Cardiac output and cerebral blood flow during carotid surgery in regional versus general anesthesia: A prospective randomized controlled study

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ABSTRACT

Objective: Carotid endarterectomy (CEA) is a preventive procedure aimed at decreasing the subsequent risk of fatal or disabling stroke in patients with significant carotid stenosis. It is well-known that carotid surgery under ultrasound-guided regional anesthesia (US-RA) causes a significant increase in blood pressure, heart rate and stress hormone levels owing to increased sympathetic activity. However, little is known about the effects on cardiac output (CO), cardiac index (CI), and cerebral blood flow (CBF) under US-RA as compared with general anesthesia (GA).

Methods: Patients scheduled for CEA were randomized prospectively to receive US-RA ($n = 37$) or GA ($n = 41$). The primary end point was the change in CI after induction of anesthesia and the change from baseline over time at four different times during the entire procedure in the respective randomized US-RA and GA groups. In addition to systolic blood pressure and heart rate, we also recorded peak systolic velocity, end-diastolic velocity, and minimum diastolic velocity as seen from transcranial Doppler ultrasound examination, as well as regional cerebral oxygenation (rSO_2) as seen from near-infrared refracted spectroscopy to evaluate cerebral blood flow.

Results: In the US-RA group, the CI increased after induction of anesthesia (3.7 ± 0.8 L/min/m^2) and remained constant until the end of the procedure. In the GA group CI was significantly lower (2.4 ± 0.6 L/min/m^2; $P < .001$). After induction of anesthesia, the rSO_2 remained constant in the GA group on both the ipsilateral (63 ± 9 rSO_2) and the contralateral (65 ± 7 rSO_2) sides; in contrast, it significantly increased in the US-RA group (ipsilateral 72 ± 8 rSO_2; $P < .001$; contralateral 72 ± 6 rSO_2; $P < .001$). The transcranial Doppler ultrasound parameters (peak systolic velocity, end-diastolic velocity, and minimum diastolic velocity) did not differ between the US-RA and the GA group. The clinical outcome was similarly favorable for both groups.

Conclusions: CI was maintained near baseline values throughout the procedure during US-RA, whereas a significant decrease in CI values was observed during CEA under GA. Near-infrared refracted spectroscopy values, reflecting blood flow in small vessels, were higher in US-RA patients than in those with GA. These differences did not influence clinical outcome. (J Vasc Surg 2021;74:930-7.)

Keywords: Carotid endarterectomy; General anesthesia; Regional anesthesia; Cardiac index; Cerebral blood flow

Carotid endarterectomy (CEA) as a preventive operation is the method of choice for decreasing the subsequent risk of fatal or disabling stroke in patients with significant carotid stenosis.[1] It can be performed under ultrasound-guided regional anesthesia (US-RA) or general anesthesia (GA). Currently, the choice of anesthesia method depends on local clinical practice and patient preference, with GA being the most commonly applied technique.[2,3] A randomized, multicenter study comparing GA and US-RA for carotid procedures (GALA trial) showed no difference in morbidity or mortality.[4] In the past decade, however, increasing evidence has favored US-RA as an independent factor of decreased morbidity after CEA.[3] In fact, US-RA has been associated with a decreased incidence of postoperative respiratory failure, less circulatory instability, and less cardiovascular morbidity.[5-7]

As early as 1990, Takolander et al[5] found a clear association between elevated plasma catecholamines and hypertensive blood pressure levels in CEA during US-RA. In a previous work, our group demonstrated that the US-RA technique for CEA induces temporary hypertension and an increase in stress hormone levels, but enables safe targeted placement of local anesthetics (LA).[6]

Thus, the aim of this study was to expand our previous findings and investigate the stress response concerning CI as well as cerebral blood flow (CBF) under US-RA

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versus GA in patients undergoing CEA. The primary outcome measure was the change in CI after performing US-RA or inducing GA (t1) as compared with baseline CI before induction (t0) in patients undergoing CEA.

METHODS

Patient selection and study design. This study was approved by the Ethics Committee of the Medical University of Innsbruck (Study Code: AN2014-0146336/4.25). Signed consent was obtained from each subject prior to randomization. The study was also internationally registered (ClinicalTrials of the US National Library of Medicine: NCT02230358). Ninety patients who underwent elective intervention for symptomatic or asymptomatic stenosis of the internal carotid artery at Innsbruck Medical University Hospital between March 2015 and July 2017 were included in this prospective randomized controlled study. Indication for CEA was based on the decision of our hospital interdisciplinary board (neurologists, radiologists, and vascular surgeons), including symptomatic and asymptomatic patients. Simple, unstratified randomization using a 1:1 block randomization to allocate patients to the US-RA or the GA group was performed after written consent was obtained.

Exclusion criteria were age less than 18 years, emergency procedure, lack of consent because of a language barrier, dementia or major confusion, contralateral vocal chord or phrenicus paralysis, an anticipated difficult airway, claustrophobia, patient denial, and previous decision on anesthetic technique. All involved anesthesiologists and surgeons were equally familiar with both anesthetic techniques. A computer-generated list was used to prospectively randomize consecutive patients scheduled for elective CEA to receive US-RA or GA, observed by two independent persons not involved in the study.

