Advantages of pyruvate over lactate in peritoneal dialysis solutions

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ABSTRACT

This review discusses effects of both lactate and pyruvate, and high glucose in peritoneal dialysis solutions (PDS) on leukocytes, mainly on intracellular pH ([pH]i), glucose metabolic pathways, and apoptosis. Lactate-based PDS (L-PDS) are bioincompatible primarily due to the low pH, high lactate, and glucose excess in both individual and combination. High lactate in an acidi milieu would induce severe intracellular acidosis of leukocytes, and high glucose may disturb glucose metabolic pathways and activate protein kinase C (PKC) and nuclear factor-kappa B (NF-kappa B) of the cells, leading to apoptosis. Pyruvate-based PDS (P-PDS) are novel experimental PDS. Evidence shows that P-PDS are superior in biocompatibility. Pyruvate protection of cells has been confirmed in many fields besides the PDS area. Although the underlying mechanism whereby P-PDS preserve cell function is not fully understood, it may be associated with the maintenance of [pH]i close to physiological, due to its low buffering capacity, improvement of cellular glucose metabolic pathways and redox state, and maintenance of intracellular calcium ([Ca^2+],) homeostasis in high glucose concentrations. It may also inhibit PKC and NF-kappa B activation in high glucose. In addition, pyruvate is a strong antioxidant, a scavenger of hydrogen peroxide (H_2O_2). However, exogenous pyruvate in PDS could not be an energy source for cells and also the Crabtree effect might not occur in neutrophils. Pyruvate is a hopeful candidate of buffers in PDS in the near future. Further observation of P-PDS is strongly needed with peritoneal cells to verify the cell protection both in vitro and in vivo before clinic trials.

INTRODUCTION

Conventional lactate-based peritoneal dialysis solutions (L-PDS) are unphysiologic fluids, which have been employed in continuous ambulatory peritoneal dialysis (CAPD) for over two decades. Novel experimental pyruvate-based peritoneal dialysis solutions (P-PDS) were recently found to be superior in biocompatibility. It is possible that P-PDS would be a potent alternative in the near future. The present review discusses effects of both lactate and pyruvate, and high glucose on human leukocytes, mainly on intracellular pH ([pH]i), glucose metabolism, and apoptosis, to elucidate advantages of pyruvate in peritoneal dialysis solutions (PDS) and its probable mechanisms of the cell protection.

LACTATE-BASED PERITONEAL DIALYSIS SOLUTIONS

Abbreviations AGES; advanced glycosylation end-products; AR; aldose reductase; B-PDS; bicarbonate-based peritoneal dialysis solutions; [Ca^2+]; intracellular calcium; CAPD; continuous ambulatory peritoneal dialysis; DAG; diacylglycerol; FMLP; formylmethionyl-leucyl-phenylalanine; GDP; glucose degradation products; GLUT; glucose transporter; HBSS; Hanks' balanced salt solution; HMPS; hexose monophosphate shunt; HPNMC; human peritoneal mesothelial cells; L-PDS; lactate-based peritoneal dialysis solutions; MCT; monocarboxylate transporter; NAD; oxidized nicotinamide adenine dinucleotide; NADH; reduced nicotinamide adenine dinucleotide; NADP; oxidized nicotinamide adenine dinucleotide phosphate; NADPH; reduced nicotinamide adenine dinucleotide phosphate; NF-kappa B; nuclear factor-kappa B; NO; nitric oxide; O_2; superoxide; PDC; pyruvate dehydrogenase complex; PDS; peritoneal dialysis solutions; PK; phosphokinase; [pH]i; intracellular pH; P/K; phosphokinase; PKC; protein kinase C; P-PDS; pyruvate-based peritoneal dialysis solutions; TAC; tricarboxylic acid cycle; TNF; tumor necrosis factor.

