— Original —

From the Department of Medicine, Tokyo Jikeikai School of Medicine

**The Afferent Nerves in the Pulmonary Vessels and
Bronchial Tree in Some Mammals***

By

HIDEO UEDA, MASAHARU HORIGUCHI, KIHACHIRO SHIMANO,
MUNEHARU YOSHIDA, AKIRA KODAMA & SHOJI IIDA

(Received for Publication, Mar. 7, 1955)

It has been already morphologically and physiologically proved that pressoreceptors lie in the areas of the carotid-sinus, the brachiocephalic artery, and the arch of aorta, and that they are self-regulators of the blood pressure in the systemic circulation.

On the other hand, there are some studies on similar pressoreceptors in the pulmonary circulation, but they are not in accord with one another.

We have been engaged in studies on the pulmonary circulation for several years, and in the present article we would like to report some results of morphological studies on the problem above mentioned.

Historical Review

There are some observations on the distribution of the afferent nerves in the pulmonary vessels and bronchial tree (Dogiel, 1898; Sunder Plassmann, 1933; Takino, 1933, 1935, 1943; Nonidez, 1937, 1941; Seto, 1945, et al.).

In the pulmonary vascular system, Dogiel (1898) described the dense distribution of nerve fibers in the adventitia not only to the stem but also to the second division of the artery, and also the nodular form of the nerve endings of sensory type in the media.

Larsell (1921, 1933) observed similar findings in the cat and human lung stained with methylene blue.

Schwiegk (1935) discovered in the physiological experiment the self-regulating mechanism in the pulmonary circulation which caused bradycardia and the reflex fall of the systemic blood pressure

when the pulmonary arterial pressure was increased (so-called "Lungen-entlastungsreflex").

Daly (1937) described that the distension of the pulmonary veins and left atrium caused the reflex fall of the systemic blood pressure in the dog with various types of perfused preparations.

Takino (1933, 1935), using the method of Cajal, found the free nerve endings of sensory type in human and avian lungs similar to those of the carotid-sinus and the arch of aorta.

He described that they were densely distributed to the bronchi and intrapulmonary arteries near the hilum (about 400μ in diameter), although the findings somewhat varied according to the species examined, but the nerve endings of sensory type were scarcely found in the intrapulmonary veins.

Schwiegk explained the mechanism of the self-regulating reflex above described, based on this Takino's observation, by means of the fact that the aorta, the carotid artery, and the pulmonary artery all differentiated embryologically from the primitive paired aortae. However, Takino (1943) emphasized the innervation on the stem of the pulmonary artery rather than the intrapulmonary arteries and designated the reflex eliciting here as "the pulmonary stem reflex."

On the other hand, Nonidez (1941) described that the nerve endings of sensory type similar to those in the aorta were found in the divisions of the pulmonary arteries but not in other parts of the arterial walls in the dog and also the afferent sensory endings were found in the subendothelial portion of the pulmonary veins in the dog but not

* This research owes to the "Grant in Aid for Fundamental Scientific Research" of the Ministry of Education. An outline of this research was reported at the 18th Annual Meeting of the Japanese Circulation Society.

in the pulmonary arteries in the rabbit, cat, and guinea pig.

From these evidences, Nonidez supported Daly's opinion above described in opposition to Schwiegl and Takino.

Elftman (1943), by the method of Cajal-Nonidez, observed also the nerve endings of sensory type in the pulmonary veins near the hilum of the puppy, but not in the arteries.

Seto (1954), using the Bielschowsky-Seto's method, found that in the pulmonary vascular system sensory fibers were distributed mostly to the arterial walls and rarely to the venous walls. According to Seto, not only the distribution of sensory fibers concerned in the control of blood pressure are more widespread in the fetus than in the adult, but also the types of the nerve endings of the former are much different from those of the latter, namely in the pulmonary arteries in the fetus thick sensory fibers extend to the media through the adventitia, ending in arborization or irregular branching type, some of which extend even to the intima. But these findings are chiefly found in the proximal portions and rarely in the peripheral arteries. These sensory fibers markedly degenerate in the pulmonary arteries, as the age advances, and are hardly found in the media in the fetus 8 months old.

In the bronchial system, Larsell (1921, 1933) described that afferent fibers of sensory type were

distributed in the so-called atrium of Miller (1950) in the rabbit and human, giving off, on the way, the branches to the bronchial epithelium and the smooth muscle.

Larsell, Miller, and Takino divided the nerves distributed in the intrapulmonary bronchi into two types: extrachondrial and subchondrial. Takino (1933) confirmed the myelinated fibers in the walls of the alveoli in the rat and guinea pig.

Hayashi (1937) noted the thick myelinated fibers originating from the vagus in the human bronchial epithelium, smooth muscle, and pulmonary parenchyma.

Materials and Methods

The materials used for this study were:

Five puppies from 1 day to 4 weeks (weighing about 300 g).

Thirty guinea pigs weighing from 50 to 150 g.

Three human fetuses (3, 4, and 6 months old).

Some of the puppies and the guinea pigs were anesthetized with urethane and the others were beaten to death, and the lungs, according to Cajal-Nonidez's modification, were impregnated with silver solution after fixation in 50% alcoholic chloral hydrate in as nearly the normal expiratory condition as possible.

