Reliability of the EchoMRI Infants System for Water and Fat Measurements in Newborns

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Objective: The precision and accuracy of a quantitative magnetic resonance (EchoMRI Infants) system in newborns were determined.

Methods: Canola oil and drinking water phantoms (increments of 10 g to 1.9 kg) were scanned four times. Instrument reproducibility was assessed from three scans (within 10 minutes) in 42 healthy term newborns (12-70 hours post birth). Instrument precision was determined from the coefficient of variation (CV) of repeated scans for total water, lean mass, and fat measures for newborns and the mean difference between weight and measurement for phantoms. In newborns, the system accuracy for total body water (TBW) was tested against deuterium dilution (D2O).

Results: In phantoms, the repeatability and accuracy of fat and water measurements increased as the weight of oil and water increased. TBW was overestimated in amounts >200 g. In newborns weighing 3.14 kg, fat, lean mass, and TBW were 0.52 kg (16.48%), 2.28 kg, and 2.40 kg, respectively. EchoMRI’s reproducibility (CV) was 3.27%, 1.83%, and 1.34% for total body fat, lean mass, and TBW, respectively. EchoMRI-TBW values did not differ from D2O; mean difference, $-1.95 \pm 6.76\%$, $P = 0.387$; mean bias (limits of agreement), 0.046 kg (−0.30 to 0.39 kg).

Conclusions: The EchoMRI Infants system’s precision and accuracy for total body fat and lean mass are better than established techniques and equivalent to D2O for TBW in phantoms and newborns.

Introduction

Obesity rates have increased among obstetric populations (1,2). Increased maternal weight at conception and delivery is associated with increased risk of macrosomia, specifically higher body fat in newborns (3,4). This increase in body fat may be a significant risk factor for obesity in early childhood and in later life. The extent to which fatness/adiposity, fat distribution, and the composition of fat-free mass (FFM) are determinants of diseases such as obesity and comorbidities later in life remains to be elucidated. There is a need to understand what constitutes a healthy body fat at birth and with growth during the first years of life.

The measurement of body composition in infants continues to be “work in progress” largely because of the lack of validated measurement techniques in this age group (5). Available measurement methods are limited by issues relating to accuracy, practicality, invasiveness, and safety. There is no single technique that allows for the measurement of body composition from birth through adulthood that is radiation free and has good precision. The EchoMRI Infants technology (Echo Medical Systems, Houston, Texas) provides an opportunity to measure fat mass (FM), lean mass, and total body water (TBW) in infants beginning at birth and longitudinally for body weights up to 12 kg.

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Author contributions: TT-R and DG designed the study. TT-R and OP contributed to recruitment, study procedures, and database management. WY contributed to setting up D2O procedures, preparation of D2O samples for administration to infants, and processing and shipping of collected specimens. WW contributed to deuterium procedures and performed analysis of specimens. TT-R and JT conducted the statistical analyses. TT-R, JT, XP, and DG wrote the paper. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Quantitative magnetic resonance (QMR) is a nonimaging technique that uses an electromagnetic field to detect the hydrogen atoms in three groups: fat, lean tissue, and free water. Once excited by radio-frequency pulses, these hydrogen protons have different relaxation times per their environment or the tissue in which they are embedded (protein, fat, or unbound, as water in the bladder or stomach). The processed signal is obtained from the whole body at once as a linear combination of fat, lean tissue, and free water. The lean signal originates mainly from water bound within the lean tissues (6). Regression formulas optimized by an algorithm based on previous validation studies separate the different components based on the pulse sequences obtained (7). To assess the total water, a second independent physical measure is obtained for all the hydrogen present in the body. All hydrogen measured is the sum of all water (TBW + free water) and fat; thus, lean mass and fat are estimated independently of each other. Total body water minus free water (unbound water is that found in the bladder and stomach) is the water contained in a bound state in tissues.

