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ORIGINAL RESEARCH

Use of small volume hypertonic acetate dextran during aortic occlusion in pigs: assessment of blood flow and antioxidant status in tissues

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BACKGROUND: Hypertonic/hyperoncotic fluids may reduce overall fluid requirements and tissue edema, improve perfusion and reduce the incidence of paraplegia associated with aortic cross-clamping and subsequent reperfusion.

OBJECTIVE: We evaluated potential benefits of a hypertonic saline acetate solution on reperfusion injury following ischemia. We examined blood flow and plasma antioxidant status, spinal cord and skeletal muscle above and below the cross-clamp, as well as in the liver and the kidney.

METHOD: The aorta of anesthetized swine (n=5-6/group) was cross-clamped at the level of T9 for 30 min; animals were infused with 4 ml/kg of hypertonic acetate dextran (HAD) or 8.4% $NaHCO_3$ (Control). Pigs were euthanatized 1h later.

RESULTS: As blood flow fell to zero in lower spinal cord and muscle, it doubled in the upper cord and increased 6-fold in upper muscle. Upon reperfusion, blood flow in all regions returned to baseline levels, with no statistical differences between HAD and Controls. Lipid peroxidation in plasma was lower in HAD than Controls. Lower muscle had 41% lower glutathione levels and significantly lower activities of the antioxidant enzymes glutathione peroxidase and reductase, catalase, superoxide dismutase versus upper muscle. The lower spinal cord had 2.5 fold higher malondialdehyde levels and 50% higher catalase activity than upper spinal cord. Within a tissue, any significant differences in antioxidant status or evidence of lipid peroxidation favored HAD over Control.

CONCLUSION: HAD offered only minor advantages over $NaHCO_3$ with respect to blood flow and antioxidant status of spinal cord and muscle following this period of aortic cross-clamping and reperfusion.

KEYWORDS: ischemia/reperfusion; hypertonic saline; blood flow; oxidant stress; swine.

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INTRODUCTION

Traumatic injury resulting in exsanguinating shock has led to aortic crossclamping as a heroic measure until hemorrhage control and resuscitation can be performed.[1-3] It has even been applied in wartime environments.[4] Most recently, other techniques such as aortic balloon occlusion and an abdominal aortic tourniquet have been used.[5,6] In the past, crossclamping of the aorta was common practice as part of surgical repair for aneurysmal disease.[7] Despite the technique, reperfusion following aortic ischemia can result in hemodynamic instability and neurologic deficits.[8]

Recent studies have explored the use of hypertonic saline dextran solutions for maintaining hemodynamics and reducing fluid requirements during surgical repair of abdominal aortic aneurysms.[9,10] A hypertonic sodium acetate dextran (HAD) solution has been introduced as having similar volume expanding and hemodynamic effects as hypertonic saline dextran (HSD), but having buffering capacity to prevent the hyperchloremic acidosis sometimes seen with HSD.[11-13] However, HAD has not been explored for possible benefit in surgical or trauma scenarios where aortic crossclamping may be applied.

The literature presents much evidence that reactive oxygen species (ROS) are generated in response to ischemia and subsequent reperfusion (reoxygenation).[14-17] Major organs, including the liver, kidney, brain, heart and intestine, are susceptible to ischemic injury that may result from surgical ischemia encountered during certain procedures.[14,17,18] The present study addressed whether 30 min of aortic crossclamping resulted in evidence of ROS generation in certain tissues, including spinal cord, that could help explain the complications associated with aortic

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repair following traumatic injury or in patients with aortic disease. In addition, we examined whether a hypertonic/hyperoncotic fluid could reduce volume requirements and improve organ blood flow better than standard sodium bicarbonate solution, and thereby reduce the risk of ischemia/reperfusion injury.

MATERIALS AND METHODS

Animal Preparation and Experimental Design

This study was approved by the University of Texas Medical Branch Animal Care and Use Committee where the animal studies were performed. Guidelines for the Care and Use of Experimental Animals, National Institutes of Health, were adhered to throughout this study. Immature female Yorkshire swine (27 ± 1 kg) were anesthetized with ketamine and atropine IM, followed by isoflurane as previously described[19] and surgically instrumented with arterial and venous catheters under aseptic conditions. The descending aorta was cross-clamped at the level of T9 for 30 min followed by a gradual declamping over 5 min. During this period animals were infused with either 4 ml/kg hypertonic acetate dextran – HAD (1.9% NaCl, 7.9% Na acetate and 6% Dextran-70; n = 5) or an 8.4% sodium bicarbonate solution as control (n = 6).