The lungs of the human fetus obtained by the artificial abortion were also stained by the same method.

The tissues were embedded in paraffine and

Fig. 1. Guinea pig 80g. Intrapulmonary artery. Cajal-Nonidez's method. $\times 500$

cut serially at from 10 to 20 μ .

For the purpose of differentiation of the artery from the vein, some of the tissues were stained with Hematoxylin-Eosin and Weigert's Resorcin-fuchsin, moreover the lungs, infused with Sudan III suspension from the arterial side and with methylene blue solution from the venous side, were stained by the same technique as above described.

Results

(A) Pulmonary Blood Vessels.

In the pulmonary arteries, the thick myelinated afferent fibers of sensory type are followed to the areas considered as the third division (260 μ in diameter) of the intrapulmonary artery.

These fibers are branchy and take tortuous courses in irregular thickness and terminate in the adventitia in various types such as reticulate, clubbed, and lariat-like. Although the nerve fibers passing through the media are found, they form the terminations mostly in the adventitia and the

Fig. 2. Puppy 250g. ♀ Intrapulmonary artery. Cajal-Nonidez's method. $\times 500$

Fig. 3. Fetus 6 months old. Intrapulmonary artery. Cajal-Nonidez's method. $\times 500$

endings appearing as afferent are not found in the medial musculature.

In the pulmonary veins, the similar fibers are followed to the areas considered as the second division of the intrapulmonary vein and terminate in clubbed endings.

The nervous elements in the pulmonary vein are far less numerous than those in the pulmonary artery.

Furthermore, the similar fibers and endings are

also found in the lungs infused with Sudan III suspension from the arterial side and with methylene blue solution from the venous side for the purpose of differentiation of the artery from the vein.

The nervous elements of the fetus are more numerous, more various in thickness and more tortuous in course than those of the guinea pig and puppy.

(B) Bronchi and Alveoli.

The ganglia, mostly of the multipolar type, are

Fig. 4. Guinea pig 80g. Intrapulmonary vein. Cajal-Nonidez's method. $\times 500$

Fig. 5. Puppy 250g ♀ Intrapulmonary artery. Cajal-Nonidez's method. $\times 500$

Fig. 6. Fetus 6 month old. Intrapulmonary vein. Cajal-Nonidez's method. $\times 500$

encountered scattered or in a cluster in peribronchial connective tissues.

In extrachondrial plexuses, the bundles of sensory fibers are considerably large and chiefly consist of the myelinated fibers with small clusters of ganglion cells.

The nervous elements of subchondrial plexuses encountered in the connective tissues between the cartilages and the smooth muscles are few in number as compared with those of extrachondrial plexuses.

The nervous elements such as bundles, fibers, and endings of sensory type are frequently found about the intrapulmonary bronchi and bronchioles, and also the nerve endings are encountered within the ciliated columnar epithelia.

In the wall of the alveolus the fine myelinated afferent fibers are infrequently found, whose endings are spindle-shaped, knob-like, and clubbed.

Discussion

As already stated, histologically Dogiel (1878) in the mammal, Larsell (1921, 1933), by the methylene blue method, in the rabbit and human found the nerve fibers and endings of sensory type to the second division of the pulmonary artery.

Takino (1933, 1935), using the method of Cajal, in the bird and human noticed the dense distribution of sensory fibers in the extrapulmonary pulmonary artery and vein and in the wall of the intrapulmonary artery about 400μ in diameter. However, he

could hardly find the nerve elements in the intrapulmonary vein.

Schwiegk (1935) and Daly (1937) in the physiological experiment suggested the presence of the afferent fibers in the pulmonary vessels producing the reflex fall of the blood pressure in the systemic circulation. It is not clarified, however, by their methods whether these receptors lie on the arterial side or the venous side, or on both sides.

We confirmed in the dog that, when the blood pressure in the pulmonary artery or vein was separately increased, the reflex fall in the systemic arterial pressure was produced in each procedure. Therefore, we consider the pressoreceptors lie on both sides.

On the other hand, we morphologically confirmed, by the reduced silver method of Cajal-Nonidez, in the guinea pig, puppy, and fetus the myelinated afferent fibers of sensory type and the nerve endings of special type were distributed to the areas considered as the third division of the intrapulmonary artery about 260μ in diameter and to those considered as the second division of the vein, although compared with the artery, the vein was supplied less in number.

Dogiel and Larsell described the sensory endings terminated in the media of the pulmonary artery in small nodules and also Takino stated that abundant sensory fibers and endings were noticed in the media of the pulmonary artery.

We found the afferent fibers terminated in the adventitia, passing through the media, but could not find the sensory nerve endings in the smooth muscle of the media.

The discordance of our results with those of Dogiel, Larsell, and Takino may be explained partly, as Takino already stated, by the difference of materials, partly by the staining technique. Especially, our method is quite different from that of Larsell.

Even in our cases, there were some blocks in which the nervous elements were not found or they were encountered only in the arterial side but not in the venous side.

