TOTAL BODY WATER IN CHILDREN WITH CONGENITAL HEART DISEASE, BEFORE AND AFTER CARDIAC SURGERY

The aim of this study was to measure total body water in children with congenital heart disease before and after cardiac surgery and to compare the results of deuterium and ^{18}O oxygen dilution methods. Seventeen children (aged 4 to 33 months) were given aliquots of isotopically labeled water 1 week before and 6 hours after cardiac surgery. Isotope equilibration and analysis of the declining enrichment of daily urine samples allowed calculation of the total body water content. Before operation, total body water was significantly elevated ($p < 0.001$, Wilcoxon test); after operation it fell to approximately normal values. This finding is in contrast to those of previous reports, but may be explained in that the method used for calculation depended on measurements taken over a 7-day period rather than on a single measurement of isotope dilution as used elsewhere. Nevertheless, these results do suggest that surgery can correct the preoperative fluid overload. Comparison of deuterium and ^{18}O oxygen dilution methods showed a 2% to 2.5% overestimation of the total body water content with deuterium sampling. (J THORAC CARDIOVASC SURG 1995;110:633-40)

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Body water accounts for a significant proportion of body weight, and in a malnourished person this proportion increases. Because children with congenital heart disease are frequently undernourished and nutritionally depleted,¹⁻⁵ it might be expected that their total body water content would be abnormally high. Recent studies have demonstrated the ubiquity of undernutrition in this group,⁶ and it would therefore seem likely that an increase in water content might also be more widespread than expected and not just confined to those persons with congestive cardiac failure who are visibly edematous.

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The technique of cardiopulmonary bypass, required for the correction of most congenital heart abnormalities, is associated with an initial period of hypervolemia. In small infants, subsequent capillary leakage often leads to gross peripheral edema, particularly if circulatory arrest or profound hypothermia has been required.⁷⁻⁹ Such visible compartmental shifts in the intracellular and extracellular fluid volumes, however, may obscure changes in the total body water content of a patient, and although previous studies have demonstrated an increase in total body water in the immediate postoperative period^{7, 10, 11} it is unknown what effects are produced by the improvement in hemodynamics that should follow either the successful correction or the successful palliation of a congenital abnormality. A better understanding of the perioperative state of hydration is important, however, for patient management and the satisfactory maintenance of an adequate fluid balance.

An assessment of the total body water content can be made from studies of fluid balance, body weight, and, more recently, bioelectric impedance,^{12, 13} but the most accurate method depends on isotopic dilution with the use of either ^{18}O oxygen, tritium, or, more commonly, deuterium-labeled water. Comparison with direct measurement (desiccation) suggests

Table I. Patient data

Patient	Weight (kg)	Age (mo)	Diagnosis	Sex	Operation	CPB
1	6.22	7	TOF	F	BT shunt	No
2	4.22	4	VSD	M	PA band	No
3	11.47	19	Coarctation	M	Patch repair	No
4	8.65	18	ASD	F	Closure	Yes
5	7.78	12	ASD/TVM	F	Closure/resection	Yes
6	7.00	7	VSD	M	Closure	Yes
7	13.10	32	ASD	F	Closure	Yes
8	6.10	11	TOF	M	Correction	Yes
9	8.69	11	ASD	M	Closure	Yes
10	15.00	26	ASD	F	Closure	Yes
11	14.00	33	DOLV/TGA	M	Switch/conduit	Yes
12	7.60	11	AVSD	M	Repair	Yes
13	8.66	20	UVH/TGA	M	DSK/BCPS	Yes
14	8.91	11	TOF	M	Correction	Yes
15	8.12	16	TOF	M	Correction	Yes
16	10.33	27	ASD	F	Closure	Yes
17	4.40	4	VSD	M	Closure	Yes

CPB, Cardiopulmonary bypass; TOF, tetralogy of Fallot; F, female; BT, Blalock-Taussig; VSD, ventricular septal defect; M, male; PA, pulmonary artery; ASD, atrial septal defect; TVM, tricuspid valve membrane; DOLV, double-outlet left ventricle; TGA, transposition of the great arteries; AVSD, atrioventricular septal defect; UVH, univentricular heart; DSK, Damus-Stansel-Kaye; BCPS, bidirectional cavopulmonary shunt.

that the former provides the best assessment of total body water content, but prohibitive costs have resulted in deuterium being the most frequently used isotope.

