PURE BICARBONATE-BASED PD SOLUTIONS

Serkan Kubilay Koc, MD
Country Medical Director, Turkey
Congress
Dec 14th 2023 |Tehran, Iran

DISCLOSURE

- I work as the country medical director for Fresenius Medical Care, Turkey.

PERITONEAL DIALYSIS: AN UNDERUTILIZED MODALITY

- Despite the 40 years history, the comparable survival of HD and PD, and the improved PD technique survival, the percentage of patients performing PD is low.[1]
- Currently, **PD accounts only for 11% of all dialysis treatments** and 9% of all kidney replacement therapy globally,[2] being **available in 75% of 154 countries** (ranging from 96% in high-income countries to **23%** in low-income countries).[3]
- However, PD was not available in 39 of the 154 (25%) countries, particularly in countries in Africa (24/41) and low-income countries (17/22) in a published survey.[3]
- Considering the overall benefits of PD, these numbers are far from ideal.

[1]Moreiras-Plaza MM. Nefrologia. 2014 Nov 17;34(6):756-67. [2]Pecoits-Filho R et al. Kidney Int Suppl (2011). 2020 Mar;10(1):e3-e9. [3]Bello AK et al. BMJ. 2019 Oct 31;367:l5873.

PD IS A VIABLE OPTION FOR ALL PATIENTS REQUIRING KIDNEY REPLACEMENT THERAPY

PD is linked to multiple distinct benefits compared to HD, which makes it especially attractive:

- Technically less complex[1,2]
- Less nurse-to-patient ratios[2]
- Less infrastructure needs and less transportation[3]
- More feasible in rural and remote communities[2,3]
- Fewer management challenges during natural disasters[2]
- Greater cost-effectiveness (in most countries)[1,2]
- Potentially improved access equity to dialysis in resource-limited settings[1]
- Possibly better survival in the first few years[2]

[1]Cho Y et al. Am J Kidney Dis. 2021 Mar;77(3):315-325. [2]Bello AK et al. Nat Rev Nephrol. 2022 Dec;18(12):779-793. [3]Bassuner J et al. Semin Intervent Radiol. 2022 Feb 18;39(1):47-50.

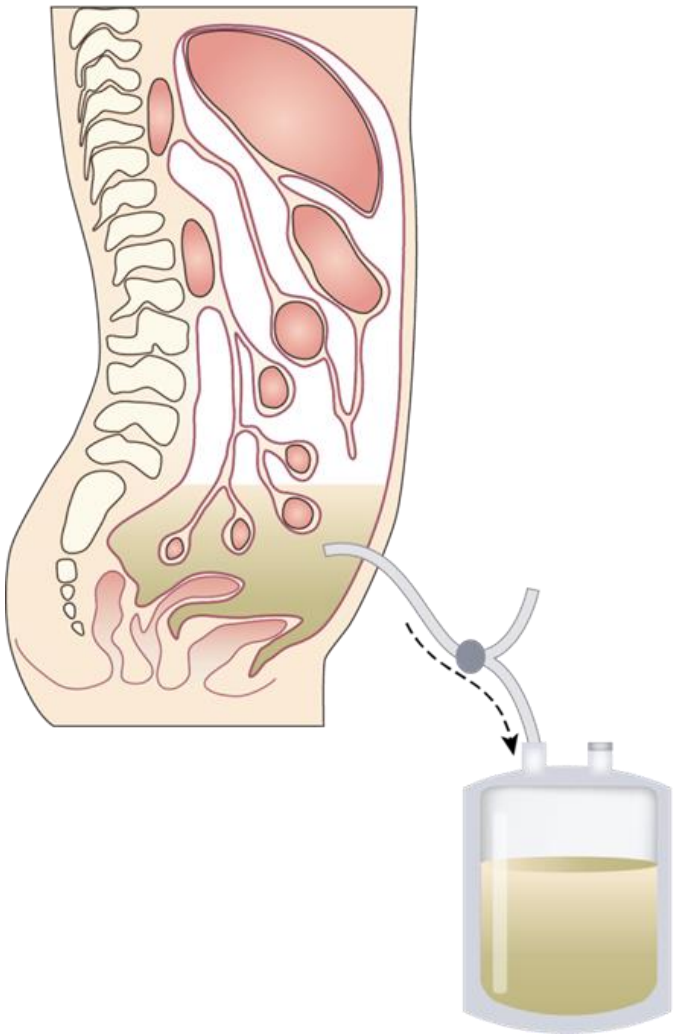
PD IS A VIABLE OPTION FOR ALL PATIENTS REQUIRING KIDNEY REPLACEMENT THERAPY

Additionally:

- Enhanced patient satisfaction and improved quality of life[1,2]
- Better preservation of residual kidney function[1,2]
- Greater ability to travel[2]
- Fewer dietary restrictions[2]
- Better outcomes following subsequent kidney transplantation[2]
- Delayed need for vascular access (especially in small children)[2]
- Reduced need for erythropoiesis-stimulating agents[2]
- Lower risk of blood-borne virus infections and of SARS-CoV-2 infection[2]

[1]Cho Y et al. Am J Kidney Dis. 2021 Mar;77(3):315-325. [2]Bello AK et al. Nat Rev Nephrol. 2022 Dec;18(12):779-793.

