

# Treatment of Post-Revascularization Syndrome: Brief Communication

REVIEW

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## Abstract

Post-Revascularization Syndrome (PRS), also described as, Ischemic Reperfusion Injury (IRI), is the main cause of failure in the revascularization of limbs. The etiology of Post-Revascularization Syndrome is not fully known, but it is accepted as a multifactorial chain with a time-dependent molecular and structural change of the affected tissues. Current clinical treatments of PRS are supportive only notwithstanding numerous intervention strategies have been proposed aiming at reducing IRI. The present perspective aimed to explain all the available treatments in studies of IRI, and their potential effects in the future medicine. Since there are almost no articles covering this topic, we believe that this perspective will clarify the necessity of more researchers and studies on IRI. Our main findings leads to believe that there are many possible therapies for ischemic reperfusion injury, but most of them are still not used in practical scenarios because of it small samples studies, or *in vitro* techniques or the clinical trials are still not concluded. Although, significant work remains to be done.

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## Keywords

Post-Revascularization Syndrome; Treatment; Review.

Post-Revascularization Syndrome (PRS), also described as, Ischemic Reperfusion Injury (IRI), is the main cause of failure in the revascularization of limbs and the transfer of free flaps with 'non reflow' phenomenon [1]. It involves microcirculatory collapse during revascularization following an ischemic insult, that constitutes an acute inflammatory process by which cells are damaged first by temporary ischemia, hypoxia and accumulation of toxic metabolites and later by reperfusion [2, 3]. It may result from thrombotic occlusion, embolism, trauma or surgical intervention through tourniquet application and subsequent restoration of blood flow.

The etiology of Port-Revascularization Syndrome is not fully known, but it is accepted as a multifactorial chain with a time-dependent molecular and structural change of the affected tissues: inflammatory cascades are activated with excessive complement deposition on the vascular endothelium; endothelial cells and white blood cells are activated; great production of free radicals responsible for increasing capillary permeability, edema and cell aggregation; and release of vasoactive factor that causes further damage to local and remote tissues [3, 7].

Firstly, ischemia leads to muscle necrosis, than reperfusion results in edema, inflammation and excessive release of reactive oxygen and nitrogen species that induces more muscle damage, such as atrophy and weakness [4].

Current clinical treatments of PRS are supportive only [12] notwithstanding numerous intervention strategies have been proposed aiming at reducing IRI. These strategies include reperfusion with various resuscitation fluids, infusion or injection of agents aimed at reducing oxidative stress, inflammation, vascular injury, to provide energy supply, and different surgical approach, if possible, for tissue reoxygenation. Being possible to conclude that the more investigation into the multiple pathophysiological mechanisms of the effects of PRS more possible treatments will become available and effective.

The aim of the present review is to display the role of those treatments and their level of success, reporting the effective ones in reducing the extension of the injury caused by reperfusion and its aspects [1, 2, 3, 5, 6, 7, 8, 11, 12, 13, 15, 16, 17, 18].

The process of re-establishing perfusion after an ischemic period in tissue that worsens the initial ischemic injury is known as ischemia/reperfusion injury (IRI) it may occur in an ischemic extremity or organ (local injury) or in distal parts far from ischemic areas [5]. Already proved by RICCIO *et. al.*, [1] IRI it is the main cause of failure in the revascularization of limbs and the transfer of free flaps with the non-reflow phenomenon.

The present perspective aimed to explain all the available treatments in studies of IRI, and their potential effects in the future medicine. Since there are almost no articles covering this topic, we believe that this perspective will clarify the necessity of more researchers and studies on IRI. Our main findings are the following:

### **Nitrite Anion Therapy**

BIR *et. al.*, [6] proved that sodium nitrite therapy is a useful modality for diabetic peripheral vascular disease stimulating ischemic vascular growth and tissue cytoprotection by hypoxic endothelial cell proliferation and migration in presence of high glucose in a nitric oxide/vascular endothelial growth factor-dependent manner.

### **C1 Esterase Inhibitor (C1 INH)**

C1 INH regulates IRI associated inflammatory cascade and thrombotic process, preventing fibrin deposition and significant reduction of C1q and C3b/c in the reperfused limb but does not reduce edema. DUEHRKOP *et. al.*, [7] affirms that C1 INH may provide a promising therapy to reduce peripheral IRI as well distant lung injury in complicated and prolonged surgical interventions requiring tourniquet application.

