Reproducibility of Plasma and Extracellular Fluid Volume Measurements in Critically Ill Patients

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Plasma and extracellular fluid (ECF) volume measurements may provide valuable complementary data to the hemodynamic measurements currently used to compare fluid infusions in critically ill patients. To assess the reproducibility of plasma and extracellular fluid volume measurements in critically ill patients, we injected ^{131}I-labeled albumin (10 μCi) and ^{35}S-sodium sulfate (50 μCi), respectively, into 15 stable patients on two occasions 150 min apart. Plasma was sampled at 20, 30, and 40 min after each injection and the volume of distribution of each radioisotope was calculated from the extrapolated zero time counts. We found that plasma and ECF volume did not differ significantly between the first (42.4 ± 4.7 ml/kg and 186 ± 39 ml/kg) and second (42.8 ± 5.5 ml/kg and 193 ± 48 ml/kg) measurements. Specifically, the mean difference between the two measurements was 0.4 ± 3.2 ml/kg and 7 ± 17 ml/kg respectively. We conclude that measurements of plasma and ECF volume are reproducible over 150 min in stable critically ill patients.

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Serial measurements of plasma and extracellular fluid (ECF) volumes by radioisotope dilution techniques, before and after the infusion of different fluids, would be useful in comparing the distribution of these infusions. In particular, the extent to which the infused fluid expands the plasma volume could be quantified and correlated with the corresponding changes in hemodynamic measurements, which are currently used to compare fluid infusions in critically ill patients (*1,2*). This correlation may help to resolve the crystalloid versus colloid controversy, regarding the optimal treatment of hypovolemia in these patients (*3*). However, the validity of such serial measurements of plasma and extracellular fluid volumes is dependent on the reproducibility of individual measurements. The purpose of this study was to determine the reproducibility of plasma and EFV measurements by radioisotope dilution techniques in critically ill patients.

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MATERIALS AND METHODS

Patients

Fifteen stable critically ill patients in our intensive care unit consented to participate in this study, which was approved by the St. Paul's Hospital and the University of British Columbia Ethics Committees. Stable patients were identified as those who did not require changes in their ventilatory and hemodynamic support during the study period. Clinical characteristics of the patients are shown in Table 1. The mean age of the patients was 64 yr (range 18–87 yr). All patients required oxygen therapy, eight patients (53%) were mechanically ventilated, and six patients (40%) required dopamine and/or dobutamine for hemodynamic support. The mean APACHE II score was 14 ± 5 (s.d.) (*4*).

Protocol

Iodine-131-labeled albumin (10 μCi in 1 ml) and ^{35}S-sodium sulfate (50 μCi in 5 ml) were injected into each patient on two occasions, 150 min apart, for the measurement of plasma and EFV, respectively. Blood was sampled (7 ml) immediately before and 20, 30, and 40 min after each injection for the calculation of the extrapolated zero time plasma counts for each radioisotope. Mean arterial pressure, pulmonary capillary wedge pressure, central venous pressure and cardiac output were measured at the time of each injection. The net liquid balance was calculated as the difference between liquid input and output during the interval between the injections.

Calculation of Plasma and ECF Volume

The volume of distribution of each radioisotope was calculated from the extrapolated zero time counts relative to the counts of a prepared standard. The extrapolated zero time counts were calculated by linear regression from the logarithms of plasma counts versus time plot for each radioisotope (Figs. 1 and 2).

Calculation of Plasma Volume. To prepare the plasma volume standard, 1 ml (10 μCi) of ^{131}I-albumin stock solution (Iodinated serum albumin, Merck Frosst Canada Inc., Pointe-Claire, Québec, Canada) was injected and mixed into 1000 ml of 0.9% saline, from which four 1-ml aliquots were pipetted as standard aliquots. To prepare the patients' plasma samples, blood samples were centrifuged at 2000 rpm for 10 min, from which two 1-ml aliquots of plasma from each blood sample were pipetted as patient aliquots. Both standard and patient aliquots were counted in a gamma counter (1282 Compugamma, LKB, Stockholm, Sweden). Plasma volume was calculated from the formula (*5*):

$$\text{Plasma volume} = \frac{(\text{Standard counts} - \text{Background}) \times 1000}{(\text{Zero time counts} - \text{Background})},$$

where all counts are expressed as cpm/ml and 1000 is the product of the dilution factor (1000) and volume injected (1 ml). Injected

