Balloon-Protected Carotid Artery Stenting
Relationship of Periprocedural Neurological Complications With the Size of Particulate Debris

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Background—Carotid artery stenting (CAS) has been advocated as an alternative to endarterectomy. To prevent cerebral atheroembolism during CAS, distal balloon occlusion of the target artery increasingly is employed during the procedure. A correlation of the size of captured particles with the incidence of periprocedural neurological complications (PNCs) has not been attempted.

Methods and Results—In a 4-center, phase-1 trial, 54 patients (46 men; age, 69 ± 8 years) underwent 58 CAS procedures using the PercuSurge GuardWire system for distal protection. Aspirated debris was sent for histological/cytological analysis. Stent placement was successful in all cases. Mean balloon occlusion time was 10.4 ± 4.0 minutes (range, 3.0 to 22.0 minutes). Three patients (5.2%) experienced PNCs: 1 prolonged reversible ischemic neurological deficit that resolved in ≤ 48 hours, 1 stroke, and 1 transient ischemic attack. Relevant particles (those with an area ≥ 10 000 μm²) were found in 48 aspirates (83%). The median number of particles, their maximum diameter, and their maximum area were all significantly higher in the aspirates obtained during procedures associated with PNCs than in aspirates obtained during procedures not associated with PNCs. However, pronounced overlap in the distributions (PNCs versus no PNCs) of the number and maximum diameter of particles precluded any predictive inferences. In contrast, a maximum particle area > 800 000 μm² (> 0.8 mm²) was associated with a 60% chance of having a PNC.

Conclusions—Despite balloon protection, PNCs occurred in 5.2% of patients who underwent CAS procedures. The maximum area of aspirated particles seems to be an indicator of increased risk for PNCs. (Circulation. 2001;104:2791-2796.)

Key Words: carotid arteries ■ embolism ■ angioplasty ■ stents

For decades, the treatment of carotid artery disease has been the domain of vascular surgeons.1–4 In recent years, technological improvements in endoluminal equipment, based on the experience with coronary interventions, have paved the way for angioplasty and stent implantation in carotid arteries.5–8 To reduce the risk of distal embolization, a catheter-based protection system initially developed for saphenous vein graft interventions5 has been modified and made available for carotid interventions. By occluding the vessel distal to the target lesion with an inflatable balloon, this system allows the capture of particulate debris released during the intervention and the retrieval of debris with an aspiration catheter. In a minority of patients, however, periprocedural neurological complications (PNCs) have been observed despite balloon protection.

Little is known about the type, number, and size of the particles retrieved during protected carotid artery stenting. The present study sought to attain a correlation between particle characteristics and the patients’ neurological outcome.

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Methods

Patients

Between January 1999 and January 2000, sixty-nine patients referred for elective stenting of the internal carotid artery were enrolled in the Carotid Angioplasty Free of Emboli (CAFE) Germany trial. All interventions were performed using the PercuSurge balloon protection system. Symptomatic patients with an angiographic diameter stenosis (according to the North American Symptomatic Carotid Endarterectomy Trial criteria) ≥ 60% and asymptomatic patients with a diameter stenosis ≥ 70% were entered into a protocol approved by the local Ethics Committees and gave their written informed consent. Major exclusion criteria were a total occlusion of the contralateral internal carotid artery in the presence of ipsilateral vertebral or intracranial disease, as well as stroke or myocardial infarction within the past 14 days. In a subgroup of 54 consecutive patients (46 [85%] men; age, 69 ± 8 years; 5 [9%] > 80 years old), captured particles were collected and analyzed.

Clinical Protocol

An independent neurologist established the indication for intervention. The neurological examination was repeated postintervention.
and, in cases of in-hospital neurological symptoms, before discharge. Patients were discharged on a regimen of clopidogrel (75 mg/d for 1 month) and aspirin (100 mg/d). Clinical follow-up was obtained at 30 days.

