Enhancement of the Erythropoietic Response of Cats to Hypoxia Following Removal of the Carotid Body[1] (36876)

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The kidney is known to be the primary source of erythropoietin (ESF) (1–5). However, a basal level of erythropoiesis still persists after nephrectomy (6), suggesting an extra-renal source of ESF. The carotid body has recently been postulated by Tramezzani *et al.* (7) to be an extrarenal source of erythropoietin. Latner (8) also reported several years ago that ablation of both carotid bodies in rabbits produced an initial anemia and reticulocytosis which was followed later by a normalization of the blood picture.

In an attempt to confirm a possible role of the carotid body in the control of erythropoiesis, the erythropoietic response of carotid body-ablated and sham-operated cats to hypoxia was compared.

Material and Methods. The carotid bodies of 7 male or female cats (3.5–5 kg) were removed surgically under pentobarbital anesthesia. Sham operations were also performed on 7 additional cats. Forty-eight hours after surgery the sham-operated and carotid body-ablated cats were exposed in pairs to hypoxia in a hypobaric chamber at 0.50 atm for 18 hr. They were again exposed to hypoxia for 18 hr 2 weeks later. Immediately following removal of the cats from the hypobaric chamber, blood was withdrawn in heparinized syringes via cardiac puncture. After centrifugation, the plasma was removed and stored at −84° until assayed for erythropoietic activity in ex-hypoxic polycythemic mice (9). HAM/ICR strain female mice (22–25 g) used in the assay for erythropoietin were made polycythemic by exposure to 0.42 atm for two weeks. The mice were injected subcutaneously with 1/2 the total dose of either saline, human urinary ESF, standardized against the International Reference Preparation or the equivalent of 0.06 ml of cat plasma on the fourth and fifth days following removal from the hypobaric chamber. Each mouse received 0.5 μCi of ^{59}Fe in the tail vein on the sixth post-hypoxic day. Two days later each animal was exsanguinated via cardiac puncture, blood sample counted in a Packard Scintillation counter and the percent ^{59}Fe incorporation in red blood cells determined. Dunnett's test for comparing several treatments with a single control was used for the statistical analyses (10).

Results. Sham-operated cats (48 hr after sham-operation) placed in a hypobaric chamber for 18 hr showed a marked increase in ESF production. As seen in Table I, the mean ESF plasma levels in the sham-operated and the carotid body-ablated groups (48 hr after carotid body-ablation) were 0.74 ± 0.11 and 1.29 ± 0.16 units/ml of plasma, respectively. The plasma ESF levels in the carotid body-ablated group were significantly higher ($p < .05$) than that of the sham-operated controls following exposure to hypoxia. However, as seen in Table II, no significant difference in plasma ESF levels was seen between the carotid body-ablated and the sham-operated cats when they were exposed to hypoxia two weeks after the operation. Thus, it seems that the cats are able to compensate 2 weeks after removal of the carotid bodies and respond to hypoxia in a manner similar to the control cats.

Discussion. The present findings indicate that plasma ESF levels are significantly higher in carotid body-ablated cats exposed to 18 hr hypoxia two days after surgery when compared to that of sham-operated cats exposed

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TABLE I. Plasma ESF Levels in Carotid Body Ablated or Sham-Operated Cats Exposed to Hypoxia for 18 Hours.[a]

Sham-operated			Carotid body ablated		
Expt. no.	Units of ESF/ml of plasma	^{59}Fe (%) incorporation into RBC	Expt. no.	Units of ESF/ml of plasma	^{59}Fe (%) incorporation into RBC
1	0.64	8.14	1	1.04	14.09
2	0.80	6.80	2	2.03	16.27
3	1.20	10.07	3	1.36	10.47
4	0.40	3.49	4	0.80	11.55
5	1.02	14.14	5	1.20	17.01
6	0.76	2.65	6	0.96	5.33
7	0.36	1.10	7	1.62	23.45
Mean	0.74 ± 0.11	6.62 ± 1.73	Mean	1.29 ± 0.16	14.02 ± 2.16

[a] Cats were exposed to hypoxia (0.50 atm) 48 hr after carotid body ablation or sham-operation.

