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The Influence of Chronically Hypoxemic States on Human Carotid Body Structure and Cardiac Hypertrophy*

Robert C. Janzer and Jakob Schneider
Institut für Pathologie der Universität Zürich (Prof. Chr. Hedinger, J.R. Rüttner)

Summary. Quantitative and qualitative changes in the human carotid body morphology, and their relationship to changes in the weight of right and left ventricles were investigated in 10 patients with a history of chronic hypoxemia. 5 patients without a history of cardiac, pulmonary or cerebral respiratory failure served as the control group. In the chronically hypoxemic group, a 2.67-fold increase in the total specific glomus cell volume was found. Up to a critical volume this increase is due to hypertrophy, beyond that it is due to hyperplasia. The course of the morphologic changes under the influence of slowly progressive chronic hypoxemia is discussed in a frame work of three stages (stage I = hypertrophy, stage II = nodular hyperplasia, stage III = atrophy). Plasmacellular infiltrates are constant though sometimes sparse. They are mostly perineural in location, less often intralobular and if so almost exclusively periglomoidal. In one case, we found an increase of Schwann cells in the interstitial and periglomoidal space without demonstrable degeneration of the nerve fibres themselves. Our hypothesis suggests that degeneration of special nerve terminals of the reciprocal type occurs in afferent nerve fibers. The increase of right ventricular weight (by a factor of 2.05) is significant, in contrast to that of the left. A linear correlation between the increase of right ventricular weight and the increased total glomus cell volume was not established. In 4 cases, however, we found pulmonary hypertensive vascular changes, which might be responsible for the disparity in the linear relationship.

Key words: Carotid body – Chronic hypoxemia – Cor pulmonale – Glomus cell volume.

Introduction

The work of Arias-Stella (1969, 1973), Heath et al. (1970, 1973), and Edwards et al. (1971a, b, 1973) has shown that human carotid bodies increase in size

* Dedicated to Prof. Dr. J.R. Rüttner on the occasion of his 60th birthday

For offprints contact: Dr. R.C. Janzer, Institut für Pathologie der Universität Zürich, Kantonsspital, CH-8091 Zürich, Switzerland

and weight in chronically hypoxemic states. In the same patients these authors also demonstrated an increase in weight of both right and left ventricles of the heart. These findings have been generally confirmed by morphometric studies on rats (Blessing and Wolff, 1973; Laidler and Kay, 1975a). It is our opinion that it is essential, especially in human carotid bodies, to estimate not only the weight of the whole organ but the total volume of the specific glomus cells. Histologically the human carotid body is of the disseminated type and contains a variable amount of interstitial and non-specific tissue. Several authors (see Adams, 1958) have found the grade of fibrosis dependent on age, while we noted considerable differences not only within comparable age groups but even between right and left sides in a few cases.

The first task of our study consisted in re-examining the volume increase of the spedific glomus cells type I in chronically hypoxemic patients. Secondly, we wished to establish whether there was a relation ship between qualitative changes in carotid body morphology and grade and/or duration of hypoxemia. Finally, we were interested in the correlation between morphological changes in the carotid bodies an the weight of the right and left ventricles of the heart.

