Proceedings of the Iowa Academy of Science

Volume 67 | Annual Issue Article 59

1960

Direct and Indirect Measurements of Arterial Blood Pressure in Normal and Propylthiouracil-treated Rats

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Direct and Indirect Measurements of Arterial Blood Pressure in Normal and Propylthiouracil-treated Rats[1]

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Abstract. Systolic and diastolic blood pressures were lowered in male rats by treatment with 0.1 percent dietary propylthiouracil for a period of ten to twelve weeks. At the best comparison levels systolic pressure measurements of experimental rats dropped 15.0 percent by the indirect method and 26.9 percent by the direct method when compared to the levels of control rats. The diastolic values of experimental animals dropped 18.3 percent as measured by the indirect method and 28.9 percent as measured by the direct method when compared to controls. Thus, the hypothyroid state induced by the drug propylthiouracil is accompanied by reduced systolic and diastolic blood pressures.

The antithyroid drug, propylthiouracil (PTU), prevented in rats the elevated blood pressure associated with bilateral encapsulation of the kidneys with latex envelopes, and reduced the elevated blood pressure of rats whose kidneys were encapsulated nine weeks previously (Fregly, 1958). PTU also reduced the blood pressure of control rats (Fregly, 1958). The measurements were indirect systolic pressures obtained both by means of the microphonic manometer technique (Friedman and Freed, 1949), but without anesthesia (Fregly, 1954), and the technique of Alexander (1957).

The reduction in blood pressure of rats by propylthiouracil treatment could occur as a result of either decreased cardiac output or decreased peripheral resistance, or both. Measurement of diastolic blood pressure as a criterion of peripheral resistance seemed worthwhile in order to assess the level of activity of the drug. In this study, both indirect and direct blood pressure measurements were made and correlated.

METHODS

Seventeen male rats of the Holtzman strain were used. They were twenty-six to thirty-one weeks old at the beginning of any experimental phase and were kept in a thermoregulated room maintained at 25 ± 1° C. and illuminated from approximately 8:00 A.M. to 5 P.M. Control animals were fed finely ground Purina laboratory chow as well as pellets. Experimental animals were given 0.1 per-

[1]This research was supported by a grant from the Iowa Heart Association to Dr. Kenneth M. Cook, Department of Biology, Coe College, Cedar Rapids, Iowa.

cent PTU[2] mixed thoroughly in the ground laboratory chow. All animals were given tap water to drink. Body weights of the animals were measured weekly.

Direct measurements following the technique of D'Amour and Blood (1954, Experiment 10) were performed first on five normal animals and five animals fed 0.1 percent PTU for ten to twelve weeks. Later the pressures of two normal and three PTU-treated animals were measured by this technique. All the animals used are treated in this paper as one group.

The direct measurement procedure involved carotid artery cannulation with fluctuations of systolic and diastolic pressures being recorded through a double membrane, saline-filled system onto a moving kymograph drum. A pneumograph, attached to a separate membrane, was placed around the thorax of the rat and calibrated kymograph paper was used. Thus, systolic and diastolic pressures, heart rate, and respiratory rate were recorded simultaneously. To anesthetize the rats a basic dose of 50 mg. of Nembutal per kilogram of body weight was administered subcutaneously.

Seven animals (three normal diet and four fed 0.1 percent PTU for ten weeks) were used for the indirect determinations following the tail plethysmograph technique as illustrated by D'Amour and Blood (1954, Experiment 21). Weekly measurements of all animals were taken during a two week control period and throughout the experimental period. The tail plethysmograph method was modified to obtain more satisfactory air and water seals and a more adequate

