Carotid baroreceptor pathological findings regarding carotid plaque status and aging

José Milei MD PhD¹, Anna M Lavezzi MD PhD², Barbara Bruni MD², Daniel R Grana VMD¹, Francisco Azzato MD¹, Luigi Matturri MD PhD²

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BACKGROUND: Carotid baroreceptor pathological lesions have been studied in animals, but few human necropsies have been performed. Therefore, data rely on case patients following surgery, radiotherapy and carotid endarterectomy. Almost no data are available regarding whether the effect of aging prevails over pathological conditions, despite the classic description that glomic fibrosis increases with age.

OBJECTIVE: To morphometrically characterize the alterations of the carotid baroreceptors and their supplying arteries.

METHODS: Patients (n=23) who had suffered and died from stroke, with and without complicated internal carotid atheromatosis, were divided by age (group 1: older than 80 years; group 2: 65 to 80 years; and group 3: younger than 65 years). Carotid segments were obtained at autopsy. The specimens were stained for light microscopy and immunohistochemistry.

RESULTS: Carotid glomus presented from moderate-to-severe atrophy and fibrosis. A focal decrease in vascularization (CD34-positive) of the glomus (greater than 50%) was observed in areas of atrophy and fibrosis. Damaged nerve endings (S100 protein-positive) were observed at the media of the carotid sinus. Morphometric data showed no differences between groups for glomus area, number of type 1 and 2 cells, and the wall to lumen arteriole ratio. No statistical differences were demonstrated in the pathological findings of the carotid glomus when comparing complicated with noncomplicated plaques or age groups.

CONCLUSION: Severe carotid chemoreceptor damage exists in patients who have died from stroke and suffered from carotid atheromatosis. These findings were independent from aging and plaque type. However, damage was correlated with a marked narrowing of the supplying arterioles as a consequence of hemodynamic and/or metabolic alterations (dyslipidemia, diabetes).

Key Words: Aging; Atherosclerosis; Carotid body; Carotid glomus; Hypertension

Anomalies anatomopathologiques baro- et chimiorécepteurs carotidiens, statut des plaques carotidiennes et vieillissement

HISTORIQUE : Les anomalies anatomopathologiques touchant les barorécepteurs et les chimiorécepteurs carotidiens ont fait l'objet d'études chez l'animal, mais on dispose de peu de données anatomopathologiques chez l'être humain. Les données disponibles proviennent de spécimens prélevés chez des patients qui ont subi une chirurgie, des traitements de radiothérapie ou une endartériectomie carotidienne. On ne dispose pour ainsi dire d'aucune donnée pour vérifier si l'effet du vieillissement supplante celui d'autres pathologies, malgré la description classique de l'aggravation de la fibrose glomique avec l'âge.

OBJECTIF : Recenser les altérations morphométriques des baro- et chimiorécepteurs et des artères qui les irriguent.

MÉTHODES : Des patients (n = 23) décédés des suites d'un accident vasculaire cérébral (AVC), atteints ou non d'athéromatose carotidienne interne compliquée, ont été répartis selon l'âge (groupe 1 : 80 ans et plus; groupe 2 : de 65 à 80 ans et groupe 3, moins de 65 ans). Les segments de carotides ont été prélevés à l'autopsie. Les spécimens ont été colorés pour examen microscopique et analyse immunohistochimique.

RÉSULTATS : Le glomus carotidien présentait une atrophie et une fibrose de modérées à graves. Les auteurs ont noté une diminution en foyers (CD34-positifs) de la vascularisation du glomus (plus de 50 %) dans les zones d'atrophie et de fibrose. Ils ont observé une atteinte (protéine S100-positifs) des terminaisons nerveuses au niveau de la média du sinus carotidien. Les données morphométriques n'ont montré aucune différence entre les groupes pour ce qui est de l'aire du glomus, du nombre de cellules de types 1 et 2 et du rapport paroi-lumière artériolaires. Les auteurs n'ont observé aucune différence statistique entre les anomalies du glomus carotidien lorsqu'ils ont comparé les groupes d'âge ou les plaques compliquées et non compliquées.

CONCLUSIONS : On note de graves anomalies des chimiorécepteurs chez les patients qui sont décédés des suites d'un AVC et qui souffraient d'athéromatose carotidienne. Ces observations étaient indépendantes de l'âge et du type de plaque. Toutefois, les atteintes étaient en corrélation avec un rétrécissement marqué de la lumière des artérioles en cause, consécutif à des anomalies hémodynamiques et/ou métaboliques (dyslipidémie, diabète).