Material and Methods

We investigated 10 patients of both sexes (2 females, 8 males) with a mean age of 68.8 years, who had come to necropsy with a known history of chronic hypoxemia of minimally 3 months and maximally 16 years duration (Table 1). The control group consisted of 5 patients in whom cardiac, pulmonary or cerebral chronic hypoxemia was excluded. Necropsy and histologic procedures were the same in both groups. The common carotid arteries were severed 2–3 cm on either side of their bifurcation. The carotid bodies were separated from their surrounding connective tissue, blood vessels and larger nerve bundles using a dissecting microscope, and fixed in Bouin's solution. We assumed the grade of shrinkage to be equal in the two groups. Each carotid body was embedded in paraffin wax; serial sections, 5 μ thick, were cut vertical to the longitudinal axis at 50 μ intervals throughout each block. Every second section was stained with hematoxylin and eosin, leaving the other sections unstained. We renounced the precise calculation of section thickness as published by Marengo (1944), being more interested in comparing both groups than in obtaining an absolute measurement while assuming the error in this procedure to be equal for both groups. The proportional volume of specific glomus cells was calculated using the point-counting method. An integration plate incorporated in the eye piece of the microscope was used to project a grid of 400 squares and 441 crosspoints onto the tissue structure. Only points lying on specific glomus cells were counted while the periglandular and interstitial connective tissue was neglected. The distance between any two cross-points at a chosen magnification, as well as the total net area, could be calculated with a standardized glass slide. The proportion of hitting points to total number of grid points correspond to the proportional area. Since, among other factors, the precision of this approximation is dependent on the total number of grid points, we rotated the grid in random directions, projecting it four times on the same field of vision, and in this manner counted up to 5000 points per case. We used Simpson's rule as quoted by Dunnill (1968) for the calculation of the absolute volume. In every case the number of nuclei of type I glomus cells were counted in 5 high-power fields on each of 10 randomly chosen sections, taking care to avoid non-specific elements. Again, we left out of consideration the correction factor given by Floderus (1944) for the true value of nuclei, being more interested in a comparison of both groups than in an absolute measurement and assuming the error to be equal in both groups. The hearts were dissected following the method of Fulton (1952), in a manner that allows the free wall of the right ventricle and the left ventricle with the septum to be weighed separately. The ventricular quotient ($VQ = L + S/R$) could thus be determined. The right lung was fixed in toto by injecting 4% buffered formalin under standardized pressure of 50 cm water through the right pulmonary artery. During fixation of at least 48 h

Table 1

Case Nr.	Age, Sex	Diagnosis	Duration of clin. symptoms of resp. insuffiencieny	pO_{2art}	pCO_{2art} (mm Hg)[a]
1	63, ♀	Syndrome of Thibierge-Weissenbach	3 months	35	53
2	70, ♂	Panlobular emphysema of lungs	12 years	36	65
3	63, ♂	Centrilobular emphysema of lungs	"since years"	not known	
4	68, ♂	Panlobular emphysema of lungs	4 years	not known	
5	63, ♀	Interstitial fibrosis of lungs	1 year	37	36
6	73, ♂	Panlobular emphysema of lungs	5 years	50	70
7	56, ♂	Asbestosis of lungs	16 years	53	25
8	86, ♂	Centrilobular emphysema of lungs	"since many years"	51	43
9	60, ♂	Eosinophilic granuloma of lungs	6 years	not known	
10	84, ♂	Panlobular emphysema of lungs	"since many years"	32	59

[a] Values taken during the last hospitalization

the pulmonary veins were clamped. Ten to twelve randomized sections were taken, embedded in paraffin, and stained by the combined van Gieson-elastin method. The significance of mean differences and the correlation between the various parameters were statistically investigated by the *t*-test and linear regression analysis.

Results

The total volume of glomus cells per case is demonstrated in Figure 1 for both investigated groups. The mean value difference turns out to be significant ($P<0.001$). The group with chronic hypoxemia shows a 2.67-fold increase of the mean total volume of glomus cells as compared to the control group. The spread is much greater in the chronically hypoxemic group.

The number of nuclei of type I glomus cells per high-power field is shown in Figure 2. The mean value difference turns out to be significant ($P<0.01$). The chronically hypoxemic group shows a 1.84-fold mean decrease of nuclei per field of vision as compared to the control group (see also Fig. 6).

Figure 3 illustrates the correlation between total glomus cell volume and number of type I glomus cell nuclei. There is no significant linear correlation,

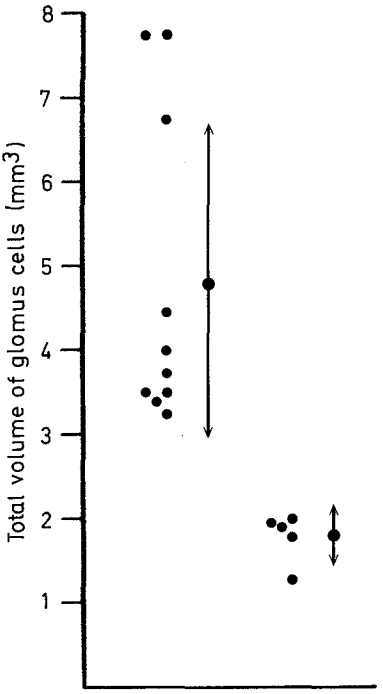

Fig. 1. Total volume of glomus cells type I (mm^3). Representation of single values, of mean values, and of twice the standard error. Respiratory insufficiency group on the left, control group on the right. Significance of differences between mean values ($P < 0.001$)

