EFFECT OF CERVICO-THORACIC GANGLIONECTOMY ON THE ADRENALINE AND NORADREN ALINE CONTENT IN THE MAMMALIAN HEART

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EFFECT OF CERVICO–THORACIC GANGLIONECTOMY ON THE ADRENALINE AND NORADRENALINE CONTENT IN THE MAMMALIAN HEART [1]

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Loewi (1) in 1921 showed that after sympathetic stimulation there was released from the frog heart an adrenaline-like substance. Cannon and Lissák (2) in 1939 found that cat hearts contained a sympathomimetic substance which they concluded to be adrenaline. Shaw (3) found that mammalian heart extracts contained an adrenaline-like substance which gave an arsenomolybdate color reaction. However, since there was a slight increase of color in Shaw's reaction after adding alkali, it was apparent to him that the color was due only in part to adrenaline. Raab (4) repeating Shaw's experiments with extracts of rat and human hearts found that they contained another catechol in addition to the adrenaline. Euler (5) in 1946 using extracts prepared from cattle heart demonstrated the presence of a sympathomimetic compound which differed from adrenaline and which had the characteristics of noradrenaline. Goodall (6) in 1950 determined the quantity of adrenaline and noradrenaline in cattle heart. Subsequently Holtz, Kroneberg, and Schümann (7) and Hökfelt (8) also demonstrated the presence of adrenaline and noradrenaline in mammalian heart. Raab and Gigee (9) compared the adrenaline and noradrenaline content of normal human hearts to that of various pathological human hearts. In 1952, Outschoorn and Vogt (10) showed that, on stimulation of the cardioaccelerator nerves in the dog, noradrenaline was released in the coronary blood.

The neurohormone of the sympathetic nerves is now believed to be noradrenaline (5, 6, 10–23). Adrenaline on the other hand apparently serves the purpose of enhancing the myocardial metabolism (24–27) and increasing the cardiac rate (28–30). Both of these catechols dilate the coronary arteries (31, 32). In view of the important cardiac action of noradrenaline and adrenaline (24–37), and in view of the lack of evidence regarding cardiac sympathetic innervation, the experiments herein described were carried out with the express purpose of trying to establish and clarify the relationship of the various cardiac ganglia to the noradrenaline (norepinephrine) and adrenaline (epinephrine) content of mammalian heart, and further, to determine whether or not the sympathetic nerves to the heart regenerate after cardiac sympatho-ganglionectomy, and if so, how soon.

METHODS

The cardiac sympathetic ganglia and nerves were divided into four anatomically related groups and resected in stages accordingly; 1) right superior, middle and inferior cervical ganglia with sympathetic nerves, 2) left superior, middle and inferior cervical ganglia with sympathetic nerves, 3) right first five thoracic ganglia and sympathetic nerves, and 4) left first five thoracic ganglia and sympathetic nerves. Because of a difference in the cardiac concentration of adrenaline and noradrenaline in various animal species these experiments were performed on two widely divergent species, *i.e.*, sheep and dogs.

The operative procedure in both types of animals was essentially the same. Male and female sheep weighing 20 Kg. to 40 Kg. and dogs weighing 10 Kg. to 15 Kg. were used. All animals were anesthetized with Nembutal®. Complete cardiac sympathectomy was done in four stages (right cervical, left cervical, right thoracic, and left thoracic) with a recovery period of two to three weeks between each stage of operation. The sheep were killed after various operative combinations, some receiving only one stage operation, some two, some three and some four. Those receiving complete cardiac sympathectomy were killed at various times up to sixteen weeks post operatively. Each of the dogs received only one type (right cervical, left cervical, right thoracic or left thoracic) of operation and was killed three weeks post operatively.

(A) *Operative procedure.* To approach the cervical ganglia and sympathetic nerves an incision was made ventrally, 2 cm. to the right or left of the mid cervical line, depending on whether the right or left cervical chain was to be removed. At a point lateral and dorsal to the thyroid cartilage the sympathetic nerve separates

from the vagus nerve. It was here that the dissection of the sympathetic nerve was begun. The nerve was dissected cephalically to the superior cervical ganglion. After removing the superior cervical ganglion the dissection was extended caudally to include the middle and inferior ganglia. The position and the presence of the middle and inferior ganglia was inconstant. Similar anomalies have been noted in sheep by Waites (38) and Ellenberger (39), and described by Gillilan (40) in the human. The inferior ganglion in the sheep was often fused to the first thoracic ganglion forming the stellate, and in such a situation was removed with the cardiac thoracic ganglia and nerves. To prevent undue stimulation, the sympathetic nerves and ganglia were frequently bathed in 1 per cent xylocaine. Subsequent to closure 250,000 units of penicillin were given intramuscularly.