PD: A THERAPY WITH DIVERSE OPTIONS AND MORE PHYSIOLOGICAL

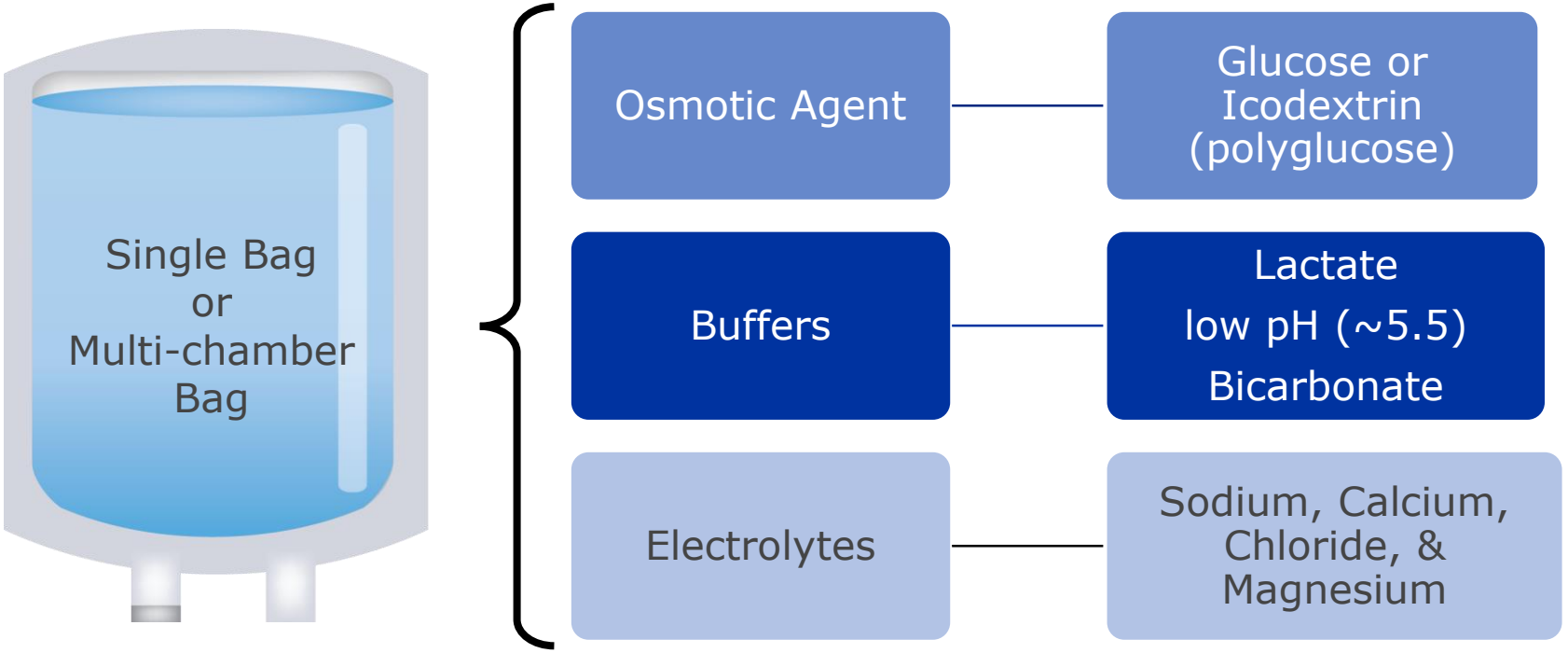


Peritoneal Dialysis Modalities[1-3]			
Manual	**Automated**		
CAPD Continuous Ambulatory PD	CCPD Continuous Cycler PD	IPD Intermittant PD	Tidal PD
	PD Plus	NIPD Nightly Intermittant PD	

Individualization

[1]Heimbürger O, Blake PG. Apparatus for Peritoneal Dialysis. In: Handbook of Dialysis. 2015:408-424. [2]Kathuria P, Twardowski ZJ. Automated Peritoneal Dialysis. In: Textbook of Peritoneal Dialysis. 2009:303-334. [3]Correa-Rotter R, Cueto-Manzano A, Khanna R. Peritoneal Dialysis. In: Brenner and Rector's The Kidney. 2012:2347-2377.

THE CRITICAL ROLE OF PD SOLUTIONS IN PD[1-3]

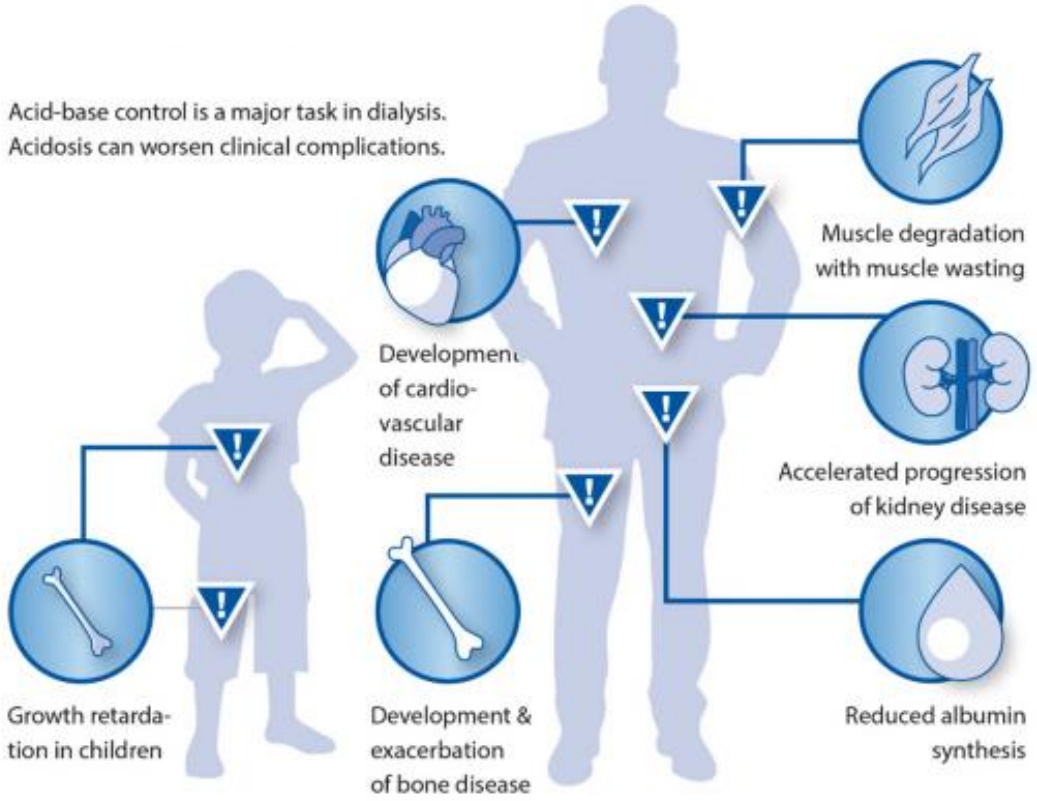


The composition of PD solutions will impact the treatment outcomes.

[1]Heimbürger O, Blake PG. Apparatus for Peritoneal Dialysis. In: Handbook of Dialysis. 2015:408-424.
[2]Teitelbaum I, Burkart J. Peritoneal dialysis. Am J Kidney Dis. 2003;42(5):1082-1096. [3]Schmitt CP et al. Kidney Int. 2002 Apr;61(4):1527-36.

METABOLIC ACIDOSIS HAS MANY NEGATIVE IMPACTS ON CLINICAL OUTCOMES

- Increased degradation of muscle protein with muscle wasting[1,2]
- Decreased albumin synthesis with predisposition to hypoalbuminemia[1,2]
- Stimulation of inflammation[1,2]
- Retardation of growth in children[1,2]
- Development or exacerbation of bone disease[1,2]
- Impairment of insulin secretion and responsiveness[1,2]
- Progression of chronic kidney disease[1,2]
- Stimulation of amyloid accumulation[2]
- Increased risk of death[1,2]



Adverse effects of metabolic acidosis.
Based on Kraut and Madias 2011[1], and Kraut and Madias 2016[2]

[1]Kraut JA, Madias NE. Pediatr Nephrol. 2011 Jan;26(1):19-28. [2]Kraut JA, Madias NE. Am J Kidney Dis. 2016 Feb;67(2):307-17.

