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Norepinephrine Induced Hypertension During Carotid Endarterectomy Clamping Decreases Cardiac Stroke Volume and Regional Cerebral Oxygenation in Patients with Low Ejection Fraction

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Abstract...

Introduction: To maintain cerebral perfusion during Carotid Endarterectomy (CEA) blood pressure is often increased with vasopressors. Several studies compare the effects of different vasoactive agents to treat hypotension during CEA but none during clamping of the stenotic carotid artery when concomitant measuring the effects on cardiac Stroke Volume (SV) and cerebral oxygenation (rSO2).

Methods: In this observational study we analyzed 40 consecutive adults during one year scheduled for CEA. Echocardiography was performed in all patients preoperatively and they were separated into two groups: 1) normal Ejection Fraction (EF): 50% and higher; or 2) low EF: 45% and lower. 3 minutes after clamping Mean Arterial Pressure (MAP) was increased by 20% from baseline with norepinephrine. The effects on SV and rSO_2 were measured.

Results: SV deceased in both groups, but significantly only in patients with EF 45% and lower: *Before increase*: SV 60.2 ± 2.1 ml and *5 min after*: 51.8 ± 2.2 ml; p<0.001. When comparing the percentage decrease in SV between patients with EF 50% or more and EF 45% or lower, there was a strong significant difference (-2.4 ± 1.4 % vs -12.6 ± 0.9%) p<0.001.

In patients with low EF there was a concomitant decrease in ipsilateral rSO2 from 65 +/-2.3 to 56 +/- 2.6 %; p<0.034.

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Conclusions: We could not find any support to increase arterial blood pressure by 20% during CEA with cerebral hypoxia. Quite the opposite this decreased rSO_2 in patients with EF 45% or lower. There seems to be an obligate need for monitoring cardiac performance during CEA under general anesthesia at least in patients with low EF.

***Key words**: Carotid endarterectomy; norepinephrine; cerebral oxygenation; mean arterial pressure; stroke volume.*

Introduction

Carotid Endarterectomy (CEA) is performed in patients with critical obstruction of the carotid artery, who are at risk of ischemic cerebral stroke. The surgical procedure requires temporary closure of the carotid artery, which implies a considerable risk for cerebral ischemic complications as well as general anesthesia itself [1]. Studies though, have not shown any benefit in outcome when using local compared to general anesthesia despite the possibility of better neurologic monitoring during surgery in awake patients [2-4]. The normally autoregulated cerebral blood flow and the carotid baroreceptor function is often impaired and dysfunctional during CEA and cerebral perfusion pressure is usually maintained by using vasopressors to treat vasodilatation and hypotension [5-6]. It has also been difficult to show if intraoperative shunting during CEA decreases the incidence of postoperative stroke [7].

Near Infrared Spectroscopy [7] is frequently used for neurological monitoring during CEA under general anesthesia and often in combination with stump pressure [9-11]. The cardiovascular monitoring is often limited to an arterial line at the contralateral arm to the surgery and there is an old recommendation to keep blood pressure +/- 20% from baseline during vascular surgery and + 20% during carotid clamping to maintain or restore cerebral perfusion pressure and blood flow [1,12]. There are several studies comparing the effects of different inotropic and vasoactive agents to treat hypotension during general anaesthesia[13-17], but only a few during CEA with concomitant measuring the influence on cerebral oxygenation [16-19]. There are no studies investigating the concomitant effects of neither norepinephrine nor any other inotropic agent during carotid clamping on both cardiac stroke volume and cerebral blood oxygenation. Pure alfa-agonists e.g. phenylephrine have been shown to negatively affect cerebral perfusion during anesthesia [20,21].

