Research Article

Monitoring of Intraperitoneal Fluid Volume during Peritoneal Equilibration Testing using Segmental Bioimpedance

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Keywords

Ultrafiltration volume · Bioimpedance · Peritoneal membrane · Peritoneal dialysis · Ultrafiltration failure

Abstract

Background: Ultrafiltration failure and fluid overload are common in peritoneal dialysis (PD) patients. Knowledge of intraperitoneal volume (IPV) and time to peak IPV during a dwell would permit improved PD prescription. This study aimed to utilize trunk segmental bioimpedance analysis (SBIA) to quasi-continuously monitor IPV (IPV_{SBIA}) during the peritoneal dwell. **Methods:** IPV_{SBIA} was measured every minute using lower-trunk SBIA (Hydra 4200; Xitron Technologies Inc., CA, USA) in 10 PD patients during a standard 240-min peritoneal equilibration test (PET). The known dialysate volume (2 L) rendered IPV_{SBIA} calibration and calculation of instantaneous ultrafiltration volume (UFV_{SBIA}) possible. UFV_{SBIA} was defined as IPV_{SBIA} – 2 L. **Results:** Based on dialysate-to-plasma creatinine ratio, 2 patients were high, 7 high-average, and 1 low-average transporters. Technically sound IPV_{SBIA} measurements were obtained in 9 patients (age 59.0 ± 8.8 years, 7 females, 5 African Americans). Drained ultrafiltration volume (UFV_{drain}) was 0.47 ± 0.21 L and correlated ($r = 0.74$; $p < 0.05$) with end-dwell UFV_{SBIA} (0.55 ± 0.17 L). Peak UFV_{SBIA} was 1.04 ± 0.32 L, it was reached 177 ± 61 min into the dwell and exceeded end-dwell UFV_{SBIA} by 0.49 ± 0.28 L (95% CI: 0.27–0.7) and UFV_{drain} by 0.52 ± 0.31 L (95% CI: 0.29–0.76), respectively. **Conclusion:** This pilot study demonstrates the feasibility of trunk segmental bioimpedance to quasi-continuously monitor IPV_{SBIA} and identify the time to peak UFV_{SBIA} during a standard PET. Such new insights into the dynamics of intraperitoneal fluid volume during the dwell may advance our understanding of the underlying transport physiology and eventually assist in improving PD treatment prescriptions.

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Published by S. Karger AG, Basel

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Background

Recent studies have shown that 25–70% of peritoneal dialysis (PD) patients experience fluid overload [1]. Its prevalence is due to many factors, including a decline in residual renal function, high salt and water intake, chronic inflammation, poor nutritional status, and small solute transport characteristics. Fast transporters are especially prone to fluid overload given the rapid dissipation of the peritoneal-to-plasma glucose gradient after instillation of dialysis solution, resulting in potential ultrafiltration failure during longer dwells [2, 3]. Improved knowledge of the time course of intraperitoneal volume (IPV) during PD dwells may provide insights into fluid transport characteristics beyond the information provided by a standard peritoneal equilibration test (PET) and may eventually help to optimize and personalize PD prescriptions. Although ultrasound studies can provide a snapshot image of IPV, they are not practical for continuous IPV monitoring.

Bioimpedance analysis (BIA) has been used for many years to measure fluid volumes in body compartments. Information from BIA can provide useful information on the fluid status [4–8]. However, due to fundamental physical and technical issues, standard BIA has not been able to measure fluid volume in the peritoneal cavity. To overcome that limitation, we developed an abdominal segmental BIA (SBIA) technique that allows for quantitative measurement of IPV (IPV_{SBIA}) in a quasi-continuous manner [9]. The present study aimed to explore the potential usefulness of IPV measurements and to relate IPV dynamics to transport characteristics obtained from standard 240-min PET.

Methods

Study Population

Ten PD patients were studied during routine PET at the Rogosin Institute in New York.

