Rebound Phenomenon in the Premature Infant during Exchange Transfusion

By

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(Received June 27, 1962)

A great mass of bilirubin streams from the extravascular space into the circulation during the blood exchange of newborn infants, so that the decrease in the serum bilirubin level lags behind the extent of erythrocyte exchange. Brown and Zuelzer [2] have coined the term "rebound phenomenon" for the reflux of pigment into the intravascular compartment. Since this rapid reflux continues for some time after the transfusion, the phenomenon in question may be divided into a first phase coinciding with, and a second following, the exchange of blood.

The reduction in the serum bilirubin level during exchange transfusion performed on full-term newborns has been recorded serially [11], and it was thus possible to estimate the extent and time of the first phase of the phenomenon. The reduction of the serum bilirubin level was increasingly inhibited during the first half of the intervention, whereas the effect was practically stationary during the second half when the exchanged amount had reached the threefold of the circulating blood volume.

Further observations [12] and the analysis of records regarding a total of 50 transfusions performed under identical conditions have made it possible to establish certain mathematical relationships. The formulation of the exponential function expressing the arithmetic mean of the bilirubin values, and the narrow range of scattering allowed to compute the bilirubin level to be expected in any given case of blood exchange.

The distribution of bilirubin in the organism depends on numerous factors such as the proportion of the fluid compartments, the permeability of the membranes between these compartments, and also on whether a given tissue binds the bilirubin reversibly or irreversibly. Since the investigations of Martin [6] and Odell [8] indirect bilirubin circulating in the blood and the interstitial spaces is assumed to be attached to albumin. The proteins of the organism are therefore highly significant in the metabolism of bilirubin.

A consideration of these factors makes it clear that the factors being at play during blood exchange in premature babies must be substantially different from those in normal

newborns. It was for this reason and also with a view to collecting data concerning the possible results of exchange transfusions that we have studied the rebound phenomenon in prematurely born babies.

Material and Method

Fifty-one premature infants subjected to exchange transfusion have been studied. In every case the serum bilirubin level was determined at least three times during the intervention.

The body weight of the babies was
1000 to 1500 g, in 15 cases;
1501 to 2000 g, in 25 cases;
2001 to 2500 g, in 11 cases.

The serological distribution was,
Rh incompatibility in 10 cases, whereof 3 were sensitized;
ABO incompatibility in 12 cases, whereof 9 were sensitized;
Double incompatibility in 3 cases, whereof 1 was sensitized.

Sensitization was ascertained on the evidence of Coombs' direct and indirect reactions, as also by the presence in the maternal blood of anti-A and anti-B incomplete antibodies of adequate titre [1].

While maternal-foetal blood-group incompatibility could be demonstrated in 24 cases, it was not possible to prove sensitization in more than 13 instances. Exchange transfusion was resorted to in the other 38 cases on account of hyperbilirubinaemia above the permissible level [19].

Blood was exchanged by withdrawal from the radial artery and injection into the superficial temporal vein [4]. With this technique the disturbing influence of the dead space of catheters inserted in the umbilical vein is eliminated [17]. The average rate of blood exchange amounted to 100 ml/kg body weight/hour.

Results

The results are shown in percentage of the initial serum bilirubin level. Considering that the weight, and also the volume, of circulating blood varied consideraby, it seemed more convenient to refer the changes in bilirubin concentration not to the absolute amount of exchanged blood but to the extent of exchange, in other words to express the ratio, exchanged blood volume per circulating blood volume. Thus, on the abscissa in Fig. 1 the upper scale indicates that fraction of the prematures' circulating blood which has already been exchanged, while the lower scale shows (in ml) the corresponding amounts in the exchange transfusion of full-term babies.

The volume of circulating blood was taken to amount to 10 per cent of body weight on the basis of pertaining data for normal newborns [10] and prematures [15]. Accordingly, points $^1/_3$, $^1/_2$, etc., on the upper scale of Fig. 1 correspond to 100, 150, etc. ml on the lower scale.

