Respiratory Influences upon Depressor and Pressor Responses to Stimulation of the Aortic Nerve in the Decerebrate Cat[1]

DOUGLAS and SCHAUMANN[2] have reported that in cats under urethane anaesthesia stimulation of an aortic nerve with pulses of increasing amplitude or duration successively activates low threshold depressor fibres, intermediate threshold pressor fibres and high threshold depressor fibres. As the excitation of the intermediate component is also associated with the appearance of hyperpnoea, this group of fibres has been interpreted as composed of chemoceptive afferents, while the two depressor components have been recognized to be made up of pressoceptive fibres. DOUGLAS and SCHAUMANN[2] have also observed that changes in pulmonary ventilation have marked influences upon sign and intensity of some of these responses. The recent studies of DALY's group[3,4] on the interaction between respiratory and cardiovascular effects of natural chemoceptive stimuli have further contributed to this problem. The researches here reported have been performed to define mechanisms and importance of the respiratory influences upon the circulatory responses to aortic nerve stimulation.

Our observations were made on 33 unanaesthetized decerebrate cats. Decerebration was electrolytically performed at the intercollicular level by means of a stereotactically oriented electrode. The left aortic nerve was carefully isolated from the vagus trunk at mid cervical levels, cut as distally as possible, and its proximal stump was stimulated through fine bipolar silver electrodes connected to a Tektronix Series 160 Unit. Both carotid sinus nerves as well as the right vagus-aortic trunk were always severed before the stimulating trials were started. Only the left vagus trunk was left intact to be subsequently cut during the experiment. When necessary, the decerebrate animals were immobilized by gallamine (Sincurarina®, Farmitalia) and artificially ventilated at variable speed and amplitude by means of a positive-pressure pump. The pump input could be connected at will to ambient air or to a large Douglas bag filled with either low oxygen or high carbon dioxide gas mixtures. Arterial pressure was measured from a cannulated femoral artery by means of a Sanborn differential transformer and spontaneous ventilation by a crystal capsule. In most animals carbon dioxide concentration in the expired air was continuously measured by means of a fast infrared analyser, the final part of the curve being used as an index of carbon dioxide concentration in the alveolar air. All three phenomena were simultaneously displayed on a suitable multichannel ink-writer (Battaglia-Rangoni, M.10).

Stimulation of the aortic nervewith repetitive (50 to 100/sec) pulses of either constant duration (0.01–0.1 msec) and increasing amplitude, or of constant amplitude (1–2 V) and increasing duration has substantially confirmed the observation of DOUGLAS and SCHAUMANN[2]. As shown in the first row in Figure 1, 0.01 msec, 1–2 V pulses applied to the aortic nerve could induce a definite blood pressure fall associated to slight hypopnoea, a response pattern which can be ascribed to selective stimulation of low-threshold pressoceptive fibres. Mere rise of the stimulating voltage to 3 V elicited a weak, slowly incrementing hyperpnoea, while the blood pressure fall was still conspicuous, though somewhat smaller than during 2 V stimuli. A further rise of the pulse amplitude to 4 V immediately yielded strong hyperventilation; simultaneously arterial pressure, after an initial decrease, quickly returned to prae-stimulus levels to show a late moderate fall with the progression of hyperpnoea. These effects appear to result from co-activation of intermediate threshold fibres, presumably chemoceptive in origin (see below). Finally an important hypotensive reaction, probably due to high threshold pressoceptive afferents, could be brought forth by an increase of the stimulus voltage (6 V); at this strength the respiratory response always maintained its strong excitatory character.

The effect of changes in pulmonary ventilation on the various blood pressure responses induced by the three groups of aortic fibres is shown in the second and third rows of Figure 1. When the decerebrate preparation was immobilized with gallamine, and exposed to rather severe hypoventilation resulting in hypercapnia (measured from a conspicuous rise in carbon dioxide end-tidal concentration) and hypoxia (judged from the presence of cyanosis), the depressor response to low voltage (1–2 V) aortic stimulation remained substantially unmodified, while activation of the intermediate and high threshold fibres resulted either in a weak blood pressure fall (3 V) or in a hypertension of increasing size (from 4 to 6 V). Quite different changes were induced by artificial hyperventilation: conspicuous depressor effects resulted from either stimulation of low threshold fibres (1–2 V) or from bringing into action the higher threshold afferents (6 V); smaller responses, though still hypotensive in sign, were obtained by using intermediate voltage stimuli (3–4 V). The effects of ventilatory changes on the blood pressure responses to stimulation of the intermediate threshold 'chemoceptive'

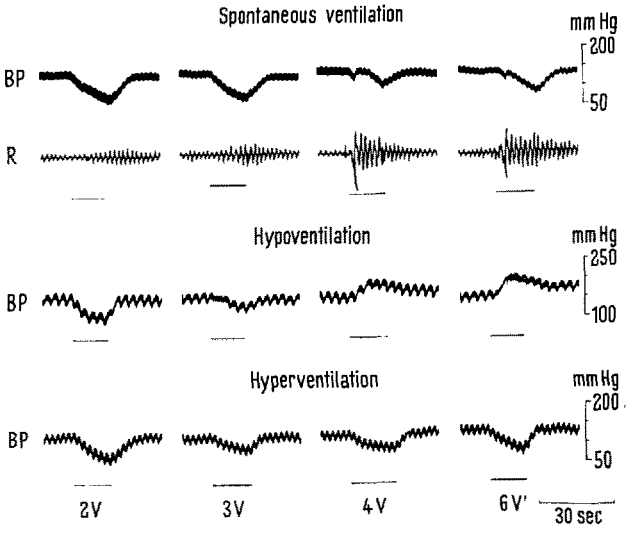

Fig. 1. Blood pressure and respiratory responses to electrical stimulation of the left aortic nerve with rectangular pulses 0.01 msec in duration, at a repetition rate of 100/sec; voltages employed are indicated above each vertical column. BP: arterial pressure, R: respiration. First row: during spontaneous ventilation. Second row: during artificial hypoventilation. Third row: during hyperventilation. Decerebrate animal with both carotid sinus nerves and the right vago-aortic trunk severed.