The main aim of this observational diagnostic study was to evaluate cerebral oxygenation and concomitant cardiac stroke volume after norepinephrine-induced blood pressure elevation by 20% during CEA. The patients were divided into two groups with normal left ventricular function (defined as ejection fraction 50% and higher) and patients with reduced left ventricular function (ejection fraction 45% and lower). Our hypothesis is that vasoconstriction and blood pressure elevation per se is not a guarantee for an increased cerebral blood flow during CEA, since the increase in afterload might reduce stroke volume and therefore cardiac index [18,20], especially if the heart function is impaired.

Materials and methods

Ethics

Ethical approval for this study (Dnr 2018/010) was approved by the Ethical committee of Uppsala University Hospital, Uppsala, Sweden on April 2018. Each participant received verbal and written information about the study protocol before giving their written informed consent for participation, data acquisition and analysis.

Participants

Consecutive patients over 18 years scheduled for carotid endarterectomy after multidisciplinary team discussion at the Central hospital of Karlstad, Sweden between May 2018 and May 2019 were asked to participate in the study. Exclusion criteria were: Age under 18, major heart valve failures (defined as moderate to severe tricuspid, pulmonal, mitral and aortic insufficiency or stenosis), patient refusal and inability of the patient to understand the information and sign the consent form. Consent was obtained from all 40 patients participating in the study. Baseline characteristics in Table 1.

Transthoracic echocardiography

A preoperative echocardiography was performed in each patient participating in the study. GE Vivid S-70s ultrasound unit with a 1.5-4.6 MHz phased array transducer was used. On the day before surgery all patients underwent a simplified echocardiography. Measurements included parasternal long axis views of left ventricular dimensions, apical five, four and two-chamber views revealing any wall motion hypokinesia or heart valve dysfunction. Ejection Fraction (EF) was calculated according to the methods of Simpson and Teicholz and a mean of the two methods was used. For later comparisons the patients were divided into two groups: A) EF 50% and more and B) EF 45% and less. Values between 45 and 50 were rounded to five.

Carotid endarterectomy

All patients were premedicated with acetaminophen 1g and the patient´s standard medication with betablockers, calcium-channelblockers, lipid lowering medication, acetylsalicylates and clopidogrel. ACE-inhibitors and AT-II receptor antagonists were not given on the day of surgery. Standard patient monitoring (Philips) consisted of 5-lead electrocardiography, pulse oximetry, neuromuscular monitoring, invasive blood pressure (radial artery contralateral to surgical site) and bispectral index (BIS) [8]. Baseline MAP was calculated from the mean of the first blood pressure obtained, a blood pressure measured at the ward and two days before surgery. This mean from several days was used since patients often present with a higher stress induced blood pressure on the day of surgery.

Cerebral oxygenation (rSO2) was measured with Near Infrared Spectroscopy (NIRS) [8,9], by two cutaneous sensors at both sides of the forehead (INVOS, Medtronic) ipsilateral and contralateral to surgery. They were calibrated before anesthesia with baseline saturation values representing an awake patient without any oxygen supply.

Cardiac performance was measured with an oesophageal doppler probe (Deltex medical) [22] inserted and fixated after induction and intubation. Stroke Volume (SV), Cardiac Index (CI)

peak Velocity (PV) and Flow Time Corrected (FTC) were measured.

Study design and data collection

Anesthesia was standardized. General anesthesia was induced with propofol, remifentanil and rocuronium. After oral intubation anesthesia was maintained by sevorane (MAC: 0.7 ± 0.2 and BIS values of 40-60) and remifentanil. Mechanical ventilation was started aiming at a partial arterial carbon dioxide pressure ($paCO_2$) of 5.0 +/- 0.2 kPa and fraction of inspired oxygen concentration (FiO2) was set to 0.30. When oesophageal Doppler FTC was measured <320ms and Stroke Volume Variation (SVV) > 15% indicating hypovolemia, a small fluid bolus of 250ml ringer acetat was administered to achieve euvolemia. A norepinephrine infusion (0.01-0.09 ug/kg/min; separate iv line; standard of care at our hospital) was started to counteract the vasodilatatory effects of the anesthetics, and blood pressure was corrected to the calculated baseline value in time before clamping of the carotid artery. The norepinephrine infusion was carefully individualized and titrated by the anesthesiologist to obtain as far as possible exact values of the blood pressure both before and after clamping of the carotid artery (below). We used norepinephrine in this study because it has to our knowledge never been investigated in these circumstances and because it besides pure α-agonistic effects also has a mild inotropic stimulating effect on the beta-1 receptor in contrast to phenylephrine [14].

