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REVIEW ARTICLE

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Evidence on continuous flow peritoneal dialysis: A review

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Abstract

Clinical application of continuous flow peritoneal dialysis (CFPD) has been explored since the 1960s, but despite anticipated clinical benefits, CFPD has failed to gain a foothold in clinical practice, among others due to the typical use of two catheters (or a dual-lumen catheter) and large dialysate volumes required per treatment. Novel systems applying CFPD via the existing single-lumen catheter using rapid dialysate cycling may solve one of these hurdles. Novel on-demand peritoneal dialysate generation systems and sorbent-based peritoneal dialysate regeneration systems may considerably reduce the storage space for peritoneal dialysate and/or the required dialysate volume. This review provides an overview of current evidence on CFPD in vivo. The available (pre)clinical evidence on CFPD is limited to case reports/series with inherently nonuniform study procedures, or studies with a small sample size, short follow-up, and no hard endpoints. Small solute clearance appears to be higher in CFPD compared to conventional PD, in particular at dialysate flows ≥100 mL/min using two single-lumen catheters or a double-lumen catheter. Results of CFPD using rapid cycling via a single-lumen catheter are too preliminary to draw any conclusions. Continuous addition of glucose to dialysate with CFPD appears to be effective in reducing the maximum intraperitoneal glucose concentration while increasing ultrafiltration efficiency (mL/g absorbed glucose). Patient tolerance may be an issue since abdominal discomfort and sterile peritonitis were reported with continuous circulation of the peritoneal dialysate. Thus, well-designed clinical trials of longer duration and larger sample size, in particular applying CFPD via the existing catheter, are urgently required.

1 | INTRODUCTION

Peritoneal dialysis (PD) has several advantages compared with hemodialysis (HD).[1] It allows for continuous and gradual removal of fluid and solutes, does not require vascular access or systemic anticoagulation, and provides more patient autonomy as treatment is performed outside the hospital. In addition, residual kidney function is preserved for a longer period of time compared with HD.[2–4] However, PD has several disadvantages: solute clearance is relatively low compared with HD—which is particularly problematic when residual kidney function declines—and technique survival is limited.[1,5,6] Main reasons to switch to HD are infectious complications (peritonitis and catheter infection), PD catheter malfunction, and inadequate dialysis (including ultrafiltration failure).[7] Chronic exposure to hypertonic

glucose solutions has detrimental effects on the peritoneal membrane which is associated with peritonitis and ultrafiltration failure.[8,9] Continuous flow peritoneal dialysis (CFPD), based on a continuous flow of "fresh" dialysate along the peritoneal membrane, may address some of these disadvantages and improve both dialysis efficacy and technique survival as outlined below. CFPD has been explored for decades, but despite important anticipated clinical benefits, CFPD has so far failed to gain a foothold in clinical practice, among others due to the need for a separate in- and outflow catheter (either two single-lumen catheters or one double-lumen catheter), the requirement for large dialysate volumes, and higher costs. Novel systems applying CFPD via the existing single-lumen catheter using rapid dialysate cycling and recent progress in sorbent technology allowing use of a small dialysate volume that is continuously regenerated and recirculated in a closed loop have renewed interest in CFPD. Two sorbent-based miniature CFPD devices have recently been tested in first-in-human clinical trials.[10–12] In addition, a system for on-demand generation of peritoneal dialysate has recently been developed which also allows for a considerable reduction in storage space for dialysate.[13]

CFPD is presumed to improve clearance in three ways. First, the continuous flow of dialysate along the peritoneal membrane increases the mass transfer area coefficient (MTAC) of solutes, defined as the theoretical maximal diffusive clearance of a solute when no solute accumulation in the PD fluid has occurred.[14] This is due to elimination of stagnant/saturated layers of dialysate at the peritoneal membrane surface therewith reducing diffusion resistance and an increase of the effective membrane surface area. Second, continuous replacement of the dialysate with fresh (regenerated) PD fluid will maintain a high plasma to dialysate concentration gradient, increasing diffusive solute transport even further. Third, effective dialysis time is increased by reducing the number of exchanges, which limits effective dwell time in automated PD (APD) as this is characterized by multiple ([near] complete) exchanges in 8 h. A second advantage of CFPD is that it may improve technique survival by prolonging preservation of peritoneal membrane function. With CFPD, a constant glucose concentration for osmotic fluid removal can be applied,[15] thereby circumventing the need for very high (harmful) initial glucose concentrations, as required with conventional PD to maintain an osmotic gradient up to the end of the dwell. This may prolong preservation of peritoneal membrane integrity since exposure to very high glucose concentrations induces fibrotic changes, eventually resulting in ultrafiltration failure.[8] Furthermore, CFPD allows for a reduction in the number of exchanges to 1–2 per day versus ±4–6 with CAPD/APD, thereby lowering the number of (dis)connections of the peritoneal catheter and/or connections of dialysate bags to the APD machine and therewith the associated risk of (infectious) peritonitis.[16,17]

The aim of this review is to provide a comprehensive overview of all reports on the efficacy of CFPD in terms of (small) solute clearance and ultrafiltration, especially in the light of recent developments such as the AWAK PD device[12] and Baxter's on-demand PD solution system.[13] Because the available evidence is limited and study design (incl. dialysate flow rates, treatment duration, and dialysis prescription of the control treatment) is highly variable, all article types (i.e., clinical trials, case reports/series, and abstracts) describing in vivo data—either in humans or animals—were included, thus excluding in vitro and in silico data.

2 | SELECTION

All human and animal studies/reports on CFPD that reported either clearance, MTAC, or ultrafiltration data were included in this review. CFPD was defined as any form of PD in which a continuous flow of dialysate was established. We included CFPD performed via a single-lumen catheter with alternate in- and outflow of fluid with continuous rapid cycling since for the enhancement of the MTAC of uremic solutes, we deemed the direction of the flow (patient in or out) irrelevant, as both result in a net flow of dialysate passing the peritoneal membrane. In total, 21 records were included for review.[11,12,18–37]

3 | BASELINE CHARACTERISTICS

A summary of the study characteristics and patient demographics is displayed in Table 1, and detailed dialysis prescription is presented in Table 2. Six animal studies were identified and 15 human studies, mostly concerning adult patients with end-stage kidney disease (ESKD) ($n = 9$ studies) and pediatric patients with acute kidney injury (AKI) ($n = 3$ studies). Among the human studies, there were six (40%) clinical trials, two (13%) case reports, and seven (47%) case series. "Conventional" PD for comparison with CFPD was performed in eight (53%) out of these 15 clinical studies, but actual results for conventional PD were reported in only seven reports (47%). Follow-up ranged between only one CFPD session and ~11 months. The majority of all included studies (both human and animal) used two single-lumen catheters per subject (57%, $n = 12$) or one double-lumen catheter (24%, $n = 5$), and only 19% ($n = 4$) of the studies employed one single-lumen catheter (with continuous rapid cycling of the dialysate). With regard to catheter location, there were three commonly applied configurations if two catheters were employed: (1) a "one up, one down" configuration (e.g., Amerling et al, Shinaberger et al) in which the inflow catheter was located near the liver, with the outflow in the "standard" location in the lesser (true) pelvis, (2) two catheters opposite to each other (e.g., left vs. right, left upper vs. right lower quadrant; e.g., in Cruz et al, Kostic et al, Raja et al); and (3) the inflow catheter located between umbilicus and upper iliac crest, with the outflow catheter in the "standard" position (e.g., Raaijmakers et al, Nourse et al). The majority of studies applied high dialysate flows during CFPD, with 12 studies employing flow rates of ≥100 mL/min.[20,21,23–33] Seven studies (33%) applied CFPD by passing peritoneal dialysate in a single-pass mode through the abdominal cavity[18,27,28,34–37] (e.g., by using a CVVH machine), while one study recirculated dialysate from a reservoir.[23] Thirteen studies (62%,) applied dialysate regeneration, either directly with the peritoneal dialysate circuit passing a purification unit based on (modified)