After declamping, all animals received lactated Ringer's and phenylephrine as needed to maintain left atrial pressures, as described.[19] Regional blood flow to the brain, upper and lower spinal cord, abdominal organs and muscle was estimated by injection of fluorescent microspheres using the reference aortic sampling method described by Prinzen and Bassingthwaighte.[20] Microspheres were injected before aortic crossclamping (baseline), at 5 min and 30 min during clamping and at 5, 30 and 60 min after release of the clamp. After this 60 min reperfusion period, animals were euthanatized using a veterinary euthanasia solution and tissues collected and frozen at −70ºC until assayed. Tissues were analyzed for antioxidant status within 3 months of collection.

Hemodynamic Measurements

Hemodynamic measurements were taken at baseline (time 0), during the 30 min aortic crossclamping period and at 15, 30 and 60 min after release of the clamp. Systolic and diastolic arterial pressures were measured above and below the clamp and pulmonary and left atrial pressures, as well as SvO_2 were measured continuously. Cardiac output was determined by thermodilution. The total volumes of fluid infused during the reperfusion period were recorded.

Biochemical Measurements

Selected tissues were assayed for antioxidant status. Spinal cord and skeletal muscle (deltoid and gastrocnemius) above and below the aortic clamp, as well as, liver and kidney were homogenized in 50 mM potassium phosphate buffer, pH 7.4. Malondialdehyde concentrations in plasma and tissues were determined as thiobarbituric acid reactive substances (TBARs) in the butanol phase using 1,1,3,3-tetraethoxypropane as standard, as described by the method of Naito et al.[21] Lipid peroxide concentrations in plasma were determined by a commercial kit (Cayman Chemical Co, Ann Arbor, MI). Antioxidant enzyme activities such as gluthathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), catalase and myeloperoxidase were determined as previously described.[22] Reduced glutathione (GSH) concentrations were determined enzymatically as described by Anderson et al.[23] Protein concentrations were determined by a commercial kit (BioRad Laboratories, Hercules, CA).

Statistical Analysis

Data are presented as mean ± SEM. The Wilcoxon 2-sample test was used to assess differences between groups regarding fluid requirements. Hemodynamic data were analyzed by ANOVA for 2-factor experiment with repeated measurements on time. Antioxidant status data were analyzed by non-paired t-test. A $p < 0.05$ was considered significant.

RESULTS

In this model, aortic crossclamping essentially eliminated blood flow to the lower spinal cord, gastrocnemius muscle, liver and kidney during the 30 min clamping period (Figs 1-3). Blood flows above the clamp in the upper spinal cord and deltoid muscle were equally maintained between the 2 groups during the 30 min clamp period (Figs 1 and 2). After release of the clamp, blood flows in the lower spinal cord, gastrocnemius and deltoid muscles, liver and kidney tended to return to pre-clamp levels. However, in the upper spinal cord after release of the clamp, blood flow over at

