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THE ACTIVITY OF THE MEDULLARY CENTRES IN DIFFUSION RESPIRATION

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In 1947 Draper, Whitehead & Spencer described experiments in which dogs were kept alive for periods up to 1 hr after respiratory movements had been arrested by deepening the level of anaesthesia until the respiratory centre was paralysed. These authors applied the term 'diffusion respiration' to the mechanism by which the animals were able to replenish the oxygen in their lungs without the aid of respiratory movements.

In a previous paper (Joels & Samueloff, 1956) we reported the finding of a 'metabolic' acidosis during diffusion respiration and discussed some of the theoretical considerations on which diffusion respiration is based. In this study we have examined the activity of the medullary centres during diffusion respiration in animals in which natural breathing had been abolished (i) by deep thiopentone anaesthesia which directly depresses the respiratory centre or (ii) by succinylcholine (Scoline) which blocks neuromuscular transmission. By comparing the results obtained under these two experimental conditions it is possible to study the effects of impulses radiating from the respiratory to the vasomotor and cardiac centres, since in the latter case the respiratory centre is still discharging, while in the former it is not. It is also possible to study the influence of an increasing CO_2 tension on the medullary centres in the absence of anoxia, under circumstances in which neither impulses from actively contracting respiratory muscles nor from rhythmically inflated lungs reflexly modify the central discharge.

METHODS

The experiments were carried out on dogs and cats. The dogs were anaesthetized with thiopentone, a 5% solution of which was gradually injected intravenously until complete surgical anaesthesia was obtained. Pentobarbitone 30 mg/kg body weight was injected intraperitoneally to anaesthetize the cats. The operative procedure and breathing circuit were similar to those which we have

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previously described (Joels & Samueloff, 1956). After a preliminary period of breathing 100% oxygen, respiratory movements were arrested either by gradually deepening the thiopentone anaesthesia until medullary paralysis occurred, or by the administration intravenously of succinylcholine 0·5–1·5 mg/kg body weight, the dose depending on the period for which it was desired to maintain diffusion respiration. Respiration was recorded by a tambour connected to the side arm of the tracheal cannula; arterial blood pressure was recorded from the left femoral artery with a mercury manometer. In some dogs lead II electrocardiographic records were taken during diffusion respiration with a Sanborn Cardiette electrocardiograph.

Nerve action potentials were studied, but only in cats. The nerves of the dog contain considerably more interstitial tissue than those of the cat; this makes dissection very difficult and the production of single fibre preparations too uncertain. In cats records were taken from the central end of recurrent laryngeal nerve as an index of respiratory centre activity (Green & Neil, 1955) and from the central end of the cervical sympathetic as a measure of vasomotor centre activity. Single (or a few) fibre preparations were made by successively splitting the nerves. The nerve-slips were laid on saline-wick electrodes which were connected to a resistance capacity coupled amplifier and thence to a double-beam Cossor oscilloscope from which the potentials were photographed. In some instances an electromyogram of the diaphragm was also recorded from a concentric needle electrode (Adrian & Bronk, 1929) inserted through the abdominal wall just below the costal margin and connected through a similar amplifier to the oscilloscope.

RESULTS

Changes in the arterial CO_2 *and* O_2 *contents*

Fig. 1 illustrates the changes, in the gaseous composition of the arterial blood, commonly seen in the course of diffusion respiration. This figure records the changes in the arterial CO_2 and O_2 contents of three dogs during the first 30 min of diffusion respiration. Similar alterations occurred in the cat. The pre-diffusion respiration blood samples were withdrawn towards the end of the period of denitrogenation, after the animals had been breathing pure oxygen for at least 45 min. The arterial CO_2 contents at this stage ranged between 28·5 and 36·5 vol. %. When diffusion respiration began the CO_2 contents rose sharply to reach 52–58 vol. % after only 5 min, and then continued to rise more gradually to be between 67 and 80 vol. % at the end of 30 min. These values for the arterial CO_2 content, high as they are, do not by themselves reveal the relatively enormous rise of the arterial CO_2 tension, since the rise in the CO_2 content resulting from the increasing CO_2 tension is partially masked by a fall in the CO_2 combining power of the blood. This fall in CO_2 combining power is due to the metabolic acidosis which occurs in diffusion respiration. We have previously shown (Joels & Samueloff, 1956) by means of logarithmic CO_2 dissociation curves that the arterial CO_2 tension after 30 min of diffusion respiration is generally between 200 and 220 mm Hg and subsequently rises even higher. Throughout the period of the experiments shown here there was virtually no change in the arterial oxygen content in any of the dogs. The arterial oxygen capacity of the blood of all three dogs was determined at the same time as the oxygen content, and in each case was slightly below the corresponding content. This rise of the oxygen content above the corresponding

