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Atherosclerotic Plaque Vulnerability as an Explanation for the Increased Risk of Stroke in Elderly Undergoing Carotid Artery Stenting

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Background and Purpose—Recent randomized trials showed an increased periprocedural risk for stroke with increasing age in patients undergoing carotid artery stenting. Manipulation of atherosclerotic plaques during carotid artery stenting can result in plaque rupture with subsequent superimposed thrombus formation, embolization, and cerebrovascular events. We hypothesized that atherosclerotic plaques become more unstable with increasing age and thereby might provide insight into the age-related increased risk of cerebrovascular events during carotid artery stenting.

Methods—Carotid atherosclerotic plaques were harvested from 1385 consecutive patients undergoing carotid endarterectomy between 2002 and 2010. Carotid plaques were quantitatively analyzed for macrophages, smooth muscle cells, and microvessels; and semiquantitatively analyzed for collagen, calcifications lipid cores, and intraplaque hemorrhages. Patients were divided in 4 groups by age: <60, 60 to 69, 70 to 79, and ≥ 80 years. Measures of association between age as a continuous variable and histological characteristics were also calculated.

Results—Increasing age was associated with a decrease in the amount of smooth muscle cells in the carotid plaque. More plaques with large atheroma and heavy plaque calcifications were observed among elderly patients. After correction for baseline differences, risk factors, and medication use, age was independently associated with a more vulnerable carotid plaque composition.

Conclusion—Plaque stability decreases gradually with age. Older patients with carotid stenosis have relatively unstable plaques with low smooth muscle cell content, a high amount of large lipid cores, and more calcified plaques as compared with younger patients. The underlying vulnerable plaque composition in the elderly might be an important contributing factor to the increased risk of stroke for older patients undergoing carotid artery stenting. (*Stroke*. 2011;42:2550-2555.)

Key Words: age ■ angioplasty & stenting ■ atherosclerosis ■ carotid stenosis ■ plaque composition ■ risk factors

Carotid endarterectomy (CEA) reduces the risk of ischemic stroke in patients with a recently symptomatic, significant carotid artery stenosis.¹ Subgroup analysis revealed a high benefit from surgery, particularly for patients >75 years, due to the relatively high risk for a secondary event and therefore a relatively low number needed to treat to prevent 1 ipsilateral stroke.² Besides the favorable number needed to treat, overall life expectancy is rising, indicating that CEA in the “intellectually intact” elderly can be highly beneficial.³

From observational studies, the periprocedural risk for the elderly undergoing CEA has been reported to be comparable to the risk for younger patients.³⁻⁵ Nevertheless, subgroup analyses for age in several randomized trials revealed that periprocedural risk of stroke, myocardial infarction, and death after carotid artery stenting (CAS) increases with age.⁶⁻⁹

The occurrence of periprocedural stroke for CAS has been proposed to be closely related to plaque manipulation with intra-arterial devices resulting in plaque rupture, subsequent superimposed thrombus formation, and embolization of plaque debris.^{10,11} Disruption of carotid plaques during manipulation in stenting procedures is more likely to occur in so-called vulnerable plaques with large lipid cores and thin fibrous caps.¹²

Only a few studies have reported on histological carotid plaque characteristics in relation to age. Age was found to be associated with a more fibrous plaque type in a study from Spagnoli et al including 180 symptomatic patients.¹³ Analyses from our laboratory previously showed a more atheromatous plaque type in older patients, but corrections for symptomatic presentation and cardiovascular risk factors were

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lacking.¹⁴ Recent data from Redgrave et al showed increased inflammation in plaques from younger patients and presence of larger lipid cores and more calcifications in plaques from older patients, but only symptomatic patients were included.¹⁵ In addition, the very elderly are overall underrepresented in carotid studies and histological assessment of carotid plaque composition in these patients has never been described. We hypothesized that plaque instability and vulnerability increase with age, which might help to understand underlying pathophysiological grounds for the evident increased age-related risk for periprocedural events during CAS as described by recent randomized trials.

Methods

Study Population

Athero-Express is an ongoing Biobank study for carotid atherosclerotic plaques harvested during CEA.¹⁶ Medical ethics boards of the 2 participating hospitals (University Medical Center Utrecht and St Antonius Hospital Nieuwegein, The Netherlands) approved the study. All participating patients provided written informed consent. Selection for CEA was discussed in a multidisciplinary team and was based on international guidelines for symptomatic and asymptomatic carotid stenoses.^{1,17} Baseline characteristics and medication use were gathered preoperatively from admission charts and standardized questionnaires. Diabetes mellitus was defined as use of insulin or oral glucose inhibitors; hypertension was defined as systolic tension >130 mm Hg or use of blood pressure-lowering drugs. Patients were considered as current smokers if they reported to be smoking until the year of CEA. Clinical presentation was divided into stroke, transient ischemic attack, or asymptomatic presentation.

