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The expiration reflex from the trachea and bronchi

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Short title: Expiration reflex from the trachea

ABSTRACT

The expiration reflex (ER) is a forced expiratory effort against a closed glottis that subsequently opens to eject laryngeal debris and prevent aspiration of material. It is distinct from the cough reflex (CR). Its source is usually assumed to be restricted to the larynx and vocal folds, and its possible origin from the tracheobronchial (TB) tree has been suggested but never studied.

We have reanalysed some of our records with mechanical or chemical stimulation of the TB tree to see if an ER can consistently be elicited, and to see whether it has properties similar to that from the larynx and vocal folds. We have made a random review of some of the extensive literature on TB 'cough' to see if this confirms our conclusions.The TBER was consistently seen in cats and rabbits, either alone or followed by cough. These results are consistent with many studies in other species, including humans. It was enhanced, relative to cough, by inflation of the lungs and by general anaesthesia.

The TBER occurs frequently with mechanical stimulation of the TB tree. It differs fundamentally from many of the properties of 'true' cough. Its similar features to the laryngeal ER suggest that both should be labeled 'expiration reflexes' and not 'cough'. Its existence should be taken into account in experimental, and possibly clinical, studies on TB 'cough'.

Keywords: Cough, expiration reflex, larynx, tracheobronchial tree, vocal folds.

The expiration reflex (ER) is defined as the strong expiratory effort, not preceded by an inspiration or accompanied by closure and then opening of the glottis; it results from mechanical and chemical stimulation of the larynx, especially the vocal folds. It was first described, but not named, by Williams in 1841 [1], when he thrust his finger up the opened trachea of a dog and observed that when it reached the larynx the dog made powerful expiratory efforts. It was comprehensively analysed and named by Korpas and colleagues [2-8] in the 1970s.

The ER and the cough reflex (CR) differ in many physiological and pharmacological ways, and have different functions. These differences have been described elsewhere [2,5,9-11] and here it is only necessary to point out that, according to the classic definitions, the ER starts with an expiration while the CR starts with an inspiration, implying quite different sensory or afferent inputs and/or central nervous processing; that the central nervous pathways for the ER have many different features from those for the CR [12,13]; that drugs, anaesthesia, lung inflation and blood gas tensions affect the two reflexes in different ways [5,9-11,14,15]; and that the function of the ER is to prevent aspiration of material into the lower airways, while that of the CR is to draw air into the lungs to promote a more efficient subsequent expulsion of mucus and airway debris.

In nearly all the studies of the ER, especially those by Korpas and his colleagues [2-8], it is implied that the ER can only be elicited from the larynx or vocal folds, an appropriate site in view of the function of the reflex; however this does not seem to be explicitly stated (the negative, that the ER cannot be elicited from the tracheobronchial (TB) tree is also not stated).

A survey of some of the literature on ‘cough’ from the TB tree (TBCR) shows many illustrations of mechanical or occasionally electrical or chemical irritation of this region causing isolated expiratory efforts (TBER) (see Discussion) or expiratory efforts followed by cough. This is similar to the ER from the larynx (LER) where there may be expiratory efforts associated with but distinct from coughs, and sometimes followed by coughs. Yet the authors seldom comment on this phenomenon. The term ‘cough reflex’ is nearly always applied to both responses resulting from stimulation of the TB tree.

Two of us (MT, JH) have re-evaluated some of our records on mechanical and chemical stimulation of the TB tree and larynx in cats and rabbits [2-4,8,14,16], and the purpose of the present paper is to present these results and to discuss the significance of the TBER.

METHODS

These have been fully described elsewhere [2-4,8,16,17]. We have reanalysed the experimental results of these papers. Briefly, cats and rabbits of either sex and weighing 2.4-3.8 kg were anaesthetized with pentobarbitone sodium (30 $mg.kg^{-1}$, i.p. and i.v. respectively). Supplementary doses were added to maintain appropriate levels of anaesthesia; depth of anaesthesia was assessed from pattern of breathing, level and stability of end-tidal CO_2 tension and arousal responses. Tracheal tubes were inserted. Unanaesthetized cats with healed chronic tracheal cannulations were also used [14].

