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ELECTROPHYSIOLOGICAL EVIDENCE OF BARORECEPTORS IN THE PULMONARY ARTERY OF THE DOG

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There is evidence that reflex cardiovascular changes may be initiated by alterations in pulmonary arterial pressure (for references see p. 329); and endings, histologically similar to those in known baroreceptor areas, have been found in the pulmonary artery (e.g. Larsell & Dow, 1933; Takino, 1933; Nonidez, 1941). However, apart from the recording of impulses from a single receptor located in the pulmonary artery of a cat (Swan & Whitteridge, 1956), there has been no demonstration of the existence of such receptors by means of electrophysiological techniques.

In the work to be reported here impulse activity has been recorded in vagal fibres whose endings could be located with certainty in the pulmonary artery. In preliminary experiments on cats we were able to confirm the findings of Swan & Whitteridge (1956). The present account deals with experiments performed on dogs; for, technically, it is easier to locate receptors precisely in the larger pulmonary artery of the dog. A brief account of these findings has already been published (Coleridge & Kidd, 1959*a*).

METHODS

Experiments were performed on dogs (7·5–22·5 kg) anaesthetized with morphine sulphate (3 mg/kg subcutaneously) and 0·25 ml./kg (intravenously) of a 1 : 1 mixture of Dial Compound (allobarbitone-urethane, Ciba) and sodium pentobarbitone (Nembutal, Abbott Laboratories Ltd.) solutions.

A tracheal cannula was inserted, and the lungs were ventilated by a Starling 'Ideal' pump. The sternum was split in the mid line, and the internal mammary vessels were ligated and cut. The cut edges of the sternum were retracted widely to give a good exposure of the heart and great vessels. The pericardium was opened in the mid line.

Respiration was recorded with an optical manometer (Coleridge & Linden, 1954) attached to a side arm on the tracheal cannula. In some experiments arterial blood pressure was also recorded optically from the ascending aorta with a cannula inserted through the left common carotid artery.

Action potentials were recorded from afferent single-fibre preparations dissected from the cervical vago-sympathetic trunk by the technique previously described (Coleridge, Hemingway, Holmes & Linden, 1957). The action potentials were amplified by a conventional R-C coupled amplifier and were displayed with an e.c.g. on a double-beam cathode ray tube. By suitable optical systems a combined photographic recording was obtained of the two

oscilloscope traces, the beams from the optical manometers, a 50 c/s time trace and a signal marker.

In some experiments infusions of saline (NaCl solution 0·9 % (w/v)) or dextran (6 % (w/v) in NaCl solution 0·9 % (w/v); 'Dextraven', Benger Laboratories Ltd.) at body temperature were made into the femoral vein.

The site of a receptor, from which action potentials were being recorded, was explored first by temporary obstruction, in turn, of the main intrathoracic vessels. For this purpose soft string ligatures were placed round the origin of the main pulmonary artery, both lung roots and the ascending aorta; the ends of the ligatures were passed through short lengths of polythene tube to form snares. Further location was effected by distending the pulmonary artery with a balloon. This device, modified from the self-guiding catheter described by Lategola & Rahn (1953), consisted of two polyvinyl tubes (approximately 70 cm long, bore 1·0 mm) cemented side by side. One tube served to distend the balloon which consisted of a condom teat fastened by thread. The other tube, the open tip of which lay immediately proximal to the balloon, was connected through a 3-way stop-cock either to a heparinized saline drip (Pularin Evans 5000 i.u./l., in NaCl solution 0·9 % (w/v)) or to a saline manometer. The collapsed balloon was inserted into either external jugular vein. Approximately 1 ml. saline was injected into the balloon; then the catheter was pushed gently into the vein and the partially distended balloon was carried into the right heart by the blood. Its passage from atrium into ventricle and subsequently into the pulmonary artery was indicated by the pressure registered by the saline manometer. Once placed in the main pulmonary artery, the balloon was collapsed completely until required.

