

The mini-PET in pediatric peritoneal dialysis: A useful tool to predict volume overload?

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Abstract

Background Cardiovascular disease (CVD) in patients on chronic peritoneal dialysis (PD) is a major cause of death and is closely linked to hypertension and volume overload. The mini-Pet has been proposed as a useful tool to evaluate free-water transport (FWT) and characterize ultrafiltration across the peritoneum. Knowledge regarding FWT could be of great value to predict volume overload in PD patients. Our objective in this study was to characterize FWT through the peritoneum in children on PD.

Methods We studied clinically stable patients with >2 months on PD. Exclusion criteria were a peritonitis episode up to 2 months prior to entrance into the study and active nephrotic syndrome. A 1-h mini-peritoneal equilibration test (mini-PET) was performed with 3.86 % glucose. Calculations (see text for full definitions) were: Dip Na ($\text{Na dial}_{\text{min}60} - \text{Na dial}_{\text{min}1}$), Dip D/PNa ($\text{D/PNa}_{60} - \text{D/PNa}_1$), total Na removal ($\text{Na}_R = \text{total Na dial}_{60} - \text{Na dial}_1$), ultrafiltration small pores [$\text{UFSP} = \text{Na}_R \times 1,000 / \text{Na}_p$], and FWT ($\text{UF} - \text{UFSP}$). Peritoneal equilibration test (PET), left ventricular mass index (LVMI, g/m^2), daily UF, and residual renal function were evaluated. Pearson's correlation coefficient was used to establish correlation between variables.

Results Sixteen patients were included, with a mean age of 11.8 ± 3.8 years. Free water transport normalized to body

surface area (BSA) (FWT_n) was $133.9 \pm 85.7 \text{ ml/m}^2$; creatinine dialysate-to-plasma (D/P) and glucose dialysate at X dwell time-to-0 dwell time (D_x/D_0) ratios were 0.38 ± 0.1 and 0.65 ± 0.09 , respectively. LVMI was $46.6 \pm 14.8 \text{ g/m}^2$; 2-h creatinine D/P and glucose D_x/D_0 showed no correlation with FWT_n , UF, and LVMI. FWT_n showed a significant inverse correlation with LVMI ($r 0.58, p 0.02$).

Conclusions This study characterized FWT in PD children through the mini-PET. Left ventricular hypertrophy showed a high prevalence in this group, and a significant correlation between LVMI and FWT was found. FWT could be a useful tool to evaluate UF in PD children.

Keywords Mini-PET · Adequacy · Peritoneal transport · Peritoneal dialysis · Free water transport · Peritoneal equilibrium test

Introduction

Since the first description by Twardowski et al. almost 30 years ago, the peritoneal equilibrium test (PET) has been used to predict the optimal dialysis prescription [1]. Individuals who are fast transporters may achieve adequate dialysis with short dwells under automated peritoneal dialysis (APD), and low transporters are better treated with long dwells [continuous ambulatory peritoneal dialysis (CAPD)], or even switched to hemodialysis. However, even with the routine use of PET, a high percentage of PD children show evidence of volume overload [2]. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2008 data show that 57 % of nearly 4,000 dialysis patients had uncontrolled hypertension (>95th percentile), and Mitsnefes et al. found that 75 % of pediatric dialysis patients had left-ventricular hypertrophy (LVH) [3]. The International Pediatric Dialysis Network (IPPN) registry shows that only 26 % of

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PD patients have a normal cardiac condition [4]. In PD patients, hypertension and cardiac impairment are most frequent in the younger and nephrectomized patients, for whom volume overload appears to be the most important etiologic factor [5]. All these data suggest that volume overload is not well controlled in most dialyzed children.