Definitions
PNCs were defined as neurological events occurring during or within 24 hours of completion of the procedure. They comprised transient ischemic attack (TIA), prolonged reversible ischemic neurological deficit (PRIND) resolving in ≤48 hours, minor stroke (ie, new neurological deficits persisting >24 hours from onset and resolving completely in ≤30 days), and major stroke (ie, new neurological deficits persisting beyond 30 days of treatment).

Carotid Stent Protocol
The majority of patients received clopidogrel (75 mg/d) and aspirin (100 mg/d) for ≥3 days before the intervention. In patients who were not premedicated, a loading dose of clopidogrel (300 mg) and a bolus of intravenous aspirin (500 mg) were administered before the intervention. A 100-cm 5F selective Vitek catheter (Cook, Inc) was used for brachiocephalic angiography. A 0.035-inch guidewire was then introduced through the lumen of the Vitek catheter into the external carotid artery, and the Vitek catheter then was exchanged for a 7F long sheath. This was placed in the common carotid artery, and 70 to 100 IU/kg of heparin was administered to raise the activated clotting time to >225 seconds. An angiogram was taken in anteroposterior and lateral views to document cerebral blood flow. After advancement of the introducer sheath toward the carotid bifurcation, a magnified “worst-view” angiogram of the lesion was taken.

The balloon protection system (GuardWire, PercuSurge, Inc) consists of a 0.014-inch guidewire with a central lumen connected to a compliant distal occlusion balloon. Nominal balloon diameters were 3 to 4 mm or 5 to 6 mm. After testing for integrity, the balloon was fully deflated, introduced into the carotid artery, and advanced across the lesion. It was positioned at least 4 cm distally to the stenosis and was inflated until vessel size was reached. Contrast dye was applied to verify total blockage of the internal carotid artery. At this point, atropine (1 mg) was administered to prevent hypotension and bradycardia.

Lesions were stented either directly or after predilation. Self-expanding stents (Carotid Wallstent [Boston Scientific] or Memothurm [C.R. Bard Inc]) were used exclusively. All stents were postdilated with a 5.0-mm or 6.0-mm balloon on the basis of vessel size.

After postdilation, the PercuSurge Export aspiration catheter (lumen diameter of the distal tip: 1.1 mm) with a proximal vacuum syringe was advanced toward the occlusion balloon. With suction applied, this catheter was advanced and retracted several times between stent and balloon until 20 mL of blood was aspirated. At the investigator’s discretion, this procedure could be repeated once. The lesion site was not flushed with saline solution. Finally, the distal occlusion balloon was deflated and angiographic assessments were taken.

Angiographic Assessment
Target lesion morphology with respect to ulceration, calcification, and eccentricity was assessed by angiography. A lesion comprising ≥2 craters of ≥3 mm in depth or having poorly defined edges and a hazy appearance was defined as ulcerated. A lesion that appeared as a radiopaque area under fluoroscopy was defined as calcified.

Particle Analysis
Aspirate collected in 20-mL syringes was filtered through a 40-μm mesh, immersed in 4% buffered formaldehyde solution, and sent for histological and cytological analysis. Grossly visible solid fragments were removed manually and processed by paraffin embedding. From the remaining solution, cytological specimens were produced using a cytocentrifuge (Auto Smear CF-12DE, Sakura). Slides were stained by hematoxylin and eosin and Elastic von Giesson stain. The investigators performing the histological and cytological assessment were blinded to the angiographic and procedural results.

The slides were viewed under a microscope (Olympus BX50) in 20-fold magnification and digitized using a video camera (Sony DXC-950P) connected to a standard Intel-based computer by a video capture board. Particles were determined to be “relevant” if they were identified as thrombus, plaque, or intima fragments.

