Body water content of extremely preterm infants at birth

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Abstract

Background—Preterm birth is often associated with impaired growth. Small for gestational age status confers additional risk.

Aim—To determine the body water content of appropriately grown (AGA) and small for gestational age (SGA) preterm infants in order to provide a baseline for longitudinal studies of growth after preterm birth.

Methods—All infants born at the Hammersmith and Queen Charlotte's Hospitals between 25 and 30 weeks gestational age were eligible for entry into the study. Informed parental consent was obtained as soon after delivery as possible, after which the extracellular fluid content was determined by bromide dilution and total body water by $H_2^{18}O$ dilution.

Results—Forty two preterm infants were studied. SGA infants had a significantly higher body water content than AGA infants (906 (833–954) and 844 (637–958) ml/kg respectively; median (range); p = 0.019). There were no differences in extracellular and intracellular fluid volumes, nor in the ratio of extracellular to intracellular fluid. Estimates of relative adiposity suggest a body fat content of about 7% in AGA infants, assuming negligible fat content in SGA infants and lean body tissue hydration to be equivalent in the two groups.

Conclusions—Novel values for the body water composition of the SGA preterm infant at 25–30 weeks gestation are presented. The data do not support the view that SGA infants have extracellular dehydration, nor is their regulation of body water impaired.

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Keywords: body composition; water compartments; growth restriction; newborn; preterm; dehydration

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Preterm birth is often associated with nutritional compromise and impaired growth performance. Recent epidemiological research has also suggested that poor intrauterine growth may set the scene for several diseases of adult life.[1] There is therefore a legitimate interest in the composition of the preterm infant, both appropriately grown (AGA) and those small for gestational age (SGA), of whom most will have suffered intrauterine growth restriction. This study was carried out to obtain data on the body water content of preterm infants of less than 30 weeks gestation and to compare the body composition of AGA and SGA infants.

The first report of the composition of the human fetus appeared in 1857 with the work of von Bezold.[2] This was followed by a number of cadaver studies,[3–5] up to and including that of Widdowson and Spray in 1950.[6] It is not known whether the early cadaver studies involved fetuses that were AGA or SGA, and in recent years, with the development of techniques to assess body composition in vivo, few cadaver studies have been carried out. More recent in vivo studies have largely excluded the preterm SGA infant. The only available data on the body composition of such infants is from a study by van der Wagen *et al*[7] in which seven infants with gestations ranging from 32 to 39 weeks were investigated. To our knowledge, there are no published data on the body composition of SGA preterm infants of less than 30 weeks gestation.

Methods

Measurements of body water compartments at birth were made as part of a larger study investigating fluid balance in preterm infants. Inborn infants between 25 and 30 weeks gestation admitted to the neonatal units at the Hammersmith and Queen Charlotte's Hospitals, London, UK were eligible for recruitment. The study was approved by the institutional research ethics committee, and written informed parental consent was obtained. Infants with major congenital abnormalities and obvious derangements of fluid balance such as hydrops were excluded.

SGA infants were defined as those who were below the 9th centile on the Child Growth Foundation charts (Child Growth Foundation 1996/1, 2 Mayfield Avenue, London W4 1PW, UK). Gestational age was determined from maternal dates confirmed by an early ultrasound dating examination.

Total body water (TBW) and extracellular fluid volume (ECFV) were determined as soon as possible after delivery. TBW was measured using $H_2^{18}O$ dilution as previously described.[8] Briefly, after taking a baseline sample of blood, the infant was given 1 ml/kg water enriched with $H_2^{18}O$. The exact amount of water administered was determined by weighing the syringe before and after administration of the water on a chemical balance accurate to ± 0.0001 g. The water was administered by nasogastric tube, and the tube was flushed with a further 2 ml sterile water for injection. Two further blood samples were taken as close to three and six hours after $H_2^{18}O$ administration as possible, the exact time being noted (blood sampling

