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Vera Augusta Araújo Silva

Preditores hemodinâmicos e alterações durante a endarterectomia carotídea sob anestesia regional./ Hemodynamic predictors and changes during carotid endarterectomy under regional anesthesia.

Fevereiro, 2024

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Hemodynamic predictors and changes during carotid endarterectomy under regional anesthesia.

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Vera Augusta Araújo Silva , abaixo assinado, nº mecanográfico 201807389, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 27/12/2023

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Vera Augusta Araújo Silva

DEDICATÓRIA

Dedico este trabalho aos meus pais e a minha irmã, que são os pilares da minha vida. Os maiores guerreiros que conheço, aos quais devo o sucesso académico até agora alcançado.

Ao professor João Rocha Neves pela excelente orientação desta dissertação.

Aos 6 anos mais bonitos, desafiantes e enriquecedores da minha vida
…

Hemodynamic predictors and changes during carotid endarterectomy under regional anesthesia.

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1) Original paper

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Conflict of Interest Statement

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Authors' contributions

Vera A. Silva and Luís Duarte-Gamas contributed equally as first authors to the methodology, investigation and writing of the manuscript, Juliana Pereira-Macedo to the formal analysis and visualization, Mariana Carreira to review and editing and visualization, Piotr Myrcha to the validation of data, review of the manuscript and visualization, José Paulo Andrade to the validation and curation of the data and review of the manuscript, André Leite Moreira to the review of the manuscript and João Rocha-Neves to the conceptualization, methodology, validation and formal analysis of data, investigation, data curation, writing of the original draft, manuscript review, supervision and project admnistration. All authors have participated to drafting the manuscript, author A revised it critically. All authors read and approved the final version of the manuscript.

Abstract

Objectives: Carotid endarterectomy (CEA) is the standard procedure for treating carotid stenosis, but it can lead to cerebral hypoperfusion and hemodynamic stroke. Regional anesthesia (RA) and light sedation allow continuous monitoring of neurological function during the procedure. However, the relationship between perioperative hemodynamic management and neurological dysfunction has yet to be thoroughly investigated. This study aimed to identify which hemodynamic patterns are most strongly associated with intraoperative cerebral ischemia in patients undergoing CEA under RA.

Methods: The study included patients who underwent CEA at an academic tertiary referral center between January 2012 and December 2019. Cases were individuals who developed neurological deficits (ND) during CEA. Controls were patients who did not experience ND. Controls were sampled 1:1 from consecutive patients undergoing the same CEA technique at the same department.

Results: A total of 154 patients were included, 78,6% male, and the mean age was 70.1±9.1 years. Cases were older than the controls (p=0.012). Baseline systolic blood pressure (SBP) values were higher in the ND group (154.6±31.8 vs 141.8±41.2 mmHg, p=0.035) as well as pulse pressure (p=0.023). The ND group also had a statistically significant higher mean arterial pressure (MAP) at the 3rd-minute post-clamp (p=0.028) and exhibited a smaller drop in SBP between the pre-clamp and the 1st and 3rd minutes post-clamp (p=0.021 and p=0.039, respectively).

Conclusions: Focal neurological deficits during CEA showed no characteristic preditive pattern, besides a higher systolic blood pressure. Hemodynamic management at the pre-clamping stage is crucial for preventing unwanted deficits.

Introduction:

CEA is an established and beneficial procedure for treating and preventing cerebral ischemic events in patients with severe symptomatic carotid stenosis. Its efficacy has been demonstrated through randomized clinical trials (1). CEA is routinely performed as a standard procedure for eligible patients. (2, 3). This procedure is recommended for symptomatic patients or patients with a high degree of stenosis (>70%), which in turn results in an increased risk of stroke (4). However, the procedure carries a risk of clamp-associated intraoperative cerebral ischemia (5), whose currently recommended method of detection is the clinical assessment of neurologic deficits (ND) under regional anesthesia (RA) (6). It is important to note that patients who develop ND during the procedure are at a higher risk of postoperative morbidity (7-9), including an increased risk of stroke. These factors raise concerns regarding the risk-benefit profile of surgical intervention in such cases.

Lately, pre-CEA morbidity factors have been associated with worse outcomes. These factors include advanced age, body mass index (BMI) >30kg/m2, an ipsilateral low-grade carotid stenosis, contralateral high-grade stenosis, and increased red blood cell distribution width (10). These factors are associated with an increased risk of complications and poorer outcomes following CEA (9, 10). Thus, risk calculators are under development to highlight which patient variables have the greatest discriminatory power for risk and predict which patients will benefit the most from CEA (11).