Morphological identification of particles was done at 100-, 200-, or 400-fold magnification according to the following criteria: (1) A particle was identified as a thrombus fragment if it appeared to be a conglomerate of erythrocytes with embedded strands of fibrin, and if the structure of single erythrocytes could not be discerned. (2) A particle was identified as a plaque fragment if it was a conglomerate of erythrocytes with embedded strands of fibrin and localized structures corresponding to elutriated lipids, particularly so-called cholesterol clefts, with the latter’s contour either serrated or smooth but clearly different from a fissure. Foam cells surrounding elutriated lipids confirmed the diagnosis of plaque. (3) A particle was defined as an intima fragment if it consisted of small pieces of collagen fibers, sometimes covered by endothelial cells or attached to plaque fragments. These structures were embedded in fibrin or thrombus fragments, and foam cells often were included.

Particles thus identified were tagged with a yellow dot on the low-magnification digitized image for subsequent geometric analysis. The smallest dot still discernible on the digitized image was used; it had a diameter of 110 μm, corresponding to an area of ≈9500 μm². Particles that were completely covered by this dot or had an area <10 000 μm² were excluded from analysis. Areas and largest diameters of tagged particles were measured using ImageTool software (Texas Health Science Center in San Antonio). The usually nonspherical, irregular contour of tagged particles was traced manually on the digitized image, and the enclosed area was calculated automatically. The largest diameter of each particle also was determined manually and calculated automatically.

Statistics
Continuous variables are presented as median (range). Group differences among continuous variables were assessed with the Mann-Whitney U test. Nominal variables were analyzed with the χ² test. Statistical significance was assumed at P<0.05. Data were analyzed with the StatView 4.5 software package (Abacus Concepts, Inc).

Results
Short-Term Outcome
The 54 patients underwent a total of 58 interventions. The target lesion was located in the left internal carotid artery in 31 cases (53%) and in the right internal carotid artery in 27 cases (47%). Contralateral lesions were treated in the 4 patients with 2 interventions. Stent implantation (90% Wallstent) was successfully performed (residual diameter stenosis <30%) in all 58 procedures. Lesions had a mean length of 13.0±6.3 mm; they were predilated in 28 procedures and approached directly (without predilation) in 30 (51.7%). Postdilation was performed with 5.0-mm and 6.0-mm balloons in 35 (60%) and 23 procedures, respectively. The protection system was successfully employed during all procedures; mean balloon occlusion time was 10.4±4.0 minutes (range, 3.0 to 22.0 minutes). Three patients experienced PNCs, for a procedure-related incidence of complications of 5.2%:

(1) An 86-year-old man had suffered a stroke 3 months before the intervention and was referred for an intervention for an ulcerated 65% stenosis of the left internal carotid artery. At the time of the intervention, he had incomplete residual right-sided hemiparesis and no impairment of speech.
During the direct stenting procedure, he temporarily lost consciousness. After completion of the procedure, the patient developed aphasia and aggravated right-sided hemiparesis. Both symptoms resolved completely in ≈48 hours, and the patient thus was considered to have suffered a PRIND. At discharge, his neurological status was identical to that before the intervention.

(2) A 58-year-old man who was treated by balloon angioplasty and stenting for an asymptomatic ulcerated 75% stenosis of the right internal carotid artery suffered a stroke manifested by left-sided hemiplegia and hemiparesthesia in ≈30 seconds after deflation of the occlusion balloon.

(3) A 75-year-old man with a symptomatic 65% stenosis of the left internal carotid artery developed motor aphasia 5 minutes after completion of a direct stenting procedure. His symptoms resolved completely in ≈40 minutes. This patient was considered to have suffered a TIA.

Balloon occlusion times in the 3 patients were 10, 16, and 12 minutes, respectively (P=0.157 versus procedures without PNCs).

Angiographic Analysis
Of all the lesions, 83% were eccentric, 36% were calcified, and 52% were ulcerated. There were no differences in the prevalence of morphological lesion characteristics between procedures without and with PNCs (Table 1).