LACTATE AS A BUFFER[1]

- Lactate is included in the peritoneal dialysis solution to offset the hydrogen ions (via its conversion to bicarbonate) normally produced during the metabolic processes.
- Nowadays **lactate is the most commonly used buffer** in conventional PD fluids with concentrations of 35 or 40 mmol/L.
- However, despite the general thought that PD adequately corrects uremic acidosis, several studies have demonstrated that **more than 50% of patients present mild to moderate acidosis** with the solution containing 35 mmol/L of lactate, although with a 40 mmol/L solution this percentage decreases, a substantial number of patients remain acidotic.
- Bicarbonate was initially used as a buffer source in PD fluid, but it was soon replaced by lactate when it was found that calcium carbonate precipitated, and the solution became alkaline during autoclaving. **Today, this problem does not exist due to the double-chamber design of the PD solutions.**

[1]Feriani M. Semin Dial. 2000 Jul-Aug;13(4):256-60.

LACTATE AS A BUFFER: THE CHALLENGES[1]

- However:
  - **Low pH associated with lactate** is reported to result in increased **infusion pain** and directly effects **neo-angiogenesis** and **mesothelial cell damage**.
  - Together with the commercial manufacturing process, these factors also result in the production of glucose degradation products (GDPs). GDPs enhance the local and systemic production of advanced glycation end products by the reaction of the aldehyde form of glucose, in the presence of amines or proteins, to produce Amadori glycosolation products.
  - **Advanced glycation end product accumulation has been implicated in the development of structural damage of the peritoneum and vasculature.**

- Multi-bag systems are used to separate the buffer from the rest of the PD solution content to prevent precipitation and allows glucose to be stored at a low pH and minimize degradation.

[1]McIntyre CW. Kidney Int. 2007 Mar;71(6):486-90.

LIMITATIONS OF THE LACTATE CONTAINING BUFFERS

Biocompatibility of PD fluids has been intensively studied since the beginning of PD

Avoiding patient harm is a key element of all prescribed therapies

Relatively low compatibility of conventional PD solutions due to three major factors

Glucose
(Osmotic agent)

Low fluid pH
(Prevention of GDP formation during fluid sterilization)

Lactate buffer
(Source of endogenously generated bicarbonates)

Very early on, *in vitro* data have demonstrated that **acidic, lactate and GDP containing solutions** contribute to a reduced cellular response and functionality of human neutrophils and mesothelial cells thus worsening host defense combating peritoneal infection.[1-6]

- The use of a **lactate buffer** is associated with:[7,8]
  - Risk of **insufficient correction of metabolic acidosis**.
  - Risk of provoking **abdominal pain during the fluid inflow.**
- Increased **lactate load** is associated with a decrease in cellular redox state, thus **impairing numerous vital cellular functions.**[9]

GDP: Glucose Degradation Products

[1]Jörres A et al. Nephron. 1991;58(3):276-82. [2]Topley N et al. Kidney Int. 1996 May;49(5):1447-56. [3]Liberek T et al. Nephron. 1993;65(2):260-5. [4]Witowski J et al. J Am Soc Nephrol. 2000 Apr;11(4):729-39. [5]Witowski J et al. J Am Soc Nephrol. 2001 Nov;12(11):2434-41. [6]Mortier S et al. J Am Soc Nephrol. 2003 May;14(5):1296-306. [7]Coles GA et al. Perit Dial Int. 1997;17(1):48–51. [8]Mactier RA et al. Kidney Int. 1998 Apr;53(4):1061–7. [9]Feriani M et al. Kidney Int. 1998 Nov;54(5):1731–8.

THE RELAVANCE OF SERUM BICARBONATE IN ACIDOSIS CONTROL

- PD patients can use the PD fluid buffers (like lactate) to **restore plasmatic bicarbonate levels** consumed during metabolic processes.

- The level of serum bicarbonate in PD patients is determined by the **dialytic base gain**, which in turn **depends on the buffer concentration, the ultrafiltration and the metabolic acid production**.[1]

- However, in 30-50% of CAPD population (using conventional PD solutions), there is still a **wide variability of plasma bicarbonate levels** and a certain degree of **metabolic acidosis**, defined as an increase in the H^+ concentration in the systemic circulation resulting in a serum HCO_3 less than 24 mEq/L.[2-3]

[1]Feriani M et al. Perit Dial Int. 1996;16 Suppl 1:S126-9. [2]Feriani M. Kidney Int Suppl. 1996; 56:S75-80. [3]Chang TI et al. PLoS One 2013;8(12):e82912.

THE RELAVANCE OF SERUM BICARBONATE IN ACIDOSIS CONTROL

- An adequate acidosis correction is important, as decreased **serum bicarbonates levels are an independent risk factor for mortality and morbidity** in PD patients.[1,2] There is also an association between increased serum bicarbonate levels and loss of residual kidney function.[3]
- **Better correction of metabolic acidosis** is associated with an **increase in normalized catabolic rate** (nPCR), an indicator for protein break down and suggestive of improved nutrition.[2,4,5]
- This might help preventing malnutrition, frequently observed in PD patients.[6]

[1]Chang TI et al. PLoS One 2013;8(12):e82912. [2]Stein A et al. Kidney Int. 1997; 52: 1089–1095 [3]Chang TI et al. Medicine (Baltimore) 2015;94(31):e1276.
[4]Feriani M et al. Kidney Int. 1998;54(5):1731-8. [5]Montenegro J et al. Perit Dial Int. 2006;26(1):89-94 [6]Garibotto G et al. Nutr Metab Cardiovasc Dis. 2013;23 Suppl 1:S25-30.

THE RATIONALE FOR USING PURE BICARBONATE-BASED SOLUTIONS

- During a PD dwell with lactate or in combination with bicarbonate, a loss of bicarbonate into the dialysate occurs, [1-5] which increases with peritoneal ultrafiltration.

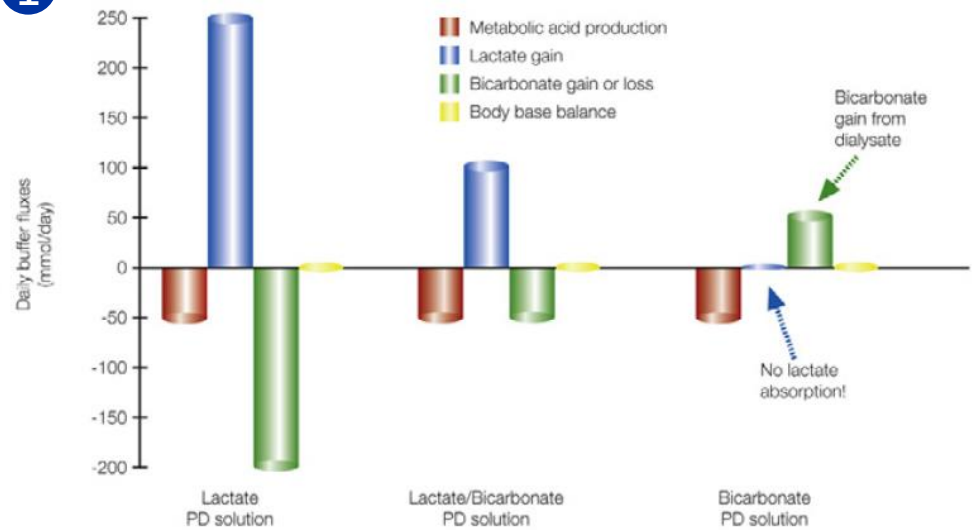
- With **pure bicarbonate**, which **does not need to be converted by the liver**, there is an absorption only dependent on the capillary concentration of bicarbonate[1], thus plateauing at this level, and its **losses are kept minimally** *(Figure 1).*[6]

- **Acidosis correction is superior** with **pure bicarbonate** solutions compared to only lactate containing solutions.[7-10]

- Furthermore, with different bicarbonate formulations, **individualization is possible and beneficial**. Studies have demonstrated improved acid base control with bicarbonate, with 60% of patients starting with acidosis being in the normal range at the end of the study.[6,11]

1

Graph based on data from Feriani et al. 1997.[6]



No loss of endogenous bicarbonate with pure bicarbonate PD solutions.