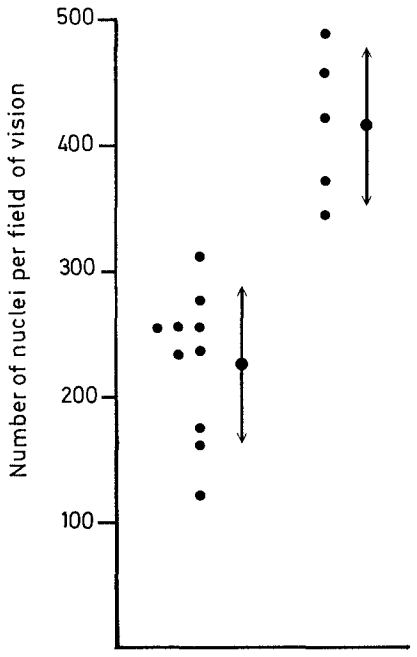

Fig. 2. Numer of nuclei per field of vision. Representation of single values, of mean values, and of twice the standard error. Respiratory insufficiency group on the left, control group on the right. Significance of differences between mean values ($P < 0.01$)

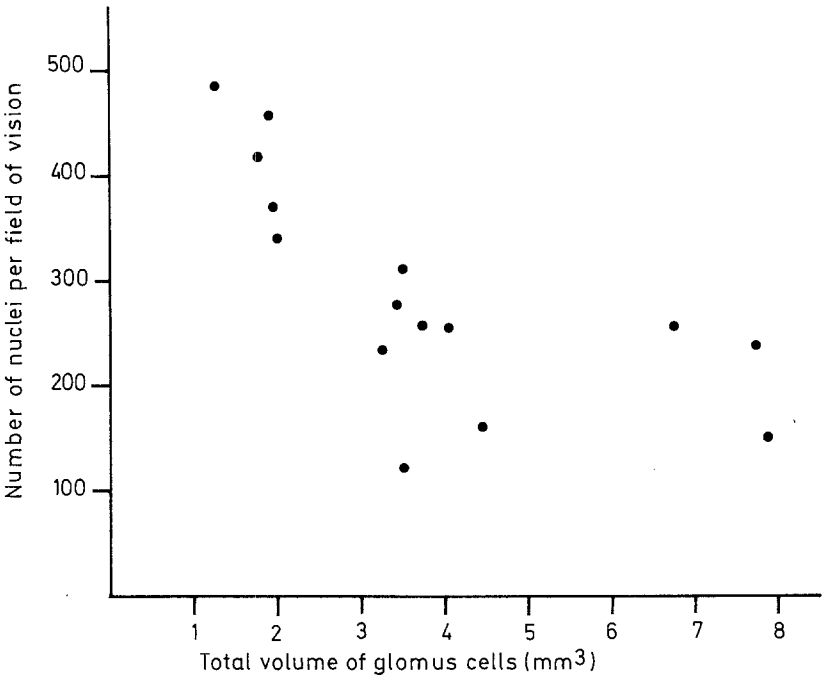

Fig. 3. Relation between total volume of glomus cells type I (mm^3) and number of nuclei per field of vision

