Perioperative stress response to carotid endarterectomy: The impact of anesthetic modality

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Objective: **Surgery for extracranial carotid artery disease has been challenged by carotid angioplasty stenting because the latter is less invasive and avoids surgical trauma. In fact, the magnitude of the perioperative stress response evoked by carotid endarterectomy (CEA) has never been evaluated. Our aim was to determine the degree of surgical trauma caused by CEA and to define differences related to the use of locoregional or general anesthesia.**

Methods: **We prospectively studied 113 consecutive CEAs performed on 109 patients admitted at a community institutional center. Patients were stratified for demographics and risk factors and operated on under locoregional (LA) or general anesthesia (GA) depending on both the surgeon preference and patient's compliance. Selective carotid shunting was performed for patients who manifested neurologic deficits under LA or had stump pressure values ≤30 mm Hg under GA. Markers of the stress response, including cortisol, adrenocorticotropic hormone, prolactin, and C-reactive protein, were measured intraoperatively, before and after carotid artery cross-clamping (CACC), and postoperatively up to the third day after surgery. Hemodynamic variability was assessed during surgery and for 24 hours postoperatively. Operative times were also measured. Surgeons were considered as independent variables for stress response. Statistics were run by means of nonparametric tests and univariate and multivariate analysis with a linear regression model.**

Results: **CEA was performed under GA in 63 cases (55.8%) and under LA in 50 (44.2%). The two groups were comparable in terms of demographics and risk factors. Intraoperatively, cortisol and adrenocorticotropic hormone levels were significantly higher in the LA group (both $P < .001$). CACC increased the intraoperative cortisol levels in both the GA ($P = .019$) and the LA groups ($P = .006$). However, in patients who underwent carotid shunting, this effect was abolished (GA group, $P = .779$; LA group, $P = 1.0$). During the early postoperative period there was no difference between the two groups. On postoperative day 1 the stress response was abolished in both groups. Prolactin levels increased intraoperatively in both the LA and GA groups and returned within preoperative values on postoperative day 1. Prolactin levels were higher in the GA group ($P = .003$ intraoperatively and $P < .001$ postoperatively). C-reactive protein significantly increased in both GA and LA groups on postoperative days 1 and 2 and started to decrease on day 3 with no differences between the two groups at any time. Hemodynamic variability and considered risk factors including individual surgeon were not significant variables. Gender-related differences were found only in prolactin secretion. The length of surgery had an impact for procedures that lasted >120 minutes. Three patients experienced an intraoperative neurologic event and had higher post-CACC cortisol values as compared to asymptomatic patients.**

Conclusions: **Intraoperative surgical stress was higher under LA and was blunted by carotid shunting under both LA and GA. Within 2 hours after surgery the anesthetic modality no longer had any impact on surgical trauma. The stress response to CEA, regardless of the type of anesthesia, was abolished within 24 hours. Intraoperative stress response, namely hypercortisolemia, directly correlated with subclinical and clinical cerebral hypoperfusion/ischemia during CACC. Hence, attenuation of the stress response to CEA might decrease the incidence of cerebral ischemic events. (J Vasc Surg 2004;39:1295-1304.)**

Surgical trauma elicits a complex biologic reaction known as the hypermetabolic stress response that is mediated by the hypothalamic-pituitary-adrenal (HPA) axis through activation of the autonomic nervous system.[1] This reaction involves hemodynamic, metabolic, inflammatory, and immunologic changes aimed at maintaining homeostasis and assisting recovery. However, surgery-related metabolic and endocrine derangements have the potential for adverse systemic effects, including increased myocardial oxygen consumption, increased catabolism, and impaired immune function, and have been associated with poor postoperative course and clinical outcome.[2,3]

Because the degree of surgical stress is related to the magnitude of the operation, the anesthetic technique, and the length of the procedure,[4-6] perioperative and postoperative stress levels have been used to compare surgical

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techniques, such as endovascular versus conventional abdominal aortic aneurysm repair,[4,5] or to evaluate the impact of anesthetic modalities, such as the use of epidural with general anesthesia during aortocoronary bypass or abdominal aortic surgery.[7,8]

Carotid endarterectomy (CEA) has been proved to be safe and effective to prevent the risk of stroke in patients with symptomatic or asymptomatic but high-grade carotid stenosis.[9,10] However, the excellent results of randomized trials might not be applicable to the total population undergoing CEA, particularly to patients with serious cardiopulmonary or renal disease who do not meet the inclusion criteria of those trials. In these patients, ill-defined as at high risk, carotid artery stenting has been proposed as an alternative to CEA because it is less invasive and avoids surgical trauma. In fact, neither the degree of perioperative stress response to CEA nor the impact of locoregional (LA) versus general anesthesia (GA) has ever been thoroughly investigated in the endless debate regarding the optimal anesthetic modality for CEA.

The aim of this study was to prospectively assess the surgical stress related to CEA, to evaluate the impact of the anesthetic modality, and to investigate the possible relationship between stress response and hemodynamic instability during CEA.

