL, USA), respectively and stored by monitoring program Anstat (Carepoint Nederland B.V., Ede, The Netherlands).

Patients were included when they were undergoing CEA for treatment of carotid artery stenosis, when they had a non-invasive blood pressure measurement before induction in operating room and when at least one preoperative BP measurement on the ward up to 3 days before surgery or on the POS was available.

The pre-induction BP was defined as an awake oscillometric non-invasive BP measurement in the OR before administration of any medication used during induction of anaesthesia (e.g. rocuronium, etomidate, atracurium, propofol, sufentanil or midazolam). When no non-invasive upper arm oscillometric BP was measured before induction of anaesthetics in the OR, patients were excluded from further analyses. If no other preoperative non-invasive BP measurements were available in addition to pre-induction BP, patients were excluded. All patients continued administration of blood pressure lowering drugs, except for diuretics in case they were not indicated for heart failure, preoperatively prior to surgery. Patients did not receive sedative premedication.

All patients underwent CEA under general anaesthesia. CEA was performed by an experienced vascular surgeon or a vascular trainee under the supervision of a vascular surgeon. All patients were neurologically monitored during surgery by electroencephalogram (EEG) and transcranial Doppler (TCD) in case there was a window. An intraluminal shunt was placed selectively in case of EEG asymmetry or a decrease of >70% of mean flow velocity in the middle cerebral artery measured by

TCD. Intraoperative target BP was between 100 and 120% of BPpreind during clamping. Postoperatively, all patients were admitted to the recovery unit for hemodynamic and neurological monitoring for at least 6 hours.

The secondary endpoint of this study was to determine if the comparability of preoperative BP-measurements and pre-induction BP-measurement differ for patients who developed a stroke within 30-days after surgery compared to patients without a 30-day stroke.

The local medical ethics committee waived the need for written informed consent (UMC Utrecht Medical Research Ethics Committee, protocol number 17-523/C). Data were collected and provided anonymously by a data manager.

Statistical analysis

Baseline characteristics of patients with differences of < 10mmHg and ≥ 10mmHg between pre-induction mean arterial blood pressure (MAP) and the mean of all preoperative BP measurements were compared. Categorical variables were compared using Chi-square tests or Fisher's exact (if the expected number of frequencies was < 5). Continuous variables were compared using Student's t-test when normally distributed or Mann-Whitney U test when non-normally distributed data.

Differences between means of preoperative BP measurement on the ward versus pre-induction BP on the OR (systolic/diastolic and mean arterial BP) were evaluated. Additionally, the difference between the average of all preoperative BP measurement of each patient and pre-induction BP were evaluated. The 'average' preoperative BP was calculated for each patient by the mean of all available preoperative BP measurements measured on the ward and POS. These differences in mean BP were assessed with paired samples t-test with 95% confidence intervals (CI). Differences between non-normally distributed paired samples were assessed by Wilcoxon signed rank Test. Mean difference between BP measurements over time of ≥ 10mmHg was considered clinically relevant.[12] These differences of 10 mmHg or more were chosen to avoid measurement errors due to the use of multiple oscillometric BP devices. Data are provided as mean (±standard deviation) for normally distributed continuous data. Non-normally distributed continuous data are provided as median (interquartile) and categorical variables as n (percentage). For baseline characteristics, a *p*-value of <0.05 was considered statistically significant. Bland-Altman plots were used to visualize the differences between BP measurements and the 95% limits of agreement.[9] To correct for multiple testing for analyses regarding the several BP measurements, Bonferroni was used. Therefore, a *p*-value of < 0.003 (0.05/15) for analyses regarding BP measurements

was considered statistically significant.[13,14] Additional to the mean (SD) the median [IQR] was calculated to adjust for possible outliers, artefacts and errors. (Supplemental Data, Table 1) Data analysis was performed using SPSS (release 24.0 for Windows; SPSS Inc., Chicago, IL).

RESULTS

In total, 1307 CEA patients were eligible for inclusion. In total 73 cases (5.6%) were excluded as no non-invasive BP measurements on the ward were registered in electronic patient records. In 54 (4.1%) patients, only a pre-induction BP in the OR was available. Due to the absence of any other preoperative BP measurements, these patients were excluded.

Of the remaining 1180 CEA patients, the majority was male (70%) with an average age of 69 years, was symptomatic (89%) and had a history of hypertension (use of hypertensive agents, 76%). (Table 1) In addition to a pre-induction BP, 850 (72%) patients had one other preoperative BP measurement, and 330 (28%) had two or more. In 684 (58%) patients, a BP measurement measured during POS was available. No differences were found for the use of any antihypertensive agents and β-blockers in particular between the patients with an increased MAP in the OR compared to preoperative BP of ≥10 mmHg (n=772) and those with an increase of less than 10 mmHg (n=408, p =.160 and p = .081, respectively, see Table 1).

Blood pressure during hospital admission

The mean BP measured on the POS was 148±22/80±12mmHg (systolic/diastolic) with a MAP of 103±14mmHg (n=684). BP measured during preoperative day three on the nursing ward was 146±25/77±13mmHg; MAP 100±15mmHg (n=143), on preoperative day two 142±23/76±13mmHg; MAP 98±15mmHg (n=128), on preoperative day one 145±23/76±12mmHg; MAP 99±14mmHg (n=517). On the day of surgery, the BP was 144±22/75±12mmHg; MAP 98±14mmHg (n=205; figure 1). All did not significantly differ from each other (p=NS).

The mean 'awake baseline BP' determined by averaging all preoperative BP measurements collected preoperatively on the ward and POS was 146±22/78±12mmHg with a MAP of 101±14mmHg (n=1180). The mean pre-induction BP in the OR directly before anaesthesia was higher; 163±27/88±15mmHg with a MAP of 117±18mmHg (p<.001; n=1180).

Blood pressure in the operating room vs awake baseline blood pressure

In 772 patients (65%) pre-induction BP in the OR was ≥ 10mmHg higher compared to preoperative BP measured on the ward or POS. In 42% the pre-induction MAP was ³ 20mmHg higher compared to preoperative BP measurements. The mean difference between all various preoperative BP measurements and the pre-induction BP in this patient cohort was 17±26, 10±15 and 16±18mmHg for systolic BP, diastolic BP and MAP, respectively (95% CI 15-18, 95% CI 9-11, 95% CI 15-17 with p<.001, p<.001, p<.001, respectively) (table 2). No statistically significant differences in results were found when the median was used instead of the use of mean. (Supplemental data, table 1)

Figure 2 shows the Bland-Altman plots of the differences for the average preoperative MAP of the total cohort compared to pre-induction MAP. This Bland-Altman plot demonstrates a mean bias of 16 mmHg with 95% limits of agreement ranging from -20 to 51 mmHg. Although wide-spread, 82% of the patients in this cohort had a higher MAP measured in the OR as compared to any other preoperatively measured MAP. Figure 3 shows the Bland-Altman plots of the differences between the separate preoperative MAP measurements in time and the pre-induction MAP. Despite a lower number of patients per preoperative measurement, the plots show a positive difference in MAP in the majority of patients with a mean bias > 10mmHg (Figure 3).

When the 'awake baseline BP' was higher, the bias between the 'awake baseline BP' and the pre-induction BP declines (from +34±14 mmHg in the 65-75 mmHg range to +8±19 mmHg in the 115-125 mmHg interval; Figure 4).

Stratification for postoperative stroke within 30 days, a significant higher pre-induction systolic BP and MAP were observed in patients who developed postoperative a stroke compared to patients who did not develop a postoperative stroke. (systolic 173±20mmHg vs 163±27mmHg, p=.034; MAP 123±15 vs 116±19mmHg, p=.042) Preoperative BP measurements did not differ significantly between groups.

DISCUSSION

In our cohort of CEA patients, the BP measured in the OR directly before induction of anaesthesia significantly overestimates the averaged BP during hospital admission in the vast majority of the patients. Moreover, the higher the pre-induction BP, the larger the overestimation of the averaged BP measuring during the entire preoperative hospital admission. Therefore, the pre-induction BP in the OR directly before surgery cannot be used to determine the awake baseline BP. All preoperative BP measurements on the nursing ward and the POS were comparable, irrespectively of the missing information of

the laterality of the measuring arm. Therefore, it seems suitable to define the 'baseline' or 'awake' BP as an average of all preoperative BP measurements found in the electronic medical records.

The overall results of the current study show a widespread distribution of the differences in BP (figures 2 and 3). However, the 95% limits of agreement for the MAP were less diverse compared to the distribution of the systolic measurements. There is a regression towards the mean in the patients with extreme preoperative or pre-induction BP values; although the majority of patients (82%) had a higher pre-induction BP measurement with a mean difference of 16 mmHg (figures 2,4). These figures also illustrate the importance of an individual BP policy per patient instead of correcting every pre-induction BP with the mean bias of 16 mmHg (figure 4). By averaging all preoperative available BP measurements not only diurnal rhythms but also stress-induced and activity effects are taken into account.

Stress-induced factors or white coat hypertension can influence in-hospital BP measurements both in the OR as well as on the ward or outpatient clinic, varying from a single increased BP measurement to consistently increased BP measurements.[15] Conversely, the use of sedative pre-medication, fasting state before surgery e.g. may lead to a decreased BP measurement. Previous studies confirmed our observations that pre-induction BP is higher than BP measured at other moments.[12,16,17] In a recent study, including 3360 patients undergoing a wide variety of non-cardiac procedures, the averaged MAP measured before induction of anaesthesia was 11 mmHg (95% CI, 10-11) higher than a single preoperative BP measurement on the POS. In 52% of their study population, a positive difference of more than 10 mmHg (which was considered clinically relevant) was found.[12]

Our study contains a vascular compromised patient group in whom adequate BP regulation is of utmost importance. To achieve and maintain an intraoperative target BP between 'normal' and 20% above baseline, as advised to minimize the risk of intraoperative complications due to hypotension and hypertension, can be challenging.[7] Especially, when the intraoperative target BP was based on a pre-induction BP measured in the OR that already overestimated the averaged awake BP during hospital admission. Maintaining this excessive high BP level can only succeed when large quantities of vasopressor and positive inotropic agents are administered. Increasing heart rate and higher systemic vascular resistance to meet BP targets increases the myocardial tissue oxygen demand.[18–20] In patients where the supply of myocardial oxygen is already jeopardized, this increase in demand may lead to an imbalance in the supply-and-demand relationship and thereby ischemia.[21] Furthermore, periprocedural hypertension

is a known leading cause of cerebral hyperperfusion and cerebral hyperperfusion syndrome.[22–24] The exact association between duration of intraoperative hypotension and hypertension and perioperative stroke need to be further investigated in future research, as well as the proposed definition of the 'awake baseline' BP and periprocedural outcome.

The majority of cerebral complications after CEA occur in the 'late' postoperative phase, between day 1-30 postoperatively.[1] Due to the timing of onset of these postoperative cerebral complications after CEA, it is difficult to simply address these complications to intraoperative BP management. International carotid stenting study (ICSS) showed that the mechanism of 'late' postoperative stroke in CEA-patients was primarily hyperperfusion and of hemodynamic origin.[1] This might imply that factors like postoperative BP variations and cerebral perfusion play a more critical role. The profit for stroke prevention after CEA primarily lies in the postoperative phase with strict postoperative BP control. Unfortunately, since large clinical trials are still missing, there is no consensus on this topic, and yet no recommendations can be made in the current international guidelines.[6,23,24] Further research on this topic is of great importance.

The study has several limitations. First, 8.5% of patients were excluded due to missing pre-induction BP measurements (4.6%) or other preoperative BP measurements additional to the pre-induction BP (3.9%). Missing pre-induction BP in the OR resulted of the chosen definition of induction, namely the administration of any induction medication. Although this was most likely a registration artefact, therefore, we excluded all patients where BP in the OR was registered during or after administration of any induction medication. Unavailable preoperative BP measurements on the ward or POS could not be retrieved in 46 patients due to the switch of non-electronic to electronic patient record system in 2003 and the introduction of a new electronic patient record system in 2011. Given the small number of these patients, we do not think this would have influenced our results.

Secondly, CEA patients often reveal an inter-arm BP difference, with one out of five CEA patients with a systolic inter-arm BP difference of > 15mmHg.[25] However, in our dataset there was no data available on whether all following BP's are measured on the same arm and with the highest BP. This might have influenced our results, although a more visual and significant difference in the several preoperative BP measurements would then have been expected (figure 1).

Third, over the years several automated non-invasive oscillometric BP devices have been used. Due to the long inclusion period, we were not possible to determine these

different devices in retrospect. This may have influenced our results, however due to the relatively short time period of preoperative admission these different NIBP-devices may only affect the between patient differences and not the intra-patient differences.

CONCLUSION

The 'baseline' or 'awake' BP should be determined by averaging all available preoperative BP values in the electronic patient medical records to guide intraoperative BP management during carotid endarterectomy. Pre-induction BP measured in the OR is significantly higher than any other preoperative BP measured on the ward or POS and should, therefore, not be used.

TABLES

Table 1. Characteristics of cohort

Patient characteristics	Total (n=1180)	MAP <10mmHg (n=408)	MAP ≥10mmHg (n=772)	*p*-value	*Missing data (%)*
Pre-induction systolic BP, mmHg [SD]	163 [27]	145 [23]	173 [24]	**<0.001**	0 (0)
Pre-induction diastolic BP, mmHg [SD]	88 [15]	80 [13]	93 [14]	**<0.001**	0 (0)
Pre-induction MAP BP, mmHg [SD]	117 [18]	102 [15]	124 [16]	**<0.001**	0 (0)
Gender, male (%)	828 (70)	276 (68)	552 (72)	0.181	0 (0)
Age, years [SD]	69 [10]	68 [10]	70 [9]	**0.007**	0 (0)
BMI [SD]	26 [4]	26.4 [4]	26.5 [4]	0.746	33 (2.8)
Renal function, eGFR [SD] *MDRD*	70 [21]	72 [20]	70 [21]	0.080	126 (11)
Alcohol use (%)	725 (61)	243 (61)	482 (64)	0.338	24 (2.0)
Smoking (%)	390 (33)	130 (32)	260 (34)	0.558	12 (1.0)
Ipsilateral stenosis	10 (1)	3 (1)	7 (1)	0.687	40 (3.4)
• 0-49%	106 (9)	33 (8)	73 (10)		
• 50-70%	1024 (87)	359 (91)	665 (90)		
• 71-99%					
Contralateral stenosis	569 (48)	201 (57)	368 (56)	0.885	167 (14)
• 0-49%	113 (10)	36 (10)	77 (12)		
• 50-70%	165 (14)	59 (17)	106 (16)		
• 71-99%	166 (14)	56 (16)	110 (17)		
• Occlusion					
History of					
• DM II (%)	281(24)	87 (21)	194 (25)	0.151	1 (0.1)
• CAD (%)	359 (30)	113 (28)	246 (33)	0.125	20 (1.7)
• PAOD (%)	233 (20)	77 (19)	156 (21)	0.539	23 (1.9)
• TIA or stroke (%)	916 (78)	313(78)	603 (79)	0.500	15 (1.3)
• Asymptomatic carotid stenosis (%)	134 (12)	47 (12)	87 (12)	0.465	29 (2.5)
• Hypertension, yes (%)	883 (75)	298 (74)	585 (77)	0.389	14 (1.2)
• Hypercholesterolemia, yes (%)	778 (66)	265 (71)	511 (74)	0.345	106 (9)
Medication use					
• Hypertension drugs (%)	842(71)	287 (74)	555 (78)	0.160	76 (6.4)
• Clopidogrel (%)	197 (17)	56 (14)	141 (18)	0.049	3 (0.3)
• B-blockers (%)	481 (41)	152 (37)	329 (43)	0.081	3 (0.3)
• Calcium channel blockers (%)	291 (25)	107 (26)	184 (24)	0.394	3 (0.3)
• ACE inhibitors (%)	354 (30)	122 (30)	232 (30)	1.000	3 (0.3)
• Diuretics (%)	408 (35)	144 (35)	264 (34)	0.748	3 (0.3)
• Angiotensin II antagonist (%)	276 (23)	94 (23)	182 (24)	0.885	3 (0.3)
• Statins (%)	989 (84)	332 (82)	657(85)	0.112	3 (0.3)
• Insulin (%)	78 (7)	20 (5)	58 (8)	0.109	3 (0.3)
• Oral antidiabetics (%)	194 (17)	65 (16)	129 (17)	0.804	3 (0.3)

P values are based on comparison of the patients with < 10 mmHg and ≥10mmHg mean difference in mean arterial pressure (MAP) between pre-induction BP and average of all preoperative BP measurements. PAOD: peripheral artery occlusive disease. BP: blood pressure. SD: standard deviation. Numbers are values (%) or in mean [SD].

Table 2. Differences in blood pressure between measurements over time.

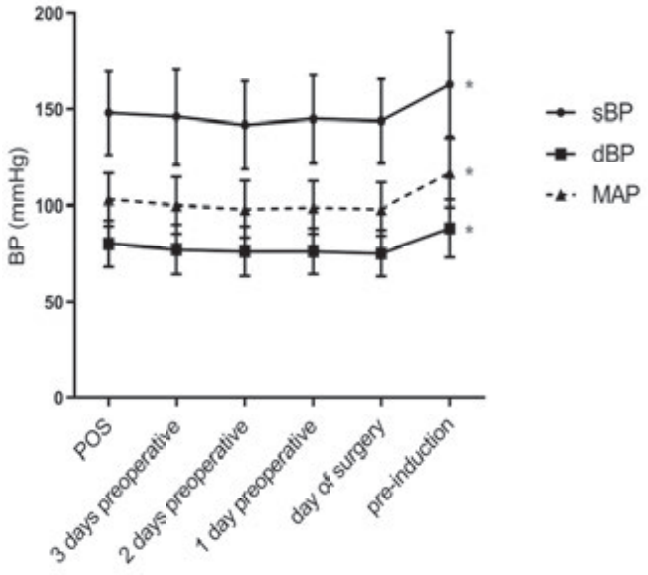
Measurement (delta in mmHg)	Number patients	Mean diff sBP (mmHg)	95% CI		Mean diff dBP (mmHg)	95% CI		Mean diff MAP (mmHg)	95% CI	
BP day0 – pre-induction BP	205	17±25*	14	21	11±14*	9	13	16±17*	14	19
BP 1 day preoperative – pre-induction BP	517	14±26*	12	17	10±15*	9	12	15±18*	13	16
BP 2 days preoperative – pre-induction BP	128	19±29*	14	24	11±17*	8	14	18±19*	14	21
BP 3 days preoperative – pre-induction BP	143	12±28*	7	16	9±15*	7	11	13±19*	10	16
POS BP – pre-induction BP	684	19±28*	16	21	10±16*	8	11	16±19*	15	17
Average all preoperative – pre-induction BP	1180	17±26*	15	18	10±15*	9	11	16±18*	15	17
BP 1 day preoperative – BP day0	183	-3±20	-6	0.3	-1±12	-3	0.2	-2±13	-4	0
BP 2 days preoperative – BP day0	62	0±20	-5	5	0±12	-3	3	0±14	-3	4
BP 3 days preoperative – BP day0	55	0±21	-6	6	0±12	-3	3	0±13	-3	4
POS BP – BP day0	11	-3±32	-25	19	-1±12	-9	7	-2±16	-13	9
BP 2 days preoperative –1 day preoperative	114	4±22	-0.2	8	0±10	-2	2	1±13	-1	4
BP 3 days preoperative – 1 day preoperative	128	-2±25	-7	2	-3±14*	-5	-.2	-2±16	-5	0
POS BP – 1 day preoperative	54	1±29	-7	9	2±14	-2	6	2±17	-3	6
BP 3 days preoperative – 2 days preoperative	74	-5±22	-10	1	-0.2±11	-3	2	-2±14	-5	2
POS BP – 2 days preoperative	17	2±22	-9	13	2±12	-4	7	2±14	-5	9
POS BP – 3 days preoperative	16	6±18	-4	15	2±10	-4	7	3±12	-3	9

Values are means ± standard deviation. * Statistical significant difference of $p < 0.05$.

MAP: mean arterial pressure. sBP: systolic blood pressure. dBP: diastolic blood pressure. 95% CI: 95% confidence interval. Mean difference of MAP (in mmHg) over time.

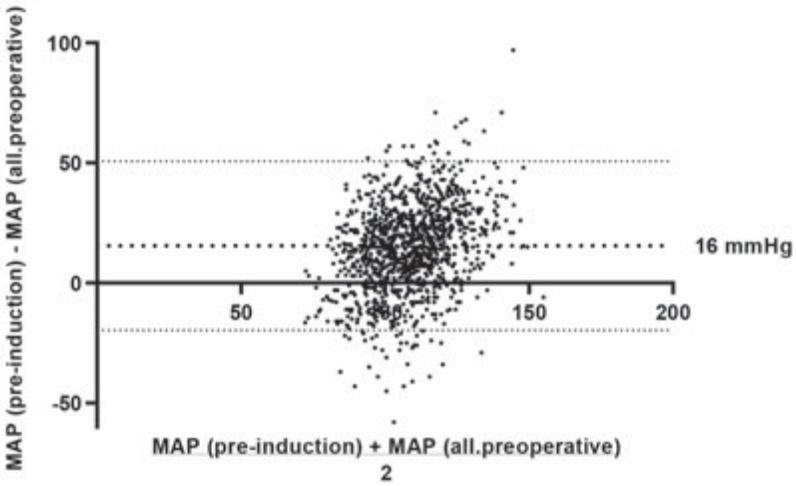
FIGURE LEGENDS

Figure 1. Changes of blood pressure over time



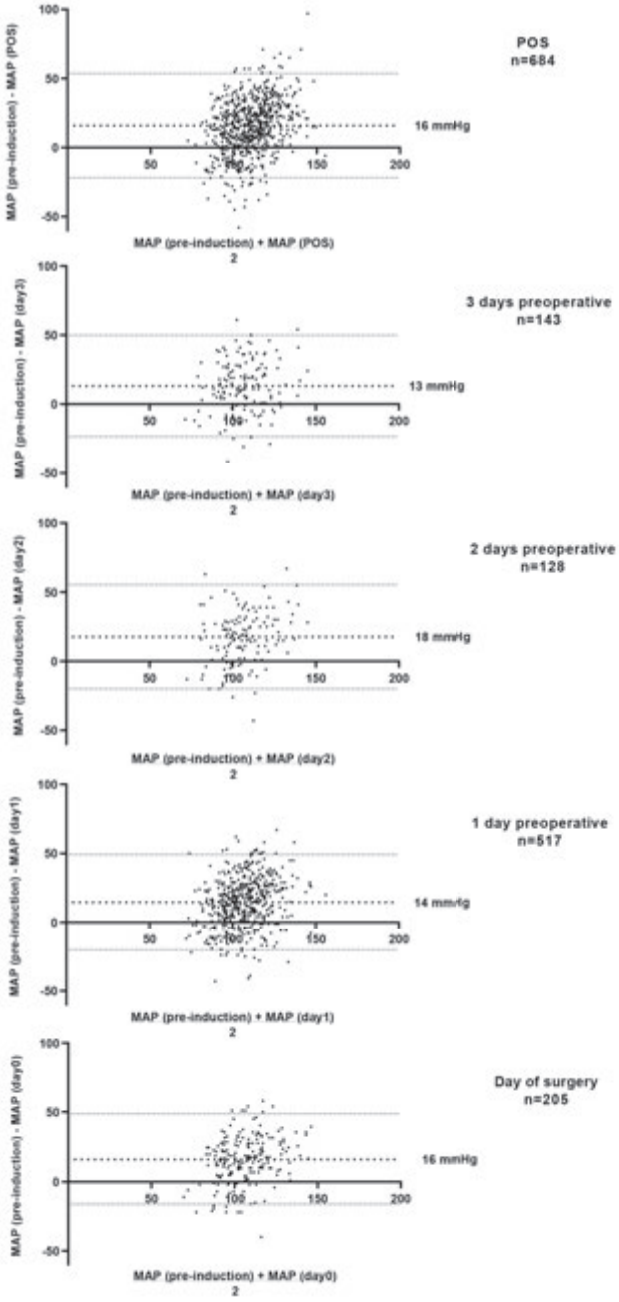
sBP: systolic blood pressure. dBP: diastolic blood pressure. MAP: mean arterial pressure. POS: preoperative outpatient screening. Data are in mean (±SD). Asterisks mark statistically significant increases.