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A pH of PDS plays an essential role in biocompatibility. In 1981, it was first demonstrated that L-PDS were bioincompatible. The detrimental effects are mainly due to the low pH (5.0–5.5), high dl-lactate (35–40 mmol·L⁻¹), and gluconeotoxicity including high concentrations of D-glucose (76–215 mmol·L⁻¹), glucose degradation products (GDP), and advanced glycosylation end-products (AGE).

It was discovered in 1991 that acidic L-PDS could create prompt and substantial intracellular acidosis in human neutrophils in vitro. The [pH]ᵢ of resting value could fall precipitously within 3 min, usually from 7.1 down to 6.0, while the extracellular pH ([pH]ₑ) was maintained at 5.2. By comparison, euglycemic L-PDS preserved a greatly higher [pH]ᵢ of 6.8. However, the severe reduction of [pH]ₑ and the inhibition of partial cell function, i.e., superoxide (O₂⁻) production, oxygen consumption, and intracellular glutathione, merely developed in an acidic medium containing a high level of lactate.

In a five-month clinic dialysis with neutralized L-PDS revealed that total leukocyte counts in the effluent decreased and the leukocyte viability increased, compared with acidic L-PDS. The phenomenon above may be explained by the hypothesis that a specialized H⁺/lactate⁻ cotransport system exists in the plasma membranes of human neutrophils. This monocarboxylate transporter (MCT) family (MCT2) with a high affinity for lactate and pyruvate, is strongly pH-dependent. Acidic [pH]ₑ enhances lactate influx along with H⁺ in symport across the membrane following the H⁺ gradient, resulting in an accumulation of intracellular protons and a suppression of respiratory burst activation and oxidative metabolism of cells. In peritoneal macrophages, lactate uptake is exclusively mediated via a specific MCT in a high pH-dependent manner as well. The lactate influx axis of neutrophils is a function of extracellular lactate levels. It is roughly twofold greater when lactate is over 20 mmol·L⁻¹ than below 10 mmol·L⁻¹. Thus, it was postulated that cell dysfunction responsible for peritoneal infection by L-PDS is primarily due to the [pH]ᵢ reduction of exposed cells in vivo. The equilibration of pH value and lactate content in L-PDS close to plasma levels takes 30–60 min dwell time in patient's peritoneal cavity. During the very first 5 min of each instillation, the pH of afferent/residual mixtures in the cavity may be still below 6.0 and the concentration of lactate over 20 mmol·L⁻¹, particularly on the catheter surface where the acidic pH is most pronounced and peritonitis is more susceptible.

Evidence has established in vitro that by exposing human neutrophils to [pH]ₑ 5.2 L-PDS for as little as 5 min, O₂⁻ generation and oxygen consumption were completely suppressed, accompanied with rapid and severe intracellular acidification. Following the transient acidosis, cell dysfunction, at least in part including O₂⁻ generation system, might be reversible although intracellular acidosis in this rather early phase could be instantaneously and entirely restored.

Findings above provide a therapeutic basis to neutralize PDS before instillation and utilize bicarbonate-based PDS (B-PDS, equimolar bicarbonate substitute for lactate or at their various ratios) and a two-chamber system for raising the pH of solutions in recent clinical trials. The [pH]ᵢ monitoring showed that both euglycemic L-PDS and euglycemic B-PDS did not cause marked changes in [pH]ᵢ. A variety of cell functions remained subsequently. Although bicarbonate/lactate based PDS, with a physiologic pH and highly reduced GDP, in double-chambered bags showed superior in biocompatibility, they might be still not perfect to entirely replace conventional L-PDS, due to unknown long-term risks and the manufacturability complexity.

