Transcranial Doppler 24 Hours after Carotid Endarterectomy Accurately Identifies Patients Not at Risk of Cerebral Hyperperfusion Syndrome

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WHAT THIS PAPER ADDS

A validated prediction model for prevention of cerebral hyperperfusion syndrome (CHS) following carotid endarterectomy (CEA) is lacking; however, early recognition of cerebral hyperperfusion (CH) is crucial to prevent this complication. Intra-operative transcranial Doppler (TCD) is the gold standard to predict the risk of CH in CEA patients under general anaesthesia, but this study finds that post-operative TCD 24 h after CEA is more effective at predicting CH and CHS and is excellent at identifying patients NOT at risk of CHS after CEA. This has clinical relevance for cerebral monitoring protocols in centres performing CEA under general anaesthesia.

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 post-operatively 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 $\geq$ 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.

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INTRODUCTION

Although multiple and heterogeneous in origin, peri-operative 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 (MCAV) with transcranial Doppler (TCD) monitoring is the gold standard for prediction of CHS after CEA.[5,7] An increase of $\geq 100\%$ in MCAV 3 min after carotid declamping compared with the MCAV 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 post-operative MCAV 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 MCAV assessments, the predictive value of MCAV 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 und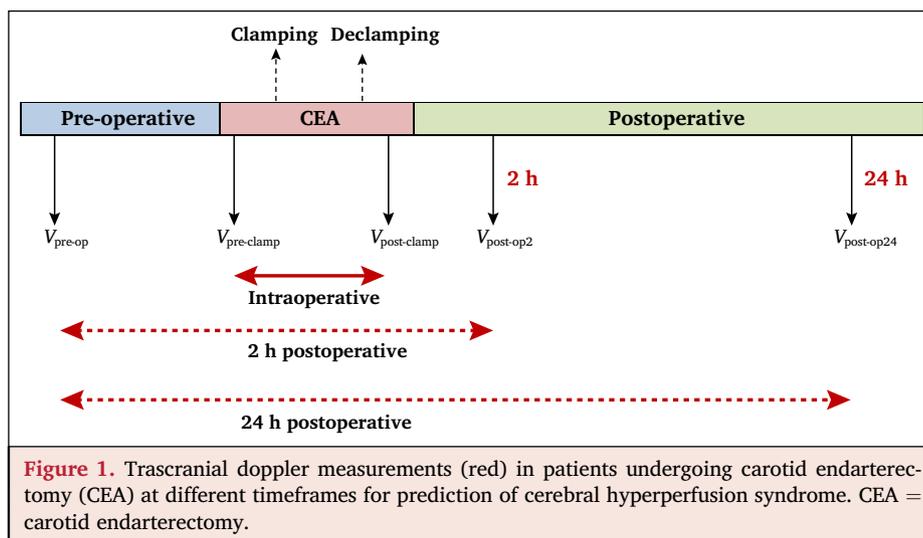erwent CEA because of a haemodynamically significant stenosis of the internal carotid artery ($\geq 50\%$ and symptomatic or $\geq 70\%$ and asymptomatic) with available data for at least pre-operative, intra-operative, and 24 h post-operative TCD monitoring were eligible for inclusion. TCD measurements 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]
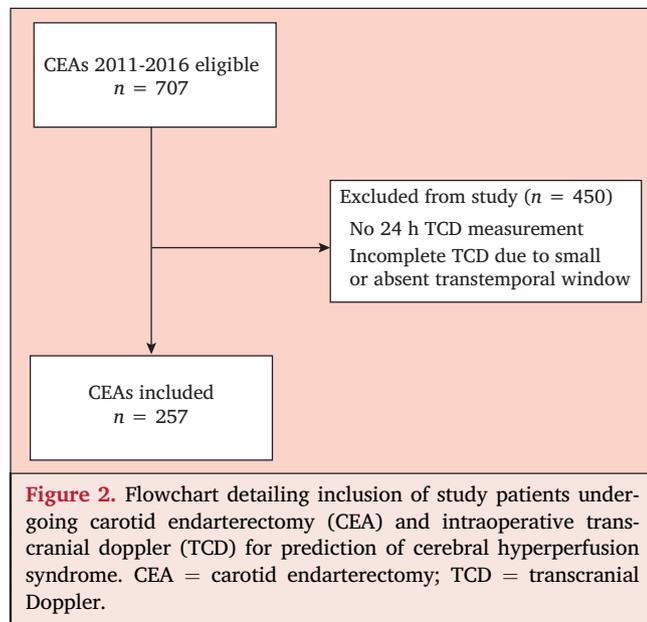
Carotid endarterectomy

