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Renin and aldosterone response in human newborns to acute change in blood volume

M. J. DILLON, K. B. RAJANI, V. SHAH, J. M. RYNESS, AND R. D. G. MILNER*

From the Institute of Child Health, University of London, and Department of Child Health, University of Manchester

SUMMARY Increased activity of the renin/aldosterone system in the neonatal period is now well established in both animals and man but the control mechanisms are poorly understood. We have monitored the plasma renin activity (PRA) and plasma aldosterone concentration (PAldo) in 14 infants undergoing 21 exchange transfusions. PRA and PAldo were measured before and at 5, 10, 15, 30, 45, and 60 minutes after the injection, and 5, 10, 15, and 30 minutes after the withdrawal of 7 ml blood/kg birthweight immediately before exchange transfusions. PRA increased to a maximum of 53% and decreased to a maximum of 39% of the resting values after withdrawal or injection of blood respectively. PAldo values did not change significantly during the same period. Thus the renin-angiotensin system in the newborn infant is responsive to changes in blood volume.

The revival of interest in renin about 40 years ago was not entirely confined to adults. Grossman and Williams (1938) found greater concentrations of renal renin in the young of rats and cattle than in the adult animals. Since then several animal studies have shown increased activity in the renin-angiotensin-aldosterone system in the newborn of various species (Broughton Pipkin *et al.*, 1971, 1974; Granger *et al.*, 1971; Malinowska and Nathanielsz, 1974). Similar findings have been reported in the human newborn (Kotchen *et al.*, 1972; Hayduk *et al.*, 1972; Beitins *et al.*, 1972; Siegel *et al.*, 1974; Katz *et al.*, 1974; Broughton Pipkin and Smales, 1975; Dillon *et al.*, 1976).

It has also been shown that in fetal and newborn animals the renin-angiotensin system responds to various stimuli that result in renin release in adults. Hypovolaemia due to haemorrhage stimulates renin release in fetal and newborn lambs (Smith *et al.*, 1974; Broughton Pipkin *et al.*, 1974) and newborn kittens (Broughton Pipkin, 1973). Suprarenal aortic constriction has been shown to have a similar effect in fetal lambs (Smith *et al.*, 1974). Saline depletion due to diuresis also increases renin production in fetal and newborn lambs (Trimper and Lumbers, 1972; Fleischman *et al.*, 1975), and peritoneal dialysis results in similar changes in newborn dogs (Granger *et al.*, 1971).

Thus evidence does exist that in both fetal and newborn animals the renin-angiotensin system responds to changes in blood volume. In the human newborn there are very limited data available. This prompted us to consider the use of exchange transfusion as a model to measure the response of the renin-angiotensin-aldosterone system to changes in blood volume. This was made possible by the development of semi-micro techniques which allowed the concurrent measurement of plasma renin activity (PRA) and plasma aldosterone concentration (PAldo) on a total volume of 750 µl plasma (Dillon, 1975; Dillon and Ryness, 1975). A preliminary report of this work has been published (Dillon *et al.*, 1975).

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*Present address: Department of Paediatrics, University of Sheffield, Sheffield S10 2TN

Patients

Fourteen newborns undergoing 21 exchange transfusions were studied (Table 1). Gestational ages varied from 31 to 40 weeks (mean 35 weeks) and birthweight from 1·50 to 3·4 kg (mean 2·3 kg). 9 infants had rhesus haemolytic disease, 3 had ABO incompatibility, in 1 there was severe bruising possibly causing the jaundice, and in 1 hyperbilirubinaemia was of unknown cause. Age at initial transfusion varied from 1 hour to 6 days. All infants were fed on SMA (humanised milk formula) and the blood used for exchange transfusion was acid-citrate-dextrose in type. There was no evidence of cardiovascular or renal disease. Any baby in whom a previous exchange transfusion had proved complicated was excluded.