Lactate excess is harmful for cellular metabolism. The addition of lactate 20 mmol·L⁻¹ to Hanks' Balanced Salt Solution (HBSS) at pH 7.0 caused a slight [pH]ᵢ decline in macrophages. By raising lactate up to 40 mmol·L⁻¹, the [pH]ᵢ of cells fell further. Acidic L-PDS could completely inhibit O₂⁻ production and mobilization of intracellular calcium ([Ca²⁺]ᵢ) by Zymosan or N-formyl-methionyl-leucyl-phenylalanine (FMLP)-stimulated neutrophils. The high lactate containing HBSS at pH 7.4 also induced an evident suppression of [Ca²⁺]ᵢ mobilization. Meanwhile, the pH adjustment of L-PDS could improve [Ca²⁺]ᵢ activation, but not entirely restore the [Ca²⁺]ᵢ response as well as O₂⁻ production. In addition, in contrast to euglycemic L-PDS, B-PDS (pH 7.4) allowed a significantly better increase of [Ca²⁺]ᵢ release in the cells, superior IL-6 release and mitochondrial dehydrogenase activity in monocytes. B-PDS even containing high glucose also revealed higher cellular ATP contents of neutrophils and human peritoneal mesothelial cells (HPMC).

There are little data available showing the effect of L-PDS on cytosolic redox state, but the presence of such a high lactate in PDS, which is a 20- to 40-fold of the blood level, could markedly reduce the cytosolic oxidation potential of leukocytes. High lactate functions prin-
cipally as a cytosolic reductant[9], which reduces oxidized nicotinamide adenine dinucleotide (NAD) to reduced nicotinamide adenine dinucleotide (NADH) by lactate dehydrogenase (LDH). The decline of NAD/NADH ratio would inhibit the glycolytic activity, leading to suppressing hexose monophosphate shunt (HMP) for $O_2^\cdot$ generation, as results showed that a euhydric L-PDS facilitated less $O_2^\cdot$ formation by neutrophils than its B-PDS counterpart[10].

All above indicate that high lactate per se in PDS would have direct deleterious impacts on cells. High lactate in an acid milieu will deteriorate harmful effects on cellular metabolism. Despite the lack of direct evidence of glucose metabolic inhibitions by L-PDS in leukocytes, it was demonstrated that human red cells (RBC) exposed to L-PDS (pH 5.5) with lactate17 mmol·L$^{-1}$ resulted in an evident depression of activities of key glycolytic enzymes and a great inhibition in glucose consumption and ATP production, accompanied simultaneously with an acute [pH] decrement[11]. Due to their similar high glycolysis rates, it would be conceivable that results from RBC are in consonance with those of leukocytes under identical conditions.

High glucose is cytotoxic In addition to its hyperosmotic effect, formation of AGE and impacts of GDP in PDS[12], high glucose-induced glucotoxicity may be mainly the stimulation of sorbitol pathway and activation of PKC in leukocytes. Human leukocytes, particularly neutrophils, belong in the category of "unusual tissues" in glucose metabolism. Although it has been well known that high glucose induces an acute depression of $O_2^\cdot$ generation by leukocytes, the mechanism of which is not fully understood[13].

Up to date yet little investigation regarding carbohydrate metabolism on leukocytes exists in peritoneal dialysis, but extensive studies in physiology, diabetes, and ischemia-reperfusion injury have revealed metabolic properties of cells. Human leukocytes are characterized with high anaerobic and aerobic glycolysis and active sorbitol pathway. The cells are specified with aldose reductase (AR) that is highly localized to certain cell types, such as lens epithelium, neuron, mesangial cells, HPMC, and RBC. In neutrophils, glucose uptake across the cell membrane is a passive process through facilitative glucose transporter molecules (GLUT family, predominantly GLUT2 and GLUT9)[34,35].

Normally, glucose is metabolized by glycolysis to produce ATP and by HMPs to create reduced nicoti-
bation with high glucose, as mentioned above in human phagocytes with L-PDS, elevated glucose levels can cause an elevation of the membranous PKC activity, which is also sorbitol pathway-dependent and crucially involved in the stimulation of O$_2^{-}$ generation. PKC is activated with glucose, because high glucose enhances de novo synthesis of diacylglycerol (DAG), a potent physiologic activator of PKC$^{(12,19)}$, and induces a rise of [Ca$^{2+}$]$_{i}$ in leukocytes. In addition, an increased O$_2^{-}$ production may also occur via auto-oxidation of glucose and/or nonenzymatic protein glutation. However, abnormal carbohydrate metabolisms need to be verified with PDS in peritoneal phagocytes.