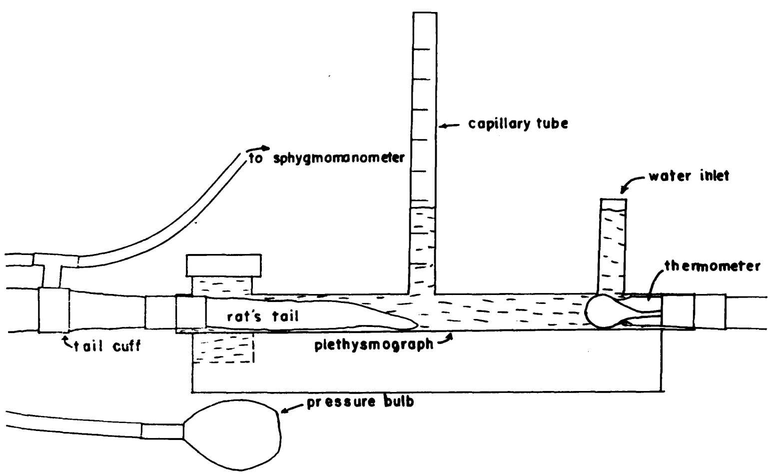

Figure 1. The plethysmograph with the rat's tail inserted and the pressure cuff wrapped around the tail.

[2]6-n-propyl-2-thiouracil, Nutritional Biochemicals, Co., Cleveland, Ohio.

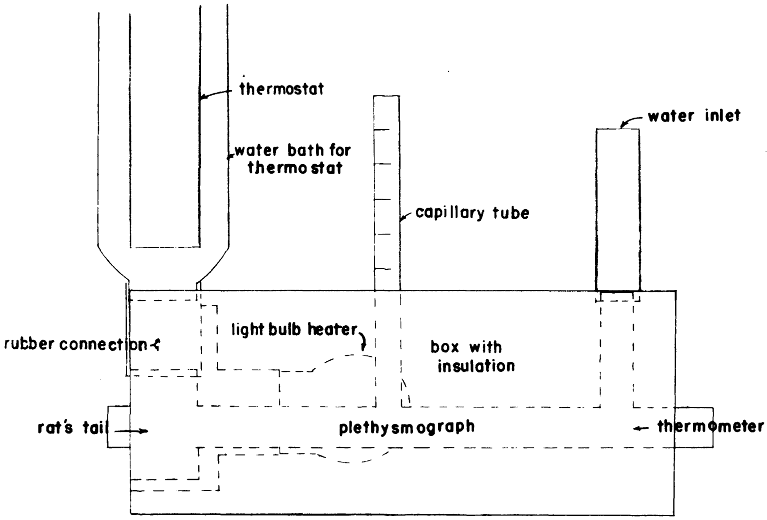

Figure 2. The apparatus showing plethysmograph and attached thermostat in the insulated box.

thermostatically controlled heating arrangement for the rat's tail. These modifications are shown in Figures 1 and 2.

As noted, the packing gland of the plethysmograph was attached to the inlet of a water-tight plastic bottle cut off at the opposite end. A partial subsurface aquatic thermostat[3] was inserted into the cut end of the bottle. The plethysmograph was placed into an insulated box containing a 15-watt light bulb. The thermostat was wired in series with the light bulb and a 120 volt source but was not connected to the voltage source until water previously warmed to 45° C. was poured into the plethysmograph and plastic bottle holding the thermostat. The thermostat was then connected and set at 42 ± 2° C.

After the animal, unanesthetized but in a holder, had been placed in the apparatus, the warmed water was poured in, the thermostat was set, and several minutes were allowed for the vessels in the tail to expand. A pressure of 150 mm. Hg was forced into the tail cuff and then gradually released. The capillary tube of the plethysmograph was watched closely, and when the water suddenly started to rise the manometer reading was taken as the systolic pressure. The gradual release of pressure in the cuff was continued until a cessation of water rise was noted and the manometer read, and then the release of pressure was completed. This procedure was performed as many times as necessary for good agreement between consecutive readings. Occasionally, however, animals became disturbed after one reading and had to be removed from the apparatus.

[3]Fenwal Thermoswitch, Fenwal, Inc.

Although there is no mention made in the reference used (D'Amour and Blood, 1954, Experiment 21) as to the interpretation of the cessation of water rise, it has been interpreted here as an indication of the diastolic pressure. However, it was much more difficult to obtain 'diastolic' values in animals with normal diet than in PTU-diet animals. Attempts were made to perform direct and indirect methods simultaneously for calibration purposes, but this proved too difficult. Direct determinations were later made on those animals whose blood pressure had been measured indirectly, so as to compare direct and indirect results.

