

REGULAR REVIEW

HARTMANN'S SOLUTION IN HAEMORRHAGIC SHOCK – NOW AND THE FUTURE

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The controversy of which fluid to use for empirical resuscitation of acute haemorrhage is long-standing and ongoing despite several large-scale studies (1-4), and has many facets: crystalloid vs. crystalloid, colloid vs. colloid and colloid vs. crystalloid. Both crystalloid and colloid may be hypertonic, hypotonic or isotonic fluids and each of these fluids have had their benefits and limitations described.

This article reviews the evidence for using Hartmann's solution - alternatively known as Ringer's Lactate (RL) in the United States of America - in the resuscitation of trauma. Recent developments in using an alternative base donor to lactate in these solutions and their potentially beneficial effect on the inflammatory response are also examined.

Background

Sydney Ringer was a British physiologist born in Norwich in 1835 who studied the action of contractile muscle using isolated frog heart preparations (5). His initial experiments perfused the hearts with 0.75% saline and Ringer was surprised to see the maintenance of cardiac contractility with saline alone.

The addition of potassium salt modified the ventricular trace. Ringer's solution was then derived serendipitously - his further experiments using saline derived from distilled water did not reproduce his earlier findings and he proceeded to analyse the original water, which he discovered had been provided by the New River Water Company and contained minute traces of calcium. Thus the foundation of Ringer's solution, saline with potassium and calcium were laid.

The solution was further modified in the early 20th century by Alexis Hartmann, a German born physician with an interest in paediatrics, with the intention of treating acidosis in children (6). Hartmann added lactate, which when metabolised predominantly by liver, muscle and kidney consumed hydrogen ions and produced glucose, water and carbon dioxide, hence acting as a base. This modification allowed the solution to become known as Lactated Ringer's Solution or, later, Hartmann's Solution. The constitution of currently commercially available Ringer's lactate is shown in Table 1.

A 70kg human contains about 45 litres of water distributed through the intracellular and extracellular spaces in a ratio of approximately 2:1 and this is maintained by a wide variety of homeostatic mechanisms, reduction in renal sodium ion excretion (and therefore retention of free water) in response to a fall in central venous volume or renal perfusion is particularly important (7). Intravenously administered fluid is redistributed across three compartments: intravascular, extracellular and intracellular, with extracellular fluid (ECF) volume being maintained by the presence of sodium ions. The fluid's eventual fate is largely dependent on its osmolality; ECF has an osmolality between 280-290 mOsmol/l and Ringer's lactate with an osmolality of 280 mOsmol/l is therefore isotonic. Due to the relative volumes of the intravascular and extracellular fluid, after homeostatic mechanisms have caused redistribution of fluids, only 1/6th of the Ringer's solution will remain in the intravascular space i.e. for every six litres replaced, one litre will remain within the blood vessels. This is mainly due to the

Table 1. Ionic contents of Various Solutions

Ionic contents Crystalloid Fluids mmol/l								
Solution	Na	Cl	K	Ca	Mg	Lactate	Acetate	Gluconate
0.9% Saline	150	150	-	-	-	-	-	-
Ringer's Solution	144	152	4	2	-	-	-	-
Lactated Ringers Solution	129	109	5	2.5	-	29	-	-
Plasma-Lyte A	140	98	5	-	1.5	-	27	23
Plasma-Lyte R	140	103	10	5	3	47	8	-

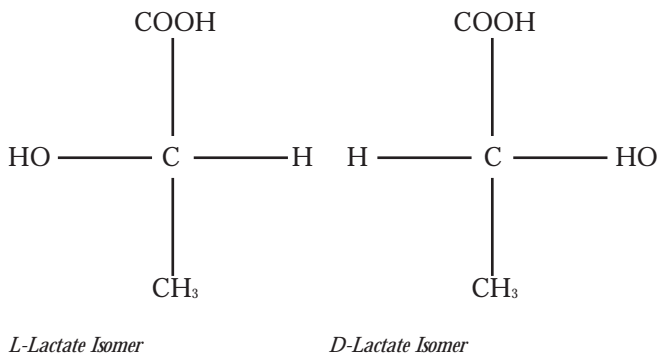
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redistribution of sodium ions across all three compartments; sodium ions cross readily between the intravascular and the extracellular fluid, but require active transport to enter the intracellular compartment. This ionic movement causes osmotic gradients across which water is forced to move.