TABLE 1
Clinical Characteristics of Critically Ill Patients

Age	64 yr (range 18–87)
Sex	9 males, 6 females
APACHE II score*	14 ± 5
Diagnosis:	Cardiac failure—post cardiac surgery (5)
	—myocardial infarction (1)
	Chronic obstructive pulmonary disease (2)
	Asthma (1)
	Drug overdose (1)
	Adult respiratory distress syndrome (1)
	Sepsis—intra-abdominal (1)
	—chest (1)
	Respiratory failure (multifactorial) (2)

Results expressed as mean ± sd.
* APACHE = acute physiology and chronic health evaluation.

counts into either the standard or patient were measured quantitatively as the difference between the activity in the syringe before and after the injection.

Calculation of ECF Volume. To prepare the ECF volume standard, 1 ml (10 μCi) of ^{35}S-sodium sulfate stock solution (Sodium sulfate, Du Pont Pharma, Montréal, Québec, Canada) was diluted volumetrically into 100 ml of 0.9% saline. From this solution, 0.5 ml was further diluted to 10 ml with 5% albumin, and then 6 ml of this final dilution was mixed with 2 ml trichloroacetic acid and centrifuged. From the supernatant, four 1-ml aliquots were pipetted as standard aliquots. To prepare the plasma samples, blood samples were centrifuged, then 3-ml samples of plasma from each blood sample were each mixed with 1 ml trichloroacetic acid and further centrifuged. From the supernatant, two 1-ml aliquots were pipetted as patient aliquots. Both standard and patient aliquots were individually placed in scintillation vials to which 10 ml of 2:1 PCS:xylene scintillation cocktail (Amersham Canada Ltd., Oakville, Ontario, Canada) were added before counting in a liquid scintillation counter (LS7500, Beckman Instruments Inc., Irvine, CA). Extracellular fluid volume was calculated from the formula (*6*):

$$\text{ECF volume} = \frac{(\text{Standard counts} - \text{Background}) \times 10000 \times 0.91}{(\text{Zero time counts} - \text{Background})},$$

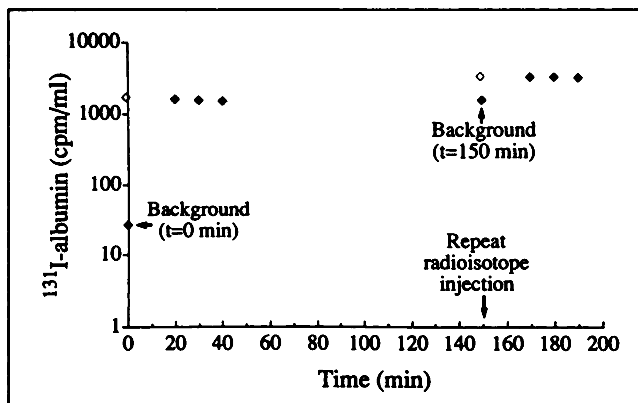

FIGURE 1. Log (^{131}I counts) versus time plot for calculation of plasma volume in one patient. ◆, measured plasma counts and ◇, extrapolated zero time plasma counts.

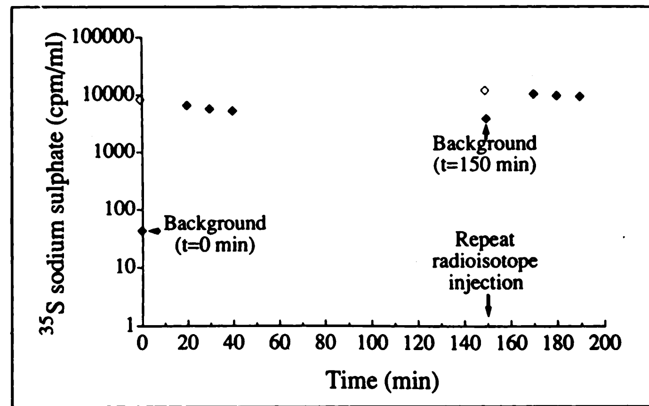

FIGURE 2. Log (^{35}S counts) versus time plot for calculation of extracellular fluid volume in one patient. ◆, measured plasma counts and ◇, extrapolated zero time plasma counts.

where all counts are expressed as cpm/ml; 10000 is the product of the dilution factor (2000) and volume injected (5 ml) and 0.91 is the correction factor for the effect of the Gibbs-Donnan equilibrium.

