

## STUDIES ON CENTRAL RESPIRATORY ACTIVITY IN ARTIFICIALLY VENTILATED RABBITS

A. HUSZCZUK and J. G. WIDDICOMBE

Laboratory of Physiology, University of Oxford, England

**Abstract.** The level of integrated phrenic nerve activity ( $C_3$  root) has been studied under various forms of impairment of respiratory muscle function, such as paralysis (gallamine), pneumothorax and phrenectomy. Experiments were performed in two groups of rabbits artificially ventilated by means of the conventional respirator and the phrenic nerve driven respirator. It was found that both paralysis and bilateral pneumothorax were very strong stimuli exciting central inspiratory activity despite the constancy of ventilation. Under the same conditions phrenectomy caused only slight persistent excitation of the activity studied. It is worth noting that activity in the  $C_3$  root contralateral to the cut phrenic nerve trunk was as a rule more strongly stimulated. As artificial ventilation preceded by administration of gallamine is commonly applied in physiological experiments, the possibility of its effect on central respiratory activity will be discussed.

Quite a large percentage of experimental models in physiology involve artificial ventilation preceded by administration of a muscle relaxant among which gallamine is most commonly used.

Besides its obvious consequence in impairment of respiratory muscle function there are several reports giving evidence for a central action of gallamine (Hougs 1963, Galindo et al. 1968, *see also* Cullen 1967/68). Thus the whole problem appears to be very complex, since it probably involves numerous afferent as well as central mechanisms.

To investigate to what extent the administration of gallamine might affect central respiratory activity we first performed 14 experiments in which we studied the level of integrated activity of cervical phrenic nerve roots after injection of gallamine followed immediately by artificial ventilation.

Gallamine was injected intravenously in a dose of 20 mg/kg. The rabbits were anaesthetised with pentobarbitone in a dose of 30 mg/kg.

The level of artificial ventilation was adjusted according to end-tidal  $\text{CO}_2$  readings and  $\text{PAO}_2$  and  $\text{PACO}_2$  analysis, to keep these variables within normal limits.

Figure 1 illustrates a typical response to gallamine injection. Marked and persistent excitation of phrenic nerve activity is clearly seen. In

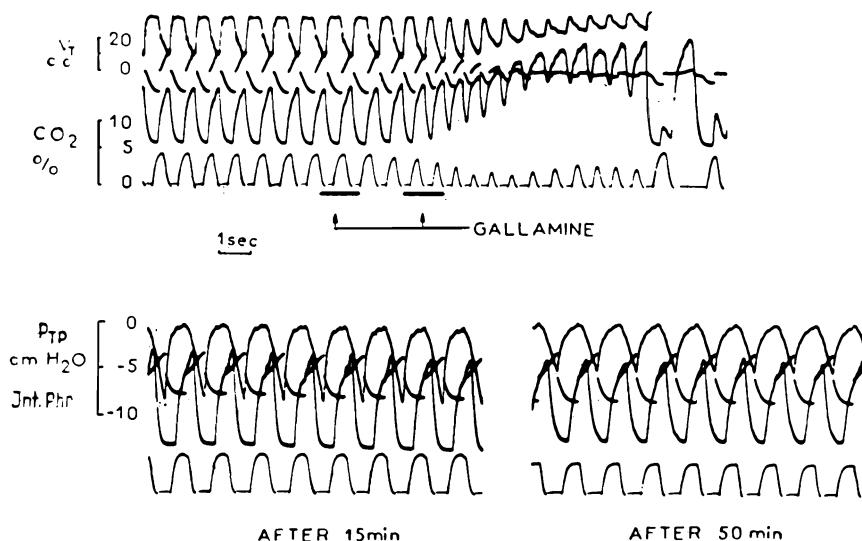


Fig. 1. An immediate response of a spontaneously breathing rabbit to gallamine injection (upper record) and states recorded after 15 and 50 min of artificial ventilation (lower records).  $\text{PTP}$ , transpulmonary pressure;  $\text{VT}$ , tidal volume;  $\text{Int. Phr.}$ , integrated phrenic nerve activity.

most cases the central respiratory rhythm locked on to the respiratory pump rate, more or less out of phase. The extreme example of such driving is illustrated in Fig. 2. Here the phrenic activity can be seen to start simultaneously with the start of the expiratory phase of the pump cycle. Occasionally there was no 1:1 correlation between pump action and respiratory rhythm. In these cases augmentation of phrenic nerve activity was even greater. Mean results indicated that the increase of phrenic nerve activity was 75% above control level, with the vagi intact. After vagotomy, the mean increase of phrenic activity was only 25%.

