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Review Article

Pathophysiology of the Intestinal Ischemic Reperfusion Injury

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ABSTRACT

The objective of this review is to approach current information about the ischemic reperfusion injury that affects the gastrointestinal system in animals, because it is classified as a complex event that can cause local and systemic injuries, leading to multiple organ failure. The deleterious events caused by the reperfusion process are greater when compared with the ischemia, due to the circulation of toxins released secondary to hypoxia, loss of cellular membrane integrity, release of free radical and endothelial injuries during reperfusion. It is known that in Veterinary Medicine most of the abdominal emergencies (acute abdomen) cause gastrointestinal microcirculatory dysfunctions and its diagnostic is still a challenge, because the clinical signs are similar to other diseases. The reperfusion injury is one of the reasons for the morbidity and mortality associated with intestinal ischemia, a common affection, especially in equines. The injuries on intestinal ischemia/reperfusion (I/R) are considerate of extreme importance due to its severity and the comprehension of the pathophysiological mechanism of these injuries is necessary to determine therapeutic strategies in the main domestic species.

Keywords: hypoxia, cellular apoptosis, free radicals, acute abdomen, microcirculatory dysfunction.

INTRODUCTION

Ischemic and reperfusion injury (R/I) is characterized by the reduction and interruption of the blood flow followed by a sequence of vascular alterations that leads to the production of free radicals during the reestablishment of the blood flow to the ischemic tissue (Matos *et al*., 2000). The sudden reintroduction of oxygen, also called reperfusion, increases the tissue and vascular injury, hastening the process of cellular necrosis (Tong *et al*., 2012). Despite all the existing studies about ischemic and reperfusion injuries, only in 1986 it was demonstrated that reperfusion would cause a greater systemic and tissue injury than the ischemic injury itself (Parks and Granger, 1986; Santos *et al*., 2008).

The intestine is irrigated by the mesenteric circulation, receiving about 20 to 25 % of the body total blood volume (Vollmar and Menger, 2011). From this volume, approximately 70 % is directed to the mucosa and sub mucosa keeping the homeostasis and the functionality of the crypts and intestinal villi. The organ is very sensitive to any kind of decrease in blood

flow, especially the small intestine (Yasuhara, 2005). Because of that, mechanisms of auto regulation that aim to mainten the flow are constantly triggered in situations of systemic blood pressure decrease or stimulation of the sympathetic tone (Vollmar and Menger, 2011).

Any injury that is capable of causing intestinal ischemia has high potential of progression, causing tissue damage (Yasuhara, 2005), such as sub mucosa edema followed by loosening of the superficial mucosa epithelium and the occurrence of ulcers and/or bleeding of the intestinal villi (Brasileiro *et al*., 2013). Consequent to the ischemic damage, the reperfusion leads to alteration of the vascular permeability and loss of the integrity of the intestinal barrier caused by the reactive oxygen species and inflammatory mediators causing damage as hemorrhages and bacterial translocation (Yasuhara, 2005; Kostopanagiotou *et al*., 2007; Vollmar and Menger, 2011; Brasileiro *et al*., 2013).

The intestinal disorders that cause the acute abdomen syndrome in animal patients, such as strangulation obstructions (torsion, volvulus, intussusceptions, strangulated hernia) and non strangulation obstruction (Rowe and White, 2002) have the potential to develop ischemic injuries and reperfusion that is associated with high mortality rates, between 60 to 70 % of the cases (Ritz *et al*., 2005; Boybeyi *et al*., 2014). Clinically, it is observed diarrhea, vomit and/or intense abdominal pain, signs that can be associated with the occurrence of acute intestinal ischemia (Ravipati *et al*., 2011).

The intestinal ischemic/reperfusion injuries (I/R) are considerate of extreme importance due to its severity (Gao *et al*., 2006; Jiang *et al*., 2011; Vollmar and Menger, 2011) and the comprehension of the pathophysiological mechanisms of these injuries are necessary to determine therapeutic strategies for the majority of the domestic species.

PATHOPHYSIOLOGY OF THE ISCHEMIC INJURY

In the moment that the tissue blood flow is interrupted, a series of metabolic and enzymatic compensatory events are triggered (Evora *et al*., 1996). The low cellular oxygen offer causes a decrease in the production of adenosine triphosphate (ATP) by the mitochondria, decreasing intracellular concentration of this molecule. Alongside an increase in adenosine monophosphate (AMP) will occur.