capacity during the period of diffusion respiration is due to the animal having breathed 100% oxygen and having thereby increased the amount of oxygen dissolved in the blood. It appears from these findings that alterations in the activity of the medullary centres during diffusion respiration cannot be attributed to a deficiency in the volume or the tension of oxygen in the arterial blood. On the other hand, the medullary centres must be greatly affected by the marked rise in the arterial CO_2 tension and content.

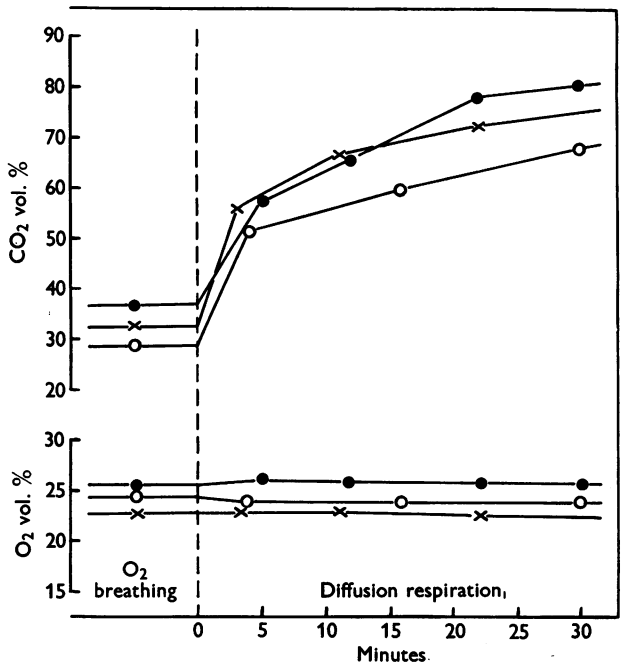
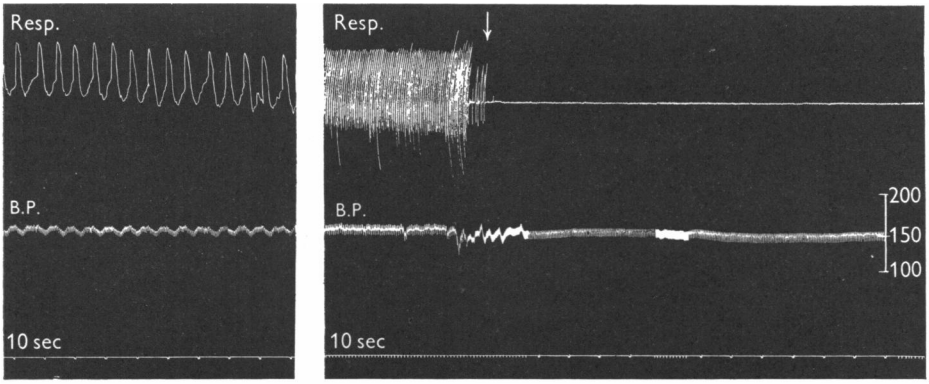


Fig. 1. Changes in the arterial CO_2 and O_2 contents of three dogs during 30 min diffusion respiration. The same symbol is used for the CO_2 contents and O_2 contents of each dog. The initial samples were drawn after the dogs had been breathing 100% oxygen for at least 45 min. When diffusion respiration commenced there was an initial very rapid rise in the CO_2 contents, followed by a more gradual increase. The O_2 contents of the individual animals remained virtually unaltered throughout the period of the experiments.