TABLE 1 Overview of study and patient characteristics

First author (year)	Article type (study design)	Subjects	Subjects (*n* [% male])	Follow-up	Age (years)	Weight (kg)	Transport status
Animal studies							
Geary (1989)	Animal study	Pigs	16 (NR)	1–2 sessions	NR	12–14	NR
Van Gelder (2020)	Animal study	Pigs	3 (0%)	3–7 sessions	NR	40–100	NR
Gordon (1976)	Animal study	Dogs	4 (NR)	Unclear	NR	18-44[a]	NR
Raja (1976)	Animal study	Dogs	10 (NR)	Single session	NR	22.7–24.9	NR
Roberts (2016)	Animal study	Pigs	6 (NR)	±1 week	NR	33.5	NR
Uechi (1993)	Animal study	(Mongrel) Dogs	15 (NR)	±3 sessions	NR	6.6 ± 0.7	NR
Human studies							
Adults							
Amerling (2003/2012)	Review/case series	Patients with AKI or ESKD	5 (80%)	1–5 sessions	66.8 ± 5.2	NR	NR
Charen (2013)	Case report	Patient with AKI	1 (100%)	±7 months	61	81.4 NR	NR
Cruz (2001)	Case series	Stable PD patients	4 (100%)	Single session	42 ± 9	90.3 ± 25.7	A (50%), HA (50%)
Freida (2003)	Clinical trial (crossover)	Stable PD patients	5 (NR)	Single session	NR	NR	L (20%), LA (20%), HA (20%), H (40%)
Htay (2021)	Clinical trial (FIH)	Stable PD patients	10 (67%)	3 days (9 sessions)	58 (35–73)	NR	H (30%), HA (47%), LA (6.7%), L (6.7%)
Mineshima (2000)	Case series	Stable PD patients	3 (67%)	1–5 sessions	49 ± 3.6	47.6 ± 7.6	NR
Passlick- Deetjen (2001)	Case series	Stable PD patients	4 (NR)	3 sessions	NR	NR	NR
Raj (2000)	Clinical trial	Stable PD patients	8 (13%)	Single session	47.7 ± 14.1	NR	NR
Samuelsson (2018)	Clinical trial (abstract; FIH)	Stable PD patients	5 (60%)	Single session	59.4 ± 10.7	NR	NR
Shinaberger (1965)	Case series	Stable PD patients	4 (NR)	Up to 22 sessions	NR	NR	NR
Stephen (1976)	Case series	Stable PD patients	8 (80%)	1–11 months	40.1 ± 10.5	NR	NR
Pediatric					Age (months)		
Kostic (2010)	Case report	Neonate with AKI	1 (0%)	Single session	0.26	2.9	NR
Nourse (2016)	Clinical trial (crossover)	Infants with AKI	5 (0%)	Single session	4.8 ± 3.7	5.6 ± 2.3	NR
Raaijmakers (2011)	Clinical trial (crossover)	Children with AKI	6 (67%)	Single session	10.7 ± 10.2	NR	NR
Sagy (1999)	Case series	Children with anasacra	6 (67%)	Single session	18.5 ± 34.7	NR	NR

Note: Values are displayed as mean ± SD, median (range), or fixed value, unless stated otherwise.

Abbreviations: A, average; AKI, acute kidney injury; ESKD, end stage kidney disease; FIH, first-in-human clinical trial; H, High; HA, high average; L, low; LA, low-average; NR, not reported; PD, peritoneal dialysis.

[a]Weight range according to inclusion criteria; actual values not reported.

TABLE 2 Overview of dialysis prescriptions

	General				CFPD	
First author (year)	Modality	Sessions (*n*)	Catheter configuration	Dialysate glucose	Session length (h)	Dialysate regeneration
Animal studies						
Geary (1989)	CFPD, IPD	CFPD: 19 IPD: 19	1 double lumen	1.5%	Short: 2 h Long: 4 h	No
Van Gelder (2020)	CFPD, CAPD	CFPD: 15 CAPD: 28	1 single lumen	0.78 ± 0.05% 0.84 ± 0.13% 1.17%	8	Yes[a]
Gordon (1976)	CFPD	>108	2 single lumen	1.5%	6	Yes[a]
Raja (1976)	CFPD, IPD	CFPD: 10 IPD: 10	2 single lumen	1.5%	2	Yes[a]
Roberts (2016)	CFPD	90	1 single lumen	2.5%	7	Yes[a]
Uechi (1993)	CFPD, IPD	CFPD: 35 IPD: 8	1 straight catheter (primary) + 1 flat disk catheter (secondary)	1.3%	3	No
Human studies						
Adults						
Amerling (2003/2012)	CFPD	16	2 single lumen	1.5% ($n = 1$) NR ($n = 4$)	6 (2–24)	Yes
Charen (2013)	CFPD	NR	1 double lumen	NR	4–6	Yes
Cruz (2001)	CFPD	5	2 single lumen	1.5%	4	No
Freida (2003)	CFPD, NTPD, NIDP, CAPD	CFPD: 6 NTPD, NIPD, CAPD: 5	2 single lumen	1.36%	4	No
Htay (2021)	CFPD	95 (131)[c]	1 single lumen	1.21% (IQR 0.99–1.37%)	3.5–7	Yes[a]
Mineshima (2000)	CFPD, CAPD	CFPD: 10 CAPD: 5	1 double lumen	2.5%. 4.25%	6	Yes
Passlick-Deetjen (2001)	CFPD, IPD	12	1 double lumen	NR	8	Yes
Raj (2000)	CFPD, APD	CFPD: 8 APD: 8	1 single lumen	2.5%	8	Yes
Samuelsson (2018)	CFPD	5	2 single lumen	1.0 ± 0.05%	8	Yes[a]
Shinaberger (1965)	CFPD, IPD	CFPD: 33 IPD: 7	2 single lumen	1.5%	NR	Yes
Stephen (1976)	CFPD, IPD	91	1 Experimental double lumen Subcutaneous catheter	1.5%	6	Yes[a]

TABLE 2 (Continued)

	General				CFPD	
First author (year)	Modality	Sessions (*n*)	Catheter configuration	Dialysate glucose	Session length (h)	Dialysate regeneration
Pediatric						
Kostic (2010)	CFPD	1	2 single lumen	1.5%	6	No
Nourse (2016)	CFPD, CAPD	CFPD: 5 CAPD: 5	2 single lumen	CFPD: 2.5%[d] CAPD: 4.25%	4.7 ± 1	No
Raaijmakers (2011)	CFPD, IPD	CFPD: 6 IPD: 6	2 single lumen	1.5% ($n = 3$)[e] 2.5%/4.25% ($n = 1$) 2.5% ($n = 1$) 4.25% ($n = 1$)	8–12	No
Sagy (1999)	CFPD	NR	2 single lumen	2.5% (or 4.25%)	127 ± 60	No