METHODS

Setting and population. Between February 2002 and May 2003, 113 consecutive CEAs performed on 109 patients admitted at the I.D.I.-IRCCS Hospital, a community institutional center, were included in the prospective study. Four patients were submitted to staged bilateral CEA. Each surgical intervention was considered as an independent procedure, and patient demographics were handled accordingly. Patients were enrolled after informed consent was obtained. The protocol of the study was approved by the Institutional Review Board.

Patients who had previously undergone ipsilateral neck surgery or needed LA or GA for medical reasons were excluded.

Patients were evaluated for demographic variables, indication for surgery, distribution of the carotid lesion, and associated vascular diseases. Patients were also stratified by preoperative risk factors including diabetes, tobacco use, hypertension, and hyperlipidemia by using a simplified grading system according to the suggested standards for reports dealing with cerebrovascular disease.[11] Preoperative cardiac assessment, including history, clinical examination, chest x-ray, standard 12-lead electrocardiogram (EKG), and laboratory tests, was performed in all cases. The resulting profile allowed for each patient the calculation of perioperative cardiac risk according to the Goldman's Revised Cardiac Risk Index (RCRI).[12]

We defined as patients at high risk those with one or more of the following preoperative risk factors: advanced age (>80 years), high cardiac risk (RCRI class III and IV; Table I), insulin-controlled diabetes mellitus (grade 2-3; Table I), poorly controlled hypertension (grade 3, Table I), and contralateral carotid occlusion.[13,14] All patients underwent carotid duplex scanning and confirmatory magnetic resonance angiography before surgery.

Surgical and anesthetic methods. CEAs were performed with both the conventional and eversion techniques according to surgeon preference. Distal intimal end point tacking sutures were used frequently. Polytetrafluoroethylene or Dacron patching was performed selectively in patients with a small distal internal carotid artery. Surgical procedures were performed by 14 surgeons with different surgical experience. Hence, for data analysis operators were divided into three groups on the basis of professional experience and analyzed as independent variables for the evaluation of the degree of stress response (Table II, online only).

The choice of anesthetic modality was determined by both the surgeon's preference and patient's compliance. LA consisted of both deep and superficial cervical plexus block supplemented with continuous intravenous 0.04 μg/kg/min remifentanil infusion as previously described in detail.[15] Cerebral perfusion was monitored with mental status evaluation. Shunting was performed for patients who manifested speech deficits, significant increases in agitation or confusion, contralateral arm weakness, seizure, or unresponsiveness. GA was induced with intravenous administration of thiopental or propofol, and tracheal intubation was facilitated with vecuronium bromide. Anesthesia was maintained with both sevoflurane and an equal mixture of oxygen and nitrous oxide by using a rebreathing system and small increments of fentanyl. The concentrations of inhaled and exhaled gases, including end-tidal CO_2 tension, were monitored. Cerebral perfusion was monitored by means of stump pressure measurement with the value of ≤30 mm Hg as the cutoff for shunting.

In both groups intraoperative monitoring also included electrocardiography, pulse oximetry, and invasive blood pressure measured from the contralateral radial artery. Patients were observed in a postanesthesia care unit for 24 hours after surgery, were sent to the surgical floor on postoperative day 1, and were discharged on postoperative day 3.

Measure of stress response. The levels of the following markers of the stress response were measured: cortisol, adrenocorticotropic hormone (ACTH), prolactin, and C-reactive protein (CRP). We decided not to measure plasma catecholamines because previous studies investigating catecholamine production during CEA failed to show any significant differences between baseline and postclamping and postoperative levels as determined in peripheral blood samples.[16] Moreover, significant pitfalls in catecholamine determination have been reported particularly in comparison to the reliability of cortisol levels.[2,17]

Venous blood samples for the measurement of cortisol, ACTH, and prolactin were taken at selected time points as follows: on the morning of surgery at the surgical floor (T0); during surgery, right before carotid artery cross-clamping (CACC) (T1), as a measure of surgical trauma

Table I. Comparison of demographics and risk factors of patients operated on under local and general anesthesia

