A Method for Producing Chronic Cardiac Failure in Dogs.* (17595)

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The difficulty of producing slowly progressive, chronic, congestive failure in lower animals has retarded the analysis of the factors involved in the pathogenesis of cardiac failure. Acute decompensation has been produced by a number of methods (see Roos and Smith(1), but attempts to simulate the chronic form have met with limited success.(2-4) Many workers have found that if the heart were sufficiently damaged to produce overt decompensation, the animals would die acutely, whereas lesser grades of damage were not followed by failure at rest. However, Landis *et al.*(5) have shown in acute experiments that minor decreases in cardiac competence, which are not apparent at rest, may lead to elevations of central venous pressure during exercise, with its increased venous return. They have suggested that these transient elevations of venous pressure during muscular activity may play an important role in the development of the signs and symptoms of congestive failure.

In order to investigate this relation between cardiac competence, exercise and venous pressure in the unanesthetized animal we have studied the changes of auricular pressure of dogs during exercise on the treadmill before and after the production of experimental cardiac damage. In the initial approach to this problem the operative lesions were limited to the right side of the heart. The following lesions were produced: (a) insufficiency of the pulmonary valve, (b) stenosis of the pulmonary artery,(6) (c) the combination of pulmonary stenosis and pulmonary insufficiency, (d) insufficiency of the tricuspid valve, and (e) the combination of tricuspid insufficiency and pulmonary stenosis. During the course of this study, which will be reported fully at a later date, it was found that chronic, congestive failure resulted from the combination of tricuspid insufficiency and pulmonary stenosis. Three dogs so treated developed cardiac failure, whereas the other lesions did not lead to overt decompensation, even with strenuous exercise. This paper describes the method for producing a form of chronic, "right-sided" cardiac failure. The salient data from the experiments on those dogs that developed congestive failure are also briefly presented.

Methods. Each dog was trained and conditioned on the treadmill with repeated observations of his work tolerance. Then, a standard control experiment was performed for comparison with the postoperative response under the same work conditions. A radiopaque catheter was inserted into the auricle through a cannula in the external jugular vein. The tip of the catheter, located fluoroscopically, was used as the zero reference point. Mean right auricular pressure was measured with a water manometer. Heart rate was recorded by a cardiotachometer. The dogs were exercised on the treadmill for successive 10-minute periods at increasing speed and grade (bottom Fig. 1) until exhausted.

Following one or more control experiments, insufficiency of the tricuspid valve was produced in each dog under nembutal anesthesia, and during positive pressure respiration. In 2 of the dogs the left thorax was entered through the fourth interspace, the heart rotated slightly to the left, purse-string sutures placed in the

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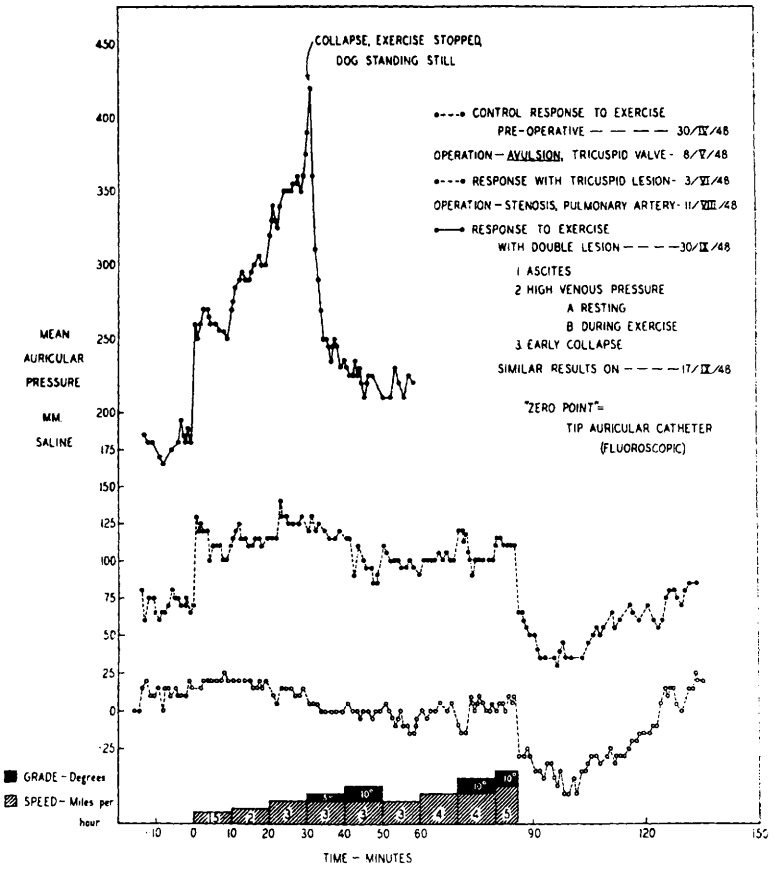