The aim of this study was therefore threefold: first, to measure the total body water content of a cohort of children with congenital heart disease, second, to determine the effects of corrective and palliative cardiac surgery on the total body water content of the same persons, and, third, to compare the results of ^{18}O oxygen and deuterium dilution methods.

Patients and methods

Patients. This study was approved by the local hospital ethics committee and informed consent was obtained from the parents of the children concerned.

Seventeen children with congenital heart disease were entered into the study. There were 11 boys and 6 girls with ages ranging from 4 to 33 months: patient details are summarized in Table I.

Operative details. A standard anesthetic technique was used and each patient received assisted ventilation until he or she was fully rewarmed, in a hemodynamically stable condition, and able to maintain adequate spontaneous respiration. The intraoperative fluid balance was maintained with 0.45% sodium chloride in 5% glucose, supplemented with plasma protein solution, fresh frozen plasma, and concentrated red blood cells as appropriate.

After operation a dextrose infusion was commenced that provided each child a total intake of 50 ml/kg per day for the first 24 hours, 75 ml/kg per day for the second 24 hours, and 100 ml/kg per day thereafter.

Cardiopulmonary bypass, when required, was instituted in a routine fashion. The bypass circuit comprised a Stöckert roller pump (Stöckert Instruments, Munich, Germany), a Cobe VPCML membrane oxygenator (Cobe Laboratories, Gloucester, England), and a Bentley AF540 (40 μm pore size) arterial filter (Baxter Healthcare, Compton, U.K.). Nonpulsatile perfusion maintained a flow rate equivalent to 2.4 L/min per square meter at 37° C, which was reduced to 1.2 to 1.6 L/min per square meter during stable hypothermia. The pump was primed with Ringer's solution, 4000 U heparin, 30 mmol sodium bicarbonate, 4 gm mannitol, potassium chloride, antibiotics, and sufficient concentrated red blood cells to achieve a hematocrit level of 25% to 30% during cardiopulmonary bypass. The prime volume was approximately 1 L. St Thomas' Hospital cardioplegic solution at 4° C was given as appropriate to stop the heart and cold saline solution was used for topical cooling. Acid-base management during bypass followed pH-stat theory, and carbon dioxide was added to the pump gases to maintain a temperature-corrected arterial pH value of 7.40.

Total body water measurement. The isotope dilution method of measuring total body water depends on the administration of a known amount of isotopically labeled water and equilibration of this with the body water pool. Because water is predominantly lost from the body as urine and this is simple to collect, it is possible to follow the declining isotopic enrichment of the total body water pool over a specific period of time by analyzing daily urine samples. Because this decline follows an exponential pattern, a plot of the logarithm of the urinary enrichment versus time is linear. Calculation of total body water content is therefore dependent on each measurement made throughout the week-long study period, but by back extrapolation it is possible to derive a measurement of

body water content at the time the isotope was first given, that is, time zero.

Although both H_2^{18}O and $^2\text{H}_2\text{O}$ may be used for total body water measurement, because of the carbonic anhydrase-mediated interchange of oxygen atoms in water and carbon dioxide, ^{18}O is lost as both water and expired carbon dioxide, whereas the deuterium isotope is lost only as water. The regression line for ^{18}O is therefore steeper than that for deuterium, which is a difference that can be exploited for the calculation of energy expenditure but that has no effect on the calculation of body water pool size, provided the losses of carbon dioxide and body water (as urine, sweat, feces, for example) are constant throughout the study period. Although some children received assisted ventilation for short periods after operation, this would not be expected to have any significant influence on body water calculation because normal respiratory rates and arterial oxygen and carbon dioxide tensions were maintained and because the calculation of total body water pool size depends not on individual data points, but on measurements taken over a 7-day period.

