REFLEX PRODUCTION OF HEART BLOCK

AND

RELATED CHANGES IN PHYSIOLOGY OF THE HEART

by

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A THESIS

Presented to the Department of Physiology
and the Graduate Division of the University of Oregon Medical School
in partial fulfillment
of the requirements for the degree of
Master of Science

May 1942

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May 26, 1942

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INTRODUCTION AND REVIEW OF LITERATURE

The Weber brothers, Eduard and Ernst, in 1846, provided the first indisputable evidence that the vagus carries inhibitory fibers to the heart (7). This, in fact, was the first evidence for the suppression or inhibition of an organ by the stimulation of an appropriate nerve. Cardiac inhibition as a result of vagal stimulation had been observed in animal experiments and reported as early as two centuries before the Webers by Boyle and Lower, Haller, and Senec. These observations failed to gain recognition not because of the obscurity of the authors or of the publications but because of "the particular orientation of the physiological thinking of those days" (2). Haller, in 1759, presented a myogenic theory for the origin of the cardiac impulse, which stated that it is based on the inherent irritability of the myocardium itself. He, however, could not entirely divorce himself from the thought that nerves probably played a part in the origin of the impulse. Accordingly, the myogenic theory was accepted by neither him nor other investigators of his time. Observations on the effect of stimulation of the vagi, together with the finding near the atrio-ventricular junction of tiny ganglia which were supposed to be affected by the sympathetic nerves, led to the neurogenic theory for origin of the cardiac impulse. This theory attributed the origin of the heart beat to spontaneous or reflex activity of the cardiac ganglia and the transmission of the cardiac impulse to the intracardiac nerve fibers originating in the ganglia. The neurogenic theory persisted in spite of the observations of other workers that the heart could continue to beat after the brain was destroyed, the animals' heads cut off and all the nerves of the heart divided (2).

Volkmann, in 1838, reported the influence of the vagus on the movements of the heart of the frog but did not point out its significance. Then in 1846, the Weber brothers, mainly Eduard, demonstrated vagal inhibition and shortly afterward Claude Bernard described cardiac arrest in response to vagal stimulation upon repeating the Webers' experiments. Since that time, the evidence for vagal inhibitory fibers has been corroborated by innumerable physiologists.

Gaskell, in 1883 (3), pointed out that stimulation of the left vagus in the frog produces an incomplete auriculo-ventricular dissociation. Hofman (9) found that in frogs stimulation of the right vagus produces a complete arrest of the heart, while stimulation of the left vagus produces only a weakening of the beat. Other animals, such as the newt (4), cat (5), horse (6), pigeons (7), as well as rats, guinea pigs, rabbits and others, were studied for differences in action of the two vagi. In dogs, observations were made by numerous investigators but in most cases no distinction was made between the right and left vagus (20) (21). Rothberger and Winterberg (8) pointed out that right vagal fibers in the dog pass predominantly to the sino-auricular node and the left to the atrio-ventricular node. Cohn, in 1912 (9), pointed out that stimulation of the right vagus produces complete arrest of all chambers of the heart, while stimulation of the left vagus has a profound effect on atrio-ventricular conduction, the effect varying from delayed P-R time to complete auriculo-ventricular dissociation. Einthoven and Wierenger (10), Cohn and Lewis (11), Lewis (12), and later many others pointed out the effect of the left vagus on junctional tissue and of the right vagus on the sino-auricular

node. Cohn and Lewis (11) pointed out that the differences in effect of the two vagi are quantitative rather than qualitative; that is, that while both nerves usually affect impulse formation and impulse conduction, the right nerve chiefly controls the former and the left nerve the latter. These experiments were done in anesthetized animals and by direct electrical stimulation of the cut peripheral ends of the nerves. Cohn, in 1913 (13), however, succeeded in producing sinus bradycardia in chronic right vagus dogs and incomplete atrio-ventricular block in chronic left vagus dogs by the intra-venous injection of morphine sulphate in dosages varying from 16 to 96 milligrams. It was assumed that his results were based on central stimulation of the vagi.