Table 1 *Clinical details of 14 patients studied*

*Patients and exchange transfusion number**	*Postnatal age at transfusion (h)*	*Gestational age (w)*	*Body weight (g)*	*Last feed in hours before transfusion*	*Underlying disease*
AI	3	33	1750	—	RHD
III	50			1	
B	72	31	1700	1	?
CI	1	36	2600	—	RHD
II	48			1·5	
III	72			3	
D	96	40	3400	3	Bruising
EI	48	31	1990	?	RHD
II	96			?	
III	96–120			?	
F	2	33	1840	—	RHD
GI	40	33	1700	1	ABO
II	58			1	
III	67			?	
H	25	32	3210	—	RHD
I	5	38	3020	2·5	RHD
J	144	39	3100	3·5	RHD
K	7	38	2880	1·5	RHD
L	144	37	2300	4	ABO
M	5	37	2840	—	RHD
N	72	33	1980	2	ABO

*Roman numerals indicate number of exchange transfusions during which the patients were studied.
RHD = rhesus haemolytic disease; ABO = ABO incompatibility.

Methods

After the siting of an umbilical venous or arterial catheter, zero time blood samples were taken with minimal delay. Blood, equivalent to 8% of the total blood volumes, was then infused into 8 newborns undergoing 10 exchange transfusions. Samples of blood were taken at 5, 10, 15, and 30 minutes, and the volume of blood taken for sampling was immediately replaced so that the infant was continuously kept in this hypervolaemic state for the study period. In 4 infants the study period was extended and samples were taken at 45 and 60 minutes. Samples were taken for measurement of PRA, PAldo, haematocrit (PCV), sodium (Na), potassium (K), and osmolality (OSM). Identical measurements were also undertaken on the donor blood used for transfusion. Similarly, 9 newborns undergoing 11 exchange transfusions were kept in a hypovolaemic state for 30 minutes by initially withdrawing 8% of their total blood volume. The exchange transfusion continued after 30 or 60 minutes in a standard fashion. The babies remained horizontal both before and during the procedure, since changes of posture have pronounced effects on renin secretion.

PRA was measured on 0·25 ml plasma by the radioimmunoassay of generated angiotensin I (AI) (Dillon, 1975) and expressed as ng AI/l per hour. PAldo was also measured by radioimmunoassay on 0·5 ml plasma using a modification (Dillon and Ryness, 1975) of the method of Mayes *et al.* (1970) and expressed as pmol/l.

Results

Tables 2–5 give the PRA and PAldo data during the blood overload and deficit experiments. Since there was considerable variation in resting PRA and PAldo values, and a lack of uniformity in the time of minimal or maximal responses to injection or withdrawal of blood, it seemed appropriate to analyse the results in terms of the percentage change of resting PRA and PAldo values.

Table 2 *PRA (ng AI/l per h) during the blood deficit experiments*

Patients	*Donor blood*	*Time (min)*				
		0	*5*	*10*	*15*	*30*
AI	310	3 600	3 730	4 000	7 990	6 900
AIII	330	6 380	11 050	9 800	9 700	6 890
B	150	7 090	6 120	10 980	6 720	4 460
CII	2430	9 050	—	—	17 020	9 790
D	110	1 210	2 080	2 520	2 650	3 360
EIII	110	10 090	11 950	12 280	7 160	12 770
F	40	4 650	5 490	6 110	5 860	7 420
GI	175	2 680	1 870	2 240	2 210	2 630
GIII	30	1 510	2 610	2 520	3 990	3 180
H	80	5 460	8 580	10 180	8 880	10 180
I	90	7 510	5 310	3 200	3 270	2 290

Note: In Tables 2 and 3 the patients are represented by letters A–N. Roman numerals indicate the number of exchange transfusions during which the patients were studied.
PRA = plasma renin activity; AI = angiotensin I.

Table 3 *PRA (ng AI/l per h) during the blood overload experiments*

Patients	*Donor blood*	*Time (min)*						
		0	*5*	*10*	*15*	*30*	*45*	*60*
J	630	3 990	2 170	1 075	2 160	1 840	—	—
K	330	330	420	770	1 160	660	—	—
CI	810	13 830	—	—	6 140	8 320	6 230	8 420
CIII	150	14 120	—	—	6 840	8 670	2 630	8 910
L	90	2 325	—	—	1 490	2 260	2 930	1 620
M	110	2 750	—	—	1 880	1 290	1 530	1 880
EI	150	7 180	6 950	8 840	9 670	5 000	—	—
EII	—	13 690	11 330	13 950	12 900	11 830	—	—
GII	210	3 360	4 140	4 100	3 180	2 470	—	—
N	70	2 850	1 160	2 630	1 185	855	—	—