This difference points to the vagi as the most important pathway by which the information resulting from paralysis is mediated. Relaxation followed by artificial ventilation must strongly affect the compliance of the total respiratory system. Furthermore the mean negative pressure

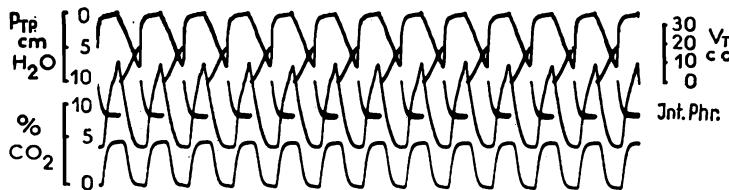


Fig. 2. The extreme example of "out of phase" driving of the central respiratory activity by the pump. Explanations as in Fig. 1.

within the pleural space no longer exists. All these factors may cause collapse of parts of the lung which may stimulate such receptors as: J receptors, irritant receptors, and deflation receptors. The already mentioned "out of phase" driving of the central respiratory activity by the pump or in other words stimulation of this activity during expiration would support this view.

More or less the same set of receptors is stimulated by pneumothorax. We therefore performed 12 analogous experiments in which gallamine administration was replaced by bilateral pneumothorax and artificial ventilation. Figure 3 shows an example of the response observed. Actually we obtained very similar results to the previous ones.

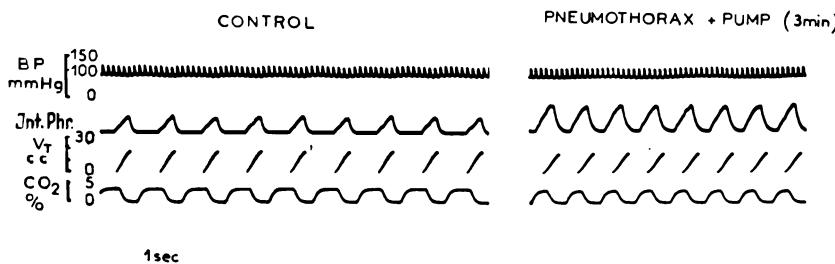


Fig. 3. States before (left) and 3 min after (right) bilateral pneumothorax followed by artificial ventilation. From top to bottom: B.P., blood pressure; Int. Phr., integrated phrenic nerve activity,  $V_T$ , inspired tidal volume and end tidal  $\text{CO}_2$ .

The mean increases in integrated phrenic activity of this group were only slightly higher. The integrated phrenic nerve activity was persistently stimulated by 94% before vagotomy and 34% after vagotomy.

The major disadvantage of the experimental model in both these groups was the procedure of artificial ventilation itself. Arbitrarily imposed parameters of classical artificial ventilation made impossible not only the observation of central respiratory rhythm which might change in response to the stimuli applied, but they could modify as well the magnitude of phrenic activity augmentation.

To avoid this disadvantage a ventilation pump driven by phrenic nerve activity has been applied (Husczuk 1970). The concept of this type of artificial ventilation was based on our finding of a close correlation between integrated phrenic nerve activity and transpulmonary pressure changes during spontaneous breathing. Figure 4 presents this correlation