Figure 2. Bland-Altman plot for differences between preoperative BP (MAP) and pre-induction BP (MAP).



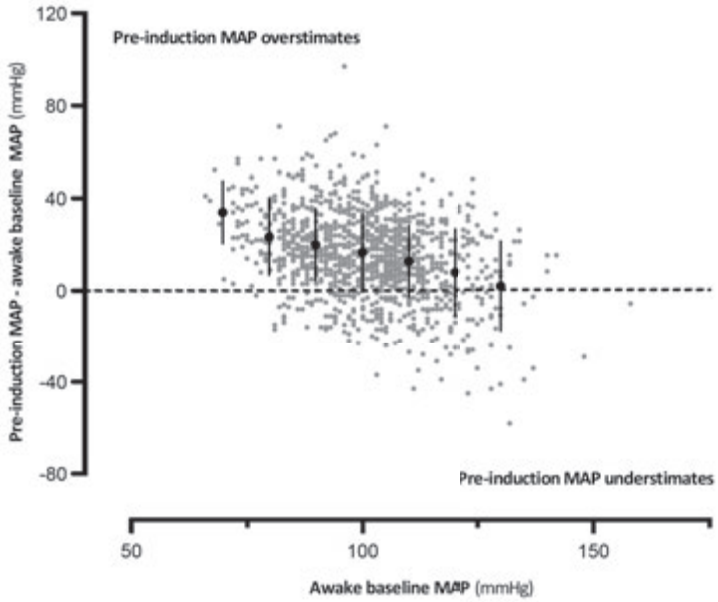
MAP: mean arterial pressure. Preoperative.all: average of all preoperative MAP measurements. Data are in mean (±SD). Dotted lines are the upper and lower 95% limits of agreement. The dashed line indicates a mean difference of 15mmHg.

Figure 3. Bland-Altman plots for differences between preoperative BP (MAP) and pre-induction BP (MAP).



Bland-Altman plots for total cohort per moment in time. MAP: mean arterial pressure. Preoperative. all: average of all preoperative MAP measurements. POS: preoperative outpatient screening. Data are in mean (±SD). Dotted lines are the upper and lower 95% limits of agreement. The dashed lines indicate mean differences.

Figure 4. Bias between pre-induction MAP and 'awake baseline' MAP related to the height of the 'awake MAP level.



MAP: mean arterial pressure. The dotted line is the line of no difference. Grey dots are individual patients (n=1078). Black dots represent the bias between awake baseline mean blood pressure and pre-induction blood pressure per 10mmHg interval. Data are in mean (±SD).

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CHAPTER 7

Intraoperative hypotension is a risk factor for postoperative silent brain ischemia in patients with preoperative hypertension undergoing carotid endarterectomy

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ABSTRACT

Objective: Intraoperative hemodynamic instability during carotid endarterectomy (CEA) has been associated with an increased risk of procedural stroke. Diffusion-weighted imaging (DWI) lesions have been proposed as a surrogate marker for perioperative silent cerebral ischemia. This study aimed to investigate the relation between perioperative blood pressure (BP) and presence of postoperative DWI-lesions in patients undergoing CEA.

Methods: A retrospective analysis was performed based on symptomatic CEA-patients included in the MRI-substudy of the International Carotid Stenting Study. Relative intraoperative hypotension was defined as a decrease of intraoperative systolic BP ≥20% compared to preoperative ('baseline') BP, absolute hypotension was defined as a drop in systolic BP <80mmHg. Primary endpoint was presence of any new DWI lesions on postoperative MRI (DWI-positive). Occurrence and duration of intraoperative hypotension was compared between DWI-positive and DWI-negative patients as was the magnitude of the difference between pre- and intraoperative BP.

Results: 55 symptomatic CEA-patients were included of whom eight were DWI-positive. DWI-positive patients had a significantly higher baseline systolic (186±31 vs 158±27 mmHg, p=.011) and diastolic BP (95±15 vs 84±13 mmHg, p=.046) as compared to DWI-negative patients. Other preoperative characteristics did not differ. Relative intraoperative hypotension compared with baseline occurred in 53/55 patients (median duration 34 minutes; range 0 – 174). Duration of hypotension did not significantly differ between the groups (p=.088). Mean systolic intraoperative BP as compared to baseline, revealed a larger drop of BP (-37±29mmHg) in DWI-positive compared to DWI-negative patients (-14±26mmHg, p=.024). Absolute intraoperative systolic BP values did not differ between the groups.

Conclusion: In this exploratory study, high preoperative BP and a larger drop of intraoperative BP were associated with periprocedural cerebral ischaemia as documented with DWI. These results call for confirmation in an adequately sized prospective study, as they suggest important consequences for perioperative hemodynamic management in carotid revascularization.

INTRODUCTION

Hemodynamic disturbances such as bradycardia and extreme hypotension are an important pathophysiological mechanism of stroke after carotid endarterectomy (CEA) and carotid artery stenting (CAS)[1,2]. However, little is known about the risks of more subtle variations in perioperative blood pressure (BP) on postoperative stroke. In addition, in patients undergoing CEA, cerebral autoregulation and collateral circulation may be compromised, which may lead to cerebral hypoperfusion even in the absence of systemic hemodynamic disturbances[3–6]. Cerebral hypoperfusion may lead directly to hypoxia and subsequently ischemia in areas of the brain or may interact with embolic mechanisms by inhibition of the washout of artery-to-artery emboli during CEA[7,8]. Micro-emboli during the dissection procedure of the carotid artery are correlated with postoperative development of new ischemic lesions on diffusion-weighted imaging (DWI) after CEA, which may be aggravated by hypoperfusion[9].

The occurrence of silent periprocedural ischemic brain lesions on MR-DWI after revascularization of the carotid artery, either with CAS or CEA, has been a topic of increasing interest[10,11]. A considerably high incidence of new postprocedural DWI lesions is reported after both CAS (50%) and CEA (17%)[11–14]. Ischemic areas can be identified on DWI within minutes of a hypoxic episode and thus DWI lesions are a useful surrogate marker for early cerebral complications. The presence of new DWI lesions after CEA and CAS is associated with a higher risk for periprocedural stroke[15] and with a higher risk for future stroke or TIA after CAS[10] or non-cardiac surgery in general[16]. Additionally, postoperative brain lesions have been associated with cognitive decline and dementia[16–18].

A small number of studies investigating the relation between intraoperative BP and its effect on the development of new DWI lesions have been performed in CEA patients[9,19,20]. Most of these studies report merely on severe intraoperative hemodynamic depression (e.g. severe hypotension, bradycardia, asystole) instead of investigating more subtle variations in BP. We hypothesized that patients with intraoperative hypotension have an increased risk for the development of new silent ischemic lesions. Therefore, we aimed to explore the association between intraoperative BP-measurements and the occurrence of new silent ischemic lesions on MR-DWI characteristics in patients undergoing CEA.

METHODS

A retrospective analysis was performed based on prospectively collected data of patients included simultaneously in the MRI-substudy of the International carotid stenting study (ICSS)[14] and the Utrecht Patient Oriented Database (UPOD)[11]. The structure and content of UPOD have been described in more detail previously[21]. Patients randomized in the ICSS for CEA in the University Medical Center (UMC) Utrecht were included. Patients included in the ICSS (between October 2003 and October 2008) had a symptomatic carotid stenosis >50% deemed to require treatment. Exclusion criteria were: previous revascularization in the randomized artery, contraindications for either treatment and planned major surgery[13]. UPOD is a data registry curated by medical experts comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated in the UMC Utrecht. UPOD data acquisition and management is in accordance with current regulations concerning privacy and ethics. BP-measurements were related to MR-DWI outcome parameters (primary outcome measure) as well as postoperative adverse events (stroke, myocardial infarction, cardiovascular death – secondary outcome measures).

Blood pressure measurement

Intraoperative blood pressure ($BP_{intraop}$) registration, both invasive radial artery BP-measurements as well as oscillometric non-invasive BP-measurements (NIBP) of brachial artery, were compared to NIBP measured prior to surgery ('baseline'). $BP_{intraop}$ was measured in the operating room (OR), non-invasively as well as invasively (112Hz, 60s-samples). Measurements were obtained by Datex-Ohmeda S/5 anaesthesia monitor (GE, Healthcare, Waukesha, WI) and Arbocath 20G (Hospira, Lake Forest, IL, USA), respectively and stored in the Anesthesia Information Management System (Anstat, Carepoint Nederland B.V.,Ede, The Netherlands).

Two types of baseline BP-measurements were used: preoperative-BP (BP_{preop}) and preinduction-BP (BP_{preind}). BP_{preop} was defined as BP measured on the outpatient clinic or ward no longer than one month before surgery, using a mean of all available BP_{preop} measurements. BP_{preind} was defined as an awake oscillometric non-invasive BP-measurement in the OR before administration of any medication used during induction of anaesthesia. Intraoperative hypotension was defined both as a decrease of ≥20% below baseline (relative hypotension) or an absolute drop in systolic BP below 80mmHg (absolute hypotension)[22]. Intraoperative hypertension was defined as an increase of ≥20% of systolic BP compared to baseline values[23]. $BP_{intraop}$ was analysed from the time of anaesthesia induction until emergence. For further data analysis, results of $BP_{intraop}$ will be compared to BP_{preop} and BP_{preind} in a separate fashion. The occurrence

of intraoperative hypotension, intraoperative hypertension and the duration of these changes in BP were associated with the presence of DWI lesions as was the magnitude of the differences in BP. Variation in BP_{intrap} was described by calculation of the standard deviation (SD) of all (invasive radial artery) systolic and diastolic $BP_{intraop}$ measurements within a patient.

CEA protocol

All patients underwent CEA under general anaesthesia and, in 53% of patients, an additional cervical plexus block. CEA was performed by an experienced vascular surgeon or a vascular trainee under the supervision of a vascular surgeon. All patients were neurologically monitored during surgery by electroencephalogram (EEG) and transcranial Doppler (TCD). An intraluminal shunt was placed selectively in case of EEG asymmetry or a decrease of >70% of mean flow velocity in the middle cerebral artery (MCA) measured by TCD. Intraoperative target BP was between 100 and 120% of BP_{preind} during clamping. Postoperatively, all patients were admitted to the recovery unit for hemodynamic and neurological monitoring for at least 6 hours.

MRI

MRI was performed on day 1-7 prior to surgery (preoperative MRI) and day 1-3 after surgery (postoperative MRI). DWI sequences were used at each scan to detect acute ischemic brain lesions. MR field strength was 1.5 or 3 Tesla. A neurologist and a neuroradiologist, both masked to intraoperative features analyzed all scans as previously described[14]. The number and volume of hyperintense lesions on DWI were measured. Volumes of separate lesions were calculated by measuring lesion diameters in three axes, converted to ml. Lesions were considered separate if there was no continuity on the same slice as well as on adjacent slices. Primary outcome parameter was presence of any new postoperative (ipsi- or contralateral) ischemic lesion on MR-DWI, secondary outcome parameter was DWI lesion volume and count.

TCD

Intraoperative routine TCD monitoring was performed for cerebrovascular monitoring whenever acoustic temporal bone window was adequate (preoperatively assessed). A pulsed Doppler transducer was placed over the temporal bone to insonate the main stem of the ipsilateral MCA, with the TCD transducer being fixed with a head frame and flow velocity measured continuously. The increase or decrease of flow velocity after cross-clamping of the carotid artery was calculated as a percentage compared to values prior to cross-clamping. Microemboli during the procedure were scored and registered as present or absent by an experienced clinical neurophysiologist.

Statistics

Data were inspected for patterns of missing values. The proportion of randomly missing values for baseline characteristics was less than 4%. Differences in binary characteristics were analysed with Pearson's Chi-square between DWI-positive and DWI-negative patients. Differences in continuous parameters were calculated with a student's t-test or a Mann-Whitney U test, as appropriate. Correlations between continuous parameters and continuous outcome (DWI lesion volume and count) were calculated using the Pearson correlation. Continuous data are provided as mean (±standard deviation) or median (range), as appropriate and categorical variables as n (percentage). A *p*-value of <.05 was considered statistically significant. Differences between BP_{preop} and $BP_{intraop}$ (non-invasive and invasive, systolic/diastolic and mean arterial pressure (MAP)) were evaluated. SPSS 25.0 (SPSS Inc, Chicago, Illinois, USA) was used for all statistical analysis.

RESULTS

Fifty-seven patients met the inclusion criteria, of which 55 had intraoperative BP-measurements available. Eight patients had DWI lesions on the postoperative MR-DWI that were not present on preoperative MR imaging (15%, DWI-positive group) in comparison to 47 patients without any new DWI lesions (85%, DWI-negative group). Five out of eight only had new ipsilateral lesions, three had both ipsi- and contralateral lesions (for example, see Figure 1). Mean lesion volume was 3.9mL (median 0.37, range from 0.05 to 19.3). The median number of new lesions in DWI-positive patients was 3.5 (range 1-14). DWI-positive patients had a significantly higher BP_{preop} systolic (186±31 vs 158±27 mmHg, *p*=.011) and diastolic BP (95±15 vs 84±13 mmHg, *p*=.046) when compared to DWI-negative patients. Other baseline characteristics did not show statistically significant differences between the groups (Table 1). All but one DWI-positive patients had a systolic BP_{preop} of ≥170 mmHg. Preoperative imaging showed DWI-lesions in 24 out of 55 patients (43.6%), no differences in preoperative systolic or diastolic BP was observed between patients with and without preoperative lesions and preoperative DWI-lesion count did not correlate with post-operative DWI lesion count and volume (see supplemental data).

Intraoperative BP-measurements

A mean number of 138 minutes of intraoperative invasive radial artery BP-measurements were available per surgical procedure (median 137, range 78-213). Absolute values of $BP_{intraop}$ and relative values related to BP_{preind} and BP_{preop} were compared between DWI-negative and DWI-positive patients (Tables 2 and 3). An example of perioperative BP of a DWI-negative and DWI-positive patient is presented in Figure 2.

Absolute $BP_{intraop}$ values

There was no difference in systolic or diastolic mean absolute $BP_{intraop}$ between DWI-negative and DWI-positive patients (Table 2). Absolute hypotension occurred in 13 patients, all of whom were DWI-negative and lasted between 1 and 7 minutes. No significant differences were found when duration of absolute hypotension was compared between DWI-negative and DWI-positive patients. Intraoperative variability of systolic and diastolic BP did not differ between the groups either.

$BP_{intraop}$ compared to BP_{preind}

Mean differences between $BP_{intraop}$ and BP_{preind} were similar between DWI-positive and DWI-negative patients for both systolic and diastolic BP (Table 3). In all patients relative hypotension occurred (median duration of 46 minutes; range 7 – 133) with a comparable duration between the groups (p=.935*).* Intraoperative hypertension rarely occurred in both groups (Table 3).

$BP_{intraop}$ compared to BP_{preop}

When mean systolic $BP_{intraop}$ was compared to systolic BP_{preop}, DWI-positive patients had a larger decrease of $BP_{intraop}$ (37±29mmHg) compared to DWI-negative patients (14±26mmHg, p=.024*).* The difference in diastolic BP was not significantly different (Table 3). All eight DWI-positive patients had a lower mean systolic and/or diastolic $BP_{intraop}$ compared to BP_{preop}. Systolic relative hypotension, as compared to BP_{preop}, endured a median of 32 (range 0-174) minutes in DWI-negative patients compared to 117 (range 29-169) minutes in DWI-positive patients (p=.088). Differences between the groups were similar for diastolic BP (p=.071). All DWI-positive patients had an intraoperative period of relative hypotension of at least 30 minutes. Systolic hypertension, as compared to $BP_{intraop}$, occurred with a median of 5 (range 0-173) minutes in DWI-negative patients compared to 1 (range 0-15) in DWI-positive patients (p=.048*).*

BP_{preind} compared to BP_{preop}

Comparison of BP_{preind} with BP_{preop} did not results in any significant differences between DWI-negative and DWI-positive patients (6±18mmHg vs 2±7mmHgs respectively*, p=.535)*

Secondary outcome measures

DWI lesion volume and count were both significantly correlated to systolic BP_{preop} (r^2= .336, p=.012 and r^2=.371, p=0.005 respectively) and mean differences between $BP_{intraop}$ and BP_{preop} (r^2= -.296, p=.028 and r^2=-.305, p=.025 respectively). Other perioperative blood pressure values or duration of hypotension was not significantly correlated to DWI lesion volume and count (see supplemental data). Intraoperative use of vasoactive medication varied between the patients but all but one patient

received phenylephrine during surgery. Maximum dosage of phenylephrine was higher in DWI-positive compared to DWI-negative patients (25.1±8.06 vs 17.0±7.07 $\cdot 10^2$ 100µg/ml *p= 0.005).* Ephedrine and atropine was used in 21 and 11 patients respectively, dosages did not differ between DWI-positive and DWI negative patients. Selective shunting based on EEG changes was indicated and used in five patients; two of them were DWI-positive. Sensitivity analysis excluding shunted patients did not affect the abovementioned results (data not shown). 42/55 patients (76%) had intraoperative TCD data available (see supplemental data). Mean flow velocity of the ipsilateral MCA during cross-clamping had changed with a median of -21% (range -100% – 59%) in DWI-negative patients versus -30% (-100% – 38%) in DWI-positive compared to velocity prior to cross-clamping (*p*=.426). Change of mean flow velocity on the contralateral side was 15% (range -10% – 94%) in DWI-negative patients versus 27% (7% – 80%) in DWI-positive patients (*p*=.086). Micro emboli were detected in 16/37 (43%) DWI-negative versus 4/5 (80%) DWI-positive patients (*p*=.122). Arteriotomy was closed by venous patch in 44 patients (80%), Dacron patch in 4 patients (7.3%), bovine patch in 1 patient (1.8%) and primary closed in 6 patients (10.9%). Six patients had a suspicion of cerebral hyperperfusion based on increased MCA flow velocity or increase in BP (all DWI-negative patients). Four of these patients developed cerebral hyperperfusion syndrome during hospital admission, of which one was complicated by intracerebral haemorrhage. The median follow-up period was three years. Of 47 DWI-negative patients, four developed a stroke of which one ischemic after 1.5 year and three haemorrhagic (two in perioperative period and one six months after CEA). One additional patient died of cardiovascular origin one year after CEA (sudden cardiac death). Of patients with new postoperative DWI lesions, one suffered from ischemic stroke in the perioperative period.

DISCUSSION

In this study, we explored the association between intraoperative BP characteristics and new silent brain ischemia as documented with DWI. Our preliminary results suggest that DWI-positive patients have a higher systolic and diastolic BP_{preop} and that drop of systolic $BP_{intraop}$ is larger than in DWI-negative patients. Without exception, all DWI-positive patients had a lower $BP_{intraop}$ compared to BP_{preop} and all DWI-positive patients experienced at least 30 minutes of intraoperative relative hypotension. We also found that these differences were only visible when intraoperative measurements were compared to preoperative baseline values and not when compared to BP just prior to induction. Absolute values of intraoperative BP did not differ between the groups.

These results may suggest that intraoperative relative hypotension contributes to the development of silent brain ischemia. This is in accordance with earlier literature suggesting that hemodynamic events after CEA increase the risk of ischemic lesions[19]. Nevertheless, this previous study investigated major hemodynamic events (bradycardia<40bpm, asystole or hypotension requiring treatment), and it was unclear how often hypotension occurred in these patients and how severe these hypotensive episodes were. It is not surprising that such extreme hemodynamic disturbances result in brain ischemia as cerebral perfusion pressure (CPP) may fall outside the range of autoregulatory mechanisms. The thirteen patients included in our study that showed a period of absolute hypotension (<80 mmHg) only had this for a very short time (maximum of 7 minutes). This may be the reason that this hypotensive episode did not result in any brain ischemia in these patients. Our study focused mainly on more subtle variations in intraoperative BP since little is known on which intraoperative target BP to strive for and how rigorous this should be maintained. One other study that randomized patients between normotension and hypertension (>110% of baseline BP) during CEA found that the hypertension group had a decreased chance of new ischemic lesions[9] which is supported by our results showing that DWI-negative patients had a systolic BP >120% of baseline for a longer time compared to DWI-positive patients.

The difference between mean $BP_{intraop}$ and baseline was only present when compared to BP_{preop} (and not to BP just prior to induction). All but one DWI-positive patient had a BP_{preop} of at least 170 mmHg. The difference between BP_{preop} and BP_{preind} may be explained by the fact that a subgroup of patients was not adequately treated for hypertension or was not compliant to their prescribed medication when first admitted to the hospital. This is consistent with the fact that although a large difference in baseline BP is present between the groups, reported hypertension or use of anti-hypertensive medication did not differ, although reported use of medication may be higher than actual use due to compliance issues. Blood pressure lowering therapy initiated or restarted upon hospital admission may have decreased the BP in this subgroup to a value lower than the patient was accustomed to. BP_{preind} may therefore not be the most ideal BP to use as a baseline to set intraoperative target values[24], and although BP_{preop} measurements were not standardized in our study, they may represent a better reflection of a patient's true BP. These results also contribute to the discussion of whether or not to perform aggressive lowering of BP in the period before revascularization[25]. Although systolic BP>180mmHg has been independently associated with an increased risk of stroke after CEA[26], is it unclear whether lowering this BP in the preoperative period reduces the risk of events.

