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THE EFFECT OF BUPIVACAINE AEROSOL ON THE ACTIVITY OF PULMONARY STRETCH AND 'IRRITANT' RECEPTORS

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SUMMARY

1. Experiments have been done on anaesthetized, paralysed and artificially ventilated cats.

2. Vagal single afferent fibres showing discharges in phase with respiration were isolated in the neck. Two types of fibres were studied at different tidal volumes: (i) showing slowly adapting discharges from the pulmonary stretch receptors; (ii) showing rapidly adapting discharges from the lung 'irritant' receptors. The effect of bupivacaine aerosol, administered by positive pressure inflations, was recorded on the pattern of fibre discharge.

3. The pulmonary stretch fibres were further classified into low-threshold and higher-threshold fibres according to the standard criteria. Bupivacaine aerosol blocked activity in all the low-threshold and in the majority of the higher-threshold fibres.

4. Of the rapidly adapting fibres, bupivacaine completely blocked activity at some tidal volumes and markedly reduced it at most others.

5. The fibre activity data are presented. It is concluded that although bupivacaine aerosol markedly reduced impulse activity in all three types of fibres, the data suggest that there is a small difference in the ease with which low-threshold fibres on the one hand and higher-threshold and 'irritant' fibres on the other hand are affected. The reasons for this difference in the behaviour are not understood.

INTRODUCTION

Intratracheal administration of an aerosol of local anaesthetic agent, 5% bupivacaine, blocked the reflex respiratory responses mediated by the pulmonary stretch receptors and the cough receptors, but left intact those from the type J receptors (rabbit: Jain, Trenchard, Reynolds, Noble & Guz, 1973; dog and rabbit: Dain, Boushey & Gold, 1975; dog and man: Cross, Guz, Jain, Archer, Stevens & Reynolds, 1976). These observations have been confirmed by one of us in the cat (S. K. Jain, unpublished data). The findings of these studies suggested that even though the Hering–Breuer inflation and deflation reflexes were blocked, activity may not be abolished in all the afferent fibres from pulmonary stretch receptors. By using a similar technique and time course of administration of bupivacaine aerosol in the cat, we have reported in a preliminary study (Jain & Fahim, 1977) that: of the

thirty-five pulmonary stretch fibres studied, activity could be blocked completely in 57 %, partially in 40 % and remained unaffected in the remaining 3 %. However, no attempt was made to investigate whether a more prolonged administration of the aerosol would abolish activity in all these fibres.

The use of differential pulmonary vagal block in man, by breathing bupivacaine aerosol, may prove to be a useful method of investigating the role of lung receptors in pulmonary diseases (Jain, 1975). It is therefore important to establish what such an aerosol can achieve by way of blocking or reducing activity in vagal afferent fibres originating from the airways. The present investigation was planned: (1) to find out whether administration of bupivacaine aerosol for a longer period than previously studied would abolish activity in all the fibres from the pulmonary stretch receptors; (2) to study the effect of the aerosol on the activity of afferent fibres showing rapidly adapting discharges from the lung 'irritant' receptors described by Mills, Sellick & Widdicombe (1969).

METHODS

Experiments were performed on sixteen cats weighing 1·5–4·0 kg, anaesthetized with 70 mg kg^{-1} chloralose given intravenously, after induction with trichlorethylene (Trilene, I.C.I.). The cat was placed in supine position; the trachea was cannulated; polyethylene catheters were inserted into the femoral artery and vein for sampling arterial blood and giving injections respectively. The muscles were paralysed with intravenous gallamine triethiodide (Flaxedil) and the cat was artificially ventilated with air at a frequency of 15 min^{-1}, with tidal volumes adjusted to 30–50 ml. The P_{a,CO_2} was maintained at 4–5 kPa and P_{a,O_2} was always more than 10·6 kPa. The basal ventilation was kept constant throughout each experiment. Respiration was monitored either by recording intratracheal pressure changes or with a Fleisch 'O' pneumotachograph interposed between the respiratory pump and the tracheal cannula (see Fig. 1). The pneumotachograph was connected to a Statham PM 97 differential strain gauge whose output was displayed on one channel of the Tektronix type 422 cathode ray oscilloscope.