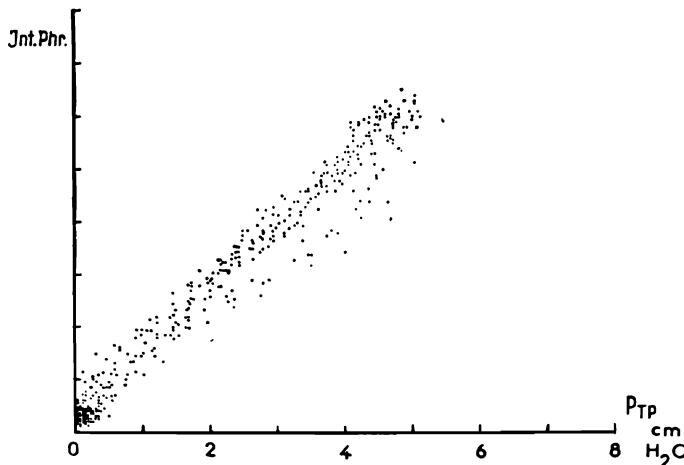


Fig. 4. Correlation between integrated phrenic nerve activity (Int. Phr.) and transpulmonary pressure ( $P_{TP}$ ) changes during spontaneous breathing.

made by computer. Samples of transpulmonary pressure and the level of integrated phrenic activity have been taken simultaneously every 20 msec. The correlation appeared to be very close to 1. We also found a very similar relationship between the peak of integrated phrenic nerve activity and tidal volume in spontaneous breathing. The construction of the phrenic nerve driven pump is based on the principle of a servo-positioning system. In other words the piston of the pump follows exactly the shape of an electric pulse which is the result of integration of a phrenic burst of activity. Figure 5 presents the block diagram of the system.

It was possible to connect the spontaneously breathing rabbits to this type of respiratory pump, so that their spontaneous breathing was assisted by the respirator. In the course of such respiration it was possible to perform unilateral followed by bilateral pneumothorax. Rabbits with intact vagi have shown responses resembling those well known in spontaneously breathing animals. Figure 6 presents a typical observation.

In all seven experiments we obtained considerable increases in the rate of breathing and a fall of tidal volume. The mean increase was 55% for rate and the mean decrease was 29% for tidal volume. Since there was no significant change in the level of phrenic activity, the fall of

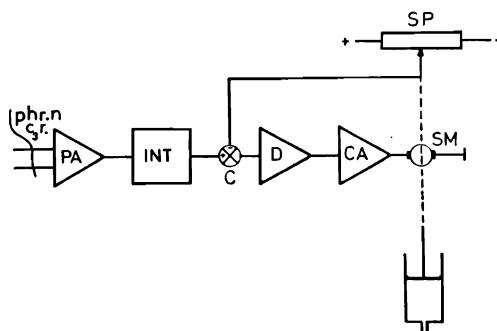


Fig. 5. Block diagram of the phrenic nerve driven respirator. PA, preamplifier; Int., integrator; C, comparator; D, driven; CA, current amplifier; SM, servo motor; SP, servo potentiometer.

tidal volume was probably due to a fall of compliance. The increase in rate of breathing was not due to a decrease of tidal volume since increase of the gain of the pump to return tidal volume to its previous value did not cause any change in respiratory rate. We observed only rapid inhibition of phrenic nerve discharges aiming to compensate the increase of tidal volume.

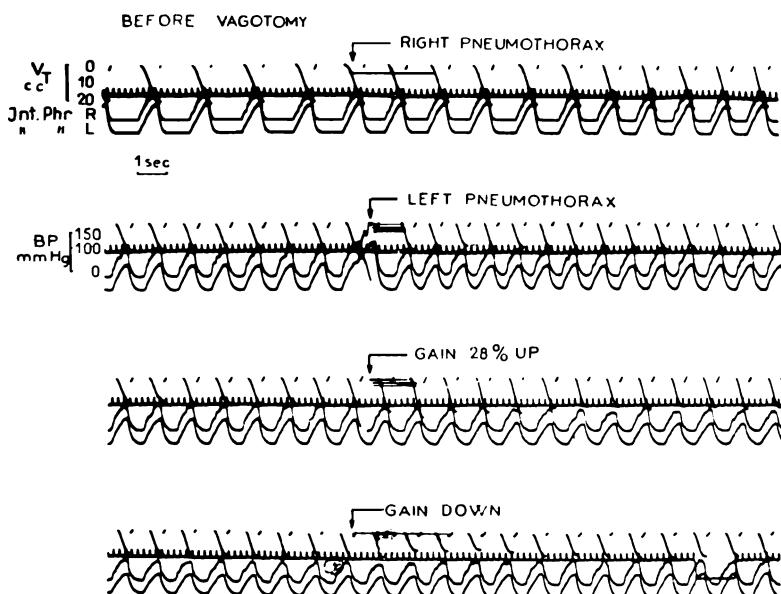


Fig. 6. Spontaneous breathing assisted by the phrenic nerve driven respirator. Responses to right and left pneumothorax and then to the servo pump gain increase aiming to compensate the fall of tidal volume. On the last record the gain was returned to the control value. Tracings from top to bottom: VT, inspired tidal volume (deflection downwards); B.P., blood pressure; Int. Phr. R. and Int. Phr. L., right and left integrated phrenic nerve ( $C_3$  root) activities.