To mitigate the risk of ischemia during carotid cross-clamping (CACC), current prevention measures emphasize the importance of avoiding intraoperative hypotension and implementing strategies to increase mean arterial pressure (MAP) by approximately 20% (8, 12). In patients undergoing CEA, it is common to observe hypotension, hypertension, and bradycardia episodes during the perioperative period. These

hemodynamic changes can be attributed to various factors such as the underlying disease, administration of vasoactive drugs, surgical manipulation of the carotid sinus, and other related factors (13). However, there are a few studies, yet not conclusive, that hypothesize that severe preoperative hypertension should predispose the patient to future cardiovascular and/or neurological complications (8, 12).

This study investigates the relationship between the hemodynamic profile during CEA under RA and the occurrence of intraoperative ND.

Materials and methods

Study Population

This study is based on a previously conducted nested case-control database. A secondary analysis was performed on 154 patients who underwent CEA under RA as a sole procedure. The study period ranged from January 2012 and December 2019, and the procedures were performed at an academic tertiary referral center.

Cases were defined as patients who developed intraoperative ND, detected through neurologic examination. A total of 77 cases were identified. Control patients (n=77) were selected in a concurrent 1:1 fashion, meaning one immediately consecutive control patient was chosen for each case. The control patients underwent the same surgical and anesthetic technique but did not develop ND (Fig.1). Patients who received an anesthetic modality other than RA or underwent concomitant cardiac surgery were excluded from the study.

Data on comorbidities and demographics of study participants were collected. Information regarding medications administered during the intraoperative period and blood pressure measurements at various time points during the carotid endarterectomy (CEA) procedure was also recorded. One month after the procedure, patients were revaluated in an outpatient setting. Subsequently, yearly follow-up assessments were conducted for a total of two years. After the two-year mark, patients were advised to continue their follow-up with their respective family physicians.

The present work follows the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria (14). The study protocol respects the Declaration of Helsinki and follows the European Union General Data Protection Regulation (GDPR). The local Ethics Committee approved the study protocol (protocol 248 -18) and it is registered at clinicaltrials.gov (NCT04347785).

CEA protocol

The degree and extent of atherosclerotic lesions were measured using Doppler ultrasound or computed angiography tomography, as indicated by clinical guidelines (15). Pre-procedure consultations with both the angiology and anesthesiology teams were carried out to evaluate the patients' overall health condition, assess potential risks, and determine the appropriate indications for the procedure. Following established clinical guidelines, patients were prescribed antiplatelet therapy and a statin for a minimum duration of two days before the CEA procedure (16). Pharmacological or mechanical thrombolysis was not administered to patients in the present study. An ipsilateral ultrasound guided "intermediate" cervical plexus block was performed on all patients for anesthesia by injecting 12-15mL of ropivacaine 0.75% posterior to the plane of the sternocleidomastoid muscle. Conscious sedation was achieved using continuous infusion of dexmedetomidine, at a maximum rate of 0.7 µg/kg/h. Benzodiazepines were optionally added to the sedation regimen based on the anesthesiologist's preference.

Hemodynamic status monitoring

During the intraoperative period, BP was continuously monitored by arterial catheterization of the upper limb contralateral to the carotid artery being operated on. The target mean BP range was set between 100 and 120% of baseline BP. Several time points were analysed, including at admission by the nursing team, after arterial catheterization, after the regional block, pre-clamping of the carotid artery, and at 1, 3, 10 minutes after clamping. The latest time point analysed was set at 10 minutes to avoid potential confounders such as surgical technique (carotid sinus denervation in eversion CEA vs. preservation in patched CEA) and shunt insertion, which usually occurred beyond that time mark. The zenith (highest) and nadir (lowest) pressures after clamping were also

recorded.

In addition to blood pressure, other hemodynamic parameters, such as pulse pressure (PP), heart rate (HR), and oxygen saturation, were also simultaneously analysed and documented for each patient.

Intraoperative Neurologic Examination

Both groups of patients underwent CEA under RA, and their neurologic status was assessed using a comprehensive neurologic examination. This examination included evaluating consciousness (response to direct commands by the anesthesiologist, simple questions) and subsequent surveillance at 5-minute intervals and continuous cerebral oximetry monitoring (INVOS, Medtronic) (6). However, neurological testing was used as the sole criterion for adjudication of diagnosis (17-19).

Surgical Technique

Depending on the surgeon's preference, the surgical technique employed for CEA included options such as patch angioplasty, eversion, or direct suture. The decision to shunt during the procedure was also at the surgeon's discretion. Carotid sinus block, as a rule, is not performed in the study center.