To analyze different age groups and analyze a specific subgroup of octogenarians and relatively young individuals, all patients were divided into 4 groups with cutoff points for age in decades: <60 years, 60 to 69 years, 70 to 79 years, and ≥80 years. To examine measures of association between age and carotid plaque characteristics, also analyses with age as a continuous variable were performed.

Atherosclerotic Plaque Examination

After endarterectomy, the atherosclerotic plaque was directly taken to the laboratory and divided into 5-mm segments. The segment with the greatest plaque burden was subjected to standardized histological examination.¹⁸ Macrophages and smooth muscle cells (SMCs) were analyzed quantitatively and expressed in positive staining per plaque area (CD68 for macrophages and α -actin for SMCs).¹⁸ Plaque microvessels were stained with CD34 and quantified in 3 hotspots per plaque and scored as an average amount of vessels per hotspot. The quantitative measurements of macrophages, SMCs, and microvessels were subjected to logarithmic transformations because they were not normally distributed. The variables were referred to a log macrophages, log SMCs, and log microvessels in the tables and were reported as original data in the text of the "Results." Semiquantitative analyses were performed for collagen (Picro-sirius Red) and calcifications (hematoxylin and eosin). "Moderate or heavy" staining was defined as a positive staining along the entire luminal border or evident parts within the lesion. Presence and size of lipid cores were assessed combining the hematoxylin and eosin and Picro-sirius Red staining. A lipid core covering ≥40% of total plaque was used as a cutoff point based on the reported correlation between lipid core size ≥40% and rupture-prone plaques.¹⁹ Presence of intraplaque hemorrhage was defined as presence of a fresh or organized hemorrhage inside the plaque. Both intraobserver and interobserver reproducibility have been reported previously and were found to be excellent ($\kappa=0.6$ to 0.9).¹⁸

Statistical Analysis

SPSS 17.0 (SPSS Inc, Chicago, IL) was used for all statistical analyses. Baseline differences between the different age groups were compared with Pearson χ^2 test for proportions, analysis of variance for means, and Kruskal-Wallis for medians. Univariate analyses of variance post hoc tests were used to examine the significant differences in plaque characteristics among the 4 age groups. To assess the independent effect of age on plaque composition and to correct for baseline differences between groups, linear and logistic regression models were used, where appropriate. Baseline differences between groups with a *P* value <0.20 were entered in multivariable model together with the 4 age groups. The statistical significance of differences for histological parameters was expressed in probability values and adjusted probability values. Measures of association between age as a continuous variable and plaque characteristics are presented as coefficients (SE) and ORs [95% CI, where appropriate. An adjusted probability value <0.05 or a CI not including 1 was considered statistically significant.

Results

Patients

Between March 2002 and April 2010, carotid atherosclerotic plaques were harvested during CEA from 1385 patients. The groups were composed of the following: patients <60 years (*n*=262), 60 to 69 years (*n*=485), 70 to 79 years (*n*=504), and ≥80 years (*n*=134). Of all patients, 14.7% (203 of 1385) were asymptomatic, 60.9% (844 of 1385) were patients with transient ischemic attack, and 24.4% (338 of 1385) had a stroke before CEA. Baseline characteristics are provided in Table 1. Older patients were less frequently smokers, had a lower body mass index, and had a lower incidence of coronary and peripheral artery disease. Furthermore, prescription of statins and aspirin was lower among the elderly, but oral anticoagulants were prescribed more frequently instead. No differences were observed in the time that elapsed between the last event and surgery. All baseline characteristics that were associated with age were added to linear and logistic regression analyses for the plaque characteristics.

Atherosclerotic Plaque Composition

The observations of all histological parameters for the 4 age groups are summarized in Table 2 with accompanying probability values and adjusted probability values.