One of the vagus nerves was exposed in the cervical region and was separated from the carotid sheath and surrounding tissues. By raising the surrounding skin flaps, a pool was made around the vagus; this was filled with liquid paraffin kept at 37–38 °C. The rectal temperature of the cat was maintained at 37 °C. The vagus was placed on a smooth black Perspex plate inside the paraffin pool. Under a binocular dissection microscope, the fibrous and epineural sheath of the nerve was removed. A thin bundle of fibres was separated from the rest of the nerve by cutting centrally, and functionally single respiratory units were isolated. The activity in the fibre was recorded with a pair of chloride coated silver wire electrodes connected to a type 122 Tektronix preamplifier; the output of the latter was displayed on the second channel of the cathode ray oscilloscope as well as fed to a speaker through an audio-amplifier. Photographs were taken from the oscilloscope screen with a C4H Grass kymograph camera at a film speed of 5 cm or 2·5 cm sec^{-1}. Two types of fibres were investigated: (1) showing slowly adapting discharges from pulmonary stretch receptors, discharges identified by their characteristic pattern (Adrian, 1933) and (2) showing rapidly adapting discharges during inflation from the lung 'irritant' receptors as described by Mills *et al.* (1969). The fibre activity was also recorded at higher than basal tidal volumes.

Administration of bupivacaine aerosol

After recording the base line discharge from single fibres, bupivacaine aerosol was administered with intermittent positive pressure inflations. The technique of preparation of the aerosol and its administration was the same as described earlier (Jain *et al.* 1973) and is shown diagrammatically in Fig. 1. 5 % bupivacaine, maintained at 56 °C was used to generate aerosol with a Wright nebulizer (Wright, 1958). The temperature of the aerosol at the point of entry into the trachea was 35–37 °C. The tracheal cannula (see Fig. 1) was blocked off from the pneumotachograph

and the respiratory pump was switched off; an aerosol of bupivacaine was produced with oxygen at a constant flow of 15 litres/min^{-1} from a pressurized cylinder. Occlusion with clamp A diverted the aerosol into the lungs of the animal. With a visual judgement of the size of lung inflation corresponding to an airway pressure between 1–2 kPa, the clamp A was released with simultaneous occlusion with clamp B. The aerosol thus trapped inside the lungs was retained there for approximately 10 sec and then let out by releasing the clamp B. The whole cycle was repeated 3–4 times per min. With experience, it was possible to administer the aerosol so that the P_{a,O_2} remained above 26 kPa and P_{a,CO_2} at 4–5·4 kPa. Occasionally, however, the airway pressure during inflation rose above 2 kPa, in which case such an inflation was immediately

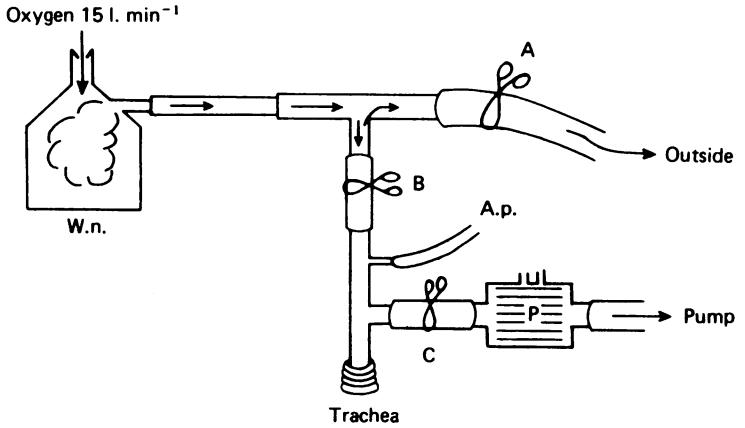

Fig. 1. Schematic diagram showing the method of administration of bupivacaine aerosol under positive pressure inflation; A.p. - to monitor the airway pressure; W.n. - Wright nebulizer to produce 5% bupivacaine aerosol, maintained at 56 °C in a water bath (not shown); clamp A diverts the aerosol into the lungs; clamp B retains the aerosol in the lungs; clamp C shut off the pneumotachograph during the aerosol administration.