Efforts to show the difference in distribution of the two vagi in man have concerned largely carotid sinus pressure, the effects of which are not confined to a single vagus and therefore are inconclusive (14) (15) (16) (22).

Anatomical attempts to follow the distribution of the right and left vagus into the heart itself have not resulted in clear-cut evidence for the differential distribution of the vagal fibers to the various portions of the conducting system. Nonidez (17) points out that preganglionic fibers terminate in ganglia above the coronary sulcus but that no ganglia are found in the ventricles. He makes no note of a differential distribution of the vagi in the heart. Woollard (18), in a study of the innervation of the heart, states merely that "it has been found experimentally that the Keith-Flack sino-auricular node is stimulated by the right nerves and the Tawara node by the left nerves (Rothberger and Winterberg)."

Since most of the evidence concerning the vagal control of the heart has concerned artificial means of stimulation, in anesthetized animals, it has seemed desirable to attempt an evaluation of the influence of the vagi on the heart under more physiological experimental conditions. Accordingly, the following experiments have been carried out on unanesthetized trained dogs.

Unselected dogs, after a suitable training period, were pre-
pared by aseptic unilateral vagotomy high in the neck. The heart beats
were recorded by a continuous electrocardiographic tracing--before,
during, and after the injection of the pressor compounds, Neo Synephrin
H Cl, Pitressin, and Angiotonin. Neo Synephrin, in 1/10,000 dilution,
was injected by means of a constant injection apparatus at the rate of
one, two, or four c.c.s per minute. Angiotonin equivalent to a
1:250,000 Adrenalin solution was injected at the rate of four c.c.
per minute through the same apparatus. Pitressin was injected intra-
venously in the dosage of one pressor unit, or intra-muscularly as 1.2
to 4.0 pressor units. Before the injection was started and the records
made, the trained dogs were allowed to rest on the table with the needle
in their veins until the heart rate was stabilized.

RESULTS

1. Neo Synephrin:

In twenty-seven out of thirty-seven experiments on fourteen
chronic left vagus dogs, a partial 2 to 1 heart block was produced.
This block was demonstrated at least once in all but one animal of the
series. In twenty-eight experiments on twelve chronic right vagus dogs,
there was no instance of a partial heart block. In four of the twenty-
eight experiments involving two animals, an atrio-ventricular nodal
rythm was produced and in one experiment, atrio-ventricular nodal beats
were observed. There were no atrio-ventricular nodal beats or rythms in
chronic left vagus dogs. In six of a series of thirteen dogs, with both
vagi intact, eight of a total of thirty-nine experiments resulted in a

partial 2 to 1 atrio-ventricular block, and in one experiment, there was an atrio-ventricular nodal rythm. In thirty-seven experiments on twenty-one completely vagotomized dogs, no heart blocks, atrio-ventricular nodal rythms, or atrio-ventricular nodal beats were observed. Ectopic ventricular beats of similar origin occurred in all four types of dogs.

2. Pitressin:

In seven of a series of ten experiments on seven chronic left vagus dogs, a partial 2 to 1 heart block was produced. Only one animal of the seven failed to develop a block. There were no cases of partial heart block in twelve experiments on six chronic right vagus dogs, although in one experiment, atrio-ventricular nodal rythm appeared and in another nodal beats. In a series of nine experiments on four dogs having both vagi intact, two experiments on two of the animals resulted in a partial 2 to 1 atrio-ventricular block. No atrio-ventricular nodal rythm or beats occurred. In four experiments on four completely vagotomized dogs, there was no incidence of partial heart block, atrio-ventricular nodal rythm, or atrio-ventricular nodal beats. There were no ectopic ventricular beats in any of the experiments with Pitressin.

3. Angiotonin:

Angiotonin was made available through the courtesy of Dr. K. K. Chen of the Eli Lilly laboratories. It was diluted to equal the potency of a 1:250,000 Adrenalin solution. A sufficient amount to try only one experiment on each of four types of dogs was available. The results showed only a sinus bradycardia in the intact and chronic right vagus dogs and a 2 to 1 heart block in the chronic left vagus dogs. There was no

slowing in the vagotomized dog.

