Intimal Hyperplasia of the Infant Parasellar Carotid Artery
A Potential Developmental Factor in Atherosclerosis and SIDS

Wolfgang J. Weninger, Gerd B. Müller, Christian Reiter, Stefan Meng, Silvi U. Rabl

Abstract—Intimal cushions that project into the lumen of arteries are precursors of atherosclerotic plaque formation. The “carotid siphon,” although frequently affected by atherosclerosis, was never analyzed for the occurrence of neonatal intimal hyperplasia. This study provides a topographic and morphometric analysis of intimal cushions in the parasellar internal carotid artery (pICA) of the human infant. A total of 35 specimens were studied in detail, using both standard histological techniques and a new method of computer-aided 3D reconstruction. Intimal hyperplasia occurred at 3 characteristic locations of the pICA: (1) the convex side of the posterior knee (C5 cushion), (2) the bottom of the horizontal segment (C4 cushion), and (3) the concave side of the anterior knee (C3 cushion). The extension of the cushions and the degrees to which they occluded the vessel lumens were measured. The complex shape of the pICA required 3D computer models for exact topographical descriptions and precise measurements. Our results suggest that the occurrence and degree of intimal hyperplasia are related to shape changes of the pICA during postnatal development. We predict that individuals who retain the relatively straight course of the fetal pICA throughout their lives are less prone to develop atherosclerotic lesions at this portion of the carotid artery. A possible contribution of neonatal intimal cushions to the origin of sudden infant death syndrome is discussed. (Circ Res. 1999;85:970-975.)

Key Words: intimal cushion ■ hemodynamics ■ 3D reconstruction ■ internal carotid artery ■ child

In the carotid artery system, the parasellar internal carotid artery (pICA) has a high propensity toward atherosclerosis, and lesions at this location frequently cause stroke.1–7 Sites of intimal hyperplasia, which appear as intimal cushions that project into the lumen of arteries, represent precursors of atherosclerosis.8,9 Such intimal cushions occur after vascular injury10–12 and vascular surgery,13–17 but they are also physiologically present near the branchings and divisions of intracranial arteries in neonates18–21 and infants.22–24 The extracranial carotid system and its intracranial branches have been studied extensively in regard to intimal hyperplasia and atherosclerosis.25–28 In contrast, information about the occurrence, position, and size of intimal hyperplasia in the pICA is scant, and information about atherosclerotic plaques is contradictory.29–35 This lack of information is caused by the hidden position of the pICA, which prevents the use of modern in vivo techniques such as ultrasound. In addition, the strongly curved course of the blood vessel impedes exact positional and morphometric analyses based on individual histological sections.

In 84% of adults, the pICA has the characteristic double-bent shape that gave rise to the term “carotid siphon,”36 but in all neonates, the pICA takes a much straighter course. This indicates that the shape of the pICA is strongly transformed during early childhood.37 This period of life also coincides with the occurrence of sudden infant death syndrome (SIDS).

One of the established factors in the multifactorial genesis of SIDS is lack of oxygen in the brain,38 which can also be caused by lumen occlusion of large arteries and the consequent deficiency of blood supply.39 We hypothesized that unusually strong intimal hyperplasia in the pICA could represent another possible cause for a reduced blood supply to the brain of neonates and infants. In this article, we demonstrate a relationship between the shape transformation of the pICA and the occurrence of intimal hyperplasia in young infants, and we discuss the consequences of these processes for the genesis of atherosclerosis and SIDS.

Materials and Methods
Parasellar regions (PSR) were collected over a period of several years from 19 male and 16 female human infants aged between 3 weeks and 9 months. None of the specimens showed vascular malformations. A total of 12 infants died from accidents and, in 23 individuals, the cause of death was diagnosed as SIDS in the forensic autopsy protocol.

