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Factors associated with hypotension and bradycardia after carotid angioplasty and stenting

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Background: Acute procedurally induced hemodynamic depression can occur after carotid angioplasty and stenting (CAS). This study was performed to determine the frequency and risk factors for hypotension and bradycardia after the CAS procedure.

Methods: The study reviewed clinical variables and angiographic data of all patients undergoing elective CAS with neuroprotection during a recent 5-year period. Intravenous atropine was given selectively in cases of bradycardia (heart rate <60 beats/min or a decrease of >20 beats/min). We further defined hemodynamic depression as bradycardia or severe hypotension (systolic blood pressure fall >30 mm Hg). Frequency and potential risk factors for hemodynamic depression were analyzed by logistic regression.

Results: During the study period, 416 patients (99% male; mean age, 74 ± 11 years) underwent the CAS procedure. The median degree of stenosis was 93% (range, 60% to 99%). The frequencies of post-CAS hemodynamic depression include hypotension in 58 (14%), bradycardia in 112 (27%), or both in 21 (5%). All patients with bradycardia received intraprocedural atropine, and all heart rates returned to the baseline level. Persistent hypotension occurred in 45 patients (11%). Increased age was associated with CAS-induced bradycardia or hypotension. Adjusted risk factors associated with hemodynamic depression include age >78 years (odds ratio [OR], 5.25; 95% confidence interval [CI], 2.32 to 15.25; P = .01) and ejection fraction of <25% (OR, 3.25; 95% CI, 0.58 to 6.58; P = .02). CEA-related restenosis was associated with a reduced risk of hemodynamic depression (OR, 0.21; 95% CI, 0.12 to 0.69, P = .001). Persistent hypotension after CAS was associated with an increased risk of an adverse clinical event (44%, P = .001).

Conclusions: Hemodynamic depression, including hypotension and bradycardia, is frequent after CAS. However, CAS-induced hemodynamic depression is rare in patients with postendarterectomy stenosis. Patients with compromised ejection fraction and increased age are at a higher risk of presenting with CAS-induced hemodynamic instability, and persistent hypotension after CAS is associated with an increased postprocedural complication rate. (J Vasc Surg 2007; 46:846-54.)

Carotid angioplasty and stenting (CAS) has become an increasingly used treatment alternative in selected patients with extracranial carotid occlusive disease. In contrast to a traditional carotid endarterectomy (CEA), CAS has become a preferred treatment strategy for many patients owing to perceived advantages of less invasiveness and discomfort related to the procedure. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial also fueled the enthusiasm of this catheter-based treatment strategy because it reported a lower incidence of stroke, death, and myocardial infarction (MI) with CAS compared with CEA in high-risk patients.[1,2]

Despite this increased enthusiasm for CAS by physicians and patients, it is widely recognized that CAS is a highly technical procedure that is associated with complications.[3,4] Neurologic impairment such as stroke remains the most feared complication of this procedure, and efforts to reduce procedurally related cerebral embolization constantly drive researchers to develop better neuroprotection devices. Other procedurally related physiologic phenomena that may influence the treatment outcome can also occur, and hemodynamic depression consisting of bradycardia or hypotension has been reported after CAS at incidence of 5% to 76%.[5-13]

Catheter-related instrumentation of the carotid bulb, such as balloon dilatation, can trigger a series of neuronal responses resulting in bradycardia and hypotension. In the event that such a hemodynamic response becomes sufficiently profound, perioperative cardiopulmonary and neurologic adverse sequelae can occur.[14,15]

This study had a twofold objective: We examined the incidence and outcome of hemodynamic instability in patients undergoing CAS at our institution and the clinical variables associated with hemodynamic depression in patients undergoing this percutaneous intervention.

METHODS

Patients. The hospital records and clinic charts for all patients who underwent percutaneous CAS from January 2002 to December 2006 were reviewed. All procedures were performed by vascular surgery staff physicians at the Michael E. DeBakey Veterans Affairs Medical Center, a hospital affiliated with the Baylor College of Medicine. A

carotid duplex scan was performed in all patients before the stenting procedure to document a high-grade carotid stenosis. Patients with symptomatic carotid stenosis of ≥60% and asymptomatic carotid stenosis of ≥80% were included in our CAS protocol.

Treatment indications were based on high-risk criteria adapted from a consensus report as well as our previous reports.[4,16-18] Briefly, these criteria are various anatomic considerations, which include high carotid bifurcation (>C2 level), contralateral carotid occlusion, presence of tracheostomy, history of ipsilateral neck irradiation, prior radical neck dissection, or CEA. Moreover, these high-risk criteria include patients with one or more medical comorbidities, such as myocardial infarction or stroke in the previous 3 months, steroid-dependent chronic obstructive pulmonary disease (defined as forced expiratory volume in 1 second if less than 30% of predicted or less than 1 L/s), and a left ventricular ejection fraction of <25% or as documented congestive heart failure (CHF) at New York Heart Association functional classification stage III or IV.

