iotic patients, that might suggest an increased plasma somatomedin activity. In a limited study, a significant difference was found between the plasma somatomedin activity of children with congenital scoliosis and normal children.

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15. We are grateful to Mr. C. W. Manning, Mr. P. F. Milling, and M. Yves Cotrel for their help in the collection of blood samples, and to Dr. J. L. Van den Brande for encouragement and technical advice.
16. This research was supported by the Wellcome Foundation, The Brompton Hospital Research Fund, and St. Mary's Hospital, Paddington UK.
17. Requests for reprints should be addressed to: G. S. G. Spencer, Growth Section, Meat Research Institute, Langford, Bristol (UK).
18. Received for publication November 3, 1976.
19. Accepted for publication January 27, 1977.

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Printed in U.S.A.

Pediat. Res. 11: 885-889 (1977)

Blood volume red cell mass
growth hormone Russell-Silver dwarfism
idiopathic short stature

The Effect of Growth Hormone Deficiency and of Growth Hormone Substitution on Blood Volume and Red Cell Parameters

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Summary

Blood volume, plasma volume and red cell mass, red cell parameters, reticulocytes, serum iron, and total iron binding capacity were investigated. Fifty-nine growth-retarded children were studied: 27 children with idiopathic short stature (ISS) and 32 children with isolated growth hormone deficiency (GHD). Fifteen of the GHD patients were studied before treatment and again 3-6 months after onset of treatment with growth hormone, 3 GHD patients only before and 14 only during treatment. Blood volume, plasma volume, and red cell mass were significantly ($P < 0.005$) decreased by 15% in the untreated GHD patients and were normal in the children studied during treatment with growth hormone compared with the values in ISS patients. In the 15 GHD patients studied before and during treatment, blood volume, plasma volume, and red cell mass increased by 17% to normal values ($P < 0.0005$) on treatment with growth hormone. No significant differences were demonstrable between values related to actual body weight and to corrected weight for height. Hematocrit, mean corpuscular volume, and reticulocytes remained unchanged. Serum iron and

total iron binding capacity were normal before treatment. Serum iron increased and total iron binding capacity decreased significantly during growth hormone substitution. In a pair of twins with Russell-Silver dwarfism and GHD, growth hormone increased blood volume, plasma volume, and red cell mass as in the other GHD patients. In another pair of twins with Russell-Silver dwarfism without GHD, growth the hormone was without effect on blood volume.

Speculation

Our results of decreased blood volume and red cell mass in children with isolated GHD and the increase of blood volume and red cell mass during growth hormone treatment provide direct evidence that growth hormone is stimulating erythropoiesis. The less pronounced decrease of blood volume and red cell mass in our patients compared with the literature data obtained on panhypopituitary and hypophysectomized subjects may indicate that growth hormone, thyroxin, and other hormones act synergistically on erythropoiesis.

In children with panhypopituitarism or isolated GHD, blood volume, plasma volume, and red cell mass were found to be decreased by approximately 30% below normal (28, 30). Therefore, Shahidi and coworkers (30) recommended checking of blood volume in order to distinguish between dwarfism due to panhypopituitarism or GHD and idiopathic short stature. Their reports, however, include only one patient with isolated GHD (28), or do not differentiate between children with isolated GHD and panhypopituitarism (30). The effect of growth hormone on blood volume in isolated GHD has not yet been studied.

MATERIALS AND METHODS

Fifteen patients with GHD, including one pair of twins with Russell-Silver dwarfism, were studied before treatment and again 3–6 months after onset of treatment with human growth hormone (10 IU/m²/week). In addition, 3 GHD patients before treatment, and 14 during treatment were examined. The control group comprised 27 children with idiopathic short stature. Furthermore, another pair of twins with Russell-Silver dwarfism but without GHD was studied before and during treatment with growth hormone. No further treatment was performed. Informed consent was obtained from patients and/or parents in every case before investigation was started. Since children with hypopituitarism are often overweight for height (17), we obtained the "appropriate" (corrected) weight for the actual height from nomograms (21). The age distribution was similar in all groups (5–18 years). The endocrine studies performed in all children included determination of growth hormone (insulin tolerance test), thyroxin, cortisol, and gonadotropins by standard procedures (radioimmunoassays). The children with ISS were without endocrine abnormalities and the patients with GHD were without further endocrine abnormalities. A possible gonadotrophic deficiency cannot be ruled out in prepubertal children.