TABLE

Neo Synephrin

Type of Animal	Number	Atrio-ventricular block	Atrio-ventricular nodal rythm	Atrio-ventricular nodal beats	Ectopic ventricular beats
Right	12 dogs	0	2	1	3
Vagus	28 exp.	0	4	1	7
Left	14 dogs	13	0	0	3
Vagus	37 exp.	27	0	0	7
Both	13 dogs	6	1	0	3
Vagi	39 exp.	8	1	0	3
0	21 dogs	0	0	0	7
Vagi	37 exp.	0	0	0	8

Pitressin

Right	6 dogs	0	1	1	0
Vagus	12 exp.	0	1	1	0
Left	7 dogs	6	0	0	0
Vagus	10 exp.	7	0	0	0
Both	4 dogs	2	0	0	0
Vagi	9 exp.	2	0	0	0
0	4 dogs	0	0	0	0
Vagi	4 exp.	0	0	0	0

DISCUSSION

These experiments support the previous contentions that the right vagus predominantly supplies the sino-auricular node and the left vagus the atrio-ventricular node. They represent an attempt to demonstrate the vagal influence on the heart under more nearly physiological conditions. Thus, the method of stimulation of the vagi is a reflex one depending on a rise of blood pressure, in unanesthetized dogs. It should be pointed out that in the chronic left vagus dogs there was a slowing of the atrial rate on an average from 93 to 54 with Neo Synephrin and from 94 to 48 with Pitressin, as compared to 89 to 50 with Neo Synephrin and 92 to 42 with Pitressin in chronic right vagus dogs. This is in accordance with the views of Cohn and Lewis (11) that direct stimulation of either vagus usually affects rate of impulse formation but the right nerve chiefly controls impulse formation and the left nerve, impulse conduction. There was no instance of heart block in chronic right vagus dogs or in vagotomized dogs. It is interesting to note that in four experiments on two dogs of a total series of twenty-eight experiments on twelve chronic right vagus dogs, an atrio-ventricular nodal rythm occurred and in another dog, atrio-ventricular nodal beats were observed. This never occurred in chronic left vagus dogs or in vagotomized animals. In these dogs, the sino-auricular node was sufficiently depressed by the right vagus to reduce its rythmicity to a level below that of the atrio-ventricular node so that the latter became the pacemaker.

Compounds having little or no direct effect on the heart but a relatively greater blood pressure raising effect were selected. However,

Neo Synephrin, a compound closely related to Adrenalin, is known to be
capable of producing direct cardiac acceleration in large doses. The
doses of this compound selected were below the threshold for more than
a slight cardiac stimulation. Keys and Violante (19), working on
humans, concluded that "Neo Synephrin produces a primary bradycardia by
inhibition of the sino-auricular node and this is relatively independent
of blood pressure reflexes over the vagus nerve." In our experiments on
dogs we find that the bradycardia is entirely dependent upon the presence
of the vagus nerves. Thus, following vagotomy, Neo Synephrin admini-
stration resulted in an acceleration from an average resting rate of
115 to an average of 135 beats per minute. In intact animals, the
slight cardio-accelerator action of Neo Synephrin is over-ridden by the
reflex inhibition produced by the rise of blood pressure. In vagotomized
animals it was not possible to produce a partial heart block, atrio-
ventricular rythm, or atrio-ventricular nodal beats by the injection of
Neo Synephrin. However, in all four types of dogs, normal, chronic right
or left vagus, and vagotomized animals, Neo Synephrin frequently pro-
duced ectopic ventricular beats, while Pitressin or Angiotonin failed to
do so.

The P-R interval was compared in both chronic right and left
vagus dogs. In 58% of the chronic left vagus dogs and 40% of the chronic
right vagus dogs, the P-R interval was lengthened 0.04 seconds as a
maximum from the resting rate. In 33% of the chronic left vagus dogs
and 14% of the chronic right vagus dogs, there was a lengthening of over
0.06 seconds. While these figures suggest a greater influence of the
left than of the right vagus on atrio-ventricular conduction, they do not

offer as striking evidence as that concerned with the development of atrio-ventricular heart block.