This suggests that under pneumothorax conditions the threshold of sensitivity of pulmonary stretch receptors is considerably lowered (Marshall and Widdicombe 1958). A group of seven vagotomised rabbits showed a smaller increase in the rate of breathing. On average it was stimulated only by 15%. The fall of tidal volume was similar to the previous group.

A difference was observed as far as the level of phrenic nerve activity was concerned. On average it was stimulated by 40%. Figure 7 illustrates

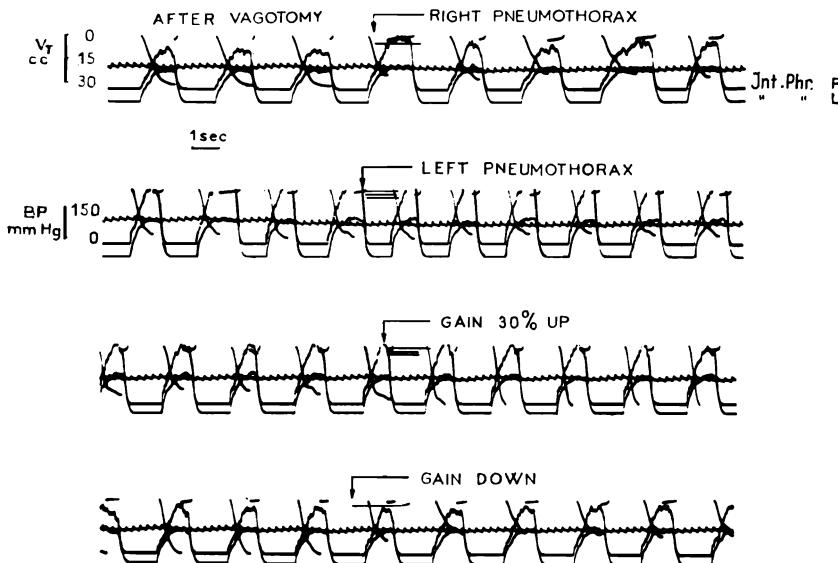


Fig. 7. Spontaneous breathing assisted by the phrenic nerve driven respirator after vagotomy. Explanations and tracings as in Fig. 6.

an example of this response. Here the augmentation of phrenic nerve activity could have been to some extent the result of a decrease in minute volume, since increased gain of the pump led in this group to slight inhibition of phrenic activity. In the last two groups with pneumothorax we have also studied the response to gallamine injection. Figure 8 summarizes all the mean results obtained and already described.

Since the phrenic nerve driven respirator gave an opportunity to study the influence of various forms of respiratory muscle impairment on central respiratory activity without depression of minute ventilation occurring under any other conditions we therefore decided to perform a group of experiments with phrenectomy. Furthermore the persistant

excitation of central respiratory activity due to gallamine after vagotomy and pneumothorax might suggest that phrenic afferent pathways could