Lactate Metabolism

Lactate, or 2-hydroxypropionate was first isolated from cows milk by Scheele in 1780 (8); It is the simplest producible hydroxycarboxylic acid and exists in 2 stereo isomeric forms, L and D-lactate (Figure 1), each thought to have differing immunological responses in vivo.

Figure 1. The L- and D- isomers of lactate



Lactate is a by-product of human anaerobic metabolism. When oxygen perfusion of tissues falls, glucose is metabolised anaerobically to form ATP and lactate; when oxygen reserves become plentiful, the lactate is then transported back to the liver where it is converted back via the intermediary pyruvate to glucose - the Cori cycle (9-11). L-lactate is rapidly metabolised back into pyruvate by the enzyme L-lactate dehydrogenase, whilst D-lactate is metabolised back at one-fifth of the rate by D- α -hydroxyacid dehydrogenase.

Controversy exists as to whether administered D-Lactate in commercial solutions is metabolised less efficiently than L-lactate, therefore, leading to an accumulation in the body (12). Lactate has a pK of 3.86; therefore at physiological pH it dissociates freely yielding a lactic ion:lactic acid ratio of 3000:1.

The normal serum levels of lactate are between 1-2 mmol/L and are considered to be entirely of the L-Lactate isomer, as the majority of mammalian cells produce this form alone. The only exception is the nanomolar concentrations of the D-Lactate isomer formed via the methylglyoxal pathway (13), D-lactate excretion is highest in the first year of life and decreases by the age of four (14).

Hartmann's Solution in Haemorrhage

ATLS (15) guidelines have resulted in an abundance of clinical data available for the usage of Ringer's lactate solution in the resuscitation of haemorrhage (1-4). It is recommended as a first line resuscitative fluid, with normal saline being used as an alternative in its absence. Due to these endorsements, Ringer's Lactate solution is the 'gold standard' to which other fluids are compared, which makes it difficult to evaluate the recent experimental data. In addition, many recent trials have examined the potential utilisation of hypotensive resuscitation, and in analysing this data, separation of the effect of the resuscitation strategy from the fluid is difficult.

Numerous studies have been undertaken by the American Armed Forces, concentrating on comparing Ringer's solution to Hypertonic Saline/Dextran. It has been demonstrated that hypertonic saline/dextran restores circulatory volume by

mobilising fluid in the extravascular compartment, which in turn increases venous return and subsequently, according to Starling's law, cardiac output.

Schierhout and Roberts (2) undertook a systematic review of 37 randomised clinical trials (of which 26 compared crystalloid to colloid) to determine the effect of resuscitation with colloid solutions compared to resuscitation with crystalloids. The trials covered a spectrum of critically ill patients ranging from major burns, those undergoing surgery or with other critically ill conditions such as sepsis. The principal outcome measure was mortality from all causes assessed at the end of each follow up period scheduled for each trial. Of the 26 trials that compared colloid vs. crystalloid resuscitation, 13 identified RL as the crystalloid employed. The results did not demonstrate a significant difference in the relative risks for all types of injury between colloids and crystalloids; however, there was an absolute risk of mortality of 4% (0-8%) associated with colloid resuscitation using the pooled relative risk.

Healey et al (16) acknowledged that there was literature available comparing Ringer's lactate to other crystalloids in the management of mild or moderate haemorrhage. However, there was no evidence of studies that compared Ringer's lactate (RL) and normal saline (NS) for the situation of massive haemorrhage and resuscitation. In order to evaluate the potential benefits, four experimental groups were established using a rat model. The first two groups underwent moderate haemorrhage attaining a mean arterial pressure (MAP) of 60mmHg for a two-hour period, and then were subjected to crystalloid resuscitation using either NS or RL for one hour. The second two groups were bled at a rate of one blood volume per hour for 2 hours. However, they were simultaneously resuscitated with blood cells and NS or RL. In the moderate haemorrhage group, there was no significant difference between resuscitation with either fluid. The animals that underwent resuscitation for massive haemorrhage with NS however demonstrated a 50% mortality compared to the RL group which had a 100% survival. Animals resuscitated with NS also had significantly worse acidosis (pH 7.14 +/- 0.06 v 7.39 +/- 0.04). The author's concluded that RL is superior to NS in the resuscitation of massive haemorrhage due to significantly less metabolic derangement and a lower mortality rate.