Table 4 *PAldo (pmol/l) during the blood deficit experiments*

patients	*Donor blood*	*Time (min)*				
		0	*5*	*10*	*15*	*30*
AI	295	3 440	3 000	3 000	2 890	3 360
AIII	1025	8 540	6 530	6 310	6 980	—
B	470	7 090	6 670	7 090	8 200	7 730
CII	620	7 810	—	—	13 200	8 620
D	—	3 225	2 410	3 590	2 750	2 750
EIII	—	6 950	5 365	3 830	7 420	5 090
F	—	2 060	2 220	2 220	2 170	2 000
GI	260	5 730	3 610	4 615	4 110	2 890
GIII	80	2 220	2 335	2 220	2 310	3 590
H	805	4 000	2 500	2 290	2 060	2 280
I	—	8 610	9 190	8 800	11 950	13 200

Note: In Tables 4 and 5 the patients are represented by letters A–N. Roman numerals indicate the number of exchange transfusions during which the patients were studied.
PAldo = plasma aldosterone.

Table 5 *PAldo (pmol/l) during the blood overload experiments*

Patients	*Donor blood*	*Time (min)*						
		0	*5*	*10*	*15*	*30*	*45*	*60*
J	450	5 950	9 450	8 900	5 870	6 230	—	—
K	330	4 730	4 280	4 920	3 000	3 840	—	—
CI	240	5 920	—	—	2 975	1 080	2 975	8 620
CIII	920	11 950	—	—	16 680	4 840	1 890	—
L	—	16 460	—	—	13 760	14 900	19 130	—
M	285	3 310	—	—	7 290	3 780	3 450	10 670
EI	—	1 610	5 560	1 110	1 835	3 030	—	—
EII	—	5 365	3 170	4 090	4 090	4 950	—	—
GII	205	2 170	4 250	2 890	2 280	2 030	—	—
N	150	1 530	1 220	1 640	1 195	2 810	—	—

Fig. 1 shows the PRA results during the overload and deficit experiments. The deficit experiments show that withdrawal of blood caused a gradual rise in PRA, reaching 53% above the resting value at 30 minutes. Similarly the overload experiments showed a fall of 39% of resting values at 45 minutes. During overload there was an unexpected early rise in PRA. If the rise in PRA on withdrawal at 30 minutes and the fall in PRA on infusion at 30 minutes are compared there is a significant difference ($P<0{\cdot}005$).

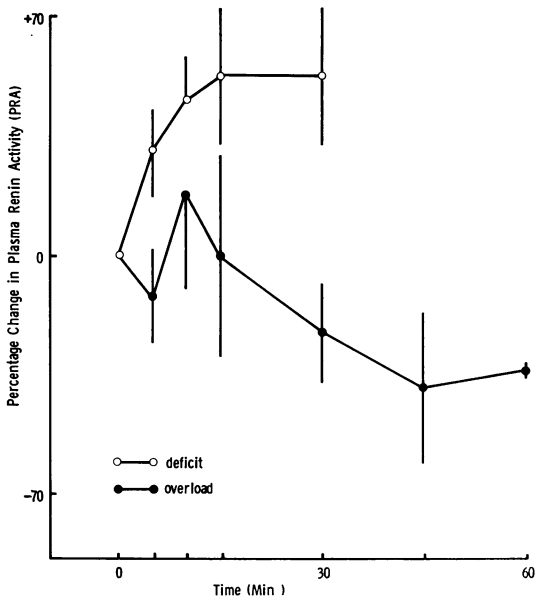


Fig. 1 *Plasma renin activity response to acute change in blood volume. Mean percentage change* (±2 *SD*).