The stroke rate observed at the center falls within the recommended range in clinical guidelines (20). The ND rate at the present center is 8% per year. Additionally, over 98% of CEA at this referral center are performed under RA. The involved vascular department has reported rates of stroke and death after CEA that list 1.10% and 0.6% in symptomatic patients, respectively (21, 22).

Patients were followed up for 30-90 days in the postoperative period through medical examinations and Doppler ultrasonography (DUS). These evaluations aimed to detect any potential complications, including early restenosis.

Definitions

The European Vascular Surgery Society clinical practice guidelines were the basis for classifying carotid stenosis as symptomatic (23). Furthermore, the first event was the first stroke identified as the first ischemic neurologic event six months before CEA.

The criteria used to define ND in this study were any persistent alteration observed during the neurologic examination that did not respond to hemodynamic adjustments during CACC (e.g., hemiparesis, aphasia, etc).

Outcomes

The primary outcome was the presence of intraoperative ND.

Statistical analysis

The sample size that was needed for a case-control study was calculated on http://sample-size.net, based on means, and the aim was to accomplish a statistical power (1-β) of 90%, an effect size of 0.6 and a type I error rate (α) inferior to 0.05. The sample was calculated at 118, with the least difference between groups at 17%(24).

Statistical analysis was run on SPSS 28.0 (IBM Corp., released 2017. IBM SPSS Statistics for Windows, version 28.0, Armonk, NY, USA)

Univariable analysis was evaluated through χ^2 or Fisher's tests regarding categorical data and Student's t-test analysis for continuous data. Continuous variables following a normal distribution are presented with mean ± standard deviation, median, and interquartile range for non-normally distributed variables. Categorical variables are presented as percentages.

Results

Demographics and baseline characteristics of patients

The study sample consisted of 154 patients, 121 (78.6%) of whom were male, and only 33 were female. The mean age of the participants was 70.1 ± 9.1 years. There was a similar distribution of men in both the control group (81.8%) and the neurologic deficit (ND) group (75.3%), and no statistically significant differences were observed in this regard (Table 1).

Patients with ND had a mean age of approximately 72.0 ± 9.90 years. In contrast, control patients had a significantly lower mean age of 68.3 ± 8.3 years (p=0.012). Approximately 50.5% of the procedures were performed on the right side. CEA was performed on the right side in 53.9% and 47% of patients in the control and ND groups, respectively (p= 0.381). (Table 1).

Regarding comorbidities, obesity was more prevalent in the ND population (22.1 vs. 9.3%, p=0.029). However, no statistically significant differences were observed in other comorbidities and cardiovascular (CV) risk factors between the two groups (Table 1).

The average degree of ipsilateral stenosis was similar in the ND population compared to the control group (85% vs. 81%, p=0.953). However, the degree of contralateral carotid artery stenosis was higher in the ND group (65.5% vs. 59.7%, p=0.05). Less than half of the patients in the study (46.1%) reported symptoms related to carotid stenosis. Among these, the majority presented with a stroke (35.3%), followed by a smaller number of cases with a transient ischemic attack (10.45%) (Table 1).

No significant differences between the two groups were observed in the number or pharmacological classes of anti-hypertensive agents used in the preoperative period.

Hemodynamic evaluation

The surgical duration of the control group showed a tendency towards a more extended period than the group with ND (123.9±49.5 vs 110.0±32.7 min, p=0.059). There was no significant difference in clamping duration between groups (46.1±23.3 vs. 49.1±23.25 min, p=0.558) (Table 2).

Pre-clamping SBP was significantly higher in patients with ND compared to controls (154.6±31.8 vs. 141.8±41.2 mmHg, p=0.035). The ND group also maintained significantly higher PP values (98.1±24.0 vs. 87.4±32 mmHg, p=0.023) (Table 3).

In the first minute after carotid clamping, the ND group maintained significantly higher SBP compared to the other group (171.0±29.7 vs. 158.3±40.0 mmHg, p=0.022) as well as PP values (96.0±23.1 vs. 84.7±27.3 mmHg, p=0.007). This difference continued until the 3rd and 10th-minute post-clamping, retaining significance for both SBP and PP. Additionally, at the 3rd post-clamping minute, the MAP obtained in the ND group (108.3±19.7 mmHg) was higher than in the control group (101.1±20.2mmHg), p=0.028 (Table 2).

Both the post-clamping SBP nadir (153.4±29.2 vs. 142.6±33.7 mmHg, p=0.042) and zenith (188.8±34.1 vs. 173.0±33.7 mmHg, p=0.006), along with their respective PP (105.5±23.1 vs. 90.3±26.0 mmHg, p=0.001), were significantly higher in the ND group (Table 2). The ND group also exhibited a statistically higher MAP at the 3rd-minute post-clamp (p=0.028). This is the only significant moment in the variation of diastolic blood pressure (DBP), as shown in Table 3; the ND group had a much smaller drop than the control group (9.3 vs. 18.0 mmHg), indicating that it maintained higher DBP. Additionally, the ND group showed a significant change in SBP, which together affected the MAP. These factors may explain this heterogeneous finding (Fig. 2).