Note: Values are displayed as mean ± SD, median (range), or fixed value/range, unless stated otherwise.
Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CFPD, continuous flow peritoneal dialysis; IQR, interquartile range; (N)IPD, (nocturnal) intermittent peritoneal dialysis; NR, not reported; (N)TPD, (nocturnal) tidal peritoneal dialysis; Qd, effective (dialysate) flow rate; TV, tidal volume.
[a]Dialysate regeneration with (modified) REcirculation DialYsis (REDY) sorbent technology or sorbent technology in general.
[b]Rapid tidal PD was performed, that is, alternate in- and efflux of dialysate via a single-lumen catheter.
[c]131 sessions were performed, but only 95 were deemed "valid" according to the authors (i.e., session length >3.5 h).
[d]Glucose concentration 2.5% by default but could be adjusted by the treating physician according to the individual needs of the patient.
[e]Dwell time, dwell volume, and glucose concentration could be adjusted according to the individual needs of the patient.

TABLE 2 (Continued)

	CFPD			Conventional	
First author (year)	Qd (mL/min)	Total dialysate volume/session (L)	Initial fill volume (L)	Description	Time-averaged Qd (mL/min)
Animal studies					
Geary (1989)	0.40 ± 0.15 0.45 ± 0.09 (mL/kg/min)	1.0 ± 0.29 1.7 ± 0.36	30 ± 1 30 ± 1 (mL/kg)	Short: one 2-h dwell of 28 ± 3 mL/ kg, total volume 379 ± 82 mL Long: two 2-h dwells of 30 ± 3 mL/kg, total volume 742 ± 26 mL	~0.25 ~0.24 mL/kg/min
Van Gelder (2020)	81 ± 11	10–12	NR	One 2-L dwell for 4 h	8.3
Gordon (1976)	40–60–80–100–120	28.8–36	NR	NA	
Raja (1976)	66–100–150–200–250	10.4–32.5	2.5	2-L exchange every 30 min for 2 h 2-L exchange every 20 min for 2 h	66 100
Roberts (2016)	NR[b]	NR	1	NA	
Uechi (1993)	30–60–90–120	2	40 (mL/kg)	One 4-h dwell of 40–60 mL/kg	0.17–0.25 mL/kg/min

TABLE 2 (Continued)

	CFPD			Conventional	
First author (year)	Qd (mL/min)	Total dialysate volume/session (L)	Initial fill volume (L)	Description	Time-averaged Qd (mL/min)
Human studies					
Adults					
Amerling (2003/2012)	200–300	NR	NR	NA	
Charen (2013)	300	72–108	NR	NA	
Cruz (2001)	200	50	2	NA	
Freida (2003)	100–150	26–38	2	NIPD: 13 L/8 h NTPD: 13 L/8 h (tidal and residual volume unknown) CAPD: 4 × 2 L exchange per 24 h	27 (NTPD/NIPD) 5.6 (CAPD)
Htay (2021)	33.3 (TV = 250 mL)[b]	≥7	NR	NA	
Mineshima (2000)	100	NR	NR	NR	
Passlick-Deetjen (2001)	200	NR	2	Overnight IPD (3 times a week)	NR
Raj (2000)	141 ± 23.7[b]	6.2 ± 0.7	NR	5 exchanges of (on average) 2.7 L in 8 h	28 ± 3
Samuelsson (2018)	NR	NR	2	NA	
Shinaberger (1965)	300	NR	3–4	2 L exchange every h for 6-8 h	33
Stephen (1976)	100–250	37.2–93	1.2–3.0	2 L dwells, 4 L/h for 6 h, total volume 24 L	0.17–0.25 mL/kg/min
Pediatric					
Kostic (2010)	5	1.8	10 (mL/kg)	NA	
Nourse (2016)	100 (mL/min/1.73m^2)	4.9	20 (mL/kg)	APD (n = 2): Exchange of 20 mL/kg every 1.5 h for 11 h ($n = 1$) and 15 h ($n = 1$) CAPD ($n = 3$): Exchange of 20 mL/kg every 1.5 h for 6 h	0.22 mL/kg/min
Raaijmakers (2011)	100 (mL/min/1.73m^2)	9.7–14.6	20 (mL/kg)	Exchange of 20 mL/kg every 1.5 h for 8–16 h[e]	0.22 mL/kg/min
Sagy (1999)	0.17–0.83 (mL/kg/min)	NR	NR	NA	

Note: Values are displayed as mean ± SD, median (range), or fixed value/range, unless stated otherwise.

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; CFPD, continuous flow peritoneal dialysis; IQR, interquartile range; (N)IPD, (nocturnal) intermittent peritoneal dialysis; NR, not reported; (N)TPD, (nocturnal) tidal peritoneal dialysis; Qd, effective (dialysate) flow rate; TV, tidal volume.

[a]Dialysate regeneration with (modified) REcirculation DialYsis (REDY) sorbent technology or sorbent technology in general.

[b]Rapid tidal PD was performed, that is, alternate in- and efflux of dialysate via a single-lumen catheter.

[c]131 sessions were performed, but only 95 were deemed "valid" according to the authors (i.e., session length >3.5 h).

[d]Glucose concentration 2.5% by default but could be adjusted by the treating physician according to the individual needs of the patient.

[e]Dwell time, dwell volume, and glucose concentration could be adjusted according to the individual needs of the patient.

REcirculation DialYsis (REDY)[38] technology ($n = 4$)[12,20–22] or indirectly using a secondary dialysate circuit separated from the primary peritoneal dialysate circuit by a (hemo)dialysis membrane ($n = 9$).[11,19,25,26,29–33] In three studies, the secondary dialysate circuit contained a sorbent unit, comprising either only activated carbon[33] or a combination of activated carbon and ion exchangers.[11,19]

4 | SOLUTE CLEARANCE

4.1 | Small solutes

In animals, direct comparison between CFPD and conventional PD was performed in four out of six studies. In only one study, a considerable increase in small solute clearance was reported (Table 3, Table S1). Uechi et al observed a ~2.5–3.5-fold increase in urea clearance and a ~3-fold increase in creatinine clearance with CFPD at dialysate flow rates of 60–120 mL/min as compared to conventional PD (one dwell of 60 mL/kg) in dogs weighing 5.5–7.5 kg. In the other two studies, only a limited increase in small solute clearance was observed. Geary et al reported minimal (28%, 2-h session) or no (4-h session) increase in small solute clearance with CFPD at low dialysate flow rates of ~5 mL/min as compared to static dwells in pigs of ~12–14 kg. Van Gelder et al, using a single-lumen catheter with continuous rapid cycling of dialysate, reported an increase in clearance for creatinine (58%), urea, (45%), phosphate (57%), and potassium (41%) with CFPD (Qd 81 ± 11 mL/min) versus a static dwell (2 L, 4 h) in pigs. However, there was a considerable effect of peritonitis on peritoneal transport, with only potassium clearance being significantly higher with CFPD compared to conventional PD in the absence of peritonitis (i.e., at lower transport status). Raja et al observed a limited increase in urea clearance of 25% (66 mL/min) and 16% (100 mL/min) and in creatinine clearance of 11% (66 mL/min) and 8% (100 mL/min) with CFPD as compared to intermittent PD at similar time-averaged flow rates (Qd 66 and 100 mL/min), which suggests that continuous circulation of dialysate per se may (slightly) increase small solute clearance.