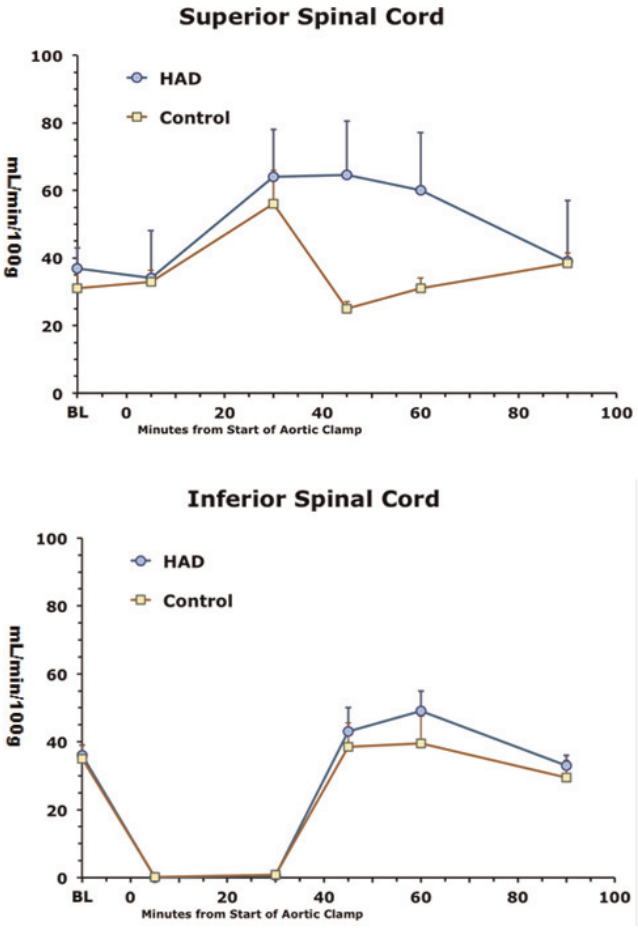

Figure 1 - Blood flows over time in spinal cord superior (top) and inferior (bottom) to the aortic clamping and HAD or bicarbonate infusion. Data expressed as mean ± SE of 5-6 animals per group.

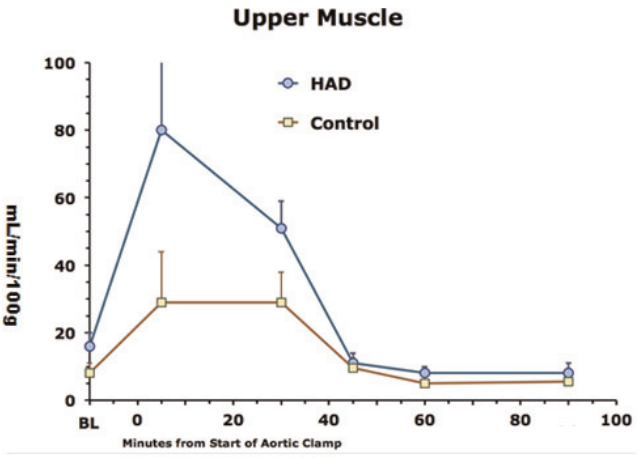

Figure 2 - Blood flows over time in upper muscle (deltoid) or lower muscle (gastrocnemius) relative to the location of the aortic clamp. Data expressed as mean ± SE of 5-6 animals per group.

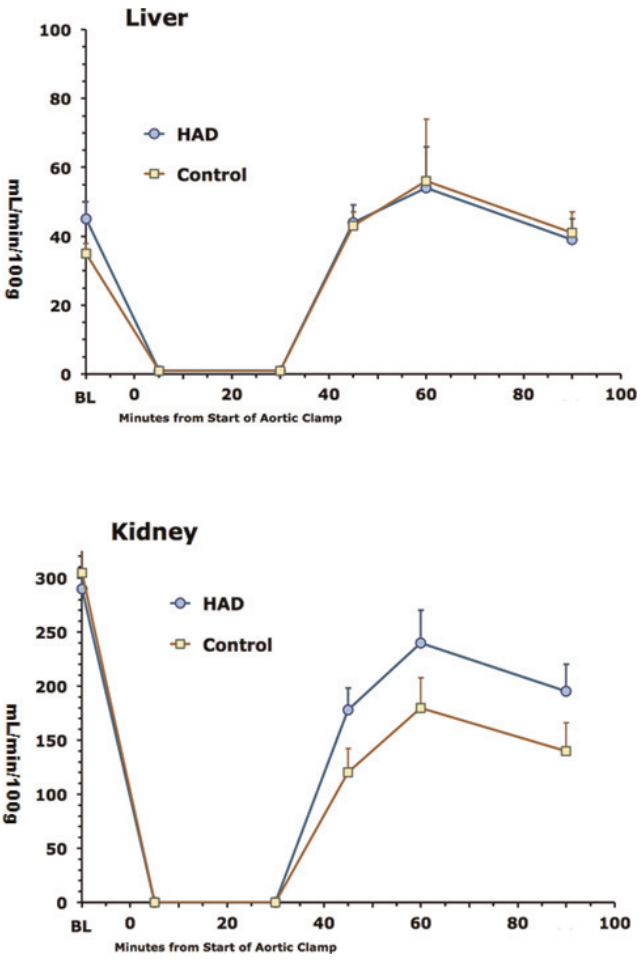

Figure 3 - Blood flows over time in liver (top) and kidney (bottom) in response to aortic clamping and release. Data expressed as mean ± SE of 5-6 animals per group.

least the first 30 min was better maintained in the HAD group than controls (Figs 1-3).

Early into the reperfusion period, cardiac index was higher in the HAD than control group (7.3 ± 0.3 vs 5.6 ± 0.2 ml/min/m^2). The HAD group also tended towards a lower net fluid accumulation than controls (39 ± 8 vs 59 ± 5 ml/kh); however, there were no statistically significant differences in total fluid needed to maintain filling pressures between the 2 groups (data not shown).