PYRUVATE-BASED PERITONEAL DIALYSIS SOLUTIONS

P-PDS improve cell function In 1994, it was first reported that experimental P-PDS, equimolar pyruvate replacement of lactate, greatly improved acute cytotoxic effects on human leukocytes, peritoneal macrophages, and HMPC in vitro. It is noteworthy that in sharp contrast to L-PDS counterparts, acidic P-PDS (pH 5.2 - 5.6) with 1.5% glucose revealed a normal viability, proliferation, and cytokine release of HMPC, even 4.25% glucose-enriched P-PDS still maintained the integrity, rate of proliferation and IL-1 release of cells. O$_2^{-}$ generation by human leukocytes (peritoneal macrophages, peripheral mononuclear cells, and neutrophils) and chemotaxis of granulocytes in pH 5.4 P-PDS were comparably as controls. Mononuclear cells preincubated in acidic P-PDS and control media exhibited comparable tumor-necrosis factor (TNF)-alpha mRNA signals, and showed by far less inhibitory effects on the production of cytokines. In conclusion, pyruvate in PDS maintained cell function even at low pH or in the presence of high glucose$^{(20,21)}$.

Although L-PDS could induce apoptosis of peritoneal phagocytes and HMPC, recent results demonstrated that high glucose per se in L-PDS could induce a dose-dependent apoptosis of leukocytes$^{(22)}$. A pilot study further indicated that pyruvate in PDS could protect cells against apoptosis in a dose- and time-dependent manner in vitro, even with 4.25% PDS. Also, a preliminary experiment in vivo showed that O$_2^{-}$ generation and TNF-alpha secretion of macrophages from uremic rats following a five-week dialysis were higher in P-PDS group than in L-PDS one. Interestingly, metabolic acidosis was more effectively corrected in the former than in the latter, and the nutritional state was better after dialysis with P-PDS than with L-PDS as well (abstracts; XXXVI Congress of ERA-EDTA; 1999 Sep 5 - 8; Madrid, Spain. p 304, 1999; J Am Soc Nephrol 1998; 9: 236A). More recently, direct evidence indicated that pyruvate in culture media protected rat peritoneal mesothelial cells against oxidant injury by H$_2$O$_2$, adding one more support of pyruvate as a potentially useful buffer for PDS$^{(23)}$.

Pyruvate preserves physiological [pH]$_e$ and may sustain activities of enzymes. It was discovered in 1995 that acidic P-PDS mixed in vitro with residual peritoneal effluent in the ratio of 10:1 created a markedly higher pH of 7.1 in contrast to a pH of 6.2 of L-PDS counterpart$^{(24)}$. The neutrophilic [pH]$_e$, monitoring in vitro indicated that P-PDS at pH 5.2 preserved a near physiological [pH]$_e$ value, due to the presence of pH 7.4 phosphate-buffered saline solution in cell suspension, whereas identical acidic L-PDS induced a severe [pH]$_e$ reduction$^{(25)}$. Alternatively, P-PDS at [pH]$_e$ 5.2 also showed a drastic depression of O$_2^{-}$ production and oxygen consumption by Zymosan or FMLP-stimulated neutrophils, accompanied with a severe [pH]$_e$ reduction. Findings above were verified by the investigation in Europe.