Before clamping values for bilateral rSO_2, SV, CI, PV and ETCO2 were registered. 3 minutes after carotid clamping bilateral rSO_2, SV, CI, PV and ETCO2 were registered again and thereafter mean arterial blood pressure (MAP) was elevated 20 +/- 5% with norepinephrine and the same values were registered 2, 5 and 10 minutes after MAP elevation (5, 8 and 13 min after ceased carotid blood-flow). When you use the time between induction of anesthesia and clamping to titrate the norepinephrine-infusion to keep baseline blood pressure you have learned how each patient responds to the drug and this is the basis to be able to increase MAP 20 ± 5 % after clamping. The primary endpoints were effects on SV and rSO2 after MAP elevation during clamping to be able to show if an increase in MAP per se means an increase in cerebral blood flow and cerebral oxygenation or the opposite.

A decrease in rSO2 with 20% or more in combination with a mean stump pressure <35mmHg were indications for shunting and the study was discontinued.

Statistical analysis

There were no missing data. Data are presented as mean (standard deviation). The sample size calculation was based on data from earlier studies [18,19,23]. Power analysis showed that a sample size of n=10 would be required (αlevel 0.05 and statistical power >80%) in order to detect an expected reduction in NIRS-determined rSO_2 of 3%. When analyzing the results the patients in group A and B were compared. Hemodynamic and echocardiographic variables were compared using repeated measure (ANOVA) for group vs time interaction. Student´s paired t-test and Wilcoxon´s signed rank test were used to evaluate changes between conditions. A confidence level of less than 5% (0.05) was considered significant.

Results

Study population and characteristics

40 consecutive patients were enrolled. There were no significant differences between the groups in perspective of baseline characteristics (Table 1). The flow chart of the study is displayed in Figure 1.

Effects of norepinephrine induced BP elevation on cardiac stroke volume (SV).

Basal stroke volumes of the patients participating in the study was measured with oesophageal doppler after induction of anesthesia and correction of mean arterial blood pressure to basal values with norepinephrine infusion +/- crystalloid boluses (Figure 2). Norepinephrine dosing was between 0.01 – 0.09 µg/kg x min, was considered a reasonable amount to counteract for the vasodilatory effects of anesthesia. Crystalloid boluses of 250ml were used if norepinephrine in the concentrations above was not enough to restore BP when FTC was < 320ms and SVV > 15% indicating hypovolemia. There were no significant differences in basal SV between patients with EF 45% or lower and EF 50% or higher p=0.080 (60 ± 11ml vs 66 ± 8ml), though there was a tendency to lower SV in patients with low EF (Table 1).

When increasing norepinephrine infusion to elevate MAP by 20% from baseline during carotid clamping SV deceased in both groups (Figure 2) but significantly only in patients with EF 45% and lower (Figure 3). SV values presented as mean ± SD at 0, 2, 5 and 10 min after increasing MAP 20% with norepinephrine in patients with EF 45% and lower: SV 60.2 ± 2.1 ml; 53.0 ± 2.4 ml (2 min) p<0.001; 51.8 ± 2.2 ml (5 min) p<0.001 and 50.8 ± 1.7ml (10 min) p<0.001 (Figure 2). In Figure 3. Stroke Volume (SV) by time stratified by EF group when clamping of the carotid artery (0min) and 2, 5 and 10 min after increasing MAP 20% from baseline with norepinephrine. 95% confidence interval for each group at each time. P-value for group vs time interaction is p=0.79 for EF 50 and p=0.009 for EF 45% and less.