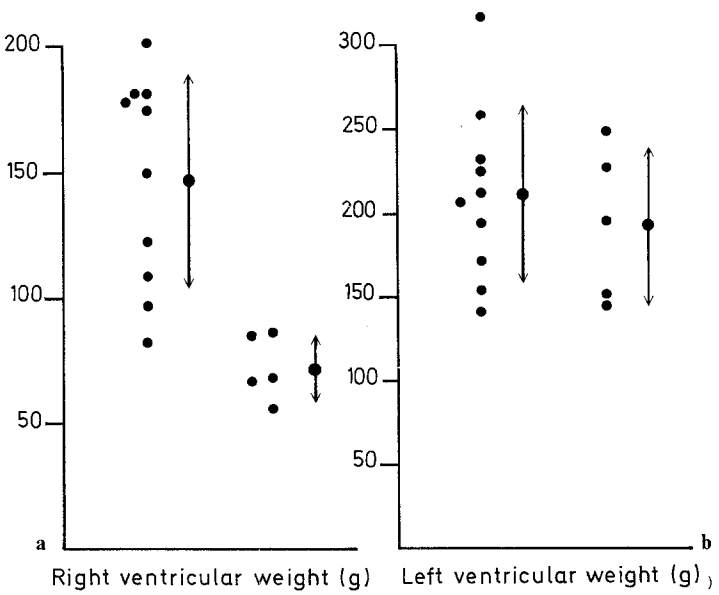

Fig. 4. a Right ventricular weight (g). **b** Left ventricular weight (g). Representation of single values, of mean values, and of twice the standard error. Respiratory insufficiency group on the left, control group on the right. The differences between mean values are significant for right ventricular weights ($P<0.01$), not for left ventricular weights

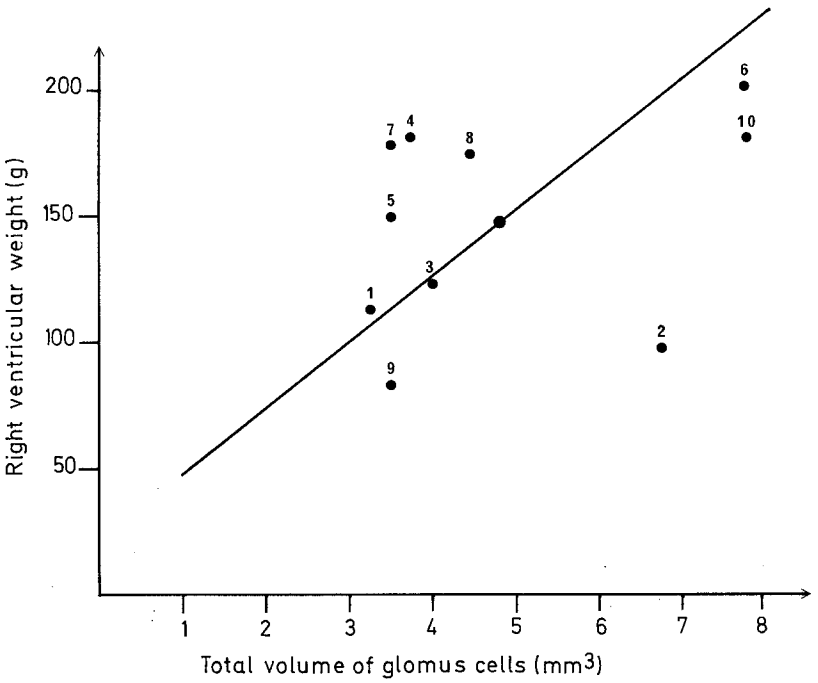

Fig. 5. Relation between total volume of glomus cells type I (mm^3) and right ventricular weight (g). No significant correlation ($P > 0.05$). The numbers 1 to 10 are identical with the case numbers of Table 1