Results

Weekly body weight measurements for normal and PTU-diet male rats in both experiments are shown in Table 1. There was either a slight increase in weight or a decrease in weight for PTU-treated animals, whereas normal animals showed an increase in average body weight.

Table 1

Effect of 0.1 Percent Propylthiouracil (PTU) Diet on Body Weights

Method Determination	Experimental Condition	No. of Rats	Initial Mean Body Weight (Gms)	Final Mean Body Weight (Gms)	Percent Increase in Body Weight
Direct:	Normal Diet	5	393.4	492.5	20.1%
	0.1% PTU Diet	5	395.4	395.0	– 0.1%
Indirect:	Normal Diet	3	319.9	406.4	21.3%
	0.1% PTU Diet	4	310.3	325.1	4.6%

In the direct method the curves obtained by the pressure recording stylus on the kymograph drum demonstrated a larger fluctuation due to the respiration pressure variations on the blood vessels of the thorax and also a fluctuation of the pulse seen within the larger respiratory curve. In Figure 3 the respiratory pressure wave is exaggerated for illustrative purposes.

The systolic pressures were read from the crests of the smaller waves (arterial pressure) and the diastolic pressures from the troughs of the waves. The difference between systolic and diastolic pressures gives the pulse pressure, and the diastolic pressure plus one-third of the pulse pressure gives the mean arterial pressure. By counting the individual fluctuations, the heart rate can be determined. Breathing rates were taken directly from the kymograph recording of the thorax pneumograph. The results of all direct measurements taken are summarized in Table 2.

Table 2

Direct Measurements

Control Rats	Systolic Pressure	Diastolic Pressure	Mean Pressure	Pulse Pressure	Heart Rate/Min.	Respiration Rate/Min.
No. 3	106.0	103.0	104.0	3	499.0	—
No. 4	139.0	136.0	137.0	3	386.0	123.0
No. 26	145.0	141.0	142.3	4	450.0	67.0
No. 44	126.0	124.0	124.7	2	426.0	86.0
No. 45	153.0	150.0	151.0	3	558.0	94.0
No. 74	134.0	132.0	132.7	2	458.0	112.0
No. 75	117.0	115.0	115.7	2	432.0	121.0
Average	131.4	128.7	129.6	2.9	458.4	100.5
Propylthiouracil						
No. 1	128.0	122.0	124.0	6	294.0	63.0
No. 5	84.0	79.0	80.7	5	284.0	52.0
No. 6	76.0	70.0	72.0	6	284.0	68.0
No. 47	113.0	109.0	110.3	4	352.0	79.0
No. 48	73.0	69.0	70.3	4	374.0	82.0
No. 49	119.0	116.0	117.0	3	326.0	98.0
No. 70	97.0	92.0	93.7	5	285.0	78.0
No. 71	79.0	75.0	76.3	4	310.0	79.0
Average	96.1	91.5	93.0	4.4	313.6	74.9

The propylthiouracil rats showed a 28.2 percent decrease in mean pressure with 26.9 percent decrease in systolic and 28.9 percent decrease in diastolic pressures. The average pressure of the treated rats was 96.1/91.5 mm.; the control rats had a much higher average of 131.4/128.7 mm. As a consequence, of course, the mean and pulse pressures also differed in the two groups. The average heart rate of propylthiouracil rats was much lower (314 beats/minute) than that of the controls (458 beats/minute).

The indirect pressure measurements are plotted in Figure 4. (As previously mentioned, diastolic pressures were more difficult to obtain in normal than PTU animals. Therefore, the plots for control period weeks 1 and 2 and experimental period weeks 3, 6, and 7 represent only one animal.) As noted, systolic and diastolic pressures agree well for PTU and control animals in the two week control period, but both pressures reached a lower value for PTU-treated animals during the third week experimental period and remained substantially at these levels for the remainder of the experiment. Thus, control animals had nearly constant values over the course of the

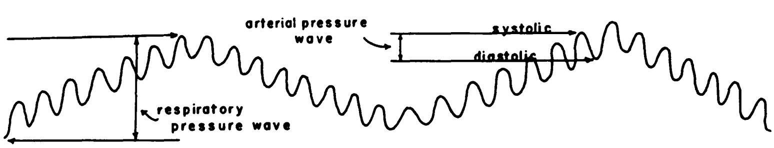

Figure 3. A pressure curve showing the greater respiratory wave and smaller arterial fluctuations.