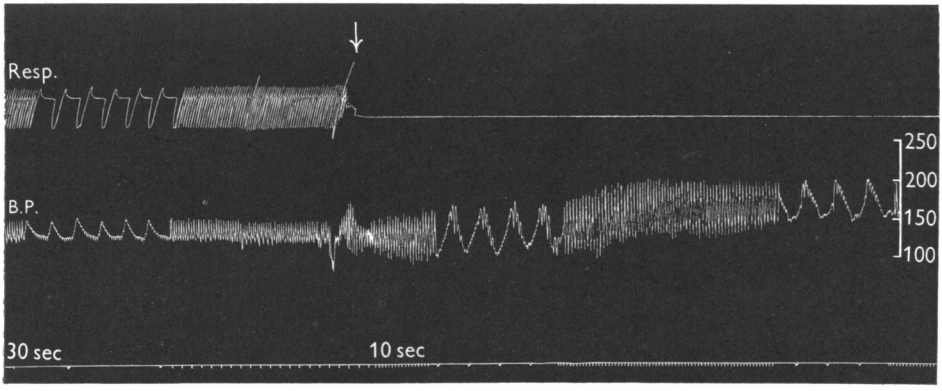
Effects on respiration, blood-pressure and heart-rate

Fig. 2 (*a*) is taken from a representative experiment in a dog in which deep thiopentone anaesthesia was used to arrest the respiratory movements by depressing the respiratory centre. During the first 5 min of diffusion respiration the blood pressure remained at its control value of 150 mm Hg. The heart rate was likewise unchanged and the cardiac rhythm remained regular. The striking difference during diffusion respiration was the complete absence of the rhythmic variations in the blood pressure which accompanied the respiratory movements in the control record.

Fig. 2 (*b*) illustrates the changes observed in an anaesthetized dog, in which the respiratory movements were arrested by completely paralysing the respiratory muscles with succinylcholine. In complete contrast with the experiment shown in Fig. 2 (*a*), rhythmic variations in the blood pressure not only continued after diffusion respiration had begun but became exaggerated. The rhythmic blood-pressure fluctuations rapidly increased in amplitude until after 2–3 min they showed a swing of 70 mm Hg. The mean level of



(*a*)



(*b*)

Fig. 2. Blood-pressure variations during diffusion respiration in a dog. Kymograph speeded at intervals to show individual heart beats. (*a*) Left-hand record shows rhythmic fluctuations normally present in the blood pressure. At arrow diffusion respiration followed arrest of respiratory movements by 87·5 mg thiopentone. The rhythmic blood-pressure variations completely disappeared. (*b*) At arrow diffusion respiration followed injection of 25 mg succinylcholine. The normal rhythmic blood-pressure fluctuations continued and were accentuated. Sinus arrhythmia can be seen on faster portions of record.

arterial blood pressure rose above the control value of 125 mm Hg, being 175 mm Hg after 15 min diffusion respiration. This rise in blood pressure was probably due to the increase in the arterial CO_2 content which, in the similar experiments illustrated in Fig. 1, was between 58 and 69 vol. % after 15 min diffusion respiration.

However, during the first 5 min of diffusion respiration shown in Fig. 2 (*b*) there was little change in the arterial blood pressure. The rise in blood pressure occurred later in the record and the corresponding period is not shown in Fig. 2 (*a*). Thus in this initial 5 min period at least there is little difference between the effects on the *mean* blood pressure of diffusion respiration during respiratory paralysis produced by thiopentone or by succinylcholine.

Fig. 2 (*b*) also shows that sinus arrhythmia was present during diffusion respiration produced by succinylcholine. Rhythmic variations in heart rate accompanied the rhythmic variations in blood pressure, there being an increase in rate accompanying the rise in blood pressure and a decrease during the fall. Electrocardiographic records taken at intervals throughout the period of diffusion respiration enabled these changes in heart rate to be measured. Fig. 3 shows a record of the blood pressure 13 min after diffusion respiration had begun. The time intervals between the peaks of the successive R waves on the electrocardiogram taken at the same time were measured and plotted beneath the corresponding portion of the blood pressure record. The R–R intervals varied from 0·40 to 0·46 sec during the course of each blood-pressure wave, indicating a change in heart rate of from 150 to 130 beats/min.