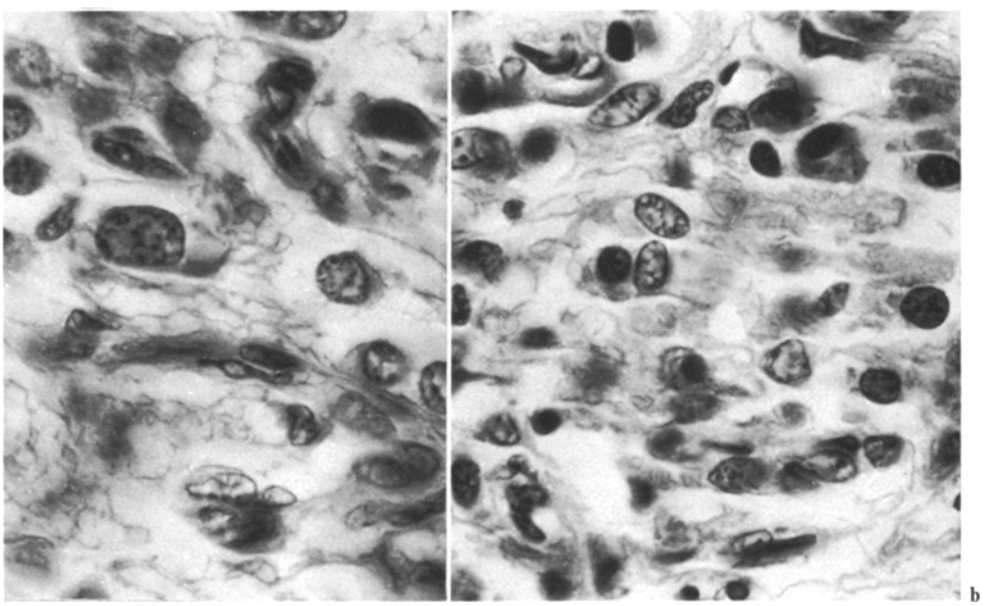

Fig. 6a and b. Detail from human carotid body (× 1000). **a** Chronically hypoxemic patient: the type I glomus cells are enlarged, with a lighter, scarcely granular cytoplasm; the nuclei are increased, lighter and have a more irregular nuclear membrane. **b** Control

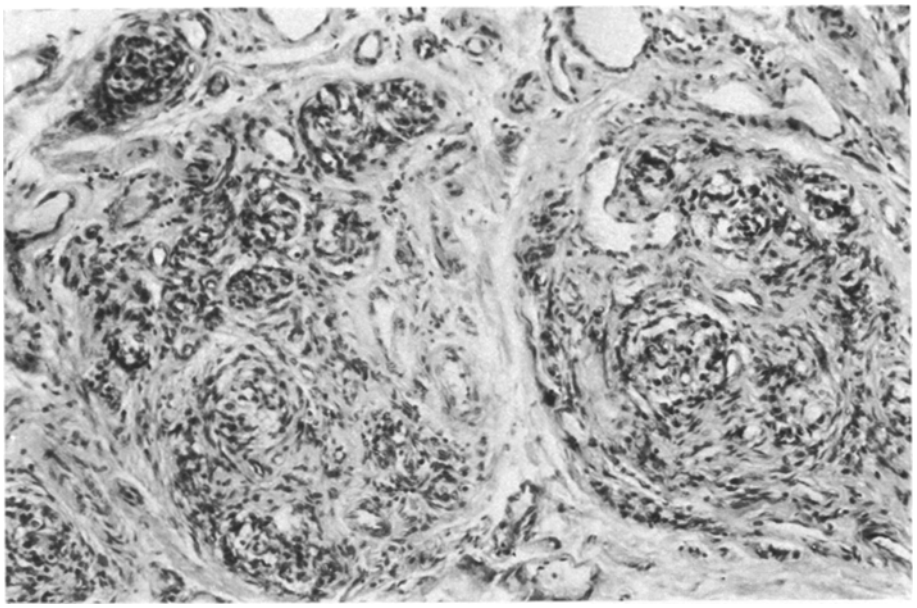

Fig. 7. Detail from human carotid body of a chronically hypoxemic patient (×130). Note enlargement and irregularity of lobuli, greater number of glomoids, and increased intralobular fibrous connective tissue. Dilatation of capillaries

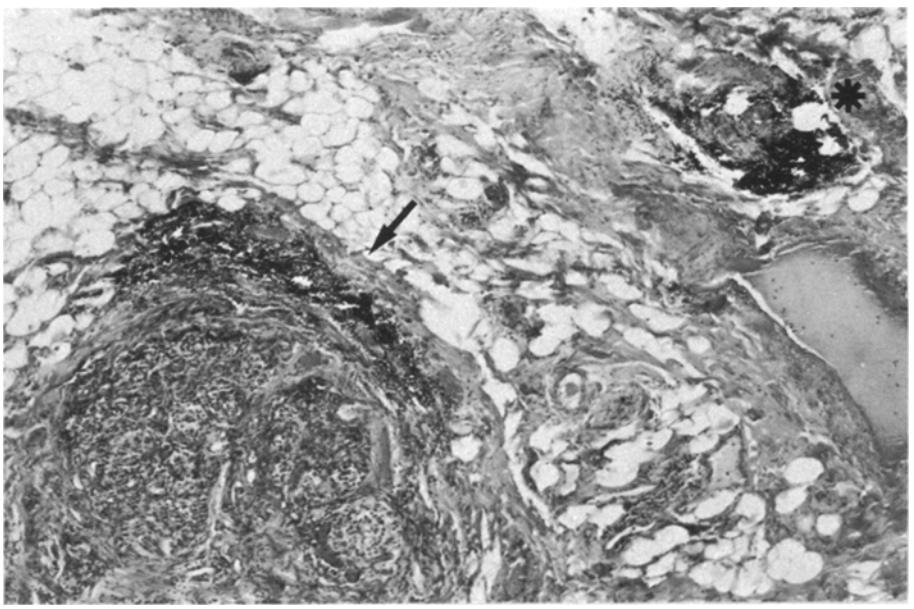

Fig. 8. Carotid body from a chronically hypoxemic patient. Perilobular (→) and perineural (*) lymphoplasmacellular infiltrates (×50)