The significance of the ability of the carotid sinus baroreceptor to sense and regulate blood pressure has been known since the publication of Hering's investigations in 1927 (1). A few years later, in 1930, Heymans unequivocally demonstrated the chemoreceptor activity of the carotid bodies (2). However, the impact of carotid baroreceptor denervation was studied only in animals. There have been few human necropsies and therefore, evidence relies on case patients with damage to the carotid sinus and glomus (carotid body) following surgery, radiotherapy and carotid endarterectomy (3,4). Moreover, the effects of these interventions on baroreceptor

structures have not been extensively studied. Therefore, little information is available on the morphology of inherent baroreceptor structures in disease (5).

The baroreflex is very important for the maintenance of arterial pressure, particularly during orthostatic stress. Chemoreflexes play an eminent role in maintaining blood gas homeostasis (6). Therefore, baroreflex failure is a disabling and potentially life-threatening condition.

Data on the long-term effect of human bilateral carotid sinus denervation on arterial blood pressure are limited and controversial (3,7-10).

¹Instituto de Investigaciones Cardiológicas, Facultad de Medicina, Universidad de Buenos Aires – Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina; ²Istituto di Patologia, Università degli Studi di Milano, Milano, Italia

Correspondence: Dr José Milei, Instituto de Investigaciones Cardiológicas, "Prof Dr Alberto C Taquini", Marcelo T de Alvear 2270, C1122AAJ, Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina. Telephone 54-11-45083836, fax 54-11-45083888, e-mail ininca@fmed.uba.ar

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It was observed that acute carotid sinus denervation, as a result of bilateral carotid glomus tumour resection, has a long-term effect on the level, variability and rapid reflex control of arterial pressure. Findings in 13 patients subjected to bilateral carotid glomus resection included increased daytime and nighttime blood pressure variability, unopposed sympathetic activation in response to physical and mental stress, and the elimination of orthostatic hypotension and normocapnic hypoxic drive as a result of peripheral chemoreflex failure (11).

Baroreceptors are compromised in diseases such as diabetic autonomic neuropathy, Guillain-Barré syndrome, arterial hypertension and heart failure (12). Fatal complications in most stroke patients likely result from baroreceptor malfunction (12).

The available experimental and clinical evidence suggests that a pattern of chronic intermittent hypoxia, with short episodes of hypoxia followed by normoxia, selectively enhances the chemosensory and ventilatory responses of the carotid body to hypoxia, suggesting this sensor has an essential role in the enhanced ventilatory and cardiovascular responses observed in animals and obstructive sleep apnea patients (13).

Recently, we found a strong involvement of the chemoreceptor structures and corresponding supplying arterioles in a selected group of elderly patients who had died from cerebral vascular disorders with critical carotid artery lesions (14).

Despite the accepted dogma that the amount of connective tissue separating the glomic lobules increases with age (3), the significant fibrotic involvement and the unquestionable reduction in the vascularity, as was found in our previous study (14), could not merely be explained by the aging process. However, a possible limitation to the interpretation of those results was the superposition of arterial hypertension, atherosclerosis and aging in the patients. Due to these facts, and to characterize the potential damage of the carotid glomus related to hemodynamic stress alone, we performed experiments using spontaneously hypertensive rats (SHRs), an animal model with arterial hypertension, in which other factors such as dyslipidemia, high blood sugar or aging were absent.

In this group, we found a significant increase in extracellular matrix expansion in the carotid glomus and autonomic nerves, along with a decreased number of neurons in autonomic ganglia compared with normotensive controls. Furthermore, all these findings were highly correlated with high blood pressure and an increase in plasminogen activator inhibitor 1 (PAI-1) and transforming growth factor-beta-1 (TGF- β -1) deposits in the carotid glomus and autonomic ganglia. Additionally, SHRs presented a higher wall to lumen arteriole ratio in small periglomic vessels, a higher number of S100 protein-positive cells (sustentacular or type 2 cells) and a decreased number of type 1 cells in the carotid glomus. Interestingly, extracellular matrix expansion was highly correlated with the blood pressure level. Because of this, these structures must be considered as target organs in the model of systemic hypertension (15).