Traverso et al (17) reported a study in which 116 anaesthetised swine were subjected to a rapid haemorrhage of 54ml/kg over 15 minutes through an aortic sideport to simulate human exsanguination and resuscitated with one of four crystalloids: normal saline, Ringer's lactate, Plasmalyte-A (PA) and Plasmalyte-R (PR). After biochemical analysis and metabolic measurements, it was concluded that RL was the superior solution due to its decreased mortality (67% survival rate compared to NS (50%), PA (40%) and PR (30%)), decreased chloride load (present in NS) and the absence of magnesium and acetate (present in PA and PR).

In a study to determine the cardiac, haemodynamic and metabolic effects of blood, plasma, saline and RL in the resuscitation of haemorrhagic shock, 30 non-splenectomised dogs were subjected to two hours of haemorrhagic shock, and then resuscitated with either shed blood alone, or a combination with plasma, saline solution or Ringer's lactate solution (18). The results were divided into initial resuscitation and late resuscitation (i.e. 180-200 minutes). All regimens demonstrated equal effectiveness in the early phase of resuscitation, with comparable correction of metabolic acidosis and decreased lactate production. During late resuscitation, however, there was a demonstrable significant decrease in myocardial and cardiac haemodynamic efficiency in the shed blood, plasma and saline solution groups. It was therefore concluded that Ringer's lactate solution was singularly effective in maintaining left ventricular

performance.

Cervera and Noss (19) compared post resuscitation arterial pH in splenectomised dogs who were subjected to continuous haemorrhage and simultaneous replacement with either Normal saline or Ringer's lactate solution. There was no significant difference between the arterial pH of controls compared to Ringer's lactate or Normal saline solution. It is suggested that due to the presence of sodium citrate in banked blood, it may be beneficial to preferentially use Normal saline than Ringer's lactate solution in massive transfusions to help prevent metabolic alkalosis.

Using another canine model of haemorrhage/resuscitation, Strodel et al (20) used whole blood, 5% albumin in RL and RL alone. In all groups pH and blood pressure approached but did not completely return to baseline levels. 5% albumin in RL and RL resuscitation demonstrated a statistically greater cardiac output compared to the group resuscitated with blood. In an attempt to identify whether the prehaemorrhage level of hydration influenced the effects of resuscitation, McKirnan et al (21) used animal models subjected to 48 hours of dehydration prior to controlled haemorrhage to simulate the likely dehydrated state of the soldier injured on the battlefield. Haemorrhagic shock was induced by removing 5ml/kg aliquots of blood via an arterial catheter at 9, 19, 31.5, 41 and 60 minutes (22). This combined 60 minute haemorrhage volume of 25ml/kg corresponded to 37% of a hydrated pig's blood volume, and the subjects divided into four groups: those resuscitated with RL, those resuscitated with hypertonic saline/dextran, non-resuscitated dehydrated controls and non-resuscitated euhydrated controls. All animals were subjected to Letterman Army Institute Haemorrhage protocol (22). This study used a resuscitation volume of 33.3ml/kg compared to 80ml/kg used in similar experiments by Bickell et al (23) previously, thereby allowing for some degree of hypotensive resuscitation. Both lactated Ringer's and hypertonic saline/dextran solution restored MAP to control levels within five minutes. However both groups suffered a drop in MAP by thirty minutes and subsequent restoration of pressure was only statistically significant in animals that received the lactated Ringer's. Overall, both resuscitative agents were comparable in effectiveness as resuscitative agents.

Acetate containing solutions are known to cause vasodilation (25) and a further US Military study compared the effects of hypertonic sodium acetate-dextran solution, hypertonic saline and RL, on gut perfusion (24). The model was a hybrid controlled/uncontrolled haemorrhage with a controlled bleed to a MAP of 30mmHg followed by creation of a free intraperitoneal haemorrhage from a 4mm aortotomy. Resuscitation with hypertonic saline acetate-dextran decreased survival without a significant difference in MAPs achieved. The volume of fluid required to maintain the target MAP was considerably higher in animals that underwent lactated Ringer's solution resuscitation however.