let out. The aerosol administration was continued till a maximum reduction in the fibre discharge, sustained for at least 4 min, was obtained. This was judged on the basis of the discharges heard from the speaker or seen on the oscilloscope during a positive pressure inflation at about 2 kPa. Soon after the termination of the aerosol administration, ventilation with the pump was resumed. About 2 min later, the fibre discharge was again recorded, as before the aerosol administration. The fibre was then allowed to recover and activity was recorded at varying intervals. If the animal's condition was satisfactory, another fibre was isolated, i.e. about 2 hr after finishing the aerosol, and the whole experiment was repeated. Control experiments were performed in three cats by administering, over the same time course, normal saline aerosol followed by the bupivacaine aerosol. No effect was observed on the fibre discharges of the slowly adapting type with saline aerosol, while complete block of activity occurred with bupivacaine.

RESULTS

The effect of bupivacaine aerosol on the activity of twenty-two pulmonary vagal afferent fibres has been studied. Of these, thirteen were from the slowly adapting pulmonary stretch receptors and the remaining nine were from the rapidly adapting 'irritant' receptors. The duration of administration of the aerosol in the two groups ranged from 8·5 to 13·0 min and 13·0 to 16·5 min respectively (see Tables 1 and 2). These Tables also give the data regarding: the number of positive pressure inflations and duration of aerosol administration; the pattern, frequency and duration of fibre

TABLE 1. Effect of intratracheal administration of bupivacaine aerosol on the activity of fibres showing slowly adapting discharges from pulmonary stretch receptors. Onset of recovery: time interval after finishing the aerosol; T_i: duration of inspiratory phase; T_d: duration of fibre discharge; T_e: duration of expiratory phase; V_T: tidal volume.

Cat/ fibre no.	High/ low threshold	Duration of aerosol adm. (min)	No. of inflations	Onset of recovery (min)	Event	V_T (ml.)	Inspiration T_i (sec)	Inspiration T_d (sec)	Inspiration No. of impulses	Expiration T_e (sec)	Expiration T_d (sec)	Expiration No. of impulses
1	2	3	4	5	6	7	8	9	10	11	12	13
30/1	Low				Control	30	1·5	1·5	164	2·6	2·6	82
						40	1·8	1·8	172	2·3	2·3	72
						58	1·8	1·8	181	2·3	2·3	74
		12	38	6	After aerosol	30		0	0		0	0
						40		0	0		0	0
						58		0	0		0	0
					Recovery (40 min)	30		1·5	143		2·6	68
						40		1·8	145		2·3	60
						58		1·8	159		2·3	54
26/2	Low				Control	40	1·4	1·4	86	2·7	2·7	97
						84	1·7	1·7	150	2·4	2·4	85
		12	43	12	After aerosol	40		0	0		0	0
						84		0	0		0	0
					Recovery (25 min)	40		1·4	71		2·7	51
						84		1·7	155		2·4	116
23/3	Low				Control	50	1·6	1·6	103	2·5	2·0	73
		12	40	7	After aerosol	50		0	0		0	0
					Recovery (48 min)	50		1·6	121		2·2	73
23/4	Low				Control	50	1·6	1·6	120	2·5	2·0	75
		12	40	36	After aerosol	50		0	0		0	0
					Recovery (60 min)	50		1·6	117		1·5	43
17/5	Low				Control	30	1·5	1·5	125	2·6	2·4	90
						50	1·6	1·6	163	2·5	1·4	50
						84	1·75	1·75	174	2·35	1·3	52
		12	40	12	After aerosol	30		0	0		0	0
						50		0	0		0	0
						84		0	0		0	0
					Recovery (24 min)	30		1·5	82		2·2	90
						50		1·6	131		1·8	54
						84		1·75	144		1·2	58
16/6	Low				Control	30	1·3	1·3	95	2·8	1·3	29
						50	1·5	1·5	129	2·6	1·6	75
						84	1·7	1·7	150	2·4	1·0	31
		10	35	5	After aerosol	30		0	0		0	0
						50		0	0		0	0
						84		0	0		0	0