Carotid artery stenting protocol. Technical details of the CAS procedure were described previously.[4,16-18] Briefly, the patient was given clopidogrel (75 mg/d; Plavix, Sanofi-Aventis, Bridgewater, NJ) and aspirin (81 mg/d) beginning 3 days before the intervention. An intravenous antibiotic (cephazolin, 1 g) was given 30 minutes before the procedure.

After a femoral artery access was established with local anesthesia using 1% lidocaine, an aortic arch angiogram was performed with power injection using a 5F pigtail catheter. Selective carotid catheterization was next performed using a 5F diagnostic catheter to delineate the carotid anatomy. Intravenous (IV) anticoagulation was initiated with a 0.75-mg/kg bivalirudin bolus, followed by an hourly infusion rate of 1.75 mg/kg.

A guidewire exchange was performed with a 0.035-in stiff Glidewire (Terumo, Elkton, Md), which was used to cannulate the external carotid artery or its branches. The groin introducer sheath and diagnostic catheter were next removed, followed by placement of a 7F, 90-cm shuttle sheath (Terumo) in the distal common carotid artery. The tracking of the shuttle sheath over the guidewire in the common carotid artery was facilitated by positioning the stiff Glidewire in the external carotid artery.

A selective digital carotid angiogram was performed through the side port of the shuttle sheath to delineate the anatomy of the common, internal, and external carotid arteries. Biplanar intracranial injections were done to document the cerebral vasculature.

The carotid lesion was crossed with the distal protection device used in all cases in this series, which was deployed in the distal internal carotid artery. Carotid balloon angioplasty was not routinely performed before stenting, and such a maneuver was only used when difficulty was encountered during crossing the carotid lesion with the neuroprotection device.

A self-expanding monorail stent then was tracked over the distal protection device and deployed across the carotid stenosis. Poststenting balloon angioplasty was routinely performed using a 5- or 6-mm-diameter angioplasty balloon on the basis of the completion carotid angiogram.

Completion angiography, which included biplanar carotid and cerebral views to document vascular anatomy and exclude cerebral thromboembolism, was then done. The cerebral embolization protection device was deactivated, and the guidewire along with the shuttle sheath were removed. The groin puncture site was closed with a 6F femoral closure device (Starclose, Abbott Lab, North Chicago, Ill). At the completion of the carotid stenting, intravenous bivalirudin was discontinued. The patient was to continue taking oral clopidogrel for 1 month and aspirin therapy indefinitely.

Assessment for hypotension and bradycardia. All CAS procedures were performed in the operating room under local anesthesia with minimal sedation. Hemodynamic status was monitored by a staff anesthesiologist, and physiologic data were registered in an electronic anesthesia record. A radial arterial catheter was placed for continual hemodynamic monitoring during all CAS procedures. Blood pressure, heart rate, and respiratory rate were recorded before, during, and after the procedure. Baseline hemodynamic information was taken before any anxiolytic premedication was administered.

After the CAS procedure, the patient was transferred to the recovery room, where hemodynamic condition was monitored continuously for another 6 hours. The patient was next transferred to the inpatient ward, where vital signs, including heart rate and blood pressure, were checked every 2 hours.

The number of patients experiencing episodes of hypotension or bradycardia after the CAS procedure was recorded. We defined bradycardia as a decrease of heart rate <60 beats/min or a decrease from the baseline level of >20 beats/min. An episode of hypotension was defined as a fall in systolic blood pressure of >30 mm Hg. Persistent hypotension is defined as a fall in systolic blood pressure for >1 hour or hypotension requiring continuous intravenous vasopressor administration.

The occurrence of CAS-induced bradycardia was promptly treated with intravenous atropine in 0.5-mg increments to a maximum of 1.5 mg. Atropine is not given prophylactically in our clinical practice. Postoperative hypotension was treated with crystalloids in 500-mL increments to a maximum of 2000 mL, depending on the patient's cardiac function and the physician's clinical assessment. In the event of persistent hypotension that was refractory to fluid resuscitation, intravenous dopamine was given with a dosage of 3 μg/kg/min and titrated to a maximum of 10 μg/kg/min. Additional measures such as admission to the surgical intensive care unit (SICU) and administration of other appropriate vasopressor agents would also be initiated.

