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Blood Volume Changes during the First Week after Birth in the Beagle and Pig (40303)

STEPHANIE I. DEAVERS, RUSSELL A. HUGGINS, AND HWAI-PING SHENG

Department of Physiology, Baylor College of Medicine, Houston, Texas 77030

Birth marks the end of the parasitic and aquatic life of the fetus and the beginning of numerous physiological adjustments which adapt the newborn to a new and different environment. Among the adjustments which occur in different species at birth are those involving the circulatory system, and within this system are the changes in red cell and plasma volumes and venous hematocrit. However, data available for the newborn human over the first few days following birth present no clear pattern of change in the plasma volume, red cell volume, blood volume, or hematocrit. A portion of the variability in these data may be the result of early or late clamping of the umbilical cord (1, 2). But even if analysis of the data is restricted to those investigations where the cord is clamped early, the results are contradictory. Plasma volume, for example, is reported to remain constant over the first 24 hr following birth (3), to increase significantly within 3–5 hr (4, 5), to decrease in the first 2½ hr (6), or to increase over the period of 4–24 hr after birth (1). Changes reported for red cell volume, blood volume, and hematocrit are equally varied, although in most of these investigations blood volume and red cell volume are calculated from the measured plasma volume and hematocrit.

There are relatively few studies examining the changes in blood volume immediately after birth for species other than the human. In the pig, McCance and Widdowson (7) report a 30% increase in plasma volume 24 hr following birth, while Ramirez *et al.* (8) report a small but significant increase in blood volume during the first 12-hr period following birth. In the rat there is a small reduction in plasma volume between days 4 and 14 (9), but, contrary to the results of these authors, in the same species Garcia (10) reports a rise in plasma volume from birth to 15 days of age, and Constable, no significant change (11).

In the present article, data are presented for both the pig and the beagle for the period between birth and day 7 following birth, and the changes in plasma, red cell, and blood volumes and hematocrits are examined.

Materials and methods. The beagles used in this investigation were from the colony maintained at the Wynne Unit of The Texas Department of Correction in Huntsville. A description of the physical facility and the routine procedures used for breeding, immunization, and diet was published previously (12). A pig colony for research purposes was established while one of us (R.H.) was serving as acting chairman of the Department of Physiology at Mahidol University in Bangkok, Thailand, and was maintained at Kasetsart University by the courtesy of university officials and The Rockefeller Foundation. Details of the management of this colony also have been published (13). Standard procedures, modified for small animals, were used to measure red cell volume with ^{51}Cr (14) and plasma volume either with ^{131}I-albumin or the dye T-1824. There was no statistically significant difference between the plasma volumes measured with ^{131}I-albumin or T-1824 (12, 15). Hematocrits were measured by the micro method; no correction was made for trapped plasma. Beagle pups up to 3 hr after birth were not sedated, while those older than 4 hr were given 0.5–1 mg of morphine sulfate, injected subcutaneously. The pigs were anesthetized with 5–10 mg/kg of pentobarbital sodium, administered intravenously. Different animals, and usually from the same litter, were used for the collection of data for each of the time periods after birth.

Results. The data for the beagles are presented in Table I. For day 0 (day of birth) data were available from 10 min to 18 hr following birth, and because there was evidence of significant changes within this time, the data were divided into three 6-hr periods. The average age of the pups was 2.5 hr for

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TABLE I. RED CELL AND PLASMA VOLUME CHANGES IN NEWBORN BEAGLES.