PET is the most common tool used to assess peritoneal permeability, but it focuses mainly on solute transport and not on ultrafiltration (UF) capacity. Sodium dialysate-to-plasma ratio (D/P) was significantly associated with drainage volume in the original PET study [1], and the magnitude of sodium (Na) sieving at 60 min has been proposed to represent the function of the ultras-small pores (USP), which could be an important factor involved in UF failure in PD [6]. The ‘three-pore model’ described by Rippe et al. [7] postulates that the major transport barrier of the peritoneum is the capillary endothelium, which contains three distinct types of pores: small pores (SP), radius 40–50 Å, correspond to clefts located between endothelial cells and account for 95 % of the hydraulic conductance; large pores, radius 250 Å, correspond to the venular interendothelial gaps, which account for 5 % of the UF coefficient and mediate an important part of UF via convection of plasma to the peritoneal cavity; and USP, water-specific pores located in endothelial cells. Ni et al. characterized the expression pattern of the *AQP* gene family in the mouse peritoneum, providing direct evidence of the role of AQP1 in transport across the peritoneal membrane [8]. They showed that AQP1 is the counterpart of USP and mediates the initial solute free-water transport (FWT) as well as half of UF during PD in mice. USP account for only 1–2 % of hydraulic conductance, but because they exclusively transport free water, they are very important during crystalloid osmosis. These pores are predicted to be responsible for Na sieving and up to 50 % of UF during a hypertonic dwell. Sodium sieving corresponds to the fall in dialysate Na concentration during a dwell with hypertonic glucose, and it has been suggested that its reduction may contribute to UF failure in PD patients [9].

In order to assess FWT through USP, La Milia et al. described the mini-PET [10]. During the first hour of a 3.86 % dwell, FWT is maximal, as glucose concentration in the dialysate is at its peak, and Na transport by diffusion is very low because of a low plasma/dialysate gradient. In PD, total Na transport is mainly due to convective transport through SP, and UF through SP (UFSP) corresponds to Na removal divided by plasma Na concentration. FWT could then be easily calculated by subtracting UFSP from total UF (FWT: total UF – UFSP). The authors of that study concluded that the mini-PET is a simple and fast method of assessing FWT.

The main objective of this study was to use the mini-PET test to characterize FWT in pediatric PD patients.

Patients and methods

A prospective protocol was applied at the Division of Pediatric Nephrology, Luis Calvo Mackenna Children’s Hospital, Santiago, Chile, between November 2011 and July 2012; a 1-h PET was performed in patients undergoing chronic PD in order to evaluate FWT. Inclusion criteria were clinically stable patients with >2 months in PD. Exclusion criteria were patients who had a peritonitis episode up to 2 months prior to entrance into the trial or had an active nephrotic syndrome condition. Mini-PET studies were performed in all selected patients according to a previously published protocol [10]. Briefly, the modified PET was applied, which differs from the classic 2.27 % glucose concentration PET, as the PD solution contained a 3.86 % glucose concentration; the duration of the test was shortened to 1 h. The night prior to the test, each patient received five exchanges of 1-h each at the same glucose concentration previously used. Afterwards, the same PD solution was used for a 4-h dwell. The exchange fill volume was 1,100 ml/m² body surface area (BSA), and the dialysate solution was Dianeal® (Baxter Healthcare, USA). The next morning, the last 4-h dwell was drained, and a transfer Y-type set Dianeal PD solution (Ultrabag) was installed. After the overnight drain, a 3.86 % glucose solution was infused over 10 min. The first PD fluid sample was taken from the bag at the end of the infusion (20 ml, minute 1). After 1 h, another dialysate sample was obtained (20 ml, minute 60). Later, the dialysate was drained and collected by gravity for at least 20 min. The volume of the infused PD solution and the drained dialysate were measured by weighing the bags and then subtracting the weight of the empty bags. A single blood sample was obtained at the start of the test. All samples obtained under noncompliance conditions were discarded. Plasma and dialysate Na (enzyme assay) was measured in each sample. The following calculations were done:

1. Absolute dip of dialysate sodium concentration:

$$\text{Dip Na}_D (\text{mEq/L}) = \text{Na dialysate out (mEq/L)} - \text{Na dialysate in (mEq/L)},$$

where Na_D is sodium in dialysate

2. Dip of sodium D/P relationship:

$$\text{Dip D/PNa} = \text{D/PNa}_{60} - \text{D/PNa}_0,$$

where D/PNa is relation dialysate/plasma of sodium, minute 60 and minute 0 of the test

3. Sodium removal during the 1 h of the test:

$$\text{Na removal} = [\text{total sodium in dialysate min 60 (out)} - \text{total sodium in dialysate min 1(in)}]$$

$$\text{Na removal} = [\text{volume dialysate out (L)} \times \text{Na dialysate out (mEq/L)}] - [\text{volume dialysate in (L)} \times \text{Na dialysate in (mEq/L)}]$$