[1]Feriani M et al. Perit Dial Int. 1995;15(8):336-41. [2]Plum J et al. Perit Dial Int. 1999;19(5):418-28. [3]Schmitt CP et al. Kidney Int. 2002;61(4):1527-36. [4]Fang W et al. Perit Dial Int. 2008;28(1):35-43. [5]Coles GA et al. Nephrol Dial Transplant. 1998;13(12):3165-71. [6]Feriani M et al. Perit Dial Int 1997;17(1):17-21. [7]Weiss L et al. Perit Dial Int. 2009;29(6):647-55. [8]Montenegro J et al. Perit Dial Int. 2006;26(1):89-94. [9]Haas S et al. J Am Soc Nephrol. 2003;14(10):2632-8. [10]Feriani M et al. Kidney Int. 1998;54(5):1731-8. [11]Feriani M, et al. Nephrol Dial Transplant 2004;19(1):195-202. [12]Feriani M et al. Perit Dial Int. 1996;16 Suppl 1:S126-9.

IMPORTANT POINTS TO REMEMBER ON METABOLIC ACIDOSIS CONTROL

Regardless of the buffer used, it is always important to remember:

- Besides the speed of acidosis correction, also the degree of acidosis control matters.
- The better the acidosis of the patient can be treated already with the PD fluid, the **less need exists for adding oral bicarbonate pills** into the treatment.
- Although these pills are no major cost issue, they contribute substantially to pill burden, the reduction of which is desired in the market as, e.g., patient compliance is often limited.

LACTATE VERSUS BICARBONATE BUFFERS ON THE PERITONEUM EXPERIMENTAL DATA

Potential prevention of long-term vascular changes of the peritoneal membrane[1]

Superfusing rat peritoneum with different PD fluids, a transient increase in arteriolar flow and capillary recruitment remained with lactate PD fluid low in GDP. This is a reaction of the peritoneum to the PD fluid, which when repeatedly occurring may induce vascular remodeling and finally reduce ultrafiltration capacity. When changing to bicarbonate-buffered solutions with neutral pH and low GDP content, arteriolar flow and capillary recruitment no longer changed during contact with the PD fluids.

Lactate PDF + High GDP	Marked increase in arteriolar blood flow and capillary recruitment
Lactate PDF + Low GDP	Transient increase in arteriolar blood flow and capillary recruitment
Bicarbonate PDF + Low GDP	No alterations in arteriolar blood flow and capillary recruitment

Vascular Remodelling Reduced UF Capacity

[1]Mortier S et al. J Am Soc Nephrol. 2002;13(2):480-9. Erratum in: J Am Soc Nephrol 2002;13(5):1419-22.

LACTATE VERSUS BICARBONATE BUFFERS ON THE PERITONEUM EXPERIMENTAL DATA

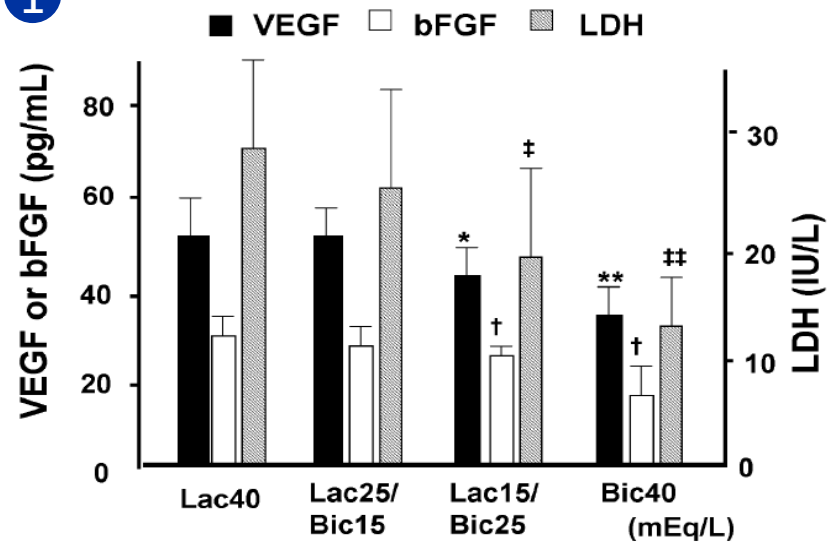
Improved viability of peritoneal mesothelial cells, and decreased concentrations of factors associated with peritoneal fibrosis and neovascularization[1]

Loss of human peritoneal mesothelial cells (HPMCs) has been suggested as a primary cause of peritoneal hyperpermeability and fibrosis.

HPMCs, when treated with **pure bicarbonate** as the buffer base (and compared with pure lactate or mixtures of lactate-bicarbonate), **showed a lesser production of vascular endothelial growth factor (VEGF)** *(Figure 1)* **and basic fibroblast growth factor (bFGF) by the HPMC.** Both are growth factors involved in peritoneal fibrosis and neovascularization. They showed also a lesser release of lactate dehydrogenase (LDH), an indicator of HPMC necrosis in used PD fluid.

In line with these results, other studies also demonstrated less peritoneal angiogenesis when using bicarbonate as the buffer base in comparison to lactate in *in vivo* experiments.[2]

1



Pure bicarbonate-based solutions have been shown to lead to:

- Lesser production of VEGF and bFGF by human peritoneal mesothelial cells.
- Lower release of LDH, an indicator of peritoneal mesothelial cell necrosis.

[1]Ogata S et al. Adv Perit Dial. 2006;22:37-40. [2]Albrektsson A et al. ASAIO J. 2006;52(3):276-81.

LACTATE VERSUS BICARBONATE BUFFERS ON THE PERITONEUM EXPERIMENTAL DATA

Augmented mesothelial cell migration capacity via upregulation of aquaporin-1[1]

Exposure to bicarbonate but not lactate augmented mesothelial cell migration capacity via upregulation of aquaporin-1. This translates into improved potential necessary for **wound healing and tissue repair processes** activated at times of damage (e.g., in case of peritonitis, as demonstrated by a significantly faster closure of a scratch in a HPMC monolayer.