TABLE 1 (*cont.*)

Cat/ fibre no.	High/ low threshold	Duration of aerosol adm. (min)	No. of inflations	Onset of recovery (min)	Event	V_T (ml.)	Inspiration T_i (sec)	Inspiration T_d (sec)	Inspiration No. of impulses	Expiration T_e (sec)	Expiration T_d (sec)	Expiration No. of impulses
1	2	3	4	5	6	7	8	9	10	11	12	13
					Recovery (19 min)	30		0·64	40		0	0
						50		1·24	71		1·6	18
						84		1·48	98		2·6	26
16/7	Low				Control	30	1·3	1·3	120	2·8	2·8	140
						50	1·5	1·5	155	2·6	2·6	102
		8·5	24	4	After aerosol	30		0	0		0	0
						50		0	0		0	0
					Recovery	30		1·3	125		2·8	130
						50		1·5	157		2·6	101
31/8	High				Control	30	1·3	1·3	57	2·8	0	0
						40	1·4	1·4	69	2·7	0	0
		12	40	9	After aerosol	30		0	0		0	0
						40		0	0		0	0
					Recovery (9 min)	30		0	0		0	0
						40		0·46	21		0	0
28/9	High				Control	40	1·8	1·6	22	2·3	0	0
		13	40	10	After aerosol	40		0	0		0	0
27/10	High				Control	40	1·6	1·6	49	2·5	0	0
						84	1·7	1·6	55	2·4	0	0
		13	45	5	After aerosol	40		0	0		0	0
						84		0	0		0	0
					Recovery (45 min)	40		0·9	12		0	0
						84		1·3	34		0	0
27/11	High				Control	40	1·6	1·1	22	2·5	0	0
						84	1·7	1·5	47	2·4	0	0
		13	45	5	After aerosol	40		0	0		0	0
						84		0	0		0	0
					Recovery (45 min)	40		0·9	7		0	0
						84		1·2	20		0	0
17/12	High				Control	40	1·6	1·1	37	2·6	0	0
						50	1·6	1·4	73	2·5	0	0
						84	1·75	1·6	104	2·35	0	0
		12	38	—	After aerosol	30		1·4	40		0	0
						50		1·35	83		0	0
						84		1·6	119		0	0
					Recovery (10 min)	30		1·1	43		0	0
						50		1·4	81		0	0
						84		1·6	110		0	0
17/13	High				Control	30	1·5	1·2	14	2·6	0	0
						50	1·6	1·6	30	2·5	0	0
						84	1·75	1·75	38	2·35	0	0
		12	40	—	After aerosol	30		1·38	14		0·8	4
						50		1·44	26			1
						84		1·75	31			1

discharge before as well as after the aerosol, and at a point of maximum recovery after the aerosol administration.

Slowly adapting receptors

The thirteen pulmonary stretch fibres were classified into two categories: low-threshold fibres (seven); higher-threshold fibres (six). The former continued to fire impulses during expiration as well as at functional residual capacity in addition to their characteristic discharge during inspiration, while the latter showed activity only during inspiration (Paintal, 1966).