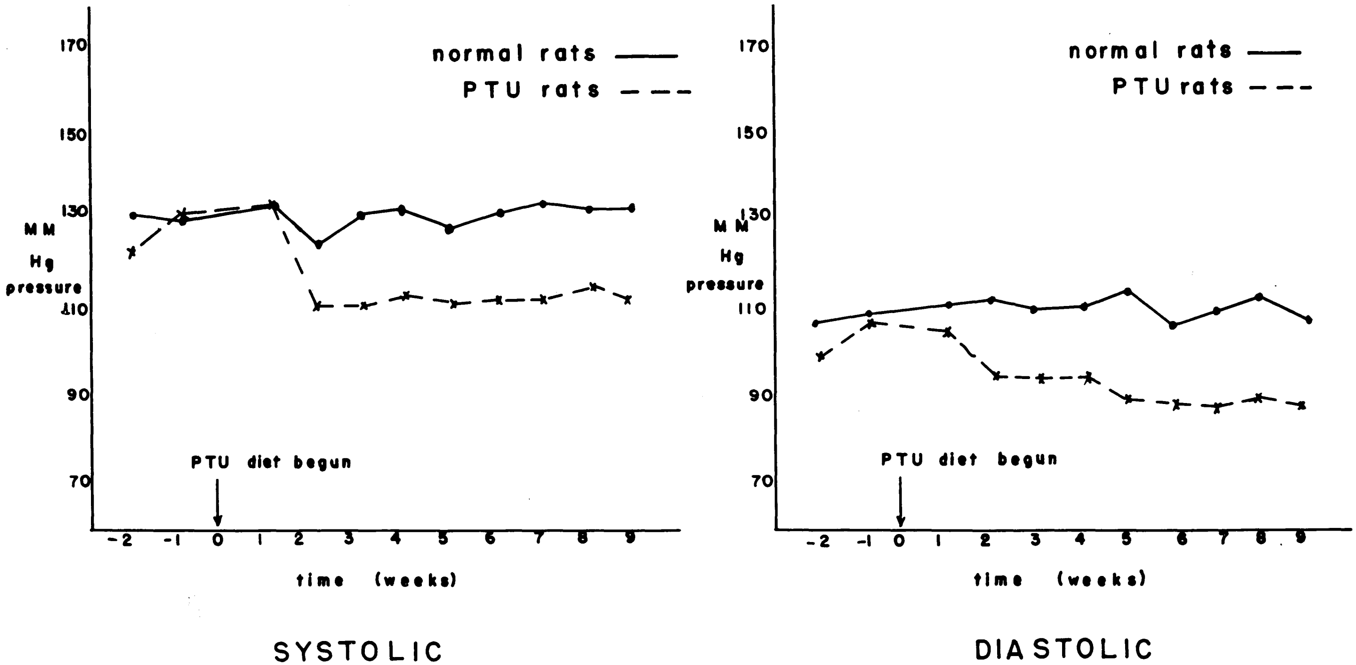

Figure 4. Weekly results from indirect measurements.

experiment, approximately 133/113, systolic over diastolic, whereas values of PTU-treated rats dropped from 133/106 during the second week of the control period to 112/96 the third week of the experimental period. This represents a 15.0 percent decrease in systolic pressure and a 9.4 percent decrease in diastolic. There appeared to be a further decrease in diastolic pressure (total 18.3 percent) over the experimental period for PTU animals, but the systolic average remained essentially the same.

Comparisons of the results obtained for animals which were part of the indirect measurement group and were later used for direct measurement are given in Table 3. Only the last indirect measurements made (tenth week) are compared to the direct results in this table.