It is seen, therefore, that when diffusion respiration was established under deep thiopentone anaesthesia there was complete disappearance of respiratory variations in the blood pressure; when succinylcholine was used to paralyse respiratory movements the blood-pressure variations which followed the control respiratory rhythm became more marked, and the cardiac rhythm, previously regular, showed marked sinus arrhythmia.

The normal respiratory fluctuations in the blood pressure are generally attributed either to the mechanical effects of the chest movements, the so-called respiratory pump mechanism, or to a phasic irradiation from the respiratory centre to the vasomotor centres, this irradiation being synchronous with the respiratory discharge. Our results show that the blood-pressure waves were absent when the respiratory centre was paralysed by thiopentone (and the respiratory muscles thereby inactivated), but were still present when the respiratory muscles were paralysed by succinylcholine, but the respiratory centre was unaffected. The blood-pressure variations in diffusion respiration after 'paralytic' doses of succinylcholine can therefore be attributed to an irradiation from the respiratory to the vasomotor centre. Under these experimental conditions the sinus arrhythmia which developed cannot be attributed to rhythmic discharges from the lungs or heart resulting from respiratory

movements. We suggest therefore that the sinus arrhythmia also was due to irradiation from the respiratory centre. During normal breathing this irradiation was presumably inadequate to produce obvious fluctuations in heart rate.

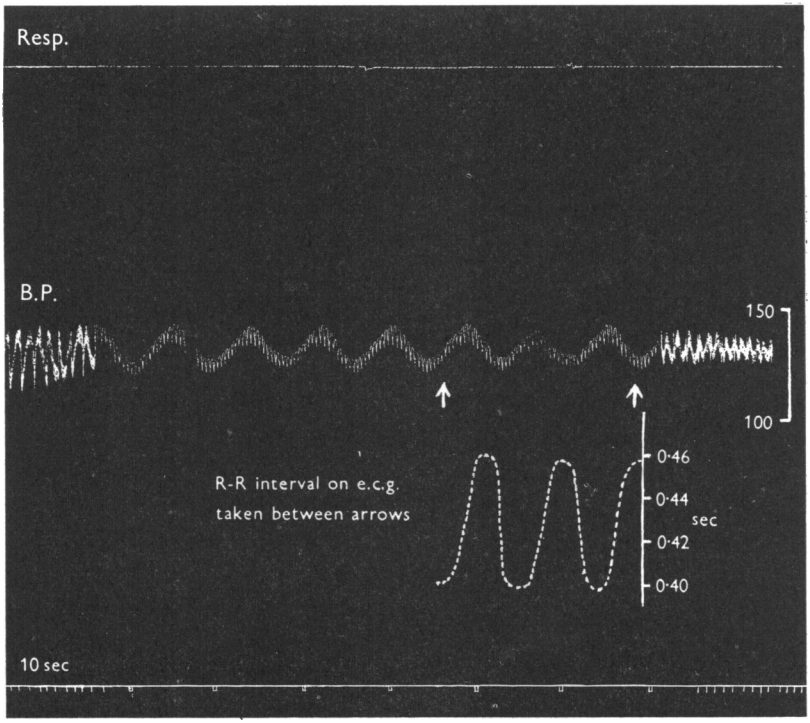


Fig. 3. Sinus arrhythmia during diffusion respiration. The figure shows a portion of the tracing obtained from a dog, 13 min after the beginning of diffusion respiration under succinylcholine paralysis. An e.c.g. was taken during the period between the arrows, the R-R intervals were measured and have been plotted beneath the corresponding portion of the blood-pressure record. The presence of sinus arrhythmia is clearly shown.