The objective of the present study was to morphometrically characterize the alterations of the carotid baroreceptor structures and their supplying arteries in patients who died from stroke with complicated versus noncomplicated internal carotid atheromatosis.

METHODS

Samples consisting of bilateral (when possible) or unilateral carotid segments were obtained at autopsy from 23 patients who died from ischemic neurological disorders. The patients consisted of 15 men and eight women, with a mean ($\pm$ SD) age of 75.7 $\pm$ 12.2 years (range 51 to 94 years). Clinical information, including age, sex, history of hypertension, left ventricular hypertrophy, diabetes, hyperlipidemia, percentage of ideal body weight, pack-years smoking and uric acid levels, was available in all cases. All patients had received long-term acetylsalicylic acid therapy (100 mg/day to 325 mg/day). Patients were undergoing chronic treatment with diuretics plus a beta-blocker (atenolol [AT]), calcium antagonist (amlodipine) or angiotensin-converting enzyme inhibitor (ACEI; enalapril) for hypertension; simvastatin for dyslipidemia; and metformin and/or glibenclamide for type 2 diabetes. All patients suffered

from transient ischemic attacks preceding their strokes, with extensive cerebral damage that precipitated death. No patient had previous surgeries or radiation treatment in the neck region.

Informed written consent was obtained from the relatives of the deceased patients to perform the autopsy and study organs with scientific aims according to national regulations.

Samples consisted of carotid segments including the distal portion of the common carotid artery (10 mm), and proximal portions of the internal and external carotid arteries (approximately 25 mm). The carotid segments were washed gently with saline, labelled for orientation and processed for optical microscopy.

Tissue processing

The specimens were fixed with 10% buffered formaldehyde and slowly decalcified with 2.5% nitric acid. Each whole specimen was embedded in paraffin and sliced frontally into two segments. Each of these segments was assessed for the degree of luminal involvement, intimal lesions, and plaque thickness and distortion. The paraffin blocks were then serially cut at a thickness of 6 μ m, and every section was alternatively stained with hematoxylin and eosin, Azan trichrome and Grimelius silver stains to detect catecholamines (16), and for immunophenotyping procedures.

Immunophenotyping of cells and nerves present in the carotid specimens was performed with monoclonal antibodies including CD34 (BioGenex, Canada) to identify endothelial cells, and nervous tissue protein S100 (Dako, Denmark) to identify Schwann cells and type 2 glomic cells. Immunocytochemical staining procedures were published elsewhere (17).

Semiquantitative morphometric analysis

Fibrosis and glomic cell preservation was assessed according to the following scale: 0 – no fibrosis between glomic structures and preservation of glomic cells; 1 – mild fibrosis between glomic structures and disappearance of at least 25% of glomic cells; 2 – moderate fibrosis between glomic structures and disappearance of at least 50% of glomic cells; and 3 – severe fibrosis, almost ‘cirrhotic’ aspect with disappearance of almost all glomic cells. Also, glomus vascularization was assessed using the following scale: 0 – preserved vascularization; 1 – disappearance of at least 25% of glomus vessels; 2 – disappearance of at least 50% of glomic vessels; and 3 – disappearance of at least 75% of glomic vessels.

The scales used for semiquantitative morphometric analysis were arbitrary.

Morphometric analysis

Morphometric analysis was performed with an Image-ProPlus version 3 image analyzer (Media Cybernetics, USA). Histological images were acquired via a CCD Color Camera (Ikegami Tsushinki Co Ltd, Japan), using a Plan Neofluar (Carl Zeiss Microimaging, USA) objective lens.

The section with the largest area was chosen to perform measurements. The following parameters were evaluated:

- The surface area of the carotid body (μ m²). The carotid body was isolated, edited, delineated and analyzed using a $\times$ 2.5 objective lens.
- The total number of cells in the carotid body and the number of type 1 and type 2 cells. The number of cells on the sections were counted using a $\times$ 20 objective lens.
- Glomus vessels (arterioles). The size of the major and minor lumen of the arteriole, the thickness of its wall and the wall to lumen arteriole ratio were recorded.

After immunotyping, plaques were pathologically characterized (17) into the following seven categories:

1. Plaque rupture plus thrombosis. Fibrous caps were highly variable in thickness. The area of rupture was covered by thrombus, in many cases embedding the lipid core, in close contact with a large pool of lipids. Borders of the rupture were infiltrated by macrophages.