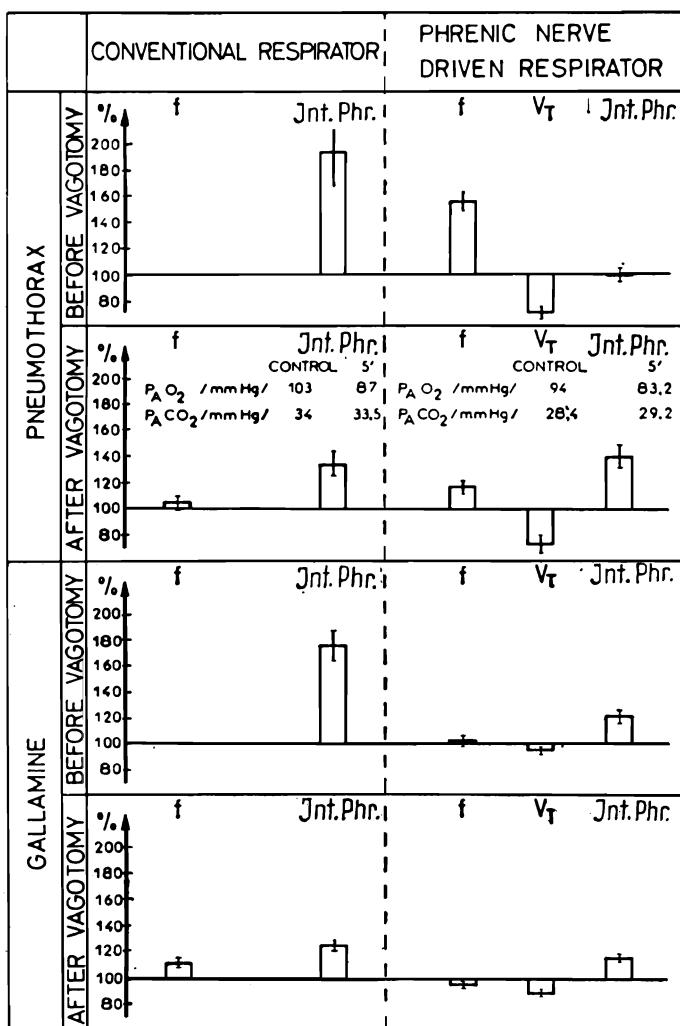


Fig. 8. Graphic comparison of the all mean results obtained.

be involved. Having the spontaneously breathing rabbits connected to the phrenic nerve driven pump we could easily cut main phrenic trunks.

Figure 9 shows the response to this manoeuvre. Generally the activity of the phrenic nerve contralateral to the cut phrenic nerve trunk was more strongly stimulated.

Figure 10 shows mean results of 11 experiments. They indicate a rather minor importance of the phrenic afferent pathway. On the contrary the results associated with connecting spontaneously breathing rabbits to the phrenic nerve driven pump were very intriguing. Despite a marked increase of tidal volume we did not observe any significant changes in the level of phrenic activity. From the physical point of view this

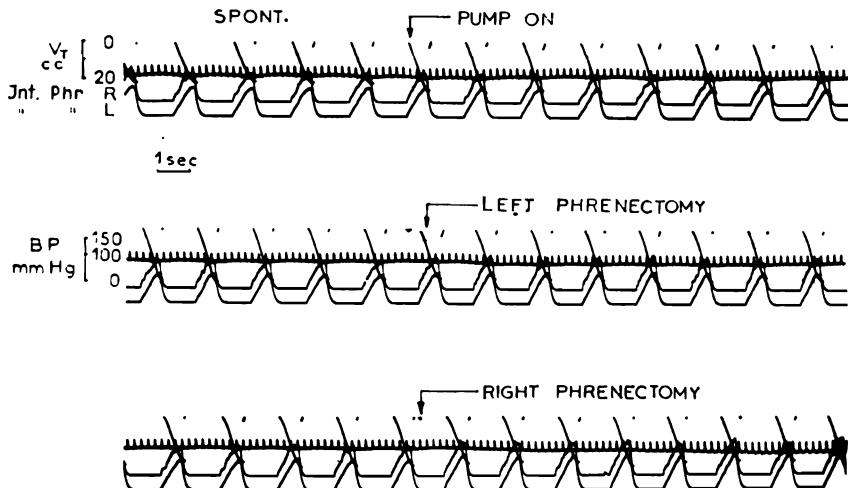


Fig. 9. Response of the spontaneously breathing rabbit to the onset of the phrenic nerve driven respirator (top record) and then to left and right main phrenic trunks sections. Explanations and tracings as in Fig. 6.

type of assisted ventilation is associated with increased transpulmonary pressure.

Thus this observation suggests that the sensitivity threshold of pulmonary stretch receptors depends upon transpulmonary pressure rather than on lung volume. This conclusion is quite obvious since the distensibility of the lung tissue may have an influence on mechanical conditions of pulmonary stretch receptors.