Hij baIn human studies (both adult and pediatric) that evaluated both CFPD and conventional PD ($n = 7$), CFPD showed a ~3-fold increase in plasma clearance of both urea and creatinine. The available evidence for the effect of CFPD on phosphate clearance is limited and heterogeneous. Raj et al and Nourse et al observed a >2-fold increase with CFPD as compared with conventional PD, while Freida et al observed a 35% increase. Of note, phosphate concentrations and removal may be influenced by other factors (e.g., intake, use of oral phosphate binders, and circadian variation), making comparison more difficult.[39] Importantly, small solute clearance with CFPD appears to increase at higher dialysate flow rates (Figure 1, Table S2). This was already predicted in a recent in silico study by Öberg et al,[40] though the expected improvement in clearance was highly dependent on the patient's transport status as well. Furthermore, this study also suggested no added value of increasing flow rates above 200 mL/min, while the included in vivo studies that employed such high dialysate flows still reported further improvement in clearance.[21,25]

Direct comparison of MTAC—one of the most important determinants of PD efficacy[15,40]—in CFPD and conventional PD was possible in only two human studies (Freida et al and Raaijmakers et al), both of which reported a ~2.3-fold increase in MTAC for creatinine compared to CAPD (Freida) and IPD (Raaijmakers), respectively. For urea, Freida found a ~1.4-fold increase in MTAC, while Raaijmakers observed an MTAC which was similar for both modalities. Regardless, urea plasma clearance with CFPD was still significantly higher with CFPD compared with conventional PD (15.1 vs. 5.0 mL/min respectively), although remarkably lower than the creatinine clearance. The theoretical positive relationship between MTAC and Qd, as suggested by Gotch, was only investigated in one subject by Freida et al, who reports a 13% and 47% increase in MTAC of creatinine and urea, respectively, when Qd is increased from 100 to 150 mL/min. In addition, both Freida et al and Cruz et al observed a more pronounced increase in MTAC with CFPD at faster transport status.

4.2 | Middle molecules and protein-bound uremic toxins

Middle molecule clearance in PD is poor, primarily due to the larger size and therewith higher diffusion resistance. Peritoneal clearance of protein-bound uremic toxins is also low since protein-binding restricts passage of the peritoneal membrane. It is difficult to improve clearance of these so-called difficult-to-remove uremic toxins, as displayed by a lack of increase in clearance with a higher volume APD schedule (12 L/day) versus a standard CAPD schedule (8 L/day).[41] For the middle molecules, this may in part be due to the fact that dwell time is more important than dialysate volume or flow employed.[42] However, modeling suggests that CFPD may enhance middle molecule clearance up to a factor of ~2.[41] Removal of middle molecules is primarily driven by convection,[40] which may be facilitated by stable glucose concentrations during CFPD. Only three studies reported β2-microglobulin removal. Freida et al showed a 1.2-fold increase in β2-microglobulin clearance with CFPD compared with conventional PD at a Qd of 100 mL/min, and Samuelsson et al observed a modest and non-significant decrease (8.8%) in β2-microglobulin serum concentrations after 8 h of CFPD (Qd not reported), while Htay et al found a significant reduction of 9.5% after up to 3 days of therapy at a Qd up to 33.3 mL/min. In theory, protein-bound uremic toxin clearance may also increase when removal of the free fraction is improved. However, there are no reports on the effect of CFPD on protein-bound uremic toxin clearance.

5 | ULTRAFILTRATION

An important advantage of CFPD could be improved ultrafiltration at lower (peak) intraperitoneal glucose concentrations, thereby possibly reducing glucose-related toxicity to the peritoneal membrane. Kinetic modeling by Gotch suggests that—in the "average"

TABLE 3 Overview of outcomes: Solute clearance and mass transfer area coefficient

	General			Clearances
First author (year)	Modality	Subjects (n)	Sessions (n)	Creatinine (mL/min)
Animal studies				
Geary (1989)	CFPD	16	Short[a], $n = 9$ Long, $n = 10$	NR
	Conventional (IPD)	16	Short[a], $n = 9$ Long, $n = 10$	NR
Van Gelder (2020)	CFPD	3	28	5.7 ± 3.4
	Conventional (CAPD)	3	15	3.6 ± 1.1
Gordon (1976)	CFPD	4	>108	16.3 (9.6–25.7) ($n = \geq 12$ sessions)
Raja (1976)	CFPD	10	10	13 ± 3
	Conventional (IPD)	10	10	12 ± 2
Roberts (2016)	CFPD	6	90	5.8 ± 1.1
Uechi (1993)	CFPD	10	10	7.1 ± 1.8
	Conventional (IPD)	4	4	2.1 ± 0.2
Human studies				
Adults				
Amerling (2003/2012)	CFPD	5	16	NR
Charen (2013)	CFPD	1	NR	Early[b]: 44.1 Late[c]: 21.4
Cruz (2001)	CFPD	4	5	28.2 ± 4.7
Freida (2003)	CFPD	5	6	22.4 ± 7.5
	Conventional (NTPD/CAPD/NIPD)	5	5	NTPD: 11.1 ± 2.2 CAPD: 4.5 ± 0.5 NIPD: 11.0 ± 2.7
Htay (2021)	CFPD	14	95	NR
Mineshima (2000)	CFPD	3	10	NR
	Conventional (CAPD)	3	5	NR
Passlick-Deetjen (2001)	CPFD	4	12	10.6 ± 1.6
Raj (2000)	CFPD	8	8	22.1 ± 9.4
	Conventional (APD)	8	8	9.8 ± 5.9
Samuelsson (2018)	CFPD	5	5	8.1 ± 2.1
Shinaberger (1965)	CFPD	4	33	34.8 ($n = 1$ subject, $n = 15$ sessions)
	Conventional (IPD)	4	7	11.5 ± NR
Stephen (1976)	CFPD	10	91	24.8 ± 4.9 ($n = 8$ subjects)
	Conventional (IPD)	1	1	22

TABLE 3 (Continued)

First author (year)	General			Clearances
	Modality	Subjects (n)	Sessions (n)	Creatinine (mL/min)
Pediatric				
Kostic (2010)	CFPD	1	1	NR
Nourse (2016)	CFPD	5	5	33.1 ± 15.5 (mL/min/1.73m^2)
	Conventional (CAPD)	5	5	7.4 ± 1.9 (mL/min/1.73m^2)
Raaijmakers (2011)	CFPD	6	6	28.8 ± 12.7 (mL/min/1.73m^2)
	Conventional (IPD)	6	6	7.6 ± 6.3 (mL/min/1.73m^2)
Sagy (1999)	CFPD	6	NR	NR

Note: Values are displayed as mean ± SD, median (range), or fixed value/range, unless stated otherwise.
Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CFPD, continuous flow peritoneal dialysis; IPD, intermittent peritoneal dialysis; MTAC, mass transfer area coefficient; NIPD, nocturnal intermittent peritoneal dialysis; NR, not reported; NTPD, nocturnal tidal peritoneal dialysis; Qd, effective (dialysate) flow rate.
[a]Short: 116 ± 18 min, Long: 250 ± 16 min.
[b]Early treatment data during the first month of continuous flow peritoneal dialysis.
[c]Late treatment data during month 4–6 of continuous flow peritoneal dialysis.