Outcome variables included all neurologic complications and non-neurologic adverse events. Neurologic complications were classified as one of the following:

1. A transient ischemic attack, which was defined as a new neurologic deficit that resolved completely ≤24 hours;
2. A minor stroke, which was defined as a new neurologic deficit that either resolved completely ≤7 days or increased the National Institutes of Health (NIH) Stroke Scale score by ≤3, or
3. A major stroke, which was defined a new neurologic deficit that persisted >7 days and increased the NIH Stroke Scale score by ≥4.[19,20]

Adverse clinical events include cardiopulmonary complications, post-CAS renal insufficiency, access-site pseudoaneurysm, and hemorrhagic complication. The latter complication was defined as major groin or retroperitoneal bleeding that required operative evacuation or blood transfusion. Adverse cardiac events included myocardial infarction on the basis of electrocardiogram tracing or cardiac enzyme elevation, worsening or renal function, or clinical signs of CHF.

Data analysis. Data analysis was performed using standard statistical methods. Categoric variables were compared by using the Fisher exact test, and continuous variables were evaluated by using analysis of variance and the Student *t* test. Univariate comparison of unpaired continuous data was done with the Mann Whitney *U* test, and the Wilcoxon paired test was used to compare paired continuous data. A multivariate binary logistic regression model was used to assess the role of hemodynamic depression and its relationship with relevant clinical risk factors and post-CAS complications. In all analyses, we only considered variables with ≥80% of the data present or recorded. A risk-factor adjustment model was used to determine potential confounding effects of other baseline variables if they appeared to differ between patients with and without hemodynamic instability. All continuous values are represented as mean ± SD, and correlations were considered significant at the $P = .05$ level. Statistical analysis was performed with SPSS 10.0 software (SPSS Inc, Chicago, Ill).

RESULTS

CAS procedures were done in 422 patients during the study period. Six patients were excluded from the analysis because of incomplete intraoperative hemodynamic data due to monitoring equipment failure (n = 4) and missing postoperative hemodynamic data in the recovery room (n = 2). The remaining 416 patients (99% male; mean age, 74 ± 11 years) were analyzed. The primary CAS technical success rate was 98% (407 of 416). Treatment indication with carotid stenting included high-risk medical comorbidities in 303 (73%), prior CEA in 96 (23%), previous tracheostomy in 6 (1%), high carotid bifurcation in 47 (11%), and prior neck radiation or dissection, or both, in 8 (2%).

Hemodynamic depression occurred in 191 patients (46%). The mean duration of the CAS procedure was 39 ± 14 minutes. There was no difference in the procedural duration among those who developed hemodynamic instability and who those remained hemodynamically stable during the stenting procedure. Among the patients with hemodynamic depression, hypotension occurred in 58 patients (14%) and bradycardia in 112 (27%). Among the those with bradycardia, 76 had a decrease in heart rate to <60 beats/min and 36 experienced a decrease in heart rate of ≥20 beats/min compared with the baseline value. Concomitant post-CAS bradycardia and hypotension developed in 21 patients (5%). The immediate onset of bradycardia, defined as the immediate onset of bradycardia after carotid artery intervention, occurred in 117 patients (28%) after carotid artery angioplasty or stent placement. Delayed onset of bradycardia (1 to 16 hours after carotid intervention) occurred in 16 patients (4%).

The 117 patients who developed intraprocedural bradycardia received immediate intravenous atropine, which effectively normalized the heart rate. Among the 79 patients (19%) who experienced hypotensive episodes, 32 episodes (41%) occurred intraoperatively, and delayed onset of hypotension developed in 47 patients (59%) at 1 to 14 hours after carotid stent placement. Thirty-eight (48%) of the hypotensive patients responded appropriately to medical treatment, which included fluid resuscitation or vasopressor agent infusion, or both. Persistent hypotension occurred in 45 (11%), and 22 (5%) required an overnight stay in the SICU for blood pressure monitoring.

The baseline hemodynamic status and the length of hospital stay were similar between the two groups (Table I), and no difference was noted in the procedural variables such as contrast usage or fluoroscopic duration. In contrast, hemodynamic depression was *less* likely to develop in patients with prior ipsilateral CEA compared with those with a primary carotid atherosclerotic lesion; similarly, no difference was noted when the presenting symptoms between the two groups were compared. Both groups also shared similar plaques characteristics and luminal diameters. Furthermore, a depressed ejection fraction (<25%) was associated with an increased incidence of hemodynamic depression (Table II).