A significant difference for the amount of SMCs per plaque area could be observed among different age groups. Median SMC for patients aged <60 years was 2.4 (0 to 20.9), 1.6 (0 to 15.1) for 60 to 69 years, 1.5 (0 to 17.6) for 70 to 79 years, and 1.2 (0 to 13.7) for ≥80 years, respectively (adjusted *P*<0.001). Post hoc analyses revealed that the patients <60 years had significantly more log SMCs compared with all older age groups. Also, a significant difference was observed between patients ≥80 years and 60 to 69 years. For the binominal histological variables, significant differences between groups were observed for large lipid cores and plaque calcifications. Large lipid cores, covering >40% of the plaque surface, were observed in 21.8% (57 of 262) of the plaques from patients <60 years, 27.2% (132 of 485) for 60 to 69 years, 32.7% (165 of 504) for 70 to 79 years, and 35.8% (48 of 134) for patients who were ≥80 years (Table 2). Heavy

Table 1. Baseline Patient Characteristics Before Carotid Endarterectomy

Patient Characteristics	Age, y				<i>P</i>
	<60 (n=262)	60–69 (n=485)	70–79 (n=504)	≥80 (n=134)	
Gender: Male	66.8% (175/262)	71.3% (346/485)	66.3% (335/504)	63.4% (85/134)	0.214
Age, y, mean (±SD)	54.3 (±4.3)	64.8 (±2.9)	74.2 (±2.9)	82.7 (±2.8)	NA
Current smoker	54.4% (130/239)	41.6% (185/445)	26.4% (117/443)	7.4% (8/108)	<0.001
Diabetes mellitus	19.0% (44/232)	23.1% (100/433)	21.7% (91/420)	14.2% (16/113)	0.170
Hypertension	81.8% (193/236)	87.4% (389/445)	88.3% (379/429)	90.2% (101/112)	0.061
BMI, kg/m ² , mean (±SD)	26.3 (±4.2)	26.7 (±3.9)	26.2 (±3.5)	25.4 (±3.0)	0.023
CAD	16.8% (44/262)	22.9% (111/485)	25.8% (130/504)	15.7% (21/134)	0.009
PAOD	20.5% (50/244)	22.0% (99/451)	20.5% (94/458)	9.1% (11/121)	0.017
Clinical presentation					
Asymptomatic	17.2% (45/262)	16.1% (78/485)	14.3% (72/504)	6.0% (8/134)	0.031
TIA	61.8% (162/262)	61.2% (297/485)	58.5% (295/504)	67.2% (90/134)	
Stroke	21.0% (55/262)	22.7% (110/485)	27.2% (137/504)	26.9% (36/134)	
Time between event and surgery, median (IQR)	48 (20–111)	46 (19–107)	52 (22–102)	47 (15–98)	0.686
Medication					
Statins	84.0% (210/250)	79.5% (373/469)	70.1% (333/475)	58.9% (76/129)	<0.001
Aspirin	90.4% (226/250)	86.4% (405/469)	80.8% (384/475)	78.3% (101/129)	0.001
Oral anticoagulants	6.8% (17/250)	10.7% (50/469)	16.6% (79/465)	17.1% (22/129)	<0.001
Clopidogrel	8.8% (22/250)	10.4% (49/469)	10.3% (49/475)	6.2% (8/129)	0.467

BMI indicates body mass index; CAD, coronary artery disease; PAOD, peripheral arterial occlusive disease; TIA, transient ischemic attack; IQR, interquartile range; NA, not applicable.

plaque calcifications were observed in 46.7% (122 of 261) for age group <60, 55.2% (267 of 484) for 60 to 69 years, 61.4% (309 of 503) for 70 to 79 years, and 58.2% (78 of 134) for patients aged ≥80 years (Table 2). Every 10-year

increase in age was associated with an adjusted regression coefficient for SMCs of -0.146 (SE 0.024) and with adjusted ORs of 1.27 (1.07 to 1.50) and 1.36 (1.16 to 1.58) for large lipid cores and moderate to heavy plaque calci-

Table 2. Histological Parameters of Carotid Atherosclerotic Plaques in Relation to Age Groups

Continuous Histological Plaque Characteristics	<60 Y (n=262)	60–69 Y (n=485)	70–79 Y (n=504)	≥80 Y (n=134)	<i>P</i>	Adjusted Coefficient	Adjusted <i>P</i>
Log macrophages (±SD)	−0.39 (±0.73)	−0.42 (±0.78)	−0.46 (±0.76)	−0.51 (±0.80)	0.420	−0.064 (0.030)	0.089
Log SMCs (±SD)*	0.26 (±0.57)	0.046 (±0.67)	0.005 (±0.65)	−0.092 (±0.68)	<0.001	−0.146 (0.024)	<0.001
Log microvessels (per hotspot) (±SD)	0.89 (±0.31)	0.89 (±0.27)	0.87 (±0.30)	0.82 (±0.30)	0.328	−0.018 (0.259)	0.579
Binominal Histological Plaque Characteristics	<60 Y (n=262)	60–69 Y (n=485)	70–79 Y (n=504)	≥80 Y (n=134)	<i>P</i>	Adjusted OR per 10-Y Increase in Age (95% CI)	Adjusted <i>P</i>
Presence of lipid core ≥40%†	21.8% (57/262)	27.2% (132/485)	32.7% (165/504)	35.8% (48/134)	0.003	1.27 (1.07–1.50)	0.005
Presence of moderate/heavy calcifications‡	46.7% (122/261)	55.2% (267/484)	61.4% (309/503)	58.2% (78/134)	0.001	1.36 (1.16–1.58)	<0.001
Presence of moderate/heavy collagen	77.8% (203/261)	81.9% (397/485)	78.5% (395/503)	80.6% (108/134)	0.478	0.92 (0.77–1.11)	0.384
Presence of intraplaque hemorrhage§	48.3% (126/261)	61.9% (300/485)	59.2% (298/503)	50.7% (68/134)	0.006	1.02 (0.87–1.18)	0.837