Several further assumptions must also be made. First, the accuracy of the isotope dilution method depends on complete equilibration of the ^{18}O and deuterium atoms with body water and free exchange of these atoms between the aqueous and nonaqueous pools.

If any isotope was permanently lost to a nonaqueous pool it could not be detected by measurement of body fluid enrichment, and if the rate constants for the exchange of isotopes between the aqueous and nonaqueous pools affected the monoexponential nature of the decline in body fluid isotope enrichment, this would seriously affect the mathematic treatment of the data. Although this question has not been studied in infants or children, a study in young adults that applied single pool and two pool mathematics to the data did suggest that a single pool model is appropriate.¹⁴

Because the use of stable isotopes in the measurement of total body water has already been proved after major operations,¹⁵ we would not expect isotope equilibration to be affected by the trauma of cardiac operations or cardiopulmonary bypass in the postoperative period.

A second assumption is that there must be no fractionation of water (vapor) or carbon dioxide leaving the body that would lead to a disproportionate loss of heavy and light isotopes.

Third, both ^2H and ^{18}O are naturally occurring isotopes present in small quantities in the normal body water pool and also in the environment. Drinking water is the main source of isotope intake, but the degree of enrichment varies slightly depending on the source. This can be taken into consideration by analyzing both the patient's home drinking water and a prestudy urine sample. The method of body water calculation assumes that background enrichment from the environment remains constant throughout the study period; although this is usually the case, if marked changes did occur, they would have a profound effect on the accuracy of the technique. Because each subject came from a different part of Scotland and then spent time in the hospital receiving a normal diet and also received various intravenous fluids during operation, samples of home and hospital drink-

ing water and commercially prepared intravenous fluids were all collected and their deuterium and ^{18}O levels taken into consideration in the calculation of energy expenditure.

Experimental details. Total body water content was measured in the week before corrective or palliative cardiac surgery and again in the week immediately after the operation. Only three children underwent surgery that did not involve the use of cardiopulmonary bypass.

Samples of home tap water were collected for each child participating in the study, together with samples of hospital tap water, commercially prepared milks, and, for the postoperative studies, samples of intravenous fluids and transfused whole blood. Isotope enrichments from this information and from predose urine samples were measured and used to modify the calculations previously described herein.

Accurately measured aliquots of the two stable isotopes of water, $^2\text{H}_2\text{O}$ and H_2^{18}O (Delta Isotopes, Crewe, Cheshire, England) were administered (orally) to each child in doses equivalent to 0.28 gm/kg body weight of 100% H_2^{18}O and 0.1 gm/kg body weight of 99% $^2\text{H}_2\text{O}$ for children younger than 1 year old and 0.15 gm/kg body weight of 100% H_2^{18}O and 0.05 gm/kg body weight of 99% $^2\text{H}_2\text{O}$ for children older than 1 year (because the water turnover is lower in older children, less isotope is required). In the preoperative study, the isotopically enriched water was given 1 week before the operation, and in the postoperative study it was administered nasogastrically 6 hours after the patient's return to the intensive care unit, once his or her condition was hemodynamically stable (time zero). It was assumed that each dose was fully absorbed because it has been demonstrated that even with an ileus there is a free exchange of water molecules across gastric mucosal cell membranes. Although it may be possible to aspirate a large volume of water from the stomach 1 hour after administration, previous studies have shown that this will contain only 1% of the labeled dose.¹⁵ Nasogastric aspiration was nevertheless not permitted for 6 hours after administration of the deuterium and ^{18}O .

The child's weight was accurately recorded at the beginning and end of each study period. In the postoperative study the child's predose weight was taken to be that obtained on the morning of operation. Urine samples were collected from urinary catheters, urine bags, or directly from the diaper¹⁶ on the morning after deuterium and ^{18}O administration and for 6 days thereafter, and the precise time of each sample was carefully recorded. All samples were frozen and stored for batch analysis of deuterium and ^{18}O by the MRC Dunn Nutrition Unit, Cambridge, by isotope-ratio mass spectrometry (Aqua-Sira model, VG Isogas, Cheshire, England).