Finally, the position of a receptor was determined accurately by careful exploration of the pulmonary artery with a fine probe immediately after the animal had been killed and the heart and great vessels dissected.

RESULTS

In twenty-nine instances impulses recorded from a slip of the vagus nerve were found to originate from receptors in the pulmonary artery between the main bifurcation and the lung roots. The discharges in these fibres were affected in characteristic ways by various experimental procedures. These are now described in the order in which they were usually applied in the course of locating a receptor.

Identification of pulmonary arterial fibres

All pulmonary arterial receptors displayed a cardiac rhythm (e.g. Fig. 1), usually very similar to that of aortic baroreceptors (e.g. Fig. 3) in that the main discharge began in ventricular systole soon after the opening of the pulmonary and aortic valves, as judged by the relation of the discharge to the QRS complex of the electrocardiogram.

Effect of occluding the main pulmonary artery. Occlusion of the main pulmonary artery near its junction with the right ventricle invariably reduced or abolished the discharge from a pulmonary arterial receptor (Fig. 2). Clearly this receptor was not in the right atrium or ventricle but lay beyond the occluding ligature. The pattern of discharge during the first 4–5 heart beats after release of the vessel was similar to that of an aortic baroreceptor. But in Fig. 2 it will be seen that the discharge

disappeared and reappeared with the first heart beat after obstructing and releasing the pulmonary artery; moreover, the impulse activity attained its maximum frequency in the first 1–2 beats after release of the ligature, thereafter the frequency rapidly diminished. Its behaviour thus differed

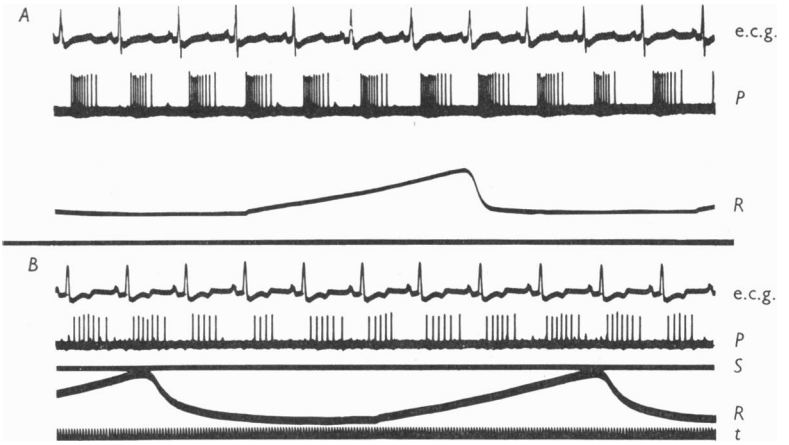

Fig. 1. Fibres from two receptors in the pulmonary artery showing burst of impulses during ventricular systole. In this and subsequent figures the following abbreviations are used: e.c.g., electrocardiogram; *P*, action potentials from vagal slip; *t*, time trace (1/50 sec); *R*, tracheal pressure (upstroke representing inflation); *S*, signal marker.

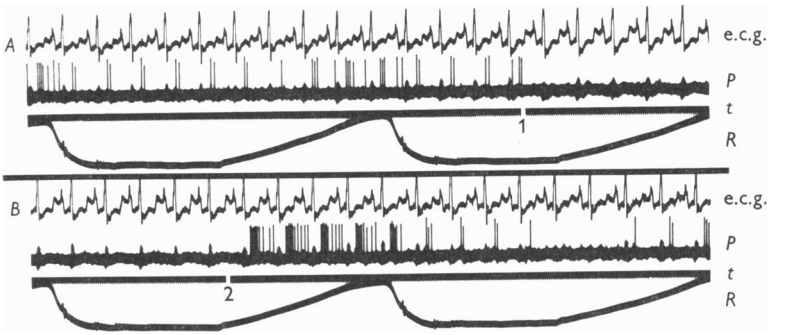

Fig. 2. Effect of occluding main pulmonary artery on discharge from pulmonary arterial receptor. Records *A* and *B* are continuous. At 1 the ligature around the proximal part of the main pulmonary artery was tightened; the ligature was released at 2.

from that of an aortic baroreceptor, as shown in Fig. 3. With aortic receptors there was always a delay of several beats before occlusion and release of the pulmonary artery affected the discharge.