Possibly, patients with high baseline BP are at risk of brain ischemia because of failure of autoregulatory mechanisms. Under physiological conditions, cerebral blood flow (CBF) is generally unaffected by changes in cerebral perfusion pressure (CPP), which is the difference between the MAP and intracranial pressure. If CPP is outside its normal range, reflex vasodilation occurs to maintain CBF due to cerebral autoregulation[27]. Studies have previously shown that CAD patients may have impaired cerebral autoregulation[5] and additionally have attenuated baroreflex sensitivity as a result of reduced distensibility of the carotid bulbs infiltrated by atherosclerosis[6]. During cross-clamping of the carotid artery, ipsilateral CPP may be reduced and baroreceptor sensitivity may be further compromised by surgical trauma to sensory nerves within the arterial wall[3]. We hypothesize that ischemic brain lesions may develop in patients that have a diminished baroreceptor sensitivity for (relatively) low arterial pressure, perhaps in combination with an impaired cerebral autoregulation. Patients with pre-existing untreated or inadequately treated hypertension may be particularly susceptible to perioperative hemodynamic complications as their baroreceptors may be even more affected due to continuous exposure to high BP[28]. This theory is supported by the observation that a higher maximum dose of vasoactive medication was used in the DWI-positive group, suggesting that in these patients maintaining adequate blood pressure is more challenging.

All patients had cerebral monitoring by EEG and TCD and selective shunting was used. There were no differences between the groups in monitoring results and shunt use. This suggests that possibly differences in CBF resulting in DWI lesions may not be prominent enough to be detected by cerebral monitoring techniques.

Future perspectives

Our preliminary results suggest that suboptimal perioperative hemodynamics may contribute to the development of cerebral complications after CEA. However, no strong conclusions can be drawn on what the true cause of the increased risk of DWI lesions is; either high preoperative BP or relatively low intraoperative BP. We do believe that perioperative blood pressure management should focus on maintaining adequate CPP during cross-clamping despite complicating factors such as impaired collateral circulation and decreased baroreceptor sensibility. Aggressive reduction of BP during the time interval between hospital presentation and surgery may unjustly lead to a too low target BP during surgery in patients with already impaired autoregulatory mechanisms. The optimal strategy for preoperative normalization of hypertensive BP should be a topic for further research. This should also include the consideration whether or not to omit anti-hypertensive medication on the morning of surgery. Additionally, a trial randomizing between high versus low intraoperative target BP

like previously performed in patients undergoing cardiac surgery[29], can be helpful for determining optimal intraoperative BP management in CEA patients.

Limitations

We are aware of the chance of type II statistical error or overfitting of our statistical model as a result of the small patient cohort. We were only able to include a limited amount of patients in this study due to its retrospective design. Although there are some differences detected in $BP_{intraop}$ between the two groups, many of the investigated parameters approached but did not reach statistical significance. Correlation between systolic BP_{preop} and postoperative DWI lesion volume and count was significant but weak. Nonetheless, the investigated features all show the same direction of effect between DWI-negative and DWI-positive patients with a difference between the groups that seems clinically relevant. Furthermore, the detailed information on pre- and intraoperative BP that was available in this exploratory study provides unique inside in perioperative hemodynamics and it's relation to brain ischemia on MR-DWI.

Because of the limited number of events, we deliberately chose not to correct for potential confounders. Yet, baseline variables (except for BP at hospital intake) were very similar between the groups. We cannot distinguish whether relatively low $BP_{intraop}$ alone or other mechanisms resulting from a high baseline BP contribute to the risk of DWI lesions. Correcting for baseline BP in our analysis would eliminate the effect of $BP_{intraop}$ on the outcome because of their interaction. Earlier literature already described high BP_{preop}, both systolic and diastolic, to be an independent predictor for periprocedural events[30,31]. These studies also suggest that this correlation may be a result of intraoperative impairment of CBF due to failed autoregulatory mechanisms. However, more research in larger patient cohorts, stratifying for differences in pre- and intraoperative characteristics, is warranted to identify factors that increase the risk of brain ischemia. TCD data was only available in a limited amount of patients. As such no conclusions can be drawn on presence or absence of any association between TCD measurements and intraoperative blood pressure or DWI lesions.

BP_{preop} was adopted from the patient's medical file and measurements used for further analysis were not standardized in time of measurement. BP_{preop} was measured using NIBP, while invasive radial artery BP-measurements were used for $BP_{intraop}$. Additionally, high BP's measured at intake or hospital admission may sometimes be due to white coat hypertension[32]. Last, in this study only relative intraoperative hypertension (defined as >20% above baseline) was scored. No absolute threshold for intraoperative hypertension was defined, as threshold described in literature are ambiguous and vary from 140 mmHg to >180 mmHg. Furthermore, relative intraoperative hypertension is

more patient specific[33]. Although these are limitations of our study design, our results can be easily translated to clinical practice.

CONCLUSION

In this exploratory study high preoperative BP and a larger drop of intraoperative BP are associated with the occurrence of periprocedural cerebral ischaemia. Patients with untreated or inadequately treated hypertension might be more prone to suffer from cerebral hemodynamic disturbances due to a relatively low intraoperative BP and may therefore be at risk for development of ischemic lesions. We are in need of prospective studies that investigate pre- and intraoperative BP and its relation to ischemic brain lesions in larger cohorts.

TABLES

Table 1 Baseline characteristics of patients with new DWI-lesions (DWI-positive) compared to those without new DWI-lesions (DWI-negative) after carotid endarterectomy.

Characteristic	DWI-negative N=47	DWI-positive N=8	*p*-value
Age	68.7±1.4	67.24±2.5	.674
Male gender	33 (70.2)	6 (75)	.783
Hypertension	34 (72.3)	5 (62.5)	.571
Systolic blood pressure	158±28	186±31	**.010**
Diastolic blood pressure	84±13	95±15)	**.045**
Anti-hypertensives use	35 (74.5)	6 (75)	.975
Diabetes Mellitus	11 (23.4)	1 (12.5)	.490
Hypercholesterolemia	29 (61.7)	6 (75.0)	.470
Statin/other lipid lowering drugs used	41 (87.2)	7 (87.5)	.983
Antiplatelet use	43 (91.5)	7 (87.5)	.717
Oral anticoagulants	5 (10.6)	1 (12.5)	.876
Currently smoking	17 (36.2)	2 (25.0)	.539
BMI	25.0 (23.9 – 27.1)	26.6 (23.3 – 28.2)	.495
History of CAD	10 (21.3)	4 (50.0)	.085
History of PAOD	8 (17.0)	1 (12.5)	.749
Qualifying symptom = hemispheric stroke	15 (31.9)	2 (25.0)	.696
• Major stroke	9 (17.0)	0 (0)	.313
• Minor stroke	7 (14.9)	2 (25)	
• Cerebral TIA	25 (53.2)	6 (75)	
• Amaurosis fugax	7 (14.9)	0 (0)	
Stenosis grade ≥ 70%	43 (91.5)	8 (100)	.734
Artery operated on (right side)	29 (61.7)	6 (75.0)	.522
Contralateral stenosis ≥ 50%	15 (31.9)	0 (0)	.061
Contralateral occlusion	3 (6.4)	0 (0)	.462
Additional cervical plexus block	26 (55)	3 (38)	.351
Use of intraoperative shunting	3 (6.4)	2 (25.0)	.090
Carotid clamping time in minutes	37 (13 – 104)	41 (21 – 51)	.782

Data are given n (%), as mean ± standard deviation (SD) in case of normally distributed data, or as median (range) in case of not normally distributed data. Hypertension was defined as previously diagnosed by an MD or use of antihypertensive drugs. Systolic and diastolic blood pressure were measured at intake/ hospital admission, in case not available the first available pre-operative blood pressure was used. Diabetes mellitus was defined as previously diagnosed by an MD or use of antidiabetic medication. LDL; mmol/L measured within 1 month prior to surgery. Antiplatelet use; dipyridamole, acetylsalicylic, carbasalate calcium or clopidogrel, anti-coagulation; coumarone or direct acting oral anticoagulant. History of CAD was defined as a composite of angina pectoris, myocardial infarction, percutaneous coronary interventions or coronary bypass surgery. PAOD; peripheral artery disease was defined as a history of peripheral interventions or intermittent claudication or ankle-brachial index<0.7. Use of intraoperative shunting was based on neuromonitoring. Carotid clamping times were compared for a selection of patients in whom no shunting was performed.

Table 2 Results of absolute intraoperative BP-measurements

	DWI-negative (n = 47)	DWI-positive (n = 8)	*p*-value
Absolute blood pressures			
Mean systolic $BP_{intraop}$, mmHg *mean (SD)*	145 (15)	149 (20)	.399
Mean diastolic $BP_{intraop}$, mmHg *mean (SD)*	62 (8)	66 (10)	.655
Duration of absolute hypotension			
Systolic $BP_{intraop}$ < 80 mmHg in minutes *median (range)*	0 (0 – 7)	0 (0 – 0)	.224
Variability			
Variability of systolic $BP_{intraop}$ (SD) *median (range)*	24.5 (16.2 – 35.2)	25.7 (13.6 – 36.3)	.459
Variability of diastolic $BP_{intraop}$ (SD) *median (range)*	10.3 (5.4 – 31.1)	11.3 (4.4 – 15.5)	.788

SD = standard deviation. Data are given as mean with standard deviation in case of normally distributed data or as median with range in case of not normally distributed data. Differences in continuous parameters were calculated with a student's t-test when data were normally distributed and otherwise using a Mann-Whitney U test. $BP_{intraop}$ was analysed from time of anaesthesia induction until emergence.

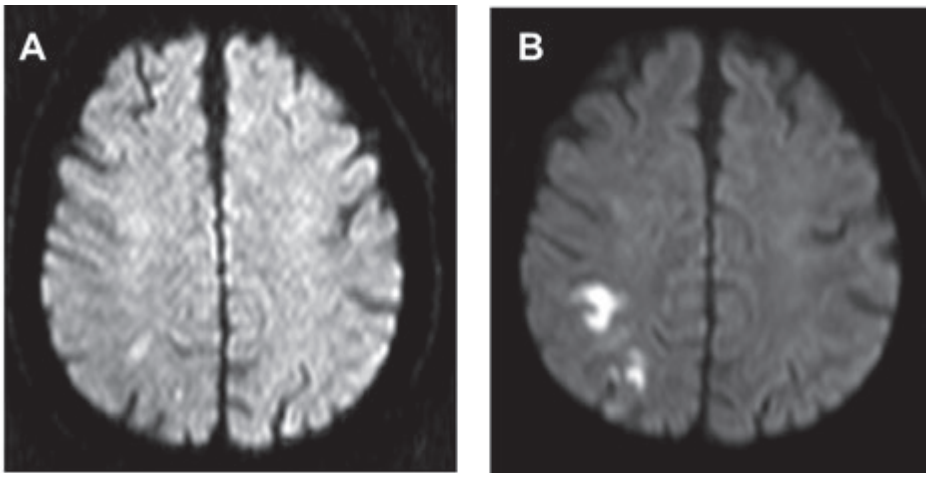
Table 3 Results of relative intraoperative BP-measurements

Compared to BP$_{preind}$	**DWI-negative (n = 47)**	**DWI -positive (n = 8)**	***p*-value**
Mean differences			
Mean systolic BP$_{intraop}$ – systolic BP$_{preind}$ in mmHg *Mean (std)*	1 (39)	-8 (23)	.558
Mean diastolic BP$_{intraop}$ – diastolic BP$_{preind}$ in mmHg *Mean (std)*	-13 (19)	-19 (11)	.370
Duration of relative hypotension			
Systolic BP$_{intraop}$ decrease ≥20% of BP$_{preind}$ in minutes *median (range)*	43 (7 – 140)	47 (30 – 134)	.935
Diastolic BP$_{intraop}$ decrease ≥20% of BP$_{preind}$ in minutes *median (range)*	111 (36 – 209)	139 (91 – 169)	.173
Duration of relative hypertension			
Systolic BP$_{intraop}$ increase ≥20% of BP$_{preind}$ in minutes *median (range)*	1 (0 – 67)	0 (0 – 5)	.417
Compared to BP$_{preop}$			
Mean differences Mean systolic BP$_{intraop}$ – systolic BP$_{preop}$ in mmHg *Mean (std)*	-14 (26)	-37 (29)	**.024**
Mean diastolic BP$_{intraop}$ – diastolic BP$_{preop}$ in mmHg *Mean (std)*	-19 (14)	-28 (14)	.113
Duration of relative hypotension			
Systolic BP$_{intraop}$ decrease ≥20% of BP$_{preop}$ in minutes *median (range)*	32 (0 – 174)	69 (15 – 140)	.088
Diastolic BP$_{intraop}$ decrease ≥20% of BP$_{preop}$ in minutes *median (range)*	67 (0 – 168)	117 (29 – 169)	.071
Duration of relative hypertension			
Systolic BP$_{intraop}$ increase ≥20% of BP$_{preop}$ in minutes *median (range)*	5 (0 – 173)	1 (0 – 15)	**.048**

Data are given as mean with standard deviation in case of normally distributed data or as median with range in case of not normally distributed data. Differences in continuous parameters were calculated with a student's t-test when data were normally distributed and otherwise using a Mann-Whitney U test. BP$_{intraop}$ was analysed from time of anaesthesia induction until emergence, BP$_{preind}$ was defined as an awake oscillometric non-invasive BP-measurement in the OR before administration of any medication used during induction of anaesthesia, BP$_{preop}$ was defined as BP measured on the outpatient clinic or ward maximum 1 month before surgery.

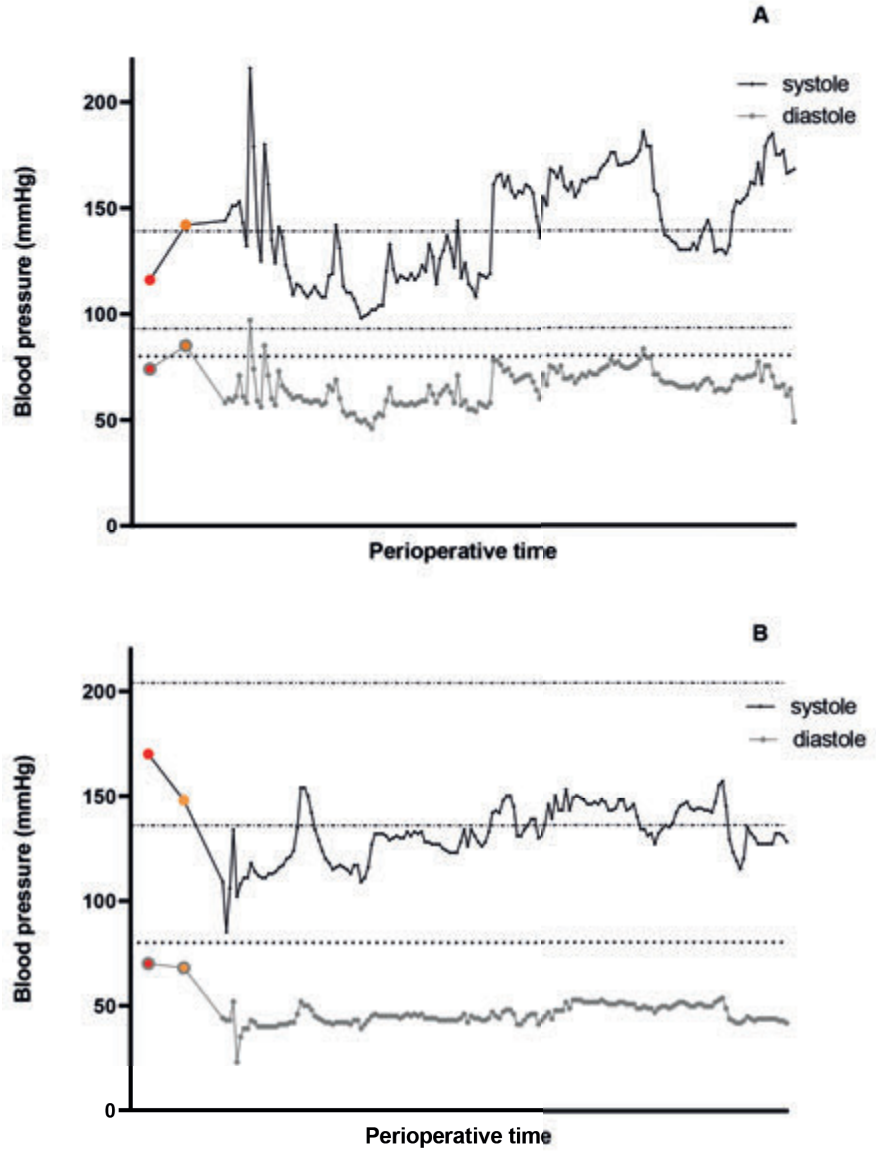
FIGURES

Figure 1. DWI lesions on MRI



Typical MRI made 1 day prior to CEA (A) and 1 day after CEA (B) MRI. In this patient, a total of 14 (13 ipsilateral and 1 contralateral) lesions were seen on MR-DWI that were not present on the preoperative scan with a total volume of 19.2 mL.

Figure 2. Perioperative blood pressure course DWI- (A) and DWI+ (B) patient.



Typical example of systolic and diastolic blood pressure course in perioperative period of patient without (A) versus with (B) postoperative DWI lesions. In each of the panels, the *red dot* represents BP_{preop}, the *orange dot* represents BP_{preind} and subsequent measurements reflect $BP_{intraop}$. The two (upper) *dashed horizontal lines* represent the relative hypo- (≥20% decrease) and hypertension (≥20% increase) limits compared to BP_{preop}. The lower *dotted line* represents the cut-off for absolute hypotension (80mmHg). The graph in panel B illustrates how the preinduction blood pressure, which is considerably decreased compared to the earlier preoperative blood pressure, determines intraoperative target BP and very often exceeds the limit of relative hypotension whereas both patients never cross the limit of absolute hypotension. The two example patients were randomly selected from each group.

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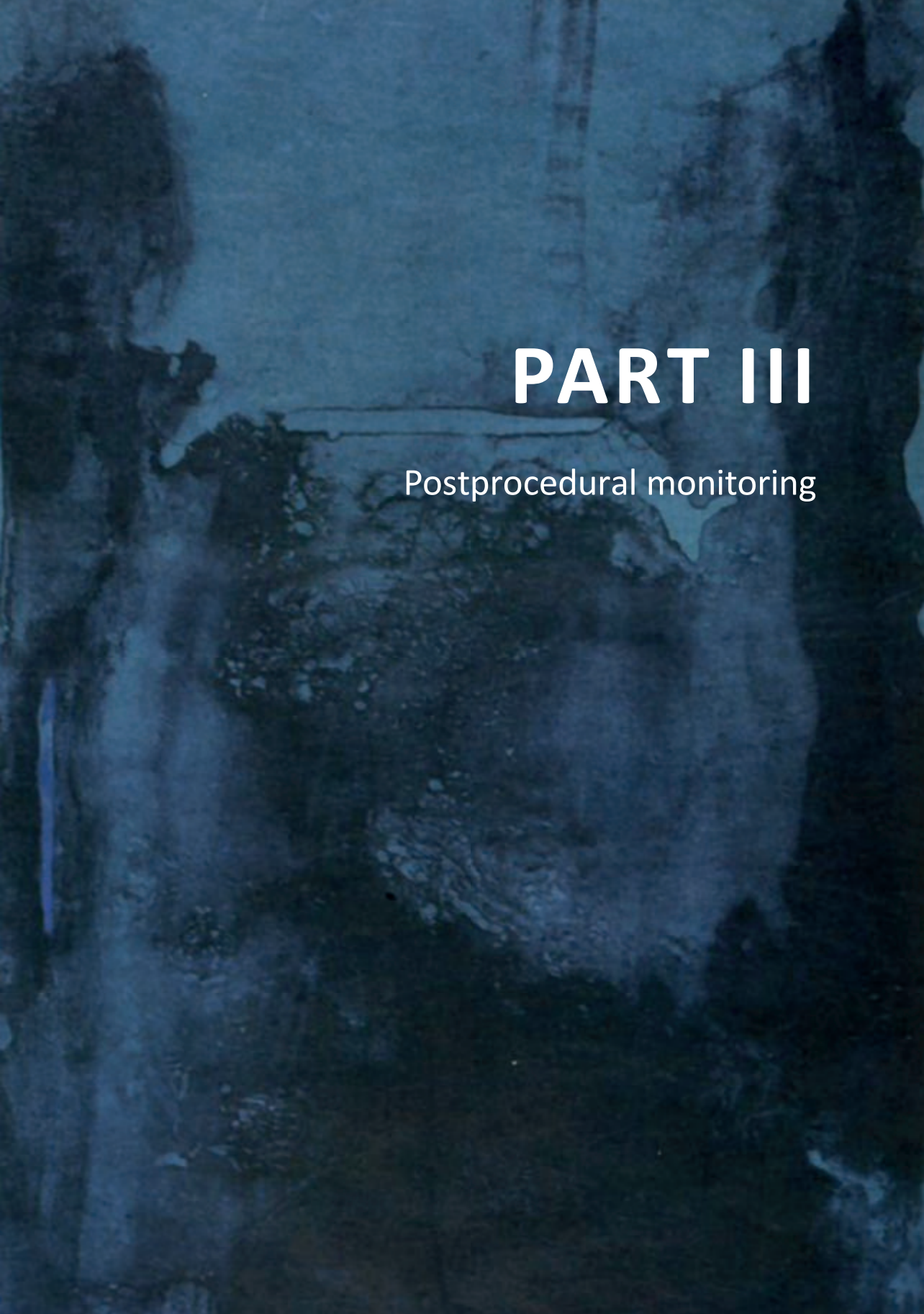

PART III

Postprocedural monitoring

CHAPTER 8

The ClearSight system for postoperative arterial blood pressure monitoring after carotid endarterectomy: a validation study

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Submitted

ABSTRACT

Objective: The majority of postoperative events in patients undergoing carotid endarterectomy (CEA) are of hemodynamic origin, requiring preventive strict postoperative arterial blood pressure (BP) control. This study aimed to assess whether BP monitoring with non-invasive beat-to-beat ClearSight finger BP (BP_{CS}) can replace invasive beat-to-beat radial artery BP (BP_{RAD}) in the postoperative phase.

Methods: Single-centre, clinical validation study using a pre-specified study protocol. In 51 patients with symptomatic carotid artery stenosis, BP_{CS} and BP_{RAD} were monitored ipsilateral in a simultaneous manner during a 6-hour period on the recovery unit following CEA. Primary endpoints were accuracy and precision of BP derived by ClearSight (Edward Lifesciences, Irvine, CA, USA) versus the reference standard (Arbocath 20 G, Hospira, Lake Forest, IL, USA) to investigate if BP_{CS} is a reliable non-invasive alternative for BP monitoring postoperatively in CEA-patients. Validation was guided by the standard set by the Association for Advancement of Medical Instrumentation (AAMI), considering a BP-monitor adequate when bias(precision) is <5(8)mmHg. Secondary endpoint was percentage under- and overtreatment, defined as exceedance of individual postoperative systolic BP-threshold by BP_{RAD} or BP_{CS} in contrast to BP_{CS} or BP_{RAD}, respectively.