This technique does not pose any health or safety concerns (no use of ionizing radiation) and can be repeated many times within or across days, allowing for the assessment of short-term changes in infant body composition. The latter theoretically would allow for greater sensitivity and smaller sample sizes in clinical research studies. The advantages of the QMR device for studies involving humans include rapid data collection, no special participation requirements on the part of the subject, no sedation, no ionizing radiation, and the highest precision (in adult and animal studies) to date for available measurement methods.

The QMR measurement approach has been validated in adults (6,8) and small animals (9-12), in which it has detected small changes in body fat with high precision, making it a highly promising tool for use in longitudinal studies involving infants. Two studies in piglets, a well-accepted research model for infant body composition, have reported high precision for the measurement of FM, with a mean coefficient of variation (CV) of 1.8% compared to 3.1% for dual-energy x-ray absorptiometry (DXA) in piglets weighing 2 to 12 kg (12) and CV of 1.5% for QMR versus CV of 3.5% for DXA in pigs weighing 3 to 50 kg (11). A smaller version of the adult QMR (EchoMRI-AH Small) also performed with high precision for infants, children, and adolescents weighing 3 to 50 kg, and its accuracy was improved after mathematical adjustment (13). The EchoMRI Infants system has not previously been validated for accuracy and precision in infants.

The aim of this study was to assess the accuracy and precision of the infant QMR system (EchoMRI Infants) for infant body composition, particularly fat and TBW. A secondary aim was to assess the level of agreement between body composition measures by QMR and PEA POD (COSMED, USA).

Methods

Four linked studies were conducted to test the QMR system, one with phantoms and three with human subjects. Canola oil and water phantoms were separately scanned in increments of 10 g through 100 g and increments of 100 g through 1.9 kg at 37°C, with two consecutive scans in the morning and two scans in the afternoon performed on the same day. Three consecutive scans were acquired in a convenience sample of 42 healthy term newborns born at Mount Sinai-Roosevelt Hospital between 12 and 70 hours post birth. Instrument reproducibility was assessed from three scans with repositioning between scans (within a 10-minute period) in newborns. Instrument precision was determined from CV of repeated scans for TBW, lean mass, and fat measures for newborns and the mean difference between known weight and measurement for phantoms. The infant studies were conducted in three parts: (1) infant scanned alone, (2) a subset of infants scanned with phantoms, and (3) a subset of infants who completed deuterium dilution (D2O) assessment and QMR scanning. Thirteen infants were measured with 10 g of oil, 21 infants were measured with 30 g and 50 g of oil, and 20 infants were measured with 100 g of oil. Fifteen infants were measured with 10 g of water, 23 infants were measured with 30 and 50 g of water, and 22 infants were measured with 100 g of water. The accuracy of the QMR for TBW measurement was compared to deuterium dilution in this subsample of 10 infants.

Inclusion criteria were women 18 to 40 years with singleton newborns who were healthy term (>37 weeks) or preterms who were stable and did not require intubation or mechanical ventilation, and exclusion criteria were mothers with poorly controlled gestational diabetes (fasting capillary blood glucose level higher than 105 mg/dL and postprandial capillary blood glucose level higher than 140 mg/dL at 1 hour and higher than 120 mg/dL at 2 hours), preeclampsia, HIV, or other infectious diseases. Infants with known birth defects, congenital abnormality, inability to urinate, or an admission to the neonatal intensive care unit were excluded. Informed consent was obtained, and infants were tested while still inpatients. Delivery and newborn data (gestational age, mode of delivery, obstetric complications, birth weight, Apgar scores, and immediate neonatal complications) were retrieved from the medical chart. The study was approved by the IRBs of Mount Sinai School of Medicine (IRB#12-159) and Columbia University (IRB-AAAP4521).

Infant QMR

The infant was placed supine on a flat tray with an infant pad that slides into an enclosed chamber that can be visually monitored through a screen door. The QMR chamber was at room temperature, and the infant was wrapped in a blanket for comfort. The body composition of the infant was measured. The infant QMR system has a subject capacity of up to 12 kg. The system’s external dimensions are 120 × 60 × 180 cm³ (L × W × H). The resistive magnet generates a static magnetic field of about 0.0145 Tesla in a bore size of 120 × 30 × 30 cm³ (L × W × H). The field of view is a 25-cm-diameter, 60-cm-long cylinder in the center of the bore, and the system is self-shielded. The operating system is based on Windows XP Professional Edition. Measuring time is <4 minutes, and there is a recommended daily system calibration test. The system output includes FM, lean tissue mass, free water, and TBW in grams.