Low-threshold fibres. Seven low-threshold slowly adapting receptors were studied at 15 volumes and in all cases found to be completely silenced following bupivacaine aerosol (Table 1). The effect on the fibre activity was fairly uniform both qualitatively as well as quantitatively. The discharge, as heard from the audio-amplifier,

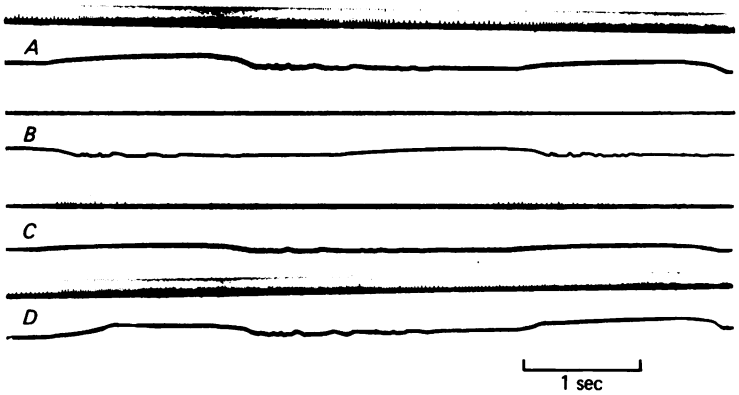

Fig. 2. The effect of bupivacaine aerosol on the slowly adapting discharge from a pulmonary stretch receptor of low threshold type. In each panel the upper trace shows the action potentials in the fibre and the lower trace shows the airflow from a pneumotachograph; inspiration writing upwards and expiration downwards. *A*, before aerosol. *B*, after aerosol; the fibre is completely silent. *C*, recovery from the effect of aerosol starts at 12 min after the termination of the aerosol, with appearance of a few impulses during the earlier part of inspiration. *D*, complete recovery occurs at 25 min after the aerosol.

was appreciably reduced after 3–4 inflations with the aerosol and then came down steadily till the fibre became silent. The aerosol was continued for 4–6 min after the discharge was abolished except in one fibre (16/7, Table 1), in which case it had to be stopped (soon after the fibre had become silent) due to failure of the aerosol generator.

The pattern of recovery of these fibres from the effect of bupivacaine was variable. In the solitary example where the aerosol had to be stopped soon after the fibre became silent, recovery started about 3–4 min later and was nearly complete in about 6 min. In cases where the aerosol administration could be continued for some time after the apparent silencing of the fibre, recovery started 5–36 min after finishing the aerosol and the pre-aerosol pattern of discharge returned in 19–60 min after the aerosol administration (Table 1). During recovery, the phase of respiration in which the impulses first appeared was variable: towards the latter part of

inspiration in two fibres, in the earlier part of inspiration in four fibres and during expiration in the remaining one fibre. A typical example of low-threshold fibre is shown in Fig. 2.

Higher-threshold fibres. The behaviour of higher-threshold fibres was slightly different from the low-threshold fibres. Six higher-threshold fibres were studied at 13 volumes; of these four at 7 volumes were silenced by bupivacaine, but in the remaining two fibres at 6 volumes there was either little or no effect (three) or a