Particle Analysis
Two 20-mL syringes of blood were drawn in 32 of the 58 procedures (55%), whereas only 1 syringe was drawn in the remaining procedures. A subanalysis of 17 two-syringe cases performed in Hamburg revealed that the median number, median maximum diameter, and median maximum area of particles contained in the first aspirate were all significantly higher than in the second aspirate (4 versus 0 particles [P=0.0032], 475 versus 0 µm [P=0.0097], and 101 672 versus 0 µm² [P=0.0016], respectively). In only 2 cases, the largest maximum particle area was found in the second aspirate. In procedures associated with PNCs, 2 syringes of blood were drawn in 2 cases and 1 in the other case.

No relevant particles were found in the aspirates retrieved during 10 procedures (17%) in 10 patients. None of these patients experienced PNCs. The numbers of particles identified as thrombus, plaque, and intima fragments are given in Table 1.

The total number of particles found in the aspirates retrieved during the 55 procedures without PNCs ranged from 0 to 32 (median, 4), whereas 10, 18, and 24 particles were counted in the aspirates of the 3 patients who experienced PNCs (Tables 1 and 2). Despite a statistically significant difference between the distributions (P=0.012), there was complete overlap (Figure 1). When particles were differentiated by type, a statistically significantly higher number of plaque particles was found in the aspirates of patients with PNCs (median of 10 particles in patients with PNCs versus 1 in procedures without PNCs; P=0.016) (Table 1). There was nearly complete overlap of ranges, however.

The maximum diameter of captured particles ranged from 130 µm to 2846 µm (median, 584 µm) in patients without PNCs and was measured at 1725, 2649, and 7301 µm in patients with PNCs (Tables 1 and 2). Again, the difference in distributions was statistically significant (P=0.009), but only the largest particle diameter in the latter group fell outside the range of maximum particle diameters in the former (Figure 2).

### Table 1. Angiographic Lesion Morphology and Characteristics of Relevant Particles

<table>
<thead>
<tr>
<th></th>
<th>All Procedures</th>
<th>No PNC</th>
<th>PNC</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lesions, n</td>
<td>58</td>
<td>55</td>
<td>3</td>
<td>0.417</td>
</tr>
<tr>
<td>Eccentric lesions</td>
<td>48 (82.8)</td>
<td>45 (81.8)</td>
<td>3 (100)</td>
<td>0.915</td>
</tr>
<tr>
<td>Calcified lesions</td>
<td>21 (36.2)</td>
<td>20 (36.4)</td>
<td>1 (33.3)</td>
<td>0.086</td>
</tr>
<tr>
<td>Ulcerated lesions</td>
<td>30 (51.7)</td>
<td>27 (49.1)</td>
<td>3 (100)</td>
<td>0.012</td>
</tr>
<tr>
<td>Total particles, n</td>
<td>4 (0–32)</td>
<td>4 (0–32)</td>
<td>18 (10–24)</td>
<td>0.016</td>
</tr>
<tr>
<td>Thrombus particles</td>
<td>1 (0–19)</td>
<td>1 (0–19)</td>
<td>0 (0–9)</td>
<td>0.785</td>
</tr>
<tr>
<td>Plaque particles</td>
<td>1 (0–20)</td>
<td>1 (0–19)</td>
<td>10 (3–20)</td>
<td>0.161</td>
</tr>
<tr>
<td>Intima fragments</td>
<td>0 (0–8)</td>
<td>0 (0–8)</td>
<td>4 (0–6)</td>
<td>0.161</td>
</tr>
<tr>
<td>Lesions with relevant particles, n</td>
<td>48</td>
<td>45</td>
<td>3</td>
<td>0.012</td>
</tr>
<tr>
<td>Maximum particle diameter, µm</td>
<td>592 (130–7301)</td>
<td>584 (130–2846)</td>
<td>2649 (1725–7301)</td>
<td>0.009</td>
</tr>
<tr>
<td>Maximum particle area, µm²</td>
<td>107 676 (14 589–2 987 993)</td>
<td>102 852 (14 589–834 686)</td>
<td>1 844 541 (811 506–2 987 993)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data are number, number (percentage), or median (range).

*No PNC vs PNC.