Pure bicarbonate-based solutions have been proposed to lead to:

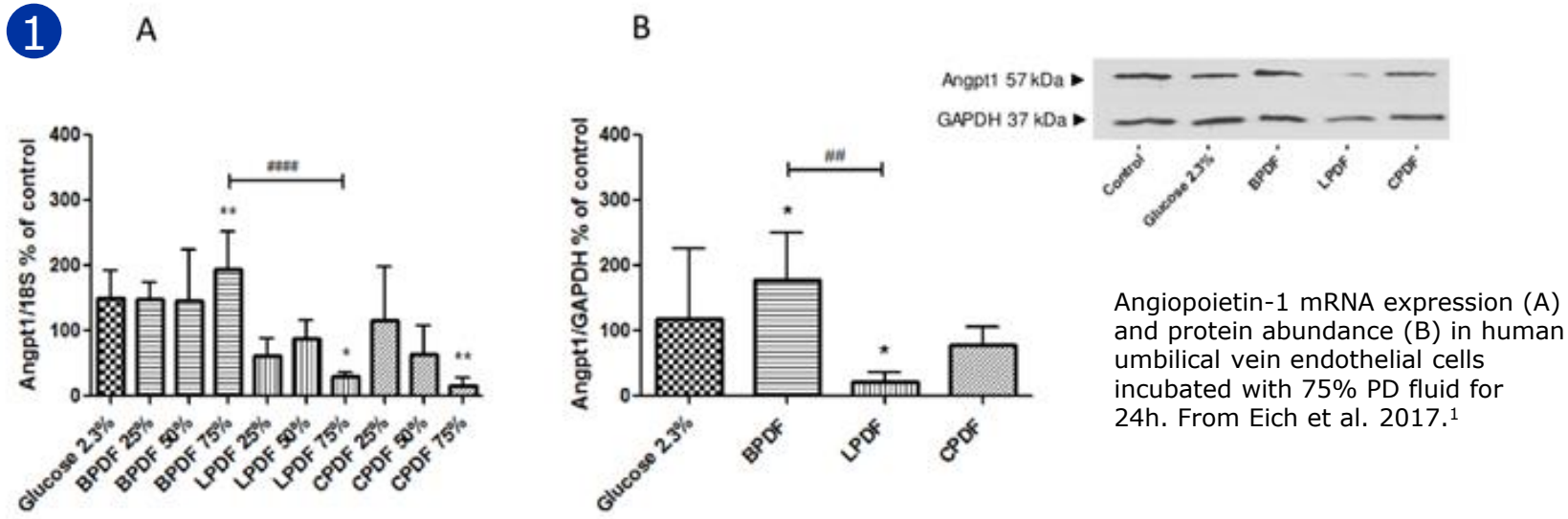
- improved potential necessary for wound healing and tissue repair processes activated at times of damage

[1]Zhai Y et al. Pediatr Nephrol. 2012;27(7):1165-77.

LACTATE VERSUS BICARBONATE BUFFERS ON THE PERITONEUM EXPERIMENTAL DATA

Induction of less endothelial tube formation[1]

In vitro, bicarbonate-buffered low-GDP fluid induced less endothelial tube formation than the respective lactate-based fluid, due to an increase in angiopoietin 1/18S ratio, that is, a shift towards vessel maturation, and tyrosine kinase receptor (TEK) translocation to the endothelial cell membrane, where it co-localized with vascular-endothelial cadherin, which stabilizes vessels *(Figure 1).* TEK plays a pivotal role in the regulation of sprouting and maturation of the vessels.[3] The finding was supported by a larger cross-sectional area of peritoneal vessels in eight bicarbonate fluid treated, peritonitis free children, as compared to the vessel area in age and glucose exposure matched children treated with the respective second-generation lactate PD fluid. Vessel size is an indicator of maturation.[2]



Angiopoietin-1 mRNA expression (A) and protein abundance (B) in human umbilical vein endothelial cells incubated with 75% PD fluid for 24h. From Eich et al. 2017.[1]

[1]Eich G et al. PLoS One 2017;12:e0189903. [2]Eklund L and Saharinen P. Exp. Cell Res. 2013;319: 1271–1280. [3]Suri C et al. Science 1998;282:468–471.

LACTATE VERSUS BICARBONATE BUFFERS ON THE PERITONEUM CLINICAL DATA (LAB-ORIENTED)

Confirming experimental studies, improvement in effluent markers signaling better biocompatibility with pure bicarbonate solutions have also been reported in several clinical studies:

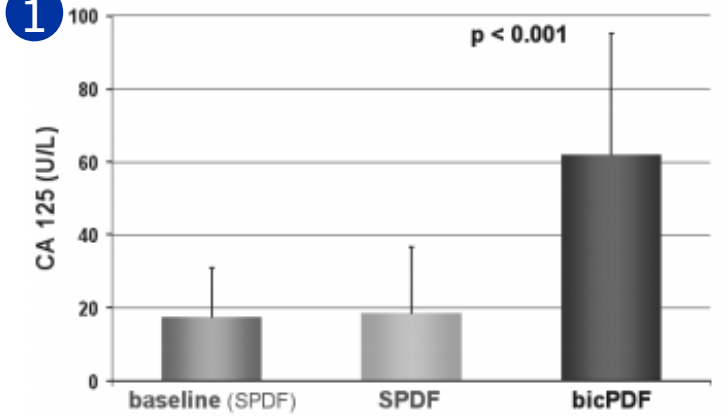
Higher concentration of cancer antigen 125 (CA125) in effluent[1]

CA125 is considered a marker for mesothelial cell mass.[1-4] Increased CA125 concentrations in dialysis effluents suggested high mesothelial mass, in comparison to effluents from lactate-based fluids *(Figure 1).*

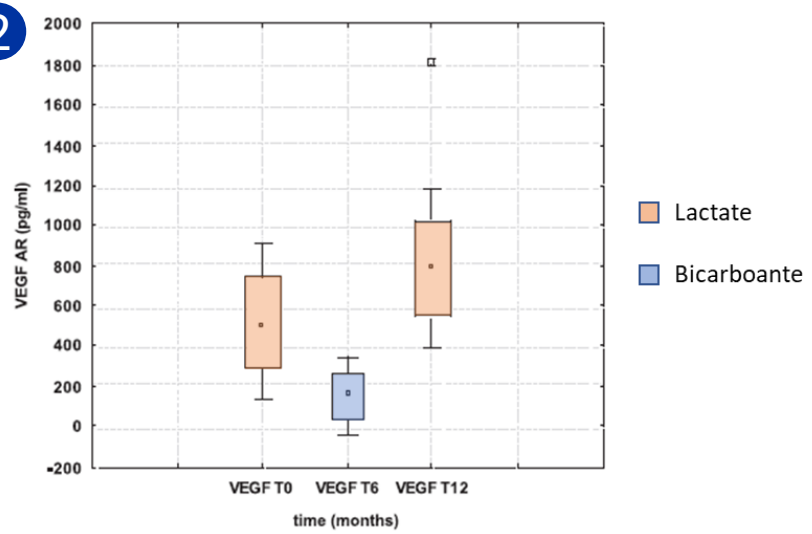
Less VEGF and HA in effluent[1,3]

