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Effect of Digitoxin on Hypoxia-Produced Cardiac Hypertrophy in Rats[1] (37781)

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The influence of digitalis on cardiac hypertrophy has been of interest for many years. Christian (1) in 1933 wrote that he firmly believed that digitalis administered daily to patients who had enlargement of the heart produced beneficial effects. He maintained that cardiac enlargement is functionally harmful and that digitalis not only retards cardiac enlargement, but delays the appearance of symptoms and signs of cardiac insufficiency. His observations obviously were of a clinical nature and were not substantiated by objective data.

Williams and Braunwald (2) in 1965 produced data tending to support Christian's thesis. They reported that digitoxin administered to rats in which the aorta was experimentally restricted developed a significantly lesser degree of myocardial hypertrophy than in those which had not received digitoxin. It was deemed worthwhile to study the effect of digitoxin further by employing a more physiologic method of producing cardiac hypertrophy, namely, hypoxia, rather than one of restricting the circulation in any way.

Materials and Methods. One hundred Sprague–Dawley albino rats (235 g) were used in this study. They were fed a diet of Purina chow *ad libitum* and kept in an air-conditioned room at a constant temperature of 75° F. They were originally divided into four groups of 25 each as follows: group I served as control animals and were injected daily with the vehicle used to dissolve the digitoxin (2.5 parts ethanol, 1.5 parts glycerine, and 1 part water). Group II was also injected daily with the vehicle, but subjected to a simulated altitude; group III was injected intramuscularly with 0.9 mg/kg digitoxin (in the vehicle), and group IV was likewise given digitoxin, but subjected to altitude.

In order to produce hypoxia the animals were placed in a respiratory chamber and exposed to a simulated altitude of 24,000 ft (7135 m), corresponding to a pressure of 294.4 mm Hg for 8 hr a day for 3 weeks. In order to acclimatize the animals a period of 6 days was used to reach the desired altitude. They were first exposed to a simulated altitude of 14,000 ft (4267 m) and each day the altitude was raised 2000 ft until 24,000 ft had been gained.

At the end of the experiment, in order to ascertain the existence of cardiac hypertrophy, the rats were weighed and decapitated. The hearts were then removed, trimmed, washed with tap water, blotted, and weighed; they were then partitioned by the method outlined by Keen (3). Each ventricle was weighed separately and the weight recorded.

Results. Table I shows the affect of digitoxin on cardiac hypertrophy after exposure to altitude. It will be observed that exposure to altitude produces a significant degree of hypertrophy of both the left and right ventricles ($P<.001$). Those animals, however, which were given digitoxin and then exposed to altitude showed no significant hypertrophy of the left ventricle ($P<0.55$). The right ventricle showed approximately the same degree of hypertrophy. On the whole, the right ventricle showed proportionally a greater degree of hypertrophy than the left, both at altitude

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TABLE I. Effect of Digitoxin on Cardiac Hypertrophy After Exposure to Altitude.

	Number of rats	Body wt. (g)	Heart wt.[a] (g)	*P*	Left vent. wt.[a] (mg)	*P*	Right vent. wt.[a] (mg)	*P*
Control	25	308	1.090 ± 0.088		567 ± 63		214 ± 23	
				.001		.001		.001
Altitude	24	269	1.250 ± 0.129		633 ± 89		282 ± 31	
Control	25	308	1.090 ± 0.088		567 ± 63		214 ± 23	
				.02		.55		.001
Altitude + digitoxin	24	297	1.169 ± 0.098		574 ± 48		292 ± 32	

[a]Values are mean ± standard deviation.

and when exposed to altitude plus digitoxin. This is due primarily to the increased pulmonary arterial hypertension produced by hypoxia.

Discussion. It probably would be expected that cardiac hypertrophy produced by hypoxia is greatly lessened by administration of digitoxin, because it is known that this drug reduces the amount of cardiac hypertrophy when the aorta is experimentally constricted. Digitoxin, however, apparently affected only the left ventricle since the right ventricle showed a significant hypertrophy. This is difficult to explain. It is known that during exposure to hypoxia the right ventricle hypertrophies proportionally more than the left, due to a marked increase in pulmonary arterial hypertension which accompanies hypoxia. Apparently digitoxin did not significantly lower this arterial resistance.

The mechanism by which digitoxin decreases hypertrophy of the left ventricle is not entirely known, but presumably the glycoside lessens the hemodynamic burden of the heart. It is known that the contractile force of the ventricle is increased by cardiac glycosides, so that the capacity of cardiac muscle to do work is increased. It has also been shown that cardiac glycosides increase the capacity of the contractile proteins for converting energy into mechanical work.

Summary. Administration of digitoxin prevented hypertrophy of the left ventricle of the rat during exposure to hypoxia. The right ventricle was not affected by the drug and showed a significant degree of hypertrophy. Presumably digitoxin greatly lessened left ventricular hypertrophy by increasing the capacity of cardiac muscle to do work.

1. Christian, H. A., J. Amer. Med. Ass. **100**, 789 (1933).

2. Williams, J. F., Jr., and Braunwald, E., Amer. J. Cardiol. **16**, 534 (1965).

3. Keen, E. N., J. Anat. **89**, 484 (1955).

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