When comparing the percentage decrease in stroke volume between patients with 50% and higher and low EF 45% and lower there was a strong significant difference (-2.4 ± 1.4 % vs -12.6 ± 0.9%) p<0.001 (Figure 4).

Effects of norepinephrine induced BP elevation on regional cerebral oxygenation rSO2.

Cerebral oxygenation was measured on both sides of the forehead with NIRS technology. There were no significant differences in ipsilateral and contralateral rSO_2 between the groups of patients with EF 50% and higher or EF 45% and lower before anesthesia (Table 1). When increasing BP 20% during clamping, ipsilateral rSO_2 decreased significantly in patients with low EF from 65 ± 2.3 to 56 ± 2.6 p<0.034, but did not change significantly in patients with normal EF from 68 ± 1.6 to 71± 1.7 p=0.28. The rSO_2 values shown are registered 5 min after 20% increase in MAP (Figure 5).

Patients scheduled for CEA.

Transthoracic echocardiography.

Group A: EF 50% and more. (n=27)

Group B: EF 45% and less. (n=13)

Day of surgery:

A-line; BIS; INVOS(rSO_2)-baseline; Oesophageal doppler

Remifentanil + Propofol

Remifentanil +Sevoflurane, Norepinephrine (NE).

Study design:

FTc- correction.

NE-infusion to baseline systolic BP.

$ETCO_2$ 5,0 ± 0,2 kPa

Measure SV, PV

Carotid clamping

0 min: SV + rSO_2 registration

3min: SV + rSO_2 registration

MAP + 20 ± 5%.

Measure:

rSO_2: 2, 5, 10min

SV: 2, 5, 10 min

Figure 1: NE: Norepinephrine: rSO2: Regional cerebral saturation; PV: Peak velocity.

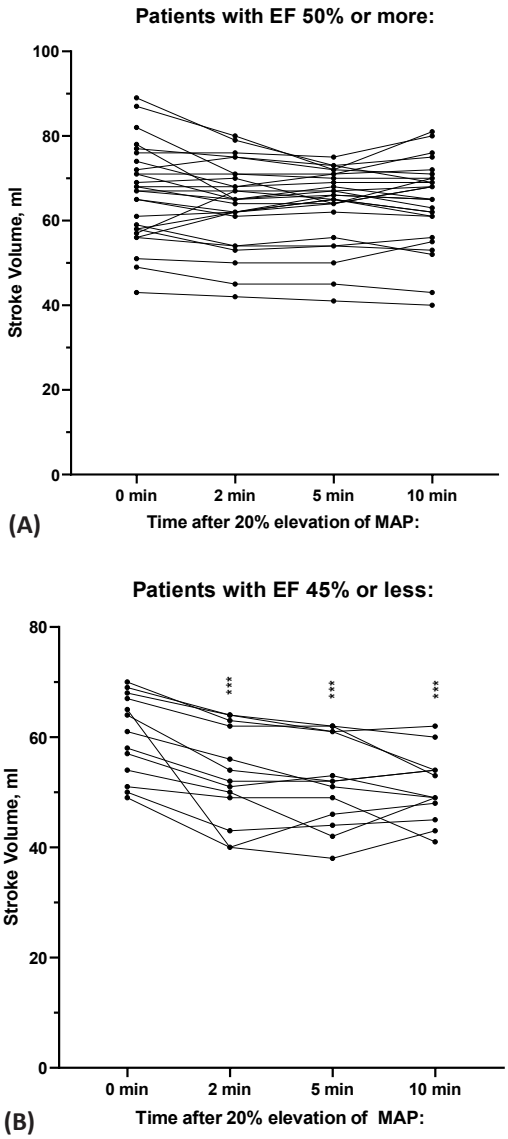

Figure 2: Stroke Volume (SV) in patients with Ejection Fraction (EF) 50% and more **(A)** and 45% and less **(B)** when clamping of the carotid artery (0min) and 2, 5 and 10 min after increasing MAP 20% from baseline with norepinephrine.