When the association between hemodynamic depression and CAS-related complications was examined, no difference was found between the patients with and without hemodynamic instability. However, persistent hemodynamic instability was associated with an increased incidence of neurologic complications (Table III). More specifically, the 30-day death rate in patients with and without persistent hemodynamic depression was 4% and 1% ($P = .05$), and the 30-day stroke and death rate in patients with and without persistent hemodynamic depression was 7% and 2% ($P = .05$). An increase in non-neurologic complications was similarly noted in patients with persistent hypotension compared with those who did not experience persistent hypotension. Specifically, the non-neurologic clinical adverse event rate was 44% in patients with persistent hemodynamic depression, which contrasted sharply with the 3% rate among those who did not experience persistent hemodynamic depression.

Binary logistic regression analysis showed that patients with persistent hemodynamic depression were at an in-

Table I. Baseline demographic, treatment indication, and procedural variables of patients with and without hemodynamic depression undergoing carotid angioplasty and stenting

Patient characteristics*	Patients with hemodynamic depression (n = 191)	Patients without hemodynamic depression (n = 225)	P
Age, y	75 ± 8.4	73 ± 7.4	NS
Male gender	188 (98)	223 (99)	NS
Baseline systolic blood pressure pre-CAS (mm Hg)	156 ± 23	154 ± 26	NS
Baseline heart rate pre-CAS (beats/min)	72 ± 14	74 ± 13	NS
CAS technical success	187 (98)	220 (98)	NS
Hospital length of stay, d	1.6 ± 1.2	1.3 ± 1.1	NS
CAS treatment indication			
High-risk medical comorbidities	139 (73)	164 (73)	NS
Prior ipsilateral CEA	5 (3)	93 (41)	.001
Prior tracheostomy	3 (2)	3 (1)	NS
High carotid bifurcation	22 (12)	25 (11)	NS
Prior neck irradiation/dissection	3 (2)	5 (2)	NS
Procedural variables			
Fluoroscopic time, min	16 ± 8	18 ± 11	NS
Contrast used, mL	185 ± 25	179 ± 28	NS
Asymptomatic carotid lesion	128 (67)	158 (70)	NS
Symptomatic carotid lesion			
Stroke	29 (15)	38 (17)	NS
Transient ischemic attack	21 (11)	18 (8)	NS
Amaurosis fugax	13 (7)	11 (5)	NS

CAS, Carotid angioplasty and stenting; *CEA,* carotid endarterectomy; *NS,* not significant.
*Continuous data are presented with the mean ± SD; categoric data are number (%).

Table II. Clinical comorbidity and carotid plaque characteristics of patients with and without hemodynamic depression undergoing carotid angioplasty and stenting

Patient characteristics*	Patients with hemodynamic depression (n = 191)	Patients without hemodynamic depression (n = 225)	P
Comorbidities/clinical variables			
Coronary artery disease	143 (75)	153 (68)	NS
Smoking	158 (83)	194 (86)	NS
Hypertension	174 (91)	200 (89)	NS
Diabetes mellitus	115 (60)	126 (56)	NS
Chronic obstructive pulmonary disease	38 (20)	38 (17)	NS
Hyperlipidemia	162 (85)	198 (88)	NS
Renal insufficiency, creatinine >1.5 mg/dL	36 (19)	36 (16)	NS
Low ejection fraction, <25	60 (38)	31 (16)	.005
Prior stroke	34 (18)	50 (22)	NS
Prior ipsilateral CEA	5 (3)	93 (41)	.001
β-blocker usage	138 (73)	175 (78)	NS
Carotid lesion characteristics			
Carotid stenosis, %	86 ± 8	88 ± 9	NS
Carotid luminal diameter before CAS, mm	2.5 ± 0.8	2.6 ± 1.0	NS
Carotid luminal diameter after CAS, mm	6.7 ± 1.3	6.8 ± 1.2	NS
Stent diameter, mm	7.6 ± 1.5	7.8 ± 1.6	NS
Lesion involves carotid bulb	130 (68)	158 (70)	NS
Contralateral carotid occlusion	29 (15)	32 (14)	NS
Ulcerated plaque	67 (35)	74 (33)	NS
Calcified plaque	55 (29)	68 (30)	NS

CAS, Carotid angioplasty and stenting; *CEA,* carotid endarterectomy; *NS,* not significant.
*Continuous data are presented with the mean ± SD; categoric data are number (%).

creased risk for neurologic complications (odds ratio [OR], 2.67; 95% confidence interval [CI], 1.38 to 6.32; $P = .01$) and non-neurologic clinical adverse events (OR, 3.25; 95% CI, 1.58 to 7.52; $P = .02$). No other clinical or radiographic predictor was identified using a multivariate analysis for stroke, death, or clinical adverse events. Morphologic

characteristics and anatomic location of the carotid plaque were also not associated with the development of post-CAS complications.