Routine management. All antihypertensive medications except β-blockers were discontinued on day of surgery. All patients received oral midazolam (0.05 mg/kg) about 30 minutes before transport to the operating room. Contralateral to the intervention side a 20G radial artery and two peripheral venous catheters were inserted. Standard monitoring consisted of heart rate, peripheral oxygen saturation, capnography, electrocardiography, systolic blood pressure (SBP), diastolic blood pressure, and mean blood pressure measured invasively with an artery catheter connected to a monitoring kit (Edwards Lifesciences, Unterschleissheim, Germany). Baseline values were recorded either before induction of GA or before US-RA was started. Hypertension was defined as a SBP of more than 20% above baseline and treated with alpha-receptor blocker (urapidil), tachycardia as a heart rate of more than 100/min and treated with β-blocker (metoprolol), aiming for baseline values by ±5% to 10%. Hypotension (defined as SBP of <20% of baseline) was treated with atropine (0.1 mg/kg) and/or alpha receptor agonist phenylephrine (1 μg/kg), aiming for baseline values of ±5% to 10%.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospectively randomized clinical study
- **Key Findings:** Patients scheduled for endarterectomy of the carotid artery were prospectively randomized to receive ultrasound-guided regional anesthesia (US-RA) (n = 37) or general anesthesia (n = 41). The cardiac index (CI) increased after induction of anesthesia and remained constant during surgery in the US-RA group, whereas in the general anesthesia group the CI was significantly lower without affecting cerebral blood perfusion.
- **Take Home Message:** The CI was maintained near baseline values throughout surgery during US-RA, while lower values were observed during general anesthesia for endarterectomy of the carotid artery. This difference did not influence clinical outcome.

Ultrasound-guided regional anesthesia. Infiltration of the skin along the posterior border of the sternocleidomastoideus muscle was performed with 8 mL of lidocaine 2%. Visualization of the bifurcation of the carotid artery was performed with ultrasound (6- to 13-Hz M-Turbo linear array transducer; SonoSite, Bothell, Wash) guidance by inserting a SonoPlex Stim cannula (Nano Line 22G 80 mm Pajunk; Pajunk GmBH, Geisingen, Germany) using a lateral-to-medial in-plane approach in direction of the carotid artery immediately below the bifurcation.[7] Ropivacaine 0.5% (10 mL) was injected in a crescent-shaped pattern beneath the carotid bifurcation and a further 10 mL ropivacaine 0.5% in the subcutis below the sternocleidomastoideus muscle while retracting the needle. The dose of 20 mL ropivacaine 0.5% was standardized for all patients. Supplemental conscious sedation during the surgical procedure was achieved by continuous administration of remifentanil (0.04-0.06 mg/kg/min). Motor function was monitored by fixing a squeaking tool in the contralateral hand of the patient for simple questions to be answered by squeaking one time for yes and two times for no. This method permitted speech comprehension to be monitored.

General anesthesia. GA was induced with fentanyl (5 μg/kg), propofol (1.5-2.0 mg/kg), and rocuronium bromide (0.6 mg/kg) followed by remifentanil infusion (0.04-0.08 mg/kg/min) and inhaled desflurane (4-5 vol % end-tidal) for the maintenance of anesthesia. Each patient received a continuous infusion of ELO-MEL isotonic electrolyte solution (Fresenius Kabi, Graz, Austria). Piritramide (3.0- to 4.5-mg bolus) was administered as supplemental pain therapy.

Vigileo FloTrac system. To measure the cardiac index (CI), stroke volume (SV) and heart rate, the Vigileo FloTrac system (Edwards Lifesciences, Irvine, Calif) was used. It requires the FloTrac sensor (Edwards Lifesciences), which is connected to a standard radial or femoral catheter and to the Vigileo monitor (Edwards Lifesciences). For cardiac output (CO) estimation, the standard deviation of pulse pressure sampled in 20 seconds is related to a normal SV based on the patient's demographic data (weight, height, sex, and age). The Vigileo FloTrac system records the hemodynamic parameters at 20-second intervals and uses the most recent data from these 20 seconds for calculation. The processing unit applies a proprietary algorithm to the digitized wave.[8,9]

Near-infrared refracted spectroscopy. Cerebral oxygen saturation was measured by near-infrared refracted spectroscopy (NIRS) (Invos 5100, Covidien/Medtronic, Minneapolis, Minn). The monitor uses a light-emitting diode transmitting near-infrared light at two wavelengths (735 and 810 nm) and two silicone photodiodes as light detectors. The monitor thus provides a single numerical value for each hemisphere, representing the regional cerebral oxygenation (rSO_2) measured in the cerebrovascular tissue under a sensor applied to the skin on each side of the forehead.

Transcranial Doppler ultrasound imaging. Transcranial Doppler ultrasound (TCD) examination was performed by a person independent of the study using the X5-1 PureWave xMATRIX transducer (Health Systems Philips Austria, Innsbruck, Austria) and a Philips ultrasound device (CX50 xMATRIX, Health Systems Philips Austria). The middle cerebral artery was visualized through the temporal bone window. Measurements were performed in the proximal straight segment (M1) using angle compensation. Ultrasound penetration remained constant for all measurements. The peak systolic velocity (PSV), end-diastolic velocity (EDV), and minimum diastolic velocity (MDV) were automatically recorded at the defined measurement points. The mean values of three measurements were used.

Surgical technique and shunting. Depending on the anatomy and plaque morphology, CEA was performed with patch angioplasty or as eversion endarterectomy. Antiplatelet therapy was not discontinued before the intervention, and heparin (5000 IU) was given intravenously before cross-clamping. A shunt was routinely placed in the GA group. In the US-RA group a shunt was planned in case neurologic symptoms (speech deficits, contralateral arm weakness, significant increase in agitation and confusion, seizure, or unresponsiveness) developed. Patients in the GA group were not shunted if the preoperatively performed duplex ultrasound examination detected no stenosis in the contralateral carotid artery and both vertebral arteries. For quality control, intraoperative completion angiography was performed routinely, except in patients with significant impairment of renal function.