Vascular Endothelial Growth Factor (VEGF) and Hyaluronic Acid (HA) are both growth factors promoting angiogenesis *(Figures 2 and 3).*

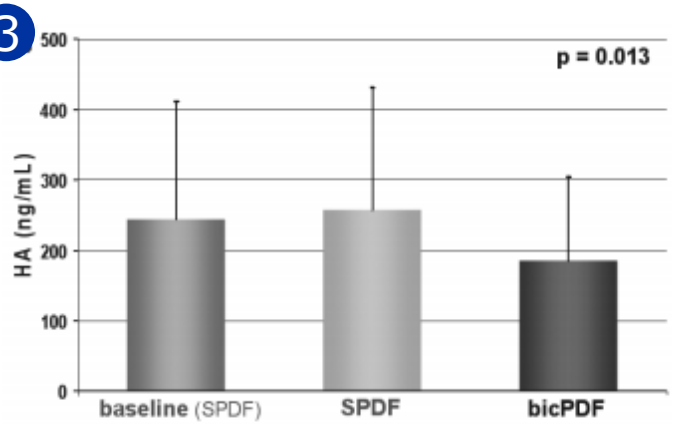
1



2



3



[1]Weiss L et al. Perit Dial Int. 2009;29(6):647-55. [2]Theodoridis M et al. Ren Fail. 2008;30(2):161-7.
[3]Theodoridis M et al. Perit Dial Int. 2011;31(2):196-9. [4]Haas S et al. J Am Soc Nephrol. 2003;14(10):2632-8.

LACTATE VERSUS BICARBONATE BUFFERS ON THE PERITONEUM CLINICAL DATA (LAB-ORIENTED)

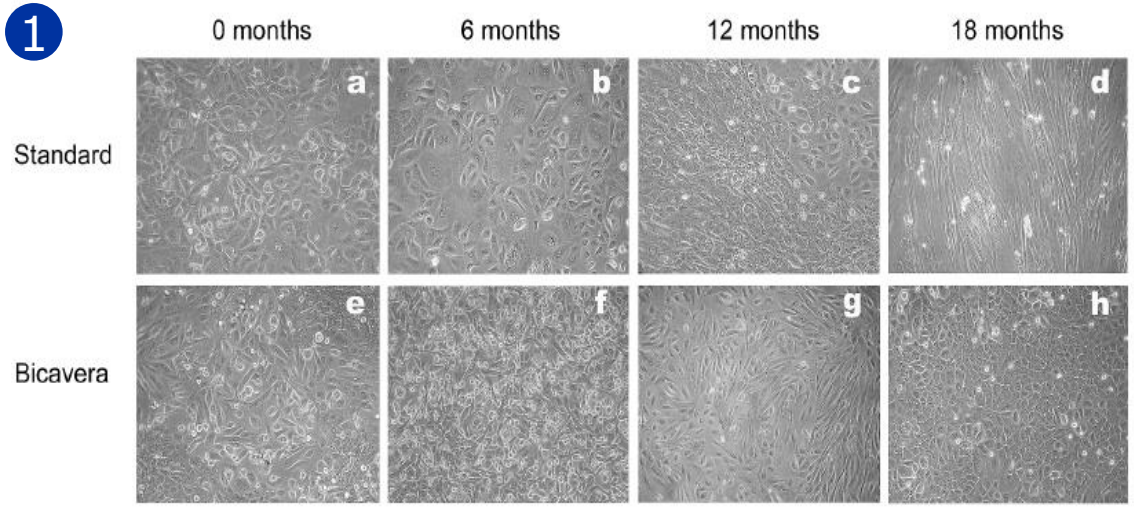
Less inflammatory cytokines as well as decreased amounts of pro-fibrotic factors and chemokines[1]

Mesothelial cells derived from cultured effluents of PD patients using bicarbonate-based solutions showed an epithelioid phenotype whereas with standard PD fluid a gradual transformation towards a non-epithelioid phenotype occurred *(Figure 1).* The latter is considered a sign of epithelial-mesenchymal transition which is linked to peritoneal fibrosis. This suggests that bicarbonate-based solutions in comparison to standard PD fluid protects the mesothelial cells long-term.

Improved removal of AGEs via the effluent as well as reduced plasma levels of AGEs[2]

Generation of advanced glycation end-products (AGEs) is a well-established consequence of GDPs and contribute to cardiovascular risk *(Figure 2).*

1



2

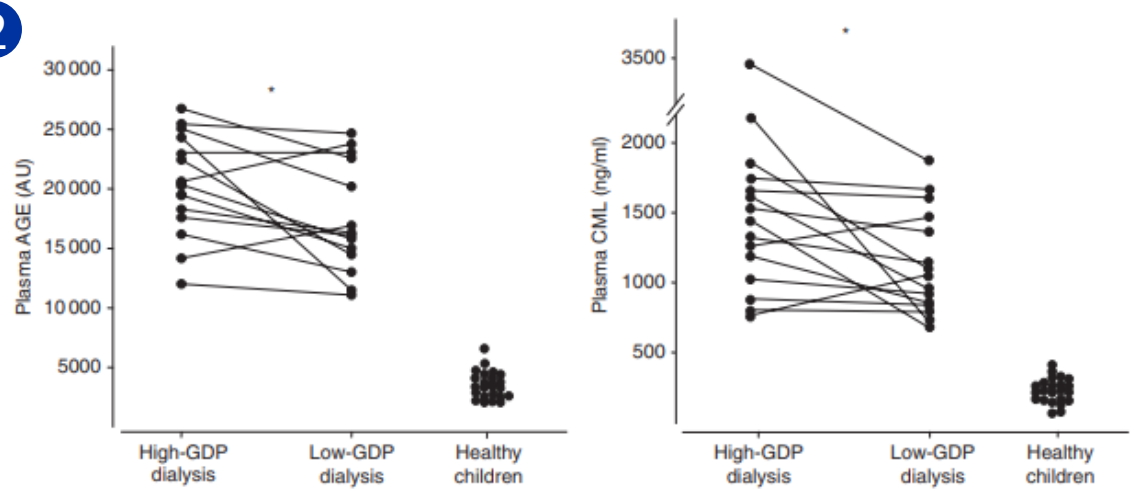


Fig. 3. Intra-individual changes in AGE and CML plasma concentrations after 12 weeks of peritoneal dialysis with low-GDP solution compared with concentrations obtained with standard GDP dialysate ($^{*}P < 0.05$). In healthy children, plasma AGE and CML concentrations are much lower.