Fig. 2 shows the percentage change in PAldo values during the overload and deficit experiments. On overload, there was an early rise in PAldo at 5 minutes but subsequent values were not significantly different from the resting values. During the deficit experiments PAldo fell slightly but this change was

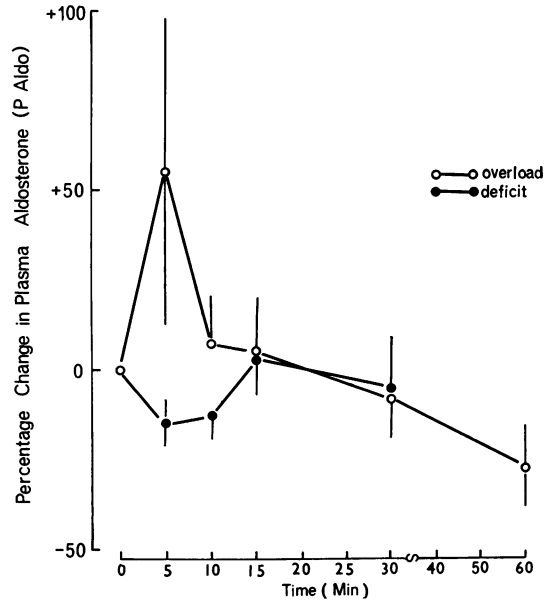
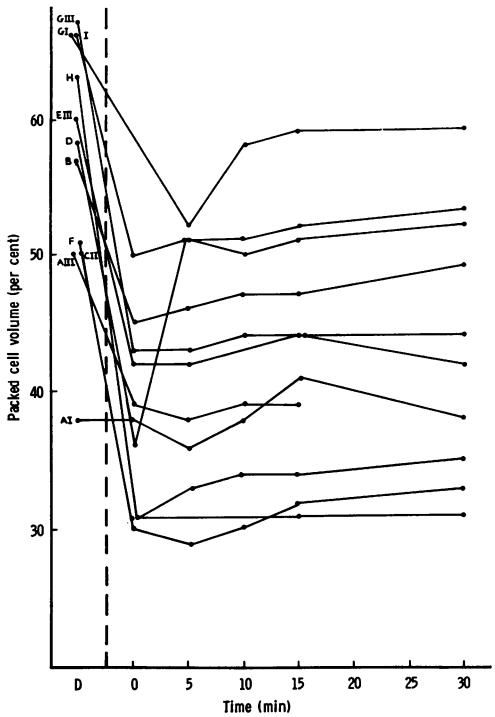


Fig. 2 *Plasma aldosterone response to acute change in blood volume. Mean percentage change* (±2 *SD*).

not statistically significant. PCVs, plasma OSM, Na, and K values in donor blood and in samples from patients before and during study periods are shown in Figs. 3–6. K values in severely haemolysed specimens were excluded but moderately haemolysed values are included, but distinguished from nonhaemolysed values.

No correlations emerged between initial PRA and PAldo values in patients and gestational age, birthweight, postnatal age at time of study, and time of last feed, even though some correlation appears to exist at other times in the study period. However, initial PRA was greater ($P<0{\cdot}01$) in infants with rhesus incompatibility than in those with other causes of jaundice although there were no significant differences detected in initial PAldo between the two groups. The relationship between donor blood PRA, PAldo, PCV, OSM, Na, and K, and subsequent values of PRA and PAldo in patients during the study was analysed. Similarly the relationship between PRA and PAldo in the infants and the above measurements at various times during the study was also analysed.

There appeared to be some positive correlation between donor blood PRA and the patients' PAldo at 5 and 10 minutes ($r = 0{\cdot}52$ and $0{\cdot}55$ respectively, $P<0{\cdot}05$) and also the patients' PRA at 15 and 45 minutes ($r = 0{\cdot}64$ and $r = 0{\cdot}95$, $P<0{\cdot}01$). Similarly, donor blood PAldo was positively correlated with patients' PRA at 5, 10, 15, and 30 minutes ($r = 0{\cdot}67$, $P<0{\cdot}05$; $r = 0{\cdot}72$; $P<0{\cdot}01$; $r = 0{\cdot}58$, $P<0{\cdot}05$;



(*a*)

Fig. 3 *Packed cell volume during (a) deficit and b) overload experiments. D = donor blood values.*