4. Convective UF through small pores (UFSP):

$UFSP \text{ (ml)} = [Na_R \text{ (mEq)} \times 1,000] / Na_p$,
 where $UFSP$ is UF through small pores, Na_R is sodium removal, and Na_p is sodium in plasma

5. Free water transport (FWT):

$FWT = \text{total UF (ml)} - UFSP \text{ (ml)}$
 where UF is UF and $FWT_n = FWT$ normalized to BSA
 where BSA is body surface area (m^2) = $\sqrt{\text{height (cm)} \times \text{weight (kg)} / 3,600}$

Daily UF and FWT were normalized by BSA (UF_n and FWT_n , respectively). An echocardiogram and a classic 2-h PET from the last 4 months were evaluated in each patient [11]. All Doppler echocardiograms were performed by a pediatric cardiologist at the Luis Calvo Mackenna Children’s Hospital. Measurements included systolic diameter, end-diastolic diameter, interventricular septal thickness, and posterior wall thickness. LVMI was calculated using the software of the IPPN (www.pedpd.org). Patients were evaluated on a routine basis by a renal dietitian for monitoring adequate protein and energy intake to meet Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations [12]. Sodium restriction was raised if hypertension (blood pressure >95 thcentile) or volume overload were diagnosed. The study was approved by the Ethical Committee, Luis Calvo Mackenna Childrens Hospital, and informed consent was obtained from all parents and/or patients.

Statistical analysis

Descriptive analysis was performed using measures of central tendency for all numeric variables (mean/standard deviation, median/range). The Shapiro–Wilk test was used to verify whether or not distribution of variables was normal. Pearson’s correlation coefficient was used to assess the association between variables. Statistical analyses were performed using SPSS software, v19.0.

Results

Sixteen patients were assessed: nine boys; median age was 11.8 ± 3.8 (range 3–16) years. The underlying kidney disease corresponds to reflux nephropathy/obstructive uropathy ($n=4$), chronic glomerulonephritis ($n=4$), renal dysplasia ($n=2$), hemolytic uremic syndrome ($n=2$), Alport syndrome ($n=2$), and unknown etiology ($n=2$). The mean time in dialysis was 35.4 ± 70.3 (range 1–188) months. All patients were on automated PD. Nine peritonitis episodes were

registered over a total of 401 months of observation time, with a rate of 0.27 episodes per year at risk. Ten of the 16 patients had LVH ($LVMI > 38 \text{ g/m}^2$). Mean LVMI value was $46.6 \pm 14.9 \text{ g/m}^2$ (range 25–78.3). Five patients showed severe cardiac hypertrophy ($>51 \text{ g/m}^2$). All those patients were treated with the angiotensin-converting enzyme inhibitor (ACEi) captopril at 0.1–0.4 mg/kg/day. Hypertension was not observed at the time of this study. Other evidence of fluid overload, such as edema or change in weight, was not observed. Mean plasma Na was 138 ± 2 (range 135–142) mEq/L. According to this, dietary Na restriction was not considered. Mean dextrose concentration was $2.05 \pm 0.55 \text{ g/dl}$, range 1.5–3.5 %, with a positive trend but without significant association to LVMI ($p=0.06$, r 0.48). Mean urine volume was 759 ± 613 (range 117–1,780) ml/m²/day. Two patients were anuric, showing an LVMI of 39.8 and 75 g/m², respectively. Peritoneal transport characteristics of the group are shown in Table 1. Dip Na_D and Dip D/PNa showed a linear correlation with FWT (Fig. 1).

The FWT_n was $133.9 \pm 85.7 \text{ ml/m}^2 \text{ BSA}$, representing 14.5 % of daily ultrafiltration. Correlation analysis showed no significant correlation between creatinine D/P and glucose dialysate at X dwell time-to-0 dwell time (D_x/D_0) ratios vs normalized UF, FWT_n , or LVMI (p value not significant). Pearson’s correlation coefficient showed a negative linear correlation between FWT_n and LVMI ($r=0.58$, $p=0.02$) (Fig. 2). Total UF during the test showed a significant correlation with Dip Na_D and Dip D/PNa ($p < 0.01$). No significant correlation was found between total and daily UF vs LVMI.