Time after birth	Body weight kg	Red cell volume ml/kg	Plasma volume ml/kg	Blood volume ml/kg	Venous hematocrit %	Circulatory hematocrit[a] %	BVR cells[b]
0–6 hr (2.5 hr)[c]	0.190 ± 0.02[d] (12)[e]	49.2 ± 2.6 (12)	46.4 ± 1.5 (4)	95.6 ± 4.9 (5)	56.0 ± 1.9 (11)	51.0 ± 1.9 (5)	0.906 ± 0.02 (5)
6.5–12 hr (8.5 hr)	0.244 ± 0.005 (4)	38.7 ± 2.3 (4) $P < 0.05$[f]	45.3 ± 0.3 (4)	84.0 ± 2.6 (4)	52.3 ± 2.6 (4)	45.9 ± 1.3 (4)	0.881 ± 0.02 (4)
12–18 hr (16.5 hr)	0.266 ± 0.01 (4)	40.5 ± 1.0 (4)	53.3 ± 1.3 (4) $P < 0.001$	93.6 ± 2.0 (4) $P < 0.05$	47.5 ± 1.5 (4)	43.2 ± 0.4 (4)	0.912 ± 0.03 (4)
Day 0 (0–24 hr)	0.275 ± 0.01 (20)	45.4 ± 1.9 (20)	48.2 ± 1.1 (13)	91.3 ± 2.5 (13)	53.5 ± 1.4 (20)	47.1 ± 1.2 (13)	0.899 ± 0.01 (13)
Day 1 (24–48 hr)	0.251 ± 0.01 (10)	56.7 ± 4.5 (10) $P < 0.02$	62.2 ± 3.1 (10) $P < 0.001$	118.9 ± 2.5 (10) $P < 0.001$	52.1 ± 2.7 (10)	47.3 ± 2.9 (10)	0.892 ± 0.01 (10)
Day 2 (48–72 hr)	0.273 ± 0.006 (10)	46.2 ± 4.0 (10) $P < 0.05$	59.1 ± 2.2 (10)	105.3 ± 4.6 (10) $P < 0.05$	46.4 ± 2.6 (10)	43.3 ± 2.3 (10)	0.933 ± 0.02 (10)
Day 7	0.436 ± 0.21 (10)	35.6 ± 2.2 (10) $P < 0.001$	62.2 ± 2.6 (8)	97.8 ± 3.1 (10)	38.8 ± 1.5 (10) $P < 0.001$	36.4 ± 2.2 (10)	0.930 ± 0.01 (10)

[a] Red cell volume/(red cell volume + plasma volume).
[b] Circulatory hematocrit/venous hematocrit.
[c] Average time.
[d] Mean ± SE.
[e] Number of animals.
[f] P value for difference from previous value.

the first 6-hr period, 8.5 hr for the second period, and 16.5 hr for the last 6-hr period.

The mean red cell volume for beagles 2.5 hr old was 49.2 ± 2.6 ml/kg. In pups 8.5 hr old the red cell volume was significantly less ($P < 0.05$), and did not change again during the next 6-hr period. The plasma volume of pups 2.5 hr old was 46.4 ± 1.5 ml/kg, with no change during the next 6 hr; however, it was significantly higher ($P < 0.001$) in pups 16.5 hr old. Blood volume was 95.6 ± 4.9 ml/kg in pups 2.5 hr after birth and decreased in pups 8.5 hr old due to the decrease in red cell volume. The blood volume, as the result of a significant increase in plasma volume between 8.5 and 16.5 hr, was only slightly less at 16.5 hr than at birth. The venous hematocrit decreased during the successive 6-hr periods, resulting in a significantly ($P < 0.01$) lower hematocrit in pups 16.5 hr old than for those at 2.5 hr. The trend for the circulatory hematocrit was the same as that for the venous hematocrit; consequently, the ratio of circulatory to venous hematocrit was essentially unaltered.

Red cell and plasma volumes were significantly higher for the day-1 than for the day-0 pups, using the pooled data for the 20 beagles on day 0. This increase in plasma and red cell volumes resulted in a significant increase in blood volume ($P < 0.001$) for the day-1 pups. On day 2 there was a significant decrease in red cell volume and blood volume ($P < 0.05$), but only a slight reduction in plasma volume. On day 7 there was a further significant decrease ($P < 0.001$) in red cell volume, while the decrease in blood volume was not significant due to an increase, although not significant, in plasma volume.

Changes in venous and circulatory hematocrits reflected those of cell and plasma volumes throughout the period of study. Since the increases in red cell and plasma volumes between day 0 and day 1 were of the same magnitude (20–23%), neither circulatory nor venous hematocrit changed significantly, and the ratios of the two hematocrits (BVR_{cells}) remained the same. From day 1 to day 2 both venous and circulatory hematocrits decreased, but not significantly; however, between days 2 and 7 there was a further significant decrease in venous hematocrit accompanied by a similar change in circulatory hematocrit. The BVR_{cells} remained relatively constant over the first 7 days after birth (0.899 ± 0.01 on day 0 and 0.93 ± 0.01 on day 7), indicating that there was no shift in the distribution of red cells and plasma in the circulation during the 7-day period.