Study protocol. The primary outcome measure of this study was the change in CI after induction of anesthesia (t1) as compared with baseline (t0, after insertion of arterial catheter in the awake patient) in patients undergoing CEA under US-RA or GA. In addition, we recorded the SV using the Vigileo FloTrac system, and PSV, EDV, and MDV with TCD imaging. Other secondary outcome variables were NIRS scores from both sides of the forehead, SBP, heart rate, the number of shunt placements, clamping time, duration of procedure and new neurologic complications up to 30 days postoperative. The hemodynamic parameters were recorded immediately after inserting the arterial line and before induction of either US-RA or GA (t0); after induction of US-RA or GA (t1); 2 minutes after cross-clamping (t2); after reperfusion (t3); and at the end of the procedure (t4; Fig 1). Finally, the biometrics and general patient data were recorded.

Postoperative complications. Transient ischemic attacks, incidence of neck hematoma after procedure requiring revision, myocardial infarction, stroke, and death were recorded up to 30 days postoperatively.

Statistics. A power analysis was performed before the trial. The prespecified outcome measure was the change in CI after induction of anesthesia (t1) as compared with baseline (t0) in patients undergoing CEA in US-RA or GA. Our sample size calculation was based on this parameter at the two time points. A sample size of 45 patients per group (90 total) was chosen because this size is required to detect a difference of at least 0.5 (L/min)/m^2 in change in CI between the US-RA and GA groups (assuming a standard deviation of 0.8) with a power of 0.8 and an alpha of 0.05 in an unpaired *t* test.

Patient characteristics and concomitant medications were analyzed descriptively using absolute and relative frequency and mean ± standard deviation. Comparisons between groups were performed with the Student *t* test. To test for differences in time course in each of the two groups, an analysis of variance using a regression model for non-continuous time series was performed. For assessment of the statistical significance of differences between the two groups at individual time points (t0 to t4) or over time, Student's *t* test was applied using the R software package 'stats'. The significance level of the two-sided *P* value was in general .05, except for analysis of the five time-points individually, where only values of less than .01 were considered statistically significant according to the Bonferroni approach for multiple testing.

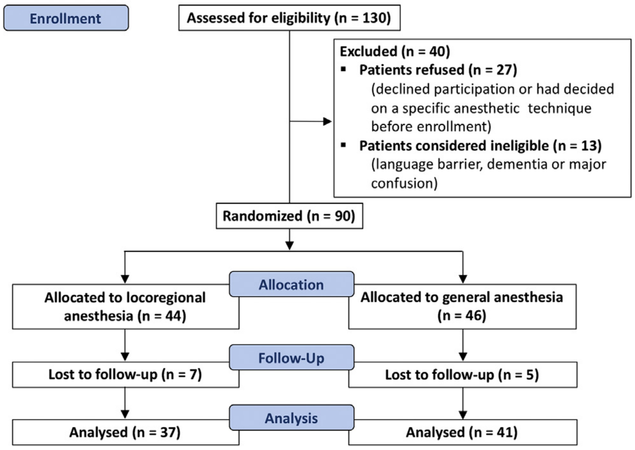

Fig 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

RESULTS

Patient characteristics. We assessed 130 Caucasoid patients for eligibility, 40 of whom were excluded (27 declined to participate or had decided on a specific anesthetic technique before enrollment and 13 were ineligible owing to a language barrier, dementia, or major confusion). A total of 90 patients were randomized (44 US-RA group, 46 GA group), 12 of whom dropped out, leaving 78 patients in the final analysis population (37 patients in the US-RA and 41 patients in the GA group) (Fig 1). The 12 patients who dropped out after enrollment did so because of logistic problems (eg, no member of the study group available on the day of the intervention or postponement of intervention) (Fig 1).

No significant differences between the two groups were found in patient characteristics (except body mass index), comorbidity, or comedication (Table I). The patients had a median stenosis of the carotid artery of 82% (70%-99%).

Intraoperative data. Regarding the operative technique, 28 patients underwent eversion endarterectomy and 50 patients patch angioplasty, whereas distribution did not differ significantly between the US-RA and the GA group (Table II). The duration of the procedure, side of the procedure, and clamping time did not differ between the groups (Table II). In the US-RA group, 28 patients had a good sensory blockade effect, whereas in 9 patients a small adjunctive dose of LA (2% lidocaine 2-5 mL) had to be supplemented by the surgeon. The absolute ischemic time defined as cross-clamping time of the carotid artery was longer in the US-RA group (24.9 ± 14.5 minutes compared with 9.05 ± 11 minutes in the GA group). A shunt was placed in 37 patients (90.2%) in the GA group, whereas no shunt was placed in the US-RA group (Table II). Intraoperative vasopressor therapy was predominantly necessary in the GA group ($P < .001$; Table II), and the same group also needed significantly more volume replacement ($P < .001$; Table II). Intraoperative antihypertensive therapy was used more frequently in the US-RA group ($P < .001$; Table II).

Cardiac index. CI, as a measure of CO per square meter of body surface area, was the primary outcome measure of this study. At baseline (t0), the CI was almost identical in the US-RA (3.5 ± 0.9 L/min/m^2) and the GA (3.3 ± 0.9 L/min/m^2; $P = .462$; Fig 2) groups. The After induction of anesthesia and before surgical incision (t1), CI increased slightly in the US-RA group (3.7 ± 0.8 L/min/m^2) and remained constant until the end of the procedure (t2: 3.7 ± 0.9, t3: 3.7 ± 1.2, t4, 3.6 ± 1.1 L/min/m^2; Fig 2). No significant change over time was observed ($P = .833$). The CI significantly decreased over time in the GA group, with every time point being significantly decreased in comparison with baseline (t0) (at t1, $P < .001$; t2, $P < .03$; t3, $P = .001$; t4 $P < .001$).