TBAR and lipid peroxide concentrations in plasma were significantly higher in the bicarbonate than HAD group at the end of ischemia and after 15 min of reperfusion (Table 1). Total antioxidant capacity of plasma increased after reperfusion in both groups ($p < 0.05$ compared with baseline), but there were no significant differences between the groups (Table 1).

Spinal cord inferior to the clamp had over 2 fold higher TBARS concentrations, over 70% higher GPx and over 50% higher catalase activities in comparison to spinal cord above the clamp (Table 2). Total antioxidant capacity was also about 30% higher in lower than upper spinal cord (Table 2). No statistically significant differences were observed in SOD

Table 1 - Indices of Oxidative Stress in Plasma at Times after Aortic Occlusion and Reperfusion[1]

		Baseline	RO	R15	R6O
TBARS[2]	Bicarb	2.8 ± 0.2	3.3 ± 0.3	2.6 ± 0.3	2.5 ± 0.3
(nmol/ml)	HAD[3]	2.1 ± 0.4	2.2 ± 0.3*	1.9 ± 0.2*	2.0 ± 0.2
Lipid Peroxide	Bicarb	22.7 ± 3.3	24.4 ± 2.8	17.1 ± 2.0	13.1 ± 1.9
(nmol/ml)	HAD	17.3 ± 3.7	14.4 ± 1.5*	11.7 ± 0.9*	11.7 ± 0.7
Antioxidant Capacity	Bicarb	285 ± 36	275 ± 35	390 ± 44	423 ± 60
(nmol/ml)	HAD	249 ± 16	264 ± 13	348 ± 25	426 ± 45

*$p < 0.05$ from bicarbonate group.
[1]Data expressed as mean ± S.E. for 5-6 animals/groups.
[2]Thiobarbituric acid reactive substances.
[3]hypertonic acetate dextran.

Table 2 - Indices of Oxidative Stress in Tissue after Aortic Occlusion and Reperfusion[1]

		Upper Spinal Cord	*Lower Spinal Cord*	*Deltoid*	*Gastrocnemius*	*Liver*	Kidney
TBAR[2]	*Bicarb*	*0.89 ± 0.11*	*2.39 ± 0.20*	*0.13 ± 0.02*	*0.14 ± 0.02*	*1.18 ± 0.18*	0.98 ± 0.09
(nmol/mg prot)	*HAD*[6]	*1.03 ± 0.12*	*2.19 ± 0.22*	*0.12 ± 0.01*	*0.09 ± 0.01*	*0.84 ± 0.07*	0.61 ± 0.07*
Glutathione Reductase	*Bicarb*	*0.59 ± 0.05*	*1.02 ± 0.12*	*0.93 ± 0.07*	*0.87 ± 0.01*	*13.3 ± 1.0*	3.7 ± 0.1
(U/mg prot)x10-2	*HAD*	*0.45 ± 0.05*	*0.80 ± 0.05**	*1.28 ± 0.15*	*0.82 ± 0.00*	*16.1 ± 0.7**	3.2 ± 0.3
Glutathione Reductase	*Bicarb*	*1.99 ± 0.06*	*2.26 ± 0.13*	*0.58 ± 0.07*	*0.38 ± 0.03*	*11.3 ± 0.5*	8.0 ± 0.6
(U/mg prot)x10-2^{-2}	*HAD*	*1.84 ± 0.05*	*2.32 ± 0.14*	*0.97 ± 0.04**	*0.39 ± 0.02*	*13.3 ± 0.9*	10.0 ± 0.9
Mn SOD[3]	*Bicarb*	*5.52 ± 0.31*	*5.03 ± 0.30*	*2.17 ± 0.37*	*1.05 ± 0.12*	*4.59 ± 0.39*	5.69 ± 0.50
(U/mg prot)	*HAD*	*4.68 ± 0.21*	*5.32 ± 0.37*	*2.74 ± 0.33*	*1.23 ± 0.12*	*5.61 ± 0.42*	5.99 ± 0.83
CuZn SOD[4]	*Bicarb*	*9.18 ± 0.56*	*10.1 ± 0.63*	*1.48 ± 0.28*	*1.02 ± 0.15*	*21.4 ± 1.4*	10.1 ± 0.8
(U/mg prot)	*HAD*	*9.45 ± 0.27*	*9.79 ± 0.78*	*2.40 ± 0.39**	*0.87 ± 0.06*	*24.9 ± 2.2*	10.9 ± 0.4
Catalase	*Bicarb*	*14.0 ± 0.5*	*21.3 ± 0.8*	*21.0 ± 1.5*	*13.6 ± 0.9*	*195 ± 4*	1359 ± 30
(U/mgprot)	*HAD*	*13.0 ± 0.6*	*21.0 ± 1.1*	*26.4 ± 2.3*	*14.8 ± 0.63*	*209. ± 13*	1395 ± 137
GSH[5]	*Bicarb*	*17.0 ± 1.3*	*17.4 ± 1.2*	*7.49 ± 0.72*	*3.84 ± 0.33*	*25.4 ± 0.9*	5.85 ± 0.79
(nmol/mg prot)	*HAD*	*22.9 ± 2.0**	*16.1 ± 0.9*	*8.72 ± 1.08*	*0.82 ± 0.47**	*26.3 ± 1.5*	4.22 ± 0.56
Antioxidant Capacity	*Bicarb*	*59.1 ± 3.4*	*76.6 ± 5.9*	*12.0 ± 2.3*	*24.7 ± 1.5*	*56.7 ± 4.1*	47.5 ± 1.5
(nmol/mg prot)	*HAD*	*59.3 ± 1.1*	*78.8 ± 6.8*	*12.1 ± 1.3*	*25.3 ± 3.0*	*57.0 ± 4.0*	47.5 ± 1.8