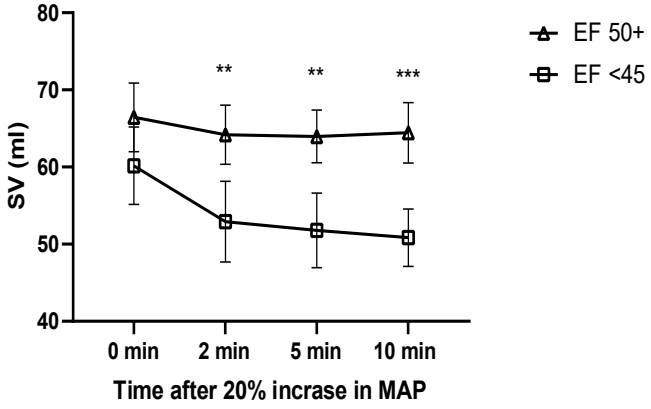

Figure 3: Mean stroke Volume (SV) by time stratified by EF group when clamping of the carotid artery (0min) and 2, 5 and 10 min after increasing MAP 20% from baseline with norepinephrine. 95% confidence interval for each group at each time. Asterisks denote probability level of random difference between the groups. ** p<0.01; *** p<0.001. P-value for group vs time interaction is p = 0.79 for EF 50 and p=0.009 for EF 45% and less.

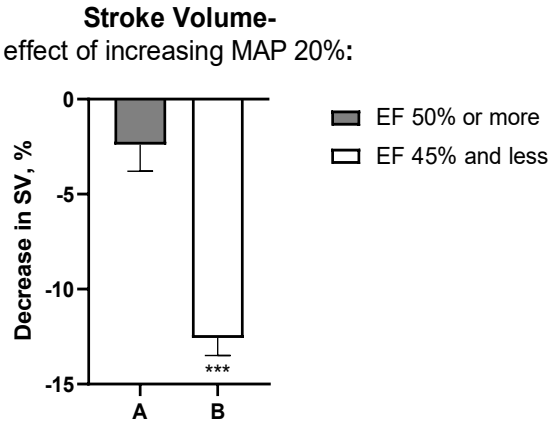

Figure 4: Percent reduction in stroke volume during cross clamping of the carotid artery 5 minutes after increasing MAP 20% with norepinephrine in patients with **(A)** EF 50% and more and with **(B)** EF 45% and less. Data are means ± SD. Asterisks denote probability level of random difference between the two groups A and B. *** p<0.001.

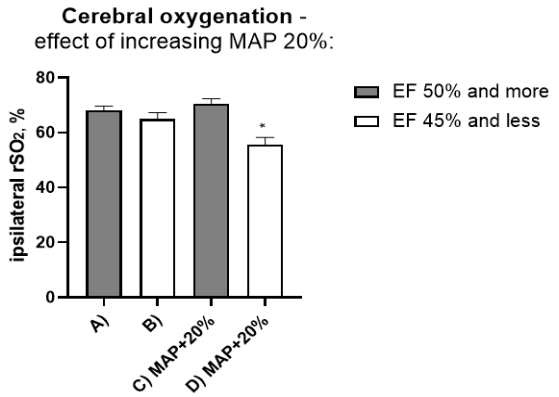

Figure 5: NIRS (Near Infrared Spectroscopy). Regional cerebral saturation (rSO2) after clamping the carotid artery before and after increasing MAP 20% with norepinephrine in patients with A+C) EF 50% and more and with B+D) EF 45% and less. Data are means ± SD. Asterisks denote probability level of random difference between group B and D. * p<0.034.

Table 1: Baseline characteristics of patients in the EF 50% and more and EF 45% and less groups.