A logistic regression model was also used to analyze risk factors for CAS-related hemodynamic instability and to adjust for other confounding risk factors, which is shown in

Table III. Association of persistent hemodynamic depression and postprocedural complications

Complications	Patients with persistent hemodynamic depression (n = 45), n (%)	Patients without persistent hemodynamic depression (n = 374), n (%)	P
Neurologic complications	4 (9)	9 (2)	.02
Transient ischemic attack	3 (7)	2 (1)	.05
Major stroke	1 (1)	2 (1)	NS
Minor stroke	0	2 (1)	NS
30-day death	2 (4)	3 (1)	.05
30-day stroke/death	3 (7)	6 (2)	.05
Clinical adverse events	20 (44)	12 (3)	.001
Cardiopulmonary	9 (20)	6 (2)	.03
Renal insufficiency	3 (7)	3 (1)	.05
Access site pseudoaneurysm	2 (4)	1 (1)	.05
Hemorrhagic	6 (13)	2 (1)	.01

NS, Not significant.

Table IV. Binary logistic regression model assessing the risk of any hemodynamic depression in patients undergoing carotid angioplasty and stenting

Factor	OR	95% CI	P
Age, y			
<65	1.02	0.85-6.52	.25
66-71	2.25	1.25-9.25	.21
72-77	2.36	1.35-10.52	.18
>78	5.25	2.32-15.25	.01
Diabetes mellitus	1.58	1.25-3.68	.125
Prior stroke	2.36	1.25-8.67	.89
Symptomatic carotid lesion	0.89	0.58-5.25	.96
History of hypertension	1.36	0.26-6.47	.136
Renal insufficiency	1.34	0.82-5.17	.87
Hyperlipidemia	3.21	0.92-10.64	.69
Low ejection fraction, <25%	3.25	0.58-6.58	.02
Contralateral carotid occlusion	1.68	0.64-6.19	.98
Prior ipsilateral CEA	0.21	0.12-0.69	.001
Lesion involves carotid bulb	1.86	1.10-2.56	.09
History of smoking	2.36	1.26-5.25	.08

OR, Odds ratio; *CI*, confidence interval; *CEA*, carotid endarterectomy.

Table IV. Age >78 years was associated with a 5.25-fold increased adjusted risk for hemodynamic depression after carotid stenting, low cardiac ejection fraction was associated with a 3.25-fold increased adjusted risk, and patients with prior ipsilateral CEA were protected from developing hemodynamic instability during carotid stent placement.

DISCUSSION

Hemodynamic alterations such as bradycardia or hypotension are a well-recognized physiologic response during catheter-based carotid artery intervention, but most of these events are transient and self-limiting in nature.[8-11] However, it has been reported that profound bradycardia and hypotension associated with CAS can result in severe hemodynamic instability that may lead to neurologic sequelae.[21,22] Therefore, our understanding of the clinical significance and potential predisposing factors of CAS-related hemodynamic instability is critical in improving the procedural safety and minimizing potential complications. In this study, we found that hemodynamic depression occurred in 46% of patients undergoing CAS procedures. Risk-factors analysis showed that predisposing conditions associated with hemodynamic instability included advanced age and low ejection fraction. Our study also showed that persistent hypotension, not hypotension alone, is associated with an increased risk of adverse clinical outcome. We postulate the latter finding is likely due to the poor tolerance of persistent hemodynamic depression in cohorts of elderly patients because cardiopulmonary adverse clinical events were the main culprit of their non-neurologic complications (Table III).

The frequency of CAS-induced bradycardia and hypotension in our series was 27% and 14%, respectively, and the incidence of combined bradycardia and hypotension was 5%. The reported incidence of CAS-induced bradycardia varies widely in the literature, from 5% to 76%.[6-13] The incidence of hypotension during CAS also ranges widely, from 14% to 28%, based on available reports.[6-13]

We postulate that this wide range of heart rate and blood pressure fluctuations may be partly due to inconsistency of hemodynamic definitions used in various clinical reports. We defined hypotension as a decrease of baseline systolic blood pressure by >30 mm Hg after carotid intervention, which is a definition others have used when analyzing hemodynamic disturbances after surgical carotid reconstruction.[8] We further defined persistent hypotension as blood pressure reduction lasting >1 hour. This variable correlates with adverse clinical outcome in our series, a finding that has been supported by others.[6,12]

Dangas et al[6] reported that persistent hypotension is more likely to occur after balloon-expandable stenting than after self-expanding stenting, a phenomenon likely due to augmented carotid sinus stimulation by the balloon-expandable stents. Furthermore, persistent hypotension correlated with increased in-hospital complications and long-term risk of death in their series. The clinical significance of CAS-induced hypotension was also highlighted by a study that showed that blood pressure reduction of >50 mm Hg, rather than the duration of hypotension, was a predictor of adverse neurologic events after carotid stenting.[23]