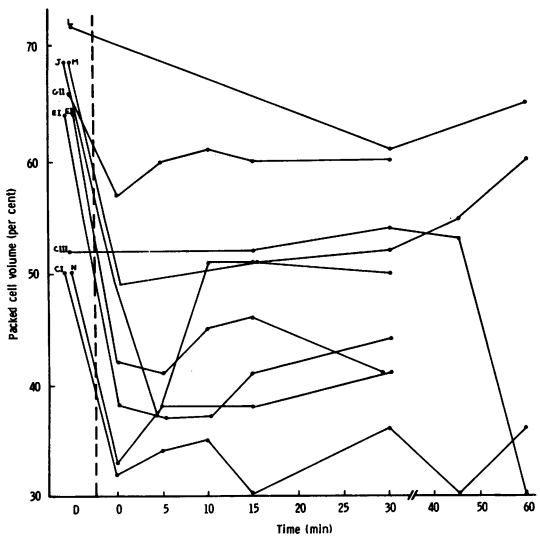


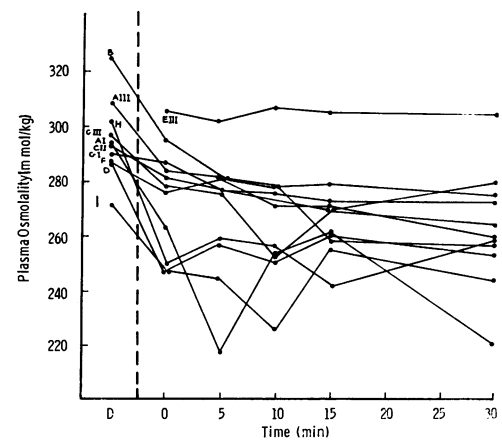
Fig. 3(*b*)

and r = 0·64, P<0·01, respectively) and with the patients' PAldo at 15 and 45 minutes (r = 0·61 and r = 0·93, P<0·05). There was a just significant positive correlation between donor OSM and the infants' 10-minute PRA (r = 0·59, P<0·05) and a negative correlation between donor K levels and the 30-minute PRA values in the patients (r = —0·57, P<0·05).

Donor PCV was negatively correlated with the 60-minute PRA (r = —0·98, P<0·001), and there were also negative correlations between gestational age and patient PRA at 10, 30, and 60 minutes (r = — 0·71, P<0·001; r = —0·46, P<0·05; and r = —0·99, P<0·001 respectively) and between birthweight and PAldo at 45 minutes (r = —0·86, P<0·05). Positive correlations were found between 45-minute PAldo and age at time of study (r = 0·84, P<0·05) and 45-minute PRA and PAldo and time of last feed (P<0·01). There were positive correlations between zero time OSM and PRA (r = 0·51, P<0·05) and between 5 and 45-minute Na and PRA (r = 0·5, P<0·05; and r = 0·93, P<0·05 respectively). Negative correlations were found between PCV and PRA at 15, 45, and 60 minutes (r = 0·49, P<0·05; r = —0·98, P<0·01; and r = —0·99, P<0·001 respectively) and between K and PRA at 45 minutes (r = —0·95, P<0·05).

Discussion

The use of exchange transfusion as a model for evaluating the renin-angiotensin-aldosterone system may be criticised. It can be argued that infants undergoing exchange transfusion for haemolytic disease or other causes of hyperbilirubinaemia are not normal and that there is evidence that neonatal



(*a*)

Fig. 4 *Plasma osmolality during (a) deficit and (b) overload experiments. D = donor blood values.*

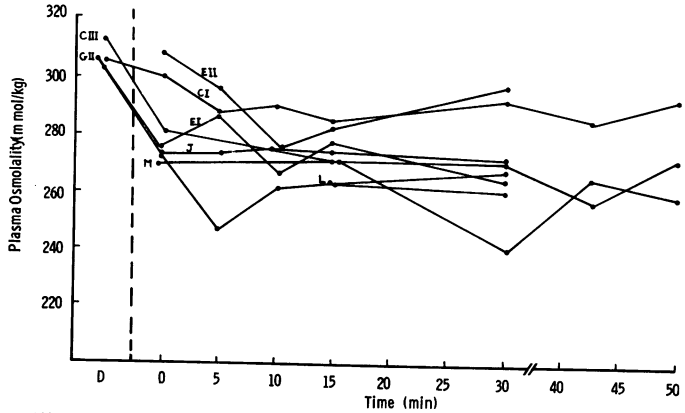
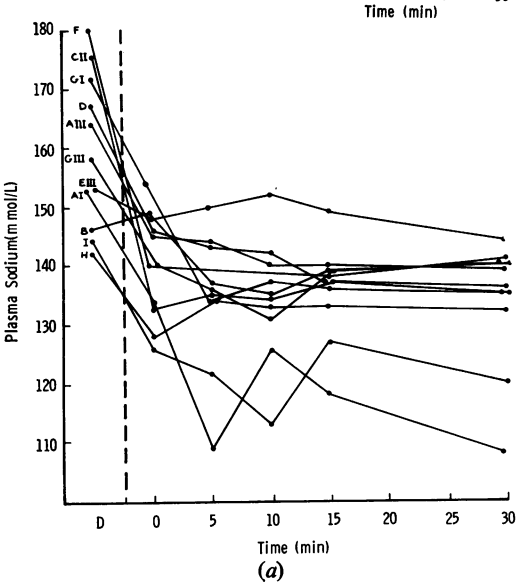