	EF 50% and more N= 27	EF 45% and less N=13
Female gender	2 (15%)	6 (22%)
Age	74 ± 6	74 ± 5
BMI	29 ± 8	32 ± 10
ASA class	3,0	2,8
Hypertension	95%	100%
Beta-blocker	13 (48%)	6 (46%)
Calcium channel blocker	9 (33%)	6 (46%)
ACE-inhibitor/ AT-II blocker	20 (74%)	12 (92%)
Diabetes Mellitus	6 (22%)	9 (69%)
Pacemaker	0	0
Current or past smoking	26 (96%)	13 (100%)
Degree of ipsilateral stenos:		
• 70-95%	12 (44%)	7 (54%)
• 50–69%	15 (66%)	6 (46%)
Degree of contralateral stenos:		
• > 50%	2 (7%)	1 (7%)
Preop MAP (mmHg)	104 ± 9	105 ± 14
Preop systole (mmHg)	151 ± 17	155 ± 24
Preop diastole (mmHg)	82 ± 9	83 ± 14
Preop ipsilateral INVOS (%)	71 ± 8	67 ± 8
Preop contralateral INVOS (%)	88 ± 8	73 ± 8
Perop shunting:	0	0
Stroke volume before clamping (ml)	66 ± 11,2	60 ± 7,6

Discussion

This study shows that individualizing blood pressure management during carotid endarterectomy under general anesthesia is absolutely necessary not to increase the risk of perioperative cerebral hypoxia. We can show that increasing blood pressure with norepinephrine by approximately 20% from baseline during the clamping period of CEA has a significant negative effect on regional cerebral saturation in patients with decreased left ventricular function defined as EF 45% and less. It seems most important to monitor cardiac output and to individualize circulatory support at least in patients with decreased LV function undergoing CEA.

Regulating and maintaining adequate cerebral blood flow during carotid endarterectomy is often based on empiric experiences and old recommendations [1]. It is especially important to be able to detect any significant decrease in cerebral blood flow and cerebral oxygenation during clamping of the carotid artery to avoid neurological complications and to guide the surgeons if a temporary shunt should be used past the stenotic artery, which is debated[7]. Since the procedure is often performed under General Anesthesia (GA), which itself impedes sympathetic control of vascular tone and cerebral autoregulation [5,24] the surgery team often increased blood pressure pharmacologically in GA patients in the GALA trial [4]. This is still one of the standard procedures to do when there are indications of declining cerebral oxygenation, hypoperfusion and thus increased risk of perioperative stroke [25].

This study shows that Norepinephrine-induced increase in systemic blood pressure decreased stroke volume and cardiac index in all ASA 3 patients participating in this study, but significantly more when EF was 45% and lower. Peak velocity (indicating systolic contractility- data not shown) also decreased when MAP was raised probably as a consequence of an increase in afterload. This was accompanied by a concomitant significant decrease in regional cerebral oxygenation ipsilateral to the clamped carotid artery. In patients with normal EF, rSO_2 was not significantly changed during the elevation of MAP. In agreement with this Brassard et al [26] suggested that norepinephrine in higher concentrations might negatively affect cerebral oxygenation even in healthy subjects. In assessment of left ventricular function, the concept ejection fraction has long been the most widespread method. It must be known however that EF, which is the ratio between stroke volume and the end-diastolic blood

volume of the left ventricle, has its limitations and in the search for alternative methods tissue doppler recordings of the systolic and diastolic velocities of the mitral annulus has gained ground in the assessment of systolic and diastolic LV function [27,28]. Patients with heart failure and preserved EF is not separately studied in this research.

There is no consensus of how to estimate normal or baseline blood pressure, but the preoperative values could be biased by stress. When starting antihypertensive treatment in patients with vascular disease the goals are blood pressures below 140 mmHg based on three different measurements at rest. Therefor it seemed reasonable to use a mean of arterial blood pressures measured preoperatively and at rest during the days before surgery in both groups. This has also been used in similar studies and both systolic and mean arterial pressures have been used without affecting the results [18].