± = Standard error of the mean.

$p < .05$ when mean plasma ESF levels were compared in the carotid body ablated and sham-operated cats exposed to hypoxia.

to the same hypoxic stimulus. These studies support the findings of earlier reports (8) that removal of the carotid body enhances the erythropoietic response to hypoxia.

Lugliani *et al.* (11) have recently reported 57 carotid body-ablated asthma patients who had undergone carotid body excision to treat asthma. They concluded that the carotid body does not play a role in erythropoiesis. However, it is interesting that 6 of their patients had secondary polycythemias requiring phlebotomy after surgical removal of the carotid bodies. A transitory increase in red-cell mass has also been reported by Nakayama (12, 13) in patients whose carotid bodies were removed to alleviate chronic asthmatic disease.

Tramezzani *et al.* (7) demonstrated that bilateral carotid-body ablation in cats resulted in a fall in hematocrit and reticulocyte counts. Injections of carotid-body extracts from phlebotomized cats into normal and carotid-body ablated cats produced an increase in reticulocyte counts. Efferent blood

TABLE II. Plasma ESF Levels in Carotid Body Ablated and Sham-Operated Cats Exposed to Hypoxia for 18 Hours.[a]

Sham-operated			Carotid body ablated		
Expt. no.	Units of ESF/ml of plasma	^{59}Fe (%) incorporation into RBC	Expt. no.	Units of ESF/ml of plasma	^{59}Fe (%) incorporation into RBC
1	2.16	23.76	1	0.72	14.41
2	0.96	16.78	2	0.56	12.99
3	0.72	4.01	3	1.44	11.20
5	0.48	5.07	5	0.80	10.99
6	0.36	2.40	6	0.49	5.24
7	0.42	9.50	7	0.72	15.15
Mean	0.78 ± 0.24	10.25 ± 3.43		0.79 ± 0.11	11.66 ± 1.45

[a] Cats were exposed to hypoxia (0.50 atm) two weeks after carotid body ablation or sham-operation.

± = Standard error of the mean.

Animal no. 4 from Table I died after the first exposure to hypoxia.

from the carotid body of their bled animals also produced an increase in ^{59}Fe incorporation in red cells of polycythemic rats. The discrepancy between our results using hypoxia as the erythropoietic stimulus and those of Tramezzani *et al.* (7) when phlebotomy was used as the stimulus may be due to the differences in the assay systems or sampling techniques used. Grant (14) using rabbits and Badger (15) using dogs also performed glomectomy and demonstrated that these animals responded with a more marked polycythemia when exposed to hypoxia (14) or high altitude (15) than that of sham-operated controls. Paulo, *et al.* (16) have also demonstrated increased ESF production in carotid body-ablated rabbits subjected to hypoxia.

It has been demonstrated that the carotid-body acts to detect changes in PO_2 of blood (17, 18). These changes in oxygen content of blood are known to modify transmission along the nerve (Hering-Castro) leading from the carotid body to the respiratory center. The more marked increase in plasma ESF levels in carotid body-ablated cats in our experiments may be due to the lack of ventilatory response to hypoxia (19).

The compensation of the carotid body-ablated cats after two weeks enabling them to respond to hypoxia similar to that of the control animals, may be due to either the increased sensitivity of the central chemoreceptors or else a compensation of the aortic bodies to play a more significant role in the ventilatory response to hypoxia.

Summary. Plasma erythropoietin levels in carotid body-ablated cats exposed to hypoxia (0.50 atm for 18 hr) 48 hr after removal of the carotid bodies were significantly higher than that of sham-operated controls exposed to the same degree of hypoxia. The mean plasma ESF levels in the carotid body-ablated group (1.29 ± 0.16 units/ml of plasma) were significantly ($p < 0.05$) higher than that of sham-operated controls (0.74 ± 0.11 units/ml of plasma). However, plasma ESF levels in cats exposed to hypoxia 2 wk after carotid body ablation or sham-operation were not significantly different. The present studies indicate that removal of the carotid bodies in cats enhances the erythropoietic response to hypoxia.

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