Deuterium dilution method

After obtaining maternal consent, a subsample of 10 infants was given an oral dose of D2O, calculated at 100 mg/kg body weight and administered using a syringe with a volume of ~1 mL/kg body weight of a 10% deuterium oxide stock solution within at least 24 hours after birth but prior to discharge from the hospital (14). At this dose, the D2O enrichment of body fluids at equilibrium is
Infant anthropometry

Infant length was measured to the nearest 0.5 cm with an infant length board. Weight was measured using the PEA POD electronic scale to the nearest 0.001 kg.

Following the daily PEA POD calibration (18), the infant was weighed and placed on a tray that slid into the transparent plastic chamber. The infant was undressed during the PEA POD measurement, except for a nylon hat, umbilical clamp, and identification bands. The PEA POD chamber was about 88°C. Infant body volume was measured using the infant’s weight and length to estimate body surface area and surface area artifact (18). Body density was obtained from body volume and body weight, from which FFM was derived, using Fomon et al.’s age- and sex-specific equations (19).

From these measures, FM was calculated. In a previous study of healthy newborns, same-day repeated tests on 29 infants gave CVs of 6.6% for %fat, 6.5% for fat, and 1.1% for FFM.

Statistics

Instrument precision was determined from the CV of the repeated scans for TBW, lean mass, and FM for newborns and phantoms and the mean difference between weight and measurement for phantoms. In newborns, the accuracy of the system was tested against D2O dilution for TBW. Bland-Altman pair-wise comparison plots were generated to examine agreement between methods. Data were analyzed using SPSS for Windows v15 (SPSS Inc., Chicago, IL). Statistical significance was set at \( P < 0.05 \).

Results

Phantoms

Precision. For each day, the CV for the oil and the CV for water of the four consecutive scans were calculated. Small amounts (10-100 g) of oil and water resulted in moderate CV values (−33.2 ± 27.1% for fat and 14.3 ± 7.2% for water measures). For 500 g of oil, the CV was 2.4%. For 1,000 g of oil, the CV was 1.5%. For TBW, the CV was 4.3% for 500 g and 4.6% for 1,000 g of water (Table 1).

Accuracy. We investigated the effect of adding incremental quantities of oil to the QMR fat measurement. It was hypothesized that the mean difference between known phantom weight and QMR-measured weight would be zero (i.e., the addition of 100 g of oil would increase the QMR fat measurement by 100 g). Figure 1 presents Bland-Altman plots showing the limits of agreement (bias ± 2 SD) between known oil and water weight and EchoMRI infants measurements of fat, free water, and TBW. Figure 1A reflects weights of 10 g to 100 g, and Figure 1B reflects 100 g to 1,900 g. The QMR underestimated fat by 5.9 g and 23.9 g (Figure 1A-1B, top), and the variability was consistent throughout the mean weight. The QMR underestimated free water by 6.1 g and 121.8 g (Figure 1A-1B, center), and there was a tendency for the difference between known phantom weight and estimated weight to increase as mean weight increased. For TBW, the QMR underestimated phantom weights between 10 and 100 g by 2.3 g (Figure 1A, bottom) with a tendency for the difference to increase as mean increased, and the QMR overestimated TBW by 34.1 g for phantoms between 100 and 1,900 g (Figure 1B, bottom) with a tendency for the difference to decrease as mean weight increased.

Table 2 shows mean fat and water differences between actual weights and QMR-measured weights. Total water differences were 6.1 g (10-100 g) and −34.1 g (100-1900 g). While free water was underestimated, total water was overestimated for amounts above 100 g.