With cats a silon fibre (0.4 mm diameter) was inserted through the tracheal cannula either to the level of the tracheal bifurcation or to the laryngeal region, and gently pushed up and down for about 7 s. With rabbits a soft venous catheter was used to stimulate the TB tree and the larynx. The TB irritation would stimulate sensors both in the trachea and in the larger bronchi. For the larynx both the vocal folds and the adjacent areas would be stimulated. To stimulate only the vocal folds in rabbits, a silon fibre loop (3-5 mm diameter) was moved across the folds from the tracheal side.

We define the CR as an inspiration followed immediately by a strong expiration, and the ER as a strong expiration not immediately preceded by an inspiration (see Discussion).

In anaesthetized animals cough and the ER were recorded as the changes in intrapleural pressure in anaesthetized animals (via an intrapleural cannula connected to a pressure transducer and electromanometer). To evaluate the effects of lung inflation in cats an oesophageal balloon catheter was connected to a pressure transducer. The lungs of cats and rabbits were inflated by 0.5, 1.0 and 1.5 kPa maintained positive pressures and the tracheobronchial region or the vocal folds were stimulated. Aerosols of capsaicin solution (100 $\mu g.ml^{-1}$, median particle diameter 6 μm) were administered to cats through the tracheal cannula for 3 to 7 breaths; tracheobronchial capsaicin is ineffective as a cough stimulant in rabbits [18]. In conscious cats, cough and the ER were recorded as the changes of lateral intratracheal pressure (via a tracheal cannula connected to a pressure transducer) [8,16].

The effects of general anaesthesia and of inflation of the lungs were statistically analysed nonparametrically, using the chi-square test. $P<0.05$ was taken as significant.

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RESULTS

Pattern of response to TB stimulation

Table 1 shows the numbers of ERs, ERs followed by cough (ER→CR), coughs and coughs followed by ERs (CR→ER) for anaesthetized cats and rabbits and for unanaesthetized cats, with TB stimulation. When the ER followed cough there was a pause between the events which showed that the ER was not the expiratory effort of a cough. In general, ERs followed by cough were seen in about one-third of tests (34-37 %) in both species (Table 1). Isolated TBERs were seen only in rabbits, but then only rarely (2%). Cough followed by TBERs were seen only in rabbits (17%). Cough due to mechanical stimulation was seen in the majority of tests (81-100 %), either alone or before or after ERs.

Stimulation of the larynx and vocal folds

Table 2 shows that stimulation of the larynx in cats evoked about equal numbers of coughs and of LERs followed by coughs (56 and 44%). In the rabbit, isolated coughs and LERs werenever seen, and the response was always an LER followed by coughs.

Stimulation restricted to the vocal folds in rabbits always caused ERs (83%) or an ER followed by cough (17%).

Anaesthesia and TB stimulation

Anaesthesia in cats decreased the proportions of coughs due to TB stimulation relative to ERs, compared with those in unanaesthetized animals (from 89 to 66%, $P<0.01$), and increased the proportion of ERs followed by coughs (from 11 to 34%, $P<0.01$) (Table 1). In other words, anaesthesia decreased cough in relation to the ER. For the larynx, anaesthesia had little effect on the proportions of ERs and coughs (Table 2).

Effects of lung inflation

In cats with inflation of the lungs at a pressure of 1.5 kPa, TB stimulation greatly increased the number of TBERs followed by cough (from 34 to 96%, $P<0.01$), and reduced the number of isolated coughs (from 66 to 4%, $P<0.01$) (Table 3). The intensity of the expiratory efforts of the TBER was increased by lung inflation from 0.92 ± 0.77 kPa to 4.81 ± 0.98 kPa ($P<0.01$). In rabbits, inflation of the lungs considerably increased the numbers of isolated TBERs (from 2 to 19%, $P<0.01$) and of TBERs followed by cough (from 37 to 48%, $P<0.05$), and reduced the numbers of isolated coughs (from 44 to 33%, $P<0.05$) and coughs followed by TBERs (from 17 to 0%, $P<0.01$). Similar but smaller effects were seen with inflation pressures of 0.5 and 1.0 kPa. In other words, inflation of the lungs enhanced the TBER at the expense of the TBCR.

