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Hypoglycaemia in Infants and Children with Cyanotic Congenital Heart Disease

By

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The fasting blood glucose concentration was measured in 44 infants and children with cyanotic congenital heart disease. In all age groups between 1 week and 16 years the blood sugar value was significantly lower than in healthy children. In 6 cases the level ranged between 20 and 40 mg per 100 ml, but no signs of hypoglycaemia were observed. It is suggested that the hypoglycaemia was due to chronic hypoxia since the lowest blood sugar values were associated with a low oxygen content. The glucose disappearance rate (Kg) was normal in cyanotic patients. The fasting insulin and the growth hormone levels were also normal. After glucagon administration the increment of blood sugar concentration was significantly lower in cyanotic patients than in normal controls, which supports the assumption that glucose release from the liver is decreased in these patients.

In infancy and childhood many pathological conditions are accompanied by hypoglycaemia. Since persistent brain damage may also develop as a consequence of a low blood sugar level, it is important to be aware of the conditions in which hypoglycaemia may arise. We have shown earlier that in cyanotic congenital heart disease the blood glucose level may be subnormal [6]. In the present report we describe our observations about hypoglycaemia in cyanotic heart disease and shall discuss some aspects of glucose homeostasis in these patients.

MATERIAL AND METHODS

Fourty-four infants and children with cyanotic congenital heart disease were studied. They were divided into three age groups of 1 to 4 weeks, 1 to 24 months, and 2 to 16 years, respectively. In most cases the diagnosis was ascertained by cardiac catheterisation. The indexes weight for age $\left(\frac{\text{actual weight}}{\text{ideal weight for age}} \times 100\right)$ and that of weight for height $\left(\frac{\text{actual weight}}{\text{ideal weight for height}} \times \right.$ $\left. \times 100\right)$ were calculated by comparison to English standards [13]. The control group included 49 healthy children studied after recovery from various acute diseases. In group I the parameters characterising development were similar in the patients and controls. In groups II and III the cyanotic patients were more or less malnourished. In order to exclude the possible effect of malnutrition on the blood glucose level, in group II a second control group was included consisting of infants suffering from congenital heart disease without cyanosis. The latter had some type of heart defect with left to right shunt and the degree of malnutrition was similar to that in infants exhibiting cyanosis (Table I).

Arterial blood for oxygen estimation was obtained during cardiac catheterisa-

tion. The studies were performed early in the morning in the fasting state, in group I, 4—6 hours; in group II, 6—8 hours; in group III, 10—12 hours after the last meal. Glucose was estimated by the orthotoluidine method.

Intravenous glucose tolerance test. 0.5 g/kg body weight glucose was administered intravenously in 2—4 minutes and venous blood was taken every 10 minutes for one hour. The glucose disappearance rate was expressed by the Kg value calculated according to DUNCAN [5], $Kg = \frac{0.693}{t^1/_2}$.

Free fatty acids were measured in fasting plasma and determined by the method of LAURELL and TIBBLING [10].

Growth hormone. No special test to provoke growth hormone secretion was performed. The maximum levels measured after fasting or in blood samples taken for different purposes are given.

Insulin was measured in fasting plasma. Growth hormone and insulin were determined by radioimmunoassay by the slightly modified method of HERBERT et al. [7]. For the calibration curves, the International Standard Preparations of WHO were used. Antibodies were purchased from Wellcome Research Laboratories.

Glucagon test. 20 μg/kg glucagon was administered intravenously and glucose was measured at 0, 20 and 40 minutes in capillary blood samples. In the statistical calculations, Student's *t*-test and the χ^2-test were used.

RESULTS

The mean fasting blood glucose concentration was in all the three groups significantly lower in the cyanotic patients than in the normal controls (Table I). Glucose was also significantly lower in group II than in the malnourished control infants with non-cyanotic heart disease. In most cases blood sugar was measured several times and was always found within the same range. In Table II we give the clinical characteristics and the laboratory findings of the cyanotic patients exhibiting glucose levels below 50 mg per 100 ml. This was the lowest glucose concentration found in healthy children. The blood sugar level was never below 20 mg per 100 ml and accordingly no cases of symptomatic hypoglycaemia were observed. During hypoxic spells, in the two cases studied the initially low blood sugar rose to hyperglycaemic levels (250 vs 30 mg and 119 vs 70 mg per 100 ml, respectively). The relation between the blood glucose and oxygen content is shown in Fig. 1. Although there was no linear mathematical correlation between the two values, the lowest blood sugar values were accompanied by a low oxygen content. The frequency distribution of the points in the four fields was significantly different: $\chi^2 = 4.89$, $p < 0.05$.