Hematocrit was measured by the microhematocrit method using a correction factor of 0.98 for trapped plasma (23). Reticulocytes were counted after staining with brilliant cresyl blue. Serum iron and total iron-binding capacity (TIBC) were determined by the use of sulfonated bathophenanthroline. Plasma volume was measured by means of Evans blue dye injected in doses of 0.2 mg/kg. Details of the method employed are described elsewhere (22). The postmix blood sample was taken 10 min after injection of the dye. In 10 patients the disappearance rate of Evans blue was estimated by taking four to six blood samples within 1 hr after injection of the dye. These studies revealed a mean error of $+1.0 \pm 2.6\%$ (SD) by dye disappearance if only one blood sample was taken 10 min after the injection of the dye. Blood volume and red cell mass were calculated from plasma volume and hematocrit using a body/venous hematocrit ratio of 0.91 (7, 10). This method causes significant error if the body/venous hematocrit ratio is markedly different from 0.91. Blood volume determination by double isotope techniques in children suffering from hypopituitarism (28) showed a mean body/venous hematocrit ratio of 0.90 ± 0.07 (SD) if the reported hematocrits were corrected for trapped plasma. Therefore, our method seems to be adequate and has the advantage of preventing the hazards of radiation exposure.

RESULTS

The individual data of blood volume and red cell mass per kg body weight are shown in Figure 1. In reference to corrected weight for height the values of the GHD patients were slightly higher. Nevertheless, blood volume, plasma volume, and red cell mass related to both actual body weight and corrected weight for height were significantly lower ($P < 0.005$) in the untreated children with GHD in comparison to the children with idiopathic short stature (Table 1).

In any of the patients studied twice, blood volume, plasma

Fig. 1. Blood volume and red cell mass in children with short stature. Values related to actual body weight.

volume, and red cell mass increased during treatment with growth hormone (Fig. 2). Furthermore, serum iron decreased and TIBC increased significantly during treatment, whereas hematocrit, mean corpuscular volume (MCV), and reticulocytes remained unchanged (Table 2). Two pairs of twins with Russell-Silver dwarfism were studied before, and 3–6 months after the initiation of growth hormone therapy (Fig. 3). One of the pairs was without endocrine abnormalities; the other pair had GHD. Blood volume, plasma volume, and red cell mass increased only in the twins with GHD during treatment.

DISCUSSION

The present study provides evidence that the total blood volume is reduced by approximately 15% below normal values in children with isolated GHD because of an equal reduction of plasma volume as well as of red cell mass. The effect of pituitary deficiency on plasma volume and red cell mass has been studied extensively by several authors in hypophysectomized animals. In hypophysectomized rats, red cell mass is decreased by about 40%, whereas plasma volume is normal or only slightly decreased, resulting in a marked peripheral anemia (1, 2, 5, 11, 12, 16, 24, 29). In dogs and monkeys, hypophysectomy does not change hematocrit but reduces plasma volume and red cell mass: in monkeys by 30% (28, 32) and in dogs by 46% (4). Few similar studies on blood volume have been done in the pituitary-deficient human. Hypophysectomy in adult patients results in a parallel decrease of plasma volume and red cell mass by about 40% (14) and in children with panhypopituitarism by 30% (28).