Newborns

Newborn characteristics are shown in Table 3. Mean weight was 3.14 ± 0.38 kg, length 49.1 ± 1.61 cm, FM 521 g (16.59%), lean mass 2.27 kg, and TBW 2.40 kg. FM was a function of body weight (Supporting Information Figure S1).

Precision. The CV for FM was 3.27% (Table 4), which translates to a precision of 17.04 g of fat in newborns. A CV of 1.83% for lean mass equates to a precision of 41.54 g and a CV of 1.34% for TBW translates to a precision of 32.16 g in newborns.

Accuracy. The effect of adding increments of oil or water with a newborn in the QMR is shown by Bland-Altman plots in Figure 2. Adding 10, 30, 50, and 100 g of oil or water resulted in QMR-measured overall differences of 3 g for fat, −8 g for FW, and 12 g for TBW. Specifically, we found differences (SD) of 0.7 g (10 g) for 10 g, 9 g (11 g) for 30 g, −2 g (10 g) for 50 g, and 5 g (13 g) for 100 g of fat; −2 g (7 g) for 10 g, −4 g (8 g) for 30 g, −6 g (9 g) for 50 g, and −17 g (33 g) for 100 g of FW; and 12 g (31 g) for 10 g, 12 g (29 g) for 30 g, 12 g (32 g) for 50 g, and 16 g (38 g) for 100 g of TBW.

We examined the accuracy of QMR estimates of TBW in newborns using D2O as the criterion method. TBW measurements did not differ between methods with QMR estimating 2.41 kg and D2O 2.37 kg (mean difference −0.046 ± 0.18 kg, \( P = 0.43 \)). The QMR overestimated TBW by 46 g, as

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**Table 1** QMR precision for oil and water phantom measurements

|          | 10-100 g |          | 100-1,900 g |
|----------|----------|----------|-------------|
|          | Mean     | SD       | Mean        | SD          |
| Fat      | 33.2\(^a\) | 27.1     | 3.9         | 3.8         |
| Free water | 14.3     | 7.2      | 3.0         | 3.0         |
| Total water | 31.9     | 15.2     | 5.6         | 8.0         |

Average CV of four scans in 1 day, where two consecutive scans were completed in the morning and two scans in the afternoon for each increment of oil or water phantom.

\(^a\)Showing mean CV\% for 20-100 g. CV\% for 10 g was an extreme outlier at \( −1.765\% \).
evident from the Bland-Altman plot (Figure 3), but the variability was consistent across the range, and 70% of subjects fell within 1 SD of the bias. The limits of agreement were clinically acceptable (1 SD: $-0.131$ to $0.223$; 2 SD: $-0.300$ to $0.392$).

QMR and PEA POD comparison. Compared to PEA POD, the QMR measured higher FM with a bias of $-191$ g ($P > 0.001$). The difference in both directions (scatter) between methods increased at a mean FM of 500 g (Supporting Information Figure S2). The QMR

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**Figure 1** Bland-Altman plot showing the limits of agreement (bias ± 2 SD) between known oil (fat) and water weight and EchoMRI Infants measurements of fat, free water, and total water. (A) Weights of 10-100 g. (B) Weights of 100-1,900 g.
measured lower lean mass than PEA POD FFM, with a bias of 502 g (P > 0.001) (Supporting Information Figure S3).

### Discussion

We conducted a series of phantom and human experiments to assess the accuracy and precision of a new infant body composition instrument. Known phantom weights more than 100 g were measured with small differences between measured weight and QMR estimated fat, free water, and total water. Small, simulated changes in body composition as created by the addition of phantoms were detected accurately. Furthermore, newborn QMR TBW did not differ from the reference D2O estimate of TBW. In infants, this technique has significant potential to measure small changes in body composition with comparable precision and accuracy to any other available technique but with no health risks and without the need for sedation.