TABLE 3 (Continued)

First author (year)	Clearances			MTAC	
	Urea (mL/min)	Weekly Kt/V	Phosphate (mL/min)	Creatinine (mL/min)	Urea (mL/min)
Animal studies					
Geary (1989)	2.7 ± 0.9 1.9 ± 0.63	NR	1.7 ± 0.6 1.2 ± 0.3	NR	NR
	2.1 ± 0.6 2.2 ± 0.3	NR	1.3 ± 0.3 1.2 ± 0.3	NR	NR
Van Gelder (2020)	8.0 ± 3.2	NR	4.4 ± 3.2	7.7 ± 6.1	14.0 ± 8.0
	5.5 ± 1.7	NR	2.8 ± 1.1	5.2 ± 2.5	10.9 ± 3.4
Gordon (1976)	33.8 (20.0–57.0) (n = ≥12 sessions)	NR	12.3 (6.9–20.8) (n = ≥12 sessions)	NR	NR
Raja (1976)	21 ± 4	NR	NR	NR	NR
	18 ± 2	NR	NR	NR	NR
Roberts (2016)	12.3 ± 1.6	5.2 ± 2.0	10.0 ± 2.8	NR	NR
Uechi (1993)	8.9 ± 2.6	NR	6.9 ± 0.8	NR	NR
	2.3 ± 0.4	NR	1.9 ± 0.4	NR	NR
Human studies					
Adults					
Amerling (2003/2012)	50.6 ± 23.5 (n = 5 pt, n = 16 sessions)	0.34 ± 0.25 (n = 4 pt, n = 13 sessions)	NR	NR	NR

TABLE 3 (Continued)

First author (year)	Clearances			MTAC	
	Urea (mL/min)	Weekly Kt/V	Phosphate (mL/min)	Creatinine (mL/min)	Urea (mL/min)
Charen (2013)	45.4 23.5	1.0–1.5 0.96–1.44	51.7 16.9	NR	NR
Cruz (2001)	40.0 ± 5.4	NR	NR	25.2 ± 4.9	40.4 ± 6.0
Freida (2003)	27.8 ± 5.8	2.3 ± NR	11.9 ± NR	23.9 ± 9.1	37.9 ± 11.9
	NR	1.2 ± NR NR 1.3 ± NR	NR NR 8.3 ± NR	NR 10.2 ± 4.5 NR	NR 26.1 ± 5.9 NR
Htay (2021)	NR	3.8 ± 1.4	NR	NR	NR
Mineshima (2000)	14.1 ± 4.4	NR	NR	NR	NR
	7.3 ± 2.1	NR	NR	NR	NR
Passlick-Deetjen (2001)	20.4 ± 3.5	NR	NR	NR	NR
Raj (2000)	26.5 ± 9.1	NR	18.2 ± 4.3	NR	NR
	11.0 ± 4.7	NR	9.8 ± 5.2	NR	NR
Samuelsson (2018)	10.6 ± 1.9	NR	6.4 ± 1.3	NR	NR
Shinaberger (1965)	57.9 ($n = 2$ subjects; $n = 22$ sessions)	NR	34.2 ± 9.27 ($n = 3$ subjects; $n = 11$ sessions)	NR	NR
	17.4 ± NR	NR	NR	NR	NR
Stephen (1976)	31–40 ($n = 2$)	NR	NR	NR	NR
	28	NR	NR	NR	NR
Pediatric					
Kostic (2010)	NR	NR	NR	NR	NR
Nourse (2016)	22.0 ± 5.1 (mL/min/1.73m^2)	NR	14.0 ± 11.1 (mL/min/1.73m^2) ($n = 2$ subjects)	NR	NR
	6.5 ± 1.1 (mL/min/1.73m^2)	NR	3.8 ± 1.7 (mL/min/1.73m^2)	NR	NR
Raaijmakers (2011)	15.1 ± 2.1 (mL/min/1.73m^2)	NR	NR	27.9 ± 16.0 (mL/min/1.73m^2)	10.6 ± 1.5 (mL/min/1.73m^2)
	5.0 ± 1.7 (mL/min/1.73m^2)	NR	NR	12.0 ± 10.8 (mL/min/1.73m^2)	10.9 ± 6.6 (mL/min/1.73m^2)
Sagy (1999)	NR	NR	NR	NR	NR

Note: Values are displayed as mean ± SD, median (range), or fixed value/range, unless stated otherwise.

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CFPD, continuous flow peritoneal dialysis; IPD, intermittent peritoneal dialysis; MTAC, mass transfer area coefficient; NIPD, nocturnal intermittent peritoneal dialysis; NR, not reported; NTPD, nocturnal tidal peritoneal dialysis; Qd, effective (dialysate) flow rate.

[a]Short: 116 ± 18 min, Long: 250 ± 16 min.

[b]Early treatment data during the first month of continuous flow peritoneal dialysis.

[c]Late treatment data during month 4–6 of continuous flow peritoneal dialysis.

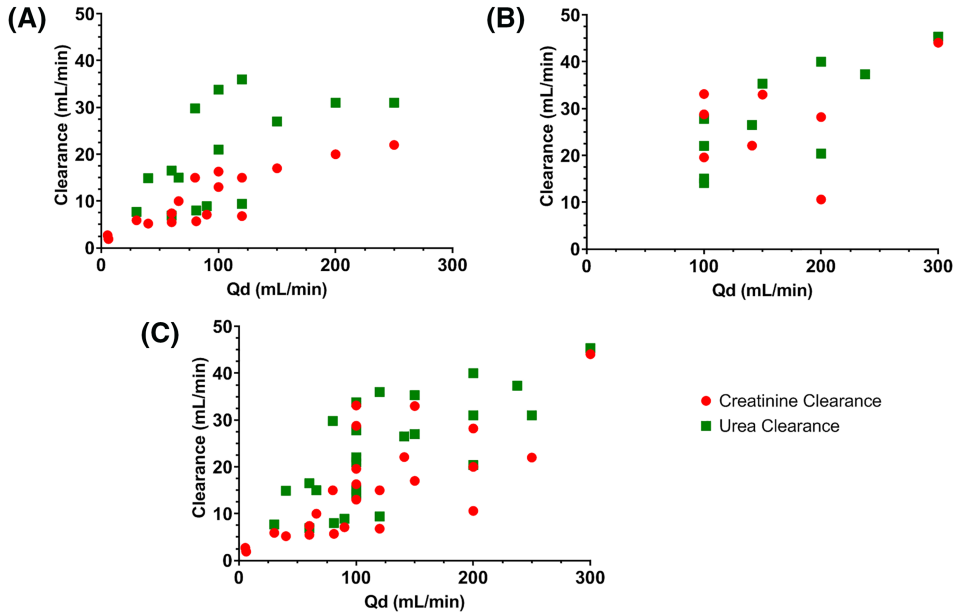

FIGURE 1 The association between dialysate flow rate (Qd) and clearance of urea and creatinine with continuous flow peritoneal dialysis derived from (A) all animal studies, (B) all human studies, and (C) all studies combined. Of note, all studies which reported both a (fixed) Qd and clearance were included.[12–15,17,19–22,24–26,31,32] Each data point represents the mean clearance for creatinine (circles) or urea (squares) at the reported mean effective dialysate flow rate (Qd). If a single study reported data for differing flow rates, each flow rate is displayed as a separate data point in this figure