In a recent study of a group of 10 children suffering from panhypopituitarism or isolated GHD a reduction of plasma volume and red cell mass by about 30% was shown (30). The blood volume values in any of these patients were below the range of children with short stature without endocrine abnormalities. The authors concluded that the determination of red cell mass and plasma volume may be of discriminating value in children with short stature. However, in contrast to this mixed group, our patients with isolated GHD showed less pronounced volume

Table 1. Hematologic values (means $\pm$ SD) of untreated and growth hormone-treated children with growth hormone deficiency (GHD) and of children with idiopathic short stature (ISS)¹

	Human GHD		
	Untreated (<i>n</i> = 18) ²	Treated (<i>n</i> = 29) ²	ISS (<i>n</i> = 27)
Blood volume (ml/kg)	65.2 $\pm$ 9.2 ³	74.5 $\pm$ 8.7	77.1 $\pm$ 8.0
Plasma volume (ml/kg)	43.1 $\pm$ 6.5 ³	49.5 $\pm$ 6.5	50.9 $\pm$ 5.3
Red cell mass (ml/kg)	22.1 $\pm$ 3.2 ³	25.0 $\pm$ 3.2	26.2 $\pm$ 4.1
Blood volume ⁴ (ml/kg)	67.1 $\pm$ 8.7 ³	79.0 $\pm$ 11.0	77.7 $\pm$ 11.1
Plasma volume ⁴ (ml/kg)	44.3 $\pm$ 5.7 ³	52.4 $\pm$ 7.6	51.3 $\pm$ 6.6
Red cell mass ⁴ (ml/kg)	22.8 $\pm$ 3.7 ³	26.6 $\pm$ 4.5	26.4 $\pm$ 4.3
Hematocrit	38.1 $\pm$ 2.9	37.7 $\pm$ 2.7	38.0 $\pm$ 3.1
MCV (fl)	84.6 $\pm$ 5.8	82.7 $\pm$ 5.4	80.1 $\pm$ 4.9
Reticulocytes (%)	1.13 $\pm$ 0.56	1.18 $\pm$ 0.71	1.01 $\pm$ 0.58
Serum iron (μ g/dl)	82.3 $\pm$ 25.3	63.4 $\pm$ 21.7 ⁵	78.9 $\pm$ 28.3
TIBC (μ g/dl)	333 $\pm$ 38	382 $\pm$ 47 ⁵	354 $\pm$ 55

¹ MCV: mean corpuscular volume; TIBC: total iron-binding capacity.² Fifteen patients included in both GHD groups, studied before and during treatment.³ *P* < 0.005 (*t*-test) when compared with ISS values.⁴ Values related to corrected weight for height.⁵ *P* < 0.05 (*t*-test) when compared with ISS values.

Fig. 2. Effect of treatment with human growth hormone on blood volume and red cell mass in 15 children with growth hormone deficiency.

reduction, and the individual values scattered over the lower half of the normal range (Fig. 1).

The comparison of blood volume data simply on the basis of body weight might be misleading, since children with hypopituitarism are often overweight for height (17). Lean body mass as reference standard for blood volume has been found to be most accurate, especially in obese subjects (13). A rough estimate of lean body mass can be obtained by using normal ("corrected") weight for height as a reference standard (13). In our patients with GHD blood volume, plasma volume, and red cell mass related to corrected weight for height were slightly, but not significantly, higher in comparison with the values referred to actual body weight. Our results of a less marked reduction in blood volume compared with the data obtained from hypophysectomized adult patients and children with panhypopituitarism may be explained by the normal thyroxine and cortisol metabolism in our patients.

In hypophysectomized animals the combined administration of thyroxine and growth hormone restores red cell mass and blood

Table 2. Effect of treatment with human growth hormone for 3–6 months on hematologic values in 15 children with growth hormone deficiency¹

	Mean differences $\pm$ SD	<i>p</i> ²
Blood volume (ml/kg)	+11.0 $\pm$ 3.9	<0.0005
Plasma volume (ml/kg)	+7.1 $\pm$ 3.3	<0.0005
Red cell mass (ml/kg)	+3.9 $\pm$ 1.7	<0.0005
Hematocrit	+0.5 $\pm$ 2.0	n.s.
MCV (fl)	-1.9 $\pm$ 4.2	n.s.
Reticulocytes (%)	+0.07 $\pm$ 0.43	n.s.
Serum iron (μ g/dl)	-27.4 $\pm$ 10.1	<0.0005
TIBC (μ g/dl)	+48 $\pm$ 38	<0.005