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[2] W. W. DOUGLAS and W. SCHAUMANN, J. Physiol. *132*, 173 (1956).

fibres are summarized in Figure 2. While tidal volumes large enough to yield end-tidal carbon dioxide concentrations between 2.5 and 3.3 vol% were compatible with a slight hypotensive reaction, a progressive decrease in ventilation such as to give 3.8 and 4.8 vol% of end-tidal carbon dioxide, changed the depressor into a pressor response of increasing amplitude. To sum up, it seems that pulmonary ventilation is without any important action upon the reflex effect of low threshold 'pressoceptive' afferents, while strongly influencing that of the intermediate threshold 'chemoceptive' fibres. Potentiation of this effect during hypoventilation appears to overwhelm also the depressor activity of high threshold pressoceptive afferents, at least when submaximally activated.

It should be recognized that most, though by no means all, of the animals behaved according to the pattern reported above. A limited number of spontaneously ventilating preparations (2 out of 33) responded with blood pressure falls of increasing size (up to a given maximum) and with decreased respiration to any type and strength of aortic stimulation. These hypotensive responses could never be changed into pressor reactions by any degree of artificial hypoventilation. The lack of hyperpnoea after left aortic excitation suggests that the intermediate threshold 'chemoceptive' component was absent or inconspicuous in the left aortic nerve of these animals.

Various mechanisms whereby ventilatory changes might affect blood pressure reactions to aortic stimulation have also been considered and subjected to experimental testing. Basal blood pressure levels are unlikely to be the crucial factor, as ventilation could influence the circulatory reflex responses even when no considerable change of the basal arterial pressure was observed. The pulmonary reflex, which has been shown by DALY et al.[3,4] to have a marked interaction with the cardiac response to natural chemoceptive stimulation, does not seem to play a fundamental role in our experimental conditions, as reversal of hypotensive to hypertensive reactions has also been observed after bilateral vagotomy. We have no data, however, as to the possible contribution of this reflex to the whole effect. Hypercapnia and hypoxia can each play an important role in the modification of the circulatory reflex response, as in 14 preparations where their effect was tested, either high carbon dioxide (5–7% CO_2 in O_2) or low oxygen mixtures (5–8% O_2 in N_2) could always shift a depressor into a pressor reaction, provided the appropriate intermediate stimulating voltage was used. The level at which both hypercapnia and hypoxia affect the circulatory response to aortic stimulation can only be surmised: the well-known excitatory effect of hypercapnia[5], and probably of hypoxia as well[6], on the vasomotor centre suggests that the excitatory state of the nervous centres controlling the circulation may be of some importance, but a peripheral action of carbon dioxide and oxygen tension on blood vessels or heart performance cannot be excluded.

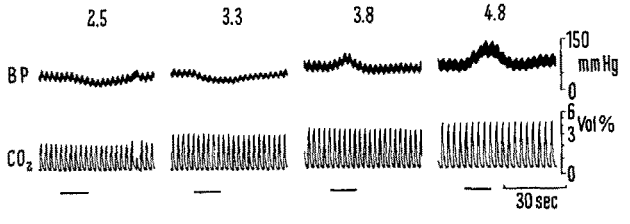

Fig. 2. Blood pressure responses to electrical stimulation of the left aortic nerve with stimuli of intermediate strength (2 V, 1 msec), during artificial ventilation at decreasing amplitudes. BP: blood pressure, CO_2: continuous records of carbon dioxide concentration in the expired air. The number on the top of each figure indicates the value of end-tidal (alveolar) carbon dioxide concentration during each stimulation trial, thus testifying that ventilation volume is decreasing from the first to the fourth trial. Decerebrate animal with both carotid sinus nerves and the right vago-aortic trunk severed.

Riassunto. Le risposte circolatorie alla stimolazione elettrica del nervo aortico sono notevolmente modificate dalla ventilazione polmonare. In particolare le risposte a stimoli di intensità intermedia ed elevata, che attivano oltre a fibre pressocettive anche fibre chemocettive, divengono da ipotensive ipertensive durante ipoventilazione. Gli effetti dell'ipoventilazione sono sempre riprodotti sia dall'ipercapnia (respirazione con CO_2 5–7% in O_2) sia dall'ipossia (respirazione di O_2 5–8% in N_2).

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The Permeation of Drugs Across the So-called Blood-Brain-Barrier at Low Temperature

The close correlation between lipid solubility of a drug and its rate of permeation from the blood into the cerebrospinal fluid (CSF) led to the assumption that the so-called blood-brain-barrier is lipoid in character[1]. The drugs are considered to penetrate passively by diffusion through a lipid layer of the membrane according to their lipid/water partition coefficients. The question arises whether the normal function of the cell is necessary to maintain these properties of the membrane or not. In order to prove this, we minimized the metabolism of cells by studying the permeation of drugs into the CSF at low temperature.

The heads of dogs weighing about 15 kg were perfused with isotonic salt solution[2] *via* the carotid arteries at a rate of 90 ml per min. The solution was saturated with oxygen and adjusted to a pH of 7.4. Haemoglobin was added in a concentration of 1% as an indicator in order to detect a leakage of the blood-brain-barrier by the appearance of a reddish tint of the CSF. The drugs investigated were added in the following concentrations: aniline

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