No statistically significant differences were observed for DBP and HR values

between both groups before induction of anesthesia, before carotid cross-clamping, or at any of the analysed time points (Table 2).

Blood pressure variation and complications after carotid clamping

Table 3 shows the variation of pre-clamp and post-clamp BP for minutes 1, 3, and 10. The drop in SBP values registered at the 1st minute post-clamping relative to pre-clamping values was significantly lower in the ND group compared to controls (11.95±16.19 vs. 19.79±24.01 mmHg, p=0.021), and this difference was observed up to the 3rd minute post-clamping (11.12±21.83 vs 19.42±26.78 mmHg, p=0.039). When observing the variation between post-clamping zenith and pre-clamping SBP values, controls group exhibited a drop in SBP of 5.6±23.6 mmHg whereas ND patients showed an increase of 5.7±23.9 mmHg (p=0.005).

Regarding the DBP variations obtained, no statistical difference was found between the groups, except for the variation between pre-clamp and post-clamp at the 3rd minute. In the ND group, the variation was 9.3±20.4 mmHg, significantly lower than the difference observed in the control group (p=0.035).

In the sample of patients who presented ND during clamping, approximately 17 (22.1%) underwent a carotid vascular shunt. In contrast, none of the patients in control group underwent this additional procedure.

Discussion

This study highlights the significance of hemodynamic values, especially SBP and pulse pressure, in determining the occurrence of clamping-associated neurologic deficits. Another finding was that patients in the ND group demonstrated a smaller drop in SBP from pre-clamping to various post-clamping time points. Moreover, the limited variation in BP exhibited by this group during the procedure suggests cerebral autoregulation might have been less effective in these patients. Secondly, PP before clamping and post-clamping was always significantly higher in the ND group. Additionally, this group had a higher prevalence of obesity and greater contralateral stenosis.

Pathophysiologically, induced hypertension seems to be a reasonable measure to ensure sufficient cerebral perfusion in presence of a high-grade ICA stenosis. The anestehsiologis intervention after the establishment of ND, might probably explain the smaller drop in SBP from pre-clamping to post-clamping time points (25). Patients with pre-existing hypertension who are said to be more dependent on a high normal pressure level had a significantly higher ND rate (25). Hypertension is an important risk factor for recurrent stroke both in the acute phase and the long-term. Moreover, hypertension is an important risk factor for complications of CEA (26). An increased pulse pressure is also associated with an increased risk of hyperperfusion syndrome (27). It might also indicate that the brain is already experiencing increased arterial stiffness or adaptation to the compromised blood flow due to the carotid artery blockade (28).

Some predictors associated with neurological deficits and a greater likelihood of post-surgical complications have already been studied (1, 29). Previous evidence has already established the relationship between obesity and a higher incidence of focal neurological deficits, which aligns with the findings of this study (9). Therefore, it would be valuable to explore how obesity interacts with BP values during CEA, considering that

individuals with higher body mass index (BMI) tend to have elevated BP profiles (30). Furthermore, other risk factors, such as ipsilateral and contralateral stenosis, have also been identified (9, 31).

Research indicates that cerebral autoregulation (CA) and arterial baroreflex (BR)are crucial to maintaining stable cerebral perfusion during stress events such as carotid endarterectomy (32, 33). This mechanism becomes especially important in patients with severe carotid stenosis and older individuals, both of whom are at risk of reduced CA effectiveness (34-37). The ND group, with a significant proportion of older patients and severe stenosis, is likely to be particularly vulnerable to perioperative blood pressure fluctuations and related neurological damage. (38).

Additionally, the ND group's persistently higher systolic and pulse pressure values from pre-clamping to post-clamping stages suggest the influence of anesthetic blockade and contralateral atherosclerotic stenosis. Thrasher et al. demonstrated the importance of BR function reserve on the contralateral side of the operated carotid artery and the baroreceptors of the aortic arch (39),(40). Specifically, severe contralateral stenosis could reduce BR sensitivity on the affected side, potentially limiting compensatory capacity during anesthesia induction. As a result, even minor interactions with the ipsilateral carotid sinus might trigger significant hemodynamic variations in the ND group compared to the control group.