Attempting to keep tissue function and in response to the increase in AMP, the cells will initiate the production of energy through an anaerobic mechanism (glycolisis), producing lactic acid and H^+ ions (Moore *et al*., 1995). The accumulated lactic acid decreases the intracellular pH which hinders the maintenance of the cellular function, due to the exhaustion of cellular energy resources. Without energy, the membrane pumps that are responsible for the flux of ions cease their functions, causing an influx of fluid and calcium ions to the intracellular space (calcium paradox), initiating the mitochondria and sarcolemma lesion, resulting in edemas (Farber *et al*., 1981; Evora *et al*., 1996; Silva-JR *et al*., 2002; Slone and Fleming, 2014).

The mitochondrial lesion will contribute to the decrease in the activity of the adenine nicotinamine dinocleotide coupled to the hydrogen (NADH) desidrogenase, the diphosphate adenosine carrier/ triphosphate adenosine (ADP/ATP) and the ATP synthase, and to the increase in the activity of phospholipase A2, creating a ionic gradient in the cellular membrane, altering the rearrangement of calcium in the citosol (Kono *et al*., 1982; Silva-JR *et al*., 2002).

This process will potentiate the increase in cytoplasmic calcium, activating a protease that can convert xantine desidrogenase (XDH) in xantine oxidase (XO) (McCord, 1985; Nilsson *et al*., 1994; Greca *et al*., 2008). At the same time there will be a depletion of ATP, accumulating AMP that will be catabolized into adenosine and inosine, ending with hipoxantine (Greca *et al*., 2008).

Among the most common causes of intestinal ischemia there are acute mesenteric obstruction and ischemic colitis, which will lead to a decrease of tissue blood supply and a

decrease in the intestinal oxygen (Yasuhara, 2005; Rowe and White, 2002). The intestinal ischemia progress rapidly causing tissue damage, especially necrosis of the tissue cells, production of toxins, loss of membrane integrity and bacterial translocation (Yasuhara, 2005; Vollmar and Menger, 2011; Brasileiro *et al*., 2013), which may cause secondary lesion in the lungs and result in multiple organs failure (Slone and Fleming, 2014).