Fig. 4(*b*)



(*a*)

Fig. 5 *Plasma sodium during* (*a*) *deficit and* (*b*) *overload experiments. D = donor blood values.*

haemolytic disease increases the levels of plasma renin concentration (Symonds *et al.*, 1974). Our findings support this view. However, the ethical considerations which precluded this type of study in normal healthy newborns were not applicable in the context of therapeutically necessary exchange transfusions.

Our results show that in the human newborn infant the renin-angiotensin system is responsive to changes in blood volume. Our findings are similar to those of Broughton Pipkin (1971, 1973) and Broughton Pipkin *et al.* (1974) in newborn animals. However, in these reports the effects of removal of 25% of blood volume were studied and shown to cause a mean increase in angiotensin-like activity of from 145 to 231% of a wide range of resting values. The same workers (Broughton Pipkin *et al.*, 1974) found that removal of as little as 3% blood volume from unanaesthetised fetal lambs was sufficient to increase plasma renin and that high values were recorded after withdrawal of blood samples at intervals for 4 hours. In these studies, plasma renin did not fall to the initial concentrations.

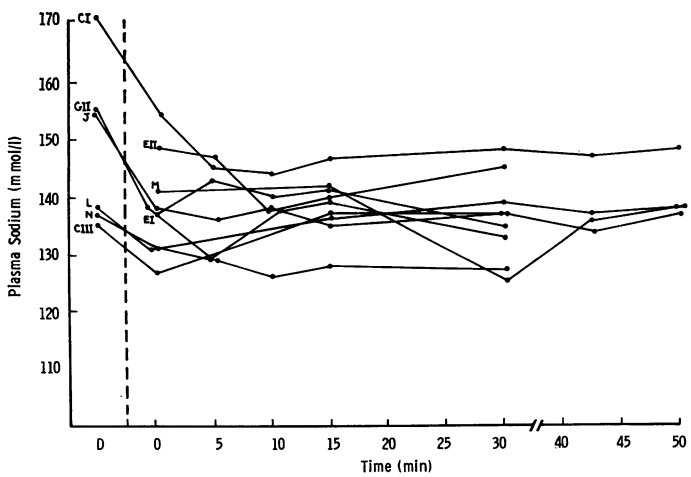
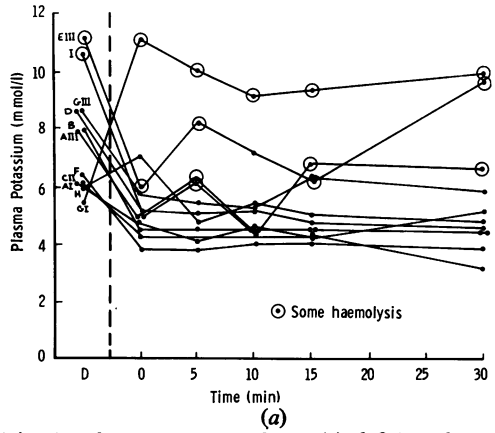
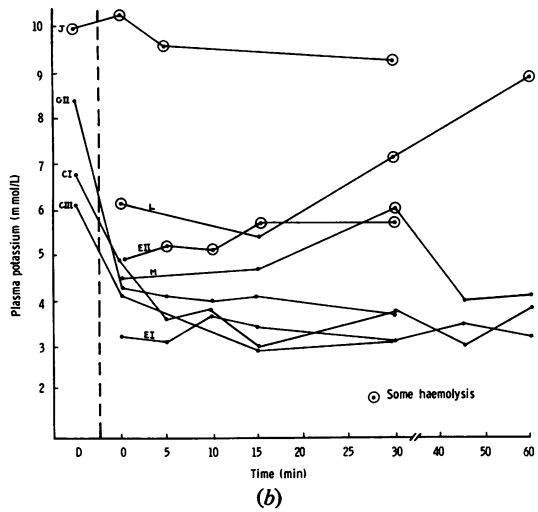