Complete blocks of PSRs were dissected out of the skull bases and were fixed in neutral buffered formaldehyde (3.7%). Four PSR blocks were histologically sectioned in their entirety at a section thickness of 0.007 mm. The sections were stained with standard eosin/hematoxylin, Goldner’s, or Mallory’s stain. One entire PSR of a 3-week-old male infant and carefully isolated pICAs from the right side of 30 other infants were reconstructed three-dimensionally using the EPI-3D method.40 The digital image series was also used for histomorphometry. Because the images were captured directly from the block surfaces.
before sectioning, they did not exhibit any distortion, shrinkage, or other artifacts that usually occur during the mounting and staining processes. All measurements were performed on the computer using NIH image 1.61. Some of the vessels were collapsed or their media were contracted because the human arteries could not be pressure-fixed. Thus, the outer diameter of the blood vessel, the inner diameter, and the area of the lumen were calculated from the circumferences. The ratio between the outer and the inner diameters of the blood vessel was termed the contraction index; it ranged between 1.151 and 1.459 and represented an estimate for the contraction status of each artery. Two groups were distinguished: noncontracted and contracted. Arteries with a contraction index \( \leq 1.305 \) (20 specimens) were part of the noncontracted group, and those with a contraction index \( >1.305 \) (10 specimens) were part of the contracted group. The lateral extension of the intimal cushions was calculated as a percentage of the total circumference of the vessel lumen, and the percentages of lumen occlusion were also calculated.

Statistical analyses were performed using the \( \chi^2 \) test for the occurrence of intimal cushions in straight versus curved arteries and for the occurrence of intimal cushions in the SIDS versus the non-SIDS groups. The Mann-Whitney U test was used to compare the occurrence of intimal cushions in the straight versus curved arteries and in the noncontracted versus the contracted group. An expanded Materials and Methods section is available online at http://www.circresaha.org.

**Results**

**Histological Findings**

In unaffected, nonhyperplastic regions of the pICA, the histological picture of the vessel wall appeared normal. The intima consisted of a single endothelial cell layer that was clearly separated from the media by an internal elastic lamina. The smooth muscle cells of the media were aligned nearly circularly. In contrast, the wall of the artery was markedly thickened at hyperplastic locations. Eccentric elevations that projected into the vessel lumen (cushions) were formed by the intima (Figure 1). In such hyperplastic regions, the internal elastic lamina and the endothelial cell layer appeared widely intact, but in some circumscribed areas, the internal elastic lamina was ruptured or split at the fringes. Elastic fiber bundles were seen within the cushions, and some contained scattered leukocytes. In other cases, only the media was thickened, and its smooth muscle cells were irregularly aligned or formed longitudinal bundles. Such thickenings were not defined as intimal cushions and were not included in this study.

**Distribution of Intimal Cushions**

The 3D computer models of the sectioned vessels permitted exact, quantitative analyses of the location, extension, size, and frequency of intimal hyperplasia in the pICAs. The 3D models of the vessel wall, the lumen, and of the intimal cushions were reconstructed from serial sections to visualize their sizes and locations. In each segment of the pICA, intimal hyperplasia occurred at a characteristic location; we developed a terminology for this in accordance with the traditional segments of the ICA (Figure 2a).

**C5 Cushion**

On the dorsomedial side of the first segment of the pICA (C5 segment), an intimal cushion was present in 24 specimens (80%) (Figure 2b). It usually began at the internal aperture of the carotid canal and extended toward the vertex of the posterior knee of the pICA. In most cases, it included the origin of the meningohypophyseal trunk (Figures 3a through 3c). In 2 cases, it merely covered the posterior knee. In 4 cases, the cushion did not reach the posterior knee, but it was seen near the internal aperture of the carotid canal. In the latter cases, the origin of the meningohypophyseal trunk was surrounded by a separate intimal cushion of small size.

**C4 Cushion**

In the horizontal segment of the pICA (C4 segment), an intimal cushion was present in 26 specimens (87%) (Figure 2b). In most cases, it began at the distal end of the concave side of the posterior knee and extended distally toward the beginning of the convex side of the anterior knee (Figures 3a through 3c). In 4 cases, the cushion extended further proximally and extensively covered the concave side of the posterior knee. In 3 cases, it extended further distally and included large parts of the convex side of the anterior knee. In 4 other cases, it extended both distally and proximally. In most cases, the origin of the inferolateral trunk of the pICA was surrounded by the lateral part of this cushion (Figure 3a).