Thus, the GA group showed significant differences to the US-RA group (t1, 2.4 ± 0.6 L/min/m^2; $P < .001$; t2, 2.8 ± 0.7 L/min/m^2; $P = .002$; t3, 2.6 ± 0.6 L/min/m^2; $P < .001$; t4, 2.8 ± 0.7 L/min/m^2 $P < .001$; Fig 2).

TCD imaging. TCD examination was used to evaluate peripheral blood flow velocity in the middle cerebral artery prior to and during CEA. Neither for PSV nor for EDV or MDV were significant differences detected between the two groups (Supplementary Fig 1, online only).

NIRS scores. NIRS was used to continuously monitor rSO_2 in the frontal lobes throughout CEA. Over time, significant differences were observed in the US-RA group for both sides (ipsilateral, $P < .001$; contralateral, $P < .001$) and in the GA group for the ipsilateral ($P = .013$), but not the contralateral side ($P = .101$). At baseline (t0), the NIRS scores were similar in the US-RA group and in the GA group for both the ipsilateral and the contralateral sides (ipsilateral US-RA, 65 ± 7 vs GA, 63 ± 8 rSO_2, $P = .117$; contralateral US-RA, 66 ± 6 vs GA, 64 ± 8 rSO_2, $P = .124$; Fig 3). After induction of anesthesia (t1) the NIRS scores remained constant in the GA group (ipsilateral, 63 ± 9; contralateral, 65 ± 7 rSO_2), but significantly increased in the US-RA group on both sides (ipsilateral, 72 ± 8 rSO_2; $P < .001$; contralateral, 72 ± 6 rSO_2; $P < .001$; Fig 3). A similar result was obtained for t2, 2 minutes after cross-clamping (ipsilateral US-RA, 70 ± 10 vs GA, 61 ± 10 rSO_2, $P = .016$; contralateral US-RA, 74 ± 7 vs GA, 66 ± 7 rSO_2; $P = .003$; Fig 3). However, after reperfusion (t3) the NIRS scores also slightly increased in the GA group, but remained significantly higher in the US-RA group until the end of the procedure (t3, ipsilateral US-RA, 74 ± 7 vs GA, 67 ± 9 rSO_2; $P < .001$; contralateral US-RA, 74 ± 8 vs GA, 67 ± 8 rSO_2; $P < .001$; t4, ipsilateral US-RA, 72 ± 8 vs GA, 68 ± 8 rSO_2, $P = .042$; contralateral US-RA, 73 ± 9 vs GA, 68 ± 7 rSO_2, $P = .011$; Fig 3). During the procedure, no significant differences between the ipsilateral and the contralateral side were observed.

Table I. Patient characteristics

Variables[a]	RA Group (n = 37)	GA Group (n = 41)	*P* value
Age, years	71.4 ± 8.9	67.3 ± 13.7	.126 (NS)
Sex			
Female	4 (10.8)	9 (22)	.233 (NS)
Male	33 (89.2)	32 (78)	.233 (NS)
Body mass index, kg/m^2	25.9 ± 3.4	27.4 ± 3.2	.047[b]
Risk factors			
Symptomatic stenosis of the internal carotid artery before surgery	18 (48.6)	24 (58.5)	.496 (NS)
Coronary artery disease	27 (73)	34 (82.9)	.411 (NS)
Peripheral arterial occlusive disease	8 (21.6)	8 (19.5)	1.000 (NS)
Hypertension	33 (89.2)	40 (97.6)	.184 (NS)
Diabetes mellitus	7 (18.9)	10 (24.4)	.595 (NS)
Smoking	14 (38.9)	18 (43.9)	.649 (NS)
Co-medication			
β-Blocker	11 (29.7)	20 (48.8)	.107 (NS)
Calcium channel blocker	10 (27)	9 (22)	.792 (NS)
Angiotensin-converting enzyme inhibitors	14 (37.8)	16 (39)	1.000 (NS)
Nitrates	0 (0)	4 (9.8)	.117 (NS)
Angiotensin II antagonists	10 (27)	18 (43.9)	.158 (NS)
α-Adrenoceptor antagonists	7 (18.9)	5 (12.2)	.534 (NS)
Diuretics	9 (24.3)	12 (29.3)	.799 (NS)
Digoxin	0 (0)	0 (0)	1.000 (NS)
Statins	33 (89.2)	37 (90.2)	1.000 (NS)

GA, General anesthesia; *NS,* not significant; *RA,* regional anesthesia.
[a]Continuous variables are shown as mean ± standard deviation and categorical variables as number (%).
[b]$P < .05$.

Systolic arterial blood pressure. As shown in our earlier study, the time course of the intraoperative SBP differed significantly between the US-RA and the GA group ($P < .001$).[9] At baseline (t0), the SBP was almost identical in the US-RA (161 ± 27 mm Hg) and the GA group (165 ± 25 mm Hg; $P = .522$; Supplementary Fig 2, online only). After induction of anesthesia and before surgical incision (t1), the SBP decreased significantly in the GA group (128 ± 33 mm Hg) as compared with the US-RA group (172 ± 27 mm Hg; $P < .001$; Supplementary Fig 2, online only).

In the US-RA group SBP during the entire procedure remained higher than in the GA group (t2, 164 ± 30 vs 132 ± 32 mm Hg, $P = .005$; t3, 155 ± 29 vs 124 ± 19 mm Hg; $P < .001$; t4, 144 ± 27 vs 131 ± 25 mm Hg; $P = .044$; Supplementary Fig 2, online only).