The total body water content (recorded as a percentage of body weight) was calculated and compared with normal values obtained from previous studies done by one of us (P.S.W.D.) with identical methods in the same institution (MRC Nutrition Unit). Because the total body water content of a child shows some variation with age, normal values were age-matched to the children participating in this study.

Table II. Preoperative total body water content and age-related normal values in 17 children with congenital heart disease measured with deuterium and ^{18}O oxygen dilution methods

Patient	TBW-d (% body wt)	Normal TBW-d (% body wt)	TBW-o (% body wt)	Normal TBW-o (% body wt)
1	65.3	60.0	62.2	58.5
2	69.2	62.5	68.1	60.5
3	66.7	60.0	64.4	58.0
4	64.4	60.0	62.5	58.0
5	83.0	60.5	79.0	58.5
6	65.0	60.0	61.7	58.5
7	71.0	60.0	69.6	58.0
8	70.0	60.5	66.3	58.5
9	67.0	60.5	65.1	58.5
10	57.9	59.5	57.0	57.5
11	62.9	60.0	61.7	58.0
12	79.6	60.5	77.1	58.5
13	68.2	60.0	67.1	57.5
14	65.5	60.5	64.1	58.5
15	78.4	60.0	76.9	58.5
16	64.2	59.5	59.7	57.5
17	84.2	62.5	81.9	60.5

TBW-d, Total body water content measured with deuterium dilution method; TBW-o, total body water content measured with ^{18}O oxygen dilution method; wt, weight.

Results

The height and weight of each child were recorded preoperatively and compared with a standard reference source for British children (Castlemead Publications, Welwyn Garden City, United Kingdom). In eight subjects height was found to be less than the 3rd percentile and in 10, weight was less than the 3rd percentile. Three children were receiving diuretic therapy before operation (patients 2, 13, and 15) and two received propranolol (patients 14 and 15). All children received a single dose of diuretic on the first postoperative morning; diuretic therapy was continued throughout the study in patients 1, 2, 5, 6, 8, and 11 through 16.

Surgical correction was complete in each child as evidenced by echocardiography. Fourteen patients were extubated either before or within 12 hours of postoperative doubly labeled water administration and made swift and satisfactory progress. Three patients received ventilator support throughout the study (8, 11, and 12). Patient 11 had bleeding after the operation and required two further explorations with delayed closure of the chest. Peritoneal dialysis was used for the first 48 hours only and transfusion requirements over the same period equaled the patient's normal blood volume. No other patient had any relevant complication.

The results of the preoperative and postoperative

total body water measurements in the 17 children with congenital heart disease are shown in Tables II and III and Fig. 1.

Comparison of normal total body water values obtained by both the deuterium and ^{18}O oxygen dilution methods in children of similar ages showed a small but significant difference, with deuterium total body water measurements being approximately 1.94% higher ($p < 0.001$, Wilcoxon test). In the study group, preoperative deuterium-calculated total body water was approximately 2.24% higher than the ^{18}O oxygen-calculated measurement and both were significantly higher than total body water measurements in normal aged-matched children without congenital heart disease ($p < 0.001$, Wilcoxon test).

After operation, the deuterium total body water measurement was again significantly higher than the ^{18}O oxygen measurement (by an average of 2.51%) ($p < 0.001$, Wilcoxon test), but the body water pool was significantly reduced in size ($p < 0.05$ for ^{18}O oxygen-derived measurements, Wilcoxon test) and no longer significantly different from the total body water content of normal aged-matched children without congenital heart disease and not undergoing an operation ($p > 0.05$, Wilcoxon test).

The presence or absence of cyanosis had no effect on the total body water pool size in children with congenital heart disease ($p > 0.05$, Wilcoxon test).

Fig. 1. Preoperative and postoperative total body water content in 17 children with congenital heart disease, together with age-matched normal values measured with an ^{18}O oxygen dilution method.