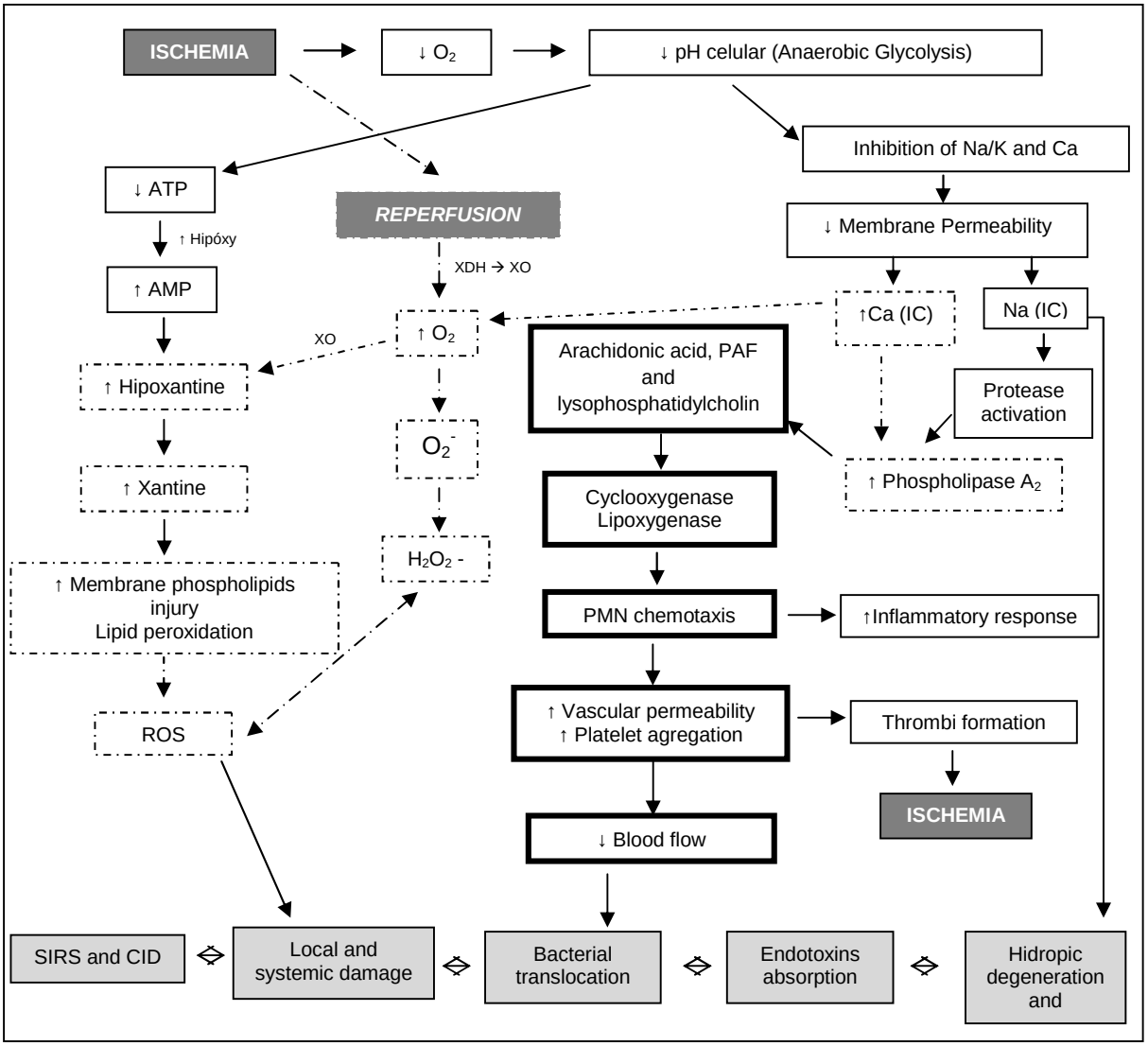

Figure 1. Representative scheme of the pathophysiological events in the intestinal ischemia reperfusion injury. After an ischemic event there will be a decrease the in supply of oxygen (O_2), a decrease in the production of adenosine triphospate (ATP), membrane permeability altering causing electrolyte imbalance and the inhibition of the body physiologic pumps, promoving influxe of intracellular calcium (Ca – IC), proteases and lipases activation, especially phospholipase A2. This enzyme will promote membrane phospholipids injury, Arachidonic acid, platelet activating factor (PAF) and lysophosphatidylcholine release. Yet, will be an increase in the production of hipoxantine. With the reintroduction of O_2, during reperfusion, it will occur activation and break of xantine desidrogenase (XDH) in xantine oxidase (XO), that will act in the hipoxantine increasing the production of reactive oxygen species (ROS), such as, superoxide anions (O_2^-) and hydrogen peroxide ($H_2O_2^-$). The sum of these events and the secondary products to the I/R can lead to or enhance the systemic inflammatory response (SIRS), disseminate intravascular coagulation (CID), bacterial translocation, endotoxins absorption, cellular apoptosis and other local and systemic damage in the body.

PATHOPHYSIOLOGY OF THE REPERFUSION INJURY

The consequences of ischemia in the different tissues and organs are dependent upon the duration of the event and many of the lesions will develop during the reoxygenation stage resulted from the tissue reperfusion (Silva-JR. *et al*., 2002). The reperfusion mechanism became much discussed because it can cause local and systemic injuries, predisposing the

formation of reactive oxygen molecules that will result in injuries throughout the body (Parks and Granger, 1986; Greca *et al*., 2001; Lock, 2002; Edward *et al*., 2003; Greca *et al*., 2008; Santos *et al*., 2010; Slone and Fleming, 2014). The deleterious effects caused by the reperfusion process will be even greater than the ischemia due to the accumulation of toxins during this event and its posterior distribution throughout the body during reperfusion (Greca *et al*., 2008).

The reperfusion stage is characterized by the feedback of the blood flow to the ischemic area. Hence, the anaerobic metabolites from the damaged tissue gain the bloodstream, causing more local and systemic tissue damage being compared with the damage caused by the ischemia (Granger and Korthuis, 1995; Greca *et al*., 2001; Lock, 2002; Edward *et al*., 2003; Chen *et al*., 2003; Greca *et al*, 2008; Köhler *et al*., 2011; Ben *et al*., 2012; Brasileiro *et al*., 2013).

The whole I/R process will cause a series of injuries **(Figure 1)**, mediated by oxygen free radicals produced by the parenchymal cells and/or by inflammatory cells. These radicals will migrate to the local and distant tissues causing damage (Ferro *et al*., 2010; Rocha *et al*., 2012).