Heart rate. At baseline (t0), the mean heart rate was similar in the US-RA (67 ± 11 bpm) and the GA group (68 ± 14 bpm; $P = .823$). After induction of anesthesia (t1) heart rate increased in the US-RA group (78 ± 17 bpm), whereas it decreased significantly in the GA group (53 ± 14 bpm; $P < .001$; Supplementary Fig 3, online only). This trend continued during the procedure, with higher values in the US-RA group than in the GA group and a significant difference between the two groups at all time points (t2, 78 ± 18 vs 59 ± 14 bpm, $P = .001$; t3, 77 ± 18 vs 55 ± 12 bpm; $P < .001$; t4, 75 ± 17 vs 57 ± 15 bpm; $P < .001$; Supplementary Fig 3, online only). Also, there was a significant increase in the US-RA group at almost every time point (except t4) as compared with the US-RA baseline (t1, $P < .001$; t2, $P < .001$; t3, $P < .001$; t4, $P < .001$), as well as a significant decrease in the GA group as compared with the GA baseline at all time points (t1, $P < .001$; t2, $P < .001$; t3, $P < .001$; t4, $P < .001$).

Postoperative complications. There were no significant differences between the groups in numbers of patients with a transient ischemic attack after the procedure, surgical neck hematomas requiring revision, myocardial infarction, stroke, death, or recurrent stenosis during the follow-up period of 30 days (Table II).

Table II. Operative details and outcomes

Variables[a]	RA Group (n = 37)	GA Group (n = 41)	*P* value
Operative technique			
Eversion endarterectomy	12 (32.4)	16 (39)	.639 (NS)
Patch angioplasty	25 (67.6)	25 (61)	.639 (NS)
Duration of surgery, minutes	96.5 ± 32.6	95.4 ± 35.0	.889 (NS)
Total clamping time, minutes	33.4 ± 12.7	34.8 ± 13.9	.659 (NS)
Clamping time without shunt, minutes	24.9 ± 14.5	9.05 ± 11.0	<.001[b]
Side of surgery			
Left	18 (48.6)	19 (46.3)	1.000 (NS)
Right	19 (51.4)	22 (53.7)	1.000 (NS)
Shunt placement	0 (0)	37 (90.2)	<.001[b]
Intraoperative therapy			
Vasopressor (norepinephrine)	13 (35.1)	37 (90.2)	<.001[b]
Antihypertensive drug (urapidil)	22 (59.5)	4 (11.8)	<.001[b]
Balanced crystalloids, mL	603 ± 219	943 ± 472	<.001[b]
Colloids	54 ± 197	305 ± 247	<.001[b]
Outcomes			
Transient ischemic attack postoperatively	1 (3)	0 (0)	.474 (NS)
Neck hematoma requiring revision	1 (3)	0 (0)	.474 (NS)
Myocardial infarction	0 (0)	0 (0)	1.000 (NS)
Stroke	0 (0)	0 (0)	1.000 (NS)
Death	0 (0)	0 (0)	1.000 (NS)
Recurrent stenosis	1 (3)	0 (0)	.474 (NS)

GA, General anesthesia; *NS*, not significant; *RA*, regional anesthesia.
[a]Continuous variables are shown as mean ± standard deviation and categorical variables as number (%).
[b]$P < .001$.

DISCUSSION

In this study, we aimed to expand the results of our previous study, which showed a temporary significant increase in SBP and an increase in stress hormone levels in patients under US-RA during CEA as compared with patients under GA.[6] The aim was to assess effects of US-RA and GA during CEA on important patient-relevant parameters. Our primary outcome measure was CI, secondary outcomes were rSO_2 and cerebral flow velocity parameters measured by means of TCD examination.

The benefits of US-RA over GA in CEA are widely accepted and known. A recent study in more than 22,000 patients demonstrated that the use of RA over GA in CEA is associated with a decreased risk for postoperative pneumonia and a reduced need for perioperative blood transfusion.[10] In contrast, a more than two-fold morbidity with GA has been shown.[2] In addition, it is known that patients with RA are significantly more stable in their circulatory system, show better early neurocognitive outcome, less often require a carotid shunt, and have shorter hospital stays and less cardiovascular morbidity.[11,12] However, the main advantage of performing CEA under RA is the real-time monitoring of the awake patient during the procedure, which affords the possibility to take immediate surgical consequences, such as shunt insertion.[12]

RA for CEA in itself entails some risks, namely, LA systemic toxicity and puncture-related complications. Systemic toxicity can cause life-threatening cardiovascular and neurologic complications. Reasons therefor might be an unintended intravascular injection or high plasma levels caused by overdosing the LA or excessively high absorption.[13]

The risk for puncture-related complications, such as vertebral artery injection, subarachnoidal or epidural injection, and local hematomas, can largely be decreased by using US-RA.[14-16]

In our study, the CI and heart rate showed no differences between US-RA and GA at baseline, but higher values were measured under US-RA at all study time points after the induction of anesthesia until the end of the procedure. We were also able to repeat our findings regarding an increase in SBP under US-RA.[6] The higher CI in US-RA seems to be caused by an increase in heart rate and not an increase in SV, which in fact showed no difference between the two groups at any study time point.