Only two patients participating in this study had been referred for an echocardiography before this study. 69% of the patients with low EF had diabetes type I or II, compared with 22% in the control group (Baseline characteristics table 1). There is a known autonomic dysfunction in patients with diabetes mellitus and the compensatory mechanisms are less prominent during cerebral clamping during general anesthesia compared to local [1,5,16]. Administration of norepinephrine to correct MAP during cardiopulmonary bypass has been shown to reduce frontal lobe oxygenation in patients with diabetes [16,29,30]. The oesophageal doppler was used in this study to measure SV and CI, since it has been shown to be a more accurate method than pure pulse contour analysis during pharmacological vasoconstriction and when clamping of the vessels are part of the surgical procedure [26,31]. It measures actual blood flow in the descending aorta and not real cerebral blood flow, but we assumed that it could be used in this study when we had corrected for preoperative hypovolemia and anesthesia induced vasodilatation. Other techniques such as transoesophageal echocardiography is almost impossible to use during this procedure, since it interacts too much with the surgical area.

Detection of cerebral ischemia is crucial and dependent on indirect measurements most often with NIRS technology and stump pressure [9,32] used in this study. Transcranial doppler assessment could also be an alternative but is more complicated to perform during surgery and shown to be less accurate than NIRS [33]. NIRS has even been suggested to improve both neurologic and major organ morbidity during surgery [34]. The sympathetic regulation of cerebral blood flow in humans [5] plays little role in regulating CBF during normal physiological conditions, but during cerebral spasm and decreased sympathetic tone it may offer therapeutic benefit. There is a direct innervation of cerebral arteries from cervical ganglia and during hypertension and increased pCO_2 this protects against an inappropriate increase in cerebral blood flow concomitant with circulating sympatomimetics [5].

Cerebral tissue oxygenation saturation is also influenced by:

- Cerebral metabolic rate of oxygen, which can be presumed almost constant during anaesthesia [19] (BIS < 60).
- Cerebral oxygenation measured with NIRS can be biased by cutaneous vasoconstriction when administrating different vasoactive drugs [35,36].
- When clamping the carotid artery during surgery, ipsilateral rSO_2 can be influenced by the degree of contralateral carotid stenosis and possible collateral circulation. In this study only 7% of the patients in each group had a contralateral stenosis > 50% (Table 1- Baseline characteristics).
- Arterial blood oxygen content and pCO_2, known to correlate with changes in cerebral blood flow, which were also kept constant.

There are many studies comparing the effects of different inotropes to maintain cerebral blood flow during anaesthesia [13,17,37], and there seems to be a preference using sympatomimetic drugs acting on both alfa and beta receptors to pure alfa agonists [18,21]. No study has to our knowledge measured the concomitant effects of vasoactive therapy on both cardiac performance and cerebral oxygenation during carotid clamping. The effects of different vasoactive drugs on cerebral blood flow are difficult to predict and will depend on volume status, absolute systemic arterial pressure, the effects of the drug on cerebral vasculature, coexisting heart disease and the extent of bilateral carotid and other cerebral vascular disease.

We can show that increasing systolic blood pressure approximately 20% during carotid clamping in patients with normal EF neither increases cardiac stroke volume nor cerebral oxygenation. In patients with decreased LV function, stroke volume and cerebral oxygenation were significantly decreased. This could be one of the reasons why there are divergent effects in the literature when using different inotropes to increase cerebral blood flow [17-21], when not measuring and not knowing the concomitant effects on heart function.

There is a need for further larger multicenter studies, where you compare different variables of cardiac performance, neurological monitoring and outcome and different pharmacologically tools to optimize cerebral perfusion during TEA.

In conclusion, we could not find any support to increase arterial blood pressure with norepinephrine to increase cerebral blood flow during carotid endarterectomy. Instead we found this to be associated with decreasing stroke volume and lower cerebral oxygenation in patients with reduced LV function.

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