Studies investigating infant body composition and longitudinal changes are limited by the size capacity of available methods and the unestablished validity of some measurement techniques in this young age group. Air displacement plethysmography is the most commonly used body composition technique in infants through ~6 months (PEA POD with an upper weight limit of 8 kg). The adult sized BOD POD can be used in children (>5 years or whose body volume >50 L) who can remain motionless during the required testing periods. The BOD POD with the pediatric option (child-sized seat) can be used in children older than 2 years (per the manufacturer), but success in the 2- to 5-year age group is low (20) because of inability to remain motionless. No option is available for the age group 6 months to 2 years. A series of QMR devices exist for a wide range of weights that are capable of high accuracy and precision. These allow for the assessment of longitudinal changes in fat, lean mass, and body water from infancy to adulthood, eliminating errors arising from the use of different body composition approaches.

### Precision

The results of this study extend Mitchell’s findings, which validated the EchoMRI Infants system in 2- to 12-kg piglets (12). Precision of the EchoMRI Infants system was evaluated in repeat phantom and newborn measures. In phantoms, precision improved as the weight of the phantom increased and was the highest for free water. Phantom water simulates free water in the QMR, as it is unbound in the body (6). It is unknown why TBW did not reflect the same precision, although it could be related to a difference in the algorithms used by the system to determine the different body composition components. Based on the study by Mitchell (12), we hypothesized that in infants, the mean within-subject difference (retest minus test) would be 1.8% at most, and the within-subject standard deviation (SD) across repeated measures would be 1.86% at most for FM measured by infant QMR. The precision in the current study was good but lower than hypothesized. Precision in newborns was 3.3%, 1.8%, and 1.3% for FM, lean mass, and TBW, respectively. Using the same device, Mitchell (12) reported a CV of 0.6% for FM in newborns using DXA. The PEA POD’s precision is lower in piglets and newborns compared to DXA and the QMR, with CVs for FM of 17% (23) and 7.9% (24), respectively. In phantoms, precision improved as weight increased (Table 1). In newborns, FM was a function of body weight (Supporting Information Figure S1).

### Accuracy

A previous study reported high accuracy (within 2% vs. carcass analysis) for body composition estimates in piglets using a larger version of the QMR (EchoMRI-AH) with a capacity up to 50 kg (11). In children ≥6 years, the EchoMRI-AH overestimated FM by 10% compared to a four-compartment model, which the authors speculated could be

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**Table 2** OMR accuracy for oil and water phantom measurements

|        | 10-100 g | 100-1900 g |
|--------|----------|------------|
|        | Mean (g) | SD         | Mean (g) | SD         |
| Fat    | 5.9      | 9.1        | 23.9     | 27.0       |
| Total water | 6.1      | 12.7       | -34.1    | 35.6       |
| Free water | 2.3      | 5.6        | 121.8    | 61.4       |

Mean is the mean difference between known phantom weight and QMR estimated weight in four scans, where two consecutive scans were completed in the morning and two scans in the afternoon of the same day for each increment of oil or water phantom.

**Table 3** Newborn descriptive characteristics (n = 42)

|                        | n | Mean | SD  |
|------------------------|---|------|-----|
| Weight (kg)            | 38| 3.14 | 0.38|
| Length (cm)            | 39| 49.1 | 1.61|
| Gestational age (wk)   | 37| 39.7 | 1.00|
| Fat (kg)               | 42| 0.52 | 0.14|
| Fat (%)                | 42| 16.53| 3.24|
| Lean (kg)              | 42| 2.27 | 0.25|
| Total body water (kg)  | 42| 2.40 | 0.25|

Mean and SD values represent the mean of three consecutive scans with repositioning.