Results: The bias(precision) of BP_{CS} compared to BP_{RAD} was -10 (13.6), 8 (7.2) and 4 (7.8) mmHg for systolic, diastolic and mean arterial pressure (MAP), respectively. Based on BP_{CS}, percentage undertreatment was 5.6% and overtreatment was 2.4%, however percentages of undertreatment quadrupled for lower systolic BP-thresholds.

Conclusion: Non-invasive mean arterial pressure, but not systolic and diastolic BP, was similar to invasive BP_{RAD} during postoperative observation following CEA, based on AAMI criteria. However, as systolic BP is currently leading in postoperative monitoring to adjust BP-therapy on, BP_{cs} is not a reliable alternative for $BP_{RAD.}$

INTRODUCTION

The benefit of carotid revascularization for severe symptomatic carotid artery stenosis is offset by stroke due to the intervention itself [1–3]. Hemodynamic disturbances are held accountable for half of the periprocedural strokes following carotid endarterectomy (CEA) and postoperative events [4–6]. Intraoperative hypotension may cause cerebral hypoperfusion which can result in hypoxia and subsequently cerebral ischemia, whereas postoperative hypertension may lead to ipsilateral cerebral hyperperfusion with haemorrhagic stroke when not timely recognized and treated [7]. Therefore, to reduce the incidence of periprocedural stroke in patients undergoing carotid endarterectomy (CEA) and to preserve adequate cerebral perfusion on the other hand, blood pressure (BP) has to remain between strict thresholds.

Today, intraoperative beat-to-beat invasive radial artery BP monitoring continues on the post-operative recovery unit for at least 6 hours following surgery. However, besides that invasive BP monitoring has a significant complication risk (i.e. failure of cannulation despite the use of ultrasound, bleedings, pseudo-aneurysm, thrombotic embolization or occlusion), it is expensive since monitoring by radial artery cannula requires admission on a recovery or medium care unit [8,9].

Recent data revealed that the ClearSight System (Edwards Lifesciences, Irvine, CA, USA), a non-invasive beat-to-beat BP-device on the finger, could be used as an alternative for intraoperative invasive BP monitoring in the radial artery in patients undergoing CEA, both under local and general anaesthesia [10,11]. However, to our knowledge beat-to-beat finger BP was not validated during the six hour lasting post-operative admission on a postoperative recovery unit.

Based on the earlier validation studies, we hypothesized that also during a prolonged monitoring period non-invasive beat-to-beat finger BP by ClearSight can be considered as a reliable and easy-to-assess alternative for invasive radial artery BP in awake patients on the post-operative recovery unit after a CEA procedure [10,11]. Therefore, we determined the accuracy and precision of BP monitored by ClearSight (BP_{CS}) compared to radial artery BP (BP_{RAD}), in line with the standard of the Association for the Advancement of Medical Instrumentation (AAMI-criteria). We also quantified the frequency of potential over- and undertreatment when invasive BP monitoring would be replaced by non-invasive BP monitoring.

METHODS

Subjects

This study was approved by the local medical ethics committee on 26 April 2017 (Medical Research Ethics Committee UMC Utrecht, protocol number 17-2573/C). Written informed consent in accordance with the Helsinki Declaration was obtained from patients undergoing CEA between July 2017 and June 2018 at a tertiary referral vascular surgery centre at the University Medical Center Utrecht in the Netherlands. Exclusion criteria were: refusal to participate and patients who underwent CEA for asymptomatic carotid artery stenosis.

Study design

All patients received standard monitoring, i.e. electrocardiography, end-tidal carbon dioxide, oscillometric non-invasive BP (NIBP) with an upper arm cuff and pulse oximetry via a Datex Ohmeda S/5 anaesthesia monitor (GE, Healthcare, Waukesha, WI). Invasive continuous BP was monitored with an artery cannula (Arbocath 20 G, Hospira, Lake Forest, IL, USA) placed preoperatively in the radial artery ipsilateral to the upper arm cuff. Standard monitoring data and invasive BP_{RAD} data of the radial artery cannula are stored by monitoring program Anstat (Carepoint Nederland B.V., Ede, The Netherlands). Postoperatively, patients were connected to the ClearSight system (Edwards Lifesciences, Irvine, CA, USA). A non-invasive beat-to-beat finger BP device was applied to the index finger, ipsilateral to the upper arm NIBP and radial artery cannula. The size of the cuff was selected to fit the size of the mid-phalanx of the index finger. The ClearSight system is based on a photoplethysmograph in a cuff and integrated into a simplified clinical platform (EV1000). The finger cuff will be inflated and deflated through the cardiac cycle in a way that the volume diameter of the finger artery becomes constant instead of pulsatile as monitored with the photoplethysmograph. The pressure in the cuff to create a constant diameter of the finger artery is the same as the BP, a technique proposed by Peňáz. A detailed description has been previously published [12]. Calibration of the ClearSight system was performed by a built-in expert system (Physiocal), detecting changes in finger arterial diameter to establish and adjust the arterial unloaded volume at least once every 70 heartbeats [13]. According to ClearSight operator's manual, a Physiocal interval >30 beats indicates stable and reliable pressure measurements [14]. A heart reference sensor (HRS) was used to correct for movements of the finger in height compared to the heart level. This reference sensor was connected to the finger cuff and the lateral side of thorax, on the position of the atria. Inflation of oscillometric NIBP was used as a marker at the start and during monitoring to synchronize BP_{CS} in time with BP_{RAD} measurements.

CEA protocol

The CEA procedure is described in detail earlier [10]. All patients underwent CEA under volatile anaesthesia performed by an experienced vascular surgeon or a vascular trainee under the supervision of a vascular surgeon. Patients were monitored neurologically during surgery by electroencephalogram (EEG) and transcranial Doppler (TCD). An intraluminal shunt was placed selectively in case of EEG asymmetry or a decrease of >70% of the mean flow velocity in the middle cerebral artery ($MCAV_{mean}$) measured by TCD during clamping. Atherosclerotic plaques were removed by longitudinal arteriotomy. Intraoperatively, mean radial artery BP was kept between 100% and 120% of the awake BP level during clamping. Postoperatively, an individual systolic BP-restriction was determined for each patient based on the intraoperative increase of $MCAV_{mean}$ after clamping assessed by TCD. This maximum systolic BP threshold could be adjusted in response to an increase of $MCAV_{mean}$ determined by a standard 2-hours postoperative TCD measurement. All patients were admitted to the recovery unit for hemodynamic and neurological monitoring for at least 6 hours.

Data collection

Both BP_{RAD} measurements (112 Hz) derived from the Datex Ohmeda S/5 monitoring system (GE Healthcare) and BP_{CS} measurements (200Hz) derived from the ClearSight system were stored on a hard disk for offline analysis. ClearSight used an algorithm to reconstruct a finger BP measurement to a brachial artery waveform. The algorithm corrects for a decrease in diastolic pressure and an increase in systolic pressure due to a pressure gradient in the smaller arteries resulting from pressure wave reflection [14,15]. For each patient, the systolic BP threshold and BP medication (either vasopressor agents or antihypertensive agents) were registered. Beat-to-beat data of the first 6 hours on the recovery unit were used in this study. BP_{CS} and BP_{RAD} were aligned in time. Data was visually inspected for any artefacts such as arterial flushing, episodes where the Physiocal frequency was more than once every 30 heartbeats, the inability for BP_{RAD} and BP_{CS} to measure due to occlusion of the arteries during oscillometric NIBP measurement. The beat-to-beat data was averaged over slots of 20 seconds. All timeslots in which the previously mentioned artefacts occurred in either the BP_{CS} or BP_{RAD} were excluded from further analysis.

Sample size calculation

The sample size for this study was calculated based on AAMI criteria and previous studies validating finger BP devices with invasive intra-arterial BP device as a reference [10,11,15]. In accordance with the AAMI criteria, a minimum of 15 patients was recommended. However, AAMI criteria do not specify for continuous non-invasive sphygmomanometers [16]. Previous studies for intraoperative validation had a sample

size of 25-30 patients. Due to expected dropouts, we believed a larger sample size was needed. Therefore, we aimed to include 50 patients.

Statistical analysis

Baseline characteristics that are normally distributed continuous data are presented as mean (± SD). Non-normally distributed continuous data are provided as median (interquartile) and categorical variables as n (percentage).

To assess whether there was sufficient agreement between the two continuous methods of measurements (i.e. ClearSight finger BP versus radial arterial BP), the Bland-Altman method and plot were used [17,18]. Herein, the mean difference and the range of these differences (in which 95% of measurements fall) are calculated using the standard deviation (SD) and graphically depicted. Whether this 95% interval (limits of agreement (LOA)) meaningfully affect the interpretation of the results, is subject to the clinical context [19]. In accordance with AAMI criteria, a mean error of <5mmHg and SD <8mmHg compared to the reference method (i.e. radial artery BP) are considered clinically acceptable [16].

However, the original Bland-Altman method was developed for *independent data*, i.e. one measurement of both methods per patient. Therefore, it is not suitable for situations in which there are multiple measurements per patient as it underestimates the true variation of the difference, although it is often misused for this purpose [19,20]. Therefore, *mixed effects* LOA, obtained through the use of random effects models in which is accounted for repeated measurements through the use of a different intercept per subject, were performed [21]. The derived total SD is used to obtain the LOA, whereas the between-subject and within-subject SD are reported and used to obtain the intra-class correlation coefficient (ICC), a measure to assess the degree of total variation explained by the between-subject variation [20].

To evaluate if baseline characteristics could partly explain the variation, the variables sex, age, BMI, diabetes mellitus, smoking, hypertension, peripheral and central arterial disease, and pulse pressure were added in another model. Pulse pressure was added to the model to correct for arterial stiffness of the smaller arteries. Assumptions checked were constant variances, residuals versus fitted values plots, q-q plots of the residuals and random effects predictions. None were substantially violated. Results were graphically visualized using Bland-Altman plots, with arterial pressure at the x-axis, as this is the reference standard [22].

Potential undertreatment and overtreatment were calculated per measurement time (20s window) and per 5 min window (mean of 15 measurements). Individual systolic BP-thresholds determined for each patient based increase of $MCAV_{mean}$ assessed by TCD, were used. Undertreatment was defined as when systolic radial arterial pressure exceeded this predetermined systolic BP-threshold, while BP_{CS} was lower than this threshold. Overtreatment was defined as when systolic radial arterial BP was below the predetermined systolic BP-threshold, while BP_{CS} was exceeding this threshold.

RESULTS

Written informed consent was obtained from 52 patients. In one patient, no measurements could be performed due to logistic reasons (directly postoperative admission to a high care unit). The measurements of two other patients were excluded for analysis due to technical problems (error of pump-unit of ClearSight system, erroneous time registration of ClearSight). In one patient, only 45 minutes were recorded and therefore not representative for a prolonged measurement. Of 48 patients (75% males, 71.5 years [50-93]), both BP_{CS} and BP_{RAD} data was analysed. Baseline characteristics are presented in Table 1.

The median duration of BP monitoring was 5.7 hours (range 178 minutes – 6 hours). Of 41606 (20s averaged) paired samples gathered from 48 patients, 5453 samples (13%) were excluded from analyses. Of these 5453 excluded samples, 2495 (6%) were excluded due to ClearSight Physiocal frequency greater than once per 30 heartbeats, 2171 (5%) samples were excluded due to artefacts of ClearSight. In 673 (2%) samples, both BP_{CS} and BP_{RAD} measurements were unreliable due to inflation of ipsilateral non-invasive upper-arm BP cuff. Lastly, 61 samples (0.2%) were excluded due to an unreliable arterial BP curve or flushing of the arterial line. A total of 36206 (87%) paired samples of BP_{CS} and BP_{RAD} measurements collected from 48 patients were suitable for analysis. This was a median of 812 samples per patient (range 249-982). (Figure 1)

AAMI validation

The levels of agreement for systolic BP, diastolic BP and MAP by ClearSight (BP_{CS}) compared to BP measured by the reference radial artery cannula (BP_{RAD}), are presented in Figure 2. The biases, precisions and LOA are presented in Table 2. The mean bias for systolic BP was -10mmHg (SD13.6, LOA -36 to 17mmHg), for diastolic BP 8mmHg (SD7.2, LOA -6 to 22mmHg) and for MAP 4mmHg (SD7.8, LOA -11 to 19mmHg). Of the MAP data, 95% of measurements met the criteria prescribed by the AAMI. Correction for baseline characteristics and pulse pressure did not substantially change bias and precision of the

measurements. (Table 2) Intra-class correlation coefficients of BP_{CS} – BP_{RAD} for systolic, diastolic and MAP were 0.58, 0.69 and 0.56, respectively. (Figure 5)

Clinical decision making

The overall percentage of overtreatment was 2.38%. The overall percentage of undertreatment was 5.56%. When specified per postoperative systolic threshold, undertreatment was almost four times as high in patients with a systolic threshold of 120 or 140mmHg. (Table 3, Figure 3)

DISCUSSION

In this single-centre validation study, we assessed if non-invasive beat-to-beat finger BP monitoring by ClearSight can replace invasive radial artery BP monitoring for postoperative hemodynamic observation in patients who underwent CEA. Both systolic and diastolic BP monitored by ClearSight are below the clinically acceptable limits of the AAMI criteria and therefore unsuitable to replace invasive BP monitoring in this population of patients undergoing CEA for symptomatic carotid disease. Besides, replacement of invasive BP_{RAD} by non-invasive BP_{CS} may lead to extensive undertreatment of patients with strict low systolic BP thresholds, as the systolic BP is the leading parameter in current postoperative hemodynamic BP monitoring of CEA-patients to adjust BP therapy on. MAP determined by ClearSight meets the AAMI criteria with expected insignificant undertreatment (due to bias +4mmHg) and may therefore be considered as a suitable non-invasive alternative in postoperative BP monitoring of CEA-patients when one wants to measure MAP.

In the majority of CEA-patients, both the baroreflex sensitivity and the cerebral autoregulation are impaired [23,24]. Periprocedurally, this can lead to larger BP fluctuations that cannot be counter-regulated by the brain vasculature [4]. Postoperative CEA-triggered changes in cerebral hemodynamics, i.e. hypertension, are assumed the underlying mechanism for the development of CHS [25–27]. Strict BP control is therefore required to maintain adequate cerebral perfusion in effort to prevent for periprocedural strokes. Recent guidelines by the European Society for Vascular Surgery (ESVS) recommend neurologic and intra-arterial BP monitoring during the first 3-6 hours on an observed postoperative recovery unit, followed by hourly non-invasive BP control during the first 24 hours [3]. However, specific recommendations how to determine postoperative BP thresholds are lacking. Some suggest a one fits all systolic BP policy by treating >170 mmHg or >160 mmHg in patients with symptoms, while others advocate implementing TCD measurements to monitor the postoperative cerebral blood flow velocity of the ipsilateral middle cerebral artery and adjust individual systolic BP thresholds upon this

[26,28–30]. Despite the different views on what is best, all agree on the clinical relevance of adequate monitoring of the postoperative BP.

In today's clinical practice, the postoperative BP monitoring policy in patients who undergo CEA is based on the systolic BP. Specific data for systolic-controlled postoperative hemodynamic monitoring as opposed to MAP-controlled postoperative monitoring have not been reported in literature.

Although no validation criteria for continuous BP monitoring systems exists, the AAMI criteria for intermittent non-invasive BP monitoring are frequently used in previous studies validating a finger BP device [16]. Our study is in line with a literature review studying the accuracy of the finger cuff method to estimate BP (CNAP, FinaPress, Nexfin and ClearSight) and concluded that although easy-in-use and able to measure a reasonable BP, finger cuff devices do not meet the criteria for clinical interchangeability with currently used invasive techniques [31]. Up to now, there are only two studies which compared non-invasive finger BP devices and invasive BP in patients undergoing carotid surgery. Both studies, one in patients undergoing CEA under general anaesthesia and the other in awake patients under regional anaesthesia, reported that MAP, but not systolic and diastolic BP, (suboptimal) met the AAMI criteria [10,11]. These results support our findings.

Our results should be put into perspective, as the patient population in the present study was vascular compromised with a high incidence of systemic atherosclerotic vascular disease and may therefore not representative for all postoperative patients. The vast majority of the patient population had a history of smoking and hyperlipidaemia and one third of the patients had diabetes mellitus type 2. Reduced quality of peripheral small vessels and increased arterial stiffness in the smaller arteries due to calcification, can be expected [32,33]. This may influence BP_{cs}, making BP_{CS} less reliable in this specific patient population and is a possible explanation for systolic and diastolic BP imprecision compared to BP_{RAD}. Despite correction for baseline characteristics and pulse pressure, different results might be found within a patient population with a more healthy vascular system.

Today, arterial BP measured invasively by radial artery cannula is still the accepted reference technique for clinical assessment of arterial BP in patients undergoing a CEA. The results of the current study represent an equation of how BP measured by ClearSight relates to BP measured by invasive radial artery cannula and not what technique is best in measuring arterial BP [19]. To address this issue, we believe that choosing the use of plotting the differences between BP_{CS} and BP_{RAD} against BP_{RAD}, the reference method,

instead of the correlation coefficient (BP_{RAD} + BP_{cs}/2) when comparing field methods, was most appropriate [22].

Limitations

The results of this study should be interpreted in light of several limitations. Firstly, several technical issues of the ClearSight and EV1000 system occurred during the measurements. The pump unit of the ClearSight system and several HRS cables had to be replaced due to failure of providing adequate pressure in finger cuff or the inability to zero and thereby level the HRS to the phlebostatic axis, respectively. In addition, HRS cable secured on the level of phlebostatic axis at the thorax may have moved during nursing on the recovery. This might have influenced our results. However, all BP measurements of the patient in whom the pump unit failed to work were excluded and failure of zeroing of HRS cable impeded to start measuring BP. Secondly, the position of the invasive radial artery cannula was ipsilateral to the finger cuff, possibly leading to decreased perfusion to the finger and underestimation of BP measured by ClearSight. However, collateral blood flow by the ulnar artery may overcome this issue. Besides, comparing BP_{CS} to contralateral BP_{RAD} is not an option since one out of five CEA patients has an inter-arm BP difference of >15mmHg [34]. Lastly, 5 of 49 patients experienced an uncomfotable tingling sensation or pain in the distal end of the finger during long-term BP measurement by ClearSight. This might have led to increased movement of the finger and influenced the BP measurements.

CONCLUSION

Non-invasive mean arterial pressure, but not systolic and diastolic BP, was similar to invasive BP_{RAD} during postoperative observation following CEA, based on AAMI criteria. However, as systolic BP is currently leading in postoperative monitoring to adjust BP-therapy on, BP_{cs} is not a reliable alternative for BP_{RAD} in this clinical setting.

Acknowlegdements

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TABLES

Table 1. Baseline characteristics

	All patients (n=48)
Age	71.5 [50-93]
Sex, male	36 (75%)
Risk factors	
• Hypertension	34 (71%)
• Hyperlipidaemia	35 (73%)
• Diabetes mellitus	13 (27%)
• Coronary artery disease	20 (42%)
• Peripheral arterial disease	11 (23%)
• Smoker (current/ex)	36 (76%)
• Symptomatic	48 (100%)
Ipsilateral stenosisal	
• 50-70%	5 (10%)
• >70%	42 (87%)
Contralateral stenosis	
• Occlusion	10 (21%)
• >70%	5 (10%)
• 50-70%	5 (10%)
• <50%	28 (58%)
Shunt-use	5 (10%)
Medication	
• Statins	39 (81%)
• Antiplatelets	41 (85%)
• Anti-coagulants	5 (10%)
• Diuretics	12 (25%)
• BP-lowering drugs	32 (67%)
Preoperative systolic BP, mmHg (SD)	147 (17)
Preoperative diastolic BP, mmHg (SD)	77 (12)
Preoperative MAP, mmHg (SD)	101 (11)
Postoperative events	
Total events	7 (15%)
• Cerebral hyperperfusion	3 (6%)
• Bleeding requiring surgery	1 (2%)
• Stroke	1 (2%)
• TIA	2 (4%)
Medium care admission	8 (17%)
Extended recovery admission	11 (23%)
Labetalol-use	11 (23%)
Norephedrine-use	4 (8%)
Clonidine use	6 (13%)

Data in median (range), or number (%). GP: general practitioner. BP: blood pressure.

Table 2. Bias, precision, ICC of BP_{CS} compared to BP_{RAD}.

	Bias	Precision	Between-subjects variability	Within-subject precision	95% Limits of agreement	ICC
Systolic BP (mmHg)	-9.58	13.64	10.43	8.79	-36;17	0.58
Diastolic BP (mmHg)	7.92	7.19	5.97	4.00	-6;22	0.69
MAP (mmHg)	4.00	7.78	5.81	5.18	-11;19	0.56
Systolic BP (mmHg) (adjusted - baseline)	-9.58	14.05	10.97	8.79	-37;18	0.61
Diastolic BP (mmHg) (adjusted - baseline)	7.92	6.47	5.09	4.00	-5;21	0.62
MAP (mmHg) (adjusted - baseline)	4.00	7.74	5.75	5.18	-11;19	0.55
Systolic BP (mmHg) (adjusted - baseline + pulse pressure)	-9.58	8.35	6.98	4.58	-26;7	0.70
Diastolic BP (mmHg) (adjusted - baseline + pulse pressure)	7.92	6.53	5.22	3.93	-5;21	0.64
MAP (mmHg) (adjusted - baseline + pulse pressure)	4.00	7.52	5.86	4.72	-11;19	0.61

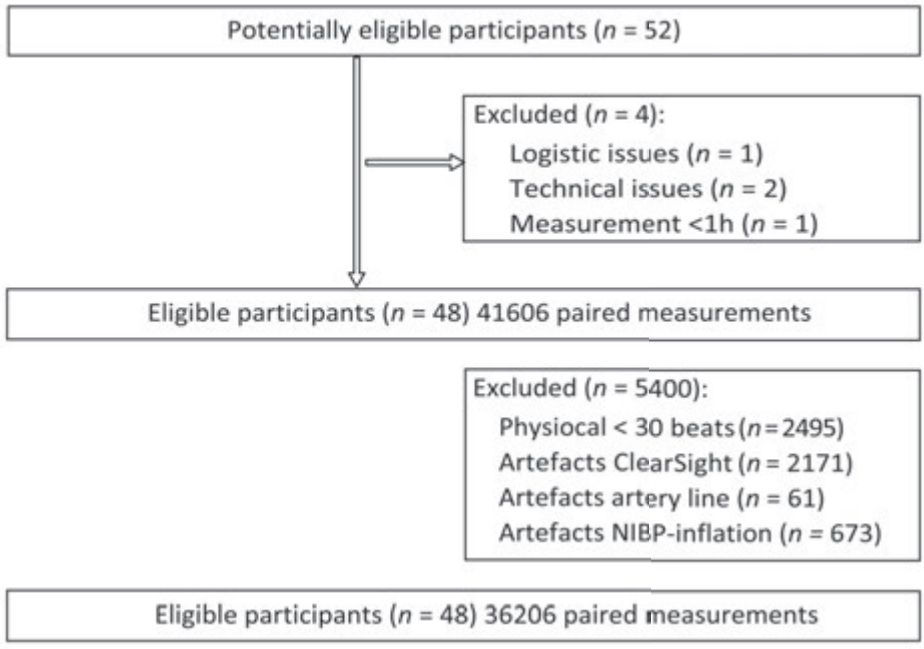
Data are presented in mmHg. BP: blood pressure. MAP: mean arterial pressure. ICC: intra-class correlation coefficient. Adjusted – Baseline: corrected for the baseline characteristics sex, age, BMI, diabetes mellitus, smoking, hypertension, peripheral and central arterial disease. Adjusted – baseline + pulse pressure: corrected for baseline characteristics and pulse pressure.