Although we did not find any demographic predictors for hemodynamic depression, our result showed that increased age and low cardiac ejection fraction (<25%) were associated with an increased adjusted risk for hemodynamic instability after CAS (Table IV). Previous reports have suggested that increased age represents a risk factor of neurologic complication after CAS.[19,24,25] Our observation is consistent with other reports that showed elderly patients and those with coronary disease are at an increased risk for hemodynamic depression after CAS.[9,11]

When physicians perform CAS in elderly patients with age-related cardiac dysfunction, they should be cognizant that these patients may have depressed cardiac output state due to low blood volume and compromised diastolic ventricular dysfunction. In the event of carotid baroreceptor stimulation triggered by balloon angioplasty or stent placement, these patients may not have a full cerebral autoregulatory response to bradycardia or hypotension partly due to age-related neuronal impairment. As a consequence, older patients or those with compromised cardiac reserve are vulnerable to hypotensive episodes after CAS. Similar findings have supported that patients with impaired cardiac function due to coronary artery disease are at an increased risk for hemodynamic depression after CAS, possibly due to chronic structural and functional impairment of myocardial function.[9,11]

Other researchers have reported that plaques involving the carotid bulb represent an increased risk for the development of hemodynamic depression after CAS.[6,12] Gupta et al[12] reviewed the incidence and predictors of bradycardia and hypotension in 400 consecutive patients. Using a multivariate analysis, these authors noted that plaques at the carotid bifurcation and calcified or ulcerated plaques were associated with a significantly higher risk of hemodynamic instability.[6,12]

The association of hemodynamic depression and carotid plaque characteristics was similarly demonstrated by Leisch et al,[26] who reported that transient asystole and hypotension developed in 40% of their patients. That study also showed that the most important predictor of hemodynamic instability was a lesion involving the carotid bifurcation and that carotid plaque characteristics that were associated with CAS-related hypotension included an ostial lesion and isolated internal carotid artery calcification.[26] Contrary to their findings, our results did not demonstrate that carotid plaque characteristics were related to either CAS-induced hemodynamic depression or post-CAS complications.

Gupta et al[12] reported interesting findings that diabetes mellitus and a history of smoking reduced the risk of hemodynamic instability after CAS.[12] They postulated that long-term smoking impairs the carotid baroreceptor response and augments the sympathetic tone, which raises the blood pressure and heart rate.[12,27,28] Similarly, diabetes mellitus is known to impair cardiovascular autonomic response by attenuating parasympathetic nerve function, which may attenuate the carotid baroreceptor stimulation triggered by carotid intervention.[29,30] Despite the high prevalence of smoking and diabetes in our patient population of veterans, we were unable to show that these variables reduced the risk of hemodynamic depression after CAS.

Patients in our study with prior CEA-related carotid stenosis constituted 23% of those who underwent CAS procedure, and hemodynamic depression was less likely to develop in these patients after CAS (OR, 0.21; 95% CI, 0.12 to 0.69; *P* < .001; Table IV), a finding that has been supported by others.[8,9,11] The adventitial baroreceptors located in the carotid sinus plays a critical role in hemodynamic alterations during and after CAS. Impulses originating in the carotid sinus reach the medullary vasomotor nuclei by way of the carotid sinus nerve and the glossopharyngeal nerve. Distension of the carotid bulb by means of balloon angioplasty or stent placement leads to baroreceptor stimulation that not only triggers a reflex inhibition of adrenergic output which reduces peripheral sympathetic tones but also increases parasympathetic activity, which ultimately leads to hypotension and bradycardia.[11,31]

In patients who have had a prior CEA, either the carotid sinus or the carotid sinus nerve, which lies in the vicinity of the carotid bulb, has been routinely divided or interrupted surgically. As the result, the carotid adventitial baroreceptors or the afferent nerve fibers are unable to send impulses to the medulla when triggered by balloon dilatation, which likely accounts for the low incidence of CAS-induced bradycardia in patients with post-CEA carotid stenosis.

The impact of hemodynamic alteration triggered by nerve interruption during CEA was also highlighted by Mehta et al,[32] who reported a higher incidence of hypertension after eversion endarterectomy. They attributed the CEA-associated hypertension to the loss of the baroreceptor reflex secondary to nerve injury caused by carotid bulb transection during an eversion endarterectomy.[32] They also reported a decreased need for perioperative vasopressors in patients whose carotid sinus nerve had been divided.