Table 1 Characterization of the study population ($n=16$)

Variables	Mean	SD	Median	Mínimum	Máximum
Age	11.81	3.85	13.05	3.00	16.10
Months on PD	35.44	70.26	12.50	1.10	288.00
D/P Na_0	0.96	0.03	0.96	0.92	1.04
D/P Na_{60}^*	0.90	0.03	0.90	0.84	0.93
Dip D/P Na*	-0.06	0.03	-0.06	-0.12	-0.03
Na removal	27.29	55.90	42.94	-96.30	93.10
$FWT_n \text{ (ml/m}^2 \text{ BSA)}^*$	133.94	85.73	105.51	32.28	175.26
UF_n	922.52	727.94	715.15	88.78	2502.58
Residual Kt/V^*	1.04	0.93	0.97	0.00	3.10
Creatinine D/P*	0.38	0.10	0.39	0.24	0.54
Glucose D_x/D_0	0.65	0.09	0.70	0.50	0.75
LVMI g/m^2^*	46.64	14.87	42.30	25.00	78.30

PD peritoneal dialysis, D/P dialysate-to-plasma ratio, Na_0 sodium at time 0, Na_{60} sodium at 60 min, FWT free-water transport, BSA body surface area, UF_n normalized ultrafiltration, Kt/V pre- and postdialysis urea concentration ratio, D_x/D_0 glucose dialysate at X dwell time-to-0 dwell time ratios, $LVMI$ left ventricular mass index

*Variables with normal distribution, Shapiro–Wilk test, $p > 0.05$

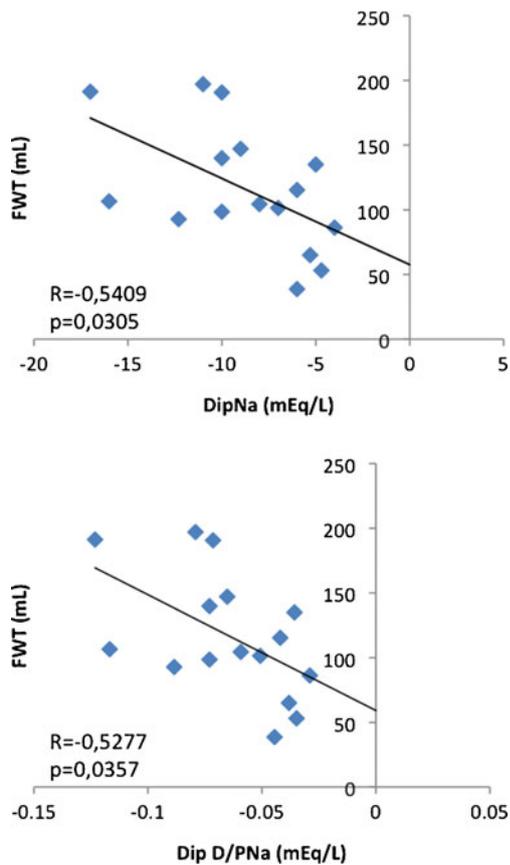


Fig. 1 Linear correlation of sodium (Na) dialysate out (mEq/L) – Na dialysate in (Dip Na_D) and relation dialysate/plasma of sodium, minute 60 and minute 0 of the test (Dip D/PNa) with free-water transport (FWT)

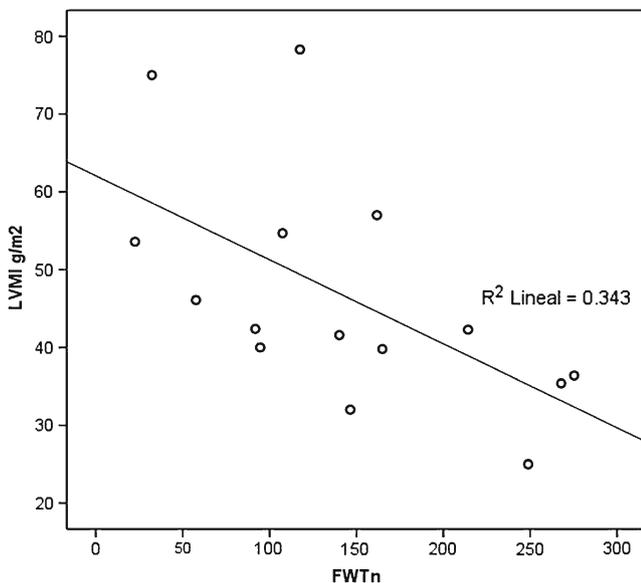


Fig. 2 Linear correlation between free-water transport (FWT) and left-ventricular mass index (LVMI); $p < 0.05$