With stimulation of the vocal folds in rabbits, lung inflation caused little change in the response, which was predominantly ERs; isolated ERs changed from 83 to 81% (NS), and ERs followed by CR changed from 17 to 19 % (NS).

Capsaicin stimulation

Capsaicin inhalation in cats provoked only cough (100%, n = 14); ERs were never seen, either alone or before or after cough. Cough was never seen with tracheobronchial administration of capsaicin in rabbits.

DISCUSSION

We analysed all appropriate and available records of previous research on cats and rabbits (conducted by MT and J H). Analysis of the results show that: (1) mechanical stimulation of the TB tree of cats and rabbits frequently causes an ER: this has been illustrated before but seldom identified as such; (2) in general the reflexes from the TB tree of cats are similar in pattern to those from the larynx, but in rabbits the ER is more frequent from the larynx than from the TB tree; (3) in cats anaesthesia significantly increases the incidence of the TBERs compared with the TBCRs, but makes little difference in the response to laryngeal stimulation; (4) inflation of the lungs in cats and rabbits makes the TBER compared with coughs significantly far more frequent, but makes little difference to the response to stimulation of the vocal folds, when the ER dominates; and (5) in cats capsaicin causes TBCRs but not TBERs.

Our definitions of the TBCR and the TBER are given above (Methods). While it is customary in clinical studies to define ‘cough’ as *all* expiratory efforts, with no distinction between the TBCR and the TBER, we believe that in analytical and laboratory studies the distinction and definitions are important, since they point to different mechanisms, as established for the larynx [2,3,5,9-11] and, as we indicate in this paper, for the TBtree. Indeed a recent Task Force Report [19] supported this use of two definitions, although it did not name them. We suggest that TBER is an appropriate name in view of its similarity with the LER, a term well-established in the literature. We appreciate that, in a bout of coughing (a cough ‘attack’ or ‘epoch’) distinction of the ER from the expiratory effort that is part of the CR is often difficult; but since the TBER can occur in isolation or before a cough it must be a genuine phenomenon distinct from cough.

We have not attempted statistical analysis of most of our results since they were derived from several experimental runs, not always under identical conditions. In addition our conclusion, that the ER can frequently be elicited from the TB tree, is essentially a qualitative one. In quantitative terms the sizes and frequencies of the responses will depend on many factors such as presence, type and depth of anaesthesia, species, and nature and duration of airway stimuli. We have only applied statistics to assess the changes due to lung inflation and anaesthesia.

We have identified at random (from reprints on our shelves) eighteen papers in which mechanical (and occasionally electrical or chemical) stimulation of the TB mucosa was used to cause ‘coughs’. Of these, eleven papers showed initial expiratory efforts, sometimes isolated and sometimes followed by cough [20-30], and the total list is almost certainly much greater. Few of the authors referred to the ER, probably because most of the papers appeared before the naming of the laryngeal ER by Korpas and his colleagues in the 1970s. Species studied include anaesthetized and unanaesthetized cats, dogs and rabbits, and humans under light anaesthesia [27,28]. Most of these studies involved a brief punctate stimulus, mechanical or electrical, and the response was often a single ER without subsequent cough. Fig. 2 (published in 1954 [15]) illustrates responses to stimulation of the trachea of an anaesthetized cat. Punctate mechanical stimulation caused an ER followed by a deep inspiration, while inhalation of sulphur dioxide (through a tracheal cannula) caused a cough. After i.v. administration of morphine, the ER was not affected but its subsequent deep inspiration and the cough due to sulphur dioxide were abolished, indicating fundamentally different neural mechanism for the tworesponses. As far as we can determine, it is the only published record that shows, in a single Figure, the two different reflexes from the TBtree and their different responses to an opiate.

For the results assessed in the present analysis the mechanical stimulus was maintained for about 7 s, so it bore little relationship to the timing of the respiratory cycle, and it is probably not surprising that the reactions were usually lengthy and generally included both ERs and cough. An ER has eventually to be followed by an inspiration (since lung volume has been greatly reduced), and this could be the first phase of a cough. In lightly anaesthetized humans, the same stimulus to larynx and trachea produced almost identical responses, an ER followed by coughs [27,28].