The hipoxantine, produced in consequence of hypoxia and accumulated during ischemia, will suffer the action of xantine oxidase (XO), with the presence of molecular oxygen (tissue reoxygenation), becoming oxygen free radicals, also called superoxide or reactive oxygen species (ROS), such as, the superoxide anions (O_2^-) and the hydrogen peroxide ($H_2O_2^-$). These can suffer reduction and transform into reactive hydroxyl that will initiate lipid peroxidation (McCord, 1985; Pitt *et al*., 1991; Moore *et al*., 1995; Hirata *et al*., 1996; Greca *et al*., 2008; Battelli *et al*., 2014).

The reperfusion event associated with the calcium influx to the intracellular space (Evora *et al*., 1996) will increase the activation of enzymes such as fosfolipase, which acts degrading the plasmatic membrane and altering the structural function of the cells. The proteases and lipases will also be activated and act degrading the organelles (Moore *et al*., 1995). These event will alter structurally and functionally the lipids present in the cellular membrane, originating an exacerbated systemic inflammatory response (SIRS), an increase in the endothelial to fluids, macromolecules and inflammatory cells, furthermore, it can aggravates the injury caused by ischemia (McCord, 1985; Moore *et al*., 1995; McQuaid and Keenan, 1997; Cohen *et al*., 1997; Greca *et al*., 2008; Belknap *et al*., 2009; Laskoski *et al*., 2012).

FINAL CONSIDERATIONS

The pathophysiology of the intestinal I/R happens in a brief and gradual manner, becoming an event highly complex due to its systemic proportion. Because it is an organ that depends on a health vascular function, in situations that culminate with I/R injuries, there will be failure in the cellular nutrition, triggering of the inflammatory mediators cascade, a response to the inflammatory process and loss of the intestinal epithelial barrier. Summed to the fact that will happen injuries in the vascular intestinal endothelium, the bacterias from the intestine can gain the system leading to bacterial translocation. The presence of bacteria in the bloodstream, as well as the systemic inflammatory response due to the endotoxin shock can directly interfere in the prognostic of the injuries associated with the acute I/R, being considered a bad prognostic.

The events are considered multifactorial and interdependent. So the comprehension of the pathophysiology is considered of great importance to improve the prognostic of patients affected by this injury.

REFERENCE

Battelli, M.G., A. Bolognesi, and L. Polito, 2014. Pathophysiology of circulating xanthine oxidoreductase: New emerging roles for a multi-tasking enzyme. *Biochimica et Biophysica Acta.* 1842: 1502-1517.

Belknap, J., J.N. Moore, and E.C. Crouser,. 2009. Sepsis: From human organ failure to laminar failure. *Veterinary Immunology and Immunopathology*. 129: 155-157.

Ben, D.F., X.Y. Yu, , G.Y. Ji, , D.Y. Zheng, , K.Y. Lv, , B. Ma, , Z.F. Xia. 2012. TLR4 mediates lung injury and inflammation in intestinal ischemia-reperfusion. *Journal of Surgical Research*. 174: 326-333.

Boybeyi, O., Y.D. Gunal, P. Atasoy, U. Kisa, , and M.K. Aslan, 2014. The effect of colchicine and low-dose methotrexate on intestinal ischemia/ reperfusion injury in an experimental model. *Journal of Pediatric Surgery*. doi: 10.1016/j.jpedsurg.2014.01.057.

Brasileiro, J.L., C.M. Inoye, R.D. Aydos, , I.S. Silva, G.R. Falcão, , G. Marks, and , D.M. Pereira. 2013. Ischemia and reperfusion of rat small intestine using pentoxyfilline and prostaglandin E1. *Acta Cirúrgica Brasileira*. 28: 767-773.

Chen, L.W., L. Egan, Z.W. Li. 2003. The two faces of IKK and NF-kB inhibition: Prevention of systemic inflammation but increased local injury following intestinal ischemia-reperfusion. *Natural Medicene*. 9: 575 – 581.

Cohen, S.M., F.A. Siddigi, , B. Darakchiev, , G.A. Fantini, , R.J. Hairi, , P.S. Barie. 1997. Attenuation of acute lung injury caused by hind-limb ischemia-reperfusion injury by butylactone anti-inflammatory agent FL 1003. *The Journal of Trauma*. 43: 247-252.

