Evidence of the Atrial Location of Receptors Influencing Urine Flow

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Receptors believed responsible for the diuresis of negative pressure breathing have been located by observing the effect on urine flow of a stepwise engorgement of the intrathoracic vascular bed. Distension of the pulmonary arterial tree (injection of plastic beads) and of the entire pulmonary circulation (snares on the pulmonary veins) were without effect. A diuresis was however elicited by expansion of a balloon in the left atrium. It is concluded that stretch receptors in the left atrium and terminal pulmonary veins are instrumental in a mechanism linking changes in the actively circulating blood volume with homeostatic responses of the kidney.

Earlier studies\(^1\) have suggested that the probable cause of the diuresis induced by negative pressure breathing is the congestion that it induces in the thoracic viscera. A mechanism may, therefore, be suspected which connects changes in intrathoracic blood volume with modifications in kidney function, and it was thought that stretch receptors in the heart or lungs may mediate the response. The present investigation was designed to determine if possible the precise location of the receptors concerned. The diuretic effect of obstructive distension of the left atrium, which increases pressures throughout the pulmonary bed, including the right ventricle and the left atrium, was compared with the effect of snares around the pulmonary veins near the hilus. The latter procedure excludes the left atrium from the congested area. In a variation of this experiment, the effect of pulmonary arterial hypertension produced by embolism of the lung bed was studied.

**METHODS**

Morphine-chloralose anesthesia was used throughout in 15 to 30 pound healthy, female mongrel dogs. Since the method of anesthesia, recording of pressures, pre- and post-operative care and the technic of obstruction are described in detail elsewhere,\(^2\) they will only be briefly mentioned.

The first and simplest obstructive technic used was to infuse an aqueous suspension of 40 to 50 micron plastic beads* in small doses until the pulmonary arterial pressure was increased from a mean control value of 16 cm. H\(_2\)O to approximately 30 cm. H\(_2\)O. A 10 per cent by weight suspension of the beads in physiologic saline was infused via the jugular vein in 2 cc. aliquots at 5 minute intervals. Approximately 1 cc./Kg. body weight was needed to increase the pressure by the desired 15 to 20 cm. H\(_2\)O.

Obstruction of the pulmonary veins was induced by snares made of flexible stainless steel cable cramped into a blunted curved 19 gage hypodermic needle shaft after the technic described by Ellison, Major, Pickering and Hamilton.\(^4\) The snare loop lay at the end of a 10 cm. length of stiff vinylite tubing stretching from the chest wall to the hilus. By using a snare the veins at the hilus could be progressively obstructed without pulling on their attachments to the lung and atrium. Since obliteration of the pulmonary veins of one lung did not raise the pressure sufficiently, the operation was performed bilaterally. Artificial ventilation with positive pressure was used while the snares were placed following bilateral resection of the fifth ribs. The ends of the wires were threaded through a button and knotted. One end of an eight-inch piece of Penrose drainage tubing was then tied firmly around the snare shaft and the other end ligatured. After chest closure and reduction of the pneumothorax, the snares could be manipulated within the Penrose tubing. The exact degree of tightening required to produce the desired pulmonary vascular hypertension was determined by watching the pressure changes on the oscillograph.

As in snare placement, thoracotomy at the fifth rib was necessary to insert an obstructing balloon in the left atrium. The 2 cm. anti-coagulant-coated† rubber balloon was attached to a 2 mm. vinylite tube which was led out through the chest wall to a 30 cc. water-filled syringe. A second vinylite tube was introduced for the recording of intra-atrial pressure. The balloon was so placed that when col-

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\(^*\) Dow Chemical Co., Midland, Mich., experimental plastic beads 772, 200 to 400 mesh.

\(^\dagger\) Dow Corning Antifoam A, silicon defoamer no. D467.
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Fig. 1. Effects of distension of a balloon in the left atrium, tensing of snares on the pulmonary veins and infusion of beads into the pulmonary vascular bed upon urine flow. Ordinate:—Mean urine flow for a period starting 10 minutes after the procedure was commenced and terminating 10 minutes after release of the obstruction (scale, cc./Kg./min. X 10^{-1}). Abscissa:—control urine flow taken as the average of flows for 40 minute periods immediately preceding and following the test procedure. (Scale, cc./Kg./min. X 10^{-1}).

Results

Obstruction of the Pulmonary Arterioles by Beads: In seven cases systemic arterial pressure and respiration rates were relatively unaffected by the beads, but they induced a mean increase in pulmonary arterial pressure from 16 cm. to 30 cm. water. This increase could be sustained for from 20 to 30 minutes by repeated small infusions. In figure 1 the effects on urine flow response are recorded by the open circles. The abscissa represents the control urine flow for 40 minutes before the bead infusion and the ordinate the mean flow. If there is no change in urine flow the data will fall on the line drawn at 45 degrees across the chart. In only one case was there a moderate increase, twice there was a decrease and the overall effect in the seven cases fell along "the line of no change."