As to the excitatory action of gallamine the results presented would rather suggest its mainly peripheral action consisting in a strong effect on the total respiratory system mechanics. Nevertheless markedly decreased but still present excitation of the central inspiratory activity in response to gallamine administration after vagotomy may be considered as a component of its central action. The problem whether it is a specific or non-specific action remains to be solved.

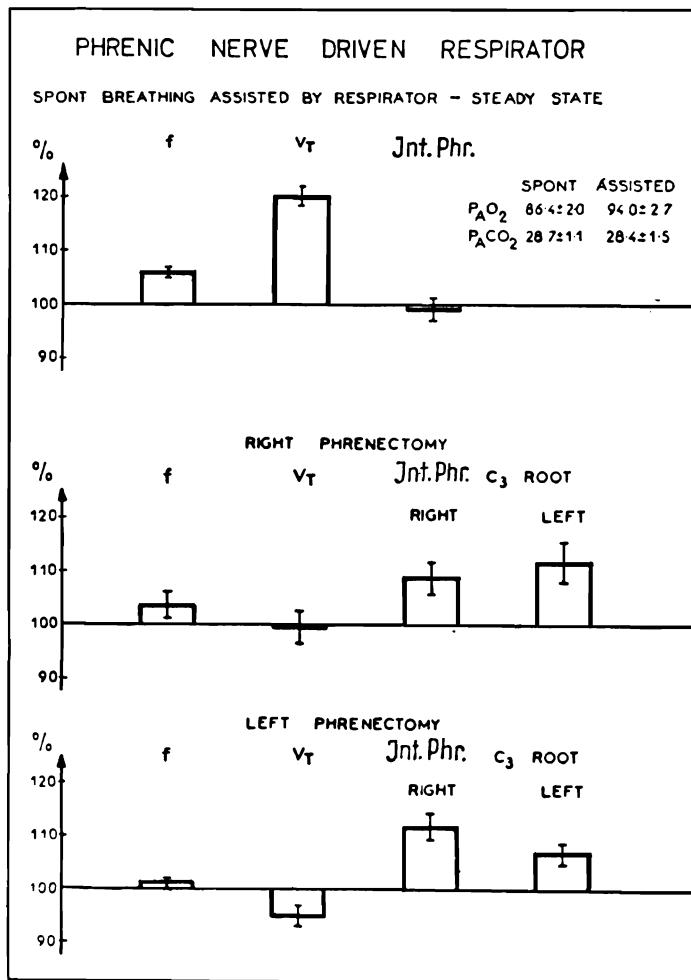


Fig. 10. Graphic presentation of the mean results associated with connecting spontaneously breathing rabbits to the phrenic nerve driven respirator (top histograms) obtained from 18 experiments and mean results of 11 experiments in which responses to left and right phrenectomy have been studied. *f*, respiratory rate; *VT*, tidal volume; *Int. Phr.*, level of integrated phrenic nerve activity.

#### REFERENCES

CULLEN, S. C. (ed.) 1967/68. The year book of anaesthesia. Flaxedil (gallamine triethiodide): Evidence for central action. Year Book Med. Publ., Chicago. 245 p.

GALINDO, A., KRNJEVIĆ, K. and SCHWARTZ, S. 1968. Patterns of firing in cuneate neurones and some effects of Flaxedil. *Exp. Brain Res.* 5: 87-101.

HOUGS, W. 1963. The effect of curarizing substances on the respiratory centre.

*In* D. M. Aviado and F. Paleček (ed.), Drugs and respiration. Pergamon Press, Oxford, p. 87-91.

HUSZCZUK, A. 1970. A respiratory pump controlled by phrenic nerve activity. *J. Physiol. (Lond.)* 210: 183P-184P.

MARSHALL, R. and WIDDICOMBE, J. G. 1958. The activity of pulmonary stretch receptors during congestion of the lungs. *Quart. J. Exp. Physiol.* 43: 320-330.

A. HUSZCZUK, Laboratory of Neurophysiology, Medical Research Centre, Polish Academy of Sciences, Dworkowa 3, Warszawa 36, Poland.

J. G. WIDDICOMBE, Laboratory of Physiology, University of Oxford, Oxford, England.