Data Analysis

Data are expressed as mean ± s.d. To compare hemodynamic variables and volume measurements, we used paired t-tests with the Bonferroni correction for multiple comparisons. To examine the relationship between the net liquid balance and changes in ECF volume, we calculated the Pearson correlation coefficient. We considered differences significant at $p < 0.05$.

RESULTS

There was no significant difference between the two measurements of plasma and ECF volume 150 min apart in these critically ill patients. Plasma volume measurements were 42.4 ± 4.7 ml/kg and 42.8 ± 5.5 ml/kg, respectively, differing by 0.4 ± 3.2 ml/kg (Fig. 3). Extracellular fluid volume measurements were 186 ± 39 ml/kg and 193 ± 48 ml/kg, respectively, differing by 7 ± 17 ml/kg (Fig. 4).

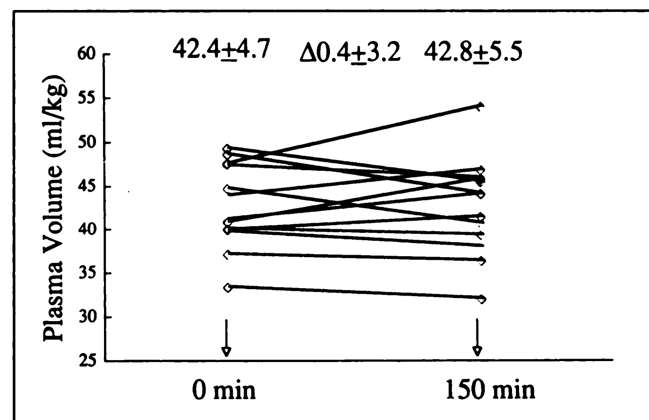

FIGURE 3. Individual changes in plasma volume over 150 min in 13 patients. Results at each measurement time and the difference between measurements (Δ) expressed as mean ± s.d.

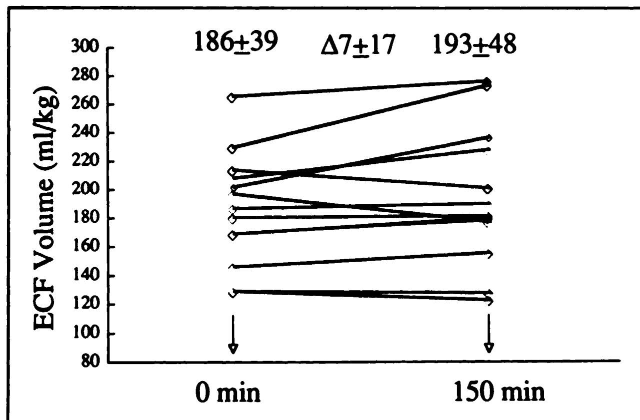

FIGURE 4. Individual changes in extracellular fluid volume over 150 min in 13 patients. Results at each measurement time and the difference between measurements (Δ) expressed as mean ± s.d. ECF = extracellular fluid volume.

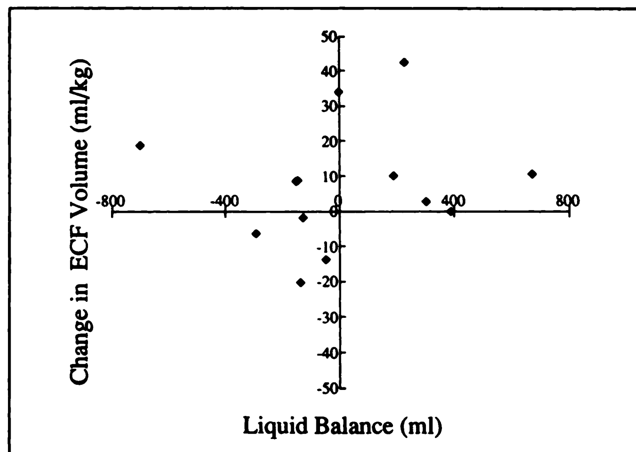

FIGURE 5. No significant correlation between changes in extracellular fluid volume and liquid balance over 150 min in 13 patients; r = 0.11, p = 0.73. ECF = extracellular fluid volume.

There was no significant difference between the two measurements of mean arterial pressure, pulmonary capillary wedge pressure, central venous pressure and cardiac output (Table 2). The mean liquid input and output during the study period was 325 ± 250 ml and 370 ± 235 ml, respectively, resulting in a net liquid balance of −50 ± 375 ml. No correlation existed between the net liquid balance and changes in extracellular fluid volume over the study period (Fig. 5), indicating that the liquid balance did not account for measured changes in the extracellular fluid volume.