### **Hyperbaric Oxygen (HBO) And Iloprost (IL) Therapy**

BOZOK *et. al.*, [5] studies showed that HBO and IL reduces lipid peroxidation minimizing the injury after reperfusion. The combined therapy is shown to be more effective than either treatment given alone. Iloprost is a stable prostacyclin analog, is a membrane stabilizer and inhibits the function of neutrophils, which are potential mediators of IRI.

### **Hyperbaric Oxygen (HBO) And WEB2170**

RICCIO *et. al.*, [1] proved a synergic effect of HBO and WEB2170, a platelet activating factor antagonist, association that decreases the infiltration of neutrophils in the ischemic tissue and reduces

muscle damage during reperfusion after 3h and 30min of ischemia in the rectus femoris rabbit muscle.

### **Hyperbaric Oxygen (HBO) And Lactate, Glucose And Glycerol Concentrations And Anti-Oxidants In Skeletal Muscle**

The study of Bosco *et. al.* [18] verified that HBO2 attenuated the ischaemia-induced increase in extracellular lactate and glycerol concentrations, whereas HBO2 had no effect on the ischaemia-induced decreases in the extracellular glucose concentration; and HBO2 attenuated the reperfusion-induced increase in CAT activity and MDA levels. The present data suggest that HBO2 treatment during skeletal muscle IR injury may be beneficial.

### **Distal Venous Arterialization (DVA)**

The results of the studies of DJORIC *et. al.*, [8] indicates that there is no statistically significant reperfusion injury after this surgical procedure, confirming the validity in these patients because it achieved the therapeutically goal –adequate re-oxygenation of ischemic tissue.

### **Muscle Progenitor Cells (MPC)**

CHEN *et. al.*, [9] proved that delayed intramuscular transplantation of muscle MPC cells improved muscle function after acute IRI by improving muscle quality, possibly through forming functional myofibers and effects on non-myofiber related components. Suggesting that this therapy could, potentially, be used as a new intervention strategy for delayed treatment of acute IRI.

### **Hydrogen Sulfide (HS)**

The findings of HENDERSON *et. al.*, [17] confirms that HS limits IRI-induced cellular damage in myotubes and skeletal muscle, even when delivered after the onset of ischemic in a murine model. Their data suggest that when given in the appropriate dose and within the proper time frame, hydrogen sul-

fide may have significant therapeutic applications in multiple clinical scenarios, but further work remains to be done.

### **Novel Liposome-Based Therapy**

GOGA *et. al.*, [10] produced a study decorating cells with SA-CVP: vaccinia virus complement control protein (VCP), a potent anti-complement protein on cell membrane to reduce complement activation and deposition, linked with Streptavidin (SA). The results were satisfactory with reduced complement activation and deposition *in vitro* and potential for application against inappropriate complement activation *in vivo* [10].

### **Carbon Monoxide**

BOUTROS *et. al.*, [11] proved that exogenous administration of carbon monoxide by inhalation at low dose prevented acute long injury post ischemia reperfusion of the lower limbs, also suggesting the necessity to study the protective effect of bilirubin at lower doses.

### **Statins**

The study of COWLED *et. al.*, [12] verified that the administration of statins has the potential to reduce the severity of pathophysiological processes during IRI. The pleiotropic effects of statins have seem them take on an ever increasing and important role in vascular surgery, but their precise role in IRI and their mechanisms of action are yet to be defined completely.

### **Phosphatidylcholine (PC)**

PC supplementation efficiently decreased the harmful consequences of limb I-R-induces microcirculatory perfusion failure and inflammatory reactions in rat according to GERA *et. al.*, [13] These data suggest a therapeutic potential for parenteral PC with a view to decreasing the harmful conditions of the bones.

### PJ34 Therapy

PJ34 is poly ADP-Ribose polymerase (PARP) inhibitor. PARP is a DNA repair enzyme that is expressed at the cellular level in range of organs and tissues. It protects the DNA from degradation. PARP activity leads to rapid depletion of cellular ATP stores that ultimately leads to cell death. Conrad et al. proved that post hoc PJ34 therapy appears to protect skeletal muscle from IRI despite increased levels of local cytokines [14]. Further study of this novel therapy is warranted. [14]

### Fluid Resuscitation

Resuscitation with Hextend or Lactated Ringer's does not adversely affect muscle viability in IRI, according to KAUVAR *et. al.*, [15] HX may be a better clinical choice when skeletal muscle ischemia reperfusion injury is a risk, despite greater edema.

### Polyclonal Anti-Thymocyte Globulins

BEIRAZ-FERNANDEZ *et. al.*, [3] in a non-human primate model supports the hypothesis