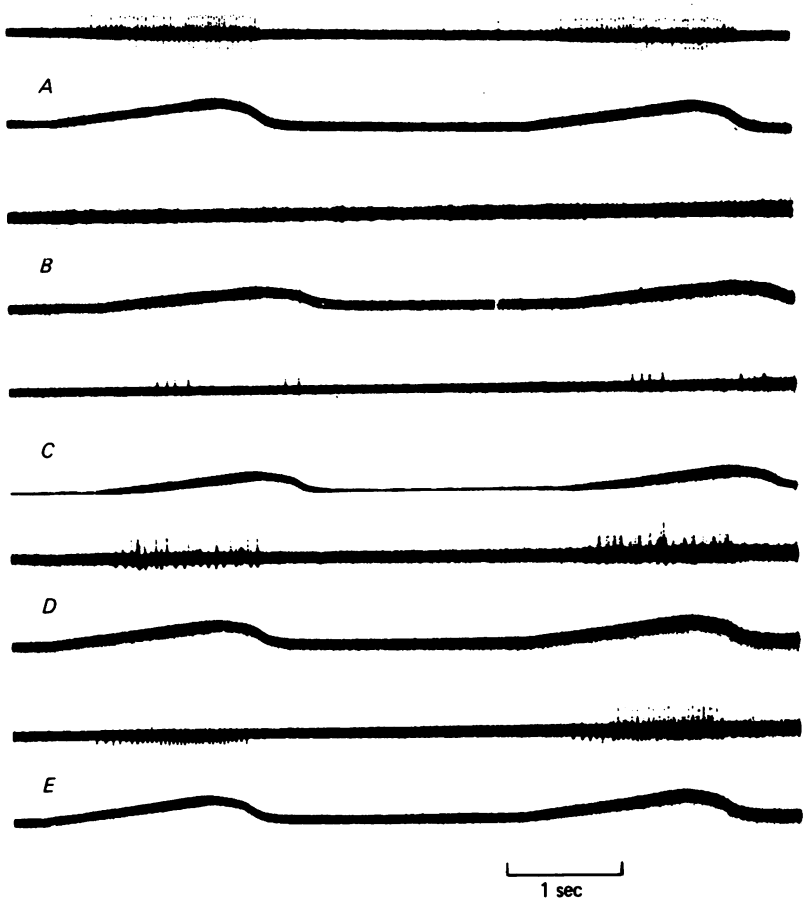

Fig. 3. The effect of bupivacaine aerosol on the slowly adapting discharge from two pulmonary stretch fibres, both of high-threshold type. In each panel the upper trace shows the action potentials and the lower trace shows airway pressure, writing upwards during inspiration and downwards during expiration. *A*, before aerosol. *B*, after aerosol; the fibres are silent. *C*, recovery starts at 5 min after the aerosol. *D*, progress of recovery at 30 min after the aerosol. *E*, recovery has progressed in both fibres, recorded 45 min after the termination of the aerosol, but the fibre discharges have not yet returned to the pre-aerosol level.

very slight reduction in activity (three). The data are presented in Table 1. From this Table it can also be seen that although recovery had started 5 min after termination of the aerosol administration, the intensity and frequency of discharge did not return to the pre-aerosol level in the two fibres (27/10 and 27/11). In

TABLE 2. Effect of bupivacaine aerosol on the activity of fibres showing rapidly adapting discharges from lung 'irritant' receptors. Abbreviations are as in Table 1.

Cat/ fibre no.	Duration of aerosol adm. (min)	No. of inflations	Onset of recovery (min)	Event	V_T (ml.)	Inspiration T_i (sec)	Inspiration T_d (sec)	Inspiration No. of impulses	Expiration T_e (sec)	Expiration T_d (sec)	Expiration No. of impulses
1	2	3	4	5	6	7	8	9	10	11	12
30/1				Control	80	1·9	0·68	11	2·2	0	0
	13·5	43	11	After aerosol	80		0	0		0	0
				Recovery (45 min)	80		0·48	4		0	0
29/2				Control	48	1·7	0·3	6	2·4	0	0
					84	1·9	0·5	14	2·2	0	0
	15·0	46	10	After aerosol	48		0	0		0	0
					84		—	1		0	0
				Recovery (18 min)	48		0·13	4		0	0
					84		0·50	9		0	0
29/3				Control	84	1·9	0·4	16	2·2	0	0
	15·0	46	10	After aerosol	84		—	1		0	0
				Recovery (18 min)	84		0·3	8		0	0
27/4				Control	108	1·7	1·2	9	2·4	0	0
	15·0	48	12	After aerosol	108		0·7	5		0	0
				Recovery (12 min)	108		0·7	6		0	0
25/5				Control	40	1·5	0·26	5	2·6	0	0
					84	1·8	0·82	15	2·3	0	0
	16·5	45	15	After aerosol	40		0	0		0	0
					84		0·26	2		0	0
				Recovery (45 min)	40		Not recorded				
					84		0·8	15		0	0
25/6				Control	40	1·5	0·64	7	2·6	0	0
					84	1·8	1·14	20	2·3	0	0
	16·5	45	15	After aerosol	40		0	0		0	0
					84		0·22	2		0	0
				Recovery (45 min)	40		Not recorded				
					84		0·64	20		0	0
24/7				Control	65	1·7	0·44	28	2·4	0	0
	13·3	43	11	After aerosol	65	1·7	0·20	3		0	0
				Recovery (20 min)	65	1·7	0·46	34		0	0