Resuscitation Fluids and Inflammation

It is apparent from numerous animal and human studies that different resuscitation fluids have different effects on the immune stimulation that occurs following trauma (26). Standard RL appears to have a proinflammatory effect, but this may be ameliorated by modification of its composition.

A study carried out by Koustova et al (13) compared the immunological effects of standard lactated Ringer's solution (a racemic mixture of D- and L-Lactate isomers) with pure L-Lactate Ringer's solution. Incubation of human leucocytes with the racemic mixture created a significant production of reactive oxygen species whilst the pure L-lactate Ringer's did not induce neutrophil activation. The study also demonstrated that TNF- α

expression was increased by two and a half times with the racemic solution suggesting that D-Lactate both interferes with and activates the immune system more readily than L-Lactate in Ringer's solution.

As well activating immunomodulating cytokines, lactated Ringer's has also been implicated in direct neutrophil activation. Rhee et al (27) reported a study in which they analysed neutrophil activation from lactated Ringer's in the presence and absence of haemorrhage. Four groups of domestic swine were used. Group 1 animals underwent a 40% controlled haemorrhage and were resuscitated with RL over an hour. Groups 2 and 3 underwent haemorrhage then resuscitation either with citrated dextrose or hypertonic saline. The final group underwent sham haemorrhage but were still subjected to the same amount of RL as Group 1. Blood samples from set time points in the resuscitation were then analysed to detect oxidative burst activity. Interestingly the data suggest that the period of resuscitation might be more harmful than the ischaemic or haemorrhagic periods. It was suspected that resuscitation would activate neutrophils due to reperfusion, however, neutrophil activation occurred only once the animals were resuscitated with RL. The authors have suggested that Lactated Ringer's may be a contributing factor to a multifactorial cause of inflammation, as a large number of individuals are resuscitated worldwide with this fluid without experiencing any ill effects.

Deb et al demonstrated that both hetastarch and RL result in increased cell apoptosis via Bax protein (29), and that resuscitation with RL increases immediate apoptosis during haemorrhagic shock fluid resuscitation (30). In a second study from Deb and colleagues at the Walter Reed Institute, rats were subjected to a controlled 40% haemorrhage followed by resuscitation by three times the volume of shed blood with a variety of resuscitation fluids. Resuscitation lasted for 1 hour followed by humane euthanasia followed by removal of the liver and small intestine for analysis. Lactated Ringer's resuscitation generated a marked and immediate increase in apoptosis compared to non-resuscitated rats, and rats resuscitated with either hypertonic saline or whole blood. There are occasional studies however that suggest that there is no upregulation of the immune response to trauma after RL resuscitation (28).

Substituted Ringer's Solutions

Ringer's solution has been modified by the replacement of the lactate with other compounds such as ketones, acetate and pyruvate in an attempt to ameliorate the immunostimulatory effects of lactated RL after trauma. Acetated Ringer's solution is relatively hypotonic (Osmolality = 270 mOsmol/l). Hahn and Drobin (31) believed that this hypo-osmolality would cause a fluid shift into the extracellular space. Ringer's acetate was infused into five healthy female volunteers (25ml/kg over 80 minutes). Urinary sodium excretion was only half of the total infused sodium load whilst there was only a slight increase in the serum sodium concentration; mass balance calculations indicated that 274 ml of water had shifted from the intracellular to the extracellular space. This fluid shift was maintained for the duration of the experiment. It was concluded that infusion with Ringer's acetate caused the kidney to promote cellular dehydration by rapid excretion of water. In the volunteers, the fluid shift contributed to 18% of the infused volume and was maintained for 2 hours. Alam et al (32) hypothesised that replacing the lactate with a potential energy substrate such as ketones would be protective against lung injury caused by lactated Ringer's. The study did successfully demonstrate that there was less expression of cellular injury markers in the ketone group compared to the lactate group.

A benefit of ketones is that they provide an energy substrate, which is actively utilised in the presence of systemic stress. It

has been described by Nakatani (33) that acetate can be metabolised by the liver and peripheral tissues to yield bicarbonate to be used as an alkalisng agent. Also Nakatani et al (34) demonstrated that ketogenesis is enhanced in the kidney and may account for hepatic loss of ketogenic function during hepatic inflow occlusion under Ringer's acetate solution administration. However, in the absence of hepatic inflow occlusion, but in the presence of hepatic dysfunction, Isosu et al (35) demonstrated no significant difference between Ringer's acetate and Ringer's lactate solution.