	LA		*GA*		
	n	%	*n*	%	P*
Overall	50	44.2	63	55.8	
Gender					
Male	35	47.9	38	52.1	
Female	15	37.5	25	62.5	.192
Age (y)					
≤69	13	40.6	19	59.4	
70–74	12	40.0	18	60.0	
75–79	17	47.2	19	52.8	
80+	8	53.3	7	46.7	.796
Indication for surgery					
Transient ischemic attack	13	52.0	12	48.0	
Stroke	3	60.0	2	40.0	
Asymptomatic	34	41.0	49	59.0	.478
Distribution of the lesion					
Unilateral	22	39.3	34	60.7	
Bilateral	24	49.0	25	51.0	
Stenosis + contralateral obstruction	4	50.0	4	50.0	.574
Renovascular hypertension	3	50.0	3	50.0	.545
PAD	22	44.9	27	55.1	.527
Abdominal aortic aneurysm	3	33.3	6	66.7	.373
Revised Cardiac Risk Index					
I (0.5 %)†	18	47.4	20	52.6	
II (1.3 %)†	24	42.1	33	57.9	
III (3.6 %)†	6	37.5	10	62.5	
IV (9.1 %)†	2	100.0	0	0.0	.381
Type of intervention					
Traditional	45	43.3	59	56.7	
Eversion	5	55.6	4	44.4	.356
Shunt	6	35.3	11	64.7	.296
Hypertension					
0 (Diastolic, <90 mm Hg)	10	58.8	7	41.2	
1 (Easily controlled, single drug)	15	48.4	16	51.6	
2 (Requires two drugs)	20	43.5	26	56.5	
3 (> Two drugs or uncontrolled)	5	26.3	14	73.7	.244
Diabetes					
0 (None)	36	43.4	47	56.6	
1 (Adult onset, no insulin)	10	45.5	12	54.5	
2 (Adult onset, insulin controlled)	2	33.3	4	66.7	
3 (Juvenile onset)	2	100.0	0	0.0	.416
Smoking					
0 (None or abstinence >10 y)	20	45.5	24	54.5	
1 (None currently, abstinence 1–10 y)	21	50.0	21	50.0	
2 (Current, >one pack/day or abstinence >1 y)	4	23.5	13	76.5	
3 (Current ≥1 pack/day)	5	50.0	5	50.0	.298
Hyperlipidemia					
0 (Cholesterol and triglycerides within normal limits for age)	31	47.0	35	53.0	
1 (Mild elevation, diet controlled)	7	53.8	6	46.2	
2 (Types II, III, or IV requiring strict diet control)	1	33.3	2	66.7	
3 (Require drug control)	11	35.5	20	64.5	.616

*χ^2 statistics.
†Major cardiac complication rates.

related to the exposure and isolation of the common, external, and internal carotid arteries; during surgery, 15 minutes after CACC (T2), as an estimate of the possible further increase of stress response due to the hemodynamic adjustments after CACC; 2 hours after the end of the surgical procedure (ie, the completion of the skin suture) (T3); and on the morning on the first (T4), second (T5), and third (T6) postoperative days as the stress response persists for 3 to 5 days after surgery.[18] High-sensitivity CRP (hs-CRP) was measured at T0, T4, T5, and T6 only, because its levels might increase within 4 to 8 hours after an acute event.

Venous blood samples were analyzed within 1 hour after collection. Cortisol (normal range, 5-25 μg/dL) and ACTH (normal range, 10-50 pg/mL) were determined with an immunoassay based on chemiluminescent enzyme-labeled immunometric reaction (Immulite System; Diagnostic Products Corporation, Los Angeles, Calif). Prolactin levels (normal ranges: male, 5-15 ng/mL; female, 5-25 ng/mL) were measured by means of a two-step Chemiluminescent Microparticle Immunoassay (Chemiflex Architect System; Abbott Laboratories, Abbott Park, Ill). Hs-CRP was assayed by an immunonephelometric assay that uses polystyrene particles coated with mouse monoclonal antibodies to CRP (BN II Systems; Dade Behring, Deerfield, Ill). This method is standardized against the IFCC/BCR/CAP reference preparation, designed to measure CRP concentrations within an overall range of approximately 0.175 to 1100 mg/L with expected values for healthy individuals of ≤3 mg/L. All assays were performed according to the manufacturers' recommendations.

Hemodynamic and cardiologic evaluation. Variability of systolic blood pressure (SBP) and heart rate (HR) and any use of supplemental vasoactive medication were monitored and registered intraoperatively before, during, and after clamping and postoperatively during the 24 hours after surgery. SBP and HR values were collected and registered every 5 minutes by using a multiparametric monitor (Datex-Engstrom, Helsinki, Finland). Quantification of hemodynamic variability was calculated according to Sternbach et al[19] as a fraction of the preoperative baseline value and expressed as a percentage according to the following equation: (HR or SBP max − HR or SBP min)/HR or SBP baseline × 100.

Postoperative cardiologic surveillance included also standard 12-lead EKG, serum creatine kinase and isoforms, lactate dehydrogenase, and troponin I levels measured 2 hours after the end of the surgical procedure, on the morning of the first, second, and third postoperative days, and whenever clinically indicated. The quantitative determination of serum troponin I levels was carried out by a commercial kit (VIDAS Troponin I; Biomerieux, Marcy-l'Etoile, France) based on the enzyme-linked fluorescent assay technique. According to the receiver operating characteristic (ROC) curve provided by the manufacturer, the cutoff value of 0.5 ng/mL was established to define the test as positive with 99% sensitivity and 94.2% specificity for the detection of myocardial ischemic damage. The postoperative EKG tracings were analyzed by the consultant cardiologist and compared with the baseline to detect the development of arrhythmias, conduction abnormalities, and new ST segment–T wave abnormalities. To guarantee that minor discrepancies in the placement of precordial leads would not interfere with the serial comparison of ST-T morphology, at baseline EKG a permanent felt-tip pen was used to mark placement of precordial leads on the patient's chest. Tracings classified abnormal for the occurrence of ST segment/T wave change, not present at baseline and suggestive of myocardial ischemia, were routinely followed by cardiologic consult and serum enzymes determination in the postanesthesia care unit.