For the pig (Table II), the exact times at which red cell and plasma volumes were measured on day 0 were not known; therefore, only the mean value was calculated. The principal changes observed in the pig were an increase in plasma volume ($P < 0.05$) between days 1 and 2 and a decrease in red cell volume between days 0 and 2 and days 2 and 7, with the decrease on day 7 significant when compared with day 0 ($P < 0.05$). Blood volume decreased progressively, and on day 7 it was significantly less than that measured on day 0 ($P < 0.05$). Venous hematocrit decreased between days 0 and 1 ($P < 0.05$), with no further significant change on day 2 or day 7. The values for BVR_{cells} were 0.85 on day 0 and 0.79 on day 7.

Discussion. During the first few days after birth there are changes in both the red cell and plasma volumes in the beagle and the pig, but the pattern of the changes is different for the two species. What the red cell and plasma volume changes are in the human over the first few days after birth is uncertain at present because of the diversity of the data. However, data by Usher *et al.* (1) suggest that in the human neonate, as in the pig and beagle, there is over the first few days following birth an increase in plasma volume and a decrease in red cell volume and venous hematocrit, although there are differences in the time relationship at which the changes occur.

In the beagle the increase in plasma volume, which may occur as early as 12 hr following birth, is accompanied by an increase in plasma protein concentration. The increase in total protein concentration is due to an increase in the globulin fractions, while the albumin concentration remains stable, so that the albumin-globulin ratio decreased significantly (15). Thus the expansion of plasma volume can be explained by a shift of fluid into the circulation due to an increase in plasma protein. This shift of fluid among body compartments is substantiated further by the finding in the beagle that between days 0 and 1 there is a significant increase in the volume of extracellular fluid, at the expense of intracellular fluid, while total body water remains constant (16).

An increase in plasma volume similar to that in the beagle occurs in the pig, although the increase is between days 1 and 2. According to McCance and Widdowson (7), who first observed an increase in plasma volume within hours following birth of the pig the increase is the result of absorption of colostrum through the gut with a marked increase in the globulin portion of total plasma protein concentration. This mechanism is suggested also as an explanation of the plasma volume expansion in the beagle.

In the immediate neonatal period, red cell volume in the beagle, but not in the pig, is

TABLE II. RED CELL AND PLASMA VOLUME CHANGES IN NEWBORN PIGS.

Time after birth	Body weight kg	Red cell volume ml/kg	Plasma volume ml/kg	Blood volume ml/kg	Venous hematocrit %	Circulatory hematocrit[a] %	BVR cells[b]
Day 0	1.7 ± 0.05[c] (16)[d]	24.8 ± 2.1 (12)	63.2 ± 2.1 (11)	88.0 ± 3.2 (9)	33.1 ± 1.3 (16)	28.1 ± 1.4 (11)	0.85 ± 0.04 (11)
Day 1	1.6 ± 0.05 (14)	—	58.0 ± 2.5 (12)	—	27.1 ± 2.7 (14) $P < 0.05$[e]	—	—
Day 2	1.5 ± 0.14 (8)	20.2 ± 1.4 (7)	66.7 ± 3.3 (6) $P < 0.05$	86.9 ± 3.4 (5)	26.6 ± 1.3 (8)	23.0 ± 1.2 (6)	0.86 ± 0.03 (6)
Day 7	2.4 ± 0.11 (23)	19.7 ± 1.0 (15)	64.4 ± 1.5 (20)	82.7 ± 1.6 (12)	29.9 ± 0.8 (23)	23.8 ± 1.9 (15)	0.79 ± 0.04 (15)

[a] Red cell volume/(red cell volume + plasma volume).
[b] Circulatory hematocrit/venous hematocrit.
[c] Mean ± SE.
[d] Number of animals.
[e] *P* value for difference from previous value.

more variable than the plasma volume, and, unlike plasma volume, the changes are difficult to explain. At 2.5 hr after birth the red cell volume is 49.2 ± 2.6 ml/kg in the beagle, decreases significantly over the next 6–18 hr, increases during the next 24 hr, then decreases between 48 and 72 hr. The venous hematocrit reflects the changes in red cell and plasma volumes fairly consistently. For example, from day 0 to day 1 there is a significant increase in both red cell and plasma volumes, and as the percentage increase for both is the same, there is no change in the venous hematocrit. On day 2 there is a significant fall (19%) in red cell volume and a 5% decrease in plasma volume, and these changes are accompanied by an 11% fall in venous hematocrit. Inasmuch as the venous hematocrit is affected by shifts in both red cell and plasma volumes, it cannot be used alone to estimate changes in either red cell or plasma volume. Shifts in the circulatory hematocrit (whole body hematocrit) follow those of the venous hematocrit, so that the ratio of the two hematocrits remains approximately the same. Therefore, for the beagle over the 7-day period after birth, it is possible to measure either red cell or plasma volume alone and, by use of this ratio (BVR_{cells}) and the venous hematocrit, estimate the other with reasonable accuracy.