**C3 Cushion**

At the concave side of the anterior knee of the pICA (C3 segment), an intimal cushion occurred in 19 specimens (63%) (Figure 2b). It was always located at the transition from the C3 to the C2 segment (Figures 3c and 3d), where the adventitia of the pICA is connected to the anterior and the middle clinoid processes by strong connective tissue strands before it enters the subarachnoidal space.41

**Ophthalmic Cushion**

In addition to the pICA cushions, an intimal cushion was present in 80% of our specimens at the origin of the ophthalmic artery. In 83% of these cases, the cushion was located at the proximal side of the orifice of the ophthalmic artery, and in 17%, the cushion surrounded the orifice almost completely (Figures 3b through 3d). The ophthalmic cushion was not further analyzed because the ophthalmic artery does not arise from the pICA proper (segments C3 through C5) but...
from the intra-arachnoidal C2 segment. In addition, the cushion represented a typical branching cushion, which was analyzed in detail in a number of earlier studies (eg, Reference 22).

Size of Intimal Cushions and Extent of Lumen Occlusion

The maximum extent of each intimal cushion was calculated in relation to the lumen circumference of the vessel. C5 cushions covered, on average, 30.7% (8.5% to 51%), C4 cushions, 33% (8% to 69.5%), and C3 cushions, 26.1% of the lumen circumference (10.5% to 42%) (Figure 2c). In each pICA, the C4 cushion covered a greater area than the C5 cushion, and the C5 cushion covered a greater area than the C3 cushion. Thus, the C4 segment of the pICA generally contained the largest region of intimal hyperplasia.

The average degree of lumen occlusion by the intimal cushions was ascertained separately for the contracted and the noncontracted blood vessel groups. In the noncontracted group (n=20), C5 cushions occluded, on average, 6.25% (0.5% to 16.5%), C4 cushions, 8.5% (1.5% to 25%), and C3 cushions, 6.5% of the vessel lumen (2% to 9.5%). In the contracted blood vessel group (n=10), C5 cushions occluded, on average, 16.6% (6.5% to 42.5%), C4 cushions, 18% (4% to 63%), and C3 cushions, 12.8% of the vessel lumen (4.5% to 25%) (Figure 2d). For the C5 cushion, the Mann-Whitney U test showed a significantly (P=0.0056) more extensive lumen occlusion in contracted blood vessels than noncontracted ones; this was not true for the C3 and the C4 cushions. In 3 contracted pICAs, >1 of the cushions occluded >30% of the lumen, and in 1 specimen, the C4 cushion occluded >60% of the lumen over a length of ~1 mm (Figure 4).

Frequencies

The C5 cushion was present in 80%, the C4 cushion in 87%, the C3 cushion in 63%, and the ophthalmic cushion in 80% of our reconstructed specimens (Figure 2b). The ophthalmic cushion does not belong to the pICA proper and, thus, it was excluded from statistical analyses. A total of 23 pICAs (77%) showed C4 and C5 cushions simultaneously (Figures 3a through 3c). In 15 pICAs (50%), C3, C4, and C5 cushions appeared together (Figure 3c).

The frequencies of the occurrence and size of intimal cushions were analyzed independently for the non-SIDS and SIDS groups. In the non-SIDS group (n=12), the C5 cushion was present in 9 specimens (75%), the C4 cushion in 10 specimens (83%), and the C3 cushion in 7 specimens (58%). In the SIDS group (n=18), the C5 cushion was present in 15 specimens (83%), the C4 cushion in 16 specimens (89%), and the C3 cushion in 12 specimens (67%) (Figure 5). This shows a slightly higher incidence of intimal cushions in the SIDS group in every cushion type, but these results were not
statistically significant. The sites of cushions did not differ significantly. The pICA that showed the highest degree of lumen occlusion by an intimal cushion (Figure 4) was part of the non-SIDS group.

Another frequency analysis distinguished between ICAs that take a very straight course through the parasellar region and those that are distinctly double curved. The first group (straight pICAs, n=8) included those vessels in which the angle of the posterior knee was $\geq 150^\circ$. In this group, a C5 cushion occurred in only 3 specimens (38%), a C4 cushion in 5 (62%), and a C3 cushion in 6 (75%). In the second group (bent pICAs, n=22), the angle of the posterior knee was $\leq 150^\circ$. In this group, a C5 cushion appeared in 19 specimens (86%), a C4 cushion in 22 (100%), and a C3 cushion in 13 (59%) (Figure 6). The $\chi^2$ test showed that the C5 cushions ($P=0.0222$, but 2 cells had an expected frequency <5) and C4 cushions ($P=0.00246$, but 1 cell had an expected frequency <5) occurred with significantly higher frequencies in the curved blood vessel group. Differences in the frequency of the C3 cushion were not significant. In 2 pICAs of the straight-course group, not a single cushion was present, and 2 other specimens merely had fragmented C3 cushions (Figure 3d). In 4 of the straight-course pICAs (13% of the entire sample), neither a C4 nor a C5 cushion was present.