Figure 1) Whole specimen of a frontally cut carotid segment. The arrow points to the glomus located in the interstitial tissue between the internal and external carotid arteries and its corresponding nerves. Multiple nonstenotic fibrolipidic and fibrotic plaques are observed along the carotid axis. Hematoxylin and eosin stain; $\times 20$ objective lens. 1 Common carotid artery; 2 External carotid artery

2. Plaque rupture plus intraplaque hemorrhage plus thrombosis.
3. Plaque rupture plus intraplaque hemorrhage.
4. Calcified ulcerated plaque.
5. Intraplaque hemorrhage without plaque rupture (despite careful search in serial sections, connections between area of hemorrhage and arterial lumen were not observed).
6. Noncomplicated calcified plaque (consisting of dense fibrous connective tissue, small amounts of lipids, cell debris and irregular masses of calcified material).
7. Soft plaque (thin fibrous cap covering a lipid-rich core, with widespread vascularization, and prone to future rupture, hemorrhage or thrombosis).

For statistical purposes, plaques were divided into two subsets: complicated (types 1 through 5) and noncomplicated.

Patients were also divided arbitrarily by age. Group 1 was older than 80 years ($n=9$; mean age 87.3 ± 3.5 years [range 82 to 94 years]). Group 2 was 65 to 80 years of age ($n=7$; mean age 76.3 ± 3.7 years [range 69 to 80 years]). Group 3 was younger than 65 years of age ($n=7$; mean age 60.1 ± 5.8 years [range 51 to 66 years]) ($P < 0.0001$).

Values are expressed as mean $\pm$ SD. All statistical analyses were performed using GraphPad InStat version 3.00 (GraphPad Software, USA; <www.graphpad.com>). For parameters with a Gaussian distribution, comparisons between groups were performed using one-way ANOVA with Dunnett's post test. For parameters following non-Gaussian distributions, comparisons were made using Fisher's exact test. $P < 0.05$ was considered significant. The Spearman rank correlation was

Figure 2) Carotid glomus showing almost normal structure and vascularization. Veins are dilated (arrow) and there is a mild increase in interstitial fibrosis (asterisk). Hematoxylin and eosin stain; $\times 100$ objective lens

performed to evaluate the relationship between histomorphometric data and age.

RESULTS

Carotid arteries

Thirty-six carotid segments were retrieved at autopsy from 23 patients who died from ischemic neurological disorders. The carotid bifurcation and the first 10 mm to 15 mm of the internal carotid artery were involved in all cases by atherosclerotic lesions. Large lipid cores with a fibrous cap and a band of fibrous tissue of variable thickness separating the plaque from the extensively damaged media were observed in all plaques. In eight cases, extensive calcified deposits were also found. The collagen border was frequently vascularized. In most cases, extensive chronic inflammatory infiltrates were observed, which consisted of macrophages and minor numbers of lymphocytes as well as extensive neoangiogenesis and calcified deposits.

Complicated plaques ($n=16$) presented with mononuclear infiltrates in the periphery, shoulders and bases in two-thirds of the cases. In contrast, only one-third of noncomplicated plaques ($n=20$) had inflammatory infiltrates ($P < 0.0001$).

The carotid glomus was located in the carotid fork, measuring approximately $3 \text{ mm} \times 1.5 \text{ mm}$, and formed by lobules compactly arranged, separated by connective tissue (14,18,19) (Figure 1). The functional units consisted of numerous small groups of cells arranged in clusters. They were grouped to form lobules organized as compact nests that were embedded in a fibrous stroma through which numerous nerve fibrils and small blood vessels were observed (Figure 2). Parenchymal cells consisted of two types: the 'chief cells' (epithelioid or type 1 cells), which were large cells with a round nucleus and a large amount of cytoplasm containing vesicles and granules stained by the Grimelius silver reaction; and elongated cells, known as 'sustentacular cells' or type 2 cells. Chief cells were arranged in the centre and sustentacular cells at the periphery (14).

Complex arrangements of afferent nerves and postganglionic sympathetic nerves, as well as autonomic ganglion cells, were found surrounding the lobules (18).

The carotid glomus showed moderate atrophy and fibrosis to severe atrophy with extensive fibrosis (cirrhotic appearance) (Figure 3). There was a loss of the characteristic chief cells (more than 50%) and loss of their argyrophilic Grimelius-staining granules, suggesting a decrease in their catecholamine content (Figure 4). Fibrosis and glomic cell loss was assessed as 2.6 ± 0.5 .