Although in most (but not all) the papers cited general anaesthesia was used, and this would depress cough relative to the ER, the TBER was also clearly seen in unanaesthetized animals [20,21,25]. Anaesthesia might preferentially inhibit inspiration and p;rolong expiration; such a change might affect the inspiratory efforts of the CR, leaving the expirations of the ER more prominent. However in cats pentobarbitone anaesthesia decreased the expiratory efforts of TBCR without significantly changing inspiratory values [14]. We have not analysed our results with this question in mind.

The distinction between the TBER and cough is reinforced by the observations, most of which are confirmed in our analysis, that: (1) inflation of the lungs enhances the ER relative to cough [4]: the inflation would stimulate slowly adapting pulmonary stretch receptors, and this might cause a preferential inhibition of inspiratory, compared with expiratory, efforts; (2) capsaicin, unlike mechanical stimulation, induces cough but not the ER [31]; (3) opioid drugs are more effective in blocking the TBCR than the TBER (Fig. 2) [15]; and (4) general anaesthesia blocks TBCR more effectively than the TBER [14,15,27,28]. Other differences between cough and the ER have been shown for the larynx; thus the LCR has glottal reflex activity [29] and central nervous pathways [12,13] different in some respects from those of the LER, but we do not know if the same is true for the tracheal reflexes.

While the teleological purpose of the LER is clear, to prevent aspiration of material into the lower airways, that of the TBER is less obvious. Presumably, if material is aspirated the TBER is a second line of defence. One can speculate that the ER is a more primitive reflex in evolution than is cough. Some fish can 'cough' either forwards or backwards [32-34]. If a chemical irritant enters the mouth, the fish makes an expulsive movement to expel the irritant forwards out of the mouth, which would protect the delicate gills behind the pharynx. If the irritant enters the gill cavity from behind, it is propelled backwards to remove it from the gills. There seems to be no equivalent in fish of the initial inspiration that is part of the definition of cough in mammals. One might suggest, perhaps with a flight of fancy, that the forward expulsion from the oropharynx is the equivalent of the ER from the larynx in mammals, and prevents entry of the irritant; while the backwards expulsion from the gills is like the ER from the TB tree in mammals (apart from the direction of flow), and expels the irritant once it has gained entry. Of course this is not to suggest that the neurological mechanisms of 'cough' and the ER are identical in fish and mammals.

Another possibility is that the TBER might be due to 'vagal overflow'. Cough can be induced from the oesophagus [35] and from the external ear [36], both innervated by the vagus nerves; these actions seem to be examples of 'unintelligent design', since they appear to provide no apparent useful function. However the TBER is not in this category; its useful function is as a reserve defense process if aspirated material overcomes the powerful LER (the laryngeal gatekeeper).

What is not clear is which neural sensors (afferent receptors) are responsible for the two reflex patterns. There is currently intensive research on the sensors for cough [see 37-39]. These must differ from those for the TBER, since the CR starts with an inspiration and the ER with an expiration. One can conceive that the same particular afferent pathway could cause either inspiration or expiration, and that the direction of the response is determined by a second input to the brainstem that acts as a gate or switch in the brainstem; but this is still saying that the neural inputs for the CR and the ER must be different. Forced expirations, such as those seen with the ER and the CR, will stimulate airway receptors and set up feedback loops that will secondarily influence the defensive reflexes. The reflex roles of these feedbacks, or even their existence, has not been established, but the forced expiration of the ER could reflexly promote inspiration as the first component of a cough. The cough response to capsaicin, coughs without ERs, may be related to the fact that capsaicin is a rather selective stimulant of nociceptors such as C-fibre sensors [37]; we do not know any stimulus that always causes ERs but never coughs, although mechanical stimulation of the rabbit vocal folds comes close to it. The ER from the larynx in humans has a latency (from laryngeal stimulation to abdominal muscular response) of about 15-25 ms [40], and in cats the latency is 30 ms [41]. Measurement of the conduction distances of sensory and motor nerves for the ER, and applying the known conduction velocities of different categories of nerve fibre, shows that it must be conducted by myelinated, and not nonmyelinated, afferent fibres [40]. The latency of the TBCR in cats is far larger, 300-5000 ms [42]; whether this delay is due to slow conduction in nonmyelinated afferent nerve fibres or due to central nervous processing has not been determined.