The approach to the right and to the left cardiac thoracic sympathetic ganglia and nerves was essentially the same. An incision was made just lateral to and parallel with the sternum, extending from the first to the seventh rib where the incision was curved dorsally. The pectoralis major and minor was divided in such a manner as to give free exposure to the second and third ribs. The periosteum of both ribs was split longitudinally and the ribs resected. On entering the pleural cavity artificial respiration was begun. The first five sympathetic thoracic ganglia and nerves were removed. The split periosteum was sutured, air removed from the pleural cavity and closure made in a routine manner. Penicillin was administered post operatively.

(B) *Preparation of extract.* Two to three weeks post operatively the animals were killed and the hearts immediately removed. The dogs were killed with a lethal dose of Nembutal® and the sheep were killed with a blow on the head immediately followed by cutting the carotid arteries. Extracts were prepared according to the method of Euler (41, 42). The whole heart was finely ground in a Waring type blendor with 10 per cent trichloroacetic acid in the ratio of 2 volumes to 1 volume of ground heart. The mixture was allowed to stand 30 to 40 minutes at room temperature and then filtered on a suction funnel. To the filtrate 20 per cent aluminum sulfate was added to the extent of 1.5 per cent of the filtrate volume. To this, 0.5 N sodium hydroxide was slowly added until pH 7.5 was reached. Precipitation began at pH 3.5 and was completed at pH 7.5. The precipitate was allowed to settle and was then filtered. After washing the precipitate twice with distilled water, the precipitate was then dissolved with 2N-sulfuric acid and readjusted to pH 3.5. To this latter filtrate was added a volume of alcohol and acetone (equal parts) four times that of the filtrate. This mixture was allowed to stand in a refrigerator (4° C.) for approximately 12 hours. Salts were then filtered off and discarded. The filtrate was concentrated *in vacuo* and adjusted to pH 3.5.

(C) *Biological assay of extracts.* Adrenaline and noradrenaline in extract may be determined if the assay is made on two different test preparations where the rela-

tive activity of these two catechols varies sufficiently, such as the cat's blood pressure and the hen's rectal caecum.

Cats were prepared in the usual manner for a blood pressure recording. The blood pressure was read from the carotid artery and injections of adrenaline, noradrenaline and heart extract were made into the femoral vein. The activity ratio of adrenaline and noradrenaline was determined at regular intervals and the heart extract assayed in terms of pure l-noradrenaline hydrochloride.

The hen's rectal caecum preparation was first described by Barsoum and Gaddum (43). Euler (44) used this method in conjunction with the cat's blood pressure for assaying adrenaline and noradrenaline. Goodall (6) used this method to determine the quantity of adrenaline and noradrenaline in cattle heart.

Two to three centimeters of the proximal portion of the rectal caecum was excised and suspended in Tyrode's solution at 39° C. The volume of the bath was 20 ml. and the load approximately 2 gm. Oxygen with 6.5 per cent CO_2 was bubbled through the solution. Injections were made into the Tyrode solution surrounding the rectal caecum. After each injection the rectal caecum was washed with fresh Tyrode solution. The effect of the injection was recorded on a kymograph. The activity ratio of pure l-adrenaline to l-noradrenaline hydrochloride was determined at regular intervals. The heart extract was assayed in terms of l-noradrenaline hydrochloride. Three to six determinations were made on each extract.

(D) *Calculation of adrenaline and noradrenaline in extract.* The method of estimating the relative amounts of noradrenaline and adrenaline in an extract depends on the use of test preparations with a sufficiently wide variance in the activity ratio of the two substances. Such is the case with the cat's blood pressure and the hen's rectal caecum. In the former the noradrenaline is two to four times more active than adrenaline, while in the hen's rectum the adrenaline is ten to sixty times more active.

Having determined the activity ratio for adrenaline and noradrenaline on the cat's blood pressure and on the hen's rectal caecum, and the activity of the extract in terms of l-noradrenaline, it is possible to calculate the relative amounts of adrenaline and noradrenaline in the heart extract.