![Figure 1](http://ccr importing link)
The maximum area of captured particles ranged from 14,589 $\mu m^2$ to 834,686 $\mu m^2$ (median, 102,852 $\mu m^2$) in patients without PNCs. In patients with PNCs, maximum particle area was measured at 811,506, 1,844,541, and 2,987,933 $\mu m^2$ (Tables 1 and 2), with the latter 2 areas clearly outside the range of maximum particle areas in patients without PNCs (Figure 3). Consequently, the difference in distributions was statistically highly significant ($P=0.005$). A slight overlap of distributions was present, with the 2 largest particle areas in patients without PNCs (828,509 $\mu m^2$ and 834,686 $\mu m^2$) roughly the same as the smallest particle area measured in patients with PNCs. Also, the corresponding maximum particle diameters were of the same order of magnitude (1757 $\mu m$ and 1549 $\mu m$, respectively, in patients without PNCs, and 1725 $\mu m$ in patients with PNCs).

Thus, captured particles with a maximum area $\geq$800,000 $\mu m^2$ were associated with a 60% (3 in 5) incidence of PNCs, as opposed to a 0% complication rate when maximum particle area was $<$800,000 $\mu m^2$. Taking the clinical manifestation of neurological complications into account, a striking correlation with particle area was apparent (Table 2). The smallest particle (patient No. 3) was associated with a minor complication (ie, a TIA) whereas the 2 largest particles with areas markedly $>1 000 000 \mu m^2$ (1 mm$^2$) were associated with major neurological complications (ie, stroke and PRIND).

### Lesion Morphology and Particle Characteristics

Ulcereated lesions did not differ from nonulcerated lesions with regard to the total number of particles, their maximum diameter, and their maximum area found in the corresponding aspirates; an analogous finding was observed for calcified versus noncalcified lesions (Table 3). Also, lesions that were neither ulcerated nor calcified, when compared with lesions either ulcerated or calcified or both, were associated with statistically identical total numbers of particles, maximum particle diameter, and maximum particle area found in the corresponding aspirates (Table 3).

### Discussion

**Major Findings**

This study showed that carotid artery stenting using the PercuSurge balloon occlusion system for cerebral protection was associated with a 5.2% incidence of PNCs. After technically successful completion of 58 interventions, stroke, PRIND, and TIA occurred in 1 patient each. These events were related neither to the duration of balloon occlusion nor to the amount of blood (one or two 20-mL syringes) aspirated after stenting. Analysis of the aspirates collected during all interventions revealed that interventions with PNCs were associated with statistically significantly higher numbers of relevant particles, larger maximum particle diameters, and larger maximum particle areas than were interventions without PNCs. Also, aspirates from procedures with PNCs contained significantly more plaque particles than did aspirates from procedures without PNCs. However, there was a complete, or nearly complete, overlap of the ranges of the total number of particles, the number of plaque particles, and maximum particle diameters for procedures without versus procedures with PNCs, thus precluding any predictive inferences. On the other hand, only minimal overlap was present for the corresponding ranges of maximum particle area, such that the incidence of PNCs was 60% when maximum area was $>800 000 \mu m^2$. In the 2 patients whose aspirates con-

**TABLE 2. Distribution and Characteristics of Particles in 3 Patients Who Experienced a PNC**

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNC type</td>
<td>PRIND</td>
<td>Stroke</td>
<td>TIA</td>
</tr>
<tr>
<td>Total particles, n</td>
<td>24</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Thrombus particles</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Plaque particles</td>
<td>20</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Intima fragments</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Maximum particle diameter, $\mu m$</td>
<td>7301</td>
<td>2649</td>
<td>1725</td>
</tr>
<tr>
<td>Maximum particle area, $\mu m^2$</td>
<td>2,987,933</td>
<td>1,844,541</td>
<td>811,506</td>
</tr>
</tbody>
</table>

**Figure 2.** Histogram of the maximum diameter of relevant particles found in the aspirates of 45 patients without and 3 patients with PNCs. Note that particle diameters of the latter are located at the upper end of the distribution, yet, except for the largest-diameter particle, are contained within the range of the former. Total number of aspirates is 48 because no relevant particles were found in 10 aspirates.