Table III. Postoperative total body water content and age-related normal values in 17 children with congenital heart disease measured with deuterium and ^{18}O oxygen dilution methods

Patient	TBW-d (% body wt)	Normal TBW-d (% body wt)	TBW-o (% body wt)	Normal TBW-o (% body wt)
1	53.0	60.0	50.4	58.5
2	61.8	62.5	59.3	60.5
3	41.9	60.0	40.5	58.0
4	68.8	60.0	68.1	58.0
5	59.0	60.5	57.5	58.5
6	65.4	60.0	62.8	58.5
7	49.6	60.0	47.8	58.0
8	73.6	60.5	71.2	58.5
9	62.5	60.5	57.9	58.5
10	58.7	59.5	52.9	57.5
11	79.2	60.0	77.5	58.0
12	79.6	60.5	77.1	58.5
13	67.9	60.0	65.7	57.5
14	66.1	60.5	64.0	58.5
15	64.5	60.0	60.7	58.5
16	63.1	59.5	58.0	57.5
17	65.7	62.5	66.4	60.5

TBW-d, Total body water content measured with deuterium dilution method; TBW-o, total body water content measured with ^{18}O oxygen dilution method; wt, weight.

Only the first three patients underwent an operation not involving the use of cardiopulmonary bypass, but there was no difference between these and other children undergoing an operation with cardiopulmonary bypass, both in terms of their preoperative and postoperative total body water content and in terms of the individual changes between the two ($p > 0.05$, Mann-Whitney test).

Discussion

Both deuterium and ^{18}O oxygen dilution methods tend to overestimate total body water content because of the exchange of atoms with nonaqueous hydrogen and oxygen within the body. Comparison with values obtained directly (by desiccation) suggests that deuterium oxide and tritium oxide ($^3\text{H}_2\text{O}$) overestimate total body water by at least 3% to

4%¹⁷⁻¹⁹ and perhaps by as much as 15%.²⁰ In contrast, because there is less exchangeable non-aqueous oxygen within the body, ¹⁸oxygen provides a much more accurate estimate of total body water that is approximately 1% to 2% greater than the true value.²¹ In this study parallel measurements of total body water before and after operation confirmed that higher values were obtained when the deuterium (rather than the ¹⁸oxygen) isotope was used. The much higher cost of ¹⁸oxygen-labeled water has, however, resulted in the more common use of deuterium in clinical practice. Nevertheless, our results are consistent with the view that ¹⁸oxygen labeling is likely to be more accurate.

Preoperative anthropometric data demonstrated that about half the children studied had a height or weight below the 3rd percentile, which is a proportion in keeping with findings of previous studies in children with congenital heart disease⁶ and that reflects the surprising ubiquity of undernutrition in this group. Three patients had congestive cardiac failure before operation of sufficient severity to require long-term diuretic therapy (patients 2, 13, and 15); as would be expected, they had an abnormally high total body water content, despite all having a height and weight below the 3rd percentile. Clearly, abnormal hemodynamics and particularly the presence of a left-to-right shunt may contribute to a degree of volume overload, even if this is not severe enough to produce overt signs of congestive cardiac failure. The remaining children, however (that is, those without clinical evidence of congestive heart failure), also had an elevated total body water content. This suggests that congenital heart disease, even when seemingly not severe, may still be associated with a more ubiquitous metabolic derangement than expected. Biochemical evidence to support this theory has already been documented.⁶ Furthermore, because many children with congenital heart disease show evidence of undernutrition¹⁻⁶ and water makes up a larger proportion of body weight in malnourished than in well-nourished children an assessment of weight loss may underestimate the true loss of cell mass, making this a less useful guide to both fluid balance and energy requirements.²²

The generalized increase in total body water demonstrated in this study is similar to that found by Novak and Feldt,²³ who used a deuterium dilution technique to demonstrate an elevated total body water content in five infants with congenital heart disease. In contrast, Brans⁹ and Huse²⁴ and their

colleagues found no difference in the total body water content of children with cardiac defects and those without, although they did observe a small shift from the intracellular to the extracellular compartments. Brans and colleagues⁹ studied 11 children and used antipyrine as a marker for total body water whereas Huse and colleagues²⁴ studied only six children and did not describe the methods used. The reasons for these differing results are unclear, but because isotope dilution is a technique that is subject to considerable error unless carefully done, the small numbers of patients and the possibility of errors may account for these discrepancies. The greater accuracy possible with ¹⁸oxygen labeling and the 7-day back extrapolation method of calculating total body water content may well enhance the validity of our results.