Using the symbols below:

a = l-noradrenaline equivalents in μg. per gm. of whole heart on cat's blood pressure

A = l-noradrenaline equivalents in μg. per gm. of whole heart on hen's rectal caecum

q = activity ratio of l-adrenaline: l-noradrenaline on cat's blood pressure

Q = activity ratio of l-adrenaline: l-noradrenaline on hen's rectal caecum

The amount of l-noradrenaline and l-adrenaline in the heart extract may be calculated as follows:

$x = $ μg. of adrenaline per gm. of whole heart or $\dfrac{A-a}{Q-q}$

$y = $ μg. of l-noradrenaline per gm. of whole heart or

TABLE I

Bioassay of known solution

Test solution	a	q	A	Q	Adr. μg./ml.	Noradr. μg./ml.	Calculated % noradr.	Actual % noradr.
0.5 μg. adrenaline/ml. 2.0 μg. noradr./ml.	2.0	0.6	15	28	0.47	1.7	78.3	80
0.5 μg. adrenaline/ml. 2.0 μg. noradr./ml.	2.0	0.6	10	17	0.49	1.7	77.6	80

$$\frac{A-xQ}{x-y} = \text{per cent noradrenaline.}$$

When a known mixture of l-noradrenaline and l-adrenaline was assayed on the cat's blood pressure and the hen's rectal caecum and calculated in accordance with the above described method, the results were satisfactory. Table I shows these results.

RESULTS

A. Sheep

Table II shows the quantity of adrenaline and noradrenaline found in normal sheep hearts and in sheep hearts after removal of various groups (right cervical, or left cervical, or right thoracic

TABLE II

*Quantity of adrenaline and noradrenaline found in sheep hearts after various stages of cervico-thoracic cardiac sympathectomy ** *

Sheep No.	Type of cardiac sympathectomy	Time killed after operation (weeks)	Adrenaline (μg./gm. whole heart)	Noradrenaline (μg./gm. whole heart)
A	Control		.065	1.075
B	Control		.085	1.265
C	Control		.073	1.343
			Av. .072	1.228
1	Right sup. and mid cervical	2	.094	1.472
2	Right sup. and mid cervical	2	.032	1.580
			Av. .063	1.526
3	Right cervical	2	.026	.680
4	Right cervical	2	.038	.800
5	Right cervical	2	.071	.787
			Av. .045	.756
6	Right thoracic	2	.201	.633
7	Right thoracic	2	.123	.734
8	Right thoracic	2	.028	.236
			Av. .117	.534
9	Left cervical	2	.051	1.465
10	Left cervical	2	.129	.953
11	Left cervical	2	.063	.880
			Av. .081	1.099
12	Left thoracic	2	.074	.760
13	Left thoracic	2	.143	.972
14	Left thoracic	2	.161	1.507
			Av. .126	1.080
15	Right cervical and right thoracic	2	.039	.208
16	Right cervical and right thoracic	2	.015	.197
			Av. .027	.203

* Each figure represents average of 3 to 6 determinations.

or left thoracic) of cardiac sympathetic ganglia and nerves. This table indicates that the left cervical sympathetics have less effect than the right cervical sympathetics on the catechols of the heart, since after resection of the left cervical sympathetics neither the adrenaline nor the noradrenaline titer is significantly changed. This also holds largely true for the left thoracic cardiac sympathetics; however, in one sheep (No. 12) there was a decrease of the cardiac noradrenaline subsequent to left thoracic cardiac sympathectomy.

After removal of either the right cervical or the right thoracic cardiac ganglia and nerves, the noradrenaline titer of the heart was significantly reduced. However, in those sheep in which only the right superior and middle cervical ganglia

were removed but the right inferior cervical ganglion was not resected, there was no significant change in either the adrenaline or the noradrenaline content of the heart. When both the right cervical (including the inferior ganglion) and the right thoracic cardiac ganglia and nerves were removed, the noradrenaline content fell to approximately one-sixth of its normal level. One would therefore conclude that so far as the noradrenaline content of the sheep heart is concerned, the right inferior cervical and the right thoracic cardiac sympathetic ganglia are preeminently the most important ganglia groups in controlling the noradrenaline content of the heart.