When the blood pressure was recorded throughout diffusion respiration during succinylcholine 'paralysis', changes were seen in the rhythmic variations. The rapid increase in the amplitude of these waves, which occurs early in diffusion respiration, has already been illustrated, Fig. 2 (*b*). Fig. 4 is from a similar experiment on a dog in which the blood-pressure waves also showed this initial increase. Seven minutes after diffusion respiration had commenced (Fig. 4*b*) these variations had gradually decreased in amplitude till they were only slightly larger than those seen during normal breathing, though their frequency was only about half the control value. The waves continued to diminish in size, and after 30–35 min of diffusion respiration they disappeared

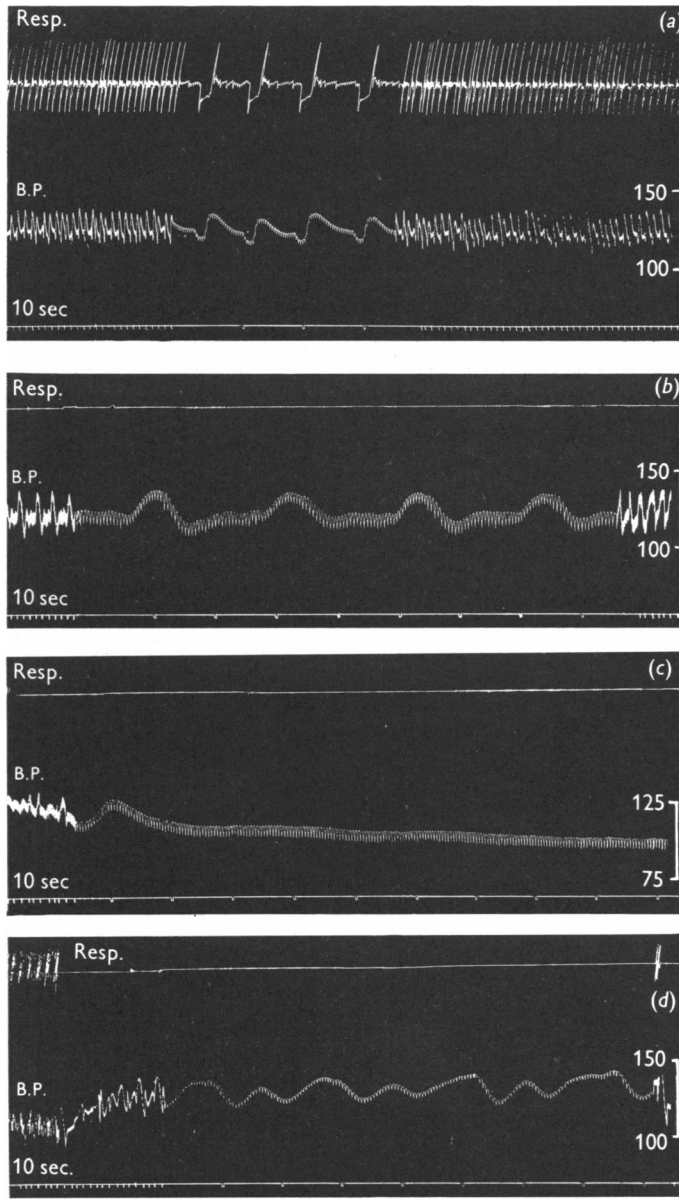


Fig. 4. Changes in the rhythmic arterial blood-pressure fluctuations during diffusion respiration in a dog. (*a*) Before diffusion respiration; blood pressure fluctuations synchronous with respiratory rhythm. (*b*) 7 min after respiratory movements arrested with 20 mg succinylcholine; rhythmic blood-pressure fluctuations still present. Sinus arrhythmia can be seen. (*c*) 34 min after commencement of diffusion respiration; blood-pressure fluctuations are just disappearing. (*d*) After 35 min artificial respiration; rhythmic blood-pressure fluctuations have returned even though respiratory movements are absent.

altogether (Fig. 4*c*). The blood-pressure record at this stage resembled that seen when respiratory movements were arrested by thiopentone. The sinus arrhythmia seen in Fig. 4 (*b*) disappeared at almost the same time as the blood-pressure waves vanished; this observation supports the suggestion that the rhythmic fluctuations in both blood pressure and heart rate had a common origin in an irradiation from the respiratory centre. We attribute the initial increase and subsequent decline of these fluctuations to the steadily mounting arterial CO_2 tension which was illustrated in Fig. 1. During the early stages of diffusion respiration this rising CO_2 tension presumably stimulated the respiratory centre and the intensity of its irradiation to the vasomotor and cardiac centres consequently increased, thus accounting for the large swings in the blood pressure and the sinus arrhythmia. Later, however, the further rise in the arterial CO_2 tension depressed the medullary centres; ultimately the respiratory centre ceased to discharge and the blood-pressure record resembled that seen during diffusion respiration under deep thiopentone anaesthesia when the respiratory centre was paralysed *ab initio*.