These effects are in accordance with the results of other experiments in which pulmonary and systemic arterial pressures were measured

simultaneously. Occlusion and release of the pulmonary artery produced alterations in arterial pressure on the right and left sides of the heart whose time course was similar to that followed by the changes in impulse frequency recorded from the corresponding arterial receptors.

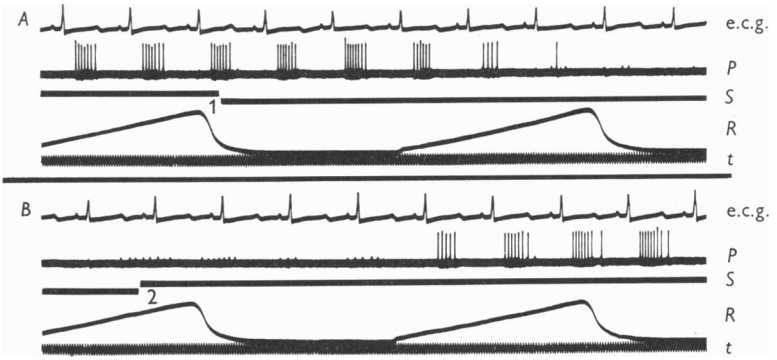

Fig. 3. Effect of occluding main pulmonary artery on discharge from an aortic baroreceptor. Interval of approximately 1 sec between records *A* and *B*. At 1 the ligature around the pulmonary artery was tightened; at 2 the artery was released.

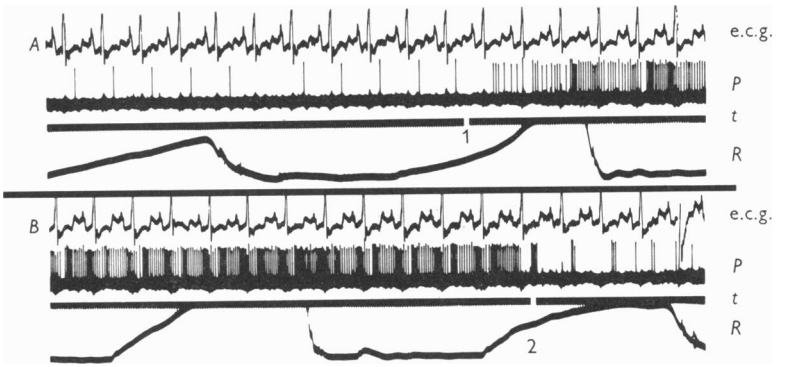

Fig. 4. Effect of occluding lung roots on discharge from receptor in pulmonary artery; same fibre as in Fig. 2. Records *A* and *B* are continuous. At 1 the snares around both right and left lung roots were tightened (note increase in tracheal pressure during period of occlusion); the snares were released at 2.

Effect of occluding the lung roots. All fibres whose impulse activity was not reduced or abolished by occlusion of the main pulmonary artery were discarded. Remaining fibres were then investigated by tightening the snares placed round the lung roots and observing the response to the subsequent increase in pulmonary arterial pressure. The effects thus produced on the discharge from a receptor in the pulmonary artery are demonstrated by the records shown in Fig. 4. Although greatly increased

by occlusion of the lung roots, the discharge was still discontinuous and showed a cardiac rhythm. By contrast, compressing the lung roots abolished the discharge from an aortic baroreceptor, as in Fig. 5. Since both pulmonary arteries and veins were included in the lung-root ligatures, there was less delay before occlusion abolished the discharge from this receptor than had been the case when the main pulmonary artery alone was occluded (Fig. 3). From the results depicted in Figs. 2 and 4, it was clear that the receptor was situated in the pulmonary artery between the conus and the snares around the lung roots.