Table 3. Clinical decision making

20 s samples	**All**	**180 mmHg**	**160 mmHg**	**140 mmHg**	**120 mmHg**
Overtreatment, n (%)	860 (2.38%)	197 (0.72%)	114 (9.30%)	83 (2.07%)	466 (15.24%)
Undertreatment, n (%)	2103(5.81%)	447 (1.63%)	15 (1.22%)	816 (20.33%)	640 (20.93%)
5 min samples	**All**	**180 mmHg**	**160 mmHg**	**140 mmHg**	**120 mmHg**
Overtreatment, n (%)	69 (2.38%)	10 (0.46%)	6 (7.41%)	6 (1.91%)	45 (17.79%)
Undertreatment, n (%)	161 (5.55%)	31 (1.42%)	2 (1.85%)	61 (19.43%)	53 (20.95%)

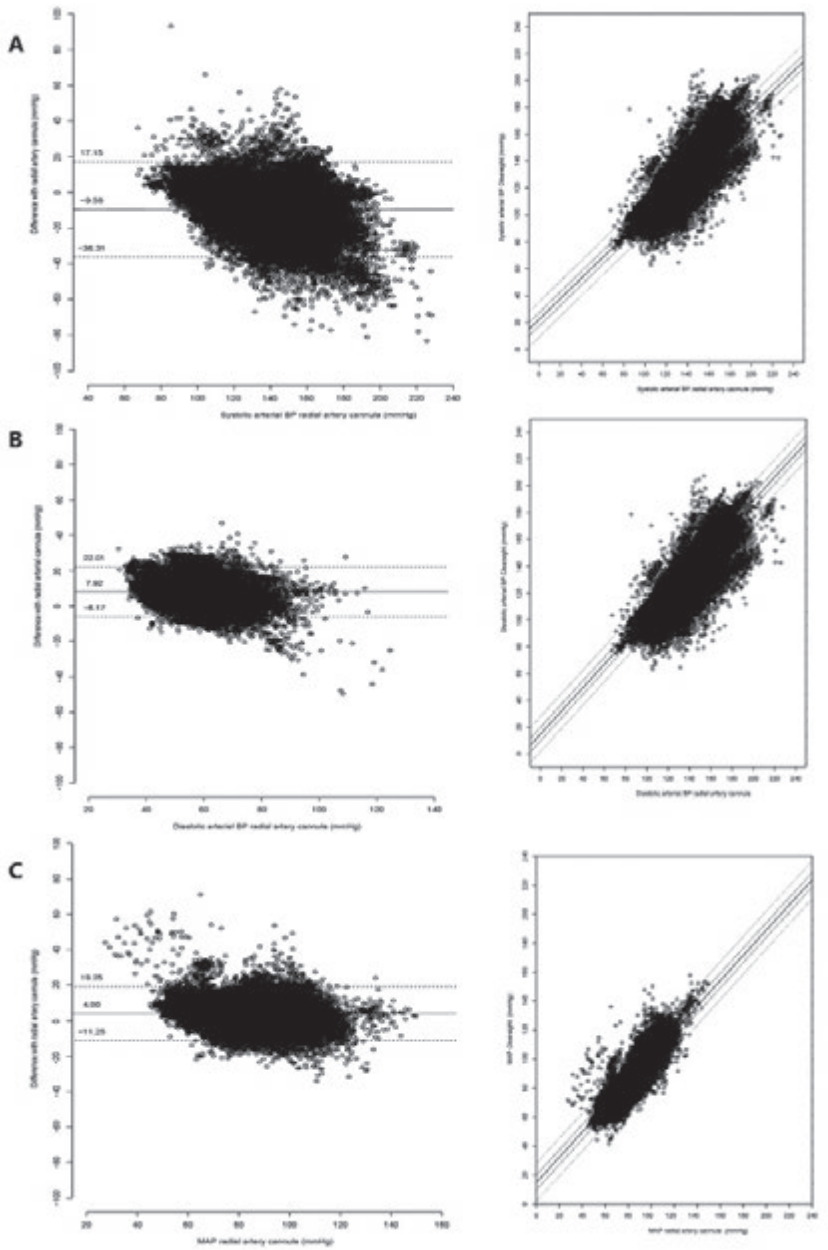
FIGURES

Figure 1. Study flowchart



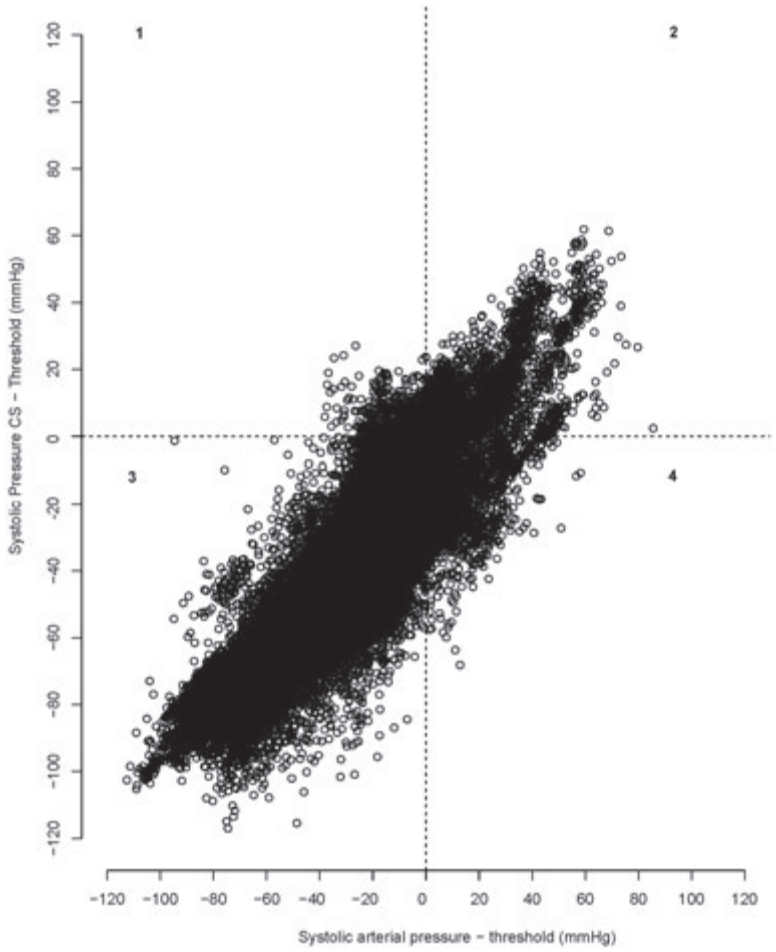
Flow chart of participants through the study. The study time frame is from the first six hours postoperative on the recovery unit.

Figure 2. Bland Altman plots systolic, diastolic and mean arterial pressure - BP_{CS} and BP_{RAD} and corresponding scatterplots.



Left: Bland-Altman plot of all 20-sec systolic (A), diastolic (B), mean arterial pressure (C) data points (n=36 290). Solid line indicates mean difference (bias) and dashed lines are the upper and lower 95% limits of agreement. *Right:* Corresponding scatterplots of systolic, diastolic and mean arterial pressure of BP_{CS} vs BP_{RAD} with lines of identity (solid line is slope, dashed lines is ±5mmHg and dotted lines ±13mmHg indicating the AAMI validation borders).

Figure 3. Scatter plot of systolic of potentially over- and undertreatment



Scatter plot with on the y-axis the difference between systolic BP by ClearSight compared to individual systolic threshold of patient (mmHg). On x-axis the difference between systolic BP by radial artery cannual and individual systolic threshold. All potentially overtreatment when using Clearsight is plotted in upper left quadrant (1), all potentially undertreatment when using ClearSight is presented in lower right quadrant (4)

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CHAPTER 9

Transcranial Doppler 24 hours after Carotid Endarterectomy accurately identifies patients not at the risk for cerebral hyperperfusion syndrome

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ABSTRACT

Objectives: Intra-operative transcranial Doppler (TCD) is the gold standard for prediction of cerebral hyperperfusion syndrome (CHS) in patients after carotid endarterectomy (CEA) under general anaesthesia. However, post-operative cerebral perfusion patterns may result in a shift in risk assessment for CHS. This is a study of the predictive value of additional post-operative TCD measurements for prediction of CHS after CEA.

Methods: This was a retrospective analysis of prospectively collected data in patients undergoing CEA with available intra- and post-operative TCD measurements between 2011 and 2016. The mean blood flow velocity in the middle cerebral artery (MCAV_{mean}) was measured pre-operatively, intra-operatively, and postoperatively at two and 24 h. Intra-operative MCAV_{mean} increase was compared with MCAV_{mean} increase two and 24 h post-operatively in relation to CHS. Cerebral hyperperfusion (CH) was defined as MCAV_{mean} increase ≥ 100%, and CHS as CH with the presence of headache or neurological symptoms. Positive (PPV) and negative predictive values (NPV) of TCD measurements were calculated to predict CHS.

Results: Of 257 CEA patients, 25 (9.7%) had CH intra-operatively, 45 (17.5%) 2 h post-operatively, and 34 (13.2%) 24 h post-operatively. Of nine patients (3.5%) who developed CHS, intra-operative CH was diagnosed in two and post-operative CH in eight (after 2 h [*n* = 5] or after 24 h [*n* = 6]). This resulted in a PPV of 8%, 11%, and 18%, and a NPV of 97%, 98%, and 99% for intra-operative, 2 h and 24 h post-operative TCD, respectively.

Conclusions: TCD measurement of the MCAV_{mean} 24 h after CEA under general anaesthesia is most accurate to identify patients who are not at risk of CHS.

INTRODUCTION

Although multiple and heterogeneous in origin, perioperative haemodynamic disturbances in patients undergoing carotid endarterectomy (CEA) are suggested to be the causative factor in one in every three procedural strokes.[1,2] Recent data revealed that the majority of post-operative strokes becoming apparent after a symptom free interval following awakening from general anaesthesia (GA) were of haemodynamic aetiology.[1,3] Intra-operative hypoperfusion may result in cerebral ischaemia, whereas post-operative cerebral hyperperfusion (CH) is associated with cerebral hyperperfusion syndrome (CHS) leading to haemorrhagic stroke and death in up to 40% of patients when left untreated.[4] In the post-operative phase, early recognition of CH can prevent serious complications because adequate BP lowering therapy is highly effective in prevention of CHS.[5,6]

In daily practice a validated prediction model for prevention of CHS is lacking. Currently, intra-operative changes in the middle cerebral artery blood velocity (MCA*V*) with transcranial Doppler (TCD) monitoring is the gold standard for prediction of CHS after CEA.[5,7] An increase of ≥100% in MCA*V* 3 min after carotid declamping compared with the MCA*V* pre-clamping is the most commonly used TCD derived parameter to predict CHS after CEA under GA. Unfortunately, intra-operative measurements have been associated with both false positive and false negative results, resulting in overtreatment and increased hospital costs.[4,8] Recently, it was found that an additional postoperative MCA*V* measurement 2 h after surgery compared with the pre-operative measurement increased the prediction rate for CHS from 13% to 41%.[5]

It was hypothesised that adding a TCD measurement 24 h post-operatively might be more accurate to predict CHS.[4] Therefore, in addition to standard intra-operative and 2 h post-operative TCD MCA*V* assessments, the predictive value of MCA*V* assessed by an additional TCD measurement 24 h after surgery was evaluated retrospectively for CH and CHS in patients undergoing CEA under GA.

MATERIAL AND METHODS

Patient population

All patients who underwent a CEA at the University Medical Centre Utrecht (UMCU) or St. Antonius Hospital (SAH), the Netherlands, between December 2011 and June 2016 were retrospectively screened for eligibility. Patients who underwent CEA because of a haemodynamically significant stenosis of the internal carotid artery (≥50% and symptomatic or ≥70% and asymptomatic) with available data for at least pre-operative,

intra-operative, and 24 h postoperative TCD monitoring were eligible for inclusion. TCD measurements 2 h and 24 h post-operatively were performed between 2012 and 2013 on a routine basis for study reasons. Before and after this period, 24 h post-operative TCD measurements were performed when medically indicated and strongly dependent on the post-operative availability of a clinical neurophysiologist (CNP). None of the patients included in the present cohort were included in the cohort of Pennekamp in 2012.[5]

Carotid endarterectomy

In all patients CEA was conducted under GA. Anaesthesia was induced with propofol, sufentanil, and rocuronium, and maintained with isoflurane or sevoflurane. After tracheal intubation, mechanical ventilation was adjusted to maintain normocapnia. All CEAs were performed by an experienced vascular surgeon or a vascular trainee under the supervision of a vascular surgeon. Atherosclerotic plaques of carotid artery were all removed by longitudinal arteriotomy. No eversion surgery was performed. In cases of asymmetry or diffuse slowing of the electroencephalogram (EEG) during clamping or a decrease of >70% of mean flow velocity in the middle cerebral artery (MCAV_{mean}) measured by TCD during clamping, an intraluminal shunt was used. Postoperatively, patients stayed on the post-anaesthesia care unit (PACU) for at least 6 h for continuous invasive radial artery blood pressure (BP) monitoring with possible extension of continuous invasive radial artery BP monitoring on the medium care unit (MCU).

Definition of study endpoints

CH was defined as an increase of TCD derived MCAV_{mean} ≥ 100% compared with baseline MCAV_{mean} without neurological complaints. CHS was defined as CH combined with clinical symptoms such as headache, confusion, seizures, intracranial haemorrhage, or focal neurological deficits after a symptom free interval. The diagnosis of CHS was made by an independent neurologist. Post-operative hypertension (PH) was defined as elevated systolic BP post-operatively >180mmHg, or a systolic BP exceeding individual BP restriction in patients with an intra-operative MCAV_{mean} ≥ 100% requiring medical antihypertensive treatment.

TCD settings

In all patients MCA*V* was determined pre-, intra- (before clamping and 3 min after declamping), and post-operatively (at two and 24 h). The technique has been reported previously in detail.[5,9] For peri-operative TCD at the UMCU, a pulsed Doppler transducer (Delica UMS-9UA system, SMT Medical, Wurzburg, Germany) with a 1.6-MHz probe was used. The transducer was adjusted in a head frame to monitor the MCA ipsilateral to the carotid artery that was being operated on. The focal depth settings were between

48 and 56 mm with a sample volume length of 10 mm. For the TCD at SAH, a pulsed Doppler transducer (Pioneer TC4040, EME, Überlingen, Germany) adjusted to a head frame was placed on the temporal bone and the MCAV_{mean} of the ipsilateral MCA was recorded continuously. The focal depth in this measurement was 45 - 60 mm. The values used for further analysis were gathered in real time on indicated data points as described below.

TCD time frames

TCD measurements were performed on five different pre-defined peri-operative moments (Fig. 1).

The mean velocity (V_{mean}) in the MCA ipsilateral to the treated carotid artery was measured:

- pre-operatively ($V_{pre\text{-}op}$), within one week prior to surgery
- 30 s before carotid cross clamping ($V_{pre\text{-}clamp}$)
- 3 min after declamping ($V_{post\text{-}clamp}$)
- 2 h post-operatively ($V_{post\text{-}op2}$)
- 24 h post-operatively ($V_{post\text{-}op24}$).

The intra-operative V_{mean} change (($V_{post\text{-}clamp}$-$V_{pre\text{-}clamp}$)/$V_{pre\text{-}clamp}$) was compared with the post-operative change after 2 h (($V_{post\text{-}op2}$-$V_{pre\text{-}op}$)/$V_{pre\text{-}op}$) and 24 h (($V_{post\text{-}op24}$-V_{preop})/$V_{pre\text{-}op}$) in relation to CHS (Fig. 1).

Post-CEA antihypertensive treatment protocol

For all patients the post-operative target systolic BP was aimed to be < 180 mmHg. When intra-operative MCAV_{mean} increased ≥100% after declamping, an individual restriction of systolic BP was set, aiming to achieve TCD controlled titration of the MCAV_{mean} < 100%. The BP restriction implied lowering of the systolic BP towards the systolic BP which accompanied a MCAV_{mean} < 100%. In these patients, invasive radial artery systolic BP was regulated to maintain below this individual restriction. This strict individualised BP control was adjusted to the post-operative TCD measurements. If the 2 h or 24 h post-operative measurements of MCAV_{mean} showed an increase of ≥100% compared with baseline or a decrease compared with the previous TCD measurement, BP restrictions could be individually adjusted by the vascular surgeon. Antihypertensive treatment consisted of intravenous labetalol (.25 - .5 mg kg^{-1} i.v. over 1 min initially, then .5 mg kg^{-1} i.v. every 5 - 10 min up to a cumulative dose of 300 mg, followed by 20 mg/h by continuous i.v. infusion) and intravenous clonidine (second choice, 75 mg i.v. over 10 min, then 25 - 75 mg/h by continuous i.v. infusion). If the BP was not controlled properly within 6 h observation on the PACU, the patient was transferred

to the MCU for continuous intra-arterial BP monitoring and treatment until the BP remained within the appropriate limits. If the BP was within the limits, intravenous antihypertensive treatment was reduced as soon as possible and commuted into an oral ß blocker (labetalol 100 - 200 mg daily to a maximum cumulative dose of 2400 mg daily or metoprolol 100 - 200 mg daily). When PH occurred on the nursing ward, treatment was started with an oral ß blocker.

Statistical analysis

The characteristics of patients who developed CHS were compared with the other patients using the chi square test for categorical variables and independent *t* test or Mann-Whitney *U* test for continuous variables, as appropriate. TCD measurements of patients were classified based on the level of increase in MCAV_{mean}, with a less or more than 100% increase at three predefined timeframes, namely intra-operatively, two and 24 h postoperatively, in relation to CHS occurrence. Of these results the positive predictive value (PPV) and negative predictive value (NPV) of the increase of MCAV_{mean} of these different timeframes were calculated in relation to CHS. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 22.0 software, IBM Analytics. A confidence level of less than 5% ($p < .05$) was considered to be significant.

RESULTS

Patient characteristics

All patients (n=707) who underwent a CEA due to high degree ICA stenosis at the UMCU or SAZ, the Netherlands, between December 2011 and June 2016 were retrospectively identified for this analysis. Patients with no available TCD derived MCAV_{mean} 24 hours postoperative or no TCD measurements at all for logistic reasons or insufficient temporal bone window were excluded. (n = 450) (Fig. 2)

A consecutive series of 257 CEA patients with available 24 h postoperative TCD measurement were included (UMC Utrecht n = 176). The average age of the patients was 70 years (range 50-92), the majority of the patients were symptomatic (93%), male (72%) and known to have hypertension (75%) and hyperlipidemia (50%). In 14% of patients intraluminal shunting was required during surgery because of EEG asymmetry or diffuse slowing or a decrease of the intraoperative MCAV_{mean} of >70%. Patient characteristics were comparable between the study populations of the two hospitals, although the incidence of PH was higher in the UMCU than in the SAH (46% vs. 26%, p=.004), respectively. In the UMCU-cohort seven patients did not have a 2 h post-operative TCD measurement (missing data). In the SAH, the 2 h post-operative TCD measurement was

missing in nine patients. Of these patients, four were diagnosed with intra-operative CH and none with 24 h post-operative CH. (Tables 1 and 2)

Thirty day outcome

Of all 257 patients, six patients (2.3%) had a peri-procedural stroke and five patients (2%) a TIA. Nine patients had a post-operative a wound hematoma and one patient died within 30 days of surgery (unknown cause after hospital discharge). The overall 30 day death/stroke rate was 2.7%. (Table 1). In total, nine patients (3.5%) developed CHS with headache (six), minor cerebellar stroke (one), both cerebellar infarction and cerebral hemorrhage (one), and TIA (one) as symptoms. Eight of nine patients had hypertension before the development of CHS, and all nine patients had been admitted to the MCU for BP control.

PH occurred in 102 patients, in 44 of these patients CH was diagnosed post-operatively and CHS in eight. Of the 154 patients without PH, 14 patients were diagnosed with post-operative CH and one patient developed CHS. (Table 1,3 and 4)

Clinical relevance

The NPV of TCD measured CH for the prediction of CHS was 97% for intraoperative TCD measurement, 98% for 2 h post-operative, and 99% for 24 h post-operative TCD measurement. The PPV of intra-operative and two and 24 hours post-operative TCD measurements were 8%, 11% and 18%, respectively (table 2-4). Separate analyses including only symptomatic patients (n = 239, excluding asymptomatic patients [n = 18]) did not influence the PPV and NPV for any of the different TCD measurements.

TCD measurements

Of the included patients, TCD measured CH (intra-operative or post-operative) occurred in 72 patients (28%). Compared with the corresponding baseline MCAV_{mean}, 25 patients (10%) had an intra-operative MCAV_{mean} increase of ≥100%, 45 patients (18%) had a MCAV_{mean} increase of ≥100% 2 h post-operatively, and 34 patients (13%) 24 h post-operatively. In 16 patients (9%) CH was diagnosed in two TCD measurements, in eight patients (3.5%) CH was diagnosed in all measurements. Of the nine patients who eventually developed CHS, an intra-operative CH was diagnosed in two, and a postoperative CH in eight (after two hours [n = 5] or after 24 hours [n = 6]). (Figure 3 and 4) Three of the nine patients (33%) who developed CHS did not reveal a 100% increase in V_{mean} by TCD either intra-operatively or 2 h post-operatively, and were adequately identified only by the 24 h post-operative measurement with a still increasing V_{mean}. These patients would have been discharged without any additional protective BP restrictions while in fact they showed at high risk for CHS within the

following 22 h (Figure 4). In one CHS-patient, with a missing two hours postoperative TCD measurement, CH was solely measured intraoperatively. (Table 2, figure 3)

Of the non-CHS group (*n* = 248), the MCAV_{mean} increase was 20%, 41% and 37% for intra-operative, 2 h post-operative and 24 h post-operative measurement, respectively. Of the CHS-group (*n* = 9), the median of MCAV_{mean} increase was 35%, 118% and 112%, respectively. This increase in MCAV_{mean} between groups 2 h and 24 h post-operatively was significantly different. (Table 5 and 6) The same applied for the relative MCAV_{mean} (Δ increase between two timeframes) of the non-CHS and CHS-group. (Table 3)

DISCUSSION

In a predominately symptomatic patient cohort with an acceptable peri-operative event rate (3.5%), we found that an increase of MCAV_{mean} < 100% at a 24 h post-operative TCD measurement accurately excludes the risk of CHS in patients undergoing CEA. In addition, the PPV of a 24 h post-operative TCD measurement for prediction of CHS was doubled compared to intra-operative TCD measurements. Although the PPV remained low, a post-operative increase of a TCD derived MCAV_{mean} at two and 24 h after CEA is more accurate for identification of patients at risk for CHS as compared to a quality strategy basing this risk solely on an intra-operative TCD determined increase of MCAV_{mean}.