¹ MCV: mean corpuscular volume; TIBC: total iron-binding capacity.² Significance level of differences (paired *t*-test). n.s.: not significant.

volume to normal values (11, 32). In the human the combined treatment with thyroxine, adrenal steroids, growth hormone, and testosterone normalizes red cell mass and increases plasma volume by 19% above normal in panhypopituitarism (20). The influence of growth hormone on blood volume has not yet been studied in children with isolated GHD. Our results show that in children with GHD administration of growth hormone normalizes total blood volume, plasma volume, and red cell mass. In the two patients with Russell-Silver dwarfism without GHD, growth hormone did not influence hematologic values. In analogy to these results growth hormone fails to increase red cell mass in intact rabbits and polycythemic mice (18).

Reduction in red cell mass can be the result of shortened red cell life span or decreased erythropoiesis. Hematologic studies in hypophysectomized animals revealed normal red cell survival time (4), reduction in the erythroid elements in bone marrow (11, 32), decreased erythropoietin activity (6, 32), decreased erythropoietic response to hypoxia (3, 19), decreased plasma iron turnover and iron uptake by red cells (3, 4, 6), and normal erythrocyte 2,3-diphosphoglycerate (28). These data and our results of normal reticulocyte counts, serum iron, and TIBC indicate that the reduction in red cell mass in panhypopituitarism and isolated GHD is solely due to decreased erythropoiesis.

On the other hand, in pituitary-deficient subjects, growth hormone increases erythropoietin activity (20, 26, 30, 32), iron incorporation into newly formed red cells (25), 2,3-diphosphoglycerate, and red cell enzyme activities that are present at a higher level in younger red cells (9, 28, 30, 31, 32). These

Fig. 3. Effect of treatment with human growth hormone on blood volume and red cell mass in two pairs of twins with Russell-Silver dwarfism. GHD: growth hormone deficiency.

observations, together with our results of an increase in red cells mass in children with isolated GHD, indicate that growth hormone stimulates erythropoiesis. Likewise, our finding of moderate iron deficiency in the growth hormone-substituted patients can be explained by stimulated erythropoiesis. Reticulocyte counts are found to be increased only during the first 10 weeks of growth hormone substitution (9), and therefore were normal in our patients studied 3–6 months after onset of treatment.

How growth hormone acts on erythropoiesis is still open to question. The widely held opinion that growth hormone influences erythropoiesis by increasing oxygen consumption (11, 14, 20, 28, 30) seems to be doubtful, at least in children, since basal metabolic rate does rise in some children with hypopituitarism, but not in all after growth hormone substitution (8, 27). A direct action of growth hormone on erythropoietin activity and/or on bone marrow seems to be more likely (15, 25).

CONCLUSION

Blood volume studies (Evans blue method) in children with isolated GHD showed the mean blood volume (BV), plasma volume (PV), and red cell mass (RCM) to be significantly lower than in children with idiopathic short stature. BV, PV, and RCM in 29 GHD patients treated with growth hormone for 3–6 months were normal. Fifteen children were studied before as well as during treatment. BV, PV, and RCM increased in all of these patients. Iron level in serum was decreased during growth hormone substitution, most probably because of increased erythropoiesis.

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- This work was presented in condensed form to the European Society of Pediatric Research, Rotterdam, June 1976. (Abstract: *Pediatr. Res.*, **10**: 888 (1976).)
- We wish to thank Dr. H. Krämer for the preparation of the Evans blue dye.

and Ms. Monika Güntner and Ms. Claudia Wohlfarth for the faultless technical assistance.

35. This work was supported by Deutsche Forschungsgemeinschaft (SFB 147).

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37. Received for publication November, 15, 1976.