After the operation the total body water content of the majority of children decreased. This also appears contrary to the results of most previous studies^{10,11} and to the clinical observation that many children become edematous after cardiopulmonary bypass, particularly if circulatory arrest or profound hypothermia has been necessary.⁷⁻⁹ Nevertheless, a postoperative increase in total body water has not been a universal finding in the past⁷ and it is possible that the clinical observation of edema could represent changes in water compartmentation rather than changes in the total body water content.⁹

In four patients (4, 6, 8, and 11) there was an increase in the total body water content after operation. In patient 6, this difference was only 1% and may therefore be a result of experimental error. Patient 11 had a stormy postoperative course with a short period of peritoneal dialysis and severe hemorrhage that necessitated massive blood transfusion. The effects of this on total body water measurement are difficult to predict and may account for the discrepancy with the general trend. Why the remaining two patients should have an elevated total body water content after operation is uncertain.

Two methods have been described for calculating total body water from measurements of isotope loss. In the first, the plateau method, the percentage enrichment of body water is plotted against time; it is assumed that a plateau is reached at about 4 to 7 hours, after which enrichment steadily declines. Total body water is measured at the peak of the curve, but this method is flawed inasmuch as a balance between water absorption and excretion can only exist instantaneously without a constant infusion of the isotope. The second method, back ex-

trapolation, depends on back extrapolation of the regression line of the graph of log enrichment versus time, but would only be valid if instantaneous mixing occurred when the isotope was injected. Although this cannot happen, the method has the clear advantage of relating the calculation of total body water to measurements of enrichment made throughout the week and not on a single measurement as with the plateau method. Nevertheless, although the value calculated theoretically represents the total body water content at the start of the experiment, that is, 6 hours after operation, in practice it can be considered as a mean value for the whole 7-day study period. As a result, the total body water content could increase in the immediate postoperative period (as clinical observation and other studies may suggest),^{10,11} but if it then fell, as the effects of surgery and the improved hemodynamics became more apparent, the overall result might appear reduced in comparison with the high preoperative values. This possibility may account for discrepancies with other series, most of which have measured total body water 24 to 48 hours after operation and have relied on only one or two measurements of isotope dilution.^{7,9} This would also be compatible with the results of the only longitudinal study of postoperative body water content, which demonstrated (by bioelectric impedance) that total body water increases initially, but generally returns to normal about 3 to 4 days after operation.¹¹

Our studies therefore suggest that a corrective operation and the consequent improvement in hemodynamics not only normalizes the body composition of children with congenital heart disease, but does so remarkably quickly.

All children received postoperative diuretic therapy for varying periods according to our normal practice and to the child's perceived clinical need. Although this policy would clearly lead to a loss of body water, it would not affect the calculation of total body water by the isotope dilution method used here. Although diuretic therapy would affect the rate at which an isotope was lost from the body and therefore the degree of body water enrichment at a given time, we have used the back-extrapolation method to determine body water at time zero. This value is independent of the subsequent speed at which enrichment declines.

We demonstrated no difference in the preoperative total body water content of children with and without cyanosis and although it has been suggested that the postoperative capillary leakage syndrome is

more frequent in children with cyanotic defects¹¹ our data do not lend support to this concept. Although it is possible that there may be a compartmental shift that favors an increase in extracellular fluid without an associated increase in the total body water content, an increase in extracellular fluid would seem unlikely in the presence of a reduction in the size of the total body water pool.

Only three children underwent operation not involving cardiopulmonary bypass yet the reduction in total body water after operation appeared no different from that in the other children. Although this is a small sample, the high preoperative values and the postoperative change do suggest that hemodynamic improvement after operation may be as important in the determination of the total body water content as fluid administration and the metabolic insult of cardiopulmonary bypass.

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