However, it is not always beneficial to have ketones as an energy substrate. Ikeya et al (36) undertook a study to demonstrate the difference between Ringer's lactate and Ringer's acetate solution on hepatic ATP levels and pH/base excess levels in rats subjected to acute haemorrhage. They demonstrated that glycogen levels in rats that were infused with Ringer's lactate were increased compared with the Ringer's acetate group. However, there was no significant difference between the pH and base excess of these two groups; however, it was significantly higher than the control group.

Similar to RL, Ringer's acetate solution is also pro-inflammatory, but compared to the L- and D- isomers of Ringer's lactate, the pharmacokinetics of the acetate enable it to be metabolised quicker(37), potentially limiting its inflammatory action. However, Ishizaka et al (38) demonstrated that post infusion of 500ml of Ringer's acetate solution; test individuals elicited an increase in polyclonal antibodies from peripheral lymphocytes, an increase in mixed lymphocyte reaction and Natural Killer cells. This response was absent in individuals who were infused with Ringer's Lactate solution, perhaps suggesting a different mechanism between the acetate and lactate varieties. A further variant of Ringer's solution contains pyruvate in place of lactate, although the relative instability of pyruvate Ringer's has led to a greater use of a more stable derivative ethyl pyruvate Ringer's (39). Reactive oxygen species are partially reduced derivatives of the oxygen molecule and the important ones in biological systems include the superoxide ion, hydrogen peroxide, hydroxyl radical and peroxynitrate (40). Reactive oxygen species are heavily implicated in the pathogenesis of ischaemia-reperfusion injury that follows haemorrhagic shock. Ringer's ethyl pyruvate can scavenge reactive oxygen species (41, 42), and decrease inflammatory effects. Compared to Ringer's lactate solution, it has clinically been demonstrated to lower circulating levels of nitrites/nitrates and the pro-inflammatory cytokine Interleukin(IL)-6, as well as increasing levels of anti-inflammatory cytokine IL-10. Although based on a rat model of endotoxic shock, these data do suggest a beneficial effect in situations where free radical scavenging would be likely to be of benefit such as resuscitation of haemorrhagic shock after trauma. A randomised trial using rats subjected to 60 minutes of gut ischaemia followed by fluid resuscitation with lactated, pyruvated or ethyl pyruvated Ringers solution (ie an ischaemia reperfusion injury) (43). The results demonstrated that, compared with controls, treatment of the rats with either pyruvate solution or ethyl pyruvate solution significantly ameliorated the development of intestinal mucosal hyperpermeability during reperfusion and also the extent of histological mucosal damage after mesenteric reperfusion.

Conclusion

It is difficult to objectively to assess the benefits of Ringer's solution as it is primarily used as the control arm 'gold standard' against which other fluids are compared, usually with the point of demonstrating the superiority of the test fluid rather than RL. It remains however the most widely used resuscitative fluid throughout the world. There still remains a significant volume

of work to be performed however to identify the precise composition of the Ringer's solution that will best treat the immune consequences of ischaemia-reperfusion after resuscitation of traumatic haemorrhagic shock. It is clear that the two isomeric versions of lactate contribute differing effects to the standard racemic mixture of lactated Ringers solution and separation of these isomers may produce benefits. Acetated Ringers has an additional energy source to be utilised by the stress response but unfortunately still elicits a pro-inflammatory effect. There is only limited data on the effects of ethyl pyruvate Ringer's but it does appear to exert a beneficial effect by its free radical scavenging capabilities. As research continues into these novel modifications of a tried and tested resuscitation fluid, it is likely that greater benefits in resuscitation of trauma will accrue.