Fig. 4 (*d*) shows that the blood-pressure variations may return (in the Scolinized animal) after 20–40 min of artificial respiration, although spontaneous respiration was still absent. It may be assumed that at this stage the artificial ventilation had lowered the CO_2 tension sufficiently to permit the return of a regular discharge from the respiratory centre, even though the respiratory movements were still absent owing to the continuing peripheral action of the succinylcholine.

Action potential studies

In the following experiments respiratory and vasomotor centre activity was studied by recording the action potentials in the central end of the recurrent laryngeal and of the cervical sympathetic nerves respectively. Diffusion respiration was maintained during succinylcholine paralysis.

Fig. 5 illustrates the activity of the respiratory centre in a cat during diffusion respiration. During normal breathing there were simultaneous discharges, synchronous with inspiration, in the recurrent laryngeal nerve and in the electromyogram from the diaphragm (Fig. 5*a*). Soon after respiratory movements had been arrested by succinylcholine there was, of course, no diaphragmatic discharge, but the discharge of the respiratory centre as evidenced by the recurrent laryngeal activity was still continuing, though at a slower rate (Fig. 5*b*). This slower rate may be attributed to the absence of the Hering-Breuer reflex from the immobile lungs. Eventually this respiratory centre activity also ceased, the arterial CO_2 tension having by then presumably reached depressant levels (Fig. 5*c*). After a brief period of artificial respiration, spontaneous breathing returned with the reappearance of rhythmic activity in both the recurrent laryngeal nerve and the electromyogram (Fig. 5*d*). The

latter potentials were still very small owing doubtless to some persistent peripheral depressant action of the succinylcholine. Though this resumption of diaphragmatic activity is only just perceptible in the figure (5*d* M.), it was clearly visible on the larger scale of the original record.

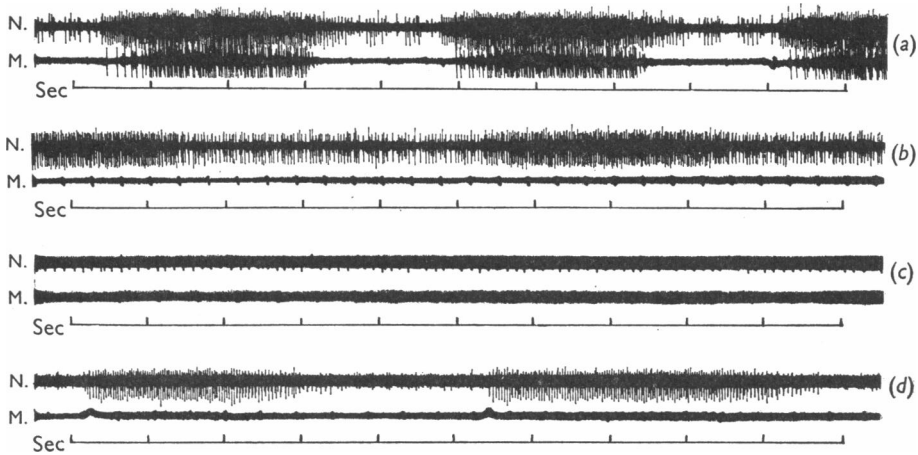


Fig. 5. Respiratory centre discharge during diffusion respiration in a cat as illustrated by activity in the recurrent laryngeal nerve. In each strip the upper record (N.) is from the central end of the recurrent laryngeal nerve and the lower record (M.) is an electromyogram from the diaphragm. Time in seconds. (*a*) Control period; with each inspiration there are synchronized bursts of activity in the recurrent laryngeal nerve and the electromyogram. (*b*) 10 min after respiratory movements arrested by succinylcholine; the rhythmic recurrent laryngeal discharge is still present but there is no diaphragmatic activity. The small spikes in the latter record are the electrocardiogram 'breaking through'. (*c*) After 47 min diffusion respiration; the rhythmic discharge in the recurrent laryngeal nerve has now also disappeared. (*d*) 63 min after the return of spontaneous respiration; the rhythmic recurrent laryngeal discharge has returned and the electromyogram shows accompanying diaphragmatic activity.