Because of its lower buffering capacity of buffer pair in P-PDS, the [pH]$_e$ of exposed cells with pH 7.4 suspensions would be higher in P-PDS than in L-PDS. The higher [pH]$_e$, via [pH]$_e$, would engender the favorable cell function. On the other hand, the ratio between the concentrations of lactate and lactate acid in L-PDS at pH 5.5 will be 50:1. If the buffer is 40 mmol·L$^{-1}$, only 0.78 mmol·L$^{-1}$ of lactate is undissociated. Correspondingly, the ratio between pyruvate and pyruvic acid in P-PDS will reach 1000:1, and merely as little as 0.339 mmol·L$^{-1}$ of pyruvate are undissociated. It suggests that a comparably extreme majority of the buffers was dissociated in an acid di mithex. The particular MCT (MCT2) of human neutrophils, which accounts for all of lactate anions uptake, has a similar affinity for both lactate and pyruvate$^{(3,4)}$. None of both permeates via nonionic diffusion to any significant degree in human neutrophils$^{(26)}$. Thus, acidic P-PDS could also bring about equally rapid and profound intracellular acidosis, the same as L-PDS if acidic [pH]$_e$ of both PDS is comparable.

Pyruvate-mediated [pH]$_e$ preservation is crucially of importance for cellular carbohydrate metabolism. It is well known that the rate-limiting enzymes of glycolysis
are extraordinarily pH-sensitive, particularly phosphofructokinase (PFK) and pyruvate dehydrogenase complex (PDC). It just took as little as 5 min that the PFK activity was markedly decreased when the pH of cell-free system was dropped from 7.6 to 7.2. An inhibition of PFK could induce severe interference with cellular energy metabolism in human neutrophils; depletion of ATP and NADPH-oxidase activity, and multifunctional inhibition including the suppression of phagocytosis, O₂⁻ generation, and cytokine production[27]. Pyruvate as an end product of glycolysis, coupled with PDC, is the sole functional link between glycolysis and TAC in human neutrophils. Normally, the activity of PDC is much low, even could not be detected in the cells[28]. Thus, it seems to be impossible that there would be a functional TAC activity, even glycolysis, in neutrophils with intracellular acidosis.

Therefore, exogenous pyruvate could not be as an energy source to enter TAC, being metabolized in neutrophilic mitochondria even with normal [ pH ]. The above conclusion was supported by preliminary experimental evidence with P-PDS in Europe.

The presumption might be impossible that the Crabtree effect occurred in human neutrophils exposed to high glucose-enriched P-PDS[20, 21], as results also indicated that both L-PDS and B-PDS at pH 7.4 did not inhibit cellular ATP contents with glucose concentrations in the cells[8], but acidic L-PDS did. Unfortunately, the [ pH ] of P-PDS/cell mixtures in the original articles was not concerned.

In addition, NADPH-oxidase that serves to transport electrons from cytosolic NADPH to molecular oxygen, producing O₂⁻ is also highly pH-dependent and ATP-required with an optimal pH 7.0 – 7.5. Enzymes in glutathione redox cycle are largely pH-sensitive as well. Thus, intracellular acidification would critically depress the main cytosolic reducing power. Conversely, one of major causes of neutrophilic apoptosis is the activation of the specific acid endonuclease. The activation is dependent on acidic [ pH ], triggering apoptosis.

Further, the motivation of [ Ca²⁺ ]i is also critically influenced with [ pH ]. A preliminary measurement showed that compared with euhydrated L-PDS, there was an evident transient increase of FMLP-stimulated neutrophilic [ Ca²⁺ ]i, motivation by P-PDS counterpart (unpublished data). In this regard, the pyruvate-mediated [ Ca²⁺ ]i activation also occurred in rat myocytes[9]. Although no data so far are available of pyruvate effects on cytosolic activities of enzymes, acidic P-PDS would probably sustain activities of key cytosolic enzymes and [ Ca²⁺ ]i, homeostasis, primarily via a near physiologic [ pH ], maintained.