Clinical evaluation. Morbidity and mortality were recorded. Myocardial infarction was suggested by electrocardiographic changes and confirmed by elevation of cardiac enzymes, regardless of symptoms. Neurologic events were defined as transient ischemic attacks for deficits that resolved within 24 hours after surgery and strokes for any new or worsening neurologic deficits that lasted for more than 24 hours, with or without computed tomographic scan changes. Operative times were also measured and registered including the duration of the surgical exposure of the carotid vessels, the duration of clamping, and the length of the whole surgical procedure.

Statistical analysis. To determine the sample size by means of the *t* test, we used the tables published by Machin and Campbell[20]; hypothesizing that the two means are 0.5 standard deviation apart (setting $\alpha = 0.05$ [one-sided, under the assumption that local anesthesia cannot induce lower stress levels than general anesthesia] and $1\text{-}\beta = 0.8$), we calculated that 50 patients per group were needed. We increased this sample size by approximately 10% to account for the loss of power that we would have incurred when using a nonparametric test.

Demographic and clinical characteristics of patients operated on under GA and LA were compared by testing the homogeneity of groups with the χ^2 statistics. Differences between levels of stress markers in GA and LA at each time point considered were tested by using the Mann-Whitney test. For each stress marker, separately for GA and LA, we tested the difference between pre-CACC and post-CACC mean values by using the Wilcoxon test for paired observations. For both GA and LA, we then investigated the relationship between post-CACC and postoperative stress marker levels and gender, age (two groups, cutoff at 80 years), duration of surgery, surgeon (three groups, depending on professional experience), hypertension, diabetes, hyperlipidemia, tobacco use, RCRI, contralateral carotid occlusion, and hemodynamic variability (tertiles). The Mann-Whitney test was performed for categorical variables with two classes and the Kruskal-Wallis test for variables with more than two classes. Spearman correlation was used to investigate the link between stress markers and duration of surgery. For post-CACC and postoperative levels of cortisol, ACTH, and prolactin we also performed a linear regression model. Independent variables were age, gender, type of anesthesia, duration of surgery (for postoperative levels) or duration of pre-CACC and CACC (for post-CACC levels), surgeon, and hemodynamic variability (regarding the period in analysis). The statistics concerning ACTH and prolactin were performed by using the natural logarithm of the values because of skewness in the distributions of the values of both measures. All analyses were run on the SPSS/PC+ version 9.0 statistical package (SPSS Inc, Chicago, Ill).

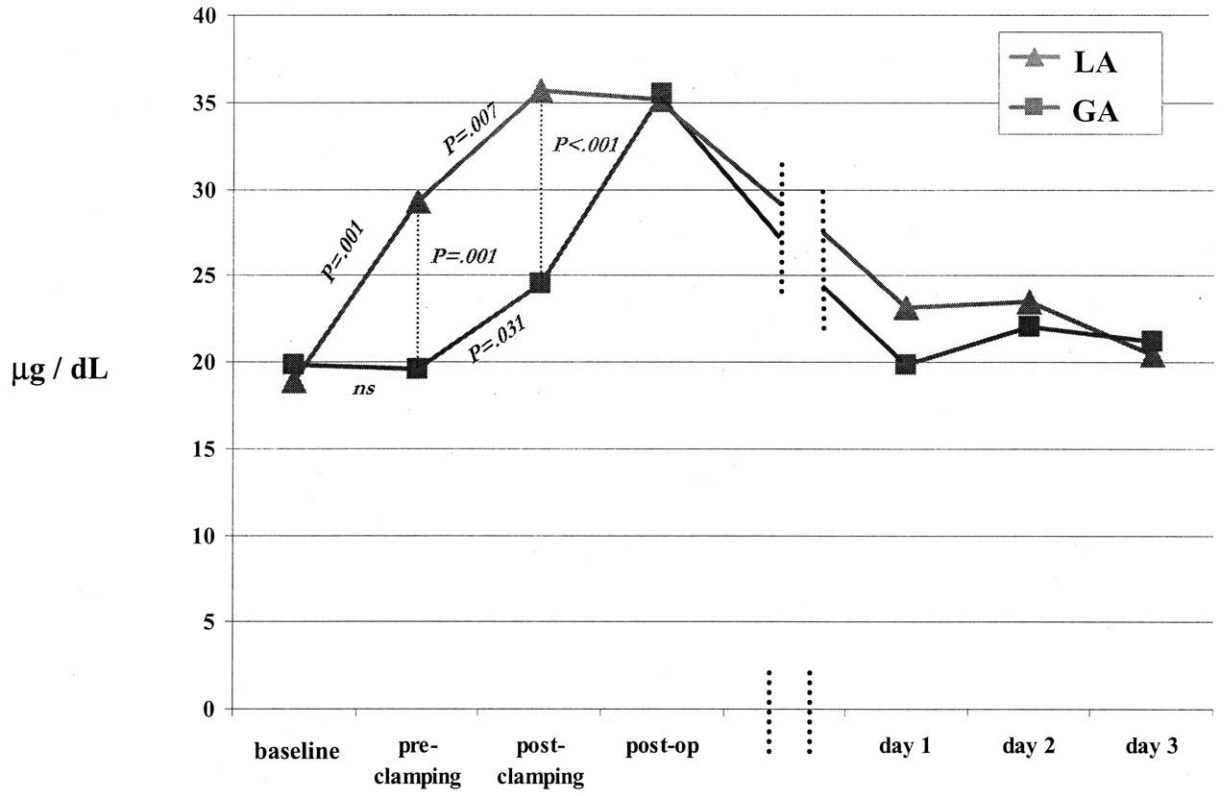

Fig 1. Baseline, intraoperative, and postoperative cortisol mean levels.