The ideal treatment of CAS-related bradycardia and hypotension remains a subject of debate. We administered intravenous atropine only when bradycardia was triggered by carotid instrumentation. We have modified our clinical practice during the CAS procedure such that a nurse will call out the heart rate on the basis of an electrocardiogram tracing during carotid balloon angioplasty or carotid stent deployment. This clinical practice allows the staff physicians to remain focused on the fluoroscopic monitor while receiving an audible feedback on the patient's heart rate and enables a clear communication among all personnel about the decision of atropine administration. Although we have reported a potential adjunctive role of temporary transfemoral cardiac pacing to treat bradycardia during CAS,[33] we have found that prompt atropine administration in selective cases is effective in reversing CAS-induced bradycardia.

In contrast, other physicians have advocated prophylactic atropine administration in all patients undergoing CAS.[5,26] It should be emphasized that prophylactic treat-

ment with atropine is not without potential harmful effects. Qureshi et al[11] reported a paradoxical finding of a higher risk of postprocedural bradycardia associated with prophylactic use of atropine in patients undergoing CAS. Other side effects of atropine include tachycardia, confusion, urinary retention, and arrhythmias.[34,35] With resultant tachycardia and arrhythmia, there is an increased cardiac oxygen demand and added myocardial workload that may lead to adverse cardiac events, particularly because many of these patients are elderly and have underlying coronary artery disease.

Our study has several limitations that are related to its retrospective nature as well as potential patient selection and treatment bias. However, an established criteria was used for patient selection, and our treatment approach adhered to a strict technical protocol that was reported previously.[4,16-18] As a consequence, we do not believe our findings are significantly influenced by any bias.

All of our procedures were performed in the operating room, and the patients were monitored by an anesthesiologist who provided anxiolytic drugs at his or her clinical discretion. Because a standardized protocol was not use for the administration of anxiolytic medications, these drugs may have influenced the heart rate and blood pressure response in our patients.

Finally, we recognize that this series represents a single-center experience that took place at a Veterans Affairs Medical Center. Nearly all patients were men, which precluded an impartial assessment of the role of gender in the hemodynamic alteration after the CAS procedure.

CONCLUSION

Our study has shown that hemodynamic fluctuation during CAS is a frequent phenomenon. Patients with postendarterectomy carotid stenosis are protected from the development of hemodynamic depression, and elderly patients and those with poor cardiac function are at risk. Because persistent hemodynamic depression is associated with adverse clinical outcome, prompt pharmacologic treatment with appropriate fluid resuscitation should be considered. Further studies are warranted to better predict patients at risk of developing this physiologic response as well as developing a treatment strategy to prevent hemodynamic instability in an effort to reduce CAS-associated adverse clinical events.

AUTHOR CONTRIBUTIONS

Conception and design: PL, WZ, PK, HE
Analysis and interpretation: PL, WZ, PK, HE
Data collection: PL, WZ, PK, HE, NB, TH
Writing the article: PL, NB
Critical revision of the article: PL, WZ, NB, PK, HE, TH
Final approval of the article: PL, WZ, PK, HE
Statistical analysis: PL, WZ, PK, HE, TH
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DISCUSSION

Dr Carlos Timaran (Dallas, Tex). Dr Lin and colleagues have presented an important study about a problem that is being seen more frequently by vascular surgeons as we embrace carotid angioplasty and stenting (CAS). As shown in this study, CAS may induce bradycardia and hypotension that may be associated with adverse outcomes if not resolved expeditiously. CAS-induced bradycardia is typically short lived, whereas hypotension is more persistent. Because CAS is currently reserved primarily for high-risk patients, hemodynamic changes could potentially result in significant morbidity and mortality, particularly in patients with severe cardiovascular disease. Moreover, this study has revealed that elderly patients and those with severely depressed cardiac function are at higher risk of developing CAS-induced hemodynamic depression. Based on the results of the current study, I have the following comments and questions:

First, in the multivariate logistic regression models included in your paper, age groups were analyzed rather than age as a continuous variable. This is a rather unfortunate, as most statisticians would agree that continuous variables should be maintained continuous. Did you analyze age as a continuous variable in separate models? If you did, what is the age cutoff value above which the risk of hemodynamic changes is more significant? It appears that octogenarians have the highest risk in this series. Do you believe that because of this additional risk factor, CAS should definitely be avoided in octogenarians?

Second, in this series, CAS-induced bradycardia was treated with atropine and hypotension with dopamine. The use of atropine during CAS is controversial as it has significant side effects, particularly in elderly and high-risk patients, including mental status changes and persistent tachycardia that may lead to myocardial ischemia. Dopamine, on the other hand, can also induce tachycardia and arrhythmias and its mechanism of action does not treat the physiologic changes induced by stretching the carotid sinus. Moreover, because atropine and dopamine produce tachycardia through different mechanisms, their actions could be additive even synergistic. What was the incidence of persistent hypertension or tachycardia related to the use of atropine and dopamine? What was the incidence of treatment-induced arrhythmias, angina and myocardial infections?