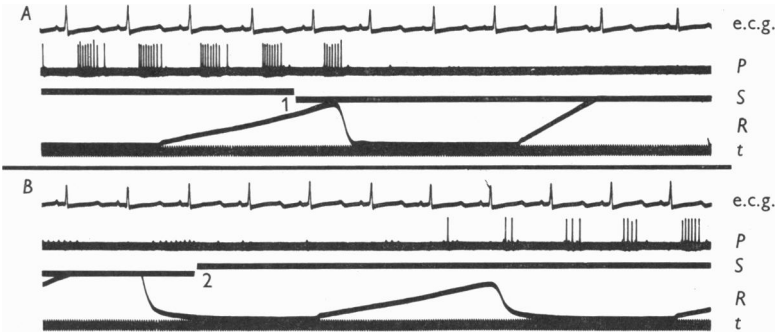

Fig. 5. Effect of occluding lung roots on discharge from an aortic baroreceptor; same fibre as in Fig. 3. Interval of approximately 2 sec between records *A* and *B*. At 1 the snares around both right and left roots were tightened (note increase in tracheal pressure during occlusion); at 2 the snares were released.

Effect of distending a balloon in the pulmonary artery. External palpation of the intact artery was of little value in locating a receptor, because much of the vessel was obscured by adjacent structures. Some dissection, with the inevitable risk of damage to nerves, was necessary. But the chances of retaining an active fibre were increased when the approximate site of the receptor was first determined in the intact vessel by distension of the balloon.

When the balloon was placed in the main artery proximal to the bifurcation, distension always reduced or abolished the discharge; hence all the receptors were apparently at or beyond the bifurcation. Distension of the balloon in the right or the left pulmonary artery produced two main types of result. Thus, distension of a balloon placed in the left artery invariably led to an increase in the impulse frequency of a receptor in the right artery (Fig. 6). This was in accordance with the observation that obstruction of flow to one lung causes an increase in pressure in the main pulmonary artery (e.g. Carlens, Hanson & Nordenström, 1951). On the other hand, when balloon and receptor were in the same branch the response to distension varied with their relative positions. Sometimes the

discharge just disappeared, when the receptor was distal to the balloon. On other occasions, distension of a balloon in the vicinity of a receptor caused an initial increase in the discharge, but with further distension the discharge was abolished, to return only when the balloon was finally collapsed (Fig. 7). This might have been due to the further distension displacing the balloon so that it moved proximal to the receptor.

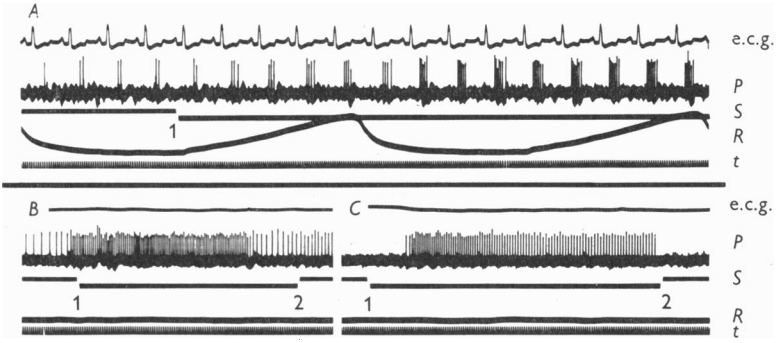

Fig. 6. Stages in the location of a pulmonary arterial receptor. *A*, inflation of balloon previously inserted into the left branch of the pulmonary artery; inflation started at 1. The obstruction of flow to the left lung produced an increase in the frequency of discharge from the receptor which was subsequently found to be situated in the right pulmonary artery. The animal was then killed, and the pulmonary artery opened. *B* and *C* show the discharge produced by punctate pressure (between 1 and 2) on the right pulmonary artery.