unless the three cases that display the greatest increase in volume are ignored. Hence it may be concluded that up to a critical point volume increase is primarily the result of hypertrophy, and beyond that, the result of hyperplasia.

A comparison of the heart weights in both groups (Fig. 4) shows a significant mean value difference for the right ($P<0.001$) but not for the left ventricle. The mean weight of the right ventricle is 2.05 times that of the control group. Also significantly differing were the mean values of the ventricular quotients ($P<0.001$), as well as of the combined weights of the right and left ventricle ($P<0.05$).

Figure 5 shows no significant linear correlation between total volume of glomus cells and right ventricular weight in the chronically hypoxemic group. If, however, we admit a linear correlation represented by the calculated straight line, we infer that cases 4, 5, 7 and 8 have an excessive right ventricular weight with respect to their total glomus cell volume. This increase of right ventricular weight must be attributable to an additional factor. Indeed, we found the following pathologic changes in pulmonary arteries of diameters in the 100–300 μ range: case 4: repeated thromboembolism, case 5: hyperplasia of medial muscle layer, cases 7, 8: medial hyperplasia and intimal fibroelastosis. In no other cases were pathologic changes in the arterial part of the pulmonary circulation observed.

Qualitative Results

The carotid bodies of chronically hypoxemic patients show some constant findings under the light microscope. The lobules are more numerous and their margins show further lobulation. The number of glomoids per lobule is increased. The interstitial connective tissue strands are narrower but the periglomoid tissue, normally represented by a delicate reticular web, is collagenized and broader. Some areas contain intralobular scars. The most evident change consists of a massive dilatation of capillaries and venules, particularly in the peripheral portions of the transversly sectioned carotid bodies. Occasionally hyalinisations, almost exlusively intra- or perivascular in location, are seen.

Predominantly plasmacellular infiltrates are constant through sometimes sparse. When intense and focal, these infiltrates are invariably arranged perineurally; when intralobular, they are found almost exclusively arround glomoids (see Figs. 8 and 9). No evidence for neural degeneration was noted. In one case with a history of chronic hypoxemia of particularly long duration an increased number of Schwann cells arranged in anastomosing cords was seen in the interstitium and around glomoids, almost totally displacing the interstitial connective tissue. The type I glomus cells are larger, contain a focally granular, lighter and vacuolated cytoplasm, and carry an enlarged, lighter nucleus with a less distinct and more irregular nuclear membrane than the normal variants. The population of the dark variant of type I glomus cells was only focally increased and never reached significantly higher amounts than in the control group. The type II glomus cells were unaltered.