Although the duration of carotid clamping did not show a statistical difference between the groups, the total duration of the surgery was shorter for the ND group. The authors suggest that upon detecting neurological alterations, surgeons probably expedite surgical procedures to minimize patients' exposure to ischemia and potentially reduce any hemodynamic exacerbation of these changes. This proposition is supported by previous studies showing an increased risk of postoperative complications with longer

surgical times in CEA (7, 41). Therefore, there is probably a bias of reverse causality relationship and a link between the shorter surgical time and the clinical outcome.

The ND group had a higher prevalence of obesity, which is associated excessive fibrosis in smooth muscle cells, increased media layer thickness, and subsequent endothelial dysfunction (42). These factors contribute to arterial stiffness and thickening, which likely justify that this group's PP is more elevated. The difference in PP is statistically significant both before and after clamping, as these are the moments when most major hemodynamic changes occur, accentuating the differences in PP between the groups.

However, it is essential to acknowledge the limitations of this study. The sample consisted of 154 individuals, predominantly male, and from a single tertiary referral center. Therefore, it is necessary to conduct multicenter studies with a larger sample size to confirm and validate the present results. Additionally, patients admitted to a tertiary referral center often have more significant comorbidities compared to those of peripheral centers, which may introduce bias when interpreting the results. Furthermore, the study did not assess differences among surgical teams due to the low incidence of events. Considering the low incidence and the limited number of events studied, potential confounders were intentionally not adjusted for, and as a result, confounding may be present in the findings.

Conclusion

This study highlights the significance of thorough perioperative assessment, as well as the importance of perioperative and intraoperative blood pressure management, in determining the outcome of CEA. The study specifically found that higher systolic blood pressure and pulse pressure, are predictive of the occurrence of clamp-associated cerebral ischemia, probably related to the patients own failling hemodynamic control. These

findings could prove useful in determining surgical risk and customizing strategies such as the use of strict and evidence-based blood pressure management protocols.

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Legend

Figure 1. – Summary of the study design

ND - Alterations on the neurologic examination during carotid clamping.

Figure 2. – Graphical representation of blood pressure values in all time points

▪Control; DBP --------- Diastolic blood pressure; MAP •••• Mean Arterial Pressure; ND ◆ Alterations on the neurologic examination during carotid clamping; Nursery – first blood pressure measurement in the nursery; Pos Clamp min 1 – blood pressure 60 seconds after carotid clamping; Pos Clamp min 3 - blood pressure 180 seconds after carotid clamping; Pos Clamp min 10 - blood pressure 600 seconds after carotid clamping; Pre-anesthesia – first blood pressure measurement after arterial catheterization and before anesthetic administration; Pre clamp – blood pressure measurement 3 minutes before carotid clamping; SBP -------- Systolic Blood pressure.

Table 1- Demographics and comorbidities of the patients.

	Control N (%) 77 (50)	ND N (%) 77 (50)	p-value
Age (years) (mean ± SD)	68.3 ± 8.3	72.0 ± 9.61	**0.012**
Side (Right)	41 (53.9)	39 (47)	0.381
Sex (Male)	63 (81.8)	58 (75.3)	0.326
Hypertension	67 (87.0)	72 (93.5)	0.174
Smoking history	44 (57.9)	35 (45.5)	0.124
Diabetes	30 (39.5)	31 (40.3)	0.921
Dyslipidemia	64 (84.2)	63 (81.8)	0.694
CKD	8 (10.5)	10 (13.0)	0.637
BMI > 30 kg /m2	7 (9.3)	17 (22.1)	**0.029**
PAD	19 (25.3)	17 (22.1)	0.637
CAD	25 (33.3)	29 (37.7)	0.577
AF	4 (5.3)	6 (7.8)	0.541
COPD	10 (13.3)	8 (10.4)	0.574
CHF	6 (8)	9 (11.7)	0.446
ASA:			0.685
II	12 (17.1)	12 (16.4)	
III	54 (77.1)	54 (74.0)	
IV	4(5.7)	7 (9.6)	
Asymptomatic	42 (55.3)	41 (53.2)	0.691
Symptomatic			
TIA	8 (10.5)	8 (10.4)	
Stroke	26 (34.2)	28 (36.4)	
ICA stenosis- ipsilateral (%)	84.9±9.4	81.4±10.6	0.953
ICA stenosis- contralateral (%)	59.7±16.1	65.5±20.7	**0.05**
Anti-hypertensive agents (numbers)	2.0±1.15	2.0±1.33	0.948

ACEI/ARB	56 (75.7)	52 (70.3)	0.459
Beta-Blocker	25 (33.8)	23 (31.1)	0.725
CCB	27 (36.5)	31 (41.9)	0.500
Thiazide diuretic	34 (45.9)	32 (43.2)	0.741
Nitrate	7 (9.5)	7 (9.5)	1

Legend: ACEI – Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; AF – Atrial fibrillation; ASA – American Society of Anesthesiologists Physical Status Classification System; CAD – Coronary artery disease; CCB - Calcium Channel Blocker; CHF – Chronic heart failure; CKD: Chronic kidney disease (creatinine = 1.5 mg/dl); COPD – Chronic obstructive pulmonary disease; ND – Alterations on the neurologic examination during carotid clamping; PAD – Peripheral artery disease; Obesity – Body Mass Index >30kg/m2; TIA – Transient ischemic attack; ICA – internal carotid.