Obstruction of the Pulmonary Veins by Snares: Figure 2 is from the oscillographic recordings of a single experiment which illustrates the pressure changes occurring during tensing of the snares. A sample control section is placed in the center. Only pulmonary arterial pressure increases significantly following snare tensing. In 13 snare experiments in ten dogs there was a mean rise of pulmonary arterial pressure from 22 to 41 cm. water. Three additional experiments in which pulmonary venous pressures were directly measured showed that this pressure increment extended throughout the pulmonary vascular bed. Left atrial, central venous and systemic arterial pressures did not change significantly during the 20 to 30 minute period of snare tension. Pulse rate rose from 100 to 130 per minute and mean respira-
Snare: Pressures during tensing of both ligatures at 470 minutes. Control: Typical control period taken after snare release at 480 minutes. Balloon: After moderate distension at 530 minutes.

FIG. 2. Pressure recordings taken during the experiment shown in figure 3. From below upwards, signal indicating the 10-minute interval when the record was taken, systemic arterial, central venous, left atrial and pulmonary arterial pressures.

Obstructive Distension of the Atrium by a Balloon: Distension of the balloon until it contained approximately 1 cc. for every kilogram body weight led, as figure 2 shows, to an increase in pulmonary arterial and left atrial pressure. In 37 balloon distensions in 13 dogs, pulmonary arterial pressure increased on the average, by 15 cm. water from a mean of 24 cm. Left atrial pressure rose from a mean of 6 to 26 cm. water. The mean pulmonary arteriovenous pressure difference was 18 cm. water when the balloon was collapsed, but fell to 13 cm. when the pulmonary bed was distended by the atrial pressure rise. There was no consistent change in right atrial or systemic arterial pressure during balloon distension. However, mean pulse rate rose from 94/min to 154/min. In two cases in which the cardiac output was measured by the Fick technic it fell with distension from 3.5 and 3.6 to 2.9 and 2.2 liters per minute, respectively.

In the sample protocol of a combined snare and balloon experiment (fig. 3), the first balloon distension at 80 to 110 minutes shows a rise in pulmonary arterial and left atrial pressures, but there was no response of urine flow. It was not known whether this was due to a high postoperative level of antidiuretic hormone or to blood loss during and after the operation. However, a 20 per cent increase of blood volume by transfusion led to a transient rise in urine flow from 3 to 5 cc. per 10 minutes. When, at 250 minutes, flow had returned to near base line, the balloon was again distended for 20 minutes. Over two hours had passed since the first distension and it was now more than five hours after the operation; this time there was a response. The urine flow following a five
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Fia. 3. Protocol of the effect of repeated distension of a balloon in the left atrium and tensing of pulmonary venous snares on urine flow, respiration, pulse and pressures in the cardiovascular system.

In the abscissa: BI, period of distension of balloon; figures in the first box (Lig) at 320 to 340 minutes, tensing of the right (1) and then of both (2) pulmonary venous snares; second box (Lig) at 430 to 450 minutes, tensing of both snares simultaneously. One-half BI represents filling of the balloon with one-half the volume used for the other trials. "INF" indicates transfusion of 30 cc. from a donor dog.

In the upper ordinate: "ART", systemic arterial pressure, each point representing a planimetric determination of a fast pressure recording (fig. 2). CV, pressure in the inferior vena cava; PA, pulmonary arterial pressure; LA, pressure in the left atrium.

Lower ordinate, urine flow in cc per 10 minutes, respiration and pulse in units of 1/10 the true rate.

minute delay rose from 4 to 13.5 cc. per 10 minutes. At 350 minutes, immediately following a 10-minute bilateral snare tensing, which did not affect urine flow, balloon distension led to an increase from 3 to 22 cc. per 10 minutes. Balloon distension at 510 minutes again caused an increase, i.e., from 4 to 20 cc. per 10 minutes. The balloon was left distended for 50 minutes and despite the continued atrial stimulation, the urine flow spontaneously started to return to base line after 30 minutes of distension. A similar falling off of the flow has been observed with prolonged negative pressure breathing. A final distension with half the amount of fluid in the balloon led only to minor pressure changes and a questionable response of urine flow.

Figure 1 summarizes the urine flow changes in 37 balloon distensions in 13 dogs. In spite of the obstruction to the circulation, only on three occasions was there any decrease in urine flow. In 14 trials, flow increased 2- to 5-fold. This was in response to a mean pressure change in the atrium and pulmonary vascular bed which was slightly less intense and lasted no longer than the pulmonary vascular distension by the snares. In five cases, the snares and balloons were successfully contrasted in the same animal, in a majority of the remaining tests balloon and snare responses were compared
with a standard negative pressure breathing stimulus to establish the sensitivity of the preparation.