The mean Kg value was similar in the cyanotic and the control groups. The individual differences in the glucose disappearance rate in the cyanotic patients were quite considerable, but the fasting blood sugar concentrations were independent of these values. The lowest concentration of insulin that can reliably be detected in our laboratory is 3 μg/ml. Values below this are given as 3 μg/ml. The fasting insulin concentrations were near this lowest limit of detectability in most cases and they were certainly not higher in the hypoglycaemic patients.

Growth hormone is considered nor-

TABLE I

Clinical characteristics and laboratory findings of patients and controls in the three groups. Mean ± SD. In parentheses the number of cases studied

	Age	Weight for age	Weight for height	Blood sugar, mg per 100 ml	Kg	Insulin, μU/ml
Group I						
cyanotic	16.7±7.0 days (8)	97.0±4.0 (8)	90.0±3.5 (8)	48.7±15.7 (8)	–	–
normal	13.4±4.2 days (9)	90.0±5.5 (9)	100.0±3.2 (9)	68.2±11.1 (8) $p < 0.02$	–	–
Group II						
cyanotic	8.3±5.1 months (11)	75.9±13.9 (11)	82.1±12.3 (11)	46.2±13.9 (11)	1.82±1.05 (7)	5.1±2.7 (6)
normal	10.0±5.4 months (20)	85.1±13.0 (20)	90.0±9.2 (20)	67.9±14.1 (20) $p < 0.001$	2.26±0.9 (7) n. s.	6.9±6.2 (20) n. s.
non cyanotic heart disease	10.5±8.8 months (14)	70.3±11.0 (14)	83.3±14.0 (14)	60.8±11.2 (14)	–	–
Group III						
cyanotic	8.9±5.0 yrs (25)	79.4±15.6 (25)	86.0±10.3 (25)	58.0±10.3 (25)	2.12±1.14 (15)	5.1±5.1 (18)
normal	9.0±3.9 yrs (20)	100.2±20.5 (20)	95.9±10.9 (20)	75.7±9.0 (20) $p < 0.001$	2.2±0.47 (9) n. s.	8.0±5.1 (18) n. s.

n. s. — not significant

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TABLE II

Clinical characteristics and laboratory findings in patients with blood sugar level below 50 mg per 100 ml. F = tetralogy of Fallot; Ftr = trilogy of Fallot; Fp = pentalogy of Fallot; Tr = transposition of great vessels; Ost = common atrioventricular canal; Trc = truncus arterio-arteriosus

Case No.	Disease	Age	Weight for height	Hgb, g per 100 ml	O_2 saturation, per cent	O_2 content, Vol per cent	Bl. sugar, mg per 100 ml	FFA, μM/l	Insulin, μU/ml	GH, mμg/ml	Increase of blood sugar after glucagon	
											20 min	40 min
1.	Ftr	8 days	100	14.0	48	9.5	27	280	—	6.2	17	3
2.	Trc	14 days	97	16.7	—	—	47	—	—	—	—	—
3.	F	17 days	90	16.7	54	12	50	—	3	—	—	—
4.	F	19 days	105	12.5	—	—	29	220	—	5.6	—	—
5.	Tr	1 mth	90	18.2	—	—	45	—	—	—	—	—
6.	Tr	2 mth	87	13.8	—	—	50	—	—	—	—	—
7.	Tr	2 mth	100	17.2	38	9.0	29	—	—	—	—	—
8.	F	5 mth	83	14.4	65	12.5	30	400	3	15.0	55	35
9.	Tr	6.5 mth	98	15.6	51	10.0	35	580	3	4.0	13	−5
10.	Ost	9 mth	65	10.6	80	11.5	42	1070	3	6.2	—	—
11.	F	15 mth	82	14.7	74	14.5	43	1560	5	10.0	—	—
12.	—	15 mth	64	15.9	—	—	32	940	8	33.5	—	—
13.	Fp	2 yr	80	15.2	—	—	46	1100	3	—	—	—
14.	F	2.5 yr	86	14.1	82	15.0	36	1200	4	—	31	−3
15.	F	2.5 yr	104	16.0	86	18.5	43	850	7	8.0	31	23
16.	F	4 yr	88	15.0	—	—	45	1120	6	—	52	17
Normal range								400−1070	3−18		42−72	−12−53

mal in our material of healthy children if it exceeds 5 mμg/ml in any blood sample. Most of the hypoglycaemic patients had at least one sample with growth hormone levels above 5 mμg/ml.

Glucagon test. Since no age-bound difference has been found between the control children belonging to groups II and III, we combined the results of these groups in Fig. 2. The increase of blood sugar was significantly less in the cyanotic patients than in the healthy control children. The blood sugar increase was, however, independent of the fasting glucose level.