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. Post-operatively, 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 MCA$V_{mean} \geq$ 100% compared with baseline MCAV_{mean} without neurological complaints. CHS was defined as CH combined with clinical

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 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.

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 > 180 mmHg, or a systolic BP exceeding individual BP restriction in patients with an intra-operative $MCAV_{mean} \geq 100\%$ requiring medical antihypertensive treatment.

TCD settings

In all patients MCAV 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 timeframes. 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-op}), within one week prior to surgery
- 30 s before carotid cross clamping ($V_{pre-clamp}$)

- 3 min after declamping ($V_{post-clamp}$)
- 2 h post-operatively ($V_{post-op2}$)
- 24 h post-operatively ($V_{post-op24}$).

The intra-operative V_{mean} change (($V_{post-clamp}$-$V_{pre-clamp}$)/$V_{pre-clamp}$) was compared with the post-operative change after 2 h (($V_{post-op2}$-V_{pre-op})/V_{pre-op}) and 24 h (($V_{post-op24}$-V_{pre-op})/V_{pre-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 $\geq$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 $\geq$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 μg i.v. over 10 min, then 25—75 μg/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 post-operatively, 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 because of high degree ICA stenosis at the UMCU or SAH, the Netherlands, between December 2011 and June 2016 were retrospectively identified for this analysis. Patients with no available TCD derived MCAV_{mean} 24 h post-operatively or no TCD measurements at all for logistical reasons or insufficient temporal bone window were excluded ($n = 450$) (Fig. 2).

A consecutive series of 257 CEA patients with available 24 h post-operative TCD measurements were included (UMCU $n = 176$). 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 hyperlipidaemia (50%). In 14% of patients intraluminal shunting was required during surgery because of EEG asymmetry or diffuse slowing or a decrease of the intra-operative 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 cohort the 2 h post-operative TCD measurement was missing for 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 transient ischaemic attack (TIA). Nine patients had a post-operative wound haematoma 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). Nine patients (3.5%) developed CHS with headache (six), minor cerebellar stroke (one), both cerebellar infarction and cerebral haemorrhage (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.

Table 1. Baseline characteristics and post-operative events of carotid endarterectomy patients who developed cerebral hyperperfusion syndrome (CHS) and who did not.

Baseline characteristics	All patients ($n = 257$)	CHS+ ($n = 9$)	CHS− ($n = 248$)	p
Age	70 ± 8.9	69 ± 10.3	70 ± 8.8	.78
Gender − male	185 (72)	6 (67)	179 (72)	.72
Diabetes mellitus	66 (26)	2 (22)	64 (26)	1.0
Hypertension	192 (75)	7 (78)	185 (75)	1.0
Hypercholesterolaemia	129 (50)	3 (33)	126 (51)	.33
CAD	76 (30)	2 (22)	74 (30)	1.0
Smoking				
Current	110 (43)	4 (44)	106 (43)	1.0
Past	102 (40)	4 (44)	98 (40)	.74
Alcohol use	149 (58)	6 (67)	143 (58)	.74
Operation side − right	126 (49)	3 (33)	123 (50)	
Symptomatic	239 (93)	9 (100)	230 (93)	1.0
Degree of ipsilateral stenosis				
>70%	234 (88.7)	9 (100)	225 (91)	.77
50−70%	22 (8.6)	−	22 (9)	
Degree of contralateral stenosis				
Occlusion	33 (12.8)	2 (22)	31 (13)	.71
>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)	.62
Post-operative events				
Stroke	6 (2)	2 (22)	4 (2)	.02
TIA	5 (2)	1 (11)	4 (2)	.16
Wound haematoma	9 (4)	−	9 (4)	1.0
Admission MC	67 (26)	9 (100)	58 (23)	<.001
Post-operatively hypertension	102 (40)	8 (89)	94 (38)	.003
Death <1 day	2 (1)	−	2 (1)	1.0