Discussion

In PD, the capacity of UF across the peritoneal membrane has been considered a major predictor of outcome [13, 14], and loss of this function is a major reason for therapy failure in adults and children. In dialyzed patients, the net UF can be very well controlled in hemodialysis, whereas in PD, it is a complex function of membrane water permeability, glucose concentration, and lymphatic flow.

Since the first description by Twardowski et al. in 1987 [1], PET has been used to assess the capacity of the peritoneal membrane to transport solutes and its ability to generate ultrafiltrate and prevent volume overload in chronic renal failure patients. The original PET is a test lasting 4 h, with a glucose 2.5 % Dianeal[®], which evaluates creatinine D/P and glucose D_x/D₀. In recent years, a short 2-h version of the original PET has been validated in pediatric clinical practice [11]. However, although most centers use this test to prescribe PD therapy, morbidity/mortality secondary to cardiovascular disturbances remains the main complication in PD patients, and the best method to quantify UF capacity of the peritoneum has become a critical question. When using the classic PET, a variability coefficient <10 % for the transport of small solutes has been reported; however, this value can increase up to 50 % when considering UF. In the original PET study [1], Na D/P showed the best correlation to drainage volume, (r 0.546); however, Na D/P is not usually evaluated in clinical practice. These observations can in part explain why—despite the wide use of this test—UF failure remains a main factor related to cardiovascular morbidity/mortality in chronic PD patients.

Lower Na and fluid removal is a powerful predictor of mortality in PD patients and is closely related to volume overload, LVH, and cardiac dilatation [13–16]. Ates et al. evaluated Na and fluid removal in 125 adult PD patients followed for 3 years [14]; 20 % died during the follow-up period, 50 % of them secondary to cardiovascular disease. The authors found a strong correlation between peritoneal Na and fluid removal ($r=0.83$) vs cardiovascular hospitalization rates, which were found to be significantly higher in patients who had a total Na removal below the median value. When patients were classified into four groups according to total Na removal (group I: patients <25th percentile value through group 4: patients >75th percentile), the 3-year patient survival rate was significantly higher in group IV vs group I (96 % vs 59 %, respectively), group II, and group III. The same difference was founded when total fluid removal was compared among groups.

To address these problems, methods focused on obtaining data on water flux across SP and USP have been evaluated. Introduction of the mini-PET by La Milia et al. has allowed quantification of the FWT through USP or aquaporin-1 channels and its separation from other components of

peritoneal UF [10]. With the aim of assessing FWT and comparing the mini-PET with the 4-h PET, those authors evaluated peritoneal transport characteristics of adult patients under chronic PD. A 3.86 %, 4-h-long PET and a 3.86 % 1-h-long mini-PET were performed in 52 stable PD patients. The authors found a mean FWT value of 215 ± 86 ml, representing 46 % of total UF, which shows a good correlation with total UF after the 4-h, 3.86 % PET. A significant inverse correlation between Dip Na and Dip D/PNa with FWT was found, concluding that absolute Dip Na_D and Dip D/PNa were better predictors of FWT than was D/PNa. In our study, mean FWT was lower than in adults (133.9 ± 85.7 ml), representing 14.5 % of total UF. Dip D/PNa showed a negative correlation with FWT, with a lower value compared with adult patients. We also analyzed creatinine D/P and glucose D_x/D_0 from an available PET from the 4 months before mini-PET was performed. Some experiences [17, 18] show that peritoneal characteristics remain stable for at least a 6-month period, allowing us to compare our results with the last available PET. In this experience, mean creatinine D/P and glucose D_x/D_0 were 0.38 ± 0.1 and 0.65 ± 0.09 , respectively, showing no correlation with FWT, total UF, dialysis dose, and LVMI. Mean residual pre- and postdialysis urea concentration ratio (Kt/V) was 1.04 ± 0.93 , without significant correlation with FWT and LVMI. LVH was previously shown to be inversely associated with residual renal function (RRF), with anuric patients showing the most severe form of cardiac hypertrophy [19, 20]. The reanalysis of the Canada–USA (CANUSA) study showed that for every 250 ml of urine output, a 36 % reduction in overall mortality could be observed [21]. The small number of patients and the age of the studied population (11.8 ± 3.8 years) could explain the lack of association between RRF and cardiac status.