The following inclusion criteria were applied:

1. Age ≥ 18 and ≤ 80 years
2. PD vintage ≥ 3 months
3. Clinically stable, with no acute medical problems in the preceding 3 months
4. Willing and able to provide informed consent

Patients with ≥ 1 of the following criteria were excluded:

1. Acute medical problems in the preceding 3 months
2. Simultaneous participation in another clinical study (except observational trials)
3. Psychological conditions which could interfere with the patient's ability to comply with or understand the study protocol
4. Pregnancy
5. Limb amputation
6. Presence of a pacemaker, implantable pump, or artificial joint
7. Hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection
8. Inability to provide informed consent

Peritoneal Equilibration Test

Segmental bioimpedance analysis was performed during a standard 240-min PET using 2 L of dialysate containing 2.5 g/dL dextrose (2.26 g/dL glucose). Serum and dialysate creatinine levels were measured 0, 120, and 240 min after PET fill infusion. Patients were stratified into peritoneal membrane transport groups based on the creatinine dialysate/plasma (D/P). Dialysate glucose levels were measured in 10-mL samples at 0, 60, 120, 180, and 240 min (in total 40 mL during the PET). Upon removal of the final 10-mL sample at 240 min, the dialysate

Fig. 1. Measurement of segmental bioimpedance in the peritoneal cavity; electrode placement: I_1 and I_2 were placed on the hands (I_{1L} and I_{1R}) and feet (I_{2L} and I_{2R}), respectively, for injecting current; 2 paired electrodes (S_1 – S_2 and S_3 – S_4) were placed at the level of the 10th rib and the buttock on both sides, respectively, for resistance measurements.

was drained and weighed. The drained ultrafiltrate volume (UFV_{drain}) was calculated as the weight difference between the instilled and drained dialysate. For these calculations, the density of both fluids was assumed to be 1 kg/L, so that 1 kg = 1 L.

Bioimpedance Measurements

The Hydra 4200 device (Xitron Technologies Inc., San Diego, CA, USA) was used. Lower-trunk segmental bioimpedance measurements were made once a minute during the PET. Eight electrodes were placed as shown in Figure 1. To deliver the bioimpedance current, 2 electrodes were placed on the hands (I_{1R} and I_{1L}) and 2 on the feet (I_{2R} and I_{2L}). To measure resistance and reactance, 2 paired electrodes were placed on each side of the body (S_1 – S_2 and S_3 – S_4) with one member of each pair at the 10th rib and the other just below the buttocks. Segmental resistance at 5 kHz (R_5 , in Ω) was computed from the multifrequency data as previously described [9]. Five to 10 min after the patient had moved into a supine position, the BIA measurement started, and after a further 5 min of baseline BIA measurements, the peritoneal cavity was filled with PD dialysate. The BIA measurement was continued throughout the entire 4-h dwell and ended after completion of the dialysate drain. Patients were asked to maintain a supine position during the entire measurement period.

Study Procedure and Measurements

Step 1. A baseline impedance measurement of the empty (“dry”) peritoneal cavity was obtained. For subsequent calculations, this baseline calculation of IPV was set to zero.

Step 2. The peritoneal cavity was filled with 2 L of dialysis solution. Once filling was initiated, impedance was recorded every minute. The change in resistance (ΔR_5) between baseline peritoneal volume and filled volume (promptly after completion of the instillation) was calculated. The ratio of resistances between empty and filled states was calculated, and this value was used to calibrate the IPV_{SBIA} measurement. The detailed calibration and calculation procedures have been reported previously [9].

Fig. 2. Indicators used to describe IPV_{SBIA} dynamics during PET. This curve has been smoothed from raw data (GraphPad Prism 5).

Step 3. Peritoneal fluid volumes were recorded using SBIA in 1-min intervals throughout the 240-min PET.

Step 4. At 240 min, the dialysate was drained and weighed.