Punctate location of receptors. The animal was killed and the right ventricle and pulmonary conus were opened. The balloon was left *in situ* to serve as a guide. The artery was opened gradually and the interior carefully probed with a fine glass rod to find the point from which a high-frequency discharge could most easily be elicited (Figs. 6, 8). It was essential to see clearly the region stimulated by the probe. To this end it was often necessary to dissect the ascending aorta and the superior vena cava (see Fig. 9), and in many cases the resultant damage to nervous structures caused action potentials to disappear before a receptor had been located precisely.

Patterns of discharge in pulmonary arterial fibres

To determine accurately the distribution of the endings in the pulmonary artery it was necessary to be able to move the balloon freely within the artery and to have ready access to the heart and great vessels. Consequently, no attempt was made to record pulmonary arterial pressure. Even so, the evidence suggested that in general the endings responded to the pressure within the pulmonary artery. Thus, the ventricular systolic

pattern of discharge seen in the majority of these fibres was similar to that recorded from aortic baroreceptor fibres (compare Figs. 1 and 3), and corresponded in time to the expected pressure variations in the pulmonary artery. Again, the changes in impulse frequency on occlusion of the pulmonary artery and lung roots were in the direction in which the pulmonary arterial pressure undoubtedly changed.

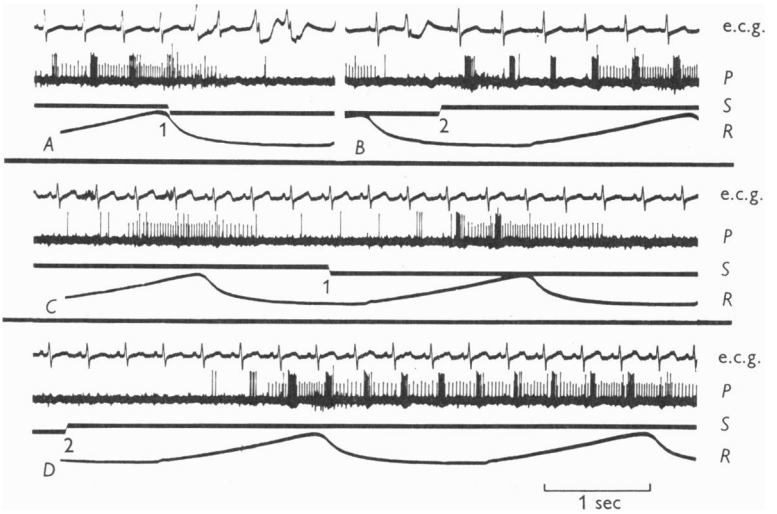

Fig. 7. Stages in the location of a pulmonary arterial receptor. *A* and *B*, effect of occlusion (at 1) and release (at 2) of main pulmonary trunk. Interval of approximately 4 sec between records *A* and *B*. *C* and *D*, alterations in the impulse activity produced by distension of a balloon in the vicinity of the receptor in the left pulmonary artery. Interval of 2 sec between records *C* and *D*. Distension of balloon started at 1, deflation at 2. Note also pulmonary stretch fibre (smaller spikes) which shows increase in discharge on deflation of balloon. In *A* and *C* some of the spikes have been retouched to aid reproduction.

However, unexpected patterns of discharge were found. For example, in the record shown in Fig. 2 there were occasional impulses during the P-R interval (i.e. synchronous with atrial systole), in addition to the main discharge starting in ventricular systole. In some instances the discharge during ventricular diastole was the most prominent. The pattern of discharge recorded when one fibre was first placed on the electrodes is shown in Fig. 8*A*; the discrete burst of activity starting in the P-R interval might well have been recorded from a type *A* receptor in the atrium or great veins (Paintal, 1953). However, infusion of 200 ml. dextran solution intravenously produced a marked alteration in the discharge (Fig. 8*B*); and although impulses synchronous with the P-R interval soon returned after the end of the infusion, main activity now occurred during ventricular systole. Consequently, it seemed worth while to try the effects of occluding

the main pulmonary artery (Fig. 8*C*). The abrupt return of a high-frequency discharge in the cardiac cycle immediately after release of the ligature suggested that this receptor was probably in the pulmonary artery. This was confirmed by occluding the lung roots. The atrial systolic discharge was thought to be due to distortion caused by atrial contraction; for all endings showing such a discharge were found, when located precisely, to be situated in the right branch of the pulmonary artery behind the superior vena cava (Fig. 8*D*).