Third, atropine is rarely used these days as an adjunct to general anesthesia because of its serious adverse effects. Glycopyrrolate is currently the anticholinergic medication of choice because of its limited half-life. Why haven't the authors used it instead of atropine? What do the authors think about using vasopressors with mechanisms of action that have more physiologic basis for the treatment of CAS-induced hypotension, such as ephedrine and norepinephrine.

Finally, I would like your input regarding a patient I had to treat several weeks ago. This was an 81-year-old patient with symptomatic carotid stenosis, unstable angina, 80% stenosis of the left main, and 99% stenosis of the right coronary arteries. His ejection fraction was 25%. According to your data, this patient has a high risk of adverse outcome. How would you treat this patient considering that his coronary artery disease was deemed nonreconstructable? I may consider transferring patients like this to Houston if you have the right answer.

I want to thank the authors for sending me their manuscript in advance and the association for the honor of discussing this important study and the privilege of the floor.

Dr Peter H. Lin: Regarding your first question, which deals with the statistical analyses of the age factor as a continuous variable as well as the categorical variable, we did perform analysis using age as a continuous variable and similarly discovered that increased age was associated with an increased risk of hemodynamic depression.

With that said, I think it is premature to draw a conclusion based on this study to say that carotid stenting is indeed contraindicated or avoided in elderly patients. There are many factors that can lead to the development of bradycardia or hypotension in elderly patients. One potential issue that comes to my mind is that many of these octogenarian patients are perhaps hypovolemic; particularly, many of these patients may have underlying left ventricular dysfunction, which may lower the threshold of sympathetic activation. As such, elderly patients who are dehydrated with suppressed cardiac function are more likely to develop hemodynamic depression following baroreceptor stimulation. One learning point that we can draw from our experience is that interventionalists should have a higher level of awareness when performing carotid stenting in elderly patients who might have compromised cardiac function. These patients should be appropriately hydrated during this procedure to reduce the likelihood of postprocedural hypotension or carotid sinus activation.

Your second question relates to the use of atropine and dopamine. In our practice, we only administer intravenous atro-

pine when a patient develops bradycardia. We have found that selective atropine administration is very effective in reversing carotid-stenting-induced bradycardia. I do want to point out a technical step in our practice with regards to atropine administration. Whenever we are about to perform balloon dilation of the carotid artery or deploy a carotid stent, we have an OR nurse or nurse anesthetist read the heart rate loudly in the operating room so that everyone in the operating room can receive an audible readout of the heart rate. The decision of atropine administration is clearly communicated with everyone participating in the stenting procedures, including the surgeons, anesthesiologists, nurses, residents, and even medical students. In no instance do we have to administer additional atropine once patients leave the operating room. I do have to emphasize that we have the advantage because all carotid stenting procedures were done in the operating room with staff anesthesiology monitoring, and we have been very satisfied with added staff support in the way these patients are monitored.

With regards to your third question, we do not have experience with glycopyrrolate to treat patients with bradycardia. Additionally, we have not experience any side effects of atropine, although we fully recognize that this drug can cause hypotension, particularly in patients who are hypovolemic. With that said, our treatment approach in patients who developed post-stenting hypotension is to provide fluid resuscitation first. After a liter or so of fluid, which obviously depends on the patient's cardiac function, we will put a central line in to monitor their intravenous pressure and follow-up by appropriate vasopressor agent administration.

With regard to your last question of an 80-year old gentleman with increased cardiac morbidities, clearly it is difficult to answer that question based on brief history. However, I do think that carotid endarterectomy under local anesthesia remains an excellent treatment option even in high-risk patients with carotid artery stenosis. I was fortunate to receive my vascular surgery fellowship training at Emory University School of Medicine where I learned the art of carotid endarterectomy under local anesthesia from surgeons such as Drs Bob Smith, Atef Salamn, Tom Dodson, and Eliot Chaikof. To this date, I continue to perform carotid endarterectomy under local anesthesia in my practice. In patients who have anatomical concern to undergo carotid stenting, we have shown in our experience that carotid endarterectomy under local anesthesia is clearly an excellent treatment option even in elderly patients. Therefore based on the scenario you provided, I would consider both options in the overall treatment strategy. The cardiac comorbidities that you had mentioned would not preclude this patient from undergoing carotid endarterectomy under local anesthesia.