SUMMARY

A review of the literature on the distribution of the cardiac branches of the two vagus nerves is presented. It reveals no previous attempts to study the problem by means of reflex activation of the nerves produced by a rise of blood pressure in the unanesthetized animal.

The compounds Neo Synephrin, Pitressin, and Angiotonin were used as pressor agents. Their influence on the heart, as judged by electrocardiographic tracings, was studied in four groups of dogs: (1) Normals; (2) Dogs whose left vagus was cut; that is, right vagus dogs; (3) Dogs whose right vagus was cut; that is, left vagus dogs, and (4) Dogs having both vagi cut.

Sinus bradycardia was commonly produced in response to pressor compounds in all except the bilaterally vagotomized dogs.

In left vagus dogs, atrio-ventricular nodal heart block was a common finding, while in right vagus dogs this block never was recorded.

In a few experiments on right vagus dogs, an atrio-ventricular nodal rythm was observed. This result indicates that the right vagus was excited reflexly to the extent that it depressed the rythmicity of the sino-auricular node to a level below that of the atrio-ventricular node.

In experiments in which it was measured, the P-R interval showed a slightly greater change in chronic left than in chronic right vagus dogs. Thus, in 33% of the left vagus dogs as compared to 14% of the right vagus dogs, there was an increase in P-R interval of over .06 seconds.

Ectopic ventricular beats occurred only with Neo Synephrin and their variable sites of origin could not be correlated with the type of animal preparation used.

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REFLEX CARDIAC DEPRESSION THROUGH RIGHT VAGUS IN RESPONSE TO HYPER-
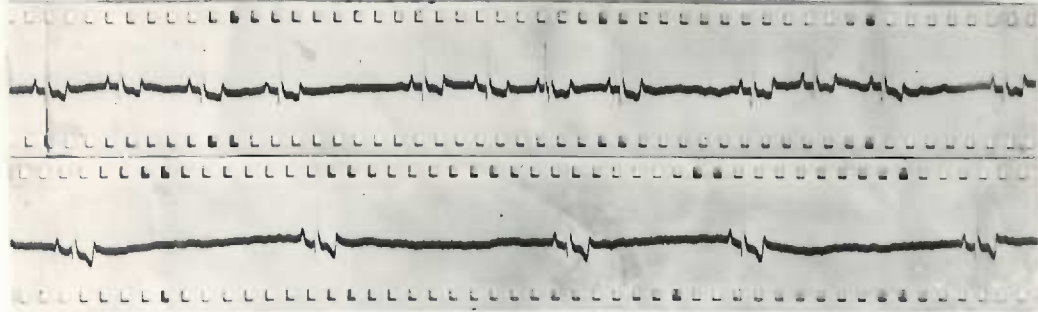TENSION INDUCED BY NEOSYNEPHRIN.