The following peritoneal fluid volume-related parameters were measured and analyzed (Fig. 2):

- Area under the curve (AUC; expressed as $L \times min$) of the IPV_{SBIA} over time was calculated using the initial “empty” value as a zero baseline. The curve was smoothed using a moving average with a window width of 5 min (GraphPad; GraphPad Software Inc., La Jolla, CA, USA).
- Peak IPV_{SBIA} was defined as the maximum IPV_{SBIA} during the 240-min PET.
- Time-to-peak IPV_{SBIA} was taken to be the time between start of infusion and the time of maximum IPV_{SBIA} .
- Bioimpedance-measured UFV (UFV_{SBIA}) was calculated as the $IPV_{SBIA} - 2 L$ (initial dialysate volume). We then added the volume of the peritoneal fluid samples drawn during the dwell (in total 40 mL, the volume of the four 10-mL intradialytic dialysate samples).
- Other parameters measured were systolic and diastolic blood pressures, heart rate, height, and pre- and post-PET body weight. Additional demographic and disease-related characteristics recorded were cause of renal failure, PD vintage (years on PD), and diabetes status; these were obtained from patient health records.

Data Analysis

Data are presented as means and SD, or percent. Values for UFV_{SBIA} , maximal IPV_{SBIA} , IPV_{SBIA} AUC, and time to peak IPV_{SBIA} were calculated for each patient. Patient results were categorized by peritoneal transport status. A p value <0.05 was considered significant.

Results

The baseline characteristics of the 10 patients studied are shown in Table 1. Per PET D/P creatinine, 2 patients were classified as high transporters (D/P creatinine 0.82 and 0.83, respectively), 7 as high-average transporters (D/P creatinine ranging from 0.66 to 0.79), and 1 as low-average transporter (D/P creatinine 0.59). Per PET D/D₀ glucose (ratio

Table 1. Patient baseline characteristics ($n = 10$)

	Mean $\pm$ SD/ n	Range
Females/males, n	7/3	
Race, n		
African American	5	
Caucasian	3	
Diabetes mellitus, n	3	
Age, years	59.0 $\pm$ 8.8	46–80
PD vintage, years	4.6 $\pm$ 2.9	1–8.5
Height, cm	161.9 $\pm$ 7.9	151–174
Weight, kg	69.8 $\pm$ 12.4	51.6–91.6
Body mass index, kg/m ²	26.7 $\pm$ 5.1	21.8–38.4
Systolic blood pressure, mm Hg	143.3 $\pm$ 21.9	93–178
Diastolic blood pressure, mm Hg	80.8 $\pm$ 11	62–95
Heart rate, beats/min	78.3 $\pm$ 10	63–93
Serum sodium, mEq/L	135.1 $\pm$ 1.9	132–138
Serum potassium, mEq/L	4.1 $\pm$ 0.9	3–5.5
Blood urea nitrogen, mg/dL	62.9 $\pm$ 23.1	25–104

Table 2. Membrane transport characteristics

Patient No.	D/P creatinine	High	High average	Low average	D4/D0 glucose	High	High average	Low average
1	0.82	x			0.25	x		
2	0.79		x		0.26		x	
3	0.59			x	0.34		x	
4	0.67		x		0.29		x	
5	0.83	x			0.22	x		
6	0.69		x		0.32		x	
7	0.67		x		0.26		x	
8	0.72		x		0.28		x	
9	0.74		x		0.30		x	
10	0.66		x		0.34		x	

of final-to-initial dialysate glucose concentrations), 2 patients were classified as high transporters (D/D₀ glucose of 0.22 and 0.25, respectively) and 8 as high-average transporters (D/D₀ glucose ranging from 0.26 to 0.34). Table 2 shows the individual patients' transport characteristics.

Measurements of intraperitoneal fluid volumes were successful in 9 patients and failed in 1 patient due to technical reasons. Figure 3 shows the IPV_{S_{BIA}} recordings in these 9 patients, and the respective IPV_{S_{BIA}} AUC calculations.

Figure 4 shows values of UFV_{S_{BIA}}, maximal UFV_{S_{BIA}}, the IPV_{S_{BIA}} AUC, and time to peak UFV_{S_{BIA}} in 9 patients stratified by peritoneal membrane transport status. Lower UFV_{S_{BIA}}, peak UFV_{S_{BIA}}, and IPV_{S_{BIA}} AUC were associated with a high transport status, while high UFV_{S_{BIA}}, maximal UFV_{S_{BIA}}, and IPV_{S_{BIA}} AUC were associated with a low transport status.