References:

1. Poole GV, Meredith JW, Pennell T et al. Comparison of colloids and crystalloids in resuscitation from haemorrhagic shock. *Surg Gynaecol Obstet* 1982;**154**:577-586.
2. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: A systematic review of randomised trials. *Br J Med* 1998;**316**:961-964.
3. Velanovich V. Crystalloid versus colloid fluid resuscitation: A meta-analysis of mortality. *Surg* 1990; **105**:65-71.
4. Virgilio RW, Rice CL, Smith DE et al, Crystalloid versus colloid resuscitation: Is one better? A randomised clinical study. *Surg* 1979;**85**(2):129-139.
5. Ringer, S. Regarding the action of hydrate of soda, hydrate of ammonia, and hydrate of potash on the ventricle of the frog's heart. *J Physiol* 1880;**3**:195-202.
6. Hartmann AF, Senn MJE. Studies in the metabolism of sodium r-lactate. II. Response of human subjects with acidosis to the intravenous injection of sodium r-lactate. *J Clin Investig* 1932;**11**(2):337-344.
7. Anderson ID. *Care of the Critically Ill Surgical Patient*. 2nd ed. 2003, London: Arnold. p126.
8. Ewaschuk JB, Naylor JM, Zello GA. D-Lactate in human and ruminant metabolism. *J Nutr* 2005;**135**:1619-1625.
9. Salway JG. *Metabolism at a Glance*. 1st ed. 1994, Oxford: Blackwell Science Ltd: pp24-25.
10. Salway JG. *Metabolism at a Glance*. 1st ed. 1994, Oxford: Blackwell Sciences Ltd: pp66-67.
11. Stryer L. *Biochemistry*. 4th ed. 1995, New York: W H Freeman and Company: pp576-577.
12. Fine A. Metabolism of D-Lactate in the dog and man. *Perit Dial Int* 1988;**9**:99-101.
13. Koustova E, Stanton K, Gushchin V, Alam HB, Stegalkina S, Rhee PM. Effects of lactated Ringer's solutions on human leucocytes. *J Trauma* 2002; **52**:872-878.
14. Haschke-Becher E, Baumgartner M, Bachmann C. Assay of D-Lactate in urine of infants and children with references values taking into account data below collection limit. *Clin Chem* 2000;**298**:98-100.
15. Committee on Trauma, American College of Surgeons, *Advanced Trauma Life Support for Doctors Student Course Manual*. 7th ed. 2004, Chicago: American College of Surgeons;77.
16. Healey MA, Davis RE, Liu FC, Loomis WH, Hoyt DB. Lactated Ringer's is superior to normal saline in a model of massive haemorrhage and resuscitation. *J Trauma* 1998;**45**(5):894-899.
17. Traverso LW, Lee WP, Langford MJ. Fluid resuscitation after an otherwise fatal hemorrhage: I. Crystalloid solutions. *J Trauma* 1986;**26**(2):168-175.
18. Horton J, Landreneau R, Tuggle D. Cardiac response to fluid resuscitation from haemorrhagic shock. *Surg Gynecol Obstet* 1985;**160**(5):444-452.
19. Cervera AL, Noss G. Dilutional re-expansion with crystalloid after massive haemorrhage: saline versus balanced electrolyte solution for maintenance of normal blood volume and arterial pH. *J Trauma* 1975;**15**(6):498-503.
20. Strodel WE, Callahan M, Weintraub WH, Coran AG. The effects of various resuscitative regimens on haemorrhagic shock in puppies. *J Paediatr Surg* 1977;**12**(6):809-819.
21. McKirnan MD, Williams RL, Limjoco U, Ragland J, Gray CG. Hypertonic saline/dextran versus lactated Ringer's treatment for haemorrhage in dehydrated swine. *Circ Shock* 1994;**44**:238-246.
22. Barrientos T, Hillman N, People JB. The effects of dehydration on the dynamics of transcapillary refill. *Am J Surg* 1982;**48**:412-416.
23. Bickell WH, Brutting SP, Millnamow GA, Benar J, Wade CE. Use of