515 **Table 2**- Hemodynamic status during carotid endarterectomy procedure.
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Positive awake test	Control n=77 mmHg (50%)	ND n=77 mmHg (50%)	p-value
Surgery duration (min)	123.9±49.5	111.0±32.7	0.059
Clamping duration (min)	49.1±39.1	46.05±23.25	0.558
Nursery			
Diastolic	60.5±24.7	69.8±14.3	0.394
Systolic	134.6±25.5	143.2±29.0	0.063
Before anesthetic induction			
SBP min	153,6±37.2	158.0±36.4	0.469
DBP min	73.6±18.7	74.9±19.7	0.661
MAP min	106.2±24.7	106.8±25.5	0.881
SBP max	169.8±36.7	176.2±33.2	0.262
DBP max	86.7±22.1	86.2±17.8	0.872
MAP max	118.3±23.7	119.6±21.7	0.722
HR max (bpm)	73.4±18,6	77.0±21.6	0.273
HR min (bpm)	63.8±12.2	65.0±13.3	0.589
$SatO_2$ min (%)	93.9±10.5	93.9±5.5	0.940
Pre-clamping			
SBP max	177.2±40.7	183.6±32.3	0.287
DBP max	89.8±32.2	85.5±24.0	0.355
MAP max	125.3±34.2	123.8±26.0	0.769
SBP min	141.8±41.2	154.6±31.8	**0.035**
DBP min	65.4±18.5	67.7±13.5	0.386
MAP min	94.8±26.5	100.8±20.5	0.124
Pulse pressure	87.4±32.5	98.1±24.0	**0.023**
HR max (bpm)	75.7±17.4	74.7±16.1	0.719
HR min (bpm)	63.3±14.0	64.3±13.1	0.678
$SatO_2$ min (%)	95.1±7.3	95.6±4.6	0.616

Post-clamping minute 1			
SBP	158.3±40.0	171.0±29.7	**0.022**
MAP	101.8±23.7	107.0±18.8	0.140
DBP	73.6±20.3	75.0±16.3	0.635
Pulse pressure	84.7±27.3	96.0±23.1	**0.007**
HR (bpm)	70.7±16.4	70.6±16.0	0.965
$SatO_2$ (%)	97.63±2.8	97.6±2.8	0.957
Post-clamping minute 3			
SBP	158.6±34.2	172.5±31.4	**0.011**
MAP	101.1±20.2	108.3±19.7	**0.028**
DBP	72.3±15.6	76.2±16.3	0.137
Pulse Pressure	86.3±25.6	96.3±23.1	**0.014**
HR (bpm)	70.3±15.0	71.1±15.8	0.762
$SatO_2$ (%)	97.4±3.2	97.7±2.6	0.469
Post-clamping minute 10			
SBP	158.6±34.2	169.0±33.6	**0.025**
MAP	101.1±20.2	105.0±19.4	0.131
DBP	72.3±15.6	72.9±14.6	0.635
Pulse pressure	84.8±24.9	96.1±25.4	**0.007**
HR (bpm)	70.3±15.0	70.0±15.6	0.861
$SatO_2$ (%)	97.4±3.2	97.6±1.8	0.576
Post-clamping nadir			
SBP min	142.6±33.7	153.4±29.2	**0.042**
MAP min	94.1±21.1	98.5±20.3	0.810
DBP min	65.1±14.9	65.7±13.7	0.810
Pulse pressure	77.5±25.4	87.7±21.0	**0.001**
HR min (bpm)	63.7±14.0	63.5±15.1	0.923
$SatO_2$ min (%)	95.5±5.4	94.3±11.4	0.400
Post-clamping Zenith			