Of the nine patients who developed CHS, all except one had post-operatively measured CH, either detected by a 2 h or a 24 h post-operative TCD measurement. Three of these patients were solely detected from the 24 h post-operative measurement, and would have been missed based on the intra-operative and 2 h post-operative measurements. In the remaining patient, CH was solely measured intraoperatively and treated directly by aggressive intravenous antihypertensive therapy, which might have affected the post-operative TCD measurements (Fig. 3)

Adequate prediction of development of CHS is essential to prevent major complications, because CHS has a very high morbidity and mortality rate.[4] As a result of the high NPV, absence of post-operative TCD measured CH obviates the need for acute aggressive invasive intravenous antihypertensive therapy directly post-operatively on a high care unit for the vast majority of post-CEA patients. Post-CEA patients with hypertension without hyperperfusion will be treated on the ward and in particular during a vascular medicine specialist follow up visit. Moreover, this will lead to a decrease in hospital costs, unlike a one size fits all postoperative systolic BP policy treating all patients with systolic pressure >160 mmHg.[10,11]

Post-operative TCD measurement, at both two and 24 h post-operatively, will help to identify more accurately patients at risk of CHS in an early post-operative phase than intraoperative TCD measurement. Intra-operative TCD with its relatively low PPV and operator dependence accompanied by logistic problems may lead to waiving the peri-operative TCD measurements completely, and in all patients, lower BP below 160mmHg to protect from CH and CHS.[10,11] However, caution is required as CH and CHS may also occur with stable normotensive systolic BP (Tables 3 and 4).

This study strengthens the results observed in an earlier and smaller study population that a 2 h post-operative TCD measurement was helpful to enable a more accurate prediction of CHS after CEA.[5,12] In the current study, 24 h postoperative TCD measurements gave a higher PPV and NPV than intra-operative and 2 h post-operative TCD measurements. The benefit of an additional TCD measurement 24 h post-operatively is primarily found in the high NPV, giving the opportunity to exclude the risk on CHS and therefore safely discharge patients to the ward or home. Unfortunately, the increase in PPV for CHS between intraoperative and post-operative TCD measurements is less notable than observed previously.[5] These differences in increase of PPV might result from more aggressive and strict intravenous antihypertensive therapy in patients with intraoperative or 2 h post-operative CH and a slightly different definition of PH, systolic BP > 180 mmHg or BP above individual restriction with need for medical treatment, used in this current study.[5]

Quantifying MCA*V* with TCD is a quick (<15 min), easily performed at bedside, convenient, and low cost method to measure the increase of the cerebral blood flow (CBF) in the MCA during and after CEA. The changes in the $MCAV_{mean}$ determined by TCD correlate well with the changes in CBF ipsilateral to the operation side.[7,9,13,14] This measurement is non-invasive with a minimal physical burden for the patient, especially in comparison with extended strict invasive BP treatment on a critical care unit. Although MCA*V* measurements by TCD are operator dependent and impossible for an absent temporal bone window (10e15% of all CEA patients), MCA*V* measurement seems to be the only method to predict or exclude development of CHS with any certainty.[5] New developments and techniques promise future TCD devices that are even more easily accessible, portable, and able to automatically identify the MCA*V* leading to a TCD device less operator dependent and more easily used by non-trained physicians.[15]

The present study has several limitations. First, patients were included retrospectively based on the availability of a 24 h post-operative TCD measurement and primarily symptomatic. In 2012 and 2013, some patients (*n* = 83) at UMCU received 2 h and 24 h post-operative TCD measurements on a routine basis for study reasons (clinical trials.

gov: NCT01451294). Before and after this period, 24 h postoperative TCD measurements were strongly dependent on post-operative availability of CNP (*n* = 174). Although the study population is a selection of a total CEA cohort, it is not believed that this selection influenced the findings and conclusion. However, results primarily apply to symptomatic CEA patients. Second, patients are included in two tertiary referral centres. Both centres used a slightly different TCD device and different technicians, which might have affected the TCD findings. Third, as a result of intra-operative or 2 h post-operative TCD measured hyperperfusion, patients were treated directly with strict BP control and admitted to the medium care unit. Because of this intervention, consecutive post-operative (2 h or 24 h) TCD measurements might have given a distorted view and an underestimation of the predictive value. However, this does not seem to apply for one third of the CHS patients who were only diagnosed by 24 h post-operative measurements. Fourth, the definition of CHS remains a matter of ongoing debate because of its partly subjective nature (headache, minor neurological events). The onset of neurological symptoms such as headache should be discussed because this is often not described in detail, which makes it harder to define the exact timing of occurrence of CHS. However, the timing of occurrence of CHS in all CHS patients was during admission, on the first or second day after surgery and after a symptom free interval. Fifth, patients without a 24 h post-operative TCD measurement were excluded from participation in this study. Included patients were a consecutive series of CEA patients with available 24 h TCD measurements. In the vast majority of patients, absence of the 24 h post-operative TCD measurement can be explained by logistics. Post-operative TCD measurements were not obtained from CEA patients operated on at the end of the day surgery starting after 2 p.m.) or during the weekends (outside of office hours), because of a lack of an available CNP to perform the measurements. Because the NPVs of both post-operative TCD measurements are similar, this logistic problem may be solved by the knowledge that timing of post-operative TCD measurements within the first 24 h can be variable. One negative post-operative TCD measurement at any time point between 2 h or 24 h, will therefore probably be sufficient to almost exclude all patients from the risk of CHS. TCD measurement in the morning (early office hours) of the first post-operative day might be a solution for these logistic issues. It is believed that logistic selection randomly excluded patients from participation in the current study and did not exclude one particular type of CEA patient. In smaller part, missing 24 h post-operative TCD measurements can be explained by absence of a temporal bone window (±10 - 15%). Unfortunately, no follow up CHS data for these excluded patients were available for analysis. Finally, the definition of PH used in this study differed slightly from the definition used by Pennekamp et al.[5] Because no correction was made for the timing of onset of PH, either directly post-operatively on PACU or on the vascular surgery ward, any post-operative systolic BP > 180 mmHg or BP increase above individual restriction in patients with an

intra-operative MCAV_{mean} ≥ 100% and requiring medical antihypertensive treatment was interpreted as PH. A systolic BP > 160 mmHg without increase of MCAV_{mean} ≥ 100% was not scored as PH but was accepted during admission because it did not require immediate BP treatment. These patients were safely discharged and received elective BP lowering intervention in the outpatient clinic. It is the authors' belief that the definition used in the current study meant that only direct postoperative clinically relevant hypertension requiring immediate treatment was diagnosed, thereby avoiding over diagnosis of hypertension.

CONCLUSION

To date, no validated pre-operative and post-operative prediction models exist for patients at risk of development of a CHS post-CEA. Only TCD measurements intraoperatively and directly post-operatively have been shown to increase the positive and negative predictive values of CHS development in post-CEA patients. Moreover, a 24 h post-operative measurement of less than 100%, accurately excludes the risk of CHS in post-CEA patients. In addition, the 24 h post-operative TCD measurement resulted in the most accurate PPV and NPV values compared with intraoperative and 2 h post-operative TCD measurements. Therefore, it is recommended that an extra measurement of the MCAV_{mean} is performed 24 h after CEA in addition to the intra-operative TCD measurement, in order to identify which patients who can safely be excluded as they are not at risk of CHS.

TABLES AND FIGURES

Table 1. Baseline characteristics and postoperative events.

Baseline characteristics	All patients (n=257)	CHS+ (n=9)	CHS- (n=248)	*p*-value
Age (SD)	70 (8.9)	69 (10.3)	70.(8.8)	0.780
Gender (male)	185 (72%)	6 (67%)	179 (72%)	0.718
Diabetes mellitus	66 (26%)	2 (22%)	64 (26%)	1.000
Hypertension	192 (75%)	7 (78%)	185 (75%)	1.000
Hypercholesterolemia	129 (50%)	3 (33%)	126 (51%)	0.334
CAD	76 (30%)	2 (22%)	74 (30%)	1.000
Smoking				
• Current	110 (43%)	4 (44%)	106 (43%)	1.000
• Past	102 (40%)	4 (44%)	98 (40%)	0.744
Alcohol use	149 (58%)	6 (67%)	143 (58%)	0.738
Operation side (right)	126 (49%)	3 (33%)	123 (50%)	
Symptomatic	239 (93%)	9 (100%)	230 (93%)	1.000
Degree of ipsilateral stenosis				0.768
• >70%	234 (88.7%)	9 (100%)	225 (91%)	
• 50-70%	22 (8.6%)	-	22 (9%)	
Degree of contralateral stenosis				0.711
• Occlusion	33 (12.8%)	2 (22%)	31 (13%)	
• >70%	42 (16.4%)	2 (22%)	40 (16%)	
• 50-70%	29 (11.3%)	1 (11%)	28 (11%)	
• <50%	141 (39.3%)	3 (33%)	138 (56%)	
• Unknown	12 (47%)	1 (11%)	11 (4%)	
Shunt use	36 (14%)	-	36 (15%)	0.618
Postoperative events	6 (2%)	2 (22%)	4 (2%)	0.015
Stroke	5 (2%)	1 (11%)	4 (2%)	0.164
TIA	9 (4%)	-	9 (4%)	1.000
Wound hematoma	67 (26%)	9 (100%)	58 (23%)	**<0.001**
Admission MC	102 (40%)	8 (89%)	94 (38%)	**0.003**
Postop. hypertension Death <1jr	2 (1%)	-	2 (1%)	1.000

CHS+: number of patients who developed CHS. (%) CHS-: number of patients who did not develop CHS (%). SD: standard deviation. CAD: coronary artery disease. TCD: transcranial Doppler. *p*-value <0.05 was considered significant.

Table 2. Predictive values of TCD measurements at different timeframes (intraoperatively, 2 hours postoperatively, 24 hours postoperatively) of all patients.

All patients (n=257)		**CHS+ (n=9)**	**CHS- (n=248)**	**PPV (%)**	**NPV (%)**
Intraoperative increase	≥100%	2	23	8	97
	<100%	7	225		
Postoperative increase total	≥100%	8	50	14	99
	<100%	1	198		
Postoperative increase – 2h	≥100%	5	40	11	98
(16 missing)	<100%	3	193		
Postoperative increase – 24h	≥100%	6	28	18	99
	<100%	3	220		
Intraoperative increase	**Postoperative increase (total)**				
≥100%	≥100%	1	10	9	97
≥100%	<100%	1	13	7	97
<100%	≥100%	7	40	15	99
<100%	<100%	0	185	0	87.5
	total	9	248		

CHS+: number of patients who developed CHS. (%) CHS-: number of patients who did not develop CHS (%).PPV: positive predictive value (%). NPV: negative predictive value (%).

Table 3a. Increase of TCD measured MCAV_{mean} (absolute increase) at different timeframes (intraoperatively, 2h postoperatively, 24h postoperatively)

All patients (n=257)	**CHS+ (n=9)**	**CHS- (n=248)**	***p*-value**
Increase MCA$V_{mean,}$ [IQR]	35% [10-93]	20% [2-43]	0.233
Intraoperatively, median [IQR]	118% [76-181]	41% [10-78]	**<0.001**
2h postoperatively, median [IQR]	112% [92-143]	37% [14-70]	**<0.001**
24h postoperatively, median [IQR]			

MCAV_{mean}: mean middle cerebral artery blood flow velocity. CHS+: number of patients who developed CHS. (%) CHS-: number of patients who did not develop CHS (%). IQR: interquartile range.

Table 3b. Delta increase of TCD measured MCAV_{mean} (relative increase) at different timeframes (intraoperatively, 2h postoperatively, 24h postoperatively)

All patients (n=257)	**CHS+ (n=9)**	**CHS- (n=248)**	***p*-value**
Δ increase MCA$V_{mean,}$ [IQR]			
Intraoperatively - 2h postoperatively, median [IQR]	77% [63]	16% [61]	**0.010**
2h - 24h postoperatively, median [IQR]	8.6% [81]	-2.13% [39]	0.329
intraoperatively - 24h postoperatively, median[IQR]	94%[69]	16% [55]	**0.001**

MCAV_{mean}: mean middle cerebral artery blood flow velocity. CHS+: number of patients who developed CHS. (%) CHS-: number of patients who did not develop CHS (%). IQR: interquartile range. Mann Whitney test.

Table 4. Postoperative hypertension (PH) and CH

All patients (n=257)	CH+ post	CH- post	PPV (%)	NPV (%)
PH – yes	44	58	43	
PH – no	14	140		91
Missing		1		
Total	58	199		

PH: postoperative hypertension.CH+ post: number of patients who developed CH postoperative (2 hour or 24 hour). CH- post: number of patients who did not develop CH postoperative (2 hour or 24 hour). PPV: positive predictive value (%). NPV: negative predictive value (%).

Table 5. Postoperative hypertension (PH) and CHS

All patients (n=257)	CHS+	CHS-	PPV (%)	NPV (%)
PH – yes	8	94	8	
PH – no	1	153		99
Missing		1		
Total	9	248		

PH: postoperative hypertension. CHS+: number of patients who developed CHS. CHS-: number of patients who did not develop CHS. PPV: positive predictive value (%). NPV: negative predictive value (%).

Figure 1. TCD measurement on different timeframes.

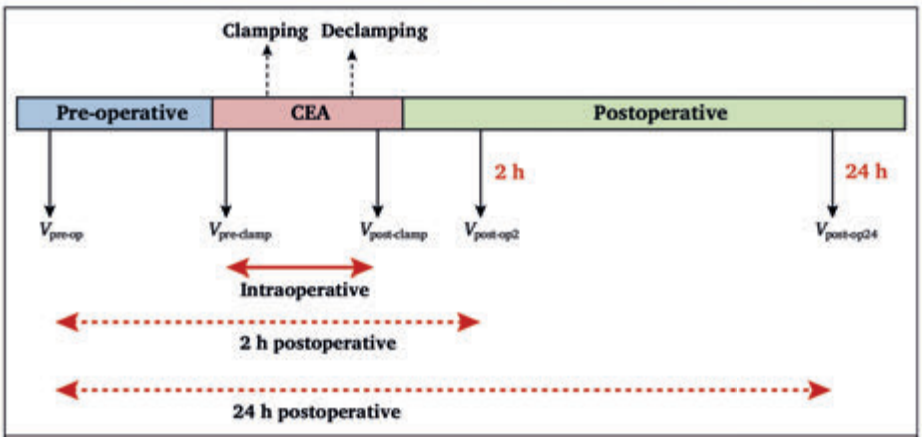

Figure 1. Trascranial doppler measurements (red) in patients undergoing carotid endarterectomy (CEA) at different timeframes for prediction of cerebral hyperperfusion syndrome. CEA = carotid endarterectomy.

Figure 2. Flowchart inclusion study patients

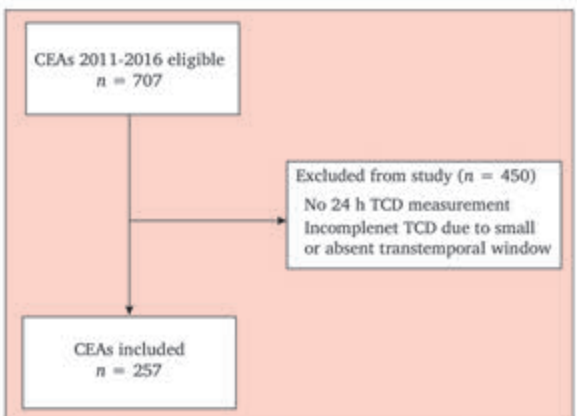

Figure 2. Flowchart detailing inclusion of study patients undergoing carotid endarterectomy (CEA) and intraoperative transcranial doppler (TCD) for prediction of cerebral hyperperfusion syndrome. CEA = carotid endarterectomy; TCD = transcranial Doppler.

Figure 3. Increase of MCAV_{mean} measured by TCD on different timeframes periprocedural, expressed as percentages, for patients who developed cerebral hyperperfusion syndrome.

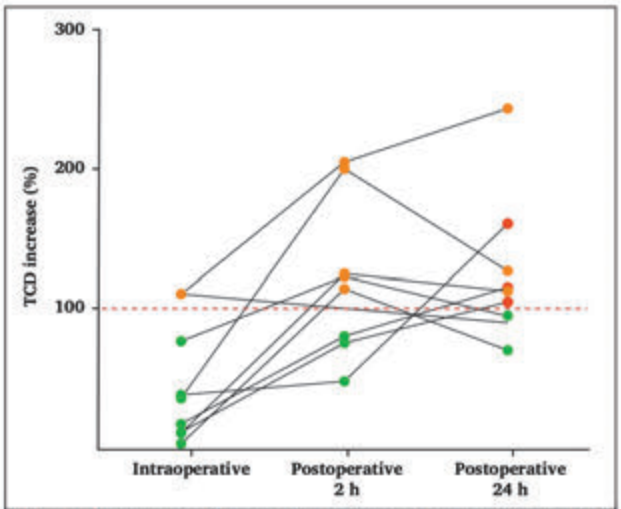

Figure 3. Increase of mean blood flow velocity in the middle cerebral artery (MCAV_{mean}) measured by transcranial Doppler (TCD) on different peri-procedural timeframes, expressed as percentages, for patients who developed cerebral hyperperfusion syndrome. Blue bullets present increase of MCAV_{mean} <100% or a decrease below 100% compared with previous measurement. Purple bullets present an increase of MCAV_{mean} ≥100%. Red bullets present an increase of MCAV_{mean} ≥100% after two previous measurements of MCAV_{mean} <100%. MCAV_{mean} = mean blood flow velocity in the middle cerebral artery; TCD = transcranial Doppler.

Figure 4. Flowchart overview intraoperative and postoperative TCD measurements

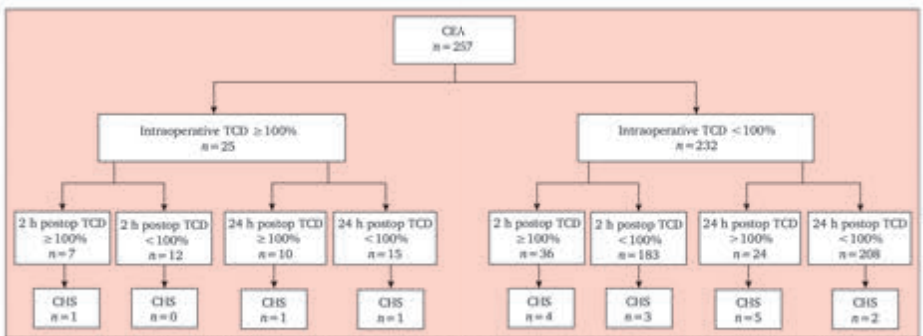

Figure 4. Flowchart overview of intra-operative and post-operative TCD measurements of carotid endaterectomy patients. CEA = carotid endarterectomy; CH = cerebral hyperperfusion; CHS = cerebral hyperperfusion syndrome; TCD = transcranial Doppler.

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CHAPTER 10

Thirty days of home blood pressure monitoring in patients following carotid endarterectomy: a feasibility study

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Submitted

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ABSTRACT

Objectives: Hemodynamic disturbances are the causative mechanism in half the perioperative strokes following carotid endarterectomy (CEA). Nevertheless, insight into individual hemodynamics after discharge is lacking. We assessed the feasibility of daily post-discharge blood pressure (BP) self-measurements at home following CEA and analysed BP-trend patterns as well as patient experiences.

Methods: Thirty CEA-patients (age 68±8 years; 87% male) measured BP at home twice daily for 30 days with an ambulatory BP-monitor. Exclusion criteria: Modified Rankin Scale score>2 or no access to WiFi. BP-values were transmitted to an online dashboard on a web application. If individually determined systolic target BP exceeded by ≥15% an alert was generated, and patients were requested to visit the outpatient clinic after 4 consecutive alerts. After 30 days, patients completed a survey regarding their experiences and perceived feasibility of home BP-monitoring. Adherence to the monitoring protocol, BP time-series, and any interventions were scored.

Results: Post-discharge, four adverse events occurred; bleeding requiring surgery (n=1), TIA (n=1), myocardial infarction (n=1), readmission due to stress-related hypertension (n=1). None of the patients had four consecutive BP-measurements exceeding the BP threshold. Patient adherence was high; 24 patients provided ≥90% of the expected BP-measurements. Eight patients visited their general practitioner with concerns regarding their observed BP-values, in two leading to changes in anti-hypertensive therapy. Over 90% of patients experienced home BP-monitoring as positive and all except one recommended adding home BP-monitoring to standard care. Median intra-individual variability of systolic and diastolic BP of all patients was 12.7mmHg and 7.4mmHg, respectively. No significant differences in systolic BP variability or absolute values were found between patients with a post-discharge event and those without.

Conclusion: Postoperative home BP-monitoring was feasible and well-accepted by CEA-patients. Future studies need to address the clinical gain of home BP-monitoring in early detection of patients at risk for postoperative hemodynamic complications.

INTRODUCTION

In patients with severe carotid artery stenosis undergoing carotid endarterectomy (CEA), cerebral autoregulation is often disturbed, making cerebral perfusion dependent on blood pressure (BP). Hemodynamic disturbances, i.e. hypertensive and hypotensive episodes, are the believed causative factor for perioperative strokes following CEA in at least half of patients, and may occur up to 30 days after surgery.[1,2] Therefore, tight perioperative BP-control is an essential component of stroke prevention after CEA.

Despite the importance of in-hospital perioperative BP-management, little is known of BP changes in the first weeks after CEA. Self-measurement of BP at home could close this knowledge gap and help to target patients who are most at risk. It might also allow earlier recognition of deterioration and early intervention.

In this pilot study, we asked CEA-patients to perform BP-measurements twice daily at home during the first 30 days after discharge and observed BP remotely. The primary aim was to assess feasibility and patient experiences with daily BP self-measurements. The secondary objective was to gain insight into postoperative BP-trends.

METHODS

Subjects

This study was approved by the local ethical committee (NL59854.041.17, 17-177/D). Written informed consent was obtained in patients undergoing CEA between October 2017 and July 2018 at a tertiary referral vascular center, University Medical Center Utrecht, the Netherlands. Exclusion criteria: Modified Rankin Scale score>2 or no access to wireless internet.