Fig. 6 shows the activity of the respiratory centre (as shown by recurrent laryngeal nerve potentials) and also that of the vasomotor centre, the latter being represented by the action potentials in the central end of the cervical sympathetic. During normal breathing (Fig. 6*a*) there was a continuous discharge in the cervical sympathetic which waxed and waned at regular intervals, each increase being synchronous with a burst of activity in the recurrent laryngeal nerve. Since the bursts of recurrent laryngeal activity were synchronous with inspiration, as shown by the diaphragmatic electromyogram (Fig. 5*a*), the periodic increases in the cervical sympathetic discharge must likewise have been synchronous with each inspiration. One minute after diffusion respiration under succinylcholine had begun (Fig. 6*b*) both the recurrent laryngeal and the cervical sympathetic discharges were intensified, though their rhythms were slightly slower. This continued synchronization of

rhythmicity in the respiratory and vasomotor centre discharges in the absence of respiratory movements confirmed that the rhythmic blood-pressure fluctuations were due to an irradiation to the vasomotor centre from the respiratory centre, when the latter had been stimulated by the rise in CO_2 tension of the arterial blood. Fifteen minutes later (Fig. 6*c*) the respiratory discharge in the recurrent laryngeal nerve had considerably diminished in intensity as the CO_2 tension reached depressant levels. The vasomotor centre, as evidenced by the cervical sympathetic potentials, showed at this stage a non-rhythmic tonic discharge of low intensity, suggesting that the weakened central respiratory discharge did not affect the vasomotor centre.

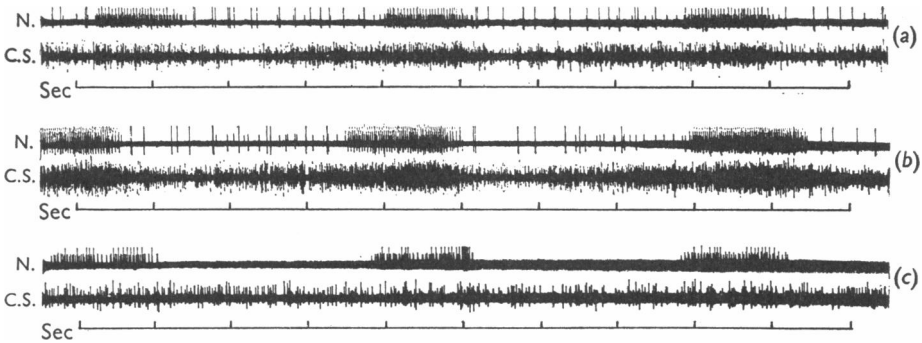


Fig. 6. Respiratory and vasomotor centre activity during diffusion respiration in a cat as illustrated by the action potential discharges in the recurrent laryngeal and cervical sympathetic nerves. In each strip, records from above downwards; recurrent laryngeal nerve (N.), central end of cervical sympathetic nerve (C.S.), time in seconds. (*a*) Control period; there is a rhythmic discharge in the recurrent laryngeal nerve, each burst of impulses being accompanied by an increase in the cervical sympathetic discharge. (*b*) 1 min after the beginning of diffusion respiration; synchronization of the recurrent laryngeal and cervical sympathetic activity is still present. Both discharges are intensified. (*c*) After 16 min diffusion respiration; the recurrent laryngeal discharge is diminished in intensity and the cervical sympathetic discharge no longer shows any rhythmicity.

DISCUSSION

Schweitzer (1945) suggested the following classification of the main rhythmic fluctuations of the arterial blood pressure:

(i) Fluctuations due to cardiac activity.

(ii) Fluctuations due to respiratory activity: (*a*) mechanical effects of the respiratory pump mechanism; (*b*) Traube-Hering waves, synchronous with respiration, and due to irradiation of impulses from the respiratory to the vasomotor centre.