Free fatty acid concentrations are given only for the hypoglycaemic cases. Most of them responded well to the low blood sugar levels, but in some very young infants the FFA level was below the normal range.

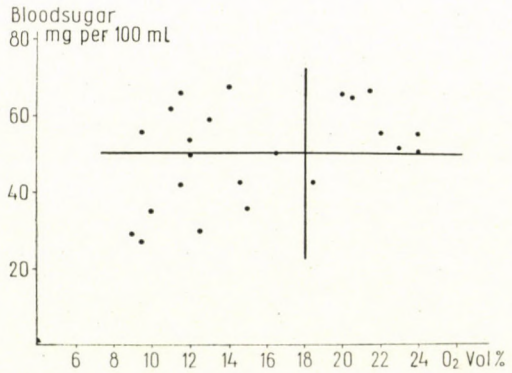

FIG. 1. Relation between blood sugar and oxygen content in cyanotic patients

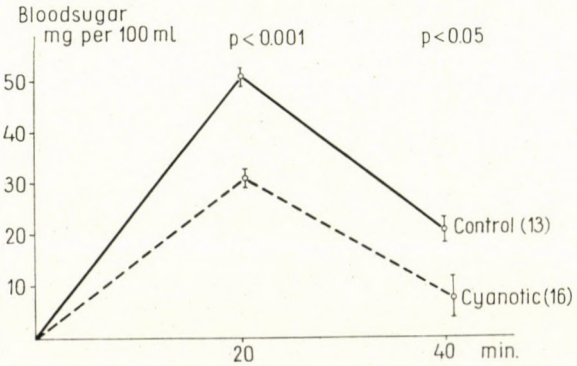

FIG. 2. Increase of blood sugar following glucagon administration. Mean ± SEM

Discussion

In all age groups the mean blood sugar concentration of cyanotic patients was found to be lower than in healthy children. As defined by Cornblath and Schwartz [3], after the newborn period glucose levels below 40 mg per 100 ml are to be regarded as hypoglycaemic. We found glucose levels not exceeding 40 mg in 6 cases and between 40 and 50 mg per 100 ml in ten more cases among the 44 cyanotic cases studied. The clinical significance of our findings cannot, however, be judged since hypoglycaemic symptoms were never observed. It seems probable that hypoxic spells are not accompanied by hypoglycaemia: in both cases studied there was a great increase in blood sugar during these spells as compared to the resting state. This is probably due to the fact that glucose utilization is reduced to a minimum in severe hypoxia.

According to the well-known homeostatic mechanism, a reduction of the blood glucose level results in an increase of FFA concentration. Free fatty acids are the source of ketone body formation which can be utilized by the brain in the case of a lack of glucose [11]. For that reason our finding that some cyanotic infants are unable to increase their FFA level in hypoglycaemia may be of some importance.

We carried out several studies to find out the mechanism of the development of hypoglycaemia in cyanotic patients. The disappearance rate of sugar from the blood (Kg) was not higher in the hypoglycaemic patients and the fasting level of insulin was also in the normal range. Hypoglycaemia is a common finding in cases of decreased pituitary function. In most of our patients the growth hormone level was, however, normal. The only difference between normal and cyanotic children was found in the glucagon test which suggests that glucose release from the liver may be impaired in these patients. Since no difference was found between the cyanotic patients with glucose levels below and above 50 mg per 100 ml, the significance of the decreased response to glucagon in the development of hypoglycaemia remains uncertain.

Concerning the possible causes of hypoglycaemia, we may consider several factors. One possibility would be congestive heart failure in which Benzing et al. [1] observed low blood sugar values, mostly in the first days of life. Congestive heart failure is, however, a rare occurrence in cases with a cyanotic heart defect, and in our material there were few patients with such symptoms.

Malnutrition is frequently accompanied by hypoglycaemia [8, 9]. Although most of our patients were to some extent malnourished, analysis of the individual cases showed that low glucose values were also found in patients with normal weight for age. The degree of malnutrition in the group of non-cyanotic heart disease was at least as pronounced as in cyanotic infants; their glucose concentra-

tions, however, were within the normal range.

The low glucose level in cyanotic patients may be due to chronic hypoxia. This assumption is supported by our finding that the lowest sugar levels were mostly accompanied by a low blood oxygen content. Our assumption of the probable effect of hypoxia is indirectly confirmed by some further facts. It was found both in animal experiments and in observations of humans living at high altitudes that chronic hypoxia results in a reduced blood glucose level. In these studies the hypoglycaemia was also ascribed to decreased glycogenolysis [2, 4, 12, 13].

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