Brain ischemia hypertension

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Summary. Hypertension was produced in anesthetized and conscious dogs when cerebral perfusion was reduced. It lasted up to 19 days in chronic studies, was not abolished by carotid sinus denervation nor with beta receptor blockade, but was absent after removal of brachiocephalic artery constriction (BCAC). The cardiovascular features of this "neurogenic hypertension" are presented.

Several reports[1-4] show that temporary occlusion of the blood flow to the head is accompanied by systemic hypertension. By sequentially ligating blood vessels supplying the head Fishback[1] and Guyton[2] produced hypertension in anesthetized dogs; Hawthorne[3] obtained hypertension in unanesthetized dogs with chronic constriction of the brachiocephalic and left subclavian arteries and we have shown that BCAC of 70% in the presence of prior left subclavian artery occlusion resulted in chronic hypertension of 19 days duration[4]. This study examines the extent of the involvement of the carotid sinus baroreceptors and presents the cardiovascular changes that are concommitant with brain ischemia effected by brachiocephalic artery constriction.

Methods. Mongrel dogs weighing between 15 and 25 kg were utilized in this study. In the acute experiments animals were anesthized with sodium pentobarbital (Nembutal, Parke Davis & Co.) 30 mg/kg i.v. The trachea was intubated and positive pressure ventillation was initiated after a left thoracotomy was performed in the 4th intercostal space. The left subclavian artery was ligated 2 cm beyond its bifurcation from the aorta. A constrictor clamp (Konisberg Instrument Co.) was placed around the brachiocephalic artery. A pressure-sensitive cell (Konisberg Instrument Co.) was inserted into the descending aorta along with a catheter to record aortic pressure (AP). A flow probe (Micron Instruments Inc., Model MC4220) was fitted around the root of the aorta to record aortic flow (AF) and for the derivation of stroke volume (SV) and cardiac output (CP). A pressure cell and a catheter similar to the ones placed in the aorta were inserted into the left ventricular cavity for recording left ventricular pressure (LVP). Wire leads were sewn to the myocardium and used to record the left ventricular electrogram (LVEG). Arterial pressure cephalad to the constrictor (SAP) was recorded with a catheter placed into the brachiocephalic artery via the right supraspinous artery. All catheters were connected to Sta-

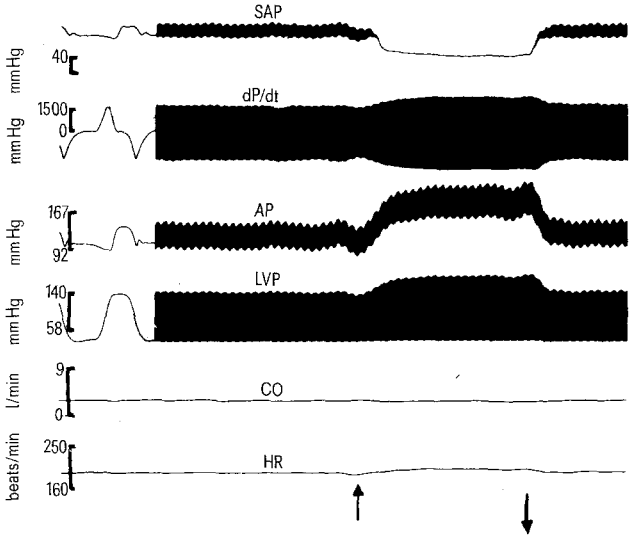

Fig. 1. Response to brachiocephalic artery constriction (BCAC) in anesthetized dog. SAP, supraspinous artery pressure; dP/dt-rate of rise of left ventricular pressure. AP, aortic pressure, LVP, left ventricular pressure, CO, cardiac output, HR, heart rate. Constriction was done between the arrows.