patient—a constant ultrafiltration rate (UFR) of 0.2–0.45 L/h can be achieved while maintaining an intraperitoneal glucose concentration of 1.0%–1.5%,[15] which is considerably higher than the "average" UFR achieved with conventional PD (~0.04 L/h based on an average daily UF volume of ~0.9 L)[43] using dialysate with glucose concentrations of 1.36%–3.86%. Out of the 21 included studies, 14 reported data on UF (Table 4). UFR was higher with CPFD compared to conventional PD in three human studies, varying from a 2.6-fold[28] to a 9.2-fold increase.[36] Using the AWAK PD device, Htay et al found—at a median intraperitoneal glucose concentration of 1.21% (IQR 0.99–1.37)—a positive UFR (median 39.6 mL/h) in patients without residual diuresis ($n = 4$), but a negative UFR (median −25.0 mL/h) in patients with residual diuresis ($n = 10$). There was no significant difference in body weight pre- versus posttreatment compared to conventional PD. In studies where no direct comparison with conventional PD was available, UF rates were mostly high, with values reaching even up to 13.4 mL/min (Cruz et al). Passlick-Deetjen et al reported disappointing UF rates at glucose 1%, although these values were not specified in their report. Finally, Heimbürger et al continuously infused glucose at a rate of 11 g/h into the abdominal cavity for 5 h with the Carry Life UF System, a novel portable ultrafiltration device, after filling patients ($n = 8$) with 1.5-L PD solution (1.36%), and found a 3.1-fold increase in UFR compared with a static 4-h dwell with 2 L glucose 2.27%.[10] Intraperitoneal glucose concentration was maintained at 1.1%–1.6% during the 5-h treatment. In addition, they showed that UF efficiency (UFV/gram absorbed glucose) improved with a factor 2.9.[10] Also, Freida and Raj found a considerable increase (~3- and ~5-fold, respectively) in UF efficiency compared to conventional PD. Thus, the available evidence appears to suggest that with continuous glucose infusion (via CFPD), the desired UFR may be achieved at lower peak intraperitoneal glucose concentrations and lower daily glucose loading.

6 | SAFETY

In general, CFPD was well tolerated by patients (Table 5), although abdominal discomfort was commonly reported (Amerling, Charen, Htay, Shinaberger, Stephen) which appeared to be related to the continuous flow (rate) of the dialysate. Htay et al observed abdominal discomfort in 73% of the patients treated with the AWAK PD device at a dialysate flow rate of ~67 mL/min, which resolved either by drainage of dialysate or spontaneously after bowel movement.[12] Stephen et al frequently observed abdominal pain, usually at later stages of a session (after ~3–4 h of a 6-h session) at high dialysate flow rates (>200 mL/min), whereas no discomfort was observed at lower dialysate flow rates. Importantly, cloudy effluent with an elevated number of polymorphonuclear neutrophils was found in a number of subjects ($n = 4$). As cultures revealed no infectious microorganism, this suggests occurrence of sterile peritonitis, possibly due to mechanical irritation of the peritoneal membrane during CFPD. In contrast, Samuelsson et al specifically state that none of the patients reported any abdominal discomfort, although Qd's were not reported in these studies, making comparison difficult.

Theoretically, increased ultrafiltration associated with CFPD may result in hypovolemia, enhanced sodium sieving due to increased free water transport, and increased intraperitoneal pressure in the absence of periodic fluid drainage. Enhanced sodium sieving was not observed in the clinical trial with the Carry Life UF system.[10] Calculated sodium concentrations in the ultrafiltrate were similar to those in a peritoneal equilibrium test. Increased intraperitoneal pressure due to overfilling was reported by Nourse et al in one pediatric patient, which was solved by peritoneal fluid drainage. However, the authors did not report which adverse events occurred due to the overfilling.[44]Ultrafiltrate could be periodically or continuously drained during treatment, for example, by setting the

TABLE 4 Overview of CFPD outcomes: ultrafiltration

First author (year)	Modality	UFR (mL/min)	UFV (L)	Dialysate glucose
Animal studies				
Geary (1989)	CFPD	NR	0.08 ± 0.06 in 2 h 0.14 ± 0.07 in 4 h	1.5%
	Conventional (IPD)	NR	0.06 ± 0.06 in 2 h 0.12 ± 0.06 in 4 h	1.5%
Van Gelder (2020)	CFPD	0.13 ± 0.15	0.06 ± 0.07 in 8 h	0.78 ± 0.05%
	Conventional (CAPD)	0.19 ± 0.89	0.05 ± 0.21 in 4 h	1.36%
Roberts (2016)	CFPD	3.04 ± 0.83	1.28 ± 0.35 in 7 h	2.5%
Human studies				
Adults				
Amerling (2003/2012)	CFPD	14.38 ± 6.19 ($n = 5$ pt, $n = 14$ sessions)	3.89 ± 0.71 in 6 h ($n = 4$ pt, $n = 11$ sessions)	1.5% ($n = 1$) NR ($n = 4$)
Charen (2013)	CFPD	NR	2.36 in 4-6 h 3.50 in 4-6 h	NR
Cruz (2001)	CFPD	13.38 ± 5.48	3.21 ± 1.31 in 4 h	1.5%
Htay (2021)	CFPD	−0.42 (−0.60, −0.12)[a] 0.66 (0.50–0.98)[b]	NR	1.21%(IQR 0.99%–1.37%)
Freida (2003)	CFPD	2.45 ± 1.03	0.59 ± 0.49 in 4 h	1.36%
	NTPD CAPD NIPD	0.89 ± 0.45 NR 0.94 ± 0.23	0.43 ± 0.22 in 8 h NR 0.45 ± 0.11 in 8 h	1.36%
Samuelsson (2018)	CFPD	NR	0.37 ± 0.05 in 8 h	1.0 ± 0.05%
Stephen (1976)	CFPD	NR	1.8 ± 0.4 in 6 h ($n = 8$ subjects)	1.5%
Pediatric				
Kostic (2010)	CFPD	1.05	0.25 in 6 h	1.50%
Nourse (2016)	CFPD	3.80 ± 1.71 (mL/min/1.73m^2)	0.18 ± 0.09 in 4.7 ± 1 h	2.5%
	Conventional (CAPD)	0.98 ± 0.79 (mL/min/1.73m^2)	0.06 ± 0.06 in 8.8 ± 4 h	4.25%
Raaijmakers (2011)	CFPD	1.84 ± 1.18 (mL/min/1.73m^2)	NR	1.5% ($n = 3$) 2.5%/4.25% ($n = 1$)
	Conventional (IPD)	0.20 ± 0.80 (mL/min/1.73m^2)	NR	2.5% ($n = 1$) 4.25% ($n = 1$)
Sagy (1999)	CFPD	4.2 ± 0.9 (mL/kg/h)	0.56 ± 0.32 (L/24 h)	2.5% (or 4.25%)

Note: Values are displayed as mean ± SD, median (range), or fixed value, unless stated otherwise.