Study design

The study was a prospective feasibility-study including 30 CEA-patients. Since a formal power calculation was not feasible due to the lack of preliminary data, a sample size of 30 was estimated for explorative analysis. Patients received an ambulatory BP monitor (OMRON HEM-9210T, Healthcare CO.Lt., Kyoto, Japan) transmitting BP-values to a secured online dashboard via telemonitoring (Luscii Vitals, Luscii Healthtech BV, Amsterdam, The Netherlands) on an iPad (Apple Inc., Cupertino, CA, USA). Patients were trained to record BP twice daily at rest (every morning and evening), for 30 days after hospital discharge. Researchers had access to an online clinician dashboard to review patients' measurements over time. In case of a missing BP-measurement, a reminder was sent. For each patient, a systolic BP upper limit was determined based on the

magnitude of postoperative increase of cerebral blood flow measured by transcranial Doppler (TCD). An alert was generated if BP exceeded this threshold with ≥15%. Two researchers (LF and MB) checked the BP-measurements daily. If four consecutive alerts were generated (i.e., exceedance of systolic BP threshold >two days), patients were requested to visit the Vascular Surgery outpatient clinic. At the end of the study, patients' experiences and perceived feasibility of home BP-monitoring following CEA was assessed by a telephone survey. The survey consisted of 14 items divided into four categories; 'Hospital admission'(3 items), 'Perceived health'(2 items), 'Patient experience'(7 items) and 'Usability'(2 items).(Supplemental data, Table 1) Patients' adherence to the monitoring protocol, BP time series, and any interventions were also scored.

The costs incurred for telemonitoring 30 study-patients for one month following hospital discharge were €76 per patient (total: €2280). This includes one telemonitoring month (application+clinicians' dashboard, €13.50 pppm), iPad lease(€29.50 pppm) and the acquisition costs of ten home BP-monitors (total: €990). These costs will likely vary when implemented in actual clinical practice.

Statistical analyses

Descriptive statistics were used to analyze the primary outcome and summarize patients' experience and satisfaction measures. Percentage of agreement was calculated by the percentage of patients scoring on a four-point Likert scale.

BP changes, patient adherence, BP time series and number of interventions are presented as mean (±SD) or median (interquartile range), as appropriate, and categorical variables as n (percentage). Intra-individual variability of BP was calculated for each patient over the 30-day monitoring period (±SD). Proportion of hypertensive episodes (BP>systolic upper limit) were calculated.

Subgroup analyses were performed based on the presence of postoperative hemodynamic complications, postoperative admission to a high-care unit and overall postoperative complications. *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient population

Of 42 eligible patients, 34 gave informed consent. Four patients withdrew before the monitoring period started due to postoperative ADL-dependency (n=2) or unwillingness

to perform measurements (n=2). In total, 30 CEA-patients (87% males, 68±8 years) completed the BP-monitoring period at home.

Neurological outcome

In-hospital, two patients (7%) developed postoperative cerebral hyperperfusion (TCD>100% increase), one patient had a postoperative bleeding requiring surgery (3%) and one patient suffered a TIA (3%). Five patients (17%) were admitted to a high-care unit for prolonged monitoring of hemodynamic parameters. Post-discharge, four patients experienced an adverse event of which two were hemodynamic events; readmission due to stress-related hypertension and postoperative bleeding requiring surgery. (Table 1)

Patient experience

Patients reported a very positive (57%) or slightly positive experience (33%) with BP-monitoring at home. Usability of home BP-monitoring was found to be 'very easy' by most patients (91%). All except one of the patients would recommend home BP-monitoring as part of the standard of care after CEA. (Figure 1)

Measurement adherence

Patient adherence to home BP-measurement was high; 24 patients provided ≥ 90% of the expected BP-measurements. Home BP-monitoring increased awareness of adequate BP control. Eight patients visited their general practitioner (GP) for concern regarding observed BP-values, leading to changes in anti-hypertensive therapy in two patients.

In 13 patients (43%) there was at least one systolic hypertensive measurement (BP > systolic upper limit) and in 3 patients (10%) BP exceeded the systolic threshold by >15%. However, in none of the patients, four consecutive BP-measurements exceeded the individual systolic BP threshold. The average number of reminders sent to the patient as a result of a missing BP-measurement was 4.2. Median intra-individual variability of systolic and diastolic BP of all patients was 12.7mmHg and 7.4mmHg, respectively. Variability (10.5 vs 13.1mmHg) and absolute values (136 vs 139mmHg*)* of systolic BP-measurements did not significantly differ between patients with an event post-discharge and those without. (Figure 2)

DISCUSSION

Within this feasibility study, postoperative home BP-monitoring was well-accepted - and even recommended - by CEA-patients. This is the first step towards closing the knowledge gap of BP changes in the first four weeks following CEA. Besides, home BP-

monitoring led to increased patient awareness resulting in self-intended visits to GP and BP-therapy changes.

The study design is unique. By implementing home BP-monitoring to postoperative care, we expanded postoperative care to the home setting. This new concept of care enables daily remote monitoring of BP-measurements by healthcare providers with the possibility to intervene, if deemed necessary. Hereby improved quality of care and safety is pursued as well as creating more patient-centered care by active participation and insight in own health.

Over the past years, home BP-monitoring has been shown to improve BP control in hypertension treatment.[3] Although the rise of telemonitoring as a novel approach and an alternative for protocolized follow-up, it is primarily used for chronic conditions while adoption in postoperative care is still in its infancy.[4-6] Implications on cost savings are still largely to be determined.

Use of telemonitoring in a selected high-risk postoperative patient group might reduce the need for outpatient visits or enable the detection of hemodynamic complications in an early stage. If such early detection and intervention could prevent post-discharge neurological complications and prevent hospital readmissions, the benefits of telemonitoring are likely to outweigh costs. In addition, patient satisfaction with postoperative BP telemonitoring was high; higher perceived safety and reduced insecurity is the most likely reason why patients recommended home BP-self measurements after hospital discharge to become standard of care.

Although home BP-monitoring seems suitable for a large group of patients, awareness is needed for possible unintended consequences when patients see their BP-values twice daily. One patient experienced stress because his BP was higher than expected. As a result, stress-related hypertension occurred, and for safety reasons, he was readmitted. However, the overall results show a very positive experience with remote monitoring at home.

Limitations

First, patients were included in a tertiary referral center which may not represent all CEA-patients. However, only five patients stated that their main reason not to participate was the anticipated burden of BP-monitoring for 30 days. Second, it was not possible to add chosen side per BP-measurement (left or right arm) in the application. This may have influenced the intra-individual BP-variability, regardless of the instruction to perform BP-measurements only on the arm that is known to provide

the highest BP readings. Finally, no conclusions can be drawn on our observation of no significant differences in postoperative BP-patterns between patients with and without postoperative events, since the study lacked the necessary statistical power to detect such differences. Therefore, we suggest addressing post-CEA BP-trends, variability and changes compared to preoperative BP as crucial new research questions.

CONCLUSION

Postoperative home BP-monitoring is well-accepted and even recommended by CEA-patients. Future larger studies need to address the potential clinical gain of home BP-monitoring in early detection and management of patients at risk for postoperative hemodynamic complications.

Sources of funding
Project was funded by eHealth & Applied Data Analytics in Medicine (ADAM) project, UMC Utrecht, The Netherlands.

Disclosures
MJMB is a part-time employee of Luscii Healthtech BV (The Netherlands).

Table 1. Baseline characteristics

	All patients(*n*=30)
Age	69(50-93)
Male	26(87)
Risk factors	
• Hypertension	26(87)
• Hyperlipidaemia	19(63)
• Diabetes	5(17)
• Coronary artery disease	10(33)
• Peripheral arterial disease	9(30)
• Smoker(current/ex)	25(83)
• Symptomatic	27(90)
Ipsilateral stenosis	
• 50-70%	2(7)
• >70%	28(93)
Contralateral stenosis	
• Occlusion	3(10)
• >70%	6(20)
• 50-70%	5(17)
• <50%	16(53)
Shunt-use	1(3)
Medication	
• Statins	26(87)
• Antiplatelets	27(90)
• Anti-coagulants	3(10)
• Antihypertensives	24(80)
• ≥2 drugs	14(47)
Postoperative events	
In-hospital:	
• Bleeding	1(3)
• TIA	1(3)
Post-discharge:	
• Bleeding	1(3)
• Myocardial infarction	1(3)
• TIA	1(3)
• Stress-related hypertension	1(3)
• BP-related GP-visit	8(27)
• BP-related medication change GP	2(7)

Data in median(range), number (%). GP: general practitioner.

Figure 1. Feasibility of home BP-monitoring

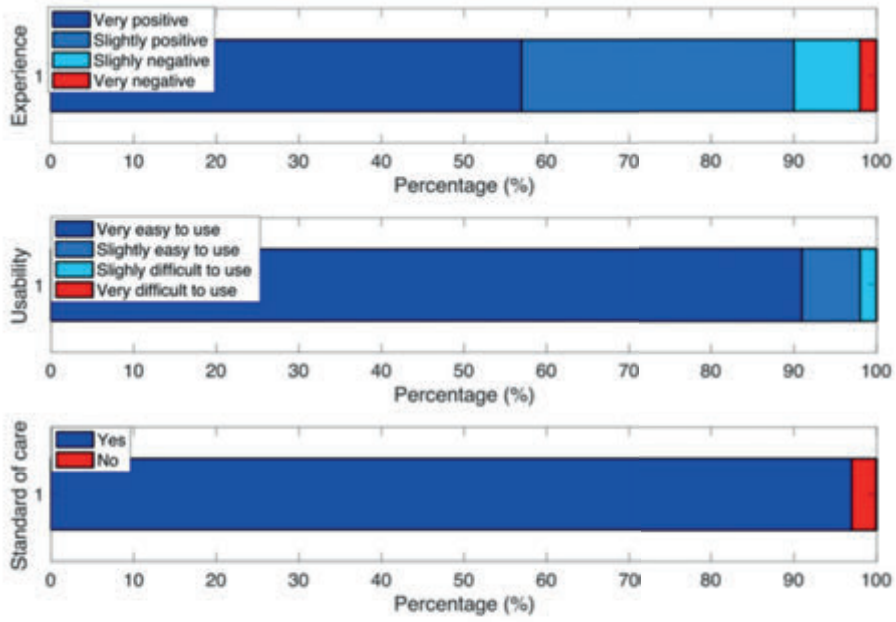
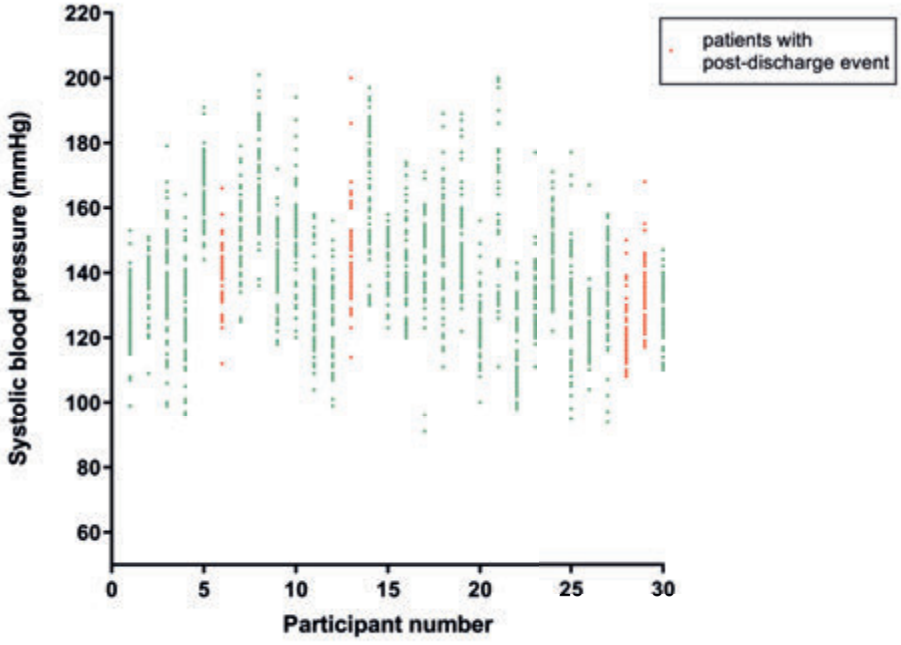


Figure 2. Intra-individual variability of systolic BP



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SUPPLEMENTARY MATERIAL

Appendix I. Survey

Supplementary material is omitted due to space limitations, and can be found in a separate file.

CHAPTER 11

Commentary on "Post-carotid Endarterectomy Hypertension. Part 2: Association with peri-operative clinical, anesthetic, and transcranial Doppler derived parameters by Jeremy E. Newman et al."

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Guidance of perioperative hemodynamics is crucial to prevent procedural stroke in carotid endarterectomy (CEA) by preserving cerebral perfusion.[1,2] Newman et al. suggest a one fits all post-operative systolic blood pressure (BP) policy treating > 170 mmHg or > 160 mmHg in patients with symptoms.[3] This policy causes significant overtreatment, as two in five CEA patients will undergo in hospital BP lowering treatment for several days, leading to a high workload, increased in hospital costs, and bed occupancy. In reality, only a subset of patients truly need immediate BP lowering therapy to prevent cerebral hyperperfusion syndrome (CHS), which occurs in 3-5% of CEA patients.[4]

Peri-operative transcranial Doppler (TCD) can identify patients at risk for CHS. Owing to the high negative predictive value of 99% no patient needing strict BP therapy will be left untreated.[4] With TCD, only one in 10 patients requires immediate and strict BP lowering on a medium care unit, thereby avoiding significant overtreatment, as the remaining 90% of patients (even when BP exceeds 170mmHg in the absence of symptoms) can be discharged safely and have elective BP lowering intervention via the outpatient clinic. Of note, Newman's protocol can never prevent all CHS cases, as CHS may also occur with stable systolic BP as low as 130mmHg! [4]

Post-CEA hypertension (PEH) is a risk factor for stroke due to CHS and intracranial hemorrhage. However, these complications are not reported as outcome parameters. From the perspective of the very small sample size, the clinical implications of the proposed one size fits all treatment approach for PEH, to direct perioperative hemodynamic therapy remain unclear. Of note, achievement of immediate and persisting BP lowering in cardiovascularly compromised patients can be very challenging! Instead, we propose a tailored approach using TCD to identify all patients that are at true high risk of PEH related complications following CEA.

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PART IV

SUMMARY AND DISCUSSION

CHAPTER 12

Summary

SUMMARY

The benefit of carotid artery revascularization for severe carotid artery stenosis is offset by stroke due to the intervention itself. One in three of periprocedural strokes and the majority of postoperative strokes are suggested to be of hemodynamic origin, making adequate cerebral perfusion of utmost importance. This thesis evaluated the several aspects of current clinical care (part I), perioperative hemodynamic monitoring (part II), and postoperative cerebral and hemodynamic (remote) monitoring (part III) in order to optimize the current periprocedural monitoring during and following carotid endarterectomy. Optimizing of monitoring will ultimately reduce the incidence of periprocedural stroke in patients undergoing carotid endarterectomy.

PART I Current clinical care

Chapter 2. Technical improvements in carotid revascularization.

This chapter provides an overview of the pathophysiological mechanism of stroke following carotid revascularization and the technical improvements that have contributed to reducing this stroke risk. Over the past years, the increased understanding of the mechanism underlying periprocedural stroke after carotid revascularization has led to multiple technical improvements. Adequate patient selection and timing of surgery, optimization of antiplatelet therapy and cerebral monitoring, and improvement of stenting techniques seem to be paying off by decreasing death/stroke risk over the recent decades.

Chapter 3. National overview of perioperative monitoring policies

The currently applied perioperative monitoring policies nationwide during carotid endarterectomy were assessed by means of a survey among vascular surgeons of all Dutch centres. This study provides an overview of perioperative hemodynamic and cerebral monitoring policies applied by Dutch CEA-centres. The findings show that type of anaesthesia, cerebral and hemodynamic monitoring policies during CEA vary widely on hospital-level. This study reaffirms the need for univocal (inter)national recommendations within a standardised protocol on hemodynamic monitoring during CEA.

PART II Procedural monitoring

Chapter 4. Preoperative blood pressure and carotid artery atherosclerosis

The associations of pre-operative systolic and diastolic blood pressure with histological carotid plaque characteristics were studied. A multiple regression analysis of patients undergoing carotid endarterectomy demonstrated that increased systolic and diastolic blood pressure levels are associated with more presence of macrophages, lipid core

and intraplaque hemorrhage in the carotid carotid plaque, representative for a more vulnerable plaque. Replication in a separate iliofemoral cohort confirmed these associations.

Chapter 5. Baseline blood pressure of carotid artery stenosis patients
In this chapter, we analyzed the comparability of preoperative blood pressure measurements of patients undergoing carotid endarterectomy to propose a uniform and standardized definition to assess the 'awake baseline blood pressure' reliably. Results of this study show that this baseline blood pressure should be determined by averaging all available preoperative blood pressure values in the electronic patient medical records to guide intraoperative blood pressure management during carotid endarterectomy. Pre-induction blood pressure measured in the operating room is significantly higher than any other preoperative blood pressure measured on the ward or POS and should, therefore, not be used.

Chapter 6. Cerebral oxygenation during surgery
Preserving adequate cerebral perfusion during surgery is expected to prevent for hemodynamic periprocedural stroke. To treat anaesthetic-induced hypotension, vasopressors are frequently administered. However, vasopressors may affect the frontal lobe cerebral tissue oxygenation. This chapter describes a randomized controlled study to evaluate the impact of both phenylephrine and ephedrine, administered to treat intraoperative hypotension, on the frontal lobe cerebral tissue oxygenation during carotid endarterectomy. Within this trial, mean arterial pressure correction by either phenylephrine or ephedrine showed to be equally effective in maintaining frontal lobe cerebral tissue oxygenation. Prioritizing the use of one of the vasopressor agents above the other during carotid endarterectomy cannot be advised.

Chapter 7. Periprocedural blood pressure and postoperative DWI-lesions
An exploratory study was conducted in order to study the association between intraoperative blood pressure measurements and the occurrence of new silent ischemic lesions on MR-DWI in patients undergoing carotid endarterectomy. Patients with preoperative hypertension were more likely to develop DWI-lesions (ipsi- or contralateral) and had a lower relative intraoperative blood pressure. This suggests that patients with preoperative hypertension are more susceptible to intraoperative hemodynamic disturbances and development of DWI-lesions.

PART III Postprocedural monitoring

Chapter 8. Postoperative non-invasive blood pressure monitoring

Strict postoperative arterial blood pressure control is required to prevent postoperative events like cerebral ischemia or hyperperfusion syndrome. This chapter determines in a prospective study design whether non-invasive blood pressure monitoring can replace invasive blood pressure monitoring in the direct postoperative phase, by comparing the accuracy and precision of non-invasive continuous ClearSight finger blood pressure to invasive radial artery blood pressure. Results of this study show that non-invasive mean arterial pressure, but not systolic and diastolic blood pressure, was equal to invasive blood pressure during postoperative observation following carotid endarterectomy, based on AAMI criteria. However, as systolic blood pressure is currently leading in postoperative monitoring to adjust blood pressure therapy on, Clearsight is not a reliable alternative for invasive blood pressure monitoring.

Chapter 9. Postoperative cerebral monitoring

Cerebral hyperperfusion syndrome is a rare, but serious complication after carotid endarterectomy and fatal when left untreated. In this chapter the predictive value of a transcranial Doppler assessment 24 hours postoperative, in addition to standard intra-operative and 2 hours post-operative TCD MCAV_{mean} assessments, was determined retrospectively for cerebral hyperperfusion syndrome in patients undergoing carotid endarterectomy under general anaesthesia. This study demonstrates that an additional transcranial Doppler 24 hours after carotid endarterectomy accurately identifies patients not at risk of cerebral hyperperfusion syndrome.

Chapter 10. Postoperative home blood pressure monitoring

To expand postoperative care to the home setting and obtain insight in postoperative blood pressure after hospital discharge, patients who underwent carotid endarterectomy performed blood pressure measurements twice-daily at home during 30 days. This feasibility study showed that postoperative home blood pressure monitoring is well-accepted and recommended by post-carotid endarterectomy patients. Future larger studies need to address the potential clinical gain of home blood pressure monitoring in early detection and management of patients at risk for postoperative hemodynamic complications.

Chapter 11. Response to one fits all post-operative systolic blood pressure

Recommendations regarding postoperative blood pressure policies are lacking in the current guidelines. Some believe that a one fits all post-operative systolic blood pressure policy for all CEA patients to prevent procedural stroke. This policy causes significant overtreatment and will not prevent for all cases of cerebral hyperperfusion

syndrome. Therefore, a tailored approach should be proposed using transcranial Doppler to identify all patients that are at true high risk of postoperative hypertension related complications following CEA.

Conclusion

Conclusions, clinical implications and future perspectives for the subjects of this thesis are discussed in Chapter 13.

CHAPTER 13

General discussion, future perspectives and conclusions

GENERAL DISCUSSION

Since the reporting of the first carotid endarterectomy (CEA) by DeBakey in 1953, significant progress has been made.[1] Today, 67 years later, increased understanding of the mechanism underlying periprocedural stroke has led to multiple improvements on intraoperative technical level as well as preoperative workup by the timing of surgery and adequate patient selection.[2,3]

Large international trials provided the evidence showing that CEA in combination with optimal medical treatment is the established standard treatment for severe symptomatic carotid artery stenosis.[4–6] Subsequent landmark clinical trials disentangled risk factors that contribute to the development of periprocedural stroke and the causative mechanism behind.[7–10] These findings reduced the risk of stroke as a result of the CEA procedure itself.

For a long time, the primary focus of stroke prevention was the prevention of the risk of intraoperative thromboembolism. Guidelines provided surgeons recommendations upon antiplatelet therapy, cerebral monitoring to reduce the risk of intraoperative emboli, type of anaesthesia, use of shunting and type of surgery. Recommendations, however, regarding intraoperative and postoperative hemodynamics are lacking and specific guidance on blood pressure (BP) thresholds seem to be allocated as ancillary matters.[2] This is in contrast with mounting evidence that hemodynamic disturbances significantly contribute to the development of periprocedural stroke.[7,8,11] Therefore, careful regulation of perioperative hemodynamics is required to maintain and preserve adequate cerebral perfusion.

This thesis focusses on hemodynamic and cerebral monitoring in patients who underwent a CEA as treatment for significant carotid artery stenosis.