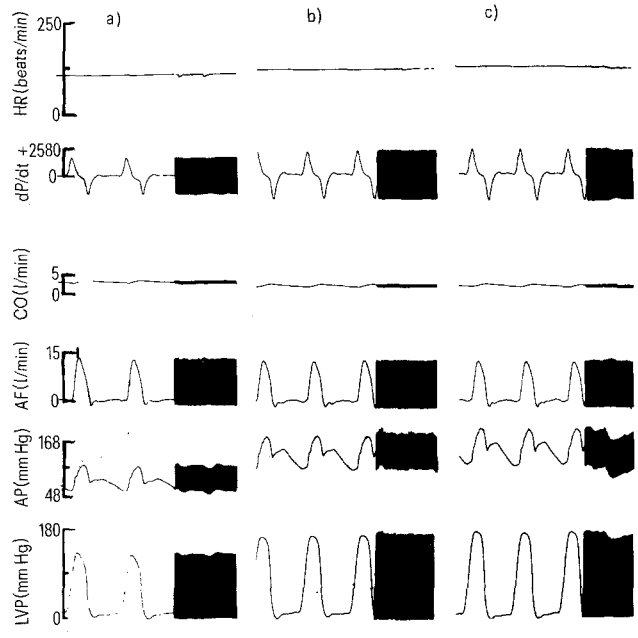

Fig. 2. Response to BCAC in conscious instrumented dog. *A* Control; *B* immediate response; *C* response at 12 h after the onset of constriction. Symbols are the same as in figure 1. AF, aortic flow.

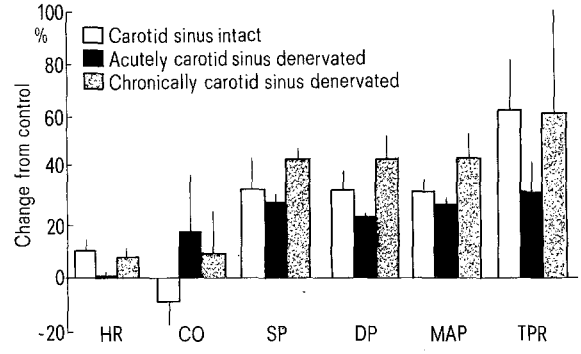

Fig. 3. Effect of removal of carotid sinuses on response to BCAC. Bars represent percent change from control ± SEM. HR, heart rate; CO, cardiac output; SP, systolic pressure; DP, diastolic pressure; MAP, mean arterial pressure; TPR, total peripheral resistance.

Percent change from control in cardiovascular variables during brachiocephalic artery constriction in left subclavian artery occluded dogs

Group	Heart rate	Stroke volume	Cardiac output	Mean arterial pressure	Total peripheral resistance	$dP/dt/P_{40}$	n
1	11.0±03*	−21.0±10*	−10.0±11	34.0±04*	64.0±24*	32.0±05*	6
2	0.8±01	19.0±22	18.0±21	27.0±02*	31.0±09*	22.0±04*	6
3	17.0±06*	−16.0±03*	1.3±07	50.0±10*	61.0±17*	21.0±05*	9
4	−9.0±03*	−2.8±04	−14.1±02*	30.9±06*	61.0±04*	−9.6±03*	5
5	30.0±25	−7.5±02*	7.5±02*	36.0±06*	23.4±06*	51.6±14*	3
6	6.4±02	1.8±14	9.6±16	45.7±07*	59.1±04*	31.2±06*	5

Groups: 1, Anesthetized carotid sinus intact; 2, anesthetized carotid sinus denervated; 3, conscious instrumented dogs (immediate response); 4, after propranolol administration; 5, conscious instrumented dogs (after chronic constriction, average of 10 days); 6, chronic carotid sinus denervated dogs; dP/dt/P, rate of rise of left ventricular pressure with time/intraventricular pressure 40 mm Hg; n, number of animals; * $p=0.05$.

tham P23DB pressure transducers (Stathan Instrument Co.). Carotid sinus denervation (CSD) was accomplished after isolation of both carotid arteries, cutting of the carotid sinus nerves, scraping and painting the vessels with 10% phenol solution. A length of vessel 1.5 cm above the carotid bifurcation and down to the thyroid artery in the opposite direction, was treated as described above. In chronic studies, the same basic preparation was used, however, all surgery was done under sterile conditions and the animals were allowed ample time to recuperate before experiments were performed. Paired Student's t-test analysis was done on groups of data. A probability value of less than or equal to 0.05 was set as the level of significant difference.