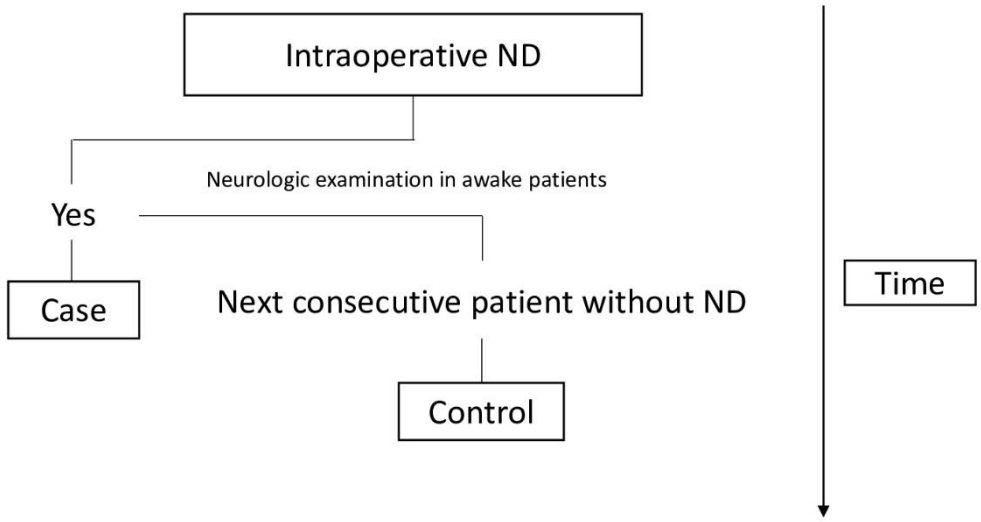
SBP max	173.0±33.7	188.8±34.1	**0.006**
MAP max	116.8±25.0	123.3±22.9	0.103
DBP max	82.7±22.6	83.3±17.6	0.850
Pulse pressure	90.3±26.0	105.5±23.1	**0.001**
HR max	78.6±26.0	77.3±19.1	0.731

Legend: ND – Alterations on the neurologic examination during carotid clamping SBP – Systolic blood pressure; DBP – Diastolic blood pressure; HR – Heart rate; MAP – Mean arterial pressure; ND: - intraoperative neurologic deficit; Nursery – first blood pressure measurement in the nursery; Pos Clamp min 1 – blood pressure 60 seconds after carotid clamping; Pos Clamp min 3 - blood pressure 180 seconds after carotid clamping; Pos Clamp min 10 - blood pressure 600 seconds after carotid clamping; Pre-anesthesia – first blood pressure measurement after arterial catheterization and before anesthetic administration; Pre clamp – blood pressure measurement 3 minutes before carotid clamping; SBP - Systolic Blood pressure; $SatO_2$ – Peripheral Oxygen Saturation

Table 3 – BP variation between pre-clamping and different post-clamping times.

Positive awake test	Control n=77 mmHg (50%)	ND n=77 mmHg (50%)	p-value
Systolic			
Δ pre-clamp _ post-clamp min1	19.79±24.01	11.947±16.19	**0.021**
Δ pre-clamp _ post-clamp min3	19.42±26.78	11.12±21.83	**0.039**
Δ pre-clamp _ post-clamp min10	21.55±31.97	14.62±30.48	0.178
Δ pre-clamp _ post-clamp zenith	5.6±23.6	-5.7±23.9	**0.005**
Diastolic			
Δ pre-clamp _ post-clamp min1	16.72±28.2	10.3±20.8	0.119
Δ pre-clamp _ post-clamp min3	18.0±28.8	9.3±20.4	**0.035**
Δ pre-clamp _ post-clamp min10	18.6±28.8	12.6±23.0	0.160
Δ pre-clamp _ post-clamp zenith	7.9±25.7	1.4±22.3	0.106
Shunt	0	17 (22.1)	0.001

Legend: BP – Blood pressure; ND – Alterations on the neurologic examination during carotid clamping; Pos Clamp min 1 – blood pressure 60 seconds after carotid clamping; Pos Clamp min 3 - blood pressure 180 seconds after carotid clamping; Pos Clamp min 10 - blood pressure 600 seconds after carotid clamping; Pre clamp – blood pressure measurement 3 minutes before carotid clamping.



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537 **Figure 1.** – Summary of the study design