Not more than one-and-half-times the amount of circulating blood having been exchanged in the examined premature infants, comparison with normal newborns was restricted to this phase of the tranfusion. Even within such limits it was up to a single exchange of the circulating blood that we obtained more numerous and so better evaluable data. The results are shown in Table I.

Fig. 1 illustrates the changes in the serum bilirubin level of 50 normal and 51 premature newborns. Both curves are based on mean values. Although the decrease in the serum bilirubin level was less pronounced in

TABLE I

	Name	Weight at birth	Exchanged blood, ml	Incompatibility		Sensitization	Serum bilirubin after the exchange of the following fractions of the circulating blood						
				ABO	Rh		Initial	1/3	1/2	2/3	1	1 1/3	1 1/2
1.	B. Á.	1000	100	+	—	+	9.6	6.2	—	5.7	5.4	—	—
2.	B. Zs.	1200	120	+	—	—	16.0	—	12,0	—	9.7	—	—
3.	I. B.	1700	170	+	—	+	14.5	—	10.6	—	5.1	—	—
4.	T. E.	1280	130	—	—	—	9.0	7.0	—	—	6.5	—	—
5.	P. M.	1410	140	—	—	—	10.0	9.7	—	—	8.6	—	—
6.	L. K.	1900	140	—	+	—	15.5	12.2	—	11.8	—	—	—
7.	F. J.	1730	120	—	+	—	17.2	—	12.7	12.0	—	—	—
8.	N. A.	1700	120	—	—	—	14.2	13.8	—	12.0	—	—	—
9.	H. I.	1500	120	—	—	—	16.5	15.4	—	14.8	—	—	—
10.	P. V.	1100	110	—	+	—	10.1	9.3	—	6.9	6.6	—	—
11.	H. S.	1770	170	+	—	+	14.0	12.2	11.0	—	7.4	—	—
12.	Sz. I.	1800	150	+	+	—	19.3	16.5	13.5	11.9	—	—	—
13.	R. A.	2050	200	+	+	—	14.2	12.3	—	9.8	8.2	—	—
14.	D. Cs.	1400	140	—	—	—	14.4	12.7	—	—	10.9	—	—
15.	M. G.	1800	180	+	—	—	18.8	14.6	—	12.3	12.0	—	—
16.	R. P.	1850	270	+	—	+	16.5	15.9	—	—	10.4	—	7.5
17.	T. E.	1850	230	—	+	—	15.1	14.6	—	—	7.9	—	4.3
18.	W. K.	2010	260	—	—	—	19.7	17.4	—	14.5	—	8.1	—
19.	V. T.	1600	160	—	+	+	18.8	12.8	—	11.7	11.3	—	—
20.	K. J.	1200	180	+	—	+	15.4	—	10.1	—	9.5	—	7.7
21.	F. A.	1670	170	—	—	—	23.0	14.5	—	13.5	10.1	—	—
22.	O. J.	2000	140	—	—	—	17.4	16.5	—	11.3	—	—	—
23.	P. Á.	2000	200	—	+	+	16.5	15.4	—	11.0	8.5	—	—
24.	H. K.	2400	240	+	—	+	20.6	18.8	—	13.3	13.1	—	—
25.	H. M.	1790	240	—	—	—	21.9	—	18.6	—	16.3	—	15.0
26.	P. L.	1470	200	—	—	—	31.0	—	25.0	—	15.0	13.2	—
27.	Sz. Gy.	1920	190	—	—	—	26.5	20.5	—	14.5	10.0	—	—
28.	B. T.	1750	160	—	—	—	41.5	33.0	—	28.0	25.0	—	—
29.	G. Cs.	1600	160	—	—	—	27.5	20.2	—	16.2	14.0	—	—
30.	Sz. E.	2060	200	—	—	—	23.1	21.2	—	16.2	14.0	—	—
31.	B. A.	2020	200	—	—	—	26.0	22.0	—	20.0	19.0	—	—
32.	R. T.	1170	180	—	—	—	19.0	16.7	—	—	11.7	—	11.0
33.	H. Z.	1900	150	+	—	+	20.0	16.0	—	13.0	—	—	—
34.	T. F.	1830	240	—	—	—	19.5	17.0	—	16.0	—	13.0	—
35.	B. K.	1670	240	+	+	+	18.7	—	17.0	—	—	—	14.2
36.	P. M.	2100	210	—	—	—	14.0	12.5	—	—	11.2	—	—
37.	V. T.	1950	250	—	—	—	24.2	21.5	—	18.2	—	12.2	—
38.	B. M.	2020	200	+	—	+	14.0	—	9.5	—	8.2	—	—
39.	B. N.	1760	180	—	+	+	15.0	13.1	—	11.7	9.2	—	—
40.	Sz. J.	1290	170	—	—	—	22.5	17.0	—	15.5	15.3	—	—
41.	M. P.	1570	210	—	—	—	13.2	—	11.0	—	—	10.2	—
42.	S. E.	2000	230	—	+	—	14.7	13.2	—	11.5	9.2	—	—
43.	N. A.	1770	280	—	—	—	12.2	11.5	—	10.2	—	—	7.7
44.	M. J.	1490	200	—	—	—	16.0	15.5	—	13.7	—	6.0	—
45.	R. Gy.	1520	200	—	—	—	18.2	14.2	—	13.7	—	11.2	—
46.	K. M.	1800	240	—	—	—	18.2	13.7	—	13.0	—	—	—
47.	R. Cs.	1270	190	+	—	+	15.0	14.7	—	13.2	—	—	4.2
48.	Cs. I.	1600	180	—	+	—	14.0	12.0	—	—	11.0	—	—
49.	G. G.	1500	230	—	—	—	16.2	14.0	—	—	10.5	9.2	3.6
50.	C. A.	2250	300	—	—	—	24.2	17.5	—	14.7	—	12.3	—
51.	L. J.	2400	330	+	—	—	22.3	16.7	—	13.0	—	12.1	—