The blood volume for newborn mongrel pups is larger, 135 ml/kg (17), than the 95.6 ml/kg measured for the beagle. This difference in the data for the newborn dog results probably from two factors. The first factor is that Lee *et al.* (17) measured plasma volume and estimated red cell volume from the venous hematocrit. The latter represents the large vessel hematocrit and therefore overestimates the red cell and blood volumes. The second factor may be even more important than the first in the estimation of blood volume. In several species including the dog, the disappearance of both ^{131}I-tagged albumin and T-1824 dye from the circulation is more rapid in the newborn than in the adult (15). Consequently, with either of these tags, when the plasma volume is calculated from a single sample, as was done in the newborn mongrels, the later the time of sampling after injection of the tag on day 0, the greater will be the error in the plasma volume measurement. For instance, in pups on day 0 a sample taken 15 min after injection of the tag may overestimate plasma volume by 15%, resulting also in an overestimation of red cell and blood volumes.

The fluctuations in red cell volume in the beagle during the first week after birth pose several questions; one of them is the possible sites from which the red cells can be sequestered or released. The volume of red cells shifting into and out of the circulation is relatively large: between 2.5 and 8.5 hr after birth the circulating red cell volume decreases by 22%, while between 18 and 48 hr after birth red cell volume increases by 28%. Changes in red cell volume of a similar magnitude for the human over the first 5-hr period after birth are reported by Sisson and Whalen (18). The difference between their results (17) and those reported for other newborn humans (6) may be explainable on the basis of the time of cord clamping during birth. This explanation, however, does not appear to be applicable to the changes seen in the beagle. Sisson and Whalen (18) also postulated, as an explanation for the changes in red cell volume in the newborn human, "an initial temporary sequestration of blood in the viscera and caudal end of the body," and the blood was later "introduced into the general circulation as vascular and pulmonary patterns were stabilized."

The spleen and bone marrow are suggested also as blood reservoirs capable of significantly increasing blood volume in the human during the first 24 hr after birth (19). In the adult dog both the spleen and the liver are known to be active red cell reservoirs (20), but whether this is true also in the newborn pup can be inferred only from indirect data. The unit red cell volume (ml/100 g) of all organs in the beagle decreases between days 0 and 1 (21, 22). The combined red cell volume of the heart, lungs, kidneys, spleen, stomach, skeletal muscle, intestines, and skin is 28% of the total red cell volume on day 0, but decreases to 16% on day 1. The decrease in the volume of red cells in these tissues coincides with an increase in the circulating red cell volume on day 1. These data, while providing no information on the mechanisms concerned in the relatively rapid fluctuations in red cell volume of the newborn beagle, do provide tentative support to the idea that there may be reservoirs of red cells in the circulation of the newborn and that red cells move in and out of these reservoirs under the control of unknown stimuli.

Summary. During the first week of postnatal life, there were significant changes in red cell volume, plasma volume, and venous and circulatory hematocrits in both the beagle and the pig. In beagle pups the mean red cell volume decreased between 2.5 and 8.5 hr after birth, then increased at 16.5 hr, with a further increase on day 1. Between days 2 and 7, red cell volume decreased. There was evidence of a release of red cells into the circulation from red cell reservoirs. In the newborn pig, red cell volume decreased between days 0 and 2, but was not significantly different on day 7 from day 2. In the beagle the mean plasma volume did not change during the first 12 hr following birth; it increased between 12 and 24 hr after birth and remained unchanged through day 7. In the pig, plasma volume decreased between day 0 and day 1, increased on day 2, and was not significantly different on day 7 from day 2. The increase in plasma volume was the result of an increase in plasma protein, which caused a redistribution of fluid among the various fluid compartments. In the beagle, blood volume decreased between 2.5 hr and 8.5 hr, increased at 16.5 hr with a further increase on day 1, then decreased on day 2, with no further change on day 7. The blood volume in the pig decreased progressively between day 0 and day 7. The changes in venous and circulatory hematocrits for both the beagle and pig reflected those of red cell and plasma volumes throughout the first week of life. The BVR_{cells} did not change significantly, indicating that there was no shift in the distribution of red cells and plasma in the circulation over this 7-day period.

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