Data are given as n (%) or mean $\pm$ standard deviation (SD).
CAD = coronary artery disease; CHS+ = number of patients who developed cerebral hyperperfusion syndrome; CHS− = number of patients who did not develop cerebral hyperperfusion syndrome; MC = medium care; TCD = transcranial Doppler; TIA = transient ischaemic attack.

Table 2. Predictive values of transcranial Doppler (TCD) measurements for development of cerebral hyperperfusion syndrome at different timeframes (intra-operatively, 2 h post-operatively, 24 h post-operatively) of 257 patients after carotid endarterectomy

Change in TCD values	CHS+ (n = 9)	CHS− (n = 248)	PPV %	NPV %
Intra-operative increase				
>100%	2	23	8	
<100%	7	225		97
Post-operative increase − total				
>100%	8	50	14	
<100%	1	198		99
Post-operative increase − 2 h[a]				
>100%	5	40	11	
<100%	3	193		98
Post-operative increase − 24 h				
>100%	6	28	18	
<100%	3	220		99
Intra- and post-operative increase − total				
>100% and >100%	1	10	9	97
>100% and <100%	1	13	7	97
<100% and >100%	7	40	15	99
<100% and <100%	0	185	0	87.5
Total	9	248		

Data are given as *n* or %. CHS+ = number of patients who developed cerebral hyperperfusion syndrome; CHS− = number of patients who did not develop cerebral hyperperfusion syndrome; NPV = negative predictive value; PPV = positive predictive value; TCD = transcranial Doppler.
[a] Measurements for 16 patients were missing.

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 (Tables 1, 3 and 4).

Clinical relevance

The NPV of TCD measured CH for the prediction of CHS was 97% for intra-operative TCD measurement, 98% for 2 h post-operative, and 99% for 24 h post-operative TCD measurements. The PPV of intra-operative and two and 24 h post-operative TCD measurements were 8%, 11%, and 18%, respectively (Tables 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

Table 3. Post-operative hypertension (PH) and cerebral hyperperfusion (CH) in 257 patients undergoing carotid endarterectomy

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

Data are given as *n* or %. CH+ post = number of patients who developed cerebral hyperperfusion post-operatively (2 h or 24 h); CH− post = number of patients who did not develop cerebral hyperperfusion post-operatively (2 h or 24 h); NPV = negative predictive value; PH = post-operative hypertension; PPV = positive predictive value.

eventually developed CHS, an intra-operative CH was diagnosed in two, and a post-operative CH in eight (after 2 h [n = 5] or after 24 h [n = 6]) (Figs. 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 of CHS within the following 22 h (Fig. 4). In one CHS patient, with a missing 2 h post-operative TCD measurement, CH was solely measured intra-operatively (Table 2, Fig. 3).