Pyruvate may improve glucose metabolism pathways and protect cells against apoptosis

Pyruvate and lactate at high concentrations have greatly opposite effects on the cytosolic redox state. An earlier experiment showed that in 5-min preincubation at pH 7.2 pyruvate 5 mmol·L⁻¹ stimulated both glucose consumption and CO₂ production of human RBC by 20 % and 40 %, respectively, whereas lactate 5 mmol·L⁻¹ had no effect on glucose consumption and reduced CO₂ production. It was recently suggested in liver epithelium and endothelial cells that high pyruvate could markedly stimulate the conversion of pyruvate to lactate by LDH with NADH and/or NADPH as co-factors, competitively inhibiting NADPH-dependent reduction of aldehyde sugars to polyols in the first step of sorbitol pathway since the enzyme, LDH, might also use NADPH for the reductive reaction[29, 30].

More importantly, pyruvate may increase the oxidation of NADH to NAD as rapidly as NAD is reduced to NADH in the second step of pathway[31]. Thus, high cytosolic pyruvate acts actually as a strong oxidant[9], raising NAD/NADH and oxidized nicotinamide adenine dinucleotide phosphate (NADP)/NADPH ratios. With an inactive TAC in leukocytes, therefore, it could be presumed that in the presence of such a supra physiologic pyruvate in P-PDS, the anaerobic utilization of exogenous pyruvate would competitively inhibit the sorbitol pathway in high glucose media and improve NAD-dependent glycolytic pathway and preserve NAD-dependent diversion of high glucose to HMPS and glutathione redox cycle[30].

Additionally, pyruvate may also inhibit PKC activity in leukocytes. In a rat skin chamber granulation model, a glucose (30 mmol·L⁻¹)-induced increase in DAG and vascular functional changes could be completely prevented by the addition of pyruvate 3 mmol·L⁻¹. The effects of exogenous pyruvate on DAG synthesis may be twofold: it reduces substrate level, dihydroxycacetone phosphate, and reduces the availability of the co-factor, NADH, needed for the reduction of substrate, resulting in an attenuation of PKC activity[19].

It was reported in 1985 that exogenous pyruvate could protect mammalian cells from H₂O₂, although it has been recognized for almost one century that H₂O₂ causes a rapid nonenzymatic and stoichiometric decarboxylation of pyruvate and related alpha-keto acids.
Subsequent studies indicated the protective role of pyruvate in H$_2$O$_2$-induced renal, neuronal, and ischemic-reperfusion injuries, and injury in transplant reject reaction in vitro or in vivo. Recently, it was also demonstrated in mouse thymocytes and human lymphoid cell lines that pyruvate protected cells from H$_2$O$_2$-mediated cell death$^{[23,33]}$. Intracellularly produced reactive oxygen species by human neutrophils would accelerate neutrophilic apoptosis$^{[34]}$. Therefore, it is likely that pyruvate as a scavenger of both exogenous and endogenous H$_2$O$_2$ would protect neutrophils against oxidative stress-induced apoptosis. In this regard, pyruvate also acts as an antioxidant. As to macrophages and HPMC, the potent effect of pyruvate may additionally be relevant to the protection against oxidative injury to DNA posed by H$_2$O$_2$. Regularly, mitochondrial DNA does not undergo fragmentation during apoptosis. The relative preservation of mitochondrial function might be associated with the copious amount of mitochondrial pyruvate. A recent study with U937 cells revealed that pyruvate 5 mmol·L$^{-1}$ in glucose 30 mmol·L$^{-1}$ could prevent cells exposed to H$_2$O$_2$ from apoptosis due to promoting the formation of intramitochondrial NADH$^{[35]}$. Moreover, it might be also possible that pyruvate suppresses AGEs formation and accumulation from high glucose in patient’s peritoneal cavity.