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CFPD, continuous flow peritoneal dialysis; IPD, intermittent peritoneal dialysis; IQR, interquartile range; NIPD, nocturnal intermittent peritoneal dialysis; NR, not reported; NTPD, nocturnal tidal peritoneal dialysis; UFR, ultrafiltration rate; UFV, ultrafiltration volume.

[a]UFR in patients with residual kidney function ($n = 10$).

[b]UFR in patients without residual kidney function ($n = 4$).

peritoneal dialysate outflow slightly higher than the inflow rate.[18,28,35,36] The theoretical risk of an empty abdomen with continuous drainage due to a discrepancy between outflow and ultrafiltration rate was not reported.

Other reported adverse events were related to the peritoneal catheter, and not specifically to the CFPD technique itself. These included bacterial peritonitis, catheter obstruction, and catheter leakage. Stephen et al used an experimental subcutaneous catheter which resulted in localized peritoneal and subcutaneous abscesses in a number of patients. In addition, Raja et al observed electrolyte disturbances (hypernatremia, hyperchloremia, and hypokalemia) which were most likely related to ion exchange by the REDY sorbent system that was used for dialysate regeneration.[38]

In addition to technique-related safety aspects and adverse events, excessive protein and amino acid losses may be a concern with single-pass CFPD as a result of continuous refreshment of dialysate. Accordingly, Freida et al reported an average total protein loss of 7.25 g (range 5.18–9.66) per 4-h CFPD session (Qd 100 mL/min), whereas this was 5.9 and 6.53 g per 8-h session of NIPD and NTPD (13 L/8 h), respectively, suggesting that protein loss with CFPD is approximately twofold higher. Although no comparison with conventional PD was performed in the study by Stephen et al, protein loss

TABLE 5 Overview of adverse events related to CFPD

First author (year)	Peritonitis[a]	Adverse events[b]	Type of event
Animal studies			
Geary (1989)	1 (6%)	7 (44%)	Catheter leakage ($n = 4$) Catheter obstruction ($n = 3$)
Van Gelder (2020)	3 (100%)	NR	NR
Gordon (1976)	NR	NR	NR
Raja (1976)	NR	Not specified	Electrolyte disturbances (hypernatremia, hyperchloremia, hypokalemia) due to REDY® system
Roberts (2018)	1 (17%)	3 (50%)	Abdominal herniation ($n = 2$) Puncture of PD catheter ($n = 1$)
Uechi (1993)	NR	NR	NR
Human studies			
Adult			
Amerling (2003/2012)	4 (80%)	1 (20%)	Dialyzer clogged with fibrin which limited clearance ($n = 1$) (Abdominal) discomfort ($n = 1$)
Charen (2013)	1 (100%)	1 (100%)	Catheter leakage Abdominal pain occurred occasionally (resolved after decreasing dialysate flow)
Cruz (2001)	0 (0%)	NR	NR
Freida (2003)	0 (0%)	0 (0%)	None related to dialysis therapy
Htay (2021)	NR	Not specified, though at least ≥60%	Abdominal discomfort ($n = 9$) Abdominal distension/bloating ($n = 7$) Fibrin in dialysate ($n = 5$) Elevated blood pressure ($n = 4$) Neck/shoulder pain/discomfort ($n = 2$)
Mineshima (2000)	NR	NR	NR
Johansson (2018)	NR	NR	NR
Passlick-Deetjen (2001)	NR	NR	NR
Raj (2000)	NR	NR	NR
Samuelsson (2018)	NR	0%	None related to dialysis therapy
Shinaberger (1965)	NR	0%	Mild abdominal discomfort; alleviated by meperidine, lidocaine, and/or reduction of flow rate
Stephen (1976)	6 (75%)[c]	Not specified, though at least ≥50%	Mechanical peritonitis ($n = 4$) No increase in clearance with CFPD due to streaming ($n = 1$) Moderate–severe abdominal pain at Qd ≥ 200 mL/min ($n = 4$) Catheter obstruction ($n = 2$) Infection(s) of the experimental peritoneal catheter ($n = 5$)
Pediatric			
Kostic (2010)	0 (0%)	0 (0%)	None related to dialysis therapy
Nourse (2016)	NR	3 (60%)	Swapped in- and outflow lines, hyperglycemia >20mM requiring insulin therapy ($n = 1$) Hypokalemia necessitating addition of potassium to dialysate ($n = 1$) Increasing IP pressure requiring fluid drainage ($n = 1$)
Raaijmakers (2011)	0 (0%)	3 (50%)	Blockage of inflow catheter which was easily resolved
Sagy (1999)	NR	0 (0%)	None related to dialysis therapy

Abbreviations: IP, intraperitoneal; NR, not reported; Qd, (effective) dialysate flow rate.

[a]Number (percentage) of patients with at least one episode of peritonitis during the study period.

[b]Number (percentage) of patients with at least one adverse events related to dialysis therapy, excluding peritonitis.

[c]Including mechanical peritonitis.

with CFPD was high: on average ~18 g (range 12–32 g) per 6-h session. Protein loss with CFPD may be reduced by application of external dialysate regeneration during which proteins are retained in the peritoneal cavity by an ultrafiltration or dialysis membrane separating the peritoneal dialysate circuit from the dialysate regeneration circuit, therewith preventing large molecules from entering the external dialysate regeneration circuit. Indeed, Samuelsson et al measured a total albumin loss of 2.0 ± 0.6 g per 8-h CFPD session using a sorbent-based external dialysate regeneration system, and Raj et al found comparable protein loss with CFPD and conventional PD (12.9 ± 6.7 vs, 14.7 ± 9.9 g, respectively, per 8-h session) using the dialysate circuit of a HD machine for external dialysate regeneration.

7 | DISCUSSION

CFPD is a promising PD modality which seems to offer improved small solute clearance and improved ultrafiltration efficiency as compared to conventional PD. However, the currently available data make it difficult to draw solid conclusions, in particular with regard to long-term effects.

The currently available data are limited by a variety of factors. First, only a small number of well-controlled clinical trials have been performed. Many reports reviewed here are case series or conference abstracts. These report types are prone to bias (e.g., indication bias and reporting bias), hamper accurate interpretation of the results due to individualized treatments (e.g., different dialysate flow rates within/between subjects) and generally prevent careful review of the methods and results due to brief reporting (abstracts) or high variability (case series). Second, most studies only included a limited number of patients (in this review overall $n = 79$ for human studies) and/or performed a limited number of dialysis sessions within a limited study duration, with the majority of the studies performing only one or two CFPD session(s) per patient (overall >281 sessions) within ≤3 days (range one session to ~11 months). Third, detailed study information was often lacking, for example on patient characteristics (e.g., age, weight, transport status, residual diuresis, and renal clearance), treatment methods (e.g., dialysate flow, initial fill volume, and description of the conventional treatment schedule), and outcome parameters (e.g., solute clearance, MTAC, and UF), complicating accurate interpretation and extrapolation of the study results. Finally, there is considerable heterogeneity regarding the methods employed (e.g., number, type and location of the catheter[s], rate and mode [continuous or rapid cycling] of the dialysate flow, and use of fresh or regenerated dialysate), which also makes it difficult to draw conclusions.