Edward, M.S., G.S. Cherr, , T.E. Craven, , A.W. Olsen, , G.W. Plonk, R.L. Geary, J.L. Ligush, , K.J. Hamsen. 2003. Acute occlusive mesenteric ischemia: surgical management and outcomes. *Annals of Vascular Surgery*. 17: 72-79.

Evora, P.R.B., P.J. Pearson, J.F. Seccombe, , H.V. Schaff. 1996. Ischemia/reperfusion injury. Pathophysiological aspects and the importance of endothelial function. *Arquivo Brasileiro de Cardiologia*. 66: 239-245.

Farber, J.L., K.R. Chien, S.J.R. Mittnnacht,. 1981. Myocardial ischemia: the pathogenesis of irreversible cell injury in ischemia. *The American Journal of Pathology*. 102: 271-281.

Ferro, C.O., V.L.A. Chagas, M.F. Oliveira, P.L. Oliveira, A. Schanaider. 2010. Catalase activity in lung, kidney and small bowel non-ischemic in rats after intestinal reperfusion. *Revista do Colégio Brasileiro de Cirurgiões*. 37: 31-38.

Gao, C. J., W. Chai, , L. Xu, , G. Zhang, H. Zhang, L. Han, X. Sun. 2006. Protective effects of hyperoxygenated solution preconditioning on intestinal ischemia-reperfusion injury in rabbits. *Journal of Surgical Research*. 135: 268-274.

Granger, D.N., R.J. Korthuis. 1995. Physiologic mechanisms of postischemic tissue injury. *Annual Review of Physiology*. 57: 311-332.

Greca, F.H., M.L.P. Biondo-Simões, S.O. Ioshii. 2001. Effects of ischemia and reperfusion on healing of bowel anastomoses experimental study in rats. *Acta Cirúrgica Brasileira*. 16: 9-15.

Greca, F.H., N.M.F.M. Gonçalves, Z.A. Souza Filho, L. Noronha, R.F.K.C. Silva, R.R. Michel. 2008. The protective effect of methylene blue in lungs, small bowel and kidney after intestinal ischemia and reperfusion. *Acta Cirúrgica Brasileira*. 23: 149-156.

Hirata, Y., T. Taguchi, , and M. Nakao, 1996. The relationship between the adenine nucleotide metabolism and the conversion of the xanthine oxidase enzyme system in ischemia-reperfusion of the rat small intestine. *Journal Pediatric Surgery*. 31: 1199-1203.

Jiang, H., L. Qu, , Y. Li, , L. Gu, Y. Shi, , J. Zhang, , W. Zhu, , J. Li. 2011. Bone marrow mesenchymal stem cells reduce intestinal ischemia/reperfusion injuries in rats. *Journal of Surgical Research*. 168: 127-134.

Köhler, H.F., I.M.S. Delluca, L. Sbragia Neto. 2011. Enteral antioxidants in ischemia/reperfusion injuries in rats. *Revista do Colégio Brasileiro de Cirurgiões.* 38: 422-428.

Kono, Y., K. Ozawa, J. Tanaka. 1982. Significance of mitochondrial enhancement in restoring hepatic energy charge after revascularization of isolated ischemic liver. *Transplantation.* 33: 150-155.

Kostopanagiotou, G., E. Avgerinos, C. Costopanaiogotu, N. Arkadopoulos, I. Andreadou, K. Diamantoupouolou, M. Lekka, , V. Smyrniotis, G. Nakos. 2007. Acute lung injury in a rat model of intestinal Ischemia-Reperfusion: the potential time depended role of phospholipases A2. *Journal of Surgical Research.*147: 108-116.

Laskoski, L.M., C.A.A. Valadão, R.O. Vasconcelos, , R.R. Faleiros, H.M.F. Mendes, D. Ferrucci, J.A.F. Silva, D.D.R.S. Machado. 2012. Neutrophil gelatinase associated lipocalin (NGAL) and calprotectin in equine laminar tissue after jejunal obstruction, treated or not with hidrocortisone. *Pesquisa Veterinária Brasileira*. 32: 817-823.

Lock, G. 2002. Acute mesenteric ischemia: classification, evaluation and therapy. *Acta Gastroenterology Belgica*. 65: 220-225.

Matos, J.J.R.T., G.E.S. Alves, R.R. Faleiros, A.D.P.M. Júnior. 2000.

intestinal ischemia-reperfusion injury in horses:pathophysiology and therapeutics. *Ciência Rural*. 30: 1083-1093.