Nitric oxide (NO) that phagocytes produced with NADPH as a co-factor also plays an essential role in cell defense and apoptosis. Although NO is bifunctional regulator of apoptosis, evidence indicated that the simultaneous enhancement of intracellular O$_2^-$ and NO specifically by high D-glucose in endothelial cells rapidly activated the transcription factor, nuclear factor-kappa B (NF-κ B), by the formation of peroxynitrite, leading to the induction of apoptosis$^{[36]}$. The NF-κ B activation may be a critical regulator of human granulocyte apoptosis. Significantly, the NF-κ B activation by high glucose could be prevented by antioxidants, including pyruvate, vitamin E, and inhibitors of NO synthase.

According to findings above, it is reasonable to speculate that pyruvate in P-PDS would be able to protect peritoneal phagocytes in high glucose against apoptosis both in vitro and in vivo. The superior biocompatibility of P-PDS and pyruvate protection of cells are certain, but the correction of abnormal metabolisms and transduction signalings by pyruvate has to be verified with P-PDS in peritoneal cells. Pyruvate is a normal intermittent of glucose metabolism, and able to freely diffuse among intercellular, intracellular, and mitochondrial compartments. An intravenous pyruvate loading test in human subjects demonstrated its safety in the clinical applicability.

CONCLUSION

Intracellular acidification of leukocytes induced by the high acidity of L-PDS is a primary detrimental effect in the bioincompatibility of PDS. High lactate and glucose excess including GDP and AGE play individually a pivotal role as well. Various combinations among them would contribute to more cytotoxic effects on host defense cells.

Pyruvate replacement of lactate in PDS preserves efficiently multiple cellular functions, almost completely overcoming harmful effects offered by lactate. Although the underlying mechanisms whereby pyruvate protects cells are not fully elucidated, the fundamental effect of pyruvate protection in P-PDS may be associated with the maintenance of a near physiologic [pH], due to its lower buffering capacity, the activities of key glycolytic enzymes remaining subsequently. In addition, studies in areas other than PDS have shown that pyruvate may improve glucose metabolic pathways and preserve cellular redox state in high glucose conditions, sustain [Ca$^{2+}$], homeostasis and protect cells against apoptosis as a potent non-enzymatic scavenger of H$_2$O$_2$. Before clinic trials, further extensive investigations are strongly needed with P-PDS both in vitro and in vivo, particularly on the interaction with cytosolic redox state among pyruvate, O$_2^-$, and NO in peritoneal phagocytes and HPMC. Pyruvate is a potent and attractive candidate as a dialyse buffer. The future of PDS will lie in combinations and additives, but P-PDS could be an entire substitute for conventional L-PDS. The observation on the cell protection of pyruvate in PDS may benefit not only in CAPD, but also in the treatment of diabetes, cardiovascular diseases, and transplantation and their complications.

REFERENCES
-morphonuclear leukocyte respiratory burst activation is related to the lowering of intracellular pH. Nephron 1993; 65: 260 – 5.


6 Zhou FQ, Zhou XJ, Yu AW, Song RH. Neutrophil trans


10 Yu AW, Olabi AZ, Gupta DK, Zhou FQ, Gandhi VC, Ing TS. Effects of euhydric peritoneal dialysis solutions containing a mixture of bicarbonate and lactate or lactate alone on neutrophil superoxide production. ASAJO J 1994; M900 – M901.


20 Mahiout A, Brunckhorst R. Pyruvate anions neutralize per


27 Anderson R, Van Rensburg CE, Joone G, Lessing A. Au-


30 Kushwagi A, Nishio Y, Asahina T, Ikubuchi M, Harada N,


35 Sestili P, Brumelli L, Cantoni O. Rotenone and pyruvate prevent the tert-butylhydroperoxide-induced necrosis of U937 cells and allow them to proliferate. FEBS Lett 1999; 457; 139–43.


丙酮酸盐在腹膜透析液中优于乳酸盐

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主题词：乳酸盐类；丙酮酸盐类；透析液；酸中毒；超氧化物；中性白细胞；细胞凋亡；葡萄糖；氧化还原；NF-κB

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