Fig.1

Dog 4. Upper record : Before injection and point of onset of injection
Lower record : Sinus Bradycardia, 75 seconds after onset of injection of
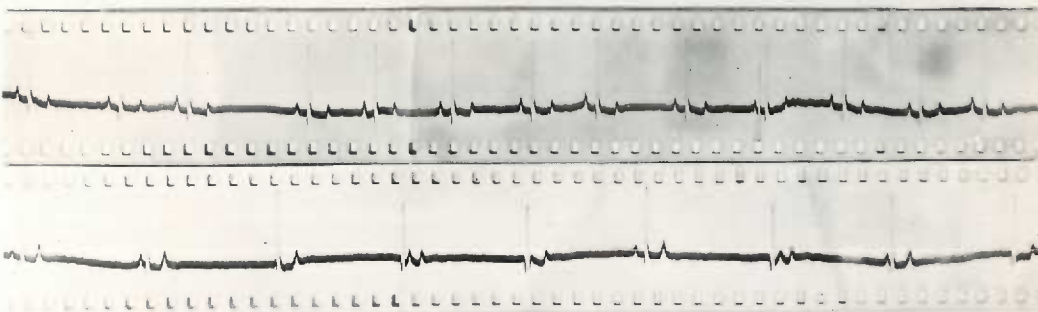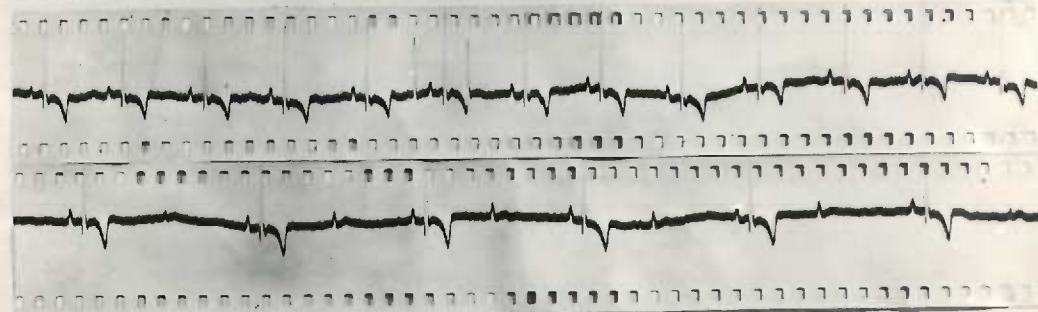neosynephrin 1-10,000 at rate of 4 cc. per minute.

Fig.2

Dog 2. Upper record : Before injection and point of onset of injection.
Lower record : A-V nodal rhythm, 90 seconds after onset of injection of
neosynephrin 1-10,000 at rate of 2 cc. per minute.

REFLEX CARDIAC DEPRESSION THROUGH LEFT VAGUS IN RESPONSE TO
HYPERTENSION INDUCED BY NEOSYNEPHRIN

Fig.3

DOG 5. Upper record : Before injection and point of onset of injection.
Lower record : 2:1 A-V heart block, 49 seconds after onset of injection
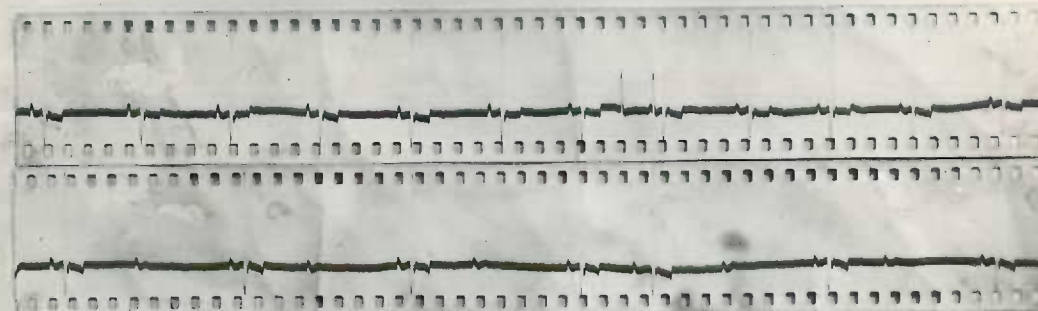of neosynephrin 1-10,000 at rate of 4 cc. per minute.

Fig.4

Dog 17. Upper record : Before injection and point of onset of injection.
Lower record : 2:1 A-V heart block, 78 seconds after onset of injection
of neosynephrin 1-10,000 at rate of 4 cc. per minute.