RESULTS

Comparison of demographics and risk factors of patients operated on under GA and LA showed no statistically significant differences for any of the considered variables (Table I). The four patients submitted to staged bilateral CEA were operated under the same anesthetic modality in both procedures (3 patients under GA and 1 patient under LA). A total of 88 patients were classified as at high risk, 33 (66%) in the LA group and 50 (79.4%) in the GA group, with no significant difference between the two groups ($P = .083$).

Mean values of cortisol, ACTH, prolactin, and hs-CRP for each time point considered separately for GA and LA are graphically presented in Figures 1 through 4. Only significant P values are shown.

Under GA, cortisol levels significantly started to increase after CACC to reach markedly high values in the early postoperative period. However, by the morning of postoperative day 1, cortisol values had returned to baseline. As expected, ACTH levels followed the same pattern. Under LA, intraoperative values of cortisol and ACTH rapidly and significantly increased as compared to baseline and GA levels. However, in the early postoperative period the hormonal concentrations started to rapidly decrease and did not differ from those measured after GA. Of note, by the morning of postoperative day 1, the stress response was completely abolished also in the LA group.

In both GA and LA groups, CACC resulted in an increase of cortisol and ACTH levels that directly correlated with cerebral blood flow. In fact, in patients who did not undergo carotid shunting, post-CACC cortisol levels were significantly higher as compared to pre-CACC values (GA group, 26.1 ± 14.2 vs 20.1 ± 11.5 μg/dL, $P = .019$; LA group, 35.7 ± 12.8 vs 28.8 ± 15.2 μg/dL, $P = .006$). On the contrary, in patients who underwent carotid shunting, 11 (17.5%) in the GA group and 6 (12%) in the LA group, no hormonal increase due to CACC was observed (GA group, 16.3 ± 14.0 vs 16.4 ± 15.1, $P = .779$; LA group, 33.0 ± 20.0 vs 31.6 ± 17.7 μg/dL, $P = 1.0$). Also post-CACC ACTH levels were not increased in patients who underwent carotid shunting under GA ($P = .893$) as compared to patients without shunting ($P = .07$), whereas this difference between the two subgroups was not observed in patients under LA probably because of the high absolute hormonal levels. No correlation was found between cortisol and ACTH changes and hemodynamic variability registered during CACC.

Prolactin levels increased significantly during surgery in both the GA and LA groups and then decreased postoperatively to reach baseline on postoperative day 1 as for cortisol and ACTH levels. However, prolactin levels were higher in the GA group during surgery and in the early postoperative period. In relation to hs-CRP levels, no difference was observed between the two groups at any time.