was timed to coincide with clinical sampling whenever possible). The sample was spun immediately, and the serum separated and frozen at −20°C until analysed. Exact times of sampling were noted in order to extrapolate backwards to a concentration at time zero (C_0). Extrapolation to time zero was performed by linear regression on the $\log_e$ values of ^{18}O concentrations (ppm). The $H_2^{18}O$ samples were analysed as previously described,[8] and TBW calculated using the method of Schoeller *et al.*[9] ECFV was determined using bromide dilution. After a baseline blood sample had been obtained, 1 ml/kg NaBr solution containing 100 mg/ml NaBr was administered intravenously, using vascular access sited for clinical purposes. NaBr equilibrates rapidly if given intravenously.[10] In addition, the half life is very long, so that once equilibration is reached only a single sample is needed to calculate ECFV. We obtained two samples after baseline, at the same time as the samples for TBW estimation, to confirm that equilibration had taken place. They were then averaged to provide a single measure. After being spun, 10 µl aliquots of serum were pipetted on to 1 cm diameter filter papers. These were dried in air before being sealed in plastic cuvettes for despatch to the Centre for Analytical Research in the Environment, Imperial College at Silkwood Park, for analysis by neutron activation. Assay results are expressed as µg bromide/ml serum and this value is used in the following equation[11]:

ECFV = (Amount of Br administered/serum [Br]) × 0.90 × 0.95 × 0.934

The amount of bromide administered was calculated as follows:

$$\text{Bromide injected} = \frac{\text{Weight of NaBr solution given (g)} \times [\text{NaBr soln}] \times \text{conversion factor}}{\text{Specific gravity of NaBr solution}}$$

The weight of NaBr solution given was measured by weighing the syringe before and after administration of the solution using a chemical balance accurate to ± 0.0001 g. ECFV was calculated as:

$$\text{ECFV (ml)} = \frac{\text{NaBr solution administered (g)} \times 10^5 \times 0.777 \times 0.9 \times 0.95 \times 0.934}{\text{Serum bromide concentration} \times 1.073}$$

where 0.90 is the correction factor for intracellular bromide, 0.95 corrects for the Donnan equilibrium across the cell membrane, 0.934 corrects for the proportion of water in serum,[12] 0.777 is the factor to convert mg/ml NaBr to mg/ml bromide, and 1.073 is the specific gravity of NaBr solution (manufactured by the Department of Pharmacology, Northwick Park Hospital, Harrow, Middlesex, UK). The Donnan equilibrium correction is necessary because intravascular anionic proteins cause differential movement of bromide ions across the capillary membrane such that the concentration of bromide in the interstitial fluid is about 5% greater than in serum water.[13][14]

Intracellular fluid volume (ICFV) was calculated by subtracting ECFV from TBW, and body solid content by subtracting TBW from body weight. We estimated the fraction of lean body mass in AGA babies as TBW for AGA babies/TBW for SGA babies based on the assumption of a 0% adipose tissue content in SGA babies. Fat content was then calculated as 1 − lean mass. We also determined whether, at this calculated fat content, there was any significant difference in lean body mass water content between the groups, as might be expected if lean body tissue hydration is the same in both groups and adipose tissue is anhydrous.

Statistical analysis was carried out using Intercooled Stata version 4.0.[15] Unless otherwise stated, results are quoted as median and range. Comparisons were made using the Mann-Whitney two sample statistic for continuous variables and Fisher's exact test for categorical variables.

Results

Forty two preterm infants were studied. Measurements were made within 18 hours of birth. Seven infants were SGA and 35 were AGA. Birth weights were 760 (420–1020) and 990 (710–1570) g and gestational ages 28 (26–29) and 27 (25–30) weeks for SGA and AGA infants respectively. There were no differences between the groups with respect to sex or gestational age (table 1).

Body composition differed between the groups (table 2). SGA infants had a significantly higher body water content, when expressed per unit body weight, than AGA infants (906 (833–954) and 844 (637–958) ml/kg respectively; p = 0.019) and therefore a correspondingly lower body solid content (94 (46–167) and 157 (42–363) g/kg respectively.

