

BODY OF REPORT

SEATO CRC Study No. 9 Cardiac Metabolism in Thyrotoxicosis

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Objective: The cardiovascular and metabolic interrelationships of the thyroid and adrenal medullary hormones in thyrotoxicosis is firmly established by a large body of evidence. The development of pharmacologic agents which permit selective blockage of the adrenergic beta receptors now permits a more precise delineation of this relationship. Studies were therefore undertaken to determine the myocardial metabolic effects of Pronethalol in 11 patients with thyrotoxicosis. The results of the 7 successful studies are reported herein.

Progress: Two males and nine females with clinical obvious thyrotoxicosis were studied. After an overnight fast and without premedication, routine right heart

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catheterization was performed, with registration of phasic brachial artery, pulmonary artery, right ventricular and right atrial pressures and oxygen saturations. Cardiac output curves were recorded by withdrawing blood from the brachial artery through a Guilford cuvette densitometer after the injection of 5-7.5 mg of Indocyanine green into a peripheral vein or the right atrium. Upon completion of these studies the catheter was manipulated into the coronary sinus, after which the patient performed a Valsalva maneuver. Blood samples were then obtained anaerobically from the brachial artery and coronary sinus in oiled syringes containing degassed heparin for blood gas analysis. Arterial and coronary sinus blood was also obtained for glucose, lactate, pyruvate, and free fatty acids (FFA). Blood for lactate and pyruvate determinations was drawn as rapidly as possible into calibrated 5 ml syringes, and the contents of the syringe were delivered into a tube containing 5.0 ml of ice-cold 0.6 N perchloric acid, after which the tubes were vigorously shaken. The time between the beginning of sampling and deproteinization was kept as short as possible, and never exceeded 60 seconds. Blood for FFA was allowed to clot, while fluoride was used as an anticoagulant for the glucose samples. Upon completion of the sampling, the patient was given Pronethalol intravenously in a dosage of 2.0 mg/Kg body weight over a 2 minute period. Records of phasic brachial artery pressure were recorded at 1 minute intervals for the first 5 minutes and at 5 minutes intervals thereafter for 30 minutes. Sampling of arterial and venous blood was repeated between 15 and 20 minutes after injection. After the 30 minute record cardiac output determination was repeated.

Hemodynamic data was tabulated, but will be reported separately at a later date.

Catheterization of the coronary sinus was successful in 8 subjects, was abandoned because of serious arrhythmias in 2, and the coronary sinus could not be catheterized in 1 subject with a very small right atrium. The withdrawal rate was so slow in 1 subject that metabolic studies were not done.

The metabolic effects of the drug are summarized in the Table. The most striking effects were upon the metabolism of FFA. All subjects had moderate to marked elevation of arterial FFA. This elevation, which is characteristic of thyrotoxicosis, may also have been in part due to excitement and the use of heparin-containing solutions to flush the cardiac catheters. Serum FFA in 2 subjects after the brachial artery needle had been inserted but before the other procedures were done were 2.10 and 1.36 mEq/L, respectively, and 2.56 and 1.75 mEq/L at the start of the metabolic studies. The administration of Pronethalol was associated with a fall in FFA in all subjects. In two the decreases were only 0.05 and 0.06 mEq/L which is within the error of the analytic method, but in the remaining 5 decreases of 0.52 to 1.83 mEq/L occurred. The magnitude of decrease was not related to the arterial concentration.

The arteriovenous difference of FFA fell in the 5 subjects whose arterial concentrations fell, but was unchanged in 1 of the two subjects without a significant

fall in arterial FFA levels , and rose in the other.

The extraction patterns of the other substrates responded variably to drug administration. In 4 of the subjects with decreased fatty acid extraction, there was a concomittant decrease in lactate and pyruvate extraction. Extraction of these substrates was increased in one subject. In both subjects who had insignificant changes in FFA, pyruvate extraction fell, while lactate extraction fell in one and rose in the other. Glucose extraction was unchanged in 3, rose in one, and fell in one. No consistent pattern was observed in the two subjects whose fatty acids did not change.

The arteriovenous difference of oxygen was consistently increased by a very small amount in all subjects. Respiratory quotient did not show any consistent changes from the control levels of approximately 0.8 .

Summary and Conclusions: The only consistent and significant metabolic results of Pronethalol administration in these subjects was a decrease in the extraction of FFA, with variable reduction in the extraction of some, and occasionally all, other substrates. The reduction in arterial FFA concentration observed in 5 of the 7 subjects would explain the decreased extraction of this substrate. However, the decreased arterial FFA levels suggest that Pronethalol may have a peripheral effect on the fat depots as well as its known effects on the adrenergic beta receptors .

Table I

		O ₂	CO ₂	Glucose	Lactate	Pyruvate	FFA
1. Control	art	15.11	42.74	96.5	9.0	0.52	2.94
	c.s.	7.85	53.46	95.5	6.4	0.32	1.07
	diff	+7.26	-10.72	+1.0	+2.6	+0.18	+0.87
Drug	art	14.84	42.34	97.0	7.8	0.41	2.26
	c.s.	7.25	45.38	96.0	7.0	0.26	1.57
	diff	+7.59	-3.04	+1.0	+0.8	+0.15	+0.69
2. Control	art			82.0	9.0	0.52	3.40
	c.s.			81.0	6.3	0.34	2.00
	diff			+2.0	+2.7	+0.18	+1.4
Drug	art			82.0	4.8	0.41	1.99
	c.s.			80.0	4.0	0.26	2.02
	diff			+2.0	+0.8	+0.15	0.00
3. Control	art	14.27		97.0	7.4	0.29	1.76
	c.s.	5.24		90.0	4.8	0.17	1.42
	diff	+9.03		+7.1	+2.6	+0.12	+0.34
Drug	art	13.55		97.3	5.7	0.23	1.24
	c.s.	3.87		87.2	5.8	0.14	1.19
	diff	+9.68		+10.1	-0.1	+0.09	+0.05
4. Control	art	16.56	40.57	95.2	7.94	0.28	3.93
	c.s.	6.41	50.16	95.8	4.25	0.21	2.63
	diff	10.15	9.59	+0.6	+3.69	+0.07	+1.30
Drug	art	16.26	38.18	103.2	6.06	0.33	2.10
	c.s.	5.64	47.84	98.2	0.50	0.18	2.17
	diff	10.62	9.66	+5.0	+5.56	+0.15	-0.07
5. Control	art	14.22	47.97	96.4		0.37	4.36
	c.s.	8.59	52.15	97.3		0.19	2.29
	diff	+5.63	-4.18	-0.9		+0.18	+2.07
Drug	art	13.95	46.97	107.0		0.27	3.47
	c.s.	5.53	53.09	106.9		0.22	2.59
	diff	+8.42	-6.12	+0.1		+0.05	+0.88
6. Control	art	15.24			24.0	0.55	1.75
	c.s.	7.37			18.7	0.35	1.57
	diff	+7.87			+5.3	+0.20	+0.18
Drug	art	14.65			19.3	0.43	1.70
	c.s.	6.95			14.5	0.28	1.50
	diff	+8.70			+4.8	+0.15	+0.20
7. Control	art	16.65	40.90	98.0	1.71	0.37	2.56
	c.s.	6.50	49.16	91.6	1.04	0.19	2.21
	diff	+10.15	-8.26	+6.4	+0.67	+0.18	+0.35
Drug	art	16.05	41.65	96.7	2.36	0.28	2.50
	c.s.	5.77	49.65	92.8	0.71	0.27	1.70
	diff	+10.28	-8.00	+3.9	+1.65	+0.01	+0.80