Part I: Current clinical practice

In current clinical practice in the Netherlands, the lack of hemodynamic and cerebral monitoring recommendations has led to a wide variation in used cerebral and hemodynamic policies on hospital-level, resulting in fragmented care **(chapter 3)**. This wide variability of the centre-specific perioperative hemodynamic and cerebral monitoring policies has not been included in the Dutch Audit of Carotid Interventions (DACI), a nationwide audit to measure and improve the quality of care in carotid interventions. It can be argued if this variability between centres may cause a distorted view of national clinical outcomes and limits the comparability. In our opinion, this wide variability emphasizes the need of alignment of centre-specific policies to one

detailed univocal (inter)national protocol on perioperative hemodynamic and cerebral monitoring during CEA to improve standardization of care and facilitate outcome comparisons (**chapter 3**). Besides, the need for multiple centres performing low volume of CEA procedures per year can be questioned. High operator and hospital volume have been associated with decreased risk of procedural death and stroke after carotid revascularisation. More centralised care may further decrease the national periprocedural complication rate.[12]

Part II: Procedural monitoring

Hypertension, both preoperative and perioperative, increases the risk of cardiovascular events.[13–17] For this, adequate BP control and treatment should start in primary care. Despite the effort of a cardiovascular risk management program in primary care, the vast majority of patients undergoing CEA were still hypertensive regardless of the use of BP lowering drugs. Also, a preoperative increased BP showed to be associated with a more vulnerable atherosclerotic plaque at risk for a cardiovascular event, underlining the systemic importance of BP and atherosclerosis. Residual hypertension with the association of high BP and a more vulnerable plaque phenotype strongly underlines that intensive BP monitoring and intensive anti-hypertensive therapy is needed for severely carotid atherosclerotic patients (**chapter 5**). Conjointly in coronary artery disease, residual hypertension was associated with vulnerable plaque characteristics, showing that adequate BP monitoring is needed in patients at risk of cardiovascular diseases.[18]

Since no intraoperative BP thresholds are specified by the guidelines due to the lack of clinical evidence, one can only speculate. It is suggested to keep the intraoperative arterial BP during CEA between baseline and 20% above baseline to minimise the risk for intraoperative stroke.[19] Unfortunately, 'baseline' was not defined, leaving this up to the anaesthesiologist or vascular surgeon to decide what BP should be used as preoperative 'baseline' BP. In both healthy patients and vascular compromised patients, BP measured in the operating room before induction (pre-induction BP) turned out to be significantly higher than any other preoperative BP **(chapter 6)**.[20] Intraoperative target BP management based on the pre-induction BP will lead in the majority of patients to administration of large quantities of vasopressor and positive inotropic agents to meet the excessive-high BP levels. By increasing the heart rate and higher systemic vascular resistance to meet BP targets, will lead to an increase of myocardial tissue oxygen demand. Especially in patients where the supply of myocardial oxygen is already jeopardized, this increase in demand may lead to an imbalance in the supply-and-demand relationship and thereby ischemia. In addition, an intended increase of the BP during clamping to maintain adequate cerebral perfusion is never proven to be more

effective than normotension to reduce stroke.[21] Besides, perioperative hypertension is a known leading cause of postoperative cerebral hyperperfusion syndrome.[11,22,23]

On the contrary, intraoperative hypotension is associated with the development of cerebral ischemia.[24] The duration and explicit thresholds of hypotension that increases the risk of ischemia is unknown. The same applies to the effect of subtler BP variations on the postoperative outcome. New surrogate markers for stroke like diffusion-weighted imaging (DWI) lesions on brain MRI may be helpful study endpoints in order to close the knowledge gap regarding these BP topics. Intraoperative hypertension seems to decrease the risk of new ischemic lesions, while relative intraoperative hypotension in patients with preoperative hypertension is a risk factor for developing postoperative new ischemic brain lesions **(chapter 7).** This underlines the importance of adequate intraoperative hemodynamic monitoring during surgery for procedural stroke prevention and the need for explicit hemodynamic guidance adopted in international guidelines. By all means, it is difficult to simply address periprocedural stroke and silent brain lesions solely to intraoperative BP management and trials upon this topic are warranted.

Part III: Postprocedural monitoring

For postoperative care, the most harmful complication is cerebral hyperperfusion syndrome (CHS). Adequate postoperative BP monitoring **(chapter 8, 11)** and the use of Transcranial Doppler (TCD) monitoring up to 24 hours after surgery **(chapter 9)** showed to be helpful in the prevention of this severe complication. Since systolic BP is leading postoperative BP management, a non-invasive BP device like ClearSight is not an alternative for postoperative CEA patients. Although these findings are in line with previous ClearSight studies, there is no evidence that systolic controlled postoperative hemodynamic monitoring is superior to MAP-controlled monitoring. Besides, in a national care system in which the health care costs are increasingly important and both the government as well as health insurance companies apply pressure to decrease hospitalization costs, the possibilities of a MAP-controlled postoperative monitoring policy should be explored.

Over the last years, eHealth made its entrance in the current clinical care leading to a shift of in-hospital care to remote care at home. An approach that fits very well in the cost-effectiveness debate. In patients who underwent CEA, implementation of eHealth by self-BP monitoring at home for remote monitoring was well-accepted and recommended by all patients **(chapter 10).** A unique concept of care that enables daily remote monitoring of BP measurements by healthcare providers with the possibility to intervene, if deemed necessary. Besides expanding postoperative care to the

home setting, this new concept of care is a step towards insight in postoperative hemodynamics the first month post-CEA. Larger studies need to address the relation between postoperative hemodynamic trends and periprocedural events, as well as the potential clinical gain of home BP-monitoring in early detection and management of patients at risk for postoperative hemodynamic complications. On the other side, one should be critical. It is questionable whether postoperative telemonitoring of CEA-patients will stipulate a decrease of postoperative events since the majority of events occur periprocedural or within the first 48 hours postoperative. With this in mind, the actual beneficial effect of postoperative telemonitoring of CEA-patients on direct postoperative outcomes is expected to be little.

FUTURE PERSPECTIVES

The risk of periprocedural stroke after CEA depends on several factors like atherosclerotic plaque vulnerability and the inability to maintain adequate cerebral perfusion by cerebral autoregulation. However, the selection of patients eligible for CEA is mainly based on symptomatology and the extent of luminal narrowing of the carotid artery. Additional imaging by MRI to visualize the atherosclerotic plaque burden by identifying the presence of intraplaque haemorrhage or a CT-perfusion scan of the brain to map the cerebral perfusion and ability to maintain adequate cerebral perfusion during clamping, can be helpful for risk stratification. Currently, the European Carotid Surgery Trial-2 randomizes symptomatic patients at low-risk for recurrent stroke for either best medical treatment or carotid revascularisation. The results of this trial will play an essential role in patient selection for CEA.

Current guidelines are based upon large trials that reported the classic clinical endpoints; procedural stroke or death and recurrent stroke. However, novel insights showed that new DWI-lesions, silent brain lesions and white matter lesions on a postoperative brain MRI are associated with increased risk of future cerebrovascular events (CVE) in patients with carotid artery disease. These markers for CVE visualized by periprocedural MRI should be implemented as new complementary surrogate endpoints for both peri-procedural outcome (DWI) and long term outcome (silent brain lesion and white matter lesions) following CEA in future trials.[25]

Our healthcare system is continually changing and innovating. In order to provide best clinical care for every patient undergoing CEA and to reduce cerebrovascular events following CEA, carotid surgery should be performed in more centralized and specialized high volume centres by an experienced vascular surgeon together with an anaesthesiologist specialized in cardiovascular procedures.[11] This enables the use of a

univocal protocol on perioperative hemodynamic and cerebral monitoring during CEA and simplifies the implementation of cerebral monitoring by TCD for postoperative monitoring.

Although this thesis provided evidence on the importance of hemodynamic and cerebral monitoring, it has also shown the gaps. The provided evidence points out into a direction but does not guide specific perioperative BP thresholds. There is a clear need for a trial randomizing intraoperative hypertension (+20% baseline preoperative BP) versus normotension during carotid surgery in relation to direct postoperative cerebrovascular events, defined as new DWI lesions and silent brain ischemia on post-procedural brain MRI as a marker for postoperative cerebrovascular events and cognitive decline as a long term outcome. The same applies for postoperative BP thresholds (one fits all policy vs individualized patient specified BP thresholds based on TCD) in order to provide a definition and range of specific BP thresholds. [26,27]

Based on the evidence provided by this thesis and with an eye on the future, hemodynamic and cerebral monitoring must play a prominent role in perioperative care in patients undergoing CEA to reduce the risk of neurologic events of the procedure itself to the bare minimum.

CONCLUSIONS

Part I Current clinical care

- Multiple technical improvements like patient selection, timing of surgery, optimization of antiplatelet therapy and intraoperative cerebral monitoring have led to a decrease of stroke following carotid revascularization over the years. *(chapter 2)*
- Nationwide, applied perioperative hemodynamic and cerebral monitoring policies during CEA are widely diverse and aim for a detailed (inter)national protocol to improve standardization of care. *(chapter 3)*

Part II Procedural monitoring

- Increased preoperative systolic and diastolic BP levels are associated with more carotid plaque macrophages, lipid core and IPH in patients undergoing CEA. *(chapter 4)*
- Average of all available preoperative in-hospital BP-values reported in the electronic patient medical records instead of a single pre-induction BP value, should be used as 'baseline' BP to guide intraoperative BP management during carotid endarterectomy. *(chapter 5)*
- Correction of mean arterial pressure by either phenylephrine or ephedrine showed to be equally effective in maintaining cerebral tissue oxygenation in patients undergoing CEA. *(chapter 6)*
- High preoperative BP with low intraoperative BP are associated with the occurrence of periprocedural new silent ischemic lesions on MR-DWI. *(chapter 7)*

Part III Post-procedural monitoring

- Non-invasive mean arterial pressure measured by ClearSight, but not systolic and diastolic BP, is equal to invasive radial artery BP during postoperative observation following CEA, based on AAMI criteria. Not usable for CEA patients, since systolic BP is leading in current postoperative BP-monitoring. *(chapter 8)*
- Transcranial Doppler 24 hours after carotid endarterectomy accurately identifies patients not at risk of cerebral hyperperfusion syndrome. *(chapter 9)*
- Postoperative home BP-monitoring for remote monitoring is well-accepted and recommended by patients who underwent carotid endarterectomy. *(chapter 10)*
- A one fits all postoperative systolic BP threshold policy should not be used for the prevention of cerebral hyperperfusion syndrome, a tailored approach should be proposed using transcranial Doppler. *(chapter 11)*

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ADDENDA

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Aan de meerderheid van de beroertes ligt een vernauwing (stenose) van de halsslagader (arterie carotis) door verkalking (atherosclerose) ten grondslag. In combinatie met optimale medicamenteuze behandeling is chirurgische behandeling middels een carotis desobstructie (endarteriëctomie) de aangewezen behandeling bij een symptomatische carotis stenose. Carotis endarteriëctomie is een operatie aan de halsslagader waarbij de atherosclerotische vernauwing chirurgisch wordt verwijderd, een preventieve behandeling om toekomstige beroertes of TIA's te voorkomen. Helaas gaat het voordeel van deze behandeling bij patiënten met ernstige carotis stenose gepaard met een risico op beroertes, veroorzaakt door de operatie zelf. Deze beroertes kunnen zowel tijdens als na de operatie optreden.

Eén op de drie beroertes voorkomend tijdens de operatie en het merendeel van de beroertes na de operatie (postoperatief) wordt geschat hemodynamische van aard te zijn. Hiermee wordt de invloed van bloeddruk op de doorbloeding van de hersenen bedoeld. Echter is er sprake van een precaire balans. Zo kan hypotensie (lage bloeddruk) tijdens de operatie leiden tot verminderde perfusie (doorbloeding) van de hersenen, met ischemie tot gevolg. Postoperatief kan juist hypertensie (hoge bloeddruk) leiden tot een cerebrale hyperperfusie, wat kan ontaarden in een hersenbloeding wanneer deze niet tijdig herkend en behandeld wordt. Om de kans op deze hemodynamische beroertes te minimaliseren, is het van groot belang om de cerebrale perfusie op peil te houden tijdens en na de operatie. Ondanks dat er veel vooruitgang is geboekt om het risico op intra-operatieve beroertes te verkleinen, zijn er nog meerdere uitdagingen op hemodynamisch vlak.

Het onderzoek in dit proefschrift is erop gericht om de huidige perioperatieve monitoring tijdens en na een carotis endarteriëctomie te verbeteren. Om dit doel te bereiken zijn de verschillende aspecten van de huidige perioperatieve zorg (deel I) in kaart gebracht en is de intra-operatieve hemodynamiek (deel II) en postoperatieve cerebrale en hemodynamische monitoring (deel III) geëvalueerd.

PART I Huidige perioperatieve zorg

Hoofdstuk 2. Technische verbeteringen in carotis revascularisatie

In dit hoofdstuk wordt een overzicht gegeven van het pathofysiologische mechanisme van een beroerte na carotis revascularisatie, zowel de chirurgische behandeling door een carotis endarteriëctomie als het verwijden van de halsslagader met behulp van een stent in de arterie carotis. Daarnaast worden de technische verbeteringen beschreven die hebben bijgedragen aan het verminderen van het risico op een periprocedurele

beroerte. In de afgelopen jaren heeft de toegenomen kennis van het mechanisme dat ten grondslag ligt aan een periprocedurele beroerte na carotis revascularisatie geleid tot meerdere technische verbeteringen. Patiënt-selectie, de timing van een chirurgische ingreep na een index event (beroerte), optimalisatie van bloedplaatjes remming, het gebruik van cerebrale monitoring en verbetering van stenttechnieken lijken hun vruchten af te werpen en hebben geleid tot een afname van overlijden en/of beroertes na carotis revascularisatie in de afgelopen decennia.

Hoofdstuk 3. Nationaal overzicht van perioperatieve monitoring
In Nederland zijn momenteel 50 verschillende medische centra die carotis chirurgie verrichten. Het huidige toegepaste perioperatieve monitoringbeleid in deze centra is in kaart gebracht door middel van een enquête onder chirurgen binnen al deze centra. De bevindingen tonen aan dat het type anesthesie en zowel het cerebrale als hemodynamische monitoringbeleid tijdens carotis endarteriëctomie sterk varieert op ziekenhuisniveau. Deze studie bevestigt de behoefte aan een eenduidig (inter) nationale aanbeveling oftewel een gestandaardiseerd protocol over perioperatieve (hemodynamische) monitoring tijdens een carotis endarteriëctomie.

PART II Procedurele monitoring
Hoofdstuk 4. Preoperatieve bloeddruk en carotis atherosclerotische plaque karakteristieken
In dit hoofdstuk worden de associaties tussen preoperatieve systolische en diastolische bloeddruk en histologische atherosclerotische karakteristieken in de carotis plaque bestudeerd. Analyses laten zien dat verhoogde preoperatieve systolische en diastolische bloeddrukken geassocieerd zijn met een meer inflammatoire en vette atherosclerotische plaque. Er werden meer ontstekingscellen en vetrijke kernen met dode cellen in de atherosclerotische plaque gevonden met aanwezigheid van intraplaque bloedingen, wat representatief is voor een instabiele atherosclerotische plaque. Dezelfde resultaten zijn gevonden in een onafhankelijk cohort patiënten met ernstige atherosclerotische vernauwing van de liesslagader, waarvoor operatieve behandeling geïndiceerd was.

Hoofdstuk 5. Baseline bloeddruk van patiënten met carotis stenose
Adequate bloeddrukregulatie tijdens carotis endarteriëctomie is van groot belang om cerebrale perfusie (doorbloeding van de hersenen) op peil te houden. Dit hoofdstuk beschrijft een voorstel voor een gestandaardiseerde en uniforme definitie van de 'wakkere baseline' bloeddruk waarop intra-operatief beleid gebaseerd dient te worden. De resultaten tonen dat de bloeddruk gemeten op de operatiekamer voor inleiding van anesthesie significant hoger is dan iedere preoperatieve bloeddrukmeting op de polikliniek of afdeling. Dit resulteert in het advies om intra-operatief beleid niet

te baseren op de pre-inductie bloeddruk, maar op het gemiddelde van aanwezige preoperatieve bloeddrukmetingen van de afdeling.

Hoofdstuk 6. Cerebrale oxygenatie tijdens carotis chirurgie
Het behoud van adequate cerebrale perfusie tijdens carotis chirurgie vermindert de kans op een hemodynamische perioperatieve beroerte. In dit hoofdstuk wordt onderzocht of de vaak gebruikte snelwerkende antihypotensiva ter behandeling van door anesthesie veroorzaakte intra-operatieve hypotensie invloed hebben op de zuurstofvoorziening (oxygenatie) van de frontale hersenkwab. Een gerandomiseerde gecontroleerde studie heeft met behulp van near infrared spectroscopie (NIRS) onderzocht wat de invloed is van fenylefrine en efedrine op de oxygenatie in de hersenen tijdens carotis chirurgie. De resultaten laten zien dat bij carotis patiënten beide antihypotensiva zowel de bloeddruk verbeteren als de cerebrale oxygenatie van de frontale hersenkwab behouden. Hierdoor kan op basis van deze studie geen voorkeur voor één van beide medicamenten worden uitgesproken tijdens carotis chirurgie.

Hoofdstuk 7. Perioperatieve bloeddruk en postoperatieve DWI-laesies
Met behulp van een oriënterend onderzoek is de associatie tussen intra-operatieve bloeddruk en postoperatieve, nieuwe, stille ischemische laesies op diffusie gewogen MRI onderzocht bij patiënten die een carotis endarteriëctomie ondergaan. Patiënten met preoperatieve hypertensie hebben meer kans om deze zogenoemde DWI-laesies te ontwikkelen, ook hebben zij een gemiddeld lagere intra-operatieve bloeddruk. Dit suggereert dat patiënten met preoperatieve hypertensie gevoeliger zijn voor intra-operatieve hemodynamische schommelingen en DWI-laesies ontwikkelen. Prospectieve studies in grotere cohorten zijn nodig om preoperatieve en intra-operatieve bloeddruk en de relatie met DWI-laesies te onderzoeken.

PART III Post procedurele monitoring
Hoofdstuk 8. Postoperatieve non-invasieve bloeddrukmonitoring
Ook postoperatief is strikte bloeddrukmonitoring van groot belang ter voorkoming van een postoperatieve beroerte of cerebraal hyperperfusie syndroom. Dit hoofdstuk omvat de validatie van een non-invasieve vingerbloeddrukmeter (ClearSight) voor continue bloeddrukmonitoring gedurende de eerste 6 uur postoperatief bij patiënten die een carotis endarteriëctomie hebben ondergaan. De referentiemethode is invasieve bloeddrukmonitoring met een arterielijn geplaatst in de arterie radialis. De non-invasieve gemiddelde arteriële bloeddruk, maar niet de systolische en diastolische bloeddruk, was vergelijkbaar met invasieve arterielijn metingen tijdens postoperatieve observatie. Echter, in het huidige praktijk is de systolische bloeddruk leidend tijdens postoperatieve monitoring. Dit maakt dat ClearSight vooralsnog geen betrouwbaar

alternatief is voor postoperatieve bloeddrukmonitoring van patiënten die een carotis endarteriëctomie ondergaan.

Hoofdstuk 9. Postoperatieve cerebrale monitoring
Het cerebraal hyperperfusiesyndroom is een zeldzame maar ernstige complicatie na carotis endarteriëctomie en dodelijk wanneer het niet tijdig herkend en behandeld wordt. In dit hoofdstuk wordt aangetoond dat een transcraniële Doppler (TCD) cerebrale flowmeting 24 uur postoperatief additioneel aan de standaard intra-operatieve en 2 uur postoperatieve TCD-metingen zeer nauwkeurig patiënten identificeert die geen risico lopen op een cerebraal hyperperfusie syndroom. Dit maakt het mogelijk een patiëntengroep te identificeren die zonder risico (naar de afdeling) ontslagen kunnen worden en bij wie de behandeling van eventuele hypertensie uitgesteld kan worden naar de afdeling of poliklinische zorg.

Hoofdstuk 10. Postoperatieve thuis bloeddrukmonitoring
Om inzicht te krijgen in het postoperatieve bloeddrukbeloop na een carotis endarteriëctomie na ziekenhuisontslag en de postoperatieve zorg uit te breiden naar de thuisomgeving, is de haalbaarheid onderzocht van tweemaal daags thuis bloeddruk meten door de patiënt zelf tijdens de eerste 30 dagen na ontslag. De bloeddrukmetingen werden dagelijks op afstand gecontroleerd via een online platform. Deze studie toonde aan dat postoperatieve bloeddrukmeting thuis goed wordt geaccepteerd en zelfs wordt aanbevolen. Toekomstige grotere studies moeten de potentiële klinische winst van thuis bloeddrukmonitoren onderzoeken met oog op uitbreiding van postoperatieve zorg en vroege detectie en behandeling van patiënten met een verhoogd risico op postoperatieve hemodynamische complicaties.

Hoofdstuk 11. Reactie op een 'one fits all' postoperatief bloeddrukbeleid
De huidige richtlijnen doen geen aanbevelingen over het postoperatieve bloeddrukbeleid na CEA. Een suggestie met betrekking tot de postoperatieve systolische bloeddruk is om voor alle CEA-patiënten dezelfde maximale systolische bloeddruk te hanteren. Echter leidt deze zogenoemde *one- fits all* policy tot significante overbehandeling en daarnaast voorkomt het niet alle gevallen van cerebraal hyperperfusie syndroom. Met behulp van een transcraniële Doppler meting kan een individueel afgestemde systolische maximale bloeddruk worden bepaald, waarbij patiënten met een verhoogd risico op hypertensie gerelateerde complicaties na CEA geïdentificeerd kunnen worden.

Conclusie
Conclusies, klinische implicaties en toekomstperspectieven voor de onderwerpen van dit proefschrift worden besproken in hoofdstuk 13.

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CURRICULUM VITAE

Leonie Madelein Maria Fassaert was born on the 20th of May 1990 in 's-Hertogenbosch, the Netherlands. She grew up with her parents, brother and sister. She graduated (Gymnasium) from Sint-Janslyceum in 's-Hertogenbosch in 2008 and started medical school at Maastricht University (MUMC+) that same year. She combined medical school with being an active member of the student association, rowing/field hockey and discovering other countries; between her bachelor and masters she travelled half a year throughout Australia. As part of her internships, she gained international work experience in Indonesia and India. Alongside her internships, she enlisted herself for the best interests of Dutch medical interns in the Netherlands by a board year of Landelijk Overleg CoAssistenten (LOCA). After finishing medical school in 2015, she started working as a surgical resident (not in training) at Sint Antonius hospital under the supervision of dr. Boerma. Following one year of residency, she started as a PhD candidate at the Department of Surgery of the University Medical Centre Utrecht, focusing on hemodynamic and cerebral monitoring in carotid surgery under supervision of Prof. dr. GJ. de Borst. The results of her research projects are presented in this thesis. All work described in this thesis is presented on international conferences and several studies were awarded on international conferences as the Charing Cross certificate of merit for excellent abstract presentation and MAC Best Short Communication Award. Currently, Leonie is working as a surgical resident (not in training) at Meander Medical Centre in Amersfoort under the supervision of prof. dr. Consten and is living in Utrecht.