Peak UFV_{S_{BIA}} was 1.04 $\pm$ 0.32 L and was attained 177 $\pm$ 61 min into the dwell; it exceeded the end-dwell UFV_{S_{BIA}} by 0.49 $\pm$ 0.28 L (95% CI: 0.27–0.7) and UFV_{drain} by 0.52 $\pm$ 0.31 L (95% CI: 0.29–0.76), respectively (Fig. 4a–c). Time-to-peak IPV_{S_{BIA}} was not related to transport status. Figure 5 shows the average IPV_{S_{BIA}} curve in 9 patients with 95% CIs.

Fig. 3. Area under curve (AUC) of the intraperitoneal volume (IPV_{SBLA}) during PET in 9 individual patients. One patient (#5) was excluded because of technical failure of the bioimpedance measurements.

Discussion

This pilot study demonstrates the feasibility of segmental bioimpedance measurements to continuously monitor changes in intraperitoneal fluid volume during a PD dwell. This novel technique permits characterization of intraperitoneal fluid volume changes during a dwell, including various patterns of volume changes that may be patient specific. Such new insights into the dynamics of intraperitoneal fluid volume during the dwell may advance our understanding of the underlying transport physiology and eventually assist in improving PD treatment prescription.

Fluid management is a clinical challenge in PD patients [1], and recent studies have indicated the presence of fluid overload in a substantial fraction. In the EuroBCM study, whole-body bioimpedance spectroscopy was used to assess volume status in a cross-sectional cohort of prevalent PD patients in 28 centers in 6 European countries [10]. The Initiative for Patient

Fig. 4. UFV_{SBIA} at the end of dwell (a), maximal UFV_{SBIA} (b), area under IPV curve (c), and time to maximal UFV_{SBIA} (d) in patients stratified by peritoneal transport status. Average maximal UFV_{SBIA} at 177 ± 61 min was significantly larger than the UFV_{SBIA} at 240 min (0.93 ± 0.44 vs. 0.5 ± 0.24 L, $p < 0.01$). High, High-ave, and Low-ave represent the transport status by dialysate/plasma creatinine. Individual patients from #1 to #10 are indicated by different colors. Patient #5 has been omitted due to technical failure of the bioimpedance measurements.

Outcomes in Dialysis-Peritoneal Dialysis (IPOD-PD) study of 1,092 incident PD patients from 135 centers in 32 countries found that 56.4% of patients were fluid overloaded before PD was initiated. These findings are in line with reports from China which reported 66.8% continuous ambulatory PD patients with fluid overload [11]. Observational studies have shown that there is no difference in volume control in patients on automated PD versus continuous ambulatory PD [12]. A recent publication reports a relationship between weight gain and maximum ultrafiltration rate [13]. In patients with fluid overload, the identification of both the magnitude and the timing of maximal UFV (IPV – instilled dialysate volume) during the dwell may assist with achieving better volume control. Bioimpedance is the only currently available, clinically viable technique for continuous measurements of IPV changes. Current clinical studies of bioimpedance in PD patients focus on fluid management and body composition [14–16]. The root cause of fluid overload in PD patients is low UFV. Therefore, increase in UFV is the fundamental solution for poor fluid management in PD treatment. Our 2 previous studies have shown the potential feasibility of using segmental bioimpedance to measure IPV [9, 17]. The present study adds a new dimension, because for the first time we were able to

Fig. 5. Average intraperitoneal volume (IPV_{SBIA}) in 10-min increments in 9 patients during PET. The bars represent 95% confidence intervals.

relate membrane transport characteristics to the time-to-peak IPV. With this technique, bioimpedance measurements are taken before and after instillation of a known volume of fluid into the peritoneal cavity, and this information is used to calibrate the bioimpedance estimate of the volume. Continuous measurement of IPV based on the known ratio of volume change to resistance changes then permits recognition of both the shape of the volume curve over time and the time-to-peak IPV, at which point the fluid could optimally be drained. In addition, the average IPV curve in 9 patients demonstrates dynamic IPV changes (Fig. 5). As far as we know, this is the first time to report that IPV changes have been observed during PET. Unlike modeling studies, this method enables us to observe the real nature of net IPV changes.