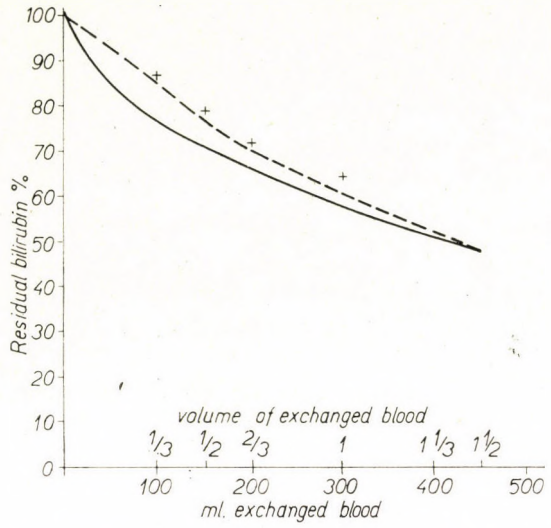

FIG. 1. Levels of the residual bilirubin in relation to the initial level are indicated on the ordinate, and the amount of exchanged blood on the abscissa. The latter is given as the actual amount of exchanged blood in the case of full-term babies, and as the fraction of circulating blood in the case of prematures.

A solid thick line indicates the mean decrease in the serum bilirubin level in normal newborns, and a thin dotted line that in prematurely born infants. Crosses stand for mean values in the lightest weight class of prematures

prematures than in fullterm infants, this difference became less and less with the progress of the transfusion. It amounted to 8 to 9 per cent (initial value = 100 per cent) at the beginning and fell to about 3 to 4 per cent after a single exchange of the amount of circulating blood, while the two curves practically coincided after one-and-half-times the volume of circulating blood had been exchanged.

The serum bilirubin level in the blood of the smallest premature infants (between 1000 and 1500 g) showed mean values in the course of transfusion that were above the mean values for all prematures; the number of examined cases was, however small so that, instead of plotting a separate curve, we have indicated these values by crosses in the diagram.