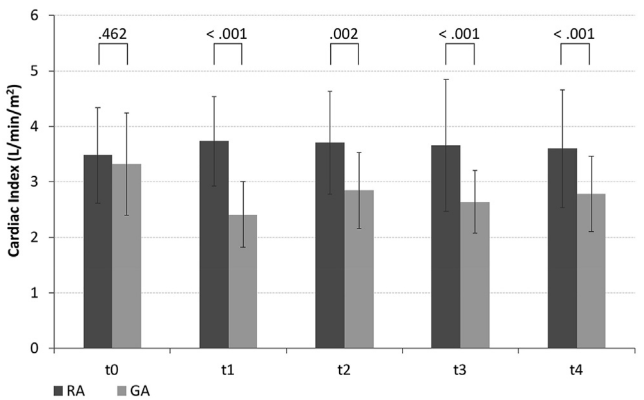

Fig 2. Cardiac index (CI) of patients undergoing carotid endarterectomy (CEA) in regional anesthesia (*RA*) or general anesthesia (*GA*) at baseline (*t0*), after induction of anesthesia (*t1*), 2 minutes after cross-clamping (*t2*), after reperfusion (*t3*), and at the end of surgery (*t4*). Data are presented as mean ± standard deviation. Only *P* values of less than .01 were considered statistically significant for individual time-point comparisons according to the Bonferroni approach for multiple testing.

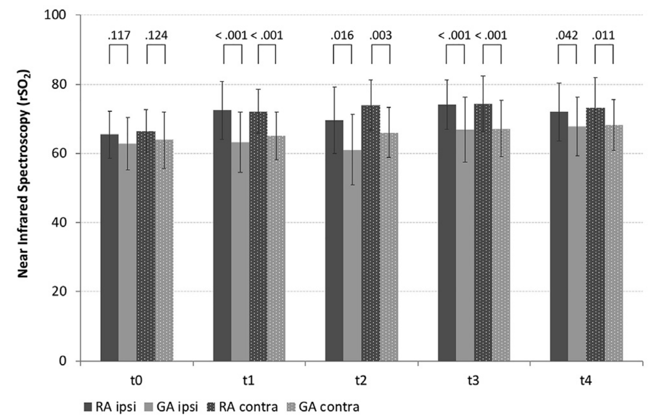

Fig 3. Regional cerebral oxygen saturation (rSO_2) with near-infrared spectroscopy (NIRS) in patients undergoing carotid endarterectomy (CEA) in regional anesthesia (*RA*) or general anesthesia (*GA*) for the ipsilateral (ipsi) and the contralateral (contra) side. Data were recorded at baseline (*t0*), after induction of anesthesia (*t1*), 2 minutes after cross-clamping (*t2*), after reperfusion (*t3*), and at the end of surgery (*t4*). Data are presented as mean ± standard deviation. Only *P* values of less than .01 were considered statistically significant for individual time-point comparisons according to the Bonferroni approach for multiple testing.

Under GA, the CI was significantly lower than under US-RA at all time points as compared with baseline, but remained in a physiologic range without affecting CBF. These findings promote the assumption that LA might have a direct influence on baroreceptors in the carotid sinus.[10-12,17-19] The baroreceptor reflex is known to be the fastest negative feedback mechanism for blood pressure stabilization.[20] Changes in stress on stretched receptors in the wall of elastic vessels (aortic arch and carotid sinus) modulate central vasomotor centers. They change the mechanical properties of the left ventricle and the vascular system to regulate blood pressure and heart rate. Because patients in the US-RA group received midazolam preoperatively and remifentanil continuously throughout the intervention to achieve sedation, the impaired baroreceptor response and not anxiety might be the reason for the increases in the CI, SBP, and heart rate. In contrast, patients under GA needed the administration of vasopressor therapy and more fluid replacement to maintain hemodynamic stability. This difference did not improve the outcome in any patients, but might indicate a theoretical benefit for US-RA during CEA in critical patients.

Importantly, even if a significant increase in SBP in the US-RA group indicates changes in systemic vascular resistance and also in CBF, TCD examination showed no significant differences between US-RA and GA during the entire procedure. We assume that neither US-RA nor GA has a clinically significant impact on CBF, probably owing to cerebral autoregulation.

NIRS allows CBF to be monitored at the frontal lobe during CEA by measuring rSO_2. In the US-RA group, patients showed significantly higher rSO_2 values ipsilaterally and contralaterally as compared with GA. Despite this finding, no difference in the CBF was detected when using TCD examination. In contrast with TCD examination, NIRS as an optical imaging technique does not directly measure blood flow, but reflects levels of oxygen-saturated hemoglobin in the venous, capillary, and arterial blood in the grey matter of the cerebral cortex, mainly from blood in small vessels, as light propagated into large vessels is almost completely absorbed.[21] It is known that cortical activation induces pial artery dilatation with redistribution of CBF in regions with stronger cerebral metabolism.[22] The prefrontal cortex plays an important role in stress response and consciousness. Recently, an increase in oxygenated hemoglobin in the bilateral prefrontal cortex during mental stress in adults, as response to an increase in cerebral metabolism and oxygen demand in this activated cerebral region, was demonstrated.[23] This finding may explain the significantly higher rSO_2 found during US-RA as compared with GA in our study population.

We also found a significantly longer total ischemia time in US-RA as compared with GA. Because shunting during cross-clamping of the carotid artery is performed at our institution in nearly all CEA patients under GA and under US-RA solely when they develop neurologic signs of transient ischemia, this finding is easily explained.

Because intraoperative completion angiography is a routine procedure at our hospital for the purpose of checking the postoperative results when there are no contraindications (hyperthyroidism, renal failure, or allergy to contrast agent), 92.4% (n = 72) of our study patients underwent intraoperative completion angiography. The clinical 30-day outcome of patients undergoing US-RA versus GA was similar. One patient in the US-RA group had a transient ischemic attack and recovered completely, one patient in the US-RA group had a recurrent stenosis during the 30-day follow-up. Intraoperative completion angiography of both patients was normal.