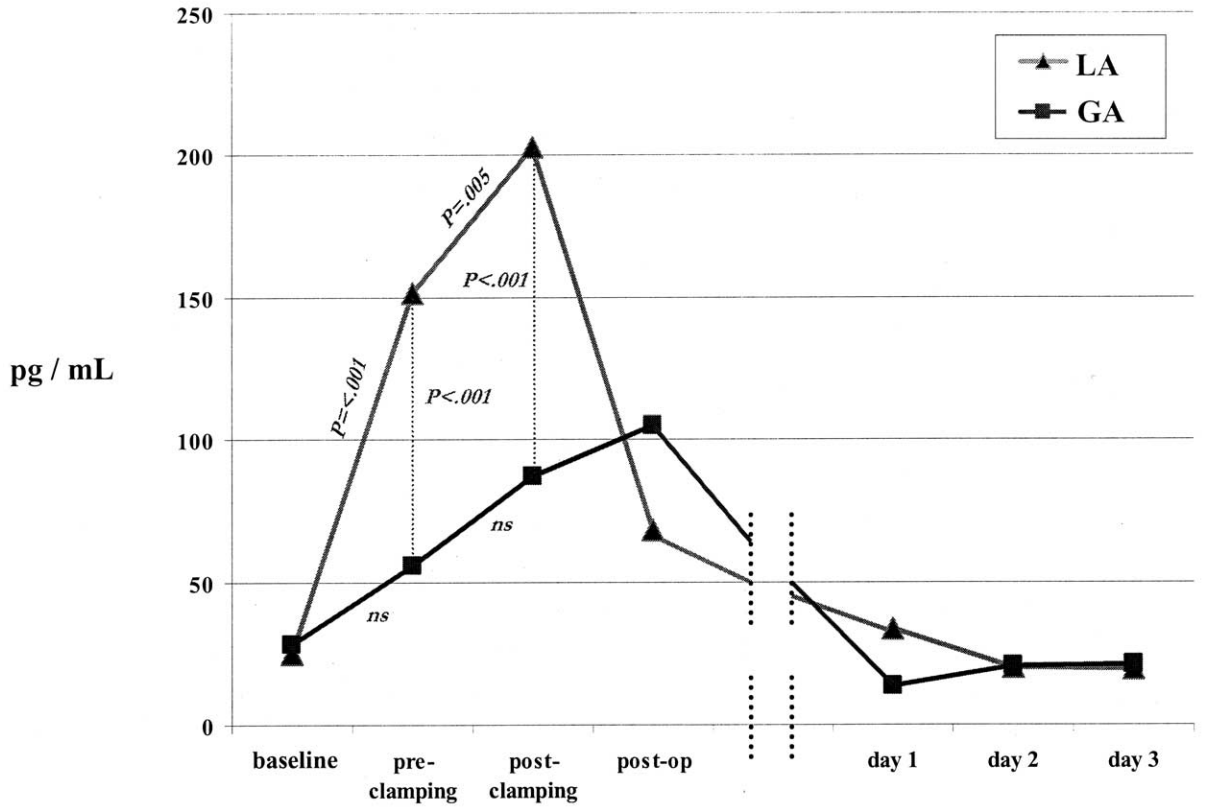

Fig 2. Baseline, intraoperative, and postoperative ACTH mean levels.

Univariate analysis of post-CACC and postoperative stress marker values showed a gender-related difference for prolactin levels with higher concentrations in women both in the GA ($P < .001$) and in the LA groups ($P < .001$). No significant influence of risk factors, including age, class of cardiac risk, hypertension, diabetes, hyperlipidemia, tobacco use, and contralateral carotid occlusion, was observed. Hemodynamic instability and individual surgeon were not significant variables. When operators were divided into three groups based on surgical experience, no direct correlation was found with postoperative stress either. The length of surgery was inversely correlated with surgical experience but had an impact only for procedures that exceeded 120 minutes of duration.

In a linear regression analysis post-CACC levels of cortisol and ACTH remained significantly higher in LA group than in GA group, also after adjusting on the other variables. No difference was observed in the postoperative values. Both post-CACC and postoperative levels of prolactin were significantly higher in women than in men. Postoperative prolactin level was also higher in GA group than in LA group. No effect of any of the considered variables was observed in hs-CPR values.

Hemodynamic variability did not significantly differ between the LA and GA groups (Table III). Patients submitted to eversion CEA did not show any increased postoperative hemodynamic instability as compared to those operated on with the standard technique.

There were no deaths in either group. Two patients, one of each anesthetic group, experienced an intraoperative transient ischemic attack, and one patient operated under LA had an intraoperative stroke. All the symptomatic patients had higher post-CACC cortisol values (47, 34, and 59 μg/dL, respectively), as compared to asymptomatic patients (mean value, 28.8 ± 14.8 μg/dL). Two patients, one of each anesthetic group, had a myocardial infarction on postoperative days 2 and 3, respectively. No significant increase of hormonal levels was detected in these patients.

DISCUSSION

Endocrine and sympathetic nervous system responses to surgical trauma have been correlated with perioperative and postoperative course and clinical outcome.[2,3] In particular, surgical stress has been associated to the development of morbid cardiac events, both in cardiac[21] and noncardiac surgery including CEA,[18] and attenuation of stress response has been reported to blunt postoperative myocardial ischemia effectively.[22] Furthermore, activation of the HPA axis in reaction to various types of stress, namely hypercortisolemia due to the well-known neurotoxicity of this hormone,[23] might exacerbate hypoxic injury to neurons during acute cerebral ischemia and has been closely