In conclusion, we believe that there is a true ER from the tracheobronchial tree (the TBER), with many physiological and pharmacological properties similar to the well-established ER from the vocal folds and larynx (the LER). Although there have been clues to this observation scattered in the literature, the present paper seems to be the first attempt to emphasize the existence of the TBER. This conclusion, if accepted, is important because the TBER must be taken into account during laboratory and clinical research on defensive reflexes from the lower airways.

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Table 1

CR and ER induced by mechanical stimulation of the tracheobronchial tree in cats and rabbits

Species		Anaest.	No.	ER (%)	ER→CR (%)	CR (%)	CR→ER (%)
Cat	(17)	Yes	100	0	34	66	0
	(12)	No	119	0	11	89	0
Rabbit	(23)	Yes	84	2	37	44	17

Numbers of animals are given in parentheses. No. gives the numbers of tests. Values are %s of the number of stimuli. All stimuli caused a response. ER→CR: ER followed by cough; CR→ER: cough followed by ER.

Table 2

CR and ER induced by mechanical stimulation of the larynx in cats and rabbits and of the vocal folds in rabbits

Species	Anaest.	Site	No.	ER (%)	ER→CR (%)	CR (%)	CR→ER (%)
Cat (17)	Yes	Larynx	94	0	44	56	0
Cat (12)	No	Larynx	113	0	46	54	0
Rabbit (13)	Yes	Larynx	17[1]	0	100	0	0
Rabbit (17)	Yes	Vocal folds	35	83	17	0	0

Numbers in parentheses are numbers of animals. No. gives numbers of tests. %s apply to of the number of responses. All stimuli caused a response, except [1], when the 17 stimuli caused only 9 responses. VF: stimulus restricted to vocal folds..

Table 3

The effect of lung inflation on reflexes evoked by mechanical stimulation of the TB tree and vocal folds.

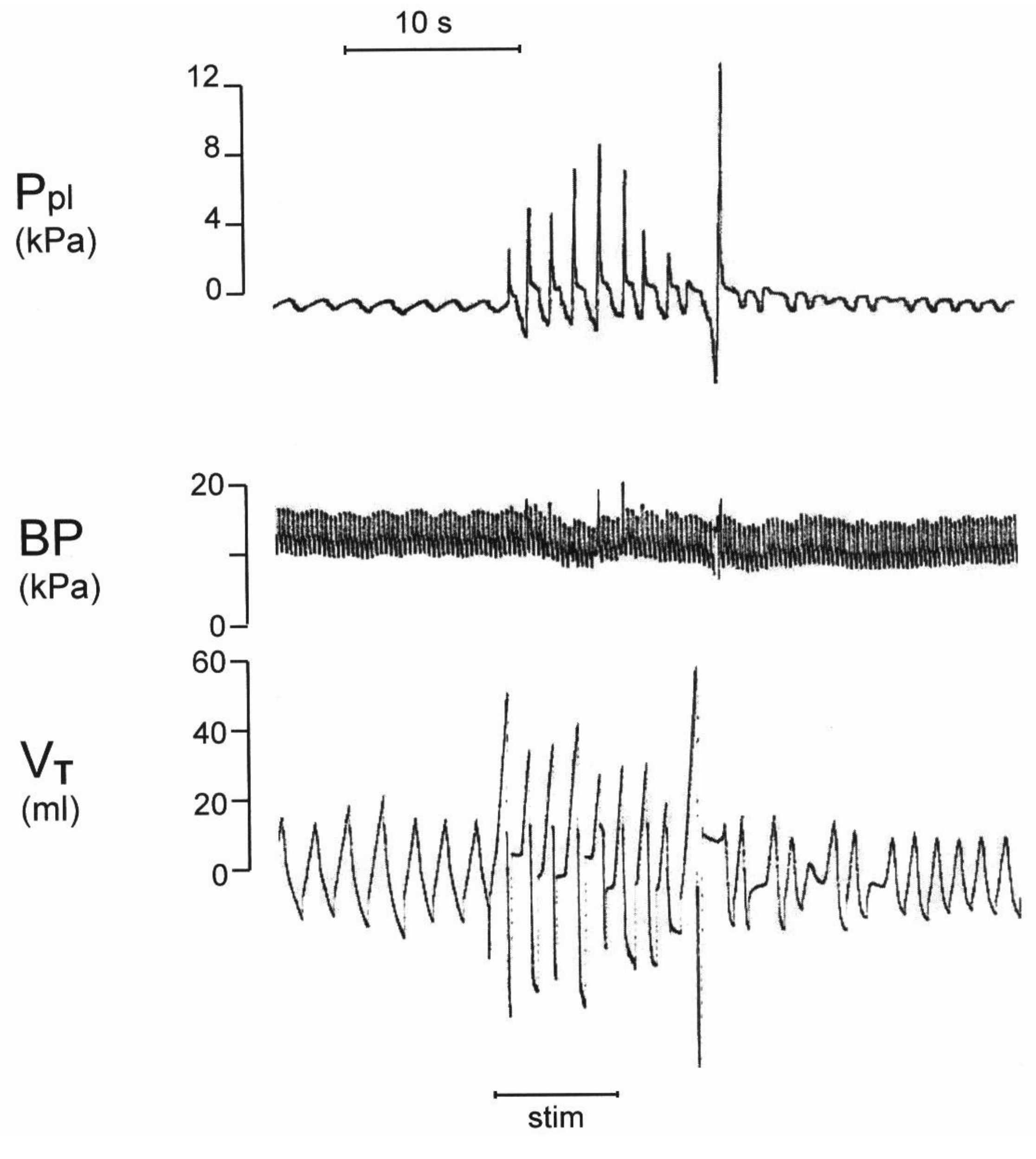
Species	Site	Lungs	No.	ER (%)	ER→CR (%)	CR (%)	CR→ER (%)
Cat (17)	TB	Normal	100	0	34	66	0
Cat (10)	TB	Inflated	27	0	96	4	0
Rabbit (23)	TB	Normal	84	2	37	44	17
Rabbit (13)	TB	Inflated	31	19	48	33	0
Rabbit (17)	VF	Normal	35	83	17	0	0
Rabbit (17)	VF	Inflated	31	81	19	0	0