[1]Fernández-Perpén A et al. Perit Dial Int. 2012;32(3):292-304. [2]Schmitt CP et al. Nephrol Dial Transplant. 2007;22:2038–2044

CLINICAL BENEFITS OF USING PURE BICARBONATE-BASED PD SOLUTIONS

- Significant **decline in pain during the fluid infusion, constipation and diarrhea** in a 6 months clinical study analyzing patient perception of the treatment.[1] Subjective patient well-being was improved mainly because of a reduction in abdominal pain induced by the standard lactate solution.
- **Less episodes of peritonitis** in a cohort of PD patients for a mean of 2.5 years.[2-3] Episodes of peritonitis limit technique survival of PD and thus negatively impact patient treatment.
- Demonstrated **beneficial effect on residual renal function**.[2-4]
- The **latest ISPD guidelines for peritoneal dialysis in acute kidney injury** recommend the use of bicarbonate containing solutions in **adult and pediatric patients** who are critically ill, especially those with significant liver dysfunction and marked elevation of lactate levels.[5,6]

[1]Feriani M et al. Kidney Int. 1998;54(5):1731-8. [2]Montenegro J et al. Perit Dial Int. 2006;26(1):89-94. [3]Montenegro J et al. Nephrol Dial Transplant 2007;22(6):1703-8.
[4]Weiss L et al. Perit Dial Int. 2009;29(6):647-55. [5]Cullis B et al. Perit Dial Int. 2021;41(1):15-31. [6]Nourse P et al. Perit Dial Int. 2021;41(2):139-157.

BETTER PRESERVATION OF ULTRAFILTRATION WITH PURE BICARBONATE-BASED PD SOLUTIONS IN PEDIATRIC PATIENTS

- **Positive effects on structural and functional cardiac alterations including an improved ejection fraction[1]**. In addition to a possible negative impact of high GDPs in the control PD fluid, also the change to a pure bicarbonate buffer might have contributed to these cardiac effects. Infusion of lactate, the traditionally used buffer base, influences the cellular redox status[2] which in turn is associated with contractile function.[3]

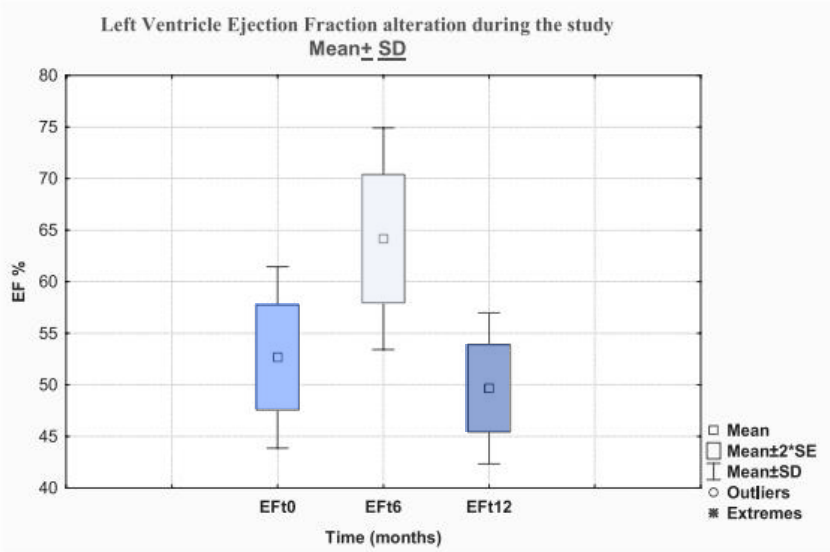


Fig. 1. Left Ventricle EF during the study period (mean ± SD). From Theodoridis et al. 2011.[1]

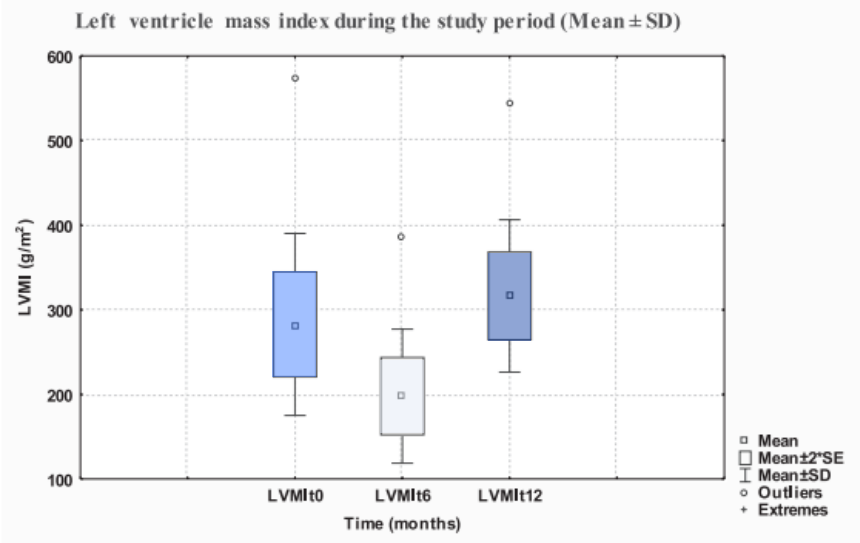
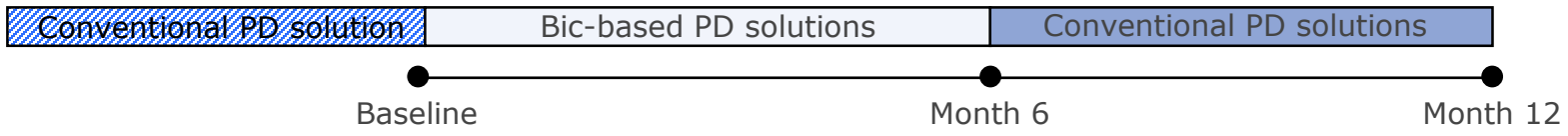


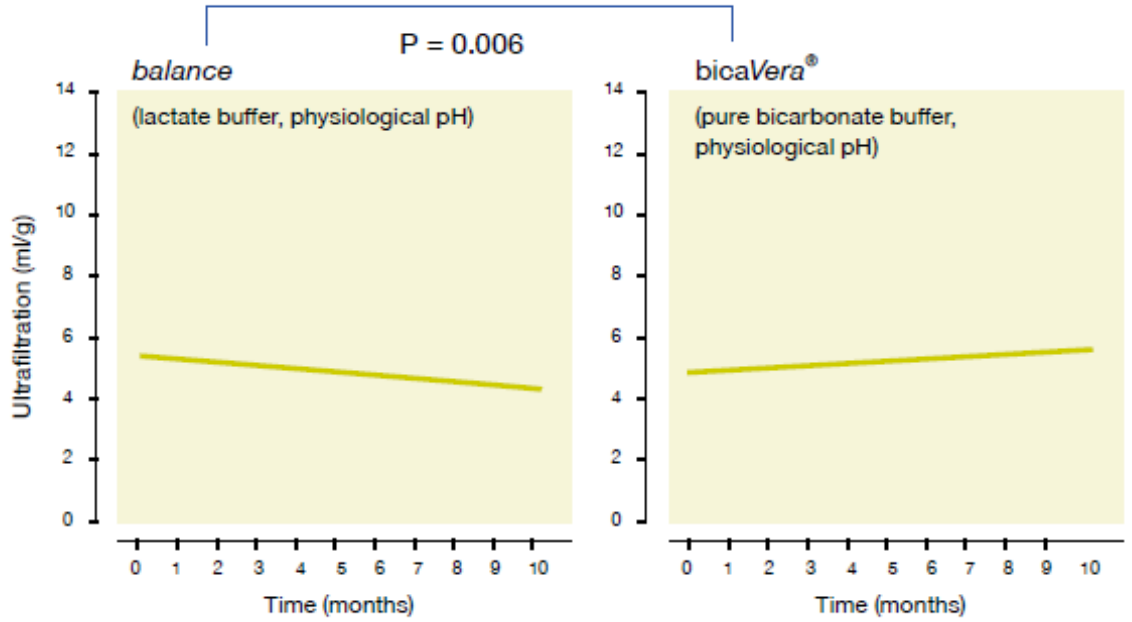
Fig. 4. LVMI during the study period (mean ± SD). From Theodoridis et al. 2011.[1]