TABLE 2 (*cont.*)

Cat/ fibre no.	Duration of aero-sol adm. (min)	No. of infla-tions	Onset of recov-ery (min)	Event	V_T (ml.)	Inspiration T_i (sec)	Inspiration T_d (sec)	Inspiration No. of im-pulses	Expiration T_e (sec)	Expiration T_d (sec)	Expiration No. of im-pulses
1	2	3	4	5	6	7	8	9	10	11	12
23/8				Control	84	1·8	0·6	18	2·3	0	0
					104	1·9	0·75	24	2·2	0	0
	13·0	40	6	After	84		0·24	3		0	0
				aerosol	104		0·5	12		0	0
				Recovery	84		0·6	12		0	0
				(48 min)	104		0·7	17		0	0
18/9				Control	58	1·5	0·84	10	2·6	0	0
	15·0	48	12	After aerosol	58		0	0		0	0
				Recovery (12 min)	58		0·5	5		0	0

another two fibres (31/8 and 28/9) adequate time for a maximal recovery could not be allowed for technical reasons. The recovery pattern of discharge was studied in three fibres. The impulses first appeared during the latter part of inspiration in two fibres and during the earlier part of inspiration in one fibre. An example of higher-threshold fibre is shown in Fig. 3.

Rapidly adapting receptors

In the case of rapidly adapting receptors the duration of aerosol administration was slightly longer than in the case of slowly adapting receptors (cf. Tables 1 and 2). Nine rapidly adapting fibres were studied at 13 volumes, four at two different tidal volumes each and the remaining five at a single tidal volume each. The analysis data are presented in Table 2. It can be seen that five of the nine fibres at 5 volumes become silent; in another six cases a very marked reduction (> 80% of the pre-aerosol number of impulses), although not complete silence, was observed; in the remaining two instances the activity was reduced by 40–50% of the control number of impulses.

The fibres started recovering from the aerosol effect 6–15 min after finishing the aerosol and attained a maximum in 12–50 min, but the discharge seldom reached the pre-aerosol level; in the fibre 19/9, however, adequate time was not allowed for a maximal recovery. Typical examples of behaviour of rapidly adapting receptors are shown in Figs. 4 and 5.

DISCUSSION

The results of these experiments provide convincing evidence that intratracheal administration of bupivacaine aerosol can affect markedly the impulse activity in single fibres from both stretch 'irritant' receptors. These two types of receptors are located in the wall of the airways; frequency of their distribution has been reported by Sant'Ambrogio and his co-workers (Miserocchi, Mortola & Sant'Ambrogio, 1973;

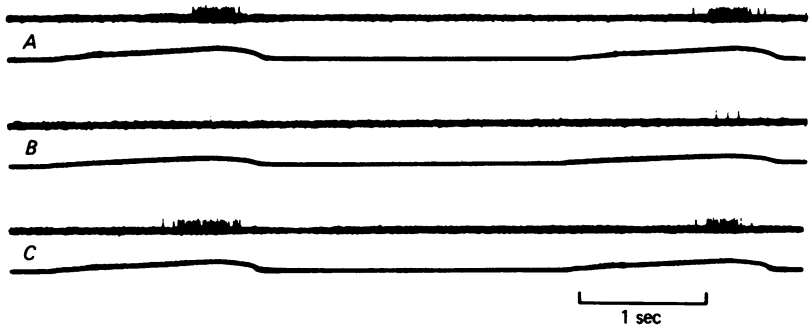

Fig. 4. The effect of bupivacaine aerosol on the rapidly adapting discharge from the lung 'irritant' receptors. In each panel the upper trace shows action potentials and the lower trace shows the airway pressure, writing upwards during inspiration and downwards during expiration. *A*, before aerosol. *B*, after aerosol; a few impulses can still be seen which represents a near complete block. *C*, recovery from the effects of the aerosol recorded at 20 min after termination of the aerosol.