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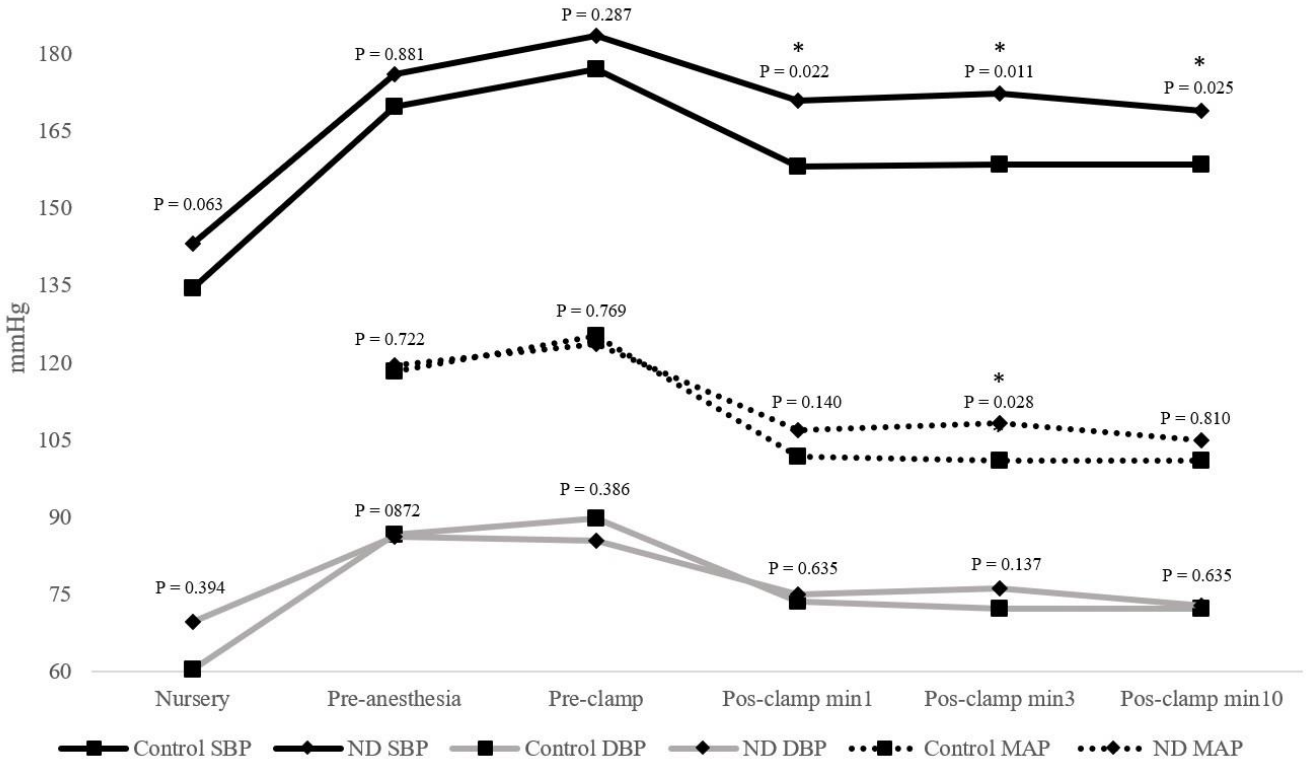

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542 **Figure 2.** – Graphical representation of blood pressure values in all time points

Anexos

A) STROBE Statement—Checklist of items that should be included in reports of case-control studies

B) Normas de publicação da revista: Annals of Vascular Surgery

C) Autorização por parte da Comissão de Ética

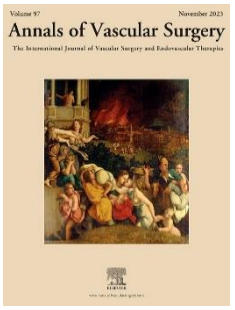
A) STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7
		(*b*) For matched studies, give matching criteria and the number of controls per case	7-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	7-10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how matching of cases and controls was addressed	10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	11-13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	11-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	11-13

Main results		16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
			(*b*) Report category boundaries when continuous variables were categorized	11-13
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		11-13
Discussion				
Key results	18	Summarise key results with reference to study objectives		14-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results		16
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		3

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.



B) Guide for authors

Preparation

Peer review

This journal operates a single anonymized review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of one independent expert reviewer to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. Editors are not involved in decisions about papers which they have written themselves or have been written by family members or colleagues or which relate to products or services in which the editor has an interest. Any such submission is subject to all of the journal's usual procedures, with peer review handled independently of the relevant editor and their research groups. More information on types of peer review.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Theory/calculation

A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

• **Title**. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• **Author names and affiliations.** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.
• **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Highlights

Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Structured abstract

A structured abstract, by means of appropriate headings, should provide the context or background for the research and should state its purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations.

Abbreviations

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[5] Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13 March 2003].
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30 de Outubro de 2018

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

Aprovado. Ao CA.

(Prof.ª Doutora Ana Azevedo)

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Nome do Investigador Principal:

João Rocha Neves

Título da Investigação:

Défices neurológicos após clampagem Carotídea durante a endarterectomia carotídea sob anestesia loco-regional, estudo de preditores de prognóstico pré, intra e pos-operatório.

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Com os melhores cumprimentos.

O Investigador/ Promotor

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