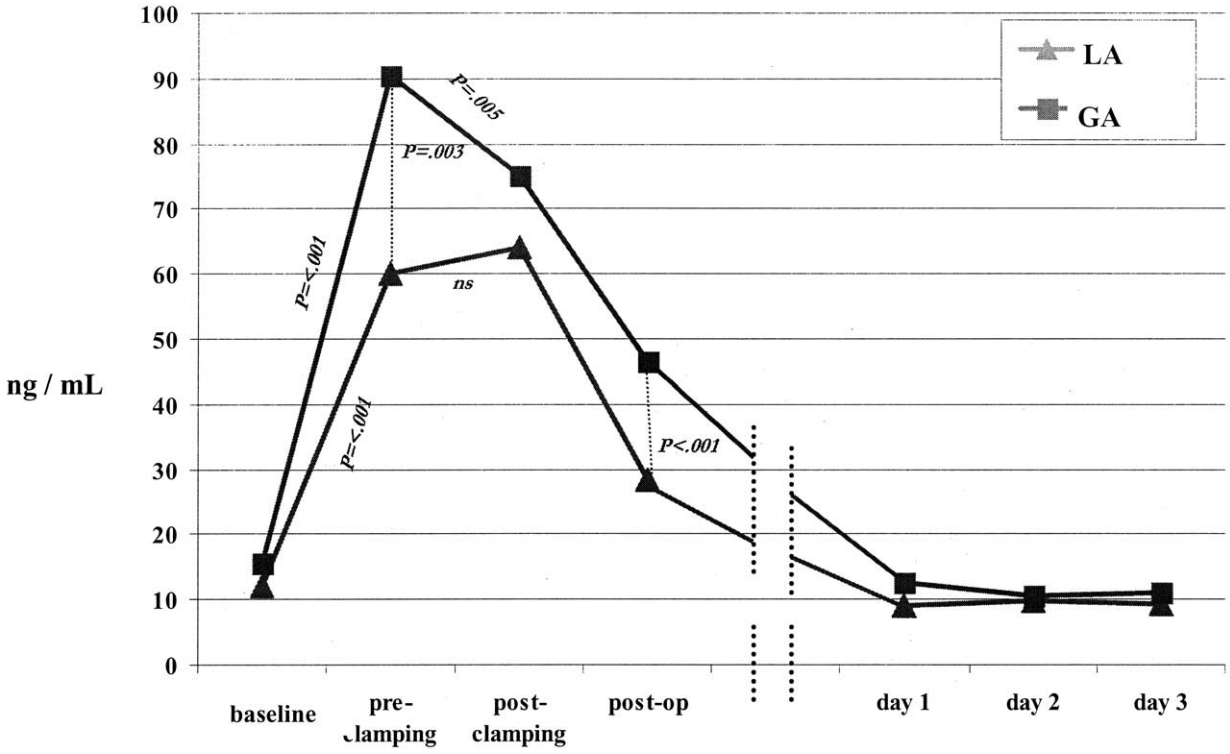

Fig 3. Baseline, intraoperative, and postoperative prolactin mean levels.

associated with cognitive disturbances and extensive motor impairment.[24] Also, a massive neuroendocrine response has been observed after acute stroke, with increased plasma levels of cortisol being an aggravating factor associated with a high mortality rate and poor functional outcome.[25]

We aimed to assess the stress response to CEA by considering the anesthetic modality as an independent variable. Whether to perform CEA under GA or LA anesthesia has been a matter of debate for years, and no throughout conclusions have been drawn thus far in particular for those patients thought to be at increased risk of complications after surgery.

LA appears to be associated with a lower morbidity and mortality even in patients considered at high risk.[13] However, LA might expose patients to an undue stress and pain during the operation, resulting in an increased risk of myocardial ischemia or in a hurried and technically poor surgical procedure.[26]

In our study, intraoperatively GA modulated but did not abolish the stress response as measured by cortisol level. During the early postoperative period a sharp increase of this hormone was detected as a result of the end of anesthesia, a finding consistent with what has been previously described in patients undergoing cardiac surgery[27] and in patients operated on under propofol-, fentanyl-, and sevoflurane-based anesthetic regimens.[28,29] As expected, ACTH levels showed the same trend. On the contrary, under LA intraoperative values of cortisol and ACTH dramatically increased as compared to baseline and GA levels. However, as early as 2 hours after the end of the surgical procedure hormonal concentrations did not differ from those measured after GA.

CACC increased the intraoperative stress response as measured by cortisol levels in both the GA and the LA groups, but its effect was blunted by carotid shunting, suggesting a protective role of the maintenance of direct cerebral perfusion. Furthermore, the patients who experienced an intraoperative neurologic event had higher cortisol levels after CACC as compared to asymptomatic patients.

Our findings are consistent with the evidence of a synergic detrimental effect on the brain of adrenocortical stress hormones and acute ischemia.[23] In fact, CACC results in a short-term cerebral hypoperfusion and/or an impairment of the blood-brain barrier,[30] activating a cerebral inflammatory and metabolic response.[31] It rarely causes a perioperative stroke,[32] but it has been associated with subclinical neurocognitive declines[33] and might also account for asymptomatic cerebral infarcts after CEA.[31] Accordingly, we believe that blunting the stress response to CEA and particularly during CACC by either technical or pharmacologic interventions might improve cerebral tolerance to clamping ischemia and prevent its sequelae.

Postoperatively, within 24 hours after surgery hormonal concentrations returned to baseline values. Because the reaction to surgical trauma persists for 3 to 5 days after

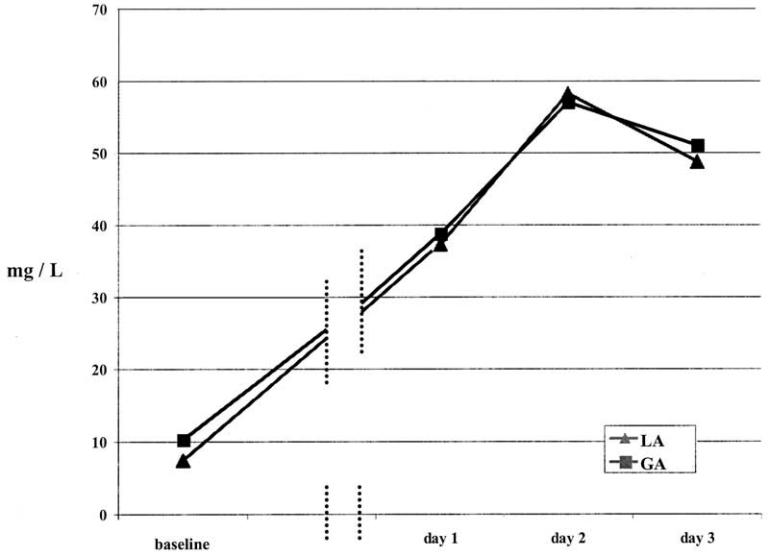

Fig 4. Baseline and postoperative CRP mean levels.