Discussion

The loss or slight increase in body weight of PTU-treated animals as compared to normals is substantially in agreement with other investigations (Fregly, 1958; Cook, 1960). In addition, it has been demonstrated (Cook, 1960) that male rats given 0.1 percent dietary PTU for ten weeks have a decrease in oxygen consumption of about 23 percent at the tenth week of treatment. The lowered heart and respiratory rates are also indicative of lowered metabolism.

Systolic blood pressures of normal rats as obtained by both the direct and indirect methods compare favorably with the indirect measurements of Fregly (1958) and Alexander (1957). The lowered systolic pressures obtained for PTU-treated rats by the indirect method are also in good agreement with those obtained by Fregly (1958). In addition, 'diastolic' pressures for PTU-treated animals are substantially in good agreement for the direct and indirect methods (see Table 2 and Figure 4), even though some apprehension is experienced about the validity of the diastolic value in the indirect method of measurement. Assuming the diastolic measurements of the PTU animals to be basically correct, the systolic pressures of the PTU-treated animals as measured by the direct method are not in good agreement with the indirect method, but are some 11 mm. Hg lower at the most valid comparison level.

The lack of agreement between systolic pressures of PTU-treated rats determined by the two methods is thought to be caused by the following factor. The anesthetic, Nembutal, was used in the direct method and perhaps had a much stronger effect on the blood pressure of PTU-treated animals than on control ones. The systolic pressure of PTU-treated rats, obtained by the direct method, was 26.9 percent lower than in control rats; whereas it was only 15.0 percent lower after ten weeks of treatment with PTU when the indirect method with no anesthesia was used. The systolic pressures of normal rats, as noted, did agree despite the use of Nembutal in the direct method. Assuming now the systolic pressures of normal animals as measured by the two techniques to be correct, the diastolic pressures are in poor agreement. It is thought that the combination of higher heart rates in normal animals with the inertia of the direct measurement system contributed to too high a diastolic pressure in normal rats. The pressures were measured through a tambour system and ink writing pen, and because of the rapid heart rate in normal animals, the pen probably did not reach its true lower level before being caused to rise again by the next systolic pulse wave. Pulse pressures were very low for normal animals as they were also for PTU-treated animals.

This study has agreed with the work of others in that the systolic blood pressure of normal rats treated with PTU is shown to be lowered (Fregly, 1958). It also has extended the work of others by including a comparative study of direct and indirect systolic measurements, as well as information on diastolic pressures. The mechanism of the action of PTU in lowering blood pressure is not apparent, however. Fregly (1958) demonstrated that the reduction in blood pressure of rats made hypertensive by encapsulation of the kidneys could not be attributed solely to the weight loss produced by PTU administration. It is reasonable to assume then that the weight loss or lack of weight gain by non-hypertensive rats given PTU does not cause the lowering of blood pressure.

Several ideas have been suggested. One of these is that the lowered pressures result from lowered cardiac output which, in turn, is caused by decreased metabolism. Another possibility is that the drug has a direct or even an indirect effect on the arterioles. This may be due indirectly to the lowered basal metabolism or directly to some relaxing action of the muscles of the arterioles. A third possibility is an inhibitory action on some regulatory function of the circulatory system. The fourth and last suggestion is concerned with a substance in the circulatory system called renin (Best and Taylor, 1945). Renin is produced in the kidneys in cases of renal hypertension. It has been suggested that renin may also be present in the blood in small amounts as a blood pressure regulatory substance. The possibility involved here is that PTU may inhibit the ability of the kidneys to produce this substance under ordinary conditions. Thus, because of a decrease in quantity of this regulatory substance, the blood pressure would be lowered. All of these are hypotheses; true cause may be a resultant of any or all of these factors.

Table 3

Comparison of Direct and Indirect Measurements

	DIRECT		INDIRECT	
Control Rats	Systolic	Diastolic	Systolic	Diastolic
No. 44	126.0	124.0	130.0	112.0
No. 45	153.0	150.0	136.0	111.0
Average	139.5	137.0	133.0	109.0
Propylthiouracil				
No. 47	113.0	109.0	116.0	90.0
No. 48	73.0	69.0	109.0	87.0
No. 49	119.0	116.0	110.0	91.0
Average	102.0	98.0	113.0	89.0

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