It is obvious that SBIA adds to the currently available repertoire of diagnostic tests to assess membrane and transport characteristics in PD patients. The modified (“two in one”) PET uses a standard PET (4-h dwell) followed by a mini PET (1-h dwell) with the same glucose concentration (3.86%) [18] or with different glucose concentrations in 2 exchanges [19]. The “two in one” PET can quickly and simply evaluate membrane transport characteristics and free water removal in the first hour. However, the first hour of dwell might not be able to predict the time to peak UFV. In this paper, the time to peak UFV was 177 ± 61 min. Clearly, current test methods lack the ability to follow the change in UFV dynamically with a 1-min signal resolution.

Segmental PD BIA does suffer from shortcomings, which must be resolved, e.g., the need for an almost static body position (supine in our patients). It is difficult to motivate patients to remain in a specific position for hours. Unless future developments of segmental PD BIA can address that inconvenience, the method is not likely to gain widespread acceptance. Potential solutions may come from “smart textiles” with integrated sensors or small adhesive skin patches that have all the necessary technology onboard [20].

Segmental PD BIA may have clinical application beyond the identification of peak UFV. For example, peritoneal overfill is a well-recognized problem in patients treated with automated PD or continuous-flow PD [21, 22]. Such overfill events could be identified and prevented with segmental PD BIA in place.

Apart from its potential clinical usefulness, results obtained from an IPV over time profile could be used to compare and help validate various mathematical models of peritoneal fluid transport; while these models have provided many useful simulations, they require confirmation by in vivo measurements in a clinical setting [23].

Relationship of Transport Status to UFV_{BIA}

The results of this study suggest a relationship between D/P creatinine transport status and UFV_{SBIA} , IPV_{SBIA} AUC, and time-to-peak UFV_{SBIA} (Fig. 4). These findings are in accord with the results of previous research that has investigated the relationship between transport status and UFV [24, 25]. Our study found high creatinine transport status to be associated with lower UFV_{SBIA} and low creatinine transport status associated with higher UFV_{SBIA} , as previously described [26]. This additional information could facilitate better understanding of UFV dynamics and improved the clinical prescription of PD for individual patients.

In addition to the above, the results of this study may inspire the development of new techniques to examine the characteristics of the peritoneal membrane, including the measurement of changes in peritoneal cavity fluid volume over time, eliminating the need for repeat PETs.

A limitation of this study is its small number of patients, especially those with low and high transporter status. In addition, the continuous BIA technique used requires improvements to reduce the impact of patient movements on the BIA signal; a simple and stable electrode system and more advanced signal processing methods need to be developed. These technical requirements may be the major obstacle for its slow application since our first publication in 2003.

Conclusions

This study demonstrates a new technique for monitoring changes in peritoneal cavity fluid volume during PD. The UFV profiles can be used to identify maximal IPV during a dwell, allowing for optimization of drain times for individual patients. This should result in larger net fluid removal. While these early results are encouraging, additional validation studies are indicated. Other required advances that would add value to our technique include the development of an algorithm to automatically detect maximum UFV_{SBIA} and methods to improve the convenience of measurement.

Acknowledgments

Part of the results from this study were presented at the Annual Meeting of the American Society of Nephrology 2017 in New Orleans. The authors thank Bambi Lanto for her performing PET. S.R.A. was supported by the *nephrocore* Fresenius Medical Care exchange program for young scientists. The authors thank Sarunas Daugirdas for editing the language of the paper.

Statement of Ethics

The study protocol was approved by the Weill Cornell Medical College (WCMC) Institutional Review Board. All patients gave informed consent prior to the study.

Disclosure Statement

P.K. and N.W.L. hold stock in Fresenius Medical Care. P.K. receives author honoraria from UpToDate. The other authors have no conflicts of interest to declare.

Funding Sources

No funding was obtained for this study.

Author Contributions

F.Z. and S.R.A. carried out the clinical study with bioimpedance measurement. R.M.B. performed the clinical PET. F.Z., N.W.L., and P.K. participated in the design of the study. F.Z. and P.K. wrote the manuscript. All authors read and approved the final manuscript.

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