Results. Figure 1 shows the typical response to BCAC obtained in an anesthetized dog, while figure 2 shows the response in an awake dog before (A), immediately following (B), and 12 h after (C) the onset of BCAC. In both figures, a marked elevation in AP (138/96–210/148 in figure 1 and 110/60–175/98 in figure 2) is evident. Cardiac output remains essentially unchanged even though HR is slightly elevated. The upper trace of figure 1 shows a severe reduction in cerebral perfusion to a mean of 40 mm Hg during the full length of BCAC. Table 1 summarizes the responses obtained with BCAC in 6 groups of dogs. The values represent percent changes from control. Significant differences from control are indicated by the asterisks. The effects of removal of the carotid sinus baroreceptors are presented in the graph of figure 3. As shown, significant changes in SP, DP, MAP, and TPR were obtained whether the carotid sinus was removed acutely or chronically and no significant difference from the intact carotid sinus experiments is evident.

Discussion. The data clearly indicates that a reduction in cerebral perfusion (brain ischemia) by BCAC, in left subclavian artery occluded dogs is accompanied by alterations in HR, SV, MAP, TPR and myocardial contractility (figures 1 and 2, table). Conceivably these adjustments occur to restore an effective pressure-flow relationship to the brain.

An attractive assumption is that the response to lowered cerebral perfusion is baroreceptor related. However, the marked hypertension obtained with BCAC could not be due to the carotid sinus reflex (CSR) alone since CSD did not abolish the response (table, groups 2 and 6, and figure 3) and the aortic arch receptors are seeing an elevated arterial pressure. A more likely, but less studied, mechanism that seems to be involved in this response is the central nervous system ischemic reflex (CNSIR). In fact, it has been argued that by its very location in relation to the brain, the CNSIR is better capable of monitoring the circulation to vital centers than does the CSR[5]. In this study, the likeliness of the involvement of the CNSIR in the response is demonstrated in figure 1 where the perfusion pressure to the brain was reduced to 40 mm Hg, a level that is well below that reported to initiate the reflex[6].

It is obvious from the table that both cardiac and peripheral vascular stimulation are consequences of initiating the CNSIR, since significant changes in MAP, TPR, HR and dP/dt/P were obtained. As previously suggested[4,6] these responses are both profound and specific. On the one hand, pronounced (well above 20%) alterations in MAP and TPR were obtained in most instances. On the other hand, specificity is indicated in that receptors mediating changes in myocardial contractility (dP/dt/P) were more influenced than those mediating heart rate changes (table). In fact, the heart rate changes may have been entirely due to the CSR, since the increase in this parameter along with the reduction in stroke volume that was obtained with BCAC were not present after CSD. Also, there was a marked difference in the TPR response between groups 1 and 2. The smaller TPR response after acute denervation could be due to the absence of peripheral sympathetic excitation that has been commonly associated with the CSR. However, the presence of a large (59.1%) increase in TPR in chronically denervated dogs indicates that peripheral sympathetic excitation is also attributable to the CNSIR, probably more so than to the CSR.

Further investigation of the long term (group 5) dogs is required to correctly characterize the chronic cardiovascular responses. However, as shown in the table, myocardial contractility is highest in this group of dogs. This suggests a time dependent mechanism, such as an increase in circulating inotropic stimulants, that may take over from the neurogenic mechanism that must be involved in the immediate response.

In conclusion, BCAC in the presence of left subclavian artery ligation produces a significant hypertension that is independent of and characteristically different from the hypertension commonly associated with the CSR. The hypertension seems to be mainly attributable to a neurogenic mechanism initiated by the cerebral ischemia obtained with BCAC and both cardiac and peripheral vascular mechanisms are involved in the response.

1 H.R. Fishback, F.E. Dutra and E.T. McCanay, J. Lab. clin. Med. *16*, 1187 (1942).
2 A.C. Guyton, Am. Physiol. *154*, 45 (1948).
3 E.W. Hawthorne and A.K. Mandal, Circulation Res. *11*, 153 (1962).
4 M.S. Holder and L.N. Cothran, Proc. 4th MBS Symposium, Xavier University, New Orleans 1976.
5 C.J. Dickinson, in: Neurogenic Hypertension, p.248. Blackwell Scient. Publ., Oxford 1965.
6 R.J. McRitchie, S.F. Vatner, G.E. Heyndrick and E. Braunwald, Am. J. Cardiol. *35*, 666 (1976).