A focal reduction of glomus vascularization (more than 50%) was also observed in the areas of atrophy and fibrosis when capillaries were

Figure 3) Carotid glomus. **A** Marked decrease in cells and moderate fibrosis. Typical rounded chief cells are shown in the centre of the section (arrowhead). Hematoxylin and eosin stain; $\times 400$ objective lens. **B** Severe atrophy and, in some areas, absence of acinar structures with replacement by dense connective tissue with a so-called 'cirrhotic' appearance (asterisk). Hematoxylin and eosin stain; $\times 100$ objective lens

Figure 4) **A** Acinar structure belonging to a carotid glomus showing a moderate-to-severe decrease in the number of chief cells, and loss of argyrophilic intracellular granules (shown in black). Grimelius stain; $\times 200$ objective lens. **B** Carotid glomus. A focal absence and global decrease of vascularization is shown in the areas of acinar atrophy and fibrosis. anti-CD34 stain; $\times 100$ objective lens

stained with anti-CD34, which was assessed as 2.76 ± 0.6 (Figure 4).

In a few cases, it was possible to observe autonomic ganglia showing moderate fibrosis, mild-to-moderate neuronal damage and lipofuscin deposits (Figure 5). Interestingly, the arterioles to the glomus showed severe fibrointimal proliferation and disruption of the internal elastic lamina, marked thickening of the media and luminal narrowing. Luminal thrombi were also observed, as well as focal areas of medial homogenization (Figure 6).

At the outer media of the carotid sinus, corresponding to the deeper layers of the plaques, it was possible to identify damaged nerve endings that reacted specifically with S100 protein.

The morphometric findings are summarized in Table 1. No differences were found among groups for glomus area, number of type 1 cells, number of type 2 cells or the wall to lumen arteriole ratio. Also, no statistical differences could be demonstrated when complicated (intraplaque hemorrhage and/or rupture and/or thrombosis) and noncomplicated plaques were compared or when comparing age groups 1, 2 and 3. No correlation between morphometric data and age was found.

Regarding the underlying diseases (cardiac hypertrophy, myocardial infarction, diabetes, hypertension and stroke) and age or sex, the group of patients was heterogeneous. Therefore, it was not possible to associate the morphological changes with either age, sex or the underlying disease. The link among them, however, was severe arterial atherosclerotic involvement.

Figure 5) Autonomic ganglia showing moderate fibrosis and mild-to-moderate neuronal damage with intracytoplasmic lipofuscin deposits (arrowhead). Hematoxylin and eosin stain; $\times 200$ objective lens

DISCUSSION

Patients with stenosis of the extracranial carotid arteries constitute a multimorbid population that frequently shows several vascular risk factors, including hypertension and diabetes. The present study demonstrated that, in patients who died from cerebral vascular disorders with critical carotid artery lesions, a strong involvement of the chemoreceptor structures and their supplying arterioles was found. Accordingly, at the outer media of the carotid sinus, corresponding to the deeper fibrocalcified layers of the plaques and in periglomic areas, damaged nerve endings were observed as well as fibrotic autonomic ganglia.

Therefore, a strong involvement of the baro- (carotid sinus) and chemoreceptor (carotid body or glomus) structures and their corresponding nerves and arterioles was observed in the present group of elderly patients. These lesions were independent of patient age, as well as the presence of a complicated carotid plaque.

Despite the observation that the connective tissue separating the glomic lobules increases with age (3), the marked fibrotic involvement and the clear decrease in its rich vascularity, shown by the CD34 immunophenotyping in the present paper, cannot be explained only in terms of aging.