After total cardiac sympathectomy the noradrenaline content of the heart was reduced to ap-

TABLE III

Quantity of adrenaline and noradrenaline found in dog hearts after various stages of cervico-thoracic cardiac sympathectomy *

Dog No.	Type of cardiac sympathectomy	Time killed after operation (weeks)	Adrenaline (μg./gm. whole heart)	Noradrenaline (μg./gm. whole heart)
A	Control		.014	.483
B	Control		.018	.528
C	Control		.024	.442
D	Control		.009	.512
E	Control		.013	.675
			Av. .016	.543
1	Right sup. ganglionectomy	3	.003	.650
2	Right sup. ganglionectomy	3	.026	.499
3	Right sup. ganglionectomy	3	.015	.676
			Av. .015	.608
4	Right cervical	3	.025	.185
5	Right cervical	3	.023	.214
6	Right cervical	3	.025	.172
7	Right cervical	3	.019	.208
			Av. .023	.195
8	Right thoracic	3	.026	.502
9	Right thoracic	3	.028	.421
10	Right thoracic	3	.027	.565
			Av. .027	.496
11	Left cervical	3	.010	.444
12	Left cervical	3	.016	.632
13	Left cervical	3	.012	.684
			Av. .013	.587
14	Left thoracic	3	.045	.515
15	Left thoracic	3	.039	.654
16	Left thoracic	3	.021	.498
			Av. .035	.556

* Each figure represents average of 3 to 6 determinations.

TABLE IV

Quantity of adrenaline and noradrenaline found in sheep hearts subsequent to total cardiac sympathectomy and after varying post operative periods *

Sheep No.	Type of cardiac sympathectomy	Time killed after operation	Adrenaline (μg./gm. whole heart)	Noradrenaline (μg./gm. whole heart)	Percentage noradrenaline (%)
	Control		.072	1.228	94.4
1	Total cardiac sympathectomy	3 weeks	.008	.133	94.3
2	Total cardiac sympathectomy	3 weeks 5 days	.014	.250	94.6
3	Total cardiac sympathectomy	5 weeks	.086	.575	86.9
4	Total cardiac sympathectomy	5 weeks 4 days	.137	.509	78.7
5	Total cardiac sympathectomy	7 weeks 4 days	.070	.418	85.6
6	Total cardiac sympathectomy	11 weeks	.044	.833	94.9
7	Total cardiac sympathectomy	16 weeks	.075	1.195	94.0

* Each figure represents average of 3 to 6 determinations.

proximately one-sixth of its normal level (see Table IV). Table IV also indicates that around five weeks after total cardiac cervico-thoracic ganglionectomy the noradrenaline of the sheep heart began to rise and by sixteen weeks had returned to normal.

As for the relationship of these cardiac sympathetic ganglia groups to the adrenaline content of the sheep heart, it appears that a decrease in adrenaline does not occur regularly. Therefore, it would seem that the cardiac sympathetics *per se* would have no effect upon the adrenaline content of the heart.

B. Dog

Because of the diversity in the absolute quantities of adrenaline and noradrenaline in the hearts of animals of different species, and because of the anatomical similarity of dog cardiac sympathetics to those of man, it was felt that the quantity of adrenaline and noradrenaline in the dog heart, subjected to the same operative procedures as described for the sheep, should also be determined. Table III indicates the amounts of adrenaline and noradrenaline in the hearts of normal dogs and in the hearts of dogs subjected to various cervical and thoracic cardiac sympathetic ganglionectomies. The control values of adrenaline and noradrenaline in dog hearts were approximately one-third that of the sheep hearts.

Of the four cardiac ganglia groups herein described, the right cervical sympathetic ganglia appeared to be the only ganglia group which had any significant effect upon the noradrenaline con-

tent of the dog heart. Subsequent to removal of the right cervical sympathetic ganglia the noradrenaline content of the heart fell to approximately one-third of its normal level. However, removal of the right superior cervical ganglion did not produce a change (see Table III). Therefore, it then follows that extirpation of the right inferior cervical ganglion, including the middle cervical ganglion when present, alone must be chiefly responsible for this fall in the cardiac noradrenaline titer. This especially seems true in that resection of the right thoracic ganglia did not produce this change nor did resection of the left cervical or left thoracic ganglia.