Of the non-CHS group (n = 248), the MCAV_{mean} increase was 20%, 41%, and 37% for intra-operative, 2 h and 24 h post-operative measurements, respectively. Of the CHS group (n = 9), the median of the 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 (Tables 5 and 6). The same applied for the relative MCAV_{mean} (Δ increase between two timeframes) of the non-CHS and CHS groups (Table 3).
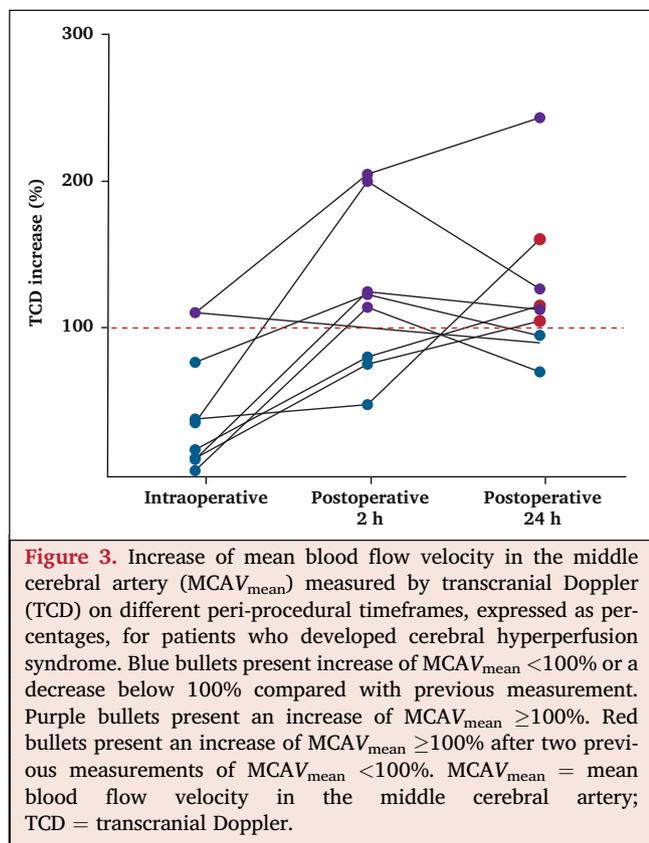
DISCUSSION

In a predominantly symptomatic patient cohort with an acceptable peri-operative event rate (3.5%), it was found

Table 4. Post-operative hypertension (PH) and cerebral hyperperfusion syndrome (CHS) in 257 patients undergoing carotid endarterectomy

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

Data are given as *n* or %. CHS+ post = number of patients who developed cerebral hyperperfusion syndrome; CHS− post = number of patients who did not develop cerebral hyperperfusion syndrome; NPV = negative predictive value; PH = post-operative hypertension; PPV = positive predictive value.

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.

that an increase of MCAV_{mean} < 100% on a 24 h post-operative TCD measurement accurately excluded 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 with 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 of CHS compared with 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 intra-operatively 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 post-operative 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 intra-operative 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 160 mmHg 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 post-operative TCD measurements gave a higher PPV and NPV than intra-operative and 2 h post-operative TCD
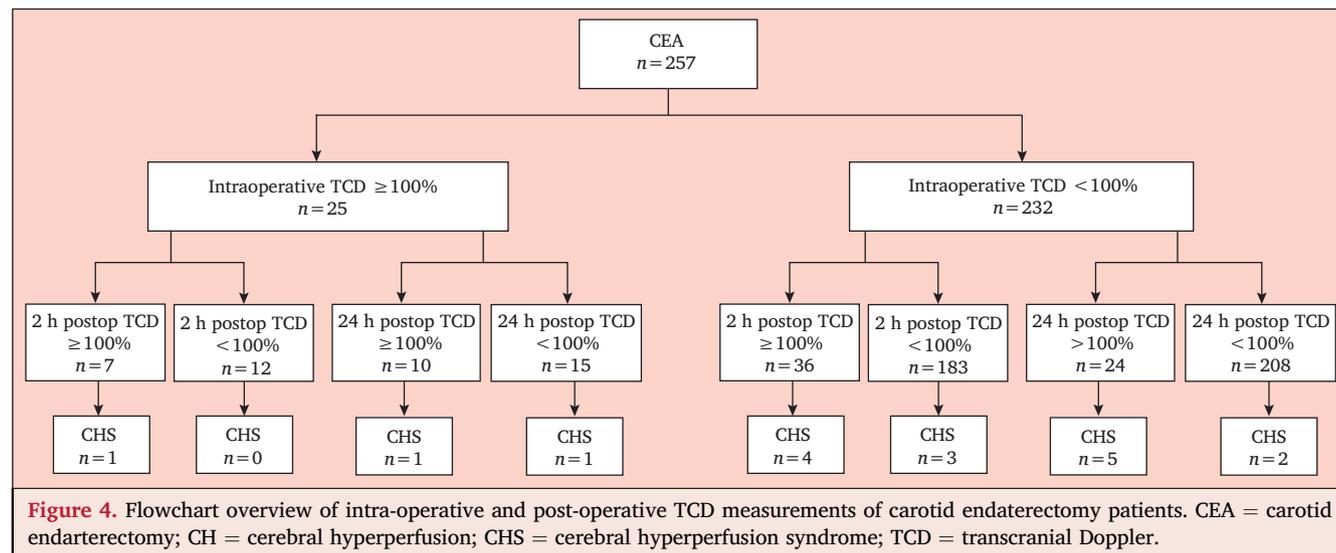

