SOME PHYSIOLOGICAL RESPONSES OF NEONATAL ARTERIAL BLOOD PRESSURE AND PULSE RATE

BY

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To assess the extent to which the neonatal vascular system is capable of responding under physiological conditions, the influence of alterations in posture and of crying on the arterial blood pressure and pulse rate was observed during the first twelve days of life.

Material and Methods

A study was made of 71 normal infants ranging from 3 hours to 12 days old. The birth weight ranged from 4 lb. 1 oz. to 9 lb. 10 oz. (1,840 g. to 4,365 g.), only two falling into the premature-weight group. All had been born by spontaneous delivery and none had been distressed. The measurements were made in the afternoon one-half to two hours after a feed; the infants were awake but quiet.

Blood-pressure measurements were made on all the infants and repeated observations on 28 of these during their first 12 days of life. The pulse rate was counted in 14 of the babies, repeated observations being made on seven of these.

The systolic blood pressure was measured by palpation as described previously (Holland and Young, 1956). The pulse rate was counted from E.C.G. records taken continuously over three two-minute periods. The record was obtained from a precordial lead and one arm; the electrodes were held in place by "selotape." The average of three blood-pressure and pulse-rate readings taken with the child lying supine were recorded.

The effect of posture was then determined, both in the "feet-down" and in the "head-down" position, by tilting the cot at an angle of 80 degrees; the child needed supporting by the shoulders during these procedures. During these

• LYING
○ UPRIGHT

FIG. 1.—Effect of tilting on the systolic pressure in the neonatal period.

manoeuvres the position of the arm in which the blood pressure was measured was kept at approximately the same level in relation to the heart and the mercury manometer. The first arterial blood-pressure measurement was made within 30 seconds of the change in posture and was followed by two more readings within two minutes. Finally, the blood pressure was measured when the infant was crying in the supine position.

On six occasions the intrathoracic pressure was recorded in quiet and in crying babies in the supine position; this was measured by a Hansen capacitance manometer from a water-filled fine "polythene" tube introduced into the oesophagus (Dornhorst and Leathart, 1952).

Results

Arterial Blood Pressure.—Fig. 1 shows that tilting into the feet-down position did not alter the systolic pressure during the first three days of life in 31 out of 36 infants;

FIG. 2.—Influence of crying on the systolic pressure in the neonatal period.

between four and six days after birth a rise was observed in 20 out of 31 infants, and in all the older infants there was a rise in systolic pressure in response to tilting. The rise did not exceed 12 mm. Hg. Tilting into the head-down position did not alter the systolic pressure in any of the infants studied at any age. Fig. 2 shows that the pattern of the response, with respect to the age of the infant, was the same for crying; the blood-pressure changes were greater, and often a rise of 20 mm. Hg was observed.

Pulse Rate.—Fig. 3 shows that in 37 out of 50 observations the heart rate rose varying amounts from a few beats to 40 beats a minute in response to tilting into the feet-down position; one-half of these showed an increase of 15–20 beats a minute. The variation in response was evenly distributed throughout the period studied, as were the occasions on which there was no acceleration of the heart rate. Crying regularly caused an increase in pulse rate of about 40 a minute. Inspection of Fig. 3 shows that the resting pulse rate increased during the first 10 days of life in the group of infants studied. To substantiate this rise the resting pulse rate was measured in a further group of 12 infants, each on at least three days during this early neonatal period; the results are shown in Fig. 4.

FIG. 3.—Influence of tilting on the heart rate during the neonatal period.

FIG. 4.—Heart rate during the neonatal period; the mean of three readings is shown, together with the lowest and the highest limit.

Discussion

The increase of heart rate of about 35 a minute which occurs during the first 10 days of life accompanies the small rise in resting systolic pressure which was observed during this time. Vierordt (1906) recorded no change in pulse rate during a similar period.