*$P < 0.05$ from bicarbonate group.
[1]Data expressed as mean ± S.E. for 5-6 animals/groups.
[2]Thiobarbituric acid reactive substances.
[3]Manganese Superoxide dismutase.
[4]Copper-Zinc Superoxide dismutase.
[5]Reduced glutathione.
[6]hypertonic acetate dextran.

or GR activities or reduced glutathione levels were observed between these 2 tissues. However, within the upper or lower spinal cord, no statistically significant differences in any of the markers of lipid peroxidation or antioxidant status were observed between the HAD and bicarbonate groups (Table 2). In addition, no detectable myeloperoxidase activity was found in either spinal cord fraction (data not shown).

In the gastrocnemius muscle (below the aortic clamp), all antioxidant enzyme activities measured and GSH concentrations were statistically lower than in deltoid muscle (above the clamp) (Table 2). In addition in deltoid muscle, GR and MnSOD activities were higher in the HAD than bicarbonate group whereas no such differences were observed in gastrocnemius muscle (Table 2).

In liver and kidney, TBARS levels were significantly lower in the HAD than bicarbonate group and in kidney, GSH levels were 28% lower in the HAD than bicarbonate group (Table 2). In addition, liver GPx activity was 21% higher in the HAD than bicarbonate group (Table 2). No other statistically significant differences were observed between groups in the other variables measured.

■ DISCUSSION

Numerous studies have reported that ischemia and reperfusion result in the generation of ROS.[14-17] This has been further supported by the evidence that pretreatment with antioxidants appears to lessen ischemia/reperfusion injury.[24-29] The results from the present study suggest that 30 min of aortic crossclamping resulted in evidence of ROS generation in plasma and in tissues below the clamp. However, these effects did not appear to be irreversible as evidence for an oxidative stress after this 30 min ischemia period and reperfusion, diminished by the 1 hr after resuscitation in the plasma and in the examined tissues. Studies by others have reported that 30 min of renal ischemia resulted in little or no injury to the kidney, whereas 60 or 90 min did.[30] In general, the results from the present study are in agreement with this observation.

In abdominal aortic operations involving aortic crossclamping, the development of paraplegia or paraparesis is of grave concern during the procedure.[31,32] A retrospective assessment of such operations where aortic cross-clamping averaged about 48 min with a range of 24-97 min, no specific cause of spinal cord ischemia could be pinpointed.[32] Other retrospective reviews found that the odds ratio for developing renal dysfunction was 10 fold higher for suprarenal aortic clamping greater than 50 min compared with 30 min or less.[33] Although aortic clamping for 30 min appeared safe in rabbits, neurological status was better if the rabbits were treated with an antioxidant.[34] In contrast, Mitteldorf et al[35] found that 30 min of aortic occlusion could be detrimental in hypovolemic dogs. In the current study, the significance of the differences in antioxidant status between spinal cord and skeletal muscle superior or inferior to the aortic clamp is unknown. We have not found other studies that compared these specific spinal cord regions or different skeletal muscle tissues under normal circumstances. Therefore, additional studies are necessary to determine whether the differences observed in the present study are a consequence of the ischemia and reperfusion, or whether they reflect normal differences for these spinal cord regions or skeletal muscles.