(iii) Fluctuations of blood pressure due to rhythmic variations in vasomotor centre tone, which are independent of respiration and are always much slower in rate (Sigmund Mayer waves, 1876).

The original observations of Traube (1865) with regard to the irradiation of impulses from the respiratory to the vasomotor centre were confirmed by Hering (1869) and many others. Hering wrote: 'We have adequately proved that the vascular system shows respiratory fluctuations which are associated with the respiratory movements, and which, like the latter, originate rhythmically from the so-called respiratory centre'.

It is these latter fluctuations, due to irradiation of impulses from the respiratory centre, that are recorded in our experiments. The variations classified by Schweitzer as being due to the mechanical effects of the respiratory pump mechanism had been abolished with the arrest of respiratory movement. Mayer waves were not observed in our records. Anderson, Kenney & Neil (1950) pointed out that such waves appear in conditions of low blood pressure, impaired circulation or anoxic anoxia, none of which was present in our experiments.

The persistence of the respiratory blood-pressure variations and recurrent laryngeal nerve activity after respiratory movements have been abolished by succinylcholine confirms that the source of the variations does not lie in the respiratory pump mechanism. The absence of these fluctuations when diffusion respiration was induced by paralysing the respiratory centre with thiopentone proves that they originate in the respiratory centre itself. As there was no fall of the blood pressure in the experiments using thiopentone, we conclude that this degree of medullary depression did not greatly affect the vasomotor centre. The results taken as a whole indicate that these blood-pressure variations are due to modification of the vasomotor centre activity by impulses arising in the respiratory centre.

The appearance of sinus arrhythmia during diffusion respiration under succinylcholine paralysis showed that there was also irradiation from the respiratory centre to the cardiac centre. The accentuation of the sinus arrhythmia during the early stages of diffusion respiration may be correlated with the increased recurrent laryngeal and cervical sympathetic discharges at this period, which indicated an increased irradiation from the respiratory to the other medullary centres. The respiratory origin of the sinus arrhythmia is confirmed by its absence once the blood-pressure variations have ceased. Thus an alternative demonstration is provided of Heymans & Heymans (1926) classical 'isolated head' experiments on the origin of sinus arrhythmia.

SUMMARY

1. The activity of the medullary centres and its relation to respiratory blood pressure variations was investigated during diffusion respiration induced during either deep thiopentone anaesthesia or paralysis of the respiratory muscles by succinylcholine.

2. The rhythmic blood-pressure variations were absent during diffusion respiration induced under deep thiopentone anaesthesia which depresses the respiratory centre; they were still present during diffusion respiration when the neuromuscular blocking agent succinylcholine was used to arrest respiratory movements. Since the blood-pressure variations cannot then be attributed to the 'respiratory pump' action of the breathing movements, the findings indicate that the rhythmic blood-pressure variations during diffusion respiration are due to an irradiation from the respiratory to the vasomotor centre.

3. Sinus arrhythmia appears during diffusion respiration induced under succinylcholine paralysis and can likewise be explained by an irradiation from the respiratory to the vasomotor centre. This irradiation is presumably subthreshold during normal quiet breathing since sinus arrhythmia does not then occur.

4. The recurrent laryngeal nerve still exhibits rhythmic bursts of action potentials after respiratory movements have been arrested by succinylcholine. Thus the respiratory centre still discharges during diffusion respiration under these conditions.

5. During normal breathing the discharge in the cervical sympathetic nerve is increased with each burst of inspiratory impulses in the recurrent laryngeal nerve. This synchronization of cervical sympathetic and recurrent laryngeal discharges persists after arrest of respiratory movements by succinylcholine and confirms that there is an irradiation from the respiratory to the vasomotor centre in these circumstances.

6. Both the rhythmic blood-pressure variations and the discharges in the recurrent laryngeal and cervical sympathetic nerves are increased during the early stages of diffusion respiration. This increase is later followed by a gradual disappearance of the blood-pressure variations and the rhythmic nerve discharges. These changes may be attributed to the great rise in the CO_2 tension during diffusion respiration, which initially stimulates but subsequently depresses the medullary centres.

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