Fig. 5(*b*)



(*a*)



(*b*)

Fig. 6 *Plasma potassium during (a) deficit and (b) overload experiments. D= donor blood values.*

Hodge *et al.* (1966) showed that a decrease in blood volume in newborn dogs stimulated the renin-angiotensin system regardless of whether there was a simultaneous fall in arterial pressure. Carver and Mott (1975) showed, also in animals, that plasma renin and angiotensin II concentrations can be reduced by expansion of fetal blood volume. These findings imply that the renin-angiotensin system may have an important role to play in the distribution of fetoplacental blood volume and hence the distribution of cardiac output between systemic and placental vascular beds (Mott, 1975). It is therefore not surprising that in the newborn human infant this system is also responsive to blood volume changes.

Our findings of an early rise in PRA during the overload experiments could be due to activation of the sympathetic system which may itself cause renin release (Kotchen *et al.*, 1972). Catheterisation of the umbilical vessels may have been a factor. In addition, McDonald and Smith (1972) have shown that an increase in PCV in dogs can cause renin release, but we were unable to show that PCV increased significantly in our patients. Moreover, we found that there was a negative concentration between PCV and PRA in the infants at 15, 45, and 60 minutes.

Our data suggest that aldosterone, as might be expected, is not as responsive as renin to changes in blood volume. From the work on adults, in which renin and aldosterone responses to various stimuli have been studied, it might be anticipated that aldosterone responses to renin stimulation are delayed by 15 to 20 minutes (Bayard *et al.*, 1971). We therefore felt that our findings reflected the shortness of the observation period. But extending this to 60 minutes in several subjects failed to clarify the aldosterone response. In fact, the maximum response appeared to occur 5–10 minutes after initial overload or withdrawal. The early rise in aldosterone during the overload experiments paralleled the similar change in PRA mentioned above and could be associated with it. On the other hand, there is no doubt that newborn levels of plasma aldosterone can change in response to other stimuli, for example, saline overload or depletion. There was no evidence however of consistent plasma electrolyte or osmolality change during the transfusions that could be correlated with plasma aldosterone values.

The initial scatter of resting values for PRA and PAldo necessitating analysis in terms of the percentage change has not been explained. No correlation between zero time values and gestational age, birthweight, postnatal age, and time of last feed could be shown although babies with rhesus incompatibility had higher values for PRA than the others. In addition, there was a positive correlation between plasma osmolality and initial PRA which just reached statistical significance, but this was the only significant finding. Overall, there were no clear differences between plasma osmolality in rhesus and nonrhesus babies although it is fair to say that some of the hydropic babies did have very high osmolalities.

The presentation of our data may be slightly misleading since not all babies behaved in the same way. Those who responded differently may have started out with different relative blood volumes so that loading or depletion of blood might have simply effected a return towards normal values, though we have no convincing evidence of this.

Donor blood levels of PRA and PAldo were positively correlated with values of PRA and PAldo in the patients at times during the study. As mentioned in the results section, several other correlations were shown between PRA and PAldo in the infants and other measurements, including gestational age,

birthweight, postnatal age, time of feed, and at various times, infant plasma OSM, Na, K, and PCV. However, no consistent pattern emerged and it was not possible to explain the PRA and PAldo changes after blood overload and deficit in terms of these findings. Moreover, many of these correlations only just reached statistical significance and we would not wish to overemphasise them.

Our findings and other published reports give compelling evidence that the renin-angiotensin-aldosterone system is extremely active in the neonatal period. The purpose this activity serves is still uncertain although there are many reasons to suppose that the newborn is dependent on the functional integrity of this system, to maintain blood pressure and sodium homoeostasis. If so, there may be advantages in preventing the suppression of the renin-angiotensin-aldosterone system in the newborn.

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Correspondence to Dr M. J. Dillon, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.