

the importance of a single attack of poliomyelitis for the production of antiviral substance.

8710 C

Oxygen Utilization, Cardiac Output, and Related Circulatory Functions in Graves' Disease.

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The increased metabolic and circulatory rates in Graves' disease have been subjected to repeated quantitative study. The relation of these two functions was indicated by Fick in 1870 and may be expressed as follows:

$$\text{Cardiac Output} \quad (\text{liters of blood per min.}) = \frac{\text{oxygen consumption (cc. of oxygen per min.)}}{\text{arterio-venous oxygen difference (cc. of oxygen per liter of blood)}}$$

Although previous workers have uniformly reported an abnormal increase both in the cardiac output and the rate of oxygen consumption, there has been a definite disagreement regarding the arterio-venous oxygen difference, which represents the number of cc. of oxygen taken up by each liter of venous blood during its passage through the lungs, or the average number of cc. of oxygen given off by each liter of arterial blood during its passage through the several tissues. It is the arterio-venous oxygen or A-V difference which is measured by the various foreign gas methods subsequently mentioned, the cardiac output being calculated from the quotient indicated above. Thus Liljestrand and Stenström,¹ using the foreign gas method of Krogh and Lindhard, and Bansi,² using the indirect Fick methods of Haldane and Christenson and of Redfield, Bock, and Meakins found the A-V (arterio-venous oxygen) difference decreased below normal. Fullerton and Harrop³ and Boothby and Rynearson,⁴ using the foreign gas method of Marshall and Grollman found no significant change in the A-V difference in Graves' disease as compared to normal. It is important to attempt to settle this disagreement for 3 reasons. First, the cardiac output

¹ Liljestrand, G., and Stenström, N., *Acta Med. Scand.*, 1925, **63**, 99.

² Bansi, H. W., *Z. für klin. Med.*, 1929, **110**, 633.

³ Fullerton, C. W., and Harrop, G. A., *Bull. Johns Hop. Hosp.*, 1930, **46**, 203.

⁴ Boothby, W. M., and Rynearson, E. H., *Arch. Int. Med.*, 1935, **55**, 542.

is indirectly proportional to, and is calculated from, the A-V difference. Secondly, the normal or abnormal utilization of oxygen in the tissues may throw light on the nature of the metabolic disturbance in Graves' disease. Thirdly, the settlement of this disagreement may indicate the comparative reliability of the methods used in determining the arterio-venous oxygen difference and cardiac output.

In the present study, the A-V difference and cardiac output have been determined under basal conditions in 4 subjects with Graves' disease, using the foreign gas method as modified by Gladstone.⁵ To allow for the subnormal vital capacity, the volumes of the gases inhaled were reduced and instead of attempting to wash out the dead space, which becomes difficult when the vital capacity is reduced, 2 mixing breaths into the front rebreathing bag were taken before drawing the first sample, and 2 more breaths before drawing the second sample. Each sample was drawn at the end of expiration. Each respiratory cycle took 2.5 seconds (the breathing and sampling being guided by the spoken directions of an accurately timed phonograph record) so that the test was completed in 10 seconds. The bag contents were as follows:

Side Bag		Front Bag
400 cc.	C_2H_2	120 cc.
	CO_2	55
100	O_2	
500	air	825

The findings are summarized in Table I. To check the adequacy of the mixing procedure an additional sample was drawn simultaneously with the first alveolar sample but from the distal end of the front rebreathing bag. The A-V difference calculated from the additional sample paired with the conventional second sample will show a deviation determined by the errors due to gas analysis and possible inadequate mixing. The sum of the last 2 errors, however, does not exceed that due to gas analysis alone. One may assume, therefore, that the mixing is adequate.

Previous studies⁶ have indicated that recirculation of the foreign gas in appreciable amounts occurs at 10 seconds or promptly thereafter in the rebreathing procedure described. Since such recirculation would increase the calculated A-V difference an additional sample was drawn at the end of the fifth breath, *i. e.*, after 12.5 seconds of rebreathing, and that sample paired with the conventional first sample. The values thus obtained are erroneously high due to the large error of recirculation.

⁵ Gladstone, S. A., *PROC. SOC. EXP. BIOL. AND MED.*, 1935, **32**, 1321.

⁶ Gladstone, S. A., *PROC. SOC. EXP. BIOL. AND MED.*, 1935, **32**, 1319.

TABLE I.
Metabolic and Circulatory Functions in Graves' Disease.

Subject	Age, yr.	Sex	Weight, lb.	Height, inch.	Blood Pressure			Oxygen Consumption, cc. per min.	Basal Metabolic Rate	A-V Difference	Cardiac Output (liters per min.)	Systolic Output, cc. per beat	Pulse Pressure, mm. of Hg.
					Pulse Rate	syst.	diast.						
W.M.	31	M	110	69	78	115	55	268	+22	35.4	7.6	97	60
M.O.	22	F	100	61	68	110	60	240	+35	38.2	6.3	71	50
D.O.	25	F	102	63	98	95	48	214	+16	23.9	8.9	91	47
J.P.	33	M	129	68	102	130	70	365	+60	38.3	9.5	93	60
Aver. Graves'					92	113	58		+33	34.0	8.1	88	54
Aver. normal ⁷					59	107	75			53.6	4.2	70	32
% change					+56	+6	-23		+33	-37	+93	+26	+69

TABLE II.
To Demonstrate Adequacy of Mixture (B) and Effect of Undue Prolongation (C) on the A-V Difference Obtained by the Method Described (A).