Figure 6 **A** Glomus arteriole showing marked intimal fibrosis with moderate thickening of the media and focal areas of medial homogenization, and severe adventitial fibrosis. Hematoxylin and eosin stain; $\times 100$ objective lens. **B** Glomus arteriole with marked fibrointimal proliferation and thickening of the wall with luminal narrowing. Azan stain; $\times 100$ objective lens. **C** Small artery supplying the glomus. Marked fibrointimal fibrosis with reduction of the lumen and medial fibrosis. Azan stain; $\times 100$ objective lens

TABLE 1
Morphometric analysis performed in the patients studied

	Complicated plaques (n=16)	Noncomplicated plaques (n=20)	Group 1* (n=7)	Group 2† (n=7)	Group 3‡ (n=9)
Glomus area (mm ²)	8.3 $\pm$ 4.1	8.4 $\pm$ 4.2	8.1 $\pm$ 3.5	8.8 $\pm$ 3.6	7.1 $\pm$ 3.3
Number of type 1 cells	1096.5 $\pm$ 243	1064.5 $\pm$ 285	1081.1 $\pm$ 389.2	1153 $\pm$ 454.1	816.4 $\pm$ 232
Number of type 2 cells	446.8 $\pm$ 177	444.9 $\pm$ 145.1	465.9 $\pm$ 146.9	450.7 $\pm$ 192.7	383.0 $\pm$ 93.3
Wall to lumen arteriole ratio	0.60	0.47	0.76	0.59	0.53
Spearman rank correlation (r)	—	—	-0.05	0.048	-0.37

All values are expressed as mean $\pm$ SD unless otherwise specified. All Spearman rank correlations were not significant. *Older than 80 years of age; †65 to 80 years of age; ‡Younger than 65 years of age

Several studies have found the grade of fibrosis to be dependent on age (20), while others have demonstrated considerable differences, not only within comparable age groups but, in a few cases, between the right and left sides (21). On the other hand, examination of surgical specimens removed from patients older than 60 years of age showed that the organ almost had a 'cirrhotic' appearance (18). This suggests an arteriolar involvement leading to fibrosis by a chronic hypoxic mechanism.

Most of the autonomic parameters, including heart rate variability and baroreflex sensitivity, decline with age (22). However, in the rat, aging of the cardiovascular system may not be associated with the attenuation of the baroreflex function (21). Accordingly, the carotid baroreceptor reflex is well maintained in both young and old dogs, suggesting a lack of morphological involvement (23). Nevertheless, the attenuation of the baroreflex is far less pronounced in patients in whom the possible effects of disease counteract the age effects (24). Therefore, it is possible that the age-related baroreflex attenuation observed in humans may not be due to aging per se but may instead reflect atherosclerotic and/or hypertensive processes (25,26).

There are few data concerning the dependency of the various kinds of chemoreflex sensitivity on age in healthy human subjects. A recent study (22), however, showed no significant correlation between chemoreflex sensitivity and age in patients with multiple organ dysfunction syndrome. The authors hypothesized that this lack of correlation can be interpreted as a confirmation that the effect of the disease prevails over aging in pathological conditions.

Early studies (27) speculated that a high systemic arterial pressure may deactivate the baroreceptor function by damaging the nerve endings in the arterial wall. An alternative explanation was issued by Heath and Smith (28), who suggested that an increased stiffness of the arterial wall would splint the baroreceptor endings, reducing their sensitivity to changes in arterial pressure instead. These authors went on to point out that, to some extent, atherosclerosis must depend on the orientation of the receptors in the arterial wall. If they are pulled circumferentially, an increased rigidity of the arterial wall should lead to a decreased baroreceptor response. In contrast, if the structure is

compressed outwards from within, an increased rigidity of the vessel wall may not have such an effect (28).

Baroreflex is aroused by changes in blood pressure that are collected by autonomic nerve 'sensors' that are distributed in the arterial tree and convey the stimuli elicited by mean pressure, rate of change in pressure (dP/dt), pulse pressure and heart rate. These mechanoreceptors, typically gathered in the outer tunica media of the carotid sinus, are found as nerve terminals and, occasionally, with the features of drumstick swellings. The smooth muscle layer is thinner there to allow for an increased vessel compliance favouring an enhanced mechanical stimulation (29).

Adjustment of the respiration rate in response to changes in levels of oxygen, carbon dioxide and hydrogen ions in body fluids are mediated by a complex interplay between central and peripheral chemoreceptors. The peripheral arterial chemoreceptors, located in the carotid and aortic glomus, are responsible for the immediate ventilatory and arterial pressure increments during acute hypoxia (2). Type 1 cells in the carotid and aortic glomus release neurotransmitters in response to hypoxia, causing depolarization of nearby afferent nerve endings (30).

Unquestionably, permanent high blood pressure causes a deleterious effect in peripheral nervous structures. However, few studies deal with the findings reported in the present paper regarding the deleterious effect of arterial hypertension on carotid glomus and autonomic ganglia.