**Table 4** Reproducibility (with repositioning) of three repeated measures in newborn (CV% = [SD/mean]*100) (n = 42)

|        | Fat | Lean | Total body water | Free water |
|--------|-----|------|------------------|------------|
| Mean CV %         | 3.27| 1.83 | 1.34             | 14.43      |
| SD (CV %)         | 2.30| 1.86 | 0.89             | 14.16      |
| Range (min) %     | 0.67| 0.18 | 0.29             | 0.59       |
| Range (max) %     | 10.72| 8.81 | 3.94             | 67.87      |
because of possible species-dependent differences in data processing and acquisition (13). The EchoMRI Infants system was less accurate in piglets up to 12 kg (12) when compared to the larger EchoMRI-AH, with an average difference from carcass analysis of 4% for FM, 2.1% for lean mass, and 2.3% for TBW. In comparison, the PEA POD has shown accuracy of 0.6% for percent fat in infants (24), whereas DXA in children overestimated FM by 1.7 kg (25) compared to a four-compartment model. We found high accuracy for phantoms in amounts greater than 100 g and in newborns when small phantom amounts were added. The QMR was unable to accurately and precisely measure small phantoms (≤100 g) placed alone (without a newborn). However, small changes in FM and TBW in newborns, simulated using small phantoms, were detected accurately, where, for example, the addition of 10 g, 30 g, 50 g, and 100 g of oil resulted in a mean increase of 9.3 g, 21 g, 48 g, and 95 g of fat, respectively (overall mean difference 3 g), and mean differences in TBW measurements were 12 g overall. TBW was overestimated in phantoms and underestimated in newborns, in agreement with findings by Mitchell in piglets, in which TBW was also underestimated (12).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Bland-Altman plot showing the limits of agreement (bias ± 2 SD) between known oil (fat) and water weight added to newborns in increments of 10 g, 30 g, 50 g, and 100 g and EchoMRI Infants measurements of fat, free water, and total water. (A) \( n = 13 \) infants measured with 10 g of oil, \( n = 21 \) measured with 30 g and 50 g of oil, and \( n = 20 \) measured with 100 g of oil. (B, C) \( n = 15 \) infants measured with 10 g of water, \( n = 23 \) measured with 30 g and 50 g of water, and \( n = 22 \) measured with 100 g of water.}
\end{figure}

In vivo QMR TBW accuracy is very high. The Bland-Altman plot (Figure 3) demonstrates that QMR overestimates TBW by 46 g or 1.95% compared to D\(_2\)O. There is a trend toward an increase in the difference between methods as the average increases (regression slope = 0.06), with overestimation of QMR TBW as the mean TBW increases. However, the scatter around the bias line does not increase as the average increases.

**QMR and PEA POD comparison**

FM and FFM comparisons to the PEA POD showed significant differences between the methods, with the QMR measuring higher FM with a bias of −191 g (36.7%) and lower FFM with a bias of 502 g (22.1%). These differences could be attributed to dissimilarities in the measurement approaches to assess fat, FFM, and lean mass. Specifically, the PEA POD employs a two-compartment model and estimates body fat from body weight and volume using assumed values for the density of fat and FFM. The density of body fat is generally considered to be constant at 0.9007 g/mL, while the density of FFM varies...
with age and maturation. The PEA POD uses fixed age- and sex-specific FFDM density constants to estimate FFDM from birth to 10 years. Newborn or birth constants were derived from infants of different ages (days) after birth but placed in a single category (19), which may not accurately represent body composition of 3-day-old infants, because of rapid changes in hydration following birth (20). Importantly, the water content of FFDM, an important determinant of FFDM density, decreases during fetal life. Fomon et al. reported TBW at birth to 68.6% in girls and 69.6% in boys (19). In the current study, we found that TBW was 76.43%, suggesting that the constants established by Fomon et al. at birth were based on older infants. QMR estimates TBW by subtracting the signal of hydrogen bound in fat from the total hydrogen signal, acquiring a measure of water in real time. Therefore, the PEA POD and QMR each measure different components using different approaches, and the QMR may give a more accurate estimate of each body component due to measuring TBW.

Study limitations

In vivo accuracy was solely reported for TBW using D2O, but FM accuracy was not assessed (with a four-compartment model). The four-compartment model implies a small radiation exposure from DXA and is therefore of limited use in infants and not appropriate for such a study (20). Furthermore, although it is the gold-standard technique, any error introduced in one of the components will influence the overall result.

Conclusion

In conclusion, the EchoMRI Infants system shows high precision and accuracy for measures of FM, lean mass, and water in phantoms and newborns and presents a method that will provide reliable longitudinal measures in body composition beginning after birth.

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