FIG. 1.

Chart showing representative changes in right auricular pressure (mm saline) during exhausting exercise. (Dog No. 2.)
A. (lower curve) Normal dog (preoperative).
B. (middle curve) Same dog following tricuspid valve avulsion.
C. (top curve) Same dog following subsequent pulmonary stenosis.

right ventricular myocardium, and a small incision made. A curved valvulotome was inserted through the incision, and the leaflets of the tricuspid valve were cut blindly. The myocardium was then closed with a mattress suture. In one dog (No. 1) a more satisfactory approach was made through the 4th interspace on the right. Purse-string sutures were placed on the right auricular appendage, and an incision made for the passage of the valvulotome. The instrument was introduced into the right ventricle through the auriculoventricular orifice and the cusps of the tricuspid valve avulsed. The animals were up and active 8 to 12 hours after operation and had uneventful recoveries.

After operation the dogs were allowed a 3-week period of recovery before a postoperative experiment was performed on the treadmill under the same conditions as the control run. After this the dogs were given daily bouts of strenuous exercise for 3 months or more, and at least one more standard treadmill experiment performed before the second operation.

The main pulmonary artery was stenosed according to the method of Hufnagel *et al.*(6) The left thorax was entered through the 4th interspace. The pulmonary artery was dissected free and a special clamp placed on the artery occluding the desired amount of the vessel (approximately 50% of the diameter in these operations). A running mattress suture was then placed along the proximal

TABLE I.
Mean Right Auricular Pressure and Heart Rate in Normal Dogs (A), and in the Same Dogs Following Tricuspid Valve Avulsion (B), and Superimposed Pulmonary Artery Stenosis (C).

Dog	Mean right auricular pressure (mm saline)			Heart rate per min.		Reduction in work tolerance
	Standing at rest on treadmill	Onset of exercise	At exhaustion	Standing at rest on treadmill	Max. heart rate	
			A. Control.			
1.	0	—10	0	85	?	0
2.	15	20	10	115	295	0
3.	0	50	—60	100	215	0
			B. Tricuspid valve avulsion.*			
1.	125	160	230	160	250	0
2.	70	125	110	125	275	0
3.	100	135	190	125	280	0
			C. Pulmonary stenosis (50% of diameter occluded).			
1.	225	310	310†	185	195	marked
2.	180	260	420	180	195	moderate
3.	175	215	335	130	250	moderate

* The extent of valvular damage determined at autopsy was: Dog No. 1, 2 cusps destroyed, 3rd damaged; Dog No. 2, 1 cusp destroyed, 1 damaged; Dog No. 3, 3 cusps damaged only.
† Collapsed after 2 min. at 2 M.P.H. on the level.

edge of the clamp. The segment of the wall thus separated from the lumen of the pulmonary artery was then resected, leaving a tapered area of stenosis. Frequent extrasystoles were noted for the first 24 to 48 hours postoperatively, but recovery was uneventful otherwise.

Observations. In the normal dog, as shown in the lowest curve of Fig. 1, auricular pressure remained constant or decreased slightly during periods of increasing exercise, with a sharp drop immediately after exercise. Following tricuspid avulsion right auricular pressure was moderately elevated at rest (Fig. 1, middle curve), rose further with the onset of exercise, but otherwise the changes in auricular pressure were similar to those of the control experiment in the example illustrated, though at a higher level throughout. The mean auricular pressure in the other 2 dogs rose 55 to 70 mm above that at the onset of exercise (Table I). None of the dogs at this stage had any detectable reduction in work tolerance, nor did any other evidence of failure appear, despite daily bouts of exhausting exercise for 3 months or more.