Effect of Posture on the Neonatal Blood Pressure

In the normal adult a passive change of posture from the supine to the feet-down position causes an immediate fall in mean arterial pressure; recovery is rapid, and after about 30 seconds the mean pressure returns approximately to the recumbent level, with a decrease in pulse pressure and an acceleration of the heart rate. These changes have been observed both by Wald, Guernsey, and Scott (1937), using a "tycos" self-recording sphygmomanometer, and by Brigden, Howarth, and Sharpey-Schafer (1950) during continuous recording of intra-arterial pressure with a condenser manometer. The present observations on the newborn infant were made at a time corresponding to the recovery period in the adult, and have two special features: firstly, during

the first four days of life there was no change in systolic pressure on tilting into the feet-down position; and, secondly, during the succeeding 10 days there was always a small rise of systolic pressure after tilting. There was usually an acceleration of the heart rate in response to tilting in both age groups.

As these findings in the infant are, at present, isolated from other circulatory data during tilting, any consideration of them can only be speculative. The neonatal circulation may differ from the adult in several respects. Firstly, the venous pressure: during the first 24 hours of life this is relatively high, +3 to +5 cm. H₂O in the supine position (Mollison and Cutbush, 1949; Bonham-Carter, Bound, and Smellie, 1956), and until it is adjusted to adult levels may influence the arterial blood-pressure response to tipping. It might be expected that hydrostatic effects due to tilting would be smaller in the infant than the adult and that the reduction in venous pressure would be proportionately less; further, the relatively large head of the infant is enclosed in a non-rigid box and will contain a greater proportion of the total blood volume than in the adult, and on account of this it is possible that the equilibrium pressure of the venous column will be higher in the upright than in the supine position. The available data (Bonham-Carter *et al.*, 1956) show that the fall in the venous pressure in response to tilting during the first 24 hours of life is of the same order as that found in the adult (Brigden *et al.*, 1950); nevertheless, the venous pressure of the infant in the upright position is higher than in the tilted adult.

The second difference between the newborn and adult circulation is likely to be the degree of vasomotor activity. The maintenance of the systolic pressure at the recumbent level after tipping during the first few days of life suggests activity of the baroreceptors, though the acceleration of the heart rate accompanying the rise of arterial pressure in the older infants is not typical of a baroreceptor response and may be from the venous side.

Thirdly, the course of the circulation in the newborn infant may also influence blood-pressure responses; Adams and Lind (1957) have shown that the ductus arteriosus may be open and that there may be a reversed flow of blood through it, for pulmonary hypertension may persist in the normal infant for two weeks after birth.

Effect of Crying on the Neonatal Blood Pressure

Since the pattern of the response is the same with respect to the age of the infant both for crying and for tilting, it is tempting to suggest: (1) common mechanisms for the responses, and (2) that there is some fundamental change in the circulation occurring four to five days after birth. However, the situation is complicated by the large pressure changes occurring in the chest during crying, which may change rapidly from a negative to a positive sign, as such transients are known to be transmitted to the arterial system. Little is known of sympathetic activity during stress in the infant, and indeed such activity may also account for the blood-pressure responses to tilting.

Summary

The response of the systolic blood pressure and of the pulse rate to tilting into the feet-down position and to crying has been studied during the first 12 days of life.

During the first three to five days of life neither tilting nor crying altered the systolic blood pressure.

In the subsequent week of life both tilting and crying caused a rise in systolic pressure; the response to the latter was the greater.

The pulse rate increased in response to tilting.

The possible mechanisms which may be concerned are discussed, and it is suggested that there is some fundamental change in the neonatal circulation four to five days after birth.

Tilting into the head-down position did not alter the systolic pressure during the first 12 days of life.

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INTRINSIC FACTOR AND VITAMIN B₁₂ ABSORPTION*

BY

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With the isolation of vitamin B₁₂ (cyanocobalamin) it soon became obvious that Castle's original hypothesis was erroneous and that intrinsic factor did not react with an extrinsic factor to form haematinic principle which was stored in the liver. The more simple concept was formed that intrinsic factor was concerned with the absorption of vitamin B₁₂ from the intestine. This led to much intensification of work connected with its isolation and possible clinical application.