DISCUSSION

Our observations have made it evident that the decrease in the serum bilirubin level during the blood exchange of premature infants lags behind that of full-term babies. This lag is more pronounced in the first phase of transfusion and tends to disappear in the further course of the intervention.

Considering that the diminution of the serum bilirubin level during blood exchange is decisively influenced by the amount of extravascular bilirubin and its reflux to the blood path, the rebound phenomenon seems

to be more pronounced in premature than in normal newborns. Investigations in full-term babies showed the rate of the pigment reflux to have increased during the first phase of transfusion, i. e. until one-and-a-half-times the amount of circulating blood had been exchanged, and to have become stationary thereafter. This, together with our observation that the higher intensity of the rebound phenomenon in prematures ceases at the same limit, suggest that those factors which promote the reflux of bilirubin during the first phase of exchange transfusion in prematures tend to lose this capacity in the further course of the operation.

What are these factors?

The first to be mentioned is a change in the interproportion of extra- and intracellular fluids with the progress of foetal development. It has been demonstrated by McCance and Widdowson [5] that, in proportion to body weight, the volume of extracellular fluids is continuously decreasing, while the mass of cells, and so the amount of fluids in them, is continuously increasing during intrauterine life. Kerpel-Fronius expressed this rule by the statement [3] that the ratio between the total amount of proteins and that of intracellular fluids does not depend on age. This is only possible if the volume of intracellular fluid increases at the expense of the interstitial fluid hand in hand with the multiplication of cell proteins. It is generally accepted [7] that the fluid compartments of newborns bear the following proportions to the body weight (and so to one another):

plasma 5 per cent (of body weight)
extracellular fluid 45 per cent (of body weight)
intracellular fluid 30 per cent (of body weight)

The more premature the newborn, the larger the proportion of the extracellular fluids. Hence, the more premature the baby, the more bilirubin will be contained in the interstitial spaces which may then increase the rate of the rebound phenomenon.

A similar effect is produced by changes in the organism's lipid contents in the course of intrauterine growth. The chemical analysis of foetuses by Widdowson and Spray [18] revealed the amount of fat per g of body weight to increase exponentially with the increase of total body weight. The amount of bilirubin, irreversibly bound in the cells, being directly proportional to the lipid contents of the given tissue, it is evident that prematures whose tissues contain but a small amount of lipids, possess a comparatively large amount of mobilizable pigment in the cells. Gaining access to the extracellular compartment and then to the blood paths, it contributes to the intensification of the rebound phenomenon.

The amount of total protein in the organism increases during foetal development both absolutely and in proportion to body weight [9]. The amount of total serum protein is likewise known to increase during foetal life but is always less in pre-

matures than in full-term newborns [13, 16]. Changes in the level of serum albumin during intrauterine development are of especial importance. Although the proportion of albumin *vs.* the other serum proteins is high in the foetus, its absolute amount is low and reaches only gradually the value usual in normal newborns [14]. Circulating indirect bilirubin is bound by albumin, and it is therefore possible that the strong bilirubin-binding capacity of the donor's higher albumin level produces a stronger effect in premature than in normal infants. This, too, may contribute to enhancing the rebound phenomenon.

The transfusion rate constitutes still another factor. It has been noted that the blood exchange was slower in the prematures than in the corresponding full-term infants (100 instead of 130 ml/kg/hr), a circumstance which likewise helped to intensify the rebound phenomenon.

The fact that the intensification of the rebound phenomenon in premature infants becomes less and less marked with the progress of the transfusion admits of the conclusion that these rebound-promoting factors gradually weaken in the course of the intervention, a phenomenon which can only partially be explained by the new level of serum albumin due to the donor's blood.

Summary

The changes in the serum bilirubin level have been studied during exchange transfusion performed in 51 premature infants. The decrease in the serum bilirubin level was less than in full-term infants, although the difference grew less and less with the progress of tranfusion. The rebound phenomenon is, accordingly, more marked in prematures. This is believed to be due to a difference in body composition and the protein relationship of premature infants.

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