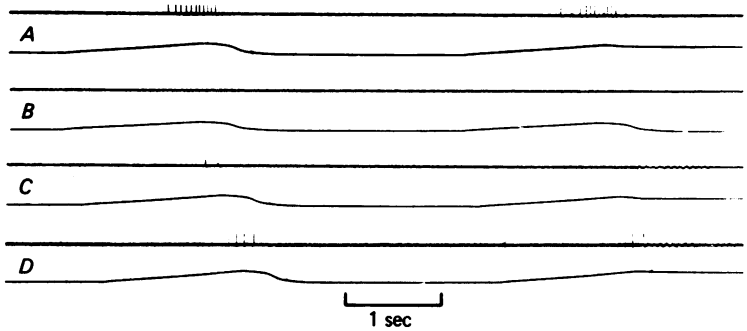

Fig. 5. The effect of bupivacaine aerosol on the rapidly adapting discharge from a lung 'irritant' receptor. In each panel, the upper trace shows the action potentials during a respiratory cycle followed by the fibre discharge during a held inspiration; the discharge shows a rapid adaptation; the lower trace shows the airway pressure, writing upwards during inspiration and downwards during expiration. In the second respiratory cycle in panel *A*, *C* and *D* the lungs are held at end-inspiratory level. *A*, before aerosol. *B*, after aerosol; the fibre becomes silent. *C*, recovery starts at 11 min after termination of the aerosol. *D*, recovery progresses; recorded at 45 min after the aerosol.

Miserocchi & Sant'Ambrogio, 1974; Mortola, Sant'Ambrogio and Clement, 1975; Bartlett, Jeffery, Sant'Ambrogio & Wise, 1976). Thus, it is generally agreed that a majority of these receptors are located in the intrapulmonary airways. The aerosol used in this investigation contained particles ranging from 5 to 9 μm in size (Jain *et al.* 1973); these are preferentially deposited in the airways and not in the alveoli (Hatch & Gross, 1964).

The histological sites for the pulmonary stretch and 'irritant' receptors are believed to be the smooth muscle and the epithelial cell lining of the airways respectively (Widdicombe, 1974). Von During, Andres & Iravani (1974) have, however, suggested that the pulmonary stretch receptors may lie just beneath the basement membrane of the bronchial wall. These findings are supported by the observations

of Bitensky, Chambers, Chayen, Cross, Guz, Jain & Johnstone (1975). These authors (including one of us, Jain, S. K.) used an aerosol of tritiated bupivacaine to block the Hering–Breuer inflation reflex in a rabbit. By using an autoradiographic technique, they demonstrated: that at a time the inflation reflex was blocked, tritium was mostly concentrated in the lamina propria and epithelial cell layer with little label in the smooth muscle. These findings would suggest that the pulmonary stretch receptors (low- as well as higher-threshold types) and the 'irritant' receptors would be equally susceptible to the effect of the aerosol. It is therefore not surprising that in the present study bupivacaine blocked activity in all three types of receptors.

It may be stated here that this study provides no information regarding the exact site of block of conduction in the receptor-fibre system, whether the block occurs at the generator or the regenerative region of the sensory endings (Paintal, 1964) or at some site on their medullated fibres. As the vagal sensory fibres enter the airway from outside the wall, the aerosol in the lumen presumably acts nearer the receptor end than any site further up on the fibre.

According to the observations of Gasser & Erlanger (1929) and Nathan & Sears (1961), the smaller diameter fibres like those of 'irritant' receptors are expected to be blocked more easily than the larger size pulmonary stretch fibres. The data of the present study, however, suggest a small difference between the ease with which activity was blocked in low-threshold fibres on the one hand and the higher-threshold and 'irritant' fibres on the other. The reasons for this difference in the behaviour of the fibres are not understood. It is possible that the receptor-fibres which proved less susceptible to the anaesthetic effect were located more deeply in the lungs and the aerosol did not reach them in adequate concentrations. Alternatively, there may be a difference in the susceptibility of these receptor-fibre systems to the blocking effects of the local anaesthetic agents (Steinman, 1967).

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