Limitations. Our data reflect a single-institution experience. The sample size was chosen to ensure that relevant differences in the primary end point CI are detected. However, we cannot exclude the possibility that the study was underpowered for the detection of differences in other parameters between the two study groups. Also, our drop-out rate was relatively high. The study does not assess long-term outcomes.

CONCLUSIONS

Our data indicate that concerns that have been prompted by a significant increase in SBP after the induction of US-RA are eased as CI also shows a slight increase or at least remains unchanged. Also, direct and indirect assessment of CBF showed favorable effects for US-RA. As it is known that CEA under US-RA diminishes neurologic risks, our data indicate that US-RA is feasible and safe for CEA.

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AUTHOR CONTRIBUTIONS

Conception and design: HT, EP, GF, CV
Analysis and interpretation: HT, WS, JG, LG, EP, MK, GF, MG, JF, CV
Data collection: HT, EP, CV
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Final approval of the article: HT, WS, JG, LG, EP, MK, GF, MG, JF, CV
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LG and CV contributed equally to this article and share co-senior authorship.

REFERENCES

1. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-87.
2. Hussain AS, Mullard A, Oppat WF, Nolan KD. Increased resource utilization and overall morbidity are associated with general versus regional anesthesia for carotid endarterectomy in data collected by the Michigan Surgical Quality Collaborative. J Vasc Surg 2017;66:802-9.
3. Dakour Aridi H, Paracha N, Nejim B, Locham S, Malas MB. Anesthetic type and hospital outcomes after carotid endarterectomy from the Vascular Quality Initiative database. J Vasc Surg 2018;67:1419-28.
4. GALA Trial Collaborative Group, Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008;372:2132-42.
5. Takolander R, Bergqvist D, Hulthen UL, Johansson A, Katzman PL. Carotid artery surgery. Local versus general anaesthesia as related to sympathetic activity and cardiovascular effects. Eur J Vasc Surg 1990;4:265-70.
6. Hoefer J, Pierer E, Rantner B, Stadlbauer KH, Fraedrich G, Fritz J, et al. Ultrasound-guided regional anesthesia for carotid endarterectomy induces early hemodynamic and stress hormone changes. J Vasc Surg 2015;62:57-67.
7. Do W, Cho AR, Kim EJ, Kim HJ, Kim E, Lee HJ. Ultrasound-guided superficial cervical plexus block under dexmedetomidine sedation versus general anesthesia for carotid endarterectomy: a retrospective pilot study. Yeungnam Univ J Med 2018;35:45-53.
8. Suehiro K, Tanaka K, Matsuura T, Funao T, Yamada T, Mori T, et al. The Vigileo-FloTrac system: arterial waveform analysis for measuring cardiac output and predicting fluid responsiveness: a clinical review. J Cardiothorac Vasc Anesth 2014;28:1361-74.
9. Manecke GR. Edwards FloTrac sensor and Vigileo monitor: easy, accurate, reliable cardiac output assessment using the arterial pulse wave. Expert Rev Med Devices 2005;2:523-7.
10. Malik OS, Brovman EY, Urman RD. The se of regional or local anesthesia for carotid endarterectomies may reduce blood loss and pulmonary complications. J Cardiothorac Vasc Anesth 2019;33:935-42.
11. Lehot JJ, Durand PG. Anesthesia for carotid endarterectomy. Rev Esp Anestesiol Reanim 2001;48:499-507.
12. Weber CF, Friedl H, Hueppe M, Hintereder G, Schmitz-Rixen T, Zwissler B, et al. Impact of general versus local anesthesia on early postoperative cognitive dysfunction following carotid endarterectomy: GALA Study Subgroup analysis. World J Surg 2009;33:1526-32.
13. Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: a systematic review of complications. Br J Anaesth 2007;99:159-69.
14. Stoneham MD, Knighton JD. Regional anaesthesia for carotid endarterectomy. Br J Anaesth 1999;82:910-9.
15. Demirel S, Attigah N, Bruijnen H, Macek L, Hakimi M, Able T, et al. Changes in baroreceptor sensitivity after eversion carotid endarterectomy. J Vasc Surg 2012;55:1322-8.
16. Martusevicius R, Swiatek F, Joergensen LG, Nielsen HB. Ultrasound-guided locoregional anaesthesia for carotid endarterectomy: a prospective observational study. Eur J Vasc Endovasc Surg 2012;44:27-30.
17. Bove EL, Fry WJ, Gross WS, Stanley JC. Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. Surgery 1979;85:633-7.
18. Lehv MS, Salzman EW, Silen W. Hypertension complicating carotid endarterectomy. Stroke 1970;1:307-13.
19. Heesch CM. Reflexes that control cardiovascular function. Am J Physiol 1999;277:S234-43.
20. Kishi T. Baroreflex failure and beat-to-beat blood pressure variation. Hypertens Res 2018;41:547-52.
21. Mancini DM, Bolinger L, Li H, Kendrick K, Chance B, Wilson JR. Validation of near-infrared spectroscopy in humans. J Appl Physiol (1985) 1994;77:2740-7.
22. Ngai AC, Ko KR, Morii S, Winn HR. Effect of sciatic nerve stimulation on pial arterioles in rats. Am J Physiol 1988;254:H133-9.
23. Nagasawa Y, Ishida M, Komuro Y, Ushioda S, Hu L, Sakatani K. Relationship between cerebral blood oxygenation and electrical activity during mental stress tasks: simultaneous measurements of NIRS and EEG. Adv Exp Med Biol 2020;1232:99-104.