Values for continuous parameters are presented as means (±SD). Values for binominal values are presented as percentages with absolute numbers. *P* values were calculated with analysis of variance tests for continuous data and Pearson χ^2 tests for binominal variables. Adjusted *P* values were calculated with linear and logistic regression models. Correction was performed for gender, smoking status, hypertension, peripheral arterial disease, coronary artery disease, symptomatic presentation, body mass index, statin use, anticoagulant use, and aspirin use.

SMCs indicates smooth muscle cells; SD, standard deviation.

Univariate analyses of variance post hoc tests revealed significant differences: *between <60 y and all other age groups; †between <60 y and 70–79 y and ≥80 y; ‡between <60 y and 70–79 y; §between <60 y and 60–69 y and 70–79 y.

Table 3. Measures of Association Between Age as a Continuous Variable and Histological Carotid Plaque Characteristics

Continuous Histological Plaque Characteristics	Coefficient (SE)	<i>P</i>	Adjusted Coefficient (SE)	Adjusted <i>P</i>
Log macrophages	−0.004 (0.002)	0.106	−0.005 (0.003)	0.095
Log smooth muscle cells	−0.012 (0.002)	<0.001	−0.011 (0.002)	<0.001
Log microvessels (per hot spot)	−0.039 (0.021)	0.061	−0.018 (0.025)	0.481
Binominal Histological Plaque Characteristics	OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	Adjusted <i>P</i>
Presence of lipid core ≥40%	1.025 (1.011–1.038)	<0.001	1.025 (1.008–1.042)	0.004
Presence of moderate/heavy calcifications	1.019 (1.008–1.031)	0.001	1.028 (1.012–1.043)	<0.001
Presence of moderate/heavy collagen	0.991 (0.977–1.005)	0.185	0.992 (0.974–1.010)	0.383
Presence of intraplaque hemorrhage	1.006 (0.994–1.017)	0.343	1.003 (0.989–1.019)	0.654

Linear and binary logistic regression models were used for the continuous and binominal variables, respectively. Adjusted measures of association represent the values corrected for gender, smoking status, hypertension, peripheral arterial disease, coronary artery disease, symptomatic presentation, body mass index, statin use, anticoagulant use, and aspirin use.

fications, respectively (Table 2). No significant differences for intraplaque hemorrhage, macrophage content, collagen, and microvessels between the groups could be observed.

Measures of association between age as a continuous variable and histological parameters were comparable to the analyses with age divided into 4 categories (Table 3). Every year of increase in age was significantly associated with a decrease in log SMCs with a coefficient of −0.011 (SE 0.002; adjusted *P*<0.001). A year of increase in age was also associated with an increased risk for lipid cores ≥40% (adjusted OR, 1.025; 1.008 to 1.042) and with an increased risk for heavy plaque calcifications (adjusted OR, 1.028; 1.012 to 1.043). No associations between age and the other histological parameters could be observed.

Discussion

The findings of the current study show that carotid plaque composition changes with age, independent of symptomatic presentation, cardiovascular risk factors, and medication use. To our best knowledge, this is the largest carotid plaque study, including 1385 plaques from consecutive patients undergoing CEA, describing the association between age and histological atherosclerotic plaque composition. Carotid plaques from elderly patients have relatively unstable carotid plaque characteristics such as large lipid cores, decreased SMC content, and heavy calcifications. The current study shows that the effect of age on carotid plaque stability is rather a gliding scale than an exponential change of plaque composition at a certain age point, like 80 years. This is in line with results from randomized trials showing that the periprocedural risk for CAS increases gradually with age.⁶ Nevertheless, when plaque composition is considered, octogenarians are at the unstable end of the spectrum, whereas patients <60 years have markedly stable plaque characteristics. The current study provides possible pathophysiological insights into underlying contributing factors for the increased periprocedural stroke risk during CAS for older patients.