DISCUSSION

We found that plasma and ECF volume measurements did not change significantly over the study period, indicating that these measurements are reproducible in critically ill patients. This finding is important because it will support the application of serial measurements of plasma and ECF volume in evaluating interventions in critically ill patients. In particular, serial measurements of plasma and ECF volume, before and after the infusion of different fluids, will provide valuable complementary data to changes in hemodynamic measurements that are currently used to compare fluid infusions in the unresolved crystalloid versus colloid controversy (*3*).

With reference to such a future application of plasma and ECF volume measurements, we required a measurement technique that was not only reproducible but also able to be completed over a relatively short time period. Iodine-131-albumin and ^{35}S-sodium sulfate were selected for these measurements because each of these radioisotopes distributes rapidly throughout its respective volume of distribution. Iodine-131-albumin distributes throughout the plasma volume, and even slow mixing of ^{131}I-albumin in the setting of circulatory shock does not invalidate the application of this indicator dilution technique to plasma volume measurement (*5*). Sulfur-35-sodium sulfate distributes throughout the extracellular fluid volume and its disappearance after intravenous injection is described by two additive single exponential rates. An initial rapid disappearance rate is completed within 20 min, corresponding to the equilibration of ^{35}S-sodium sulfate throughout the ECF volume (*7,8*). This is followed by a slower disappearance over 8–9 hr, corresponding to urinary sulfate loss, penetration into the nonfunctional ECF volumes and organic binding in various body organs, particularly muscle and liver (*9*).

Based on these characteristics of the radioisotopes, we selected a short period (40 min) for the blood sample collection and took the first sample at 20 min after each injection to ensure equilibration of ^{35}S-sodium sulfate throughout the ECF volume. To avoid corrections for radioisotope excretion or metabolism during measurements of plasma and ECF volumes, we calculated these volumes using plasma counts extrapolated to zero time. This refers to the theoretical moment when all of the injected radioisotope is uniformly distributed in its assumed volume of distribution, thereby compensating for disappearance due to excretion or metabolism (*8*).

Although previous investigators have measured plasma and ECF volume using radioisotope dilution techniques

TABLE 2
Hemodynamic Variables at each Measurement Time in Critically Ill Patients

Variable	Patients	0 min	150 min
MAP (mmHg)	15	83 ± 15	83 ± 15*
PCWP (mmHg)	9	16 ± 5	16 ± 6*
CVP (mmHg)	12	10 ± 5	11 ± 6*
Cardiac output (liter/min)	9	5.8 ± 1.5	5.8 ± 1.6*

Results expressed as mean ± sd. MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure.

* p not significant vs. 0 min.

in both healthy subjects and critically ill patients (*7–12*), only limited data concerning the reproducibility of extracellular fluid volume measurements are available. Ryan et al. (*8*) documented that the ECF volume in healthy subjects varied according to the population studied, ranging from 14.1% ± 3.2% of body weight (141 ± 32 ml/kg) in elderly males to 19.1% ± 1.7% of body weight (191 ± 17 ml/kg) in male soldiers. In five of these subjects, a repeat measurement ranging from 1 to 30 days after the first measurement differed by −0.04% ± 0.8% of body weight (−0.4 ± 8 ml/kg). The better reproducibility of the ECF volume measurement indicated by this result relative to ours might be anticipated, given the healthy, more stable nature of the population studied.

Significant changes in the liquid balance during the study period may have contributed to the measured changes in the ECF volume. To determine the extent of this contribution, we examined the relationship between the net liquid balance and changes in ECF volume. No correlation was found between these variables, a result which may be explained by changes in the intracellular fluid volume. Specifically, liquid balance reflects the net effect of liquid movement between the combined extracellular and intracellular fluid volumes and the environment, whereas changes in ECF volume reflect the net effect of liquid movement between the extracellular and intracellular fluid volumes, and between the ECF volume and the environment. Therefore, changes in intracellular fluid volume may have contributed to the liquid balance and/or changes in ECF volume, which would confound the relationship between the liquid balance and changes in ECF volume.

CONCLUSION

In summary, we found that measurements of plasma and ECF volume by radioisotope dilution techniques are reproducible over 150 min in critically ill patients. Furthermore, these measurements can be obtained within 40 min. These findings support the application of serial measurements of plasma and ECF volume in evaluating interventions in critically ill patients.

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