TABLE 1

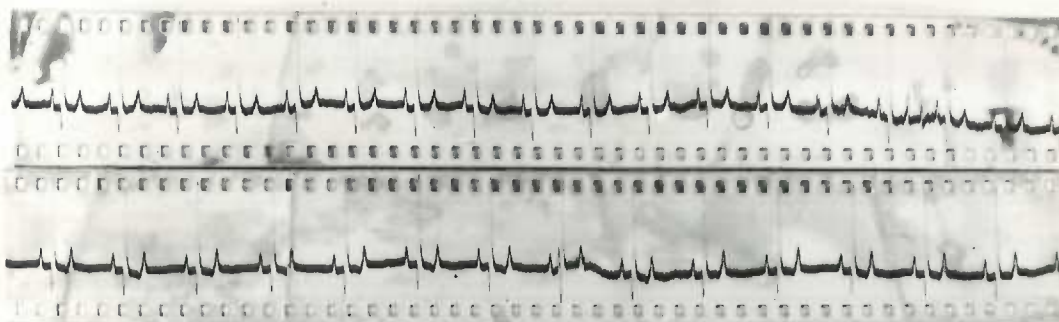# Reflex Cardiac Depression in Response to Hypertension Induced by Pitressin

Fig.5

Dog 25 - Heart denervated - Adrenals demedullated
Upper record : Before injection
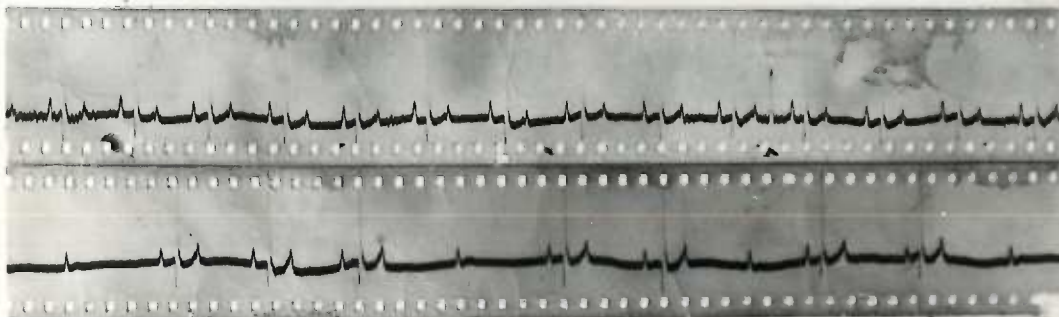Lower record : 90 sec. after i.v. injection of Pitressin 0.5 Pressor unit

Fig.6

Dog 26 - Left vagus only intact
Upper record : Before injection and point of injection
Lower record : Partial A-V block following injection of Pitressin .0625 cc.

EFFECT OF NEOSYNEPHRIN ON THE DENERVATED HEART. (Bilateral removal of the stellate and upper 5 thoracic sympathetic ganglia and section of both vagi high in the neck.
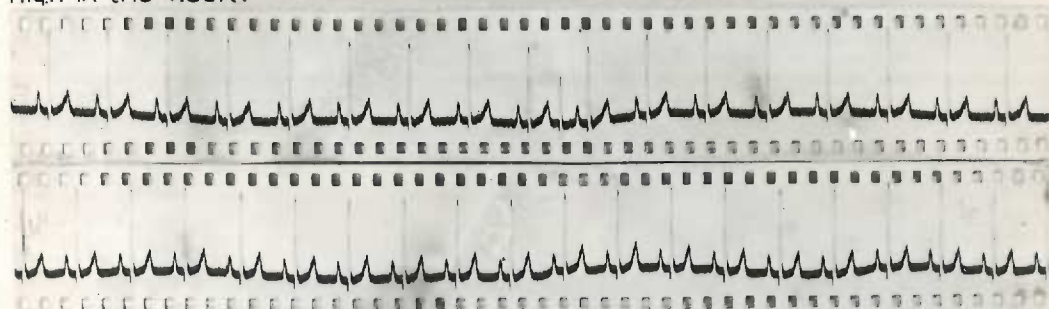

Fig.7

Dog 2. Upper record : Before injection and onset of injection of neosynephrin 1-10,000 at rate of 1cc. per minute. Rate 113 per minute.
Lower record : Moderate but definite sinus tachycardia, 60 seconds after onset of injection. Rate 128/min.

Fig.8

Dog 17: Upper record : Before injection and onset of injection of neosynephrin 1-10,000 at rate of 4 cc. per minute. Rate 120 per minute
Lower record : Tachycardia marked at 60 seconds after onset of injection Rate 150 per minute

TABLE   2