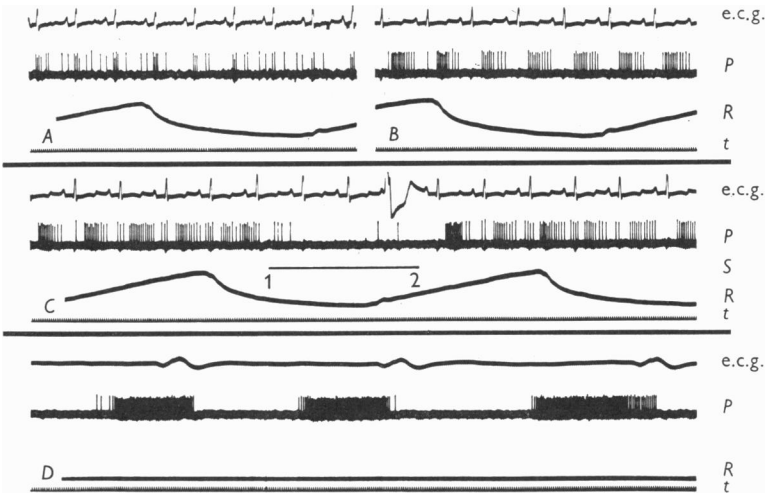

Fig. 8. Stages in the location of a pulmonary arterial receptor. *A*, pattern of discharge recorded when the fibre was first placed on electrodes. *B*, after the infusion of 200 ml. dextran solution intravenously. *C*, effect of (1) occlusion and (2) release of the main pulmonary artery. *D* shows the discharge produced by three punctate stimulations of the interior of the right branch of the pulmonary artery lying behind the superior vena cava after the animal had been killed, the pulmonary artery opened and the superior vena cava cut away.

Thus the pattern of discharge was affected not only by the degree of distension of the pulmonary artery but also by the position of the receptor in the artery. These results emphasize that a receptor cannot be assigned with certainty to a particular great vessel or chamber of the heart by inspection of the discharge and its relationship to the e.c.g.; it must be located by appropriate means in the animal with open chest. Such factors may have contributed to the previous paucity of information about receptors in the pulmonary artery.

Position of receptors in pulmonary artery

Recordings were made from twenty-nine fibres whose endings were situated in the pulmonary artery between the ligatures at the conus and

those around the lung roots. In eighteen it was not possible to determine the position of the receptor more precisely than this; for impulse activity disappeared before complete location had been achieved; but in the remainder the position of the receptor was determined precisely, as depicted in Fig. 9. All these eleven receptors were found in the vicinity of the main bifurcation, or in the right and left branches of the pulmonary artery between the bifurcation and the origins of the lobar branches.

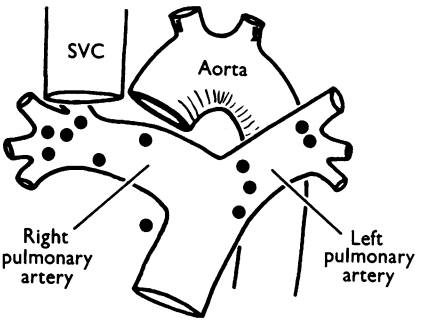

Fig. 9. The position of eleven pulmonary arterial receptors whose location had been determined accurately by punctate stimulation after the animals had been killed and the pulmonary artery dissected. The ascending aorta and the superior vena cava (SVC) near its junction with the right atrium which lie anterior to the right pulmonary artery have been omitted for clarity. In addition note the single receptor on the right of the main artery; this was situated in connective tissue between the pulmonary trunk and the first part of the ascending aorta.