Based on the limited available data, CFPD appears to provide improved (small solute) clearance compared with conventional PD, in particular at higher dialysate flow rates (>100 mL/min) and in patients with high (-average) transport status.[40] When performed for 8 h per day, small solute clearances approach the time-averaged clearances of intermittent HD (~11 mL/min for urea [or a weekly standard Kt/V of ~2.2], ~7 mL/min for creatinine with thrice weekly HD).[45,46] Therewith, CFPD may become a more attractive alternative for HD, in particular for patients without residual diuresis. Also, improvements in ultrafiltration efficiency were reported in CFPD, therewith potentially reducing glucose-related toxicity to the peritoneal membrane and possibly also adverse systemic metabolic effects of excessive intraperitoneal glucose absorption,[47] although this was not explored in any study thus far. In addition, CFPD may be used in the treatment of other causes of hypervolemia as well, such as heart failure. However, there are virtually no data available on long-term CFPD ($n = 6$ patients with treatment ≥7 months), neither with regard to outcome nor treatment tolerability. Lowering of plasma levels of (pathogenic) uremic toxins and lower daily glucose load,[48] as well as improved volume status, may all contribute to improvements in outcome parameters. These may include "hard" parameters such as mortality and (co) morbidity, as well as patient-related (and patient-reported) parameters such as quality of life, necessity for diet restrictions, pill burden, and uremic symptoms. Of note, the ADEMEX trial found that a limited increase in creatinine clearance (~35%) and peritoneal Kt/V (~40%) did not result in a survival advantage.[43] Still, the expected large improvement in clearances achieved with CFPD in combination with reduced glucose burden may result in improvements in "hard" endpoints.

As mentioned before, CFPD may theoretically improve technique survival as a result of lower (peak) glucose concentrations—leading to longer preservation of membrane integrity—and lower risk of infectious peritonitis due to less (dis)connections of the peritoneal catheter (since less exchanges are required). However, it is unknown what the effect of continuous exposure of the peritoneal membrane to high dialysate flow is on membrane integrity. The occurrence of mechanical peritonitis reported by Stephen et al in four out of eight patients treated with flow rates ≥200 mL/min for 6 h, reports of abdominal discomfort with high dialysate flow rates in several studies, and the marked decrease in dialysis efficacy after ~6 months of CFPD observed by Charen et al ($n = 1$) give cause for concern and may reflect pathogenic changes to the membrane due to mechanical irritation. Moreover, it is unclear whether maintenance of a high flow rate is feasible on the long term since catheter dysfunction is one of the main complications of PD.[49]

An important limitation to CFPD is the maintenance of a regulated volume of fluid in the peritoneal cavity. Theoretically, increased ultrafiltration associated with CFPD may result in increased intraperitoneal pressure due to overfilling when periodic or continuous drainage is not performed. Increased intraperitoneal pressure may cause abdominal discomfort, mechanical damage to the peritoneal membrane, and a decrease in solute clearance and ultrafiltration and may compromise respiratory status. On the other hand, continuous drainage without intra-abdominal volume monitoring bares the risk of an empty abdomen when the ultrafiltration rate is lower than expected. This may in theory result in damage to the peritoneal membrane at the catheter tip due to negative pressures. Yet, a system to control and/or monitor intraperitoneal volume during treatment seems important, for example, by measurement of intraperitoneal pressure (e.g., via the abdominal catheter after short cessation of the flow) or

bioimpedance,[44] although it is questionable whether these techniques are accurate enough.

Of note, 83% of CFPD studies used two single-lumen catheters or a double-lumen catheter (not commercially available), while prevalent PD patients have a single-lumen catheter. Thus far, it is unknown whether application of alternate in- and outflow with high flow rates via a single lumen catheter—as applied by Van Gelder (pigs), Roberts (pigs), Htay (patients), and Raj (patients)—can be a reasonable alternative to continuous flow via two catheter(s) (lumens). Findings by Htay and Van Gelder suggest only a limited increase in PD efficacy using this configuration, but results are too preliminary to draw conclusions, and studies providing a direct comparison with a two-catheter setup are lacking. In a recent clinical study, Bergling et al[50] compared a standard PD regimen (6×2 L 1.36% glucose) over 9 h with a novel prescription (7×2 L 2.27% glucose $+ 5 \times 2$ L 0.1% glucose over 8 h) in 21 patients. The rapid static dwells (via a single-lumen catheter) seemed to increase small solute diffusion capacities and hydraulic conductance by 27%, probably related to a stirring effect or a vasodilatation effect due to the high time-averaged dialysate flow rate. Theoretically, since MTAC seems to be one of the most important determinants of CFPD efficacy (i.e., clearance), and increases in MTAC may result from high dialysate flow rates along the peritoneal membrane, continuous rapid cycling via a single-lumen catheter using high flow rates may result in high CFPD efficacy. However, a considerable dead volume and high degree of recirculation may limit efficacy of this approach, and two single-lumen catheters or a double-lumen catheter with maximal distance between the tips may be required to ensure proper intraperitoneal fluid mixing, optimize dialysate flow along the peritoneal membrane and maximize the effective membrane area. It is questionable, however, whether use of two PD catheters is feasible in routine clinical practice, as this increases the risk of peritonitis, may limit patient comfort on the long term, and requires an additional invasive procedure in patients who only have a single catheter for conventional PD. In addition, due to the nonpelvic catheter tip location, long-term patency of the second catheter (lumen) may be an issue (e.g., due to omental wrapping or adhesions),[51] although the second catheter (lumen) will primarily be used for inflow, thus reducing the risk of catheter malfunction. However, CFPD with a temporary two-catheter setup may be employed in ICU patients with AKI.

CFPD is more complex than conventional PD. requiring additional materials and machines (e.g., an adapted CVVH machine[28,36]). The extra equipment and high dialysate volumes are impractical for use at home and render the technique more expensive than conventional PD, which may limit widespread use of the technique. However, the advent of (novel) on-demand peritoneal dialysate generation systems and sorbent-based portable/wearable CFPD devices that apply continuous dialysate regeneration may improve simplicity of this technique and result in dialysate volume requirements similar to or lower than in conventional PD. Moreover, possible improved patient outcomes and longer technique survival, postponing the necessity to switch to the more expensive hemodialysis treatment, may outweigh any additional costs of the CFPD technique.

8 | CONCLUSION

CFPD shows potential to offer superior small solute clearance and ultrafiltration compared with conventional PD. On-demand dialysate regeneration and sorbent-based portable/wearable CFPD devices, currently in the (pre)clinical development phase, may render CFPD applicable for use at home. However, there is a clear need for well-designed (long-term) clinical trials to compare CFPD with conventional PD with regard to PD efficacy, patient outcomes, long-term safety (including tolerability and long-term effects on the peritoneal membrane and transport status), and feasibility and determine the optimal catheter strategy and cost-effectiveness.

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CONFLICT OF INTEREST

JV, MG, GC, MBR, and KG are involved in the clinical validation of a continuous flow peritoneal dialysis system with dialysate regeneration in cooperation with Nanodialysis B.V. (CORDIAL, Horizon 2020 research and innovation program, grant agreement no. 945207, Dutch Kidney Foundation project PPS08).

AUTHOR CONTRIBUTIONS

JV and MG researched and reviewed literature and were involved in data collection; JV, MG, and KG were involved in data analysis. JV wrote the first draft of the manuscript. All authors were involved in conceptualization of the manuscript/study. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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