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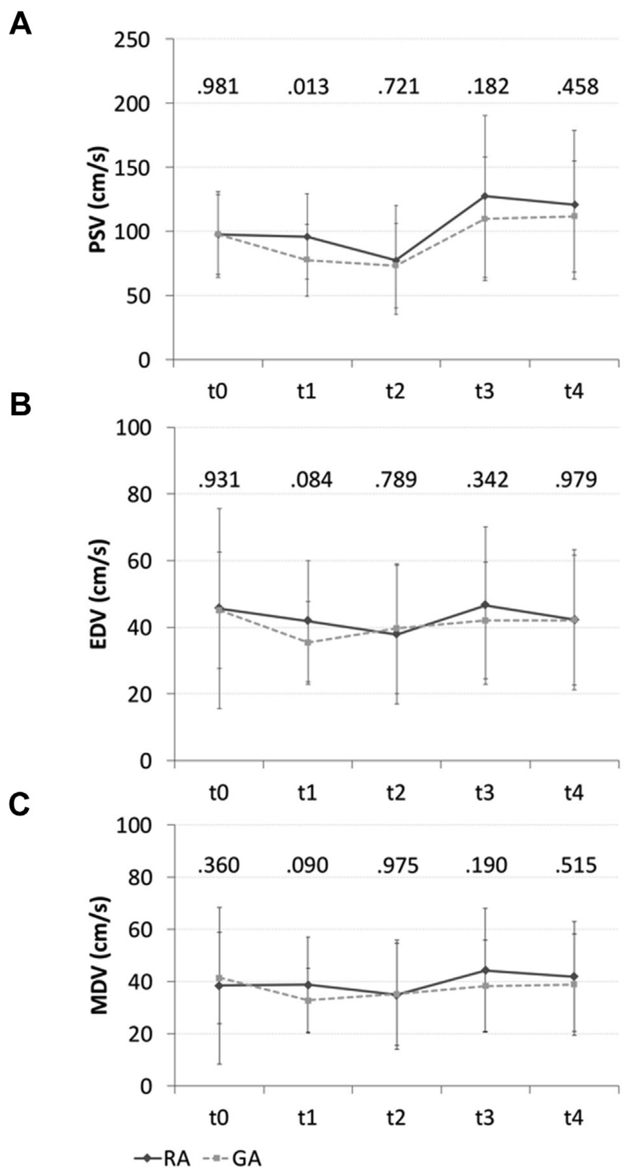
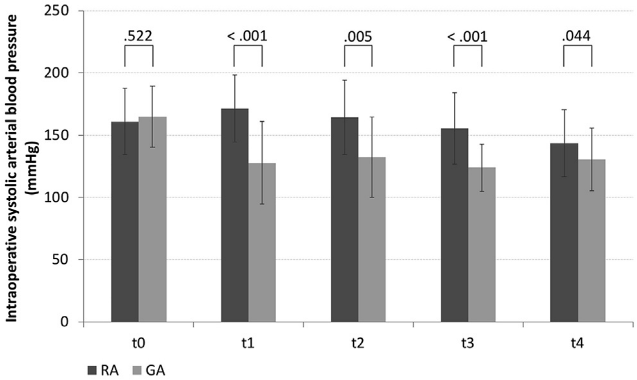
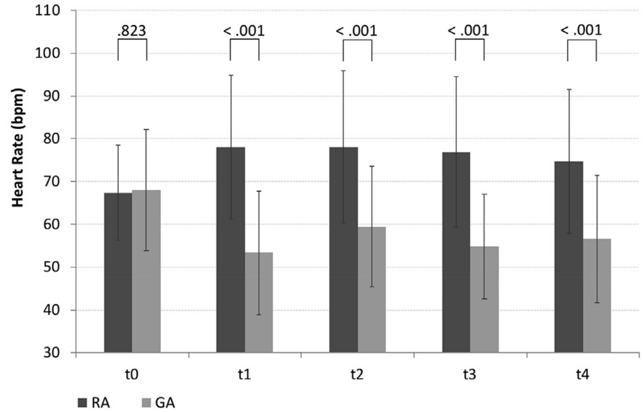


Supplementary Fig 1 (online only). Transcranial Doppler ultrasound (TCD) examination was used to record **(A)** peak systolic velocity (*PSV*), **(B)** end-diastolic velocity (*EDV*), and **(C)** minimum diastolic velocity (*MDV*) of the middle cerebral artery in patients undergoing carotid endarterectomy (CEA) in regional anesthesia (*RA*) or general anesthesia (*GA*). Measurements were performed at baseline (*t0*), after induction of anesthesia (*t1*), 2 minutes after cross-clamping (*t2*), after reperfusion (*t3*), and at the end of surgery (*t4*). Data are presented as mean ± standard deviation. Only *P* values of less than .01 were considered statistically significant for individual time-point comparisons according to the Bonferroni approach for multiple testing.



Supplementary Fig 2 (online only). Intraoperative systolic blood pressure (SBP) in patients undergoing carotid endarterectomy (CEA) in regional anesthesia (*RA*) or general anesthesia (*GA*) at baseline (*t0*), after induction of anesthesia (*t1*), 2 minutes after cross-clamping (*t2*), after reperfusion (*t3*), and at the end of surgery (*t4*). Data are presented as mean ± standard deviation. Only *P* values of less than .01 were considered statistically significant for individual time-point comparisons according to the Bonferroni approach for multiple testing.



Supplementary Fig 3 (online only). Heart rate (HR) in patients undergoing carotid endarterectomy (CEA) in regional anesthesia (*RA*) or general anesthesia (*GA*) at baseline (*t0*), after induction of anesthesia (*t1*), 2 minutes after cross-clamping (*t2*), after reperfusion (*t3*), and at the end of surgery (*t4*). Data are presented as mean ± standard deviation. Only *P* values of less than .01 were considered statistically significant for individual time-point comparisons according to the Bonferroni approach for multiple testing.