All animals were anaesthetized. Numbers in parentheses are numbers of animals. No. refers to number of tests. All tests caused a response. TB: tracheobronchial tree; VF:

vocal folds. Inflation of the lungs was at 1.5 kPa pressure. Normal values are the same as in Tables 1 and 2.

Fig 1. Effect of mechanical stimulation on the TB tree of a cat. From above down: time, 10 s; pleural pressure (expiration upwards); blood pressure; tidal volume (inspiration upwards); and stimulation at signal bar. Stimulation caused an immediate expiratory effort (the ER) followed by coughing.

Fig. 2. The effect of punctate mechanical stimulation and of the inhalation of sulphur dioxide through a tracheal cannula on breathing and blood pressure in a cat anaesthetized with pentobarbitone. From above down: tidal volume, inspiration upwards; blood pressure; time (5 s); signal mark. On the left punctuate mechanical stimulation caused an ER followed by a deep inspiration, and sulphur dioxide caused a cough. On the right, after i.v. administration of morphine (0.5 $mg.kg^{-1}$), the deep inspiration and the cough were abolished, but the ER remained. Reproduced with permission from [15].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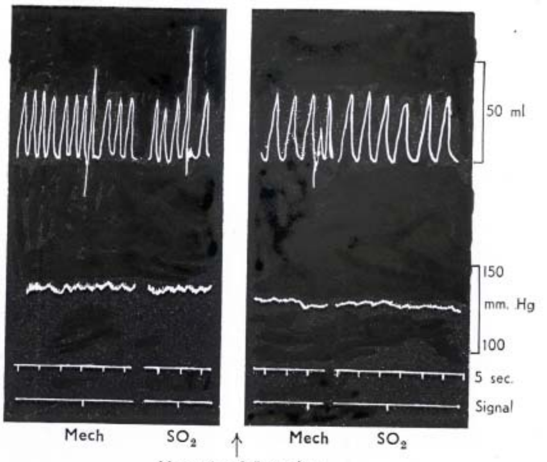

Morphine 0·5 mg./kg.