**Figure 3.** Histogram of the maximum area of relevant particles found in the aspirates of 45 patients without and 3 patients with PNCs. Particle areas of the latter constitute the top end of the distribution; overlap with particle areas of the former is present only in the $800 000 \mu m^2$ range (†).
tained a particle with an area markedly >1 000 000 \( \mu{m}^2 \) (1 mm²), major neurological complications (namely, stroke and PRIND) occurred.

Methodological Aspects
In this study, only particles with an area \( \geq 10 \, 000 \, \mu{m}^2 \) were analyzed. Such a particle, if it were spherical, would occlude a vessel 113 \( \mu{m} \) in diameter, i.e., a vessel found in the border zones of the human cerebral circulation.11 Consequently, occlusion of such a vessel would give rise only if, at all, to a border zone infarction and not to a cerebrovascular incident compatible with the types of neurological complication generally observed during carotid interventions.

Clinical Relevance
Relevant particles were found in \( >80\% \) of aspirates. The angiographic appearance (ulcerated, calcified) of the lesion allowed no prediction of the number, maximum diameter, or area of the particles released during the intervention. This finding supports experimental work with ex vivo specimens of carotid plaque.12 Apparently, the angiographic lesion characteristics do not help to decide in favor of or against the use of a balloon protection system.

The fact that the aspiration of large-area particles was related to the incidence of PNCs suggests that the type of lesion (or the outcome of the stenting procedure) was such that multiple \( (\geq 2) \) large particles were liberated but not all were aspirated. Several reasons for this are conceivable: A particle may have been too large to pass through the opening of the aspiration catheter; a free particle may have hidden in the "suction shadow" of the aspiration catheter; or a particle may have gotten stuck in the stent meshes, only to be released with the blood flow after deflation of the occlusion balloon. These assumptions point to inherent deficiencies in the system that need to be addressed in future generations.

Predilation Versus No Predilation
Of the 3 patients in the present study who experienced PNCs, only the patient who suffered a stroke underwent balloon angioplasty before stent placement. On the other hand, lesion predilation was performed in 27 other patients without complications. It cannot be determined which of the 2 interventional steps was responsible for the patient’s adverse clinical outcome. In a recent study on human ex vivo carotid artery stenosis specimens, Ohki et al12 performed stenting with predilation in 20 stenoses >80% and direct stenting in 4 stenoses \( \leq 80\% \) and found a significantly higher number of embolic particles in the former. It is impossible, however, to discern if this finding was related to predilation or to the higher degree of stenosis.

Limitations
In this study, particles with an area <10 000 \( \mu{m}^2 \) were discarded because this threshold area was the lower limit for measurement on the digitized image. Also, it was the intention of the study to characterize each particle entered into the analysis not only by its shape but also by its composition and thereby to exclude loosely aggregated erythrocytes as well as thrombogenic "dirt" particles possibly originating during preparation of the slides. It thus is conceivable that smaller "true" particles were missed that could have caused neurological events by accumulation or precipitation of thrombus formation. The number of patients enrolled in this study was too small to allow a multivariate analysis of factors predictive of PNCs.

The oval opening of the aspiration catheter has a maximum diameter of 1.1 mm. It thus is conceivable that maceration of large particles has taken place and that, consequently, (1) more large particles than those found in the aspirates were liberated during the intervention and (2) some particles may have been larger before aspiration.

Conclusions
Balloon protection during carotid artery stenting using the PercuSurge system did not prevent PNCs in 5.2% of patients. Aspiration of particles with an area >0.8 mm² was associated with a 60% chance of PNCs. The findings of this study need to be verified in a larger, prospective trial. Furthermore, it needs to be shown whether technological improvements can improve the clinical outcome of patients undergoing balloon-protected carotid interventions.

References


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