Previous studies have demonstrated a strong correlation between arterial hypertension and the development of lesions in the carotid glomus and autonomic ganglia characterized by extracellular matrix expansion, as well as a reduction in the number of ganglia neurons (15). Because lowering blood pressure is the first step in controlling the deleterious effects of arterial hypertension, we have recently evaluated the possible differences between the effects of the beta-blocker AT and the ACEI ramipril (RAM) regarding a protective role on these structures, as target organs in SHRs (31).

At the end of the experiment, SHRs receiving AT and SHRs receiving RAM (SHR-RAM) showed a similar control in blood pressure compared with untreated SHRs. However, SHR-RAM presented

with a significant reduction in extracellular matrix expansion in the carotid glomus, autonomic ganglia and autonomic nerves. Moreover, the number of neurons was preserved with AT and even more with RAM compared with the untreated SHR group. TGF- β -1 and PAI-1 were increased in the carotid glomus and autonomic ganglia in SHRs and in SHRs receiving AT, whereas SHR-RAM showed a similar expression to the normotensive group (Wistar-Kyoto rats), indicating that RAM, but not AT, provided a significant protective role against structural changes in these structures caused by arterial hypertension in SHRs. This effect seems to be independent of blood pressure reduction (31).

These structures were well preserved by an ACEI because permanent high blood pressure stimulates extracellular matrix expansion as a result of enhanced TGF- β -1 and PAI-1 production, through a mechanism regulated by the renin-angiotensin-aldosterone system (31). Previous studies have shown the existence of a local renin-angiotensin-aldosterone system in the carotid glomus (32). In agreement with this information, ACEIs could prevent fibrosis in baroreceptor structures observed in SHR by reducing local angiotensin II production (31). The clinical importance of these data could be that the baroreflex attenuation in humans might be a consequence of atherosclerotic or hypertensive processes.

Complicated carotid plaques have been implicated as the main lesions responsible for the onset of cerebral symptoms. More recent blind studies, however, indicate that a link between complicated plaques and symptomatic disease might not exist (33-36). Accordingly, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (37) demonstrated that most carotid strokes occur without warning symptoms. In a previous study (38), we could not demonstrate that complicated plaques are associated with symptoms in a very large series of 281 carotid endarterectomy specimens. Therefore, it was suggested that such plaques may occur at any time regardless of symptoms. In agreement with our previous results, the present study indicates a lack of correlation among complicated plaques, the marked fibrotic involvement of the glomic structures and the clear decrease in their rich vascularity shown by the CD34 immunophenotyping.

While the relationship between atherosclerosis and baroreflex sensitivity has been well documented in animal models (39-41), similar evidence in humans is both limited and indirect. It is possible that the age-related baroreflex attenuation observed in humans may not be

due to aging per se, but it may reflect atherosclerotic and/or hypertensive processes (14,25,26).

Carotid baroreceptors are of utmost importance in the rapid adjustment of circulation and ventilation; the different degrees of involvement of these structures may explain various clinical responses (42). These may encompass chronic hypertension, isolated systolic hypertension, blood pressure lability, postural lightheadedness and periodic orthostatic hypotension (42). Elderly hypertensive patients with these relatively common conditions could be considered as a high-risk stroke group (14,43).

Recently, Cooper et al (44) reported that the effect of both peripheral and central chemoreceptors on baroreflex function may contribute to promoting hypertension in patients with obstructive sleep apnea.

Accordingly, Kario et al (43) investigated the clinical significance and mechanism of orthostatic blood pressure dysregulation in elderly hypertensive patients. They found that silent cerebrovascular disease is advanced in elderly patients with orthostatic hypertension. Elderly hypertensive patients with orthostatic hypertension or orthostatic hypotension may have an increased risk for developing cerebrovascular disease.

CONCLUSION

Severe carotid chemoreceptor damage exists in elderly patients who died from stroke and suffered from carotid atheromatosis, independently from aging and plaque type. The damage is plausibly related to a marked narrowing of their supplying arterioles as a consequence of hemodynamic (hypertension) and/or metabolic (diabetes, dyslipidemia) disturbances.

Unfortunately, as it has been stressed (14,29), the interest in physiology, pathology and clinical studies of baroreception is hindered by the scarce information on the morphology (necroptic studies) of its inherent structures in disease (14).

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