A	B	C
35.4	35.2	
38.2	41.7	48.7
23.9	27.5	43.5
38.3		49.1
Average 34.0	35.1	47.1

Column A indicates the values for the A-V difference obtained by the method described in 4 cases of Graves' disease. Column B indicates the values obtained when the first sample is drawn from the distal end of the bag. Column C indicates the values obtained when the last sample is drawn at 12.5 seconds.

The agreement in columns A and B indicates the adequacy of the mixing procedure. The increase in column C demonstrates the effect of the error due to recirculation of the foreign gas when the rebreathing procedure is unduly prolonged.

To estimate the nature and extent of the deviation from normal in the several functions studied, the average results may be compared with the averages obtained in 6 normal young men who have been studied under the same conditions, *i. e.*, fasting, at rest, recumbent in a deck chair for 2 hours.⁷ The hyperactivity of the circulation in Graves' disease becomes even more striking when one considers that the subjects of the normal group weighed about 40% more than the hyperthyroid patients that were the subjects of the present study. In the 4 cases of Graves' disease studied on the average the B.M.R. is increased by 33%, the A-V difference is decreased by 37%, the cardiac output is increased by 93%.

It is apparent that the cardiac output and systolic output are in-

⁷ Gladstone, S. A., *Am. J. Physiol.*, 1935, **112**, 705.

directly calculated from the A-V difference, the accuracy of which will determine the reliability of the quantitative functions calculated from it. In Graves' disease as compared with normal subjects, Fullerton and Harrop⁸ as well as Ryneerson and Boothby⁴ reported no significant change in the A-V difference. Liljestrand and Stenström¹ reported a decrease of about 20%. Bansi² reported a decrease of 33%, *i. e.*, 55 cc. for the normal A-V difference, 37 cc. in Graves' disease. The present findings are in close agreement with those of Bansi, being 53.6 for the normal A-V difference and 34 cc. in Graves' disease, representing a decrease of 37%. Ryneerson and Boothby have discussed this discrepancy and have explained it as a possible effect of iodine therapy in their patients. Since the first 3 of our patients had received iodine, the consistent finding of a low A-V difference would tend to invalidate that explanation. Recent studies⁹ of the foreign gas method have indicated that after 10 seconds of rebreathing of a foreign gas under the conditions of the test, appreciable amounts of gas return to the lungs in the recirculated blood and retard the diffusion of the gas from the lungs into the blood. When the rebreathing extends beyond 20 seconds as in the Marshall-Grollman procedure used by Fullerton and Harrop as well as by Ryneerson and Boothby, the errors become large enough to render the method insensitive and unreliable. The procedure of Krogh and Lindhard as used by Liljestrand and Stenström is definitely shorter in duration (about 15 seconds) and includes a period of 10 seconds during which the breath is held. These considerations, as well as the finding by Liljestrand and Stenström that the A-V difference is somewhat decreased in Graves' disease, suggest that the error due to recirculation of the foreign gas is possibly present but is not nearly so great as in the Marshall-Grollman procedure.

In addition to subserving the metabolic needs of the tissues, the blood also acts as part of the cooling system for dissipating heat, especially through the skin capillaries. This purely physical function of the blood does not involve a loss of oxygen. The venous blood coming from the dilated capillaries of a hot skin will have a high oxygen content, will tend to increase the oxygen content of the mixed venous blood and will accordingly decrease the A-V difference, as has been found in these patients with Graves' disease.

⁸ Grollman, A., *The Cardiac Output of Man in Health and Disease*. Baltimore, 1932.

⁹ Gladstone, S. A., *Cardiac Output and Arterial Hypertension*. New York, 1935.

Since the precise nature of the underlying metabolic disturbance of Graves' disease is as yet unknown, the relation between it and our present findings is undetermined. It has been found that hyperthyroid patients require more oxygen to perform a given physical task than normal subjects.¹⁰ These findings as well as our own suggest that in Graves' disease a disproportionate amount of the energy available to the organism is dissipated as heat, and that Graves' disease may not be looked upon merely as a quickening to the same relative extent of all metabolic functions, but represents a different level of dynamic equilibrium, with an excess of certain exothermic catabolic oxidations, or a relative decrease in certain endothermic anabolic changes.

Summary. In 4 cases of Graves' disease with an average basal metabolic rate of +33%, the arterio-venous oxygen difference was found to be decreased by 37%. The average cardiac output was 8.1 liters per minute compared to a normal of 4.2, representing an increase of 93%. The relation of the present findings to those previously reported, to the question of method of cardiac output determination, and to the possible nature of the underlying metabolic disturbance in Graves' disease is briefly discussed.

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Barbiturate-Coriamyrtin Antagonism.

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At the time when we established the antidotal action of picrotoxin on the barbiturates¹ we indicated our intention of investigating the action of other picrotoxin-like substances. This paper reports the antidotal action of coriamyrtin in rabbits subjected to lethal doses of amytal, pernoston and nembutal.

The same method of procedure was followed in this work as in our early investigations of picrotoxin.^{1, 2} The animals were given

¹⁰ Boothby, W. M., and Sandiford, S., *J. Am. Med. Assn.*, 1923, **81**, 795.

¹ Maloney, A. H., Fitch, R. H., and Tatum, A. L., *J. Pharm. and Exp. Therap.*, 1931, **41**, 465.

² Maloney, A. H., and Tatum, A. L., *J. Pharm. and Exp. Therap.*, 1932, **44**, 337.