In adult PD patients, Wang et al. found that cardiac and cerebrovascular causes accounted for 65 % of mortality, describing RRF as a powerful predictor of cardiovascular mortality [20]. According to Foley et al. and Wang et al., one of the most frequent and important complication in PD patients is LVH, which was present in 74 % and 91 % of their PD patients, respectively [22, 23]. In pediatrics, children with end-stage renal disease (ESRD) show an increased risk of death, as shown in the Late Effects of Renal Insufficiency in Children (LERIC) study [24]. Those authors show that the overall mortality rate in ESRD patients was >30 times higher than in an age- and gender-matched population. The IPPN study shows that body mass index (BMI) and systolic hypertension are the main predictors of LVH; and most important, volume overload was in turn the main predictor of hypertension. In this experience, an LVMI >95th centile was considered as cardiac hypertrophy, which was found in >50 % of patients. FWT and LVMI showed a statistically significant negative correlation, with the highest

LVMI in those patients showing a lower FWT value. Normalized UF did not show a significant correlation with LVMI. However, this correlation was expected, as patients' volume status should be more correlated with total UF and Na removal as opposed to FWT, so it should be considered that UF is continuously adjusted by means of dextrose concentration in dialysate when volume overload is suspected. In this experience, mean dextrose concentration was 2.05 ± 0.55 g/dl (range 1.5–3.5 %), with a positive trend but without significant association to LVMI ($p=0.06$, $r=0.48$). The continuously adjusted dextrose concentration in dialysate to correct volume overload can also explain why hypertension was not found in these patients, although they did show a high rate of LVMI. Hypertension can be well controlled in a few weeks or even a few days with an intensive UF protocol, but ventricular mass changes could take a few months to normalize. Creatinine D/P, glucose D_x/D_0 , and dialysis dose showed no significant association with cardiac mass index.

Some authors advocate that the mini-PET could overestimate UFSP, as the test does not correct results for the small amount of Na diffusion occurring during the first hour and does not consider UF through large pores and the negative lymphatic absorption. The overestimation of UFSP has been described by Venturoli et al. [25] to be very low, nearly 3 %, and La Milia et al. [10] found that the omitted UF (UF through the large pores and through the lymphatic system) was only 15 ml after a dwell of 1 h. According to Venturoli and Rippe, it is possible to adjust the FWT for Na diffusion by the corrected formula: $\text{FWT} = \text{total UF} + 15 - (0.92 \times \text{UFSP})$. Therefore, the possible bias in UFSP can be corrected or even omitted according the small values communicated. Bernardo et al. [26] performed this test using the algorithm proposed by Venturoli and Rippe, with the formula: $\text{FWT corrected} = \text{total UF at 60 min} + 15 - 0.92 \times \text{UFSP}$, finding a small difference between FWT corrected by this formula vs FWT without correction. The same authors proposed performing a two-in-one protocol to simultaneously assess USP and SP UF using a single 4-h 3.86 % PET procedure. They conclude that this peritoneal transport test allows assessing diverse time-dependent changes of the USP and SP water transport pathways.

Conclusions

We characterized for the first time FWT in PD children across the USP of the peritoneal membrane, which correspond to AQP1 channels. In this preliminary experience in a small number of patients, we observed a negative correlation between FWT and LVMI. Further studies in more patients should be performed to characterize UF capacity

of the peritoneum and its relationship with volume status and LVMI.

When UF failure is suspected, the PD prescription is adjusted according transport categorization using the PET. However, the classic PET does not allow us to determine exactly what mechanism has generated UF failure, because PET does not determine whether peritoneal UF failure corresponds to a failure in the first part of the exchange, which means a decrease in USP function, or whether the patient produced little or no UF during the entire test, which basically involves a failure in SP function. Characterizing FWT using the mini-PET allows us to evaluate the functionality of the AQP1 channels and could be a useful tool to complement the classic information when analyzing UF and fluid overload in pediatric PD patients.

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