There was no significant difference in ECFV (SGA, 511 (461–581) ml/kg; AGA, 505 (311–569) ml/kg; p = 0.52) or the ratio of ECFV to ICFV (SGA, 1.3 (1.0–1.8); AGA, 1.4 (0.7–2.4); p = 0.7).

Assuming 0% fat content in SGA babies, we calculated the fraction of lean body mass in AGA babies as 844/906 (TBW for AGA babies/TBW for SGA babies) = 0.93. This suggests a fat content in AGA infants of 7%. Reanalysis of our data assuming 0% fat content

Table 1   Study population consisting of seven small for gestational age (SGA) and 35 appropriately grown (AGA) infants

	SGA	AGA	p Value
Birth weight (g)	760 (420–1020)	990 (710–1570)	0.009
Gestation (weeks^{days})	28^1 (26^5–29^0)	27^0 (25^5–30^0)	0.24
Male:female	5:2	19:16	0.68

Values are median (range).

Table 2   Body composition analyses

	SGA	AGA	p Value*
TBW (ml/kg)	906 (833–954)	844 (637–958)	0.019
ECFV (ml/kg)	511 (461–581)	505 (311–569)	0.52
ICVF (ml/kg)	386 (314–463)	355 (241–524)	0.33

Values are median (range).
*Mann-Whitney two sample statistic.
SGA, small for gestational age; AGA, appropriately grown for gestational age; TBW, total body water; ECFV, extracellular fluid volume; ICVF, intracellular fluid volume.

Table 3   *Values for total body water (TBW) content of lean body mass assuming different body fat content as a percentage of body weight in the appropriately grown (AGA) infants*

	TBW (ml/kg lean weight)	p (SGA v AGA)
SGA (0% fat)	906 (833–954)	—
AGA (0% fat)	844 (637–958)	0.019
AGA (2% fat)	861 (650–978)	0.058
AGA (4% fat)	879 (664–998)	NS
AGA (7% fat)	908 (685–1030)	NS

Values are median (range).
SGA, small for gestational age.

in SGA babies and a range of possible body fat content in AGA infants confirmed that, at an assumed 7% body fat content in AGA babies, there was no longer a significant difference in TBW per unit lean body mass between the groups (table 3).

Discussion

We have presented novel data on the body composition of the preterm infant and provided a baseline for longitudinal studies of growth after preterm birth. We are unaware of any previous studies reporting in vivo measurements of body water content of SGA babies below 30 weeks gestation. We have shown that the body composition of preterm SGA infants differs significantly from that of AGA babies of equivalent gestational age, with differences in TBW and both an absolute and a relative reduction in body solid mass.

Our measurements of body composition for AGA infants are comparable with the limited published data. Bauer et al[16] studied a group of infants of comparable gestational age to those in our study, although SGA babies were specifically excluded. TBW content was within our range of values. The data of Heimler et al,[17] derived from infants of slightly longer gestation (30.7 ± 2.4 weeks), are also within the range of results of the present study. All of the published cadaver studies[2–4] report values that fall within the range defined by the three in vivo studies reported here. Table 4 lists studies in which body composition was determined within the first 24 hours after birth and in which it was possible to extract values for infants below 32 weeks gestation. Results from the three cadaver studies are included for comparison.

Deuterium oxide dilution has also been used to determine TBW. However, deuterium is harmful at levels greater than 10%.[18] In addition, the hydrogen in this isotope exchanges with the labile hydrogen of both protein and other body constituents,[19] leading to an overestimate of TBW by 1–5%. We elected to use $H_2^{18}O$ enrichment because $H_2^{18}O$ is a stable, non-radioactive, non-toxic, naturally occurring isotope normally present in the body. We have previously determined dilution kinetics for this marker in preterm infants.[8]