Conclusions

These experiments attempted evaluation of the working hypothesis that the diuresis due to negative pressure breathing\(^1,2\) may result from stimulation of stretch receptor areas located in the low pressure system within the chest.\(^6\) The results narrow down the possible sensitive regions and point to a role for left atrial receptors. Although the left atrium could not, for technical reasons, be distended separately, the engorgement of the pulmonary vascular bed was only effective, if the left atrium was included in the congested area. Since right atrial pressure did not change during balloon inflation, distension of the receptor area in the right atrium and the great systemic veins\(^8\) does not appear to be essential for the diuresis accompanying negative pressure breathing. However, since direct stimulation of the right atrium has not been studied, it is possible that this region has some role in the response. The observation that distension of the inferior or superior vena cava does not elicit a diuresis\(^7\) may be related to the fact that a receptor network of the type found in the atria only extends as far as the mouths of these veins.\(^6\)

There is a striking identity between the functional topography as mapped out in these experiments and the subendocardial receptor network of Nonidez.\(^8\) According to a recent review by Dawes,\(^8\) this receptor system is well suited to record volume changes in the thoracic circulation. Recently it has been shown that stimulation of these receptors in the left atrium by the balloon distension used in the present study to induce diuresis will lead to afferent impulses in the vagus.\(^5\) Blood infusion, negative pressure breathing and balloon distension all cause an increase in impulses from left atrial stretch receptors. Pulmonary hypertension induced by snares on the veins does not result in such a response. Hemorrhage decreases the impulse frequency. Evidence was also presented that cooling of the vagus nerve in the neck to \(8\)\(^\circ\)C. abolishes both the conduction of impulses and the diuresis following balloon inflation.\(^9\)

The narrowly localized area responsible for the diuretic effect, and the concordance between our results and the anatomical\(^9\) and neurophysiologic evidence\(^8,9\) suggests that the left atrial receptor network plays an important part in the volume sensitive mechanism postulated in earlier work.\(^1,2\) Location of this sensory area in the low pressure part of the cardiovascular system would explain other responses such as the contraction of the spleen\(^10\) and of the peripheral veins\(^11\) and the release of vasoconstrictor substances\(^12\) which may occur after blood loss insufficient to change pressures in the well known sinoaortic vasosensory zones.

Summary

Location of receptors believed responsible for the diuresis of negative pressure breathing was attempted by obstructing the low pressure portion of the cardiovascular system of dogs in three places.

In thirteen dogs the left atrium was distended, together with the lung vessels, by obstructing the mitral orifice for 20 minutes with a balloon. In 33 of 37 trials a mean pressure rise of 15 cm. water induced a diuresis of various degrees. In 14 trials this diuresis attained 2- to 5-fold the control values.

In 13 tests in 10 dogs the pulmonary vascular bed was distended for 20 minutes by snares on the veins close to the hilus. A mean pressure rise of 19 cm. water induced a slight oliguria. In seven cases the pulmonary arterial tree was distended by multiple small emboli. A mean pressure increase of approximately 16 cm. water for 20 to 30 minutes failed to induce a diuresis.

The stretch receptors described by Nonidez in the left atrium and terminal pulmonary veins may be part of a mechanism linking changes in the actively circulating blood volume with homeostatic responses of the kidney and other organs.

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**Summario in Interlingua**

Esseva interprendite le tentativa de localizar receptores considerate como responsabile pro le diurese in respiratio a pression negative. Le technica usate esseva le obstruction del portion a basse pression del systema cardiovascular de canes in tres sitos.

In 13 canes le atrio sinistre, insimul con le vasos pulmonari, esseva distendite per obstruer le orificio mitral durante 20 minutas per medio de un ballon. In 33 inter 37 essayos, un augmento median del pression per 15 cm H$_2$O induceva un diurese de varie grados. In 14 essayos le diurese amontava al duple usque al quintuple del valores de controlo.

In 13 essayos con 10 canes le lecto pulmono-vascular esseva distendite durante 20 minutas per ansas applicate al venas proxime al hilo. Un augmento median del pression per 10 cm H$_2$O induceva un leve grado de oliguria.

In 7 casos le arbore pulmono-arterial esseva distendite per medio de multiple parve embolos. Un augmento median del pression per circa 16 cm H$_2$O, mantenite pro 20 a 30 minutas, non induceva ulle diurese.

Le tensoreceptores describite per Nonidez in le atrio sinistre e in le venas pulmonari terminal es possibilemente un parte de un mechanismo que establi un connection del volume sanguinee in circulation active con responsas homeostatic del renes e de altere organos.

REFERENCES


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