[1]Theodoridis M et al. Nephrol Dial Transplant 2011;26(12):4061-7. [2]Veech RL. Kidney International 1988;34:587-597. [3]Cherednichenko G et al. Circ Res. 2004;94:478-486

BETTER PRESERVATION OF ULTRAFILTRATION WITH PURE BICARBONATE-BASED PD SOLUTIONS IN PEDIATRIC PATIENTS

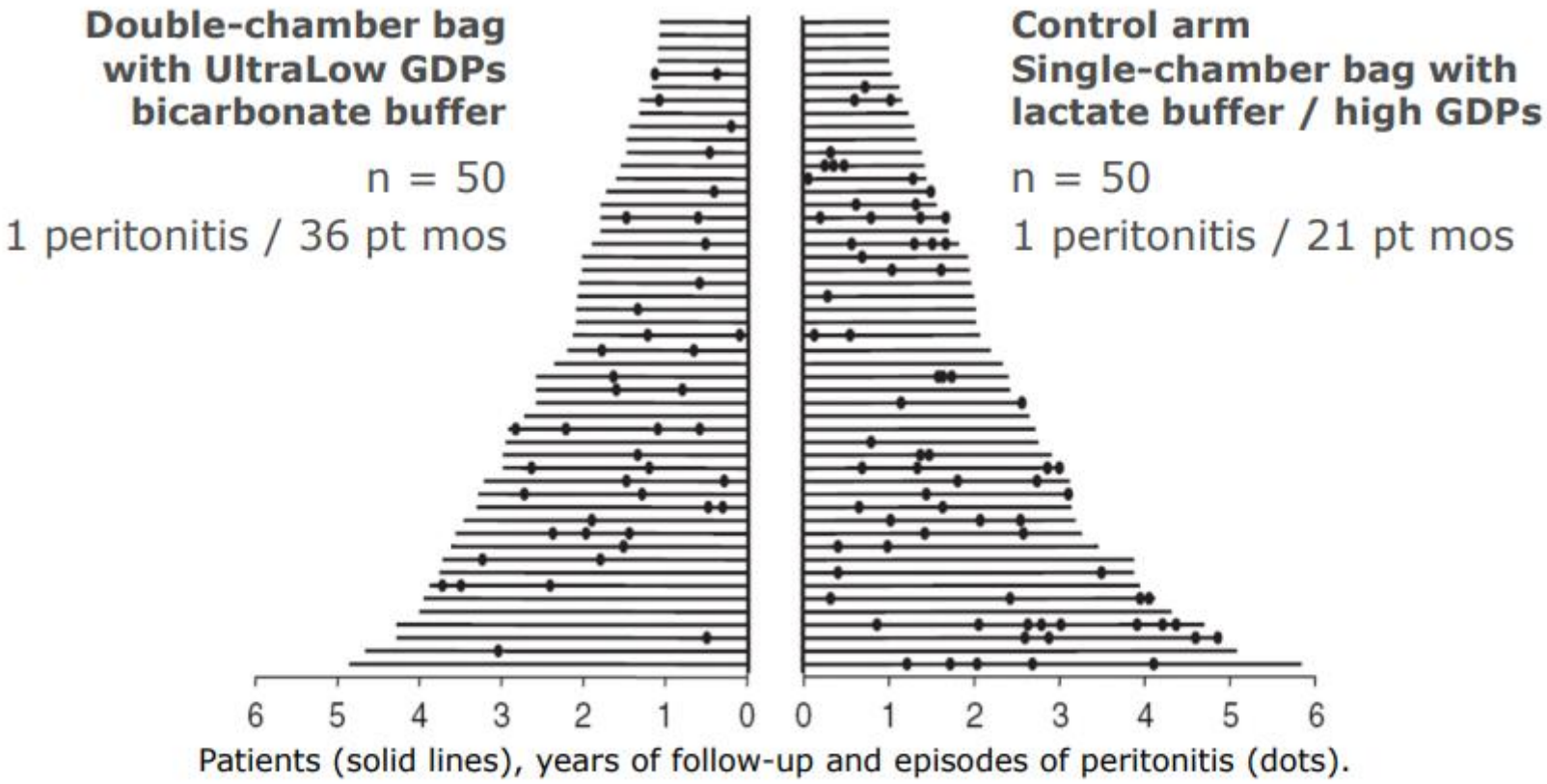
Better preservation of ultrafiltration achieved per gram of dialytic glucose exposure and body surface area in pediatric patients over 10 months[1]



Ultrafiltration per 1 g glucose administered in patients on lactate PD fluid (left) and bicarbonate PD fluid (right). Graph modified from Schmitt et al. 2013.[1]

[1]Schmitt CP et al. Clin J Am Soc Nephrol. 2013;8(1):108-15

LESS PERITONITIS WITH PURE BICARBONATE-BASED PD SOLUTIONS IN PEDIATRIC PATIENTS



Patients (solid lines), years of follow-up and episodes of peritonitis (dots).

These results are compatible with a beneficial impact of pure bicarbonate, low GDP peritoneal dialysis solutions on peritonitis rates.

Graph modified from: Montenegro et al, Nephrol Dial Transplant 2007;22: 1703-8

OVERALL SUMMARY OF THE BENEFITS OF PURE BICARBONATE-BASED PD SOLUTIONS

1. No significant alterations in arteriolar blood flow[1]
2. Preservation of ultrafiltration capacity[2]
3. Improved control of acidosis[3]
4. Improved removal of AGEs[4]
5. Protection of mesothelial cells[4,5]
6. Lower angiogenic factors in effluent[6]

[1]Mortier S et al. J Am Soc Nephrol. 2002;13(2):480-489. [2]Schmitt CP et al. Clin J Am Soc Nephrol. 2013;8(1):108-115. [3]Feriani M. Perit Dial Int. 1997;17 Suppl 2:S51-5.
[4]Schmitt CP et al. Nephrol Dial Transplant. 2007;22(7):2038-2044. [5]Weiss L et al. Perit Dial Int. 2009;29(6):647-655. [6]Theodoridis M et al. Nephrol Dial Transplant. 2011;26(12):4061-4067.

Thank you!

Head office: Fresenius Medical Care Deutschland GmbH
61346 Bad Homburg v. d. H. · Germany
Phone : +49 (0) 6172-609-0
www.freseniusmedicalcare.com