The present study used hypertonic sodium acetate dextran (HAD) as a small volume colloid for resuscitation. The premise was that replacing chloride with acetate would reduce the development of hyperchloremic acidosis and supply buffering base to optimize the hypertonic resuscitation. However, few studies have been performed with HAD in resuscitation from hemorrhagic shock and only in experimental animals. Frey [12] observed lower MAP in HAD than HSD-treated hypovolemic dogs. Similar results on MAP were seen in hemorrhaged sheep, but these authors reported improved acid-base balance, oxygen delivery and oxygen consumption in the HAD than HSD treated animals.[13] Also, Doucet and Hall observed that HAD was able to buffer against metabolic acidosis in arterial blood

and reduced fluid volumes compared to LR in a swine hemorrhage model, but transient worsening of hypotension and higher mortality were observed in the HAD group.[36]

The results of the present study cannot determine whether these data may only be relevant to the otherwise healthy individual who received a traumatic injury that requires aortic crossclamping and repair, in comparison to the less well patient undergoing aortic aneurysm repair, since the present study utilized otherwise healthy animals. Previous studies[37-39] have observed much evidence of ROS generation in aorta from patients with abdominal aneurysms that is associated with the presence of atherosclerotic disease. Thus, it is possible that in such patients, 30 min of aortic crossclamping could result in greater ROS generation and more tissue involvement that could put them at greater risk for complications after aortic surgery. However, additional studies are required to test this hypothesis.

For trauma victims and other patients requiring thoracic aorta cross-clamping and lower torso reperfusion, with the resuscitation regimen described in this study, HAD may be a suitable alternative to bicarbonate, and may have a fluid sparing effect. HAD may also preserve tissue antioxidant status, at least in the short term, based on the conditions of the present study. Additional studies are necessary to determine whether the effects of HAD would persist beyond 1 hr of reperfusion or whether it would have any benefit in maintaining tissue function and reduce the incidence of adverse events associated with aortic cross-clamping.

SUMMARY

In the current study and fluid regimen used, HAD showed some improvement in blood flows, fluid requirements, but minor effects on antioxidant status. Considering some adverse effects and limited effects on metabolic acidosis reported in other pre-clinical studies, further development of HAD as a resuscitation fluid may not be justified

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RESUMO

OBJETIVO: Soluções hipertônicas e hiperoncóticas podem reduzir as necessidades de fluidos e o edema tissular, melhorar a perfusão e reduzir a incidência de paraplegia associada com pinçamento aórtico com reperfusão subsequente. Foram avaliados os potenciais benefícios de uma solução de hipertônica de acetato de sódio mais dextrana sobre a reperfusão pós isquêmica. Avaliamos o fluxo sanguíneo e a capacidade antioxidante do plasma, a medula espinal e o músculo esquelético acima e abaixo da oclusão aórtica, bem como o fígado, rim e pâncreas.

MÉTODO: A aorta de porcos anestesiados (n = 5-6/grupo) foi ocluída ao nível de T9 durante 30 min; os animais receberam 4 ml/kg acetato de Sódio + dextrana (HAD) ou 8,4% de NaHCO3 (Controle). Os porcos foram sacrificados 1h mais tarde.

RESULTADOS: Ao reduzir-se o fluxo de sangue a zero na medula espinal e músculo distal, observou-se duplicação do fluxo espinal e aumento de 6 vezes no músculo proximal. Durante a reperfusão, o fluxo de sangue em todas as regiões voltaram aos níveis basais, sem diferenças estatísticas entre HAD e Controles. A taxa de peroxidação lipídica no plasma foi menor em HAD que nos controles. O músculo distal apresentou níveis de glutationa 41% mais baixa e atividades significativamente mais baixas dos enzimas anti-oxidantes glutationa-peroxidase e redutase, catalase, superóxido dismutase em comparação com o músculo proximal. A medula espinal distal exibiu níveis 2,5 vezes mais elevados de malondialdeído e 50% maior de atividade catalase comparados com medula espinal proximal. Para qualquer tecido, diferenças significativas na capacidade antioxidante ou evidência de peroxidação lipídica favoreceram o grupo HAD em comparação com os controles.

CONCLUSÃO: HAD apresentou vantagens discretas sobre o bicarbonato em relação ao fluxo de sangue e status antioxidante de medula espinal e muscular após este período de oclusão aórtica seguida de reperfusão.

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