When the dogs with insufficiency of the tricuspid valve were subjected to stenosis of the pulmonary artery in addition, a further rise of resting auricular pressure occurred (Fig. 1, top curve and Table I.) With the onset of the mildest grade of exercise auricular pressure rose considerably, and then rose to still higher levels with each added increment of work, reaching the remarkable height of 420 mm saline before the animal collapsed at the relatively light work load of 3 miles per hour and 5° grade. Heart rate was rapid before exercise, and only rose 15 beats a minute during exercise (Table I). Similar results were obtained in the other 2 dogs (Table I).

All 3 dogs with tricuspid regurgitation and pulmonary stenosis developed a syndrome similar to chronic, congestive failure and characterized by markedly elevated auricular pressures and distended veins, decreased work tolerance, hepatomegaly, ascites, tachycardia at rest, and a relatively fixed heart rate during exercise. The rate at which cardiac failure progressed varied from animal to animal. Ascites was noted in dog No. 1 within 2 weeks of pulmonic stenosis, and while he was still restricted to his cage. His work tolerance was extremely limited, and he collapsed after 2 minutes at 2 miles per hour on the level. Dog No. 2 developed ascites one month postoperatively, after several days of mild exercise. Dog No. 3, whose work tolerance was reduced less than the other dogs postoperatively, did not develop ascites until 6 weeks after operation, and then only after daily exhausting exercise.

For additional evidence that the syndrome was due to cardiac insufficiency, 2 of the dogs were sacrificed for study in heart-lung preparations. Cardiac output was low for both hearts. To obtain cardiac outputs approaching the normal range for fresh heart-lung preparations required extremely high auricular pressure, *e.g.*, 150 to 200 mm of saline. Calculation of the "competence index"(7) also indicated marked cardiac impairment.

The animals were sacrificed 1½ to 3 months after pulmonary stenosis was produced. Autopsies revealed dilatation and hypertrophy of the right auricle and ventricle in each dog. The pleural cavity was dry and the lungs normal. The liver was markedly enlarged and congested, and 2 to 5 liters of serosanguinous fluid were found in the peritoneal cavity.

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Summary. A form of progressive, chronic, "right-sided" cardiac failure has been produced in dogs by tricuspid valve avulsion and pulmonary artery stenosis. Three dogs so treated developed congestive failure with elevated auricular pressure and distended veins, decreased work tolerance, hepatomegaly, ascites, tachycardia at rest, and a relatively fixed heart rate during exercise. Studies of 2 of the hearts in the heart-lung preparation indicate clearly that cardiac insufficiency was present.

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Thyroid Function in the Alarm Reaction. (17596)

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The response of the body to stress of various kinds has received considerable attention in recent years; the majority of investigations have been concerned with the role of the pituitary-adrenocortical system under such conditions. It appeared *a priori* probable that the pituitary-adrenocortical system would not be the only one involved. Some rather specific forms of stress, "alarming stimuli", are quite well known to involve also the pituitary-thyroid system, *e.g.* reduced oxygen pressure (high altitude), and changes of environmental temperature. In an interesting and stimulating speculation, Means(1) considered the possibility that Graves' disease might in some way be related to an alarm reaction, a thought which he discusses in the first edition of his monograph. However, this speculation appears to have lost its appeal to its author, because it is omitted from the second edition. We decided to investigate the response of the thyroid to alarming stimuli. While our work was in progress, two reports on this subject appeared,(2,3) indicating the general interest in the complicated response to stress on the one hand, and in the adrenocortical-pituitary-thyroid interrelationship on the other hand.

Materials and methods. A total of 106 adult male rats was used in this study. Animals were kept on a stock diet of Purina dog chow. Intramuscular injection of 10% formalin was used as the stress or alarming stimulus. Thyroid function was gauged by uptake of tracer doses of I-131.* The latter

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