Although some nerves were undoubtedly damaged in the final dissection of the pulmonary artery, our failure to find any receptors in the main pulmonary trunk proximal to the bifurcation cannot be thus explained; for the main artery was never opened until it had first been explored with a probe inserted through the right ventricle. Moreover, in the twenty-nine fibres, distension of a balloon in the main pulmonary artery never caused an increase in impulse frequency.

An additional receptor was found in connective tissue between the main pulmonary trunk and the ascending aorta (Fig. 9). The alterations in impulse frequency on occlusion of different vessels had led us to believe that this receptor was situated in the wall of the pulmonary artery. It was approximately in the location of the paraganglion aorticum supracardiale (Penitschka, 1931; group 4 of the aortic bodies described by Howe, 1956). However, at present we are unable to assess the significance of this single receptor.

In early experiments single-fibre preparations were dissected from either right or left vagus nerves. But, because only one pulmonary arterial

fibre was found in the right vagus in these first few dissections, we subsequently recorded from the left vagus. This obviously precludes comment on the relative incidence of pulmonary arterial fibres in the two nerves. Nevertheless, we do not think that this probably premature exclusion of the right vagus from our investigation significantly affected the findings as to the apparent distribution of receptors within the pulmonary artery, because the left vagus carried fibres from both right and left arterial branches.

DISCUSSION

The present investigation has shown that the vagus nerves of the dog contain afferent fibres whose endings are situated in the walls of the pulmonary artery in the region of the main bifurcation and in the extrapulmonary portions of the right and left branches, but not in the main pulmonary trunk proximal to its bifurcation. In this respect our findings are in agreement with most histological observations.

Nettleship (1936) described a sensory plexus on the base of the pulmonary artery in the cat; and Boyd (1941) reported a few scattered endings of the baroreceptor type in the distal part of the pulmonary arterial trunk and in the proximal part of the right and left branches in the rabbit. Otherwise histological evidence of baroreceptors in the pulmonary trunk proximal to the main bifurcation is lacking. The endings described by Larsell (1921) and Larsell & Dow (1933) in the rabbit and man, respectively, were limited to the pulmonary arteries near the hilum of the lung. Nonidez (1935, 1941) stated that although in the guinea-pig, rabbit and cat endings of the baroreceptor type were to be found in the arterial ligament, there was a complete absence of receptors in the wall of the pulmonary trunk; and apart from some endings in the right artery in one kitten, the proximal parts of the main branches were equally devoid of receptors. In the dog, on the other hand, Nonidez (1941) found that the endings extended beyond the arterial ligament to form a baroreceptor area over the anterior surface of the pulmonary arterial bifurcation. The absence of receptors in the main pulmonary trunk of the rabbit, cat, dog and man was confirmed by Takino (1933) and Takino & Watanabe (1937). But in contrast to the findings of Nonidez, these workers described a wide distribution of baroreceptor endings on the right and left branches extending between the main bifurcation and the lung roots.

It seems that the receptor area is not limited to the extrapulmonary vessels examined in the present investigation; for similar endings have also been demonstrated histologically in the intrapulmonary branches of the artery (Dogiel, 1898; Larsell, 1921, 1922; Larsell & Dow, 1933; Takino, 1933; Takino & Watanabe, 1937). Furthermore, impulse activity with a similar ventricular systolic discharge has been recorded in fibres arising

from what were believed to be vascular receptors in the lungs (Coleridge & Kidd, 1959*b*). But it is not possible with electrophysiological methods to locate such intrapulmonary endings to a particular vessel, and they have been excluded from the present account which deals only with receptors whose situation could be determined precisely.