Figure 4. Flowchart overview of intra-operative and post-operative TCD measurements of carotid endaterectomy patients. CEA = carotid endarterectomy; CH = cerebral hyperperfusion; CHS = cerebral hyperperfusion syndrome; TCD = transcranial Doppler.

Table 5. Increase of transcranial Doppler measured mean middle cerebral artery blood flow velocity (MCAV$_{mean}$; absolute increase) at different timeframes in 257 patients undergoing carotid endarterectomy

Increase MCAV$_{mean}$	CHS+ ($n = 9$)	CHS$-$ ($n = 248$)	p
Intra-operatively $-$ %	35 [10$-$93]	20 [2$-$43]	.23
Two hours post operatively $-$ %	118 [76$-$181]	41 [10$-$78]	<.001
24 h post-operatively $-$ %	112 [92$-$143]	37 [14$-$70]	<.001

Data are given as median [interquartile range]. CHS+ = number of patients who developed cerebral hyperperfusion syndrome; CHS$-$ = number of patients who did not develop cerebral hyperperfusion syndrome; MCAV$_{mean}$ = mean middle cerebral artery blood flow velocity.

Table 6. Change (Δ) in increase of transcranial Doppler measured mean middle cerebral artery blood flow velocity (MCAV$_{mean}$; relative increase) at different timeframes in 257 patients undergoing carotid endarterectomy

Δ increase MCAV$_{mean}$	CHS+ ($n = 9$)	CHS$-$ ($n = 248$)	p
Intra-operatively to 2 h post-operatively $-$ %	77 [63]	16 [61]	.01
Two hours to 24 h post-operatively $-$ %	8.6 [81]	$-$2.13 [39]	.33
Intra-operatively to 24 h post-operatively $-$ %	94 [69]	16 [55]	.001

Data are given as median [interquartile range]. CHS+ = number of patients who developed cerebral hyperperfusion syndrome; CHS$-$ = number of patients who did not develop cerebral hyperperfusion syndrome; MCAV$_{mean}$ = mean middle cerebral artery blood flow velocity.

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 intra-operative 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 intra-operative 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 MCAV 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 MCAV measurements by TCD are operator dependent and impossible for an absent temporal bone window (10$-$15% of all CEA patients), MCAV 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 MCAV 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 post-operative 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 ($\pm$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} $\geq$ 100% and requiring medical antihypertensive treatment was interpreted as PH. A systolic BP > 160 mmHg without increase of MCAV_{mean} $\geq$ 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 post-operative clinically relevant hypertension requiring immediate treatment was diagnosed, thereby avoiding over diagnosis of hypertension.

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 intra-operatively 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 intra-operative 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.

CONFLICT OF INTEREST

None.

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