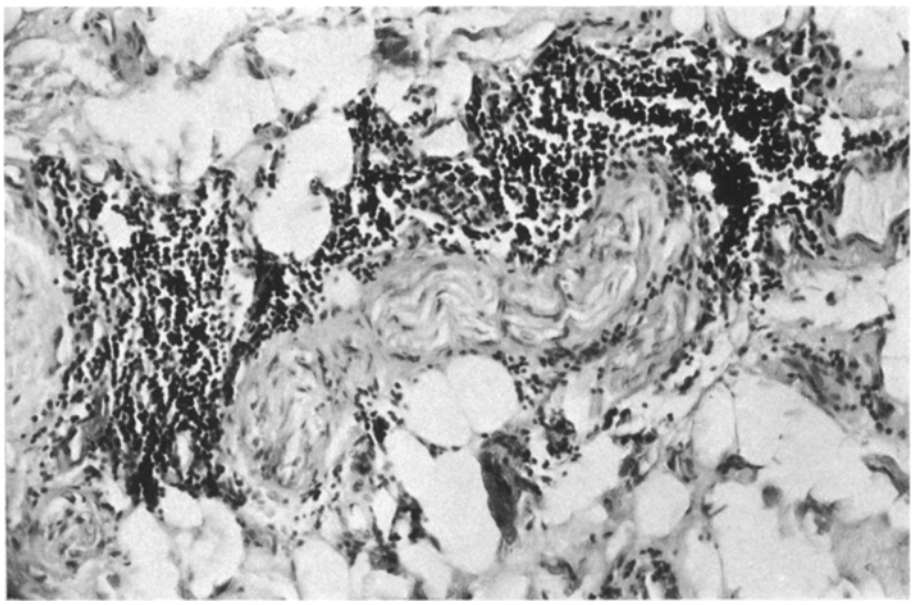

Fig. 9. Detail from the same patient. Perineural infiltrates, mostly plasmacellular (× 160)

Discussion

Our study shows a 2.67-fold increase of the total glomus cell volume in ten chronically hypoxemic patients. Similar findings were reported by Arias-Stella (1969) in 25 cases, by Heath et al. (1970) in 3 cases, an by Heath et al. (1973) in 11 cases involving a 2.2–2.7-fold increase of the medium weight of human carotid bodies under hypoxemic conditions. Although it has to be remembered that weight and volume are not primarily comparable, as the specific weight of normal and enlarged carotid bodies are not necessarily identical, our results also conform with the morphometric studies of Blessing and Wolff (1973) and Laidler and Kay (1975a). These authors found, in rats, a 4-fold increase of the total glomus cell volume (at a simulated altitude of 7500 m during 99 days) and a 3-fold increase (at a simulated altitude of 4300 m during 25–96 days) respectively. The total volume of the carotid bodies increased 4–6 times, the main reason being a 10–15-fold increase of the capillary volume. The remaining components of the volume increase were due to fibrosis and hyalin masses.

Several authors, who investigated human carotid bodies from chronically hypoxemic patients, found without using quantitative methods a volume increase of the carotid body due to hyperplasia of glomus cells. Laidler and Kay (1975b) investigated the number and nuclear diameter of type I glomus cells and found that the tacit assumption that the carotid body enlargement was due to hyperplasia of type I glomus cells, was not true in every case. Blessing and Wolff (1973) postulated preponderant hypertrophy and only possible hyperplasia. Our results head us to conclude that up to a certain critical weight and/or volume, type I

glomus cells hypertrophy and then begin to divide. In contrast with Langer (1952), we did not find mitotic figures. Since our carotid bodies were fixed 6 h post mortem at the earliest, it is conceivable that cell divisions in progress at the moment of death had reached their termination by the end of this interval.

The small number of patients investigated and the incomplete clinical information available, obviated a precise answer to the question of whether there is a correlation between duration and/or grade of hypoxemia and morphologic changes in human carotid bodies. In conformity with the assumptions of Blessing and Kaldeweide (1975), we wish, however, to outline the gradual course of histologic alterations in carotid bodies during long and slowly progressive hypoxemic states. Following a relatively weak but persistent hypoxemic stimulus, there is an increased degranulation of catecholamine bodies in the type I glomus cells, manifested in the light microscope by a lighter and vacuolated cytoplasm (Hollinshead, 1945; Bluemcke et al., 1967; Hellstroem et al., 1976). As a sign of increased cellular metabolism the nuclei swell (Langer, 1952). As a result of an increase in anaeorobic metabolism and the subsequent lowering of local pH there is an irregularly distributed vasodilatation (Arias-Stella, 1973; Blessing et al., 1973, 1975; Laidler and Kay, 1975b). These changes correspond to stage I, or hypertrophy. If these compensatory efforts are insufficient, the type I glomus cells begin to proliferate. Thus the interstitial connective tissue septae become smaller (Arias-Stella et al., 1973). These changes correspond to stage II, or nodular hyperplasia. With continuing progressive hypoxemia, there is a focal increase in the dark variants of type I glomus cells (Helpap, 1968; Heath et al., 1970), scattered nuclear pycnosis and necrosis with ultimate scarring (Blessing et al., 1973, 1975). In the dilated vessels, hyalinizations, interpreted as thrombosis, can be seen (Blessing et al., 1973, 1975; Laidler and Kay, 1975a). By these processes, the amount of intralobular connective tissue is increased. These changes correspond to stage III, or atrophy, and are considered by some authors to be normal in the elderly. These stages are not sharpely separated and can occur within the same organ, simultaneously at different foci. Histologically, nodular hyperplasia is a mode of reaction which suggests an endocrine function for the carotid body. This opinion has also been expressed in the work of Pearse (1969), who classifies the type I glomus cells as members of the APUD series. This view was also supported by the work of Tramezzani et al. (1971), who proposed a role for a hypothetic glomin hormone in erythropoiesis, and Honig et al. (1975) showing an effect of carotid body stimulation on the renal excretion of sodium.