Plaques from older patients contained less SMCs and the highest amount of large lipid cores. Differences in SMC

content were the highest between patients <60 years and older patients, but still SMC content decreased gradually among higher age groups. The finding that plaque calcifications and large lipid cores increase gradually with age is in line with recently published results from Redgrave et al.¹⁵ Although a decrease in overall plaque collagen content could not be observed, it is commonly accepted that a decline in SMC content is usually accompanied by a decrease in synthesis of collagen Types I and III, thereby weakening the strength of the fibrous cap of the plaque.²⁰ We observed a significant gradual increase in the presence of large plaque atheroma with increasing age. If the region between the lipid core and the atherosclerotic lesion surface is diminished as a result of a decrease in SMC content or an increase in lipid core size, the plaque becomes more susceptible to formation of fissures in the fibrous cap and ultimately plaque rupture.²¹ If plaque rupture occurs, lipid content is exposed to blood flow, triggering superimposed thrombus formation, which facilitates embolization and increases the risk of cerebrovascular events. During CAS, manipulation of plaques occurs by means of intra-arterial devices such as guidewires, balloon dilation, and stent placement. Manipulation of unstable plaques with thin fibrous caps and large lipid cores is accompanied by an increased risk for plaque rupture and thrombus formation. This might be an explanation for the increased periprocedural risk for stroke in the elderly undergoing CAS. Besides vulnerable plaque characteristics, also heavy carotid plaque calcifications have been reported as a contraindication due to an increased risk for periprocedural stroke and inadequate stent expansion.^{22,23} This provides an additional ground to be cautious with CAS in the elderly, who have severe calcified carotid lesions more frequently.

Besides increased risks for embolic stroke during angioplasty and stenting of vulnerable lesions, an adverse outcome has also been reported during follow-up in an imaging study by Kubo et al. Intracoronary stenting of vulnerable, lipid-rich lesions was associated with inadequate stent apposition and intracoronary thrombus formation during follow-

up.²⁴ Lipid-rich plaques are considered to be relatively avascular and contain less cells, which is detrimental for cell proliferation and proper strut endothelialization after stent placement.²⁵ Stent apposition and suboptimal endothelialization have been reported to be associated with late stent thrombosis in coronary arteries.²⁶ Ball et al recently reported a case with embolic stroke 3 years after carotid artery stenting and showed that plaque ulceration at the location of uncovered stent struts was colocalized with thrombus formation.²⁷ This confirms that also after a long term, carotid stents can give rise to renewed thrombosis and cerebrovascular symptoms due to suboptimal strut endothelialization and renewed thrombus formation. It can be hypothesized that especially the elderly are at risk for long-term adverse outcomes due to their lipid-rich carotid plaque phenotype, and therefore high risk of suboptimal stent endothelialization, but long-term results of CAS groups within randomized trials will have to be awaited.

Limitations

The current study contains certain limitations. At baseline, we observed more cardiovascular risk factors and medication use among younger patients. This is probably due to a certain amount of confounding; patients who require carotid surgery at a younger age have most likely been exposed to several risk factors for developing atherosclerotic lesions.¹⁵ Because of the design of our “real-life” prospective cohort study, this confounding factor cannot be excluded. We corrected for all baseline differences and medication use in all histological analyses through linear and logistic regression models and therefore expect that the effect of age on carotid atherosclerotic plaque composition is still evident and reliable, also due to the power and high number of patients included in this study.

The cutoff points in decades for the different age groups were chosen to focus on octogenarians, who have been reported to have a higher risk during CAS. Post hoc analyses revealed that the differences in SMC content, lipid cores, and plaque calcifications among the age groups were the most pronounced between the youngest group and the older groups. Nevertheless, the analyses with age as a continuous variable showed that per-year increase the SMC content significantly decreases and the risk of large plaque atheroma and calcifications significantly increases. This confirms that plaque destabilization is a gradual process that takes place over time and is strongly associated with age.

Conclusion

Plaque stability decreases gradually with age. Older patients with carotid stenosis have relatively unstable plaques with low SMC content and a high amount of large lipid cores as compared with younger patients. The underlying vulnerable plaque composition in the elderly might be an important contributing factor to the increased risk of stroke for older patients undergoing CAS.

Disclosures

The following authors are consultants for Cavadis, a start-up company for diagnostic plaque biomarker kits: D.P.V.d.K., F.L.M., and G.P. However, the content of this article is not related with the activities of the company.

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