- hypertonic saline/dextran versus lactated ringer's solution as a resuscitation fluid after uncontrolled aortic haemorrhage in anaesthetized swine. *Ann Emerg Med* 1992;**21**:1077-1085.
24. Burnier P, Tappy L, Jequier E et al. Metabolic and physiological effects of infused sodium acetate in healthy human subjects. *J Physiol* 1992;**263**:1271-1276.
 25. Doucet JJ, Hall IR. Limited resuscitation with hypertonic saline, hypertonic sodium acetate, and lactated ringer's solution in a model of uncontrolled haemorrhage from a vascular injury. *J Trauma* 1999;**47**(5):956-963.
 26. Sun L, Ruff B, Austin S et al. Early upregulation of ICAM-1 and VCAM-1 expression in rats with haemorrhagic shock and resuscitation. *Shock* 1999; **11**: 416-22
 27. Rhee P, Burris D, Kaufmann C et al. Lactated ringer's solution resuscitation causes neutrophil activation after haemorrhagic shock. *J Trauma* 1998;**44**:313-319.
 28. Brant K, Caragnano C, Carpenter J. Effect of resuscitation with hydroxyethyl starch and lactated ringer's on macrophage activity after haemorrhagic shock and sepsis. *Shock* 1994;**2**:141-144.
 29. Deb S, Sun L, Martin B et al. Lactated ringer's solution and hetastarch but not plasma resuscitation after rat haemorrhagic shock is associated with immediate lung apoptosis by the up-regulation of the Bax protein. *J Trauma* 2000;**49**:47-55.
 30. Deb S, Martin B, Sun L et al. Resuscitation with lactated ringer's solution in rats with haemorrhagic shock induces immediate apoptosis. *J Trauma* 1999;**46**:582-589.
 31. Hahn RG, Drobin D. Rapid water and slow sodium excretion of acetated Ringer's solution dehydrates cells. *Anaesth Analg* 2003;**97**(6):1590-1594.
 32. Alam HB, Austin B, Koustova E, Rhee P. Resuscitation-induced pulmonary apoptosis and intracellular adhesion molecule-1 expression in rats are attenuated by the use of ketone ringer's solution. *J Am Coll Surg* 2001; **193**(3):255-263.
 33. Nakatani T. Overview of the effects of Ringer's acetate solution and a new concept: renal ketogenesis during hepatic inflow occlusion. *Methods Find Exp Clin Pharmacol* 2001;**23**(9):519-528.
 34. Nakatani T, Sakamoto Y, Ando H, Kobayashi K. Enhanced ketogenesis in the kidney during hepatic inflow occlusion with the administration of Ringer's acetate solution. *Surg* 1996;**119**(6):684-689.
 35. Isosu T, Akama Y, Tase C, Fujii M, Okuaki A. Clinical examination of acetated Ringer's solution in patients with normal liver function and those with liver dysfunction. *Masui* 1992;**41**(11):1707-1713.
 36. Ikeya K, Kashimoto S, Kume M, Kumazawa T. Effects of lactated Ringer solution and acetated Ringer solution on hepatic ATP and L/P ratio in rats subjected to acute haemorrhage. *Masui* 1998;**47**(1):36-41.
 37. Hamada T, Yamamoto M, Nakamaru K, Iwaki K, Ito Y, Koizumi T. The pharmacokinetics of D-Lactate, L-Lactate and acetate in humans. *Masui* 1997;**46**(2):229-236.
 38. Ishizaka S, Kikuchi E, Tsujii T. Effects of acetate on the human immune system. *Immunopharmacol Immunotoxicol* 1993;**15**(2-3):151-162.
 39. Yang R, Gallo DJ, Baust JJ et al. Ethyl pyruvate modulates inflammatory gene expression in mice subjected to haemorrhagic shock. *Am J Physiol Gastrointest Liver Physiol* 2002;**283**(1):G212-221.
 40. Fink MP. Reactive oxygen species as mediators of organ dysfunction caused by sepsis, acute respiratory distress syndrome, or hemorrhagic shock: potential benefits of resuscitation with Ringer's ethyl pyruvate solution. *Curr Opin Clin Nutr Metab Care* 2002;**5**(2):167-174.
 41. Venkataraman R, Kellum JA, Song M, Fink MP. Resuscitation with Ringer's ethyl pyruvate solution prolongs survival and modulates plasma cytokine and nitrite/nitrate concentrations in a rat model of lipopolysaccharide induced shock. *Shock* 2002;**18**(6):507-512.
 42. Fink MP. Ringer's ethyl pyruvate solution: a novel resuscitation fluid. *Minerva Anesthesiol* 2001;**67**(4):190-192.
 43. Sims CA, Wattanasirichaigoon S, Menconi MJ, Ajami M, Fink MP. Ringer's ethyl pyruvate solution ameliorates ischemia/reperfusion induced intestinal mucosal injury in rats. *Crit Care Med* 2001;**29**(8):1513-1518.



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