Table III. SBP and HR variability

	LA	*GA*	P
SBP variability (%)			
Pre-clamping	33.6 ± 19.7	33.8 ± 22.4	.17
Clamping	26.0 ± 19.7	26.6 ± 20.2	.924
Post-clamping	24.7 ± 18.7	24.4 ± 19.1	.183
Postoperative	32.1 ± 11.4	31.9 ± 12.5	.856
HR variability (%)			
Pre-clamping	28.6 ± 29.5	23 ± 16.2	.263
Clamping	17.9 ± 13.3	14.4 ± 12	.045
Post-clamping	19.4 ± 18.5	21.9 ± 18.2	.039
Postoperative	34.3 ± 21.5	36.1 ± 17.7	.282

surgery,[18] these results imply that CEA is a procedure with low surgical stress; therefore, in this respect, carotid stenting does not appear to offer such an advantage over surgery. Our data also show that in the early and late postoperative periods, during which there is the highest risk of complications, the anesthetic modality has no impact on surgical stress. Furthermore, the fact that the stress response is completely abolished by the first postoperative day supports the safety of early discharge of patients submitted to CEA.

Prolactin is probably a more sensitive indicator of surgical stress, because its levels were increased intraoperatively in both groups and then, as for cortisol and ACTH, started to decrease during the early postoperative period to return within preoperative values on postoperative day 1. In contrast to what was observed for the other hormones, prolactin levels were higher in the GA group, but this can be ascribed to a known pharmacologic effect of fentanyl and sevoflurane.[28,34]

Hs-CRP levels significantly increased in both GA and LA groups on postoperative days 1 and 2 and started to decrease on day 3. Because the recorded values at each time point were virtually identical in all patients regardless of the anesthetic modality, we believe that these high postoperative levels reflect a systemic inflammation and stress related to the surgical procedure. On the other hand, CRP provides also an indirect measure of a specific inflammatory process of the arterial wall that is suggested to stimulate smooth cell proliferation and neointimal growth.[35] In fact, high postoperative CRP levels after carotid artery stenting were found to be associated with short-term restenosis.[36] However, whether these findings might also apply to CEA has to be demonstrated by an adequate follow-up study.

Hemodynamic instability during CEA is a major concern for its implications in perioperative morbidity.[19] Among other factors, including surgical manipulation of the carotid sinus, hemodynamic variability is a consequence of stress response due to the increase of catecholamines, but in fact it might also casually contribute to the progression of the surgical stress. In our study we specifically addressed this issue and found no direct correlation between hemodynamic variability measured at different time points during and after CEA and stress levels regardless of the anesthetic regimen.

Postoperative stress response did not correlate with the surgeon's experience, and even though the small number of patients operated by each surgeon does not allow us to make any conclusion, our finding is consistent with the evidence that operative risks of CEA do not differ among surgeons.[37] On the other hand, surgeons with less experience had, in fact, longer operative times. However, the duration of surgery was found to be relevant only for CEA that lasted >120 minutes, a period of time that is usually far enough to successfully complete the procedure. Clinical stratification for cardiac risk and the degree of hypertension, diabetes, hyperlipidemia, and tobacco use were not predictive of postoperative stress response. Patient of age >80 years, who have increased plasma norepinephrine and cortisol responses to surgical stress,[38] did not show any significantly increased hormonal levels after CEA. The presence of contralateral carotid occlusion was not a significant variable either. Gender-related differences were found only in prolactin secretion, with female patients having higher levels as previously reported in both adults[39] and children.[40]

We recognize some limits of this study, including the lack of randomization for the type of anesthesia and the limited sample size. However, an accurate evaluation of the patient characteristics showed that the two anesthesia groups were comparable. Also, significant and straightforward differences in stress response were found between the GA and LA groups despite the relatively small number of patients. Furthermore, we showed that the surgeon preference did not affect our results, and regarding patient compliance, previous studies failed to demonstrate an impact of preoperative anxiety on postoperative stress response.[41] Finally, as for similar reports focusing on the impact of the anesthetic modality,[27-29] our conclusions might apply only to the specific anesthetic regimens used in our study. This is particularly true for LA, because we supplemented the cervical block with continuous infusion of remifentanil,[15] a potent μ-opioid agonist whose buffer effect on stress response when used at low doses during LA has yet to be determined.

Overall, our study shows that LA, as compared to GA, exposes patients to a higher stress during CEA. However, in the early and late postoperative periods the anesthetic modality no longer has an impact on surgical stress. Hemodynamic instability and considered clinical and anatomic risk factors did not turn out to be independent determinants of surgical stress.

Intraoperative stress response, namely hypercortisolemia, directly correlated with subclinical and clinical cerebral hypoperfusion/ischemia during CACC. In our opinion this finding has relevant therapeutic implications, because attenuation of the stress response to CEA might decrease the incidence of cerebral ischemic events. Further studies are necessary to prove this hypothesis and to investigate anesthetic, surgical, or pharmacologic interventions that have the potential of blunting the surgical trauma evoked by CEA.

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