McCord, J.M. 1985. Oxigen-derived free radicals in postischemic injury. *The New England Journal of Medicine*. 312: 159-163.

McQuaid, K.E., and A.K. Keenan, 1997. Endothelial barrier dysfunction and oxidative stress: role for nitricoxide? *Experimental Physiology*. 82: 369-376.

Moore, R.M., W.W. Muir, and D.N. Granger, 1995. Mechanisms of Gastrointestinal Ischemia-Reperfusion Injury and Potential Therapeutic Interventions: A Review and Its Implications in the Horse. *Journal of Veterinary Internal Medicine*. 9: 115-132.

Nilsson, U. A., M.H. Schoenberg, A. Aneman. 1994. Free radicals and pathogenesis during ischemiaand reperfusion of the cat small intestine. *Gastroenterology*. 106: 629-636.

Parks, D. A., D.N. Granger. 1991. Contributions of ischemia and reperfusion to mucosal lesion formation. *The Americam Journal of Physiology*. 250: 749-753.

Pitt, R.M., G. Mckelvey, F.S. Saenger. 1991. A tungsten-supplemented diet delivered by transplacental and breast-feeding routes lowers intestinal xanthineoxidase activity and affords cytoprotection in ischemia-reperfusion injury to the small intestine. *Journal Pediatric Surgery*. 26: 930-935.

Ravipati, M., S. Katragadda, B. Go, E.J. Zarling. 2011. Acute mesenteric ischemia: a diagnostic challenge in clinical practice. *Practical Gastroenterology*. 38: 35-38.

Ritz, J.P., C.T. Germer, and H.J. Buhr, 2005. Prognostic factors for mesenteric infarction: multivariate analysis of 187 patients with regard to patient age. *Annals of Vascular Surgery*. 19: 328-34.

Rocha, B.C., R.R.S. Mendes, G.V. Lima, G.Z. Albuquerque, L.L. Araújo, M.N.S. Jesus, , W.L.C. Santos, M.C. Carreiro. 2012. Experimental model of mesenteric ischemia: reperfusion by abdominal aorta clamping in Wistar rats. *Revista do Colégio Brasileiro de Cirurgiões*. 39: 207-210.

Rowe, E. L., and N.A. White, 2002. Reperfusion injury in the equine intestine. *Clinical techniques in equine practice*. 1: 148-162.

Santos, C.H., O.M. Gomes, J.C. Pontes, , L.N. Miiji, M.A. Bispo. 2008. The ischemic preconditioning and postconditioning effect on the intestinal mucosa of rats undergoing mesenteric ischemia/reperfusion procedure. *Acta Cirurgica Brasileira*. 23: 22–28.

Santos, C.H., J.C. Pontes, L.N. Miiji, , D.I. Nakamura, C.A. Galhardo, S.M. Aguena. 2010. Postconditioning effect in the hepatic ischemia and reperfusion in rats. *Acta Cirúrgica Brasileira*. 25: 163-168.

Silva-Junior, O.C., S. Centurion, , E.G. Pacheco, , J.L. Brisotti, , A.F. Oliveira, , K .dal sasso. 2002. Basics aspects of the ischemia reperfusion

injury and of the ischemic preconditioning. *Acta Cirúrgica Brasileira*. 17: 96-100.

Slone, E. A., and S.D. Fleming, 2014. Membrane lipid interactions in intestinal ischemia/reperfusion-induced Injury. *Clinical Immunology*. 153: 228-240.

Tong, Z., Y. Fang, L. Zhonghua, , L. Haidong. 2012. Influence of ShuJinHuoXue tablets on ischemia reperfusion injury of animals' skeletal muscle. *Molecules*. 17: 8494-8505.

Vollmar, B., and M.D. Menger, 2011. Intestinal ischemia/reperfusion: microcirculatory pathology and functional consequences. *Langenbeck's Archives of Surgery*. 396: 13-29.

Yasuhara, H. 2005. Acute mesenteric ischemia: the challenge of gastroenterology. *Surgery Today*. 35: 185-195.

Zhang, F., L. Tong, H. Qiao, X. Dong, H. Jiang, X. Sun. 2008. Taurine attenuates multiple organ injury induced by intestinal ischemia reperfusion in rats. *Journal of Surgical Reasearch*. 149: 101-109.