Shaffer et al[20] and Heimler et al[17] used the bromide dilution technique to determine ECFV, and Bauer et al[16 21] used sucrose dilution. Sucrose is commonly used as a marker for ECFV estimation, as it is not metabolised and is thought to remain in the extracellular space. However, it is slow to enter connective tissue water[22] and it does not enter the cerebrospinal fluid or the gastrointestinal fluids, and this method will therefore tend to underestimate ECFV.[23] An additional problem when studying extremely small infants is that a much larger total blood sample volume is needed.[24] In contrast, bromide ions penetrate to all parts of the extracellular fluid space rapidly and evenly, although 10–13% of administered bromide is intracellular.[25 26] It is therefore conventional to correct the calculated bromide space by a factor of 10%, but for this reason measurements of ECFV using bromide dilution may be overestimates. This may explain why the ECFV values for the AGA babies in this study and that of Heimler et al,[17] although in close agreement with each other, are higher than those of Bauer et al.[16 21] Although ECFV determinations for infants from 25–31 weeks gestation carried out by Shaffer et al[20] using bromide dilution are lowest of all, this appears to be a reflection of the fact that the sample was obtained 90 minutes after the dose was administered. At this point, the bromide may well not have fully equilibrated, resulting in relatively less than 10% in the intracellular compartment and relatively more in the extracellular space, and hence an underestimate of ECFV.

Studies of term infants have also shown SGA infants to have a greater TBW content,[27 28] and this is attributed to their lower body fat content,[29] as adipose tissue in mature subjects is anhydrous. If this is also the case in extremely immature infants, for whom little is known about the composition of adipose tissue, an estimate of adiposity may be derived by determining the percentage difference in assumed fat content at which water content per unit of lean body mass is similar in AGA and SGA infants. If one assumes 0% fat content in these extremely preterm SGA infants, then reanalysis of our data suggests a fat content of about 7% in AGA infants. This would account for the differences in the TBW measurements between the AGA and SGA babies. Petersen et al,[30] using dual photon absorptiometry with ^{153}Ga, detected no fat in either AGA or SGA preterm infants, between 31 and 36 weeks gestation and at term, 2% in SGA infants, and 13% in AGA infants. However, the cadaver studies of Fehling[3] suggest a mean fat content of 2.1% in infants of 24–32 weeks gestation. This is similar to data from Iob and Swanson[5] for gestations of between 24 and 32 weeks.

Table 4   *Previously published body water compartments (ml/kg) for all gestations 22 to 32 weeks, with values from present study for comparison*

Reference	Date	TBW			ECFV		
		SGA	AGA	N/S	SGA	AGA	N/S
*von Bezold[2]	1857			808 (1)			
*Fehling[3]	1877			846 (8)			
*Givens et al[4]	1933			823 (6)			
Shaffer et al[20]	1989					410 (20)	
Bauer et al[21]	1989					452 (13)	
Bauer et al[16]	1991		792 (8)			444 (8)	
Heimler et al[17]	1993		866 (14)			504 (14)	
Present study	2000	906 (7)	844 (35)		511 (7)	505 (35)	

Numbers in parentheses are the sample size.
*Cadaver studies.
SGA, small for gestational age; AGA, appropriately grown for gestational age; TBW, total body water; ECFV, extracellular fluid volume; N/S, not stated.

Widdowson and Spray[6] present their data by body weight and suggest about 2.5% body fat at 1000 g. Enzi *et al*[31] showed a 3% difference in body fat mass, measured by anthropometric means, between AGA and SGA infants at 35 weeks gestation. Summary data from Ziegler *et al*[32] show a body fat content of 0.7–4.9% for the gestational age range 25–30 weeks. Our estimated difference therefore appears reasonable.

It is notable that the ratio of extracellular to intracellular water was not significantly different. This suggests that SGA infants are not dehydrated, as has been suggested.[33][34] Further, as it is unlikely that SGA infants would have a greater cell volume, they must either have a reduced cell volume with relative increase in cell number, with the implication that catch up growth is possible, or preservation of cell volume albeit with a reduction in cell number, in which case catch up growth is unlikely. It does, however, appear that the regulation of body water distribution is unimpaired in SGA infants.

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Notes