DISCUSSION

From these results one would deduce that in the dog the right inferior cervical ganglion, including the middle cervical ganglion when present, appears to be the ganglia group most responsible for the control of noradrenaline in the heart, since after the removal of this ganglia group the cardiac noradrenaline fell to approximately one-third of its normal level. This probably means that there are more sympathetic fibers reaching the coronary arteries and heart proper from or via the right inferior cervical ganglion and right middle cervical ganglion when present than from the other cardiac ganglia.

In the sheep, however, a somewhat different situation appears for here both the right inferior cervical ganglion and the right thoracic ganglia are the ganglia groups which influence the noradrenaline content of the heart to the greatest ex-

tent. Since removal of the right superior and middle cervical ganglia alone did not produce such a fall in the noradrenaline, this would then lead one to believe that the right inferior cervical ganglion was the ganglia group in the cervical chain which influenced most the noradrenaline content of the sheep heart. In that in sheep the inferior cervical ganglion and the first thoracic ganglion are in close proximity and often fused as a single ganglion, the cervico-thoracic ganglion (stellate), one could conclude in such a situation that the right stellate is the ganglion most responsible for the control of noradrenaline in the sheep heart.

Also in the sheep the left cervical and the left thoracic sympathetics appeared to have some influence on the noradrenaline content of the heart, but in terms of cardiac noradrenaline the degree of influence was far less on the left side than on the right (see Table II). The fact that the noradrenaline content of the sheep heart after total cervico-thoracic sympathectomy approximates the noradrenaline content of the heart after right cervical and right thoracic cardiac sympathectomy is also supportive evidence that the left cervical and left thoracic sympathetics have considerably less effect upon the heart than the right cardiac sympathetics (see Table II and Table IV).

In sheep approximately five weeks after total cardiac cervico-thoracic ganglionectomy the noradrenaline of the sheep heart began to rise and by sixteen weeks had returned to normal (see Table IV). The rise in noradrenaline is probably due to the regrowth of new sympathetic nerves taking over the function of the extirpated nerves. These new nerves probably reach the heart as post ganglionic fibers from the ganglia below those resected. Haimovici and Hodes (45) gave evidence of regeneration after removal of both sympathetic chains. Simmons and Sheehan (46), as well as Smithwick (47) have all reported instances of sweating and vasomotor constriction recurring after cervico-thoracic ganglionectomy.

The fact that the rise in cardiac noradrenaline begins about five weeks after sympathectomy and is normal by sixteen weeks fits well with the evidence given by Grimson, Wilson, and Phemister (48), who observed that after complete sympathectomy in dogs there was some recovery of reflex control of the blood pressure a few weeks after

sympathectomy and complete recovery by six months. Euler and Purkhold (22) also showed that after sympathetic denervation of the spleen, kidney, and salivary gland the sympathetic nerves regenerated in three to four months. In that the heart is not far distant from a possible sympathetic regenerative source, namely the remaining thoracic sympathetic ganglia, it follows that new sympathetics could reach the heart within a period of two to four months.

SUMMARY

1. Normal sheep and dog hearts were assayed for adrenaline and noradrenaline. The sheep hearts contained an average of .072 μg. of adrenaline and 1.228 μg. of noradrenaline per gram of whole heart. The dog hearts contained an average of .016 μg. of adrenaline and .543 μg. of noradrenaline per gram of whole heart.

2. Sheep and dogs were subjected to various stages of cardiac sympatho-ganglionectomy, *i.e.,* right cervical, left cervical, right thoracic and left thoracic.

3. In sheep the right cervical and right thoracic cardiac ganglia were the cardiac ganglia that influenced to the greatest extent the noradrenaline content of the sheep heart. Upon removal of either of these ganglia groups the cardiac noradrenaline was reduced to approximately one-half and if both groups were removed the noradrenaline titer was reduced to about one-sixth of the normal level, or to an amount approximating that of a sheep heart after total cardiac sympathectomy.

4. In dogs the right cervical cardiac ganglia were the only cardiac ganglia that significantly influenced the noradrenaline content of the heart. Upon removal of this ganglia group and more specifically after resection of the right inferior and middle cervical ganglia, the cardiac noradrenaline was reduced to approximately one-third of its normal level.

5. In both dog and sheep, removal of the cardiac sympathetics had no consistent effect upon the adrenaline content of the heart.

6. After total cardiac sympatho-ganglionectomy in sheep, the heart in terms of noradrenaline content showed signs of sympathetic regeneration five weeks post operative and complete regeneration in 16 weeks.

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