In the present experiments many more aortic baroreceptor fibres were encountered in the vagus of the dog than fibres from the pulmonary artery. But fibres could be identified only when they were active; and in view of the sparse activity exhibited by some fibres (e.g. Fig. 4), it is possible that other pulmonary arterial fibres were completely inactive under the conditions of our experiments. The prolonged exposure of the heart with repeated occlusion of the great vessels undoubtedly caused some cardiac deterioration. The right ventricle was affected more than the left by these adverse conditions because the main pulmonary artery was the vessel most commonly occluded. And since pulmonary baroreceptor discharge was dependent upon the pressure developed in the pulmonary artery by right ventricular contraction, this may have accounted in part for our impression of the relative paucity of pulmonary as compared with aortic baroreceptor fibres. However, the histological evidence also suggests that, in contrast to the rich innervation of the arch of the aorta, baroreceptor endings are distributed quite sparsely in the wall of the pulmonary artery (Takino & Watanabe, 1937; Boyd, 1941; Nonidez, 1941). This raises the question of the functional significance of the pulmonary arterial receptors.

Much evidence indicates that reflex changes can be elicited from the lesser circulation. Thus, cardiovascular and respiratory effects, resulting from stimulation of receptors in the lungs, can be elicited by injection of various chemical substances (reviewed by Dawes & Comroe, 1954). It has also been shown that a large increase of vascular pressure in a perfused lung may be followed by a reflex fall in systemic arterial pressure, brady cardia and variable changes in respiration (Churchill & Cope, 1929; Harrison, Calhoun, Cullen, Wilkins & Pilcher, 1932; Schwiegk, 1935; Schweitzer, 1936; Parin, 1947); but it was concluded that the receptors mediating these effects were mainly on the venous side of the pulmonary vascular bed (Daly, Ludány, Todd & Verney, 1937; Downing, 1957).

On the other hand, Aviado, Li, Kalow, Schmidt, Turnbull, Peskin, Hess & Weiss (1951) reported that the receptors responsible for the bradycardia were in the pulmonary arterial trunk, although they agreed with previous workers that the sensory endings concerned in the hypotensive and respiratory changes were probably situated in the pulmonary veins. Takino & Watanabe (1937) described a reflex fall in systemic arterial pressure, and bradycardia, in response to electrical and mechanical stimulation of the pulmonary artery of the rabbit. It has also been suggested that

receptors in the proximal part of the pulmonary artery may mediate the 'triad' of hypotension, bradycardia and apnoea which follows injection of capsaicine in the dog (Pórszász, Such & Pórszász-Gibiszer, 1957). Clearly such effects could be explained by the receptors now described, but their normal function remains quite unknown.

SUMMARY

1. Electrophysiological techniques have been employed in anaesthetized dogs to demonstrate baroreceptor endings in the pulmonary artery.

2. Afferent impulses were recorded from single-fibre preparations dissected from slips of the cervical vagus. Receptors in the pulmonary artery were first located approximately by tightening ligatures placed around the origin of the pulmonary artery and around the lung roots. Further location was effected by distension of a balloon passed into the pulmonary artery from the external jugular vein. Finally, the position of a receptor was defined accurately by careful exploration of the pulmonary artery with a fine probe after the animal had been killed and the heart and great vessels dissected.

3. All receptors so located were found in the vicinity of the main bifurcation of the pulmonary artery, or in the right and left branches between the main bifurcation and the origins of the lobar branches. No receptors have so far been found in the pulmonary trunk proximal to the main bifurcation.

4. Recordings made from several fibres whose endings were located in the pulmonary artery showed a ventricular systolic pattern of discharge similar to that recorded from aortic baroreceptor fibres. Other fibres showed unexpected patterns of discharge in addition.

While this manuscript was being prepared we were informed by Dr R. Bianconi and Dr J. H. Green that they have recently employed electrophysiological techniques to investigate pulmonary arterial baroreceptors in the cat (Bianconi & Green, 1959). We are indebted to Professor A. Hemingway and Dr W. J. O'Connor for helpful criticism of the manuscript. We also wish to thank Miss Barbara Thomas and Mr S. Stainthorpe for technical assistance.

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