Glass, Boyd, Rubinstein, and Svigals (1952) demonstrated that it was associated with a more or less crude mucoprotein fraction of the gastric juice, and they therefore suggested that it might also be mucoprotein in nature. In my own laboratory, work was carried out on the preparative paper strip electrophoresis of human gastric juice (Latner, Ungley, Cox, McEvoy-Bowe, and Raine, 1953). A substance with intrinsic factor activity was present on the anode section of the paper strip. It contained hexosamine and was therefore probably mucoprotein in nature. This led to further chemical procedures and the eventual preparation of highly potent material.

The first work which we carried out was concerned with precipitation at low pH and subsequently with alcohol at low temperatures (Latner, Merrills, and Raine, 1954). We soon realized that this could possibly lead to breakdown of biological material, and we therefore decided to attempt isolation of the factor by the use of ion-exchange resins. This led to the production of a highly potent product which had a molecular weight of approximately 15,000 (Latner, Merrills, and Raine, 1956). The material was homogeneous on electrophoresis at two different pH values, as well as in the ultracentrifuge. Its activity, both clinically and by the radioactive vitamin-B₁₂-absorption test, was higher than any material previously described. There was little doubt that the material was a mucoprotein.

Williams, Ellenbogen, and Esposito (1954) have prepared a substance of molecular weight 5,000 which also had high intrinsic factor activity. Since they used trypsinization in their isolation procedure it was not unlikely that they might have broken down a substance of higher molecular weight. An important point, however, was the fact that both their material and our own possessed very low vitamin-B₁₂-binding power.

Holdsworth (1957) has claimed to have isolated a substance of molecular weight 40,000 which has vitamin-B₁₂-binding power and which is highly active as intrinsic factor.

It seems that three substances with intrinsic factor activity have been prepared from pig gastric mucosa—a mucopolypeptide with a molecular weight of 5,000, and two mucoproteins, one with a molecular weight of approximately 15,000 and another with molecular weight of 40,000. This has led to some confusion. If one considers Holdsworth's material as a possible precursor of intrinsic factor produced by the gastric mucosa and that modification of this precursor both in the stomach and in the small intestine eventually leads to intrinsic factor of relatively low molecular weight, then the whole position is more or less clarified. In relation to this concept it is interesting to note that O'Brien, Taylor, Turnbull, and Witts (1955) have prepared from human gastric mucosa a substance with intrinsic factor activity which has a molecular weight of about 40,000. Its activity in human beings was much less than the pig material we ourselves have isolated. It seems, therefore, that the material in question should really be regarded as a precursor of intrinsic factor.

Absorption Tests

In order to try to shed some light on this rather confusing picture, we have for some time been undertaking isolation procedures with freeze-dried pig pyloric mucosa. After treatment by ion-exchange and precipitation procedures this has yielded a preparation which has proved remarkably potent on clinical trial (see Fig.). There is no doubt that the clinical response was completely maximal. We gave 5 mg. of our intrinsic factor preparation daily together with 5 µg. of vitamin B₁₂. We have therefore carried out intestinal absorption tests at this dosage, and we have been able to demonstrate that we were able to bring about an absorption of approximately 2 µg. daily.

It is interesting that the ion-exchange procedures have also led to the isolation of material which has proved to be inhibitory to vitamin-B₁₂ absorption (Latner and Merrills, 1957). This material is mucoprotein in nature, possesses a molecular weight approximately equal to that of the intrinsic factor mucoprotein, but has a different tyrosine: tryptophan ratio. The behaviour on electrophoresis is remarkably like that of the intrinsic factor. The existence of such a substance is of the highest significance. Recent work throwing possible doubt on the efficacy of prolonged oral treatment in pernicious anaemia (Schwartz, Lous, and Meulengracht, 1957) should not be regarded as the final word in this matter. It is obviously still necessary to test preparations which are known not to contain inhibitor. Especially is this the case since the inhibitory effect in rats is still present some weeks after a single dose of inhibitor has been taken (Latner, unpublished observations).

We will now consider the physiological mechanisms concerned with the absorption of vitamin B₁₂ and the

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