Discussion

The adult pICA is strongly affected by atherosclerosis, but information on the position and extension of atherosclerotic plaques is contradictory. Intimal hyperplasia is a precursor of atherosclerotic plaques and the reason for vascular obliteration after mechanical manipulations of arteries and veins. We studied the position, size, and extension of intimal cushions, and the degree of lumen occlusion they provoke, in the pICAs of human infants.

Traditional, 2D histological sections are not adequate for precise histomorphometric analyses or topographic descriptions of intimal cushions in strongly curved arteries. Thus, a new, computer-supported, 3D-reconstruction technique was used in the present study. The computer images were captured directly from the histologically stained surface of the paraffin block during sectioning, thus avoiding all artifacts caused by section processing. The 3D computer models exhibited resolutions between 0.006×0.006×0.012 mm and 0.01×0.01×0.012 mm per voxel. Because of the high resolution of the images and their descent from a histologically stained section series, our technique is more sensitive than computed tomography, nuclear magnetic resonance, or ultrasound techniques.

Initially, we hoped to show a relationship between SIDS and the occurrence of intimal hyperplasia, but this relationship failed to be of statistical significance. However, for every type of intimal cushion of the pICA, the frequency was slightly higher in SIDS victims compared with the non-SIDS group. Because a lack of oxygen supply to the brain has repeatedly been hypothesized as causally involved in SIDS, we suggest that the presence of extensive intimal cushions could be 1 factor in the multifactorial pathogenesis of SIDS.

High shear stress, low shear stress, and hemodynamic turbulence are discussed as triggers for physiological intimal hyperplasia elsewhere. If this is correct, the cushions found in our analyses would each be caused by different forces. Typical C4 cushions of the pICA extend from the distal concave side of the posterior curvature and further distally and reach the proximal convex side of the anterior curvature. According to hemodynamic stress exploration, hemodynamic turbulence caused by the posterior curvature would be responsible for C4 cushion formation. In contrast, C3 cushions seem restricted to the very concave side of the anterior curvature and, therefore, would be caused by low shear stress, whereas C5 cushions would be caused by high shear stress.
In contrast to purely hemodynamic models, we propose that the cushions in the pICA are associated with the developmental shape transformations of this vessel. In the majority of adults, the ICA forms a carotid siphon in the PSR, but it takes a rather straight course in 16% of adults. In fetuses and neonates, the pICA is generally less bent than in adults. In this study, a statistically significant correlation between the shape of the pICA and the degree of intimal hyperplasia in the C4 and C5 segments was shown. Strongly curving pICAs exhibited a high incidence of C4 and C5 cushions, whereas straight pICAs exhibited a low incidence of intimal cushions. We suggest that the shape-transformation process of the pICA represents a vulnerable phase of the vessel wall, in which intimal hyperplasia can easily occur, either as an active part of form transformation or because of its secondary hemodynamic consequences. This is supported by studies indicating that the mechanisms involved in both the normal assembly of vessels during development and the remodeling of the vessel wall contribute to the pathogenesis of proliferative and obliterative vascular diseases.

Our findings create the following 2 testable clinical predictions for further study: (1) Infants with a persisting straight course of the pICA do not develop intimal cushions that can extensively occlude the lumen of the blood vessel during the first year of life and, hence, should be less prone to develop SIDS, and (2) adults who retain a straight course of the pICA throughout their lives will have a lower predisposition to develop atherosclerotic plaques in these locations. As a consequence, these individuals should have a reduced risk of stroke caused by atherosclerosis of the pICA.

References
8. Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W, Richardson M, Rosenfeld ME, Schaffer SA, Schwartz CJ, Wagner WD, Wissler RW. A definition of the intima of human arteries and of its atherosclerosis-prone regions: a report from the Committee on Vascular...


Intimal Hyperplasia of the Infant Parasellar Carotid Artery: A Potential Developmental Factor in Atherosclerosis and SIDS

Wolfgang J. Weninger, Gerd B. Müller, Christian Reiter, Stefan Meng and Silvi U. Rabl

Circ Res. 1999;85:970-975
doi: 10.1161/01.RES.85.10.970

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/85/10/970

Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/1999/11/05/85.10.970.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/