The study by Dr. Mancia entitled "Influence of Carotid Baroreceptors on Vascular Responses to Carotid Chemoreceptor Stimulation" (Circ Res 36:270-276, 1975) confirms our finding (Heistad et al., J Clin Invest 53:1226-1236, 1974) that increases in carotid sinus pressure depress vascular responses to simultaneous stimulation of carotid chemoreceptors. There is, however, an important difference in the results of the two studies: we found that hypotension (either from hemorrhage or from lowering carotid sinus pressure from 150 to 75-100 mm Hg) potentiates vasoconstrictor responses to chemoreceptor stimulation, whereas Dr. Mancia found that carotid sinus hypotension attenuates vasoconstrictror responses to chemoreceptor stimulation. I suggest that several factors may have led Dr. Mancia to a conclusion different from ours.

First, hind-limb and renal vessels were profoundly constricted during carotid sinus hypotension in his study, and this vasoconstriction would be expected to reduce, in a nonspecific manner, vasoconstrictor responses to any superimposed stimulus (Folkow and Oberg, Acta Physiol Scand 47:131-135, 1959). Dr. Mancia attempted to evaluate this possibility by demonstrating that the hind-limb and renal vessels were capable of a greater degree of constriction during electrical stimulation of sympathetic nerves than that observed during combined chemoreceptor stimulation and carotid sinus hypotension. The response to sympathetic stimulation only indicates in a qualitative way that the vessels were not maximally constricted during chemoreceptor stimulation and carotid sinus hypotension. The response to sympathetic stimulation only indicates in a qualitative way that the vessels were not maximally constricted during chemoreceptor stimulation and carotid sinus hypotension and does not refute the probability that the vessels were less responsive to vasoconstrictor stimuli in their profoundly constricted state. We considered this concept extensively in the Discussion of our paper.


Third, systemic arterial blood pressure reached very high levels (mean arterial blood pressure was 219 mm Hg) during carotid sinus hypotension in Dr. Mancia's study. It is not clear what effect systemic (and cerebral vascular) hypertension might have on the chemoreceptor reflex.

Fourth, and probably most important, when carotid sinus pressure was reduced to 51 mm Hg and aortic pressure was 219 mm Hg, oxygenated arterial blood may have "leaked" into the carotid bodies, so that chemoreceptors then were not stimulated. Dr. Mancia suggested that this possibility was unlikely because tests for completeness of vascular isolation did not demonstrate a significant leak. The amount of blood that is required to perfuse the carotid bodies is extremely small (about 0.04 ml/min in cats [Purves, J Physiol (Lond) 209:395-416, 1970]) and might not be detectable as a leak by the methods used by Dr. Mancia. In early experiments in our laboratory, we found that when systemic arterial blood pressure was higher than carotid perfusion pressure the chemoreceptor reflex was reduced or abolished, which suggests that systemic blood was leaking into the chemoreceptors. This apparent leak occurred even though tests for completeness of vascular isolation, similar to those used by Dr. Mancia, did not demonstrate a leak. It is for this reason that, in our studies of cardiovascular effects of the interaction of chemoreceptor and baroreceptor reflexes (J Clin Invest 53:1226-1236, 1974) and ventilatory effects of this interaction (Heistad et al., J Appl Physiol, in press), we have maintained carotid perfusion pressure above systemic arterial blood pressure.

In conclusion, I suggest that there may be several reasons why Dr. Mancia did not observe potentiation of the chemoreceptor reflex during carotid sinus hypotension, but the primary reason may be that systemic blood with normal oxygen tension and carbon dioxide tension leaked into the chemoreceptors when carotid pressure was below systemic arterial blood pressure.

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REPLY TO THE ABOVE LETTER

Dr. Heistad regards his major criticism of my paper to be the fourth factor that he mentions: the possibility that the carotid chemoreceptors were not stimulated by perfusion with hypoxic hyper-
capnic blood when the carotid pressure was below systemic arterial blood pressure because of a leak of oxygenated blood into the carotid bodies. In my paper, specific experiments to test this point are reported (see last paragraph of Results). In these experiments, the afferent input from the carotid baro- and chemoreceptors on the left side was maintained constant. On the right side, the carotid bifurcation was isolated in the same way as it was in the main experiments except that the baroreceptors were selectively denervated (by stripping the carotid sinus), leaving afferent input only from the chemoreceptors. Under these conditions, hypoxic hypercapnic perfusion of the right carotid bifurcation induced the same pressor rise regardless of a perfusion pressure ranging from 220 to 50 mm Hg. When the right carotid pressure was 50 mm Hg, the mean aortic pressure was 163 mm Hg, that is, there was a gradient of more than 110 mm Hg between the systemic arterial circulation and the right carotid bifurcation. Thus, in my experiments, stimulation of the chemoreceptors was unaltered by reducing the carotid pressure to a much lower level than systemic arterial blood pressure. This fact seems to dispose of the major criticism of Dr. Heistad.

There still remains to be explained why in his experiments Dr. Heistad found a leak which prevented chemoreceptor stimulation when carotid perfusion pressure was lower than systemic arterial blood pressure. In my experiments, in addition to ligating the occipital artery, I carefully ligated the variable number of muscle arteries that originated between the origin of the occipital artery and the ligature beyond the carotid body (Chungharoen et al., J Physiol [Lond] 117:347-358, 1952).

Dr. Heistad also mentions three other arguments. With regard to the first argument, I certainly agree with him that chemoreceptor stimulation may add little further sympathetic vasoconstriction to the marked one caused by withdrawal of carotid baroreceptor afferent input. Indeed, this is exactly my conclusion, and I can hardly see how this argument can fit with Dr. Heistad’s statement that withdrawal of carotid baroreceptor afferent input causes a potentiation of the vasoconstrictive response to carotid chemoreceptor stimulation.

Dr. Heistad has a point in his second argument in that in the total hind-limb potentiation of constrictor responses to chemoreceptor stimulation might be masked by a simultaneous potentiation of dilator responses in cutaneous resistance vessels. However, at a carotid sinus pressure of 50 mm Hg, chemoreceptor stimulation did not cause vasoconstriction in the renal vessels.

With regard to the third argument, I am unaware of possible effects of systemic and cerebral vascular hypertension on the chemoreceptor reflex.

There are other explanations for the difference between Dr. Heistad’s results and mine. In his study, there were many more variables than just changes in carotid baroreceptor and chemoreceptor inputs. Indeed, Dr. Heistad obtained a reduction in carotid baroreceptor input by bleeding the animals until their arterial blood pressure was reduced from 127 mm Hg to 73 mm Hg and to 46 mm Hg. When the carotid baroreceptors are intact, large degrees of hemorrhage are required to reduce arterial blood pressure to such levels, and this procedure has countless effects other than decreasing carotid baroreceptor input. Just to cite a few examples, hemorrhage directly affects the discharge of the vasomotor cells in the central nervous system (Alexander, Am J Physiol 143:698-708, 1945; Brooks, Am J Physiol 114:30-39, 1935; Chien, Physiol Rev 47:214-288, 1967). It alters the activity of sympathetic afferent fibers (Malliani et al., J Physiol [Lond] 229:457-469, 1973). Also, since in the majority of the animals the vagi are left intact, it involves participation of reflexes from heart and lung receptors (Pelletier et al., Circ Res 29:626–634, 1971). Thus, the experimental situation of Dr. Heistad and co-workers was probably more complex, involving central effects of ischemia and other reflexes.

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Circ Res. 1975;37:396-397
doi: 10.1161/01.RES.37.3.396

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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World Wide Web at:
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