Indeed Nonidez in the rabbit, cat, and guinea pig, and Elftman in the puppy, using the reduced silver method of Cajal-Nonidez, found the afferent fibers of sensory type in the pulmonary veins near the hilum, but Nonidez also noticed the nerve endings of sensory type located in the division of the artery in the dog. It seems that the silver method is so difficult that these results are not in accordance with one another.

Seto, by means of the method of Bielschowsky-Seto, found the afferent fibers of sensory nature, though very small in number in the pulmonary artery of the fetus, ending in the media through the adventitia, some of which extended to the intima.

According to his observation, these fibers markedly degenerate in the pulmonary arteries and in the adult the sensory endings concerned to the pressoreceptor terminate in the connective tissues of the adventitia getting into the media.

In view of these evidences, it may be due to the grade of the degeneration that we could find no sensory nerve ending in the media of the pulmonary artery. The nerve endings found by us are reticulated, lariat-like, club-shaped, considerably large, branched, various in diameter and terminate freely in the adventitia. According to Seto, the nerve endings of sensory type in the human adult are divided into two types: One is the complex branched ending with the special fibrillar terminal plate such as Sunder-Plassmann noticed within the mucous membrane of the intrapulmonary bronchus, the other is the complex arborization ending accompanied with small arteries.

He says that, in the fetus, the endings are of arborization or irregularly branched and various in

thickness. Our observations in the fetus were in very small numbers, consequently the degenerative appearances and the structures of the endings must be left for further investigation.

Elftman described that the nerve fibers stained by Cajal's method were chiefly myelinated fibers of sensory type and terminated in small nodules in the adventitia. Nonidez said that sympathetic postganglionic fibers could not be traced with Cajal's method. Seto states that the afferent fibers are considerably thick, compared with the efferent fibers of autonomic nature.

The nervous elements found by us seem to be the afferent nerves of sensory type, judging by the staining method, the appearances of the endings, and the myelinated fibers.

Furthermore, as Larsell already stated, it will be difficult to regard them as the efferent fibers of motor system, since they are chiefly found in the adventitia. Although Seto does not support the presence of the autonomic afferent fiber, the nerve fibers noticed by us seem to be identical with those of Seto, and also they are similar to those found in the arch of aorta and the carotid-sinus in point of the myelinated fibers and the complex terminal structure.

Moreover, embryologically the pulmonary artery develops from the same organ with that of the arch of aorta and the carotid artery. In view of these morphological and physiological evidences, as Larsell and Takino stated, it seems to us that these sensory nerves derive from the myelinated fibers of vagal origin.

We confirmed, as Larsell, Miller, and Takino noticed, two types of sensory fibers distributed to the intrapulmonary bronchus; extrachondrial and subchondrial, and we also noticed, as well as Hayashi and Takino, in the walls of alveoli the thick myelinated afferent fibers of sensory type of vagal origin.

These findings will be discussed in detail on the next opportunity.

Conclusions

1. The afferent fibers of sensory type were studied by means of the reduced silver technique of Cajal-Nonidez in five puppies, thirty guinea pigs, and three human fetuses.

2. The myelinated afferent fibers of sensory type were followed to the adventitia of the areas

considered as the third divisions in the intrapulmonary arteries and as the second divisions in the intrapulmonary veins.

3. These myelinated fibers were considerably thick, branchy, tortuous in their courses, various in diameter and their endings were reticulated, lariat-like, and club-shaped.

4. It seems that these sensory nerves derive from the myelinated fibers of vagal origin.

REFERENCES

- 1) Daly, I. de Burgh, *Quat. J. exp. Physiol.* **27**: 143, 1937.
- 2) Dogiel, A. S., *Arch. Mikr. Anat.* **52**: 44, 1898.
- 3) Elftman, A. G., *Am. J. Anat.* **72**: 1, 1943.
- 4) Hayashi, S., *J. Orient. Med.* **27**: 37, 1937.
- 5) Larsell, O., *J. Comp. Neurol.* **33**: 105, 1921.
- 6) Larsell, O., *ibid.* **33**: 509, 1921.
- 7) Larsell, O. & Dow, S., *Am. J. Anat.* **52**: 125, 1933.
- 8) Miller, W. S., *The Lung* 1950, second edition 2 printing. Charles C. Thomas, Springfield Illinois.
- 9) Nonidez, J. F., *Am. J. Anat.* **61**: 203, 1937.
- 10) Nonidez, J. F., *ibid.* **68**: 151, 1941.
- 11) Schwiegk, H., *Pfluger. Arch.* **236**: 206, 1935.
- 12) Seto, H., *Acta Anat. Nipp.* **29**: 56, 1954.
- 13) Sunder Plassmann, *Dtsch. Ztsch. Chr.* **240** B. S. 249, 1933.
- 14) Takino, M., *Jap. J. Med. Scien.* Part III Biophysics. **9**: 67, 1943.
- 15) Takino, M., *Acta Scholae Med. Kioto* **15**: 303, 1933.
- 16) Takino, M. & Ezaki, Y., *ibid.* **17**: 1, 1935.
- 17) Ueda, H., *Jap. Circulation J.* **18**: 175, 1954.