38. Accepted for publication December 21, 1976.

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Printed in U.S.A.

Pediat. Res. 11: 889-893 (1973)

Adrenaline fetus
asphyxia heart rate
catecholamines noradrenaline

Catecholamine Release in the Newborn Infant at Birth

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Summary

Catecholamines were determined by a fluorimetric technique in umbilical blood which was collected from newborn infants immediately after birth. The mean catecholamine concentration was 62.1 nmol/liter in the umbilical artery and 29.3 nmol/liter in the umbilical vein of newborn full term infants delivered uneventfully. This value is considerably higher than in resting adults. Similar levels of catecholamines were seen after elective cesarean sections, whereas considerably higher levels were found after breech deliveries. In the full term asphyxiated infants about a 4-fold increase of the catecholamine concentration was found in both the umbilical arterial and venous blood. The amine concentration level correlated inversely to the pH below 7.25 ($\log$ catecholamine concentration versus pH, $r = -0.71$). Preterm infants had, in general, lower amine levels than full term infants both after uneventful deliveries and after intrauterine asphyxia. The catecholamine levels were considerably increased in the newborn infants who showed some kind of abnormal fetal heart rate variation during the last hour before birth; in particular baseline changes were associated with high levels whereas only a moderate increase was seen after loss of beat-to-beat variation.

Speculation

The high catecholamine concentrations in umbilical blood, seen even after uneventful deliveries, indicate that the sympathoadrenal system might have a functional role in the fetus at delivery. The enormous levels at asphyxia might be of importance to sustain the circulatory homeostasis.

The sympathoadrenal system is certainly of great importance for the regulation of the fetal heart rate during delivery. Determination of catecholamines (preferably in scalp blood samples) can be a valuable tool in the study of cardiocirculatory.

Studies on fetal sheep have demonstrated that adrenergic cardiovascular control is well developed at term (11, 19, 23). Probably there are fewer noradrenaline stores in the sympathetic nerve terminals of the fetus compared with the adult (11); on the other hand, there are increased catecholamine stores in the

adrenal medulla per kg body weight (7) and possibly also in the paraganglia. The isolated fetal heart is more sensitive to catecholamines than the adult heart; this supersensitivity has been compared to that of the denervated organ (11). These findings indicate that the circulating catecholamines may play a greater role in the fetus than in the adult (11). Hypoxia induces a large increase of the catecholamine secretion from the adrenal medulla (15). Even during moderate hypoxia (fetal arterial $pO_2 \approx 18$ mm Hg during 1 hr) more than 10-fold increase of the catecholamine concentration in plasma was found. Catecholamines administered to the fetal sheep in similar concentrations to these released during mild hypoxia were found to cause large cardiovascular effects (21).

On the basis of the findings in fetal sheep this study was performed to investigate the sympathoadrenal activity in the human newborn. Catecholamines were determined in umbilical blood and the levels were correlated with signs of fetal hypoxia such as Apgar score and blood gases. Particular interest was paid to the problem of whether there was any relation between the catecholamine level and abnormal fetal heart rate patterns before birth.

MATERIALS AND METHODS

Plasma catecholamines were determined in a number of newborn infants delivered at Huddinge Hospital. The infants were classified in various groups according to clinical conditions (group A) and according to fetal heart rate patterns (group B).

GROUP A: CLINICAL CONDITIONS CLASSIFICATION

Group i: Full Term Infants Delivered Uneventfully. All of these cases were delivered vaginally in vertex position; their fetal heart rate patterns were found to be essentially normal (see below) and their Apgar scores were above 7 at 1 min. The infants in this group had a gestational age of 37-43 weeks and were appropriate in weight for gestational age.

Group ii: Preterm Infants Delivered Uneventfully. These infants fulfilled the same conditions as above, except that the gestational age was less than 37 weeks.

Group iii: Infants Delivered by Elective Cesarean Section. Maternal indications such as small pelvis, long sterility, and the