Our finding of predominarly plasmacellular focal infiltrates with a perineural emphasis remains unexplained. Equally unresolved is the finding of an increase in Schwann cells in the interstitial space in a patient with a 12 year history of hypoxemia. This "proliferation", however, was not of the extent seen in degenerative peripheral nerve changes; nor were there signs of degenerative changes of the peripheral nerve fibres themselves. Without postulating a causal relation, we wish to mention the work of McDonald and Mitchell (1975), who demonstrated that specialized afferent nerve terminals of the reciprocal type are more sensitive to hypoxemic stimuli than type I glomus cells or efferent nerve endings and degenerate more readily. It has been known since 1966 (Sever-

inghaus et al.) that residents at high altitude display an irreversible insensitivity to acute hypoxemic stimuli. This has also been demonstrated in patients with congenital heart disease (Soerensen and Severinghaus, 1968), and with chronic respiratory failure (Flenley et al., 1970). This peripheral insensitivity at the level of the carotid bodies may extend to hypercapnic stimulation (Pande, 1974), which has been known to be a strong activator of carotid body discharge since the work of Heymans et al. (1930). Furthermore, it is of interest that this irreversible insensitivity cannot be demonstrated in animals, except in cats (Barer et al., 1976). So we are tempted to interprete the unusual plasmacellular infiltrates as a reaction to irreversible damage of specialized nerve terminals in chronic hypoxemia, without total degeneration of the nerve fibres. The variable capacity of animals to regain their chemoreceptive sensitivity after hypoxemic states of long duration might be explained by a generally diminished susceptibility of the specialized structures when compared with the human carotid bodies. Abraham (1970) reports a significantly higher content of nerve fibres in human carotid bodies than in those of animals.

All authors investigating the morphologic changes of carotid bodies in chronically hypoxemic patients have found a significant increase in the right ventricular as well as in the left ventricular weight. Only Blessing and Wolff (1973) describe a 2-fold increase of the total heart weight in the rat, primarily due to a hypertrophy of the right ventricle. Our results show a 2.05-fold increase for the right ventricular weight only. The weight of the left ventricle in chronically hypoxemic patients has a statistically insignificant tendency to increase. However, in 42 patients with chronic pulmonary emphysema and a singificant increase in right ventricular weight Hasleton (1973) found hypertrophy of the left ventricle only in 8 cases, and left the interrelationship of these results open to question. Rahlf and Komori (1975) in 25 cases of chronic cor pulmonale without coronary heart disease were able to show that after subtracting the relative weight of the rightsided ventricular septum, left ventricular hypertrophy was present only in cases complicated by arterio- or arteriolosclerosis of the kidneys and/or clinical hypertension. Our results likewise show a significant difference as well between the ventricular quotients between the combined right and left ventricular weights of the two compared groups.

In agreement with results of Laidler and Kay (1975a) we found no linear correlation between the total glomus cell volume and right ventricular weight in the chronically hypoxemic group, although Heath et al. (1970) and Edwards et al. (1971a, b) did establish such a correlation. 4 of our cases, however, exhibiting a right ventricular weight which was too elevated in respect to their total glomus cell volume; in these cases we observed pulmonary hypertensive vascular changes (medialhyperplasia and fibroelastosis of intima), or repeated thromboembolism. In no other case were such changes present. Other authors (Heath et al., 1973; Smith et al., 1974) had also described these alterations, but were unable to correlate them with the increase of total glomus cell volume or with right ventricular weight. Moreover, there is no obvious connection either to duration or grade of hypoxemia. Upon which causal relationship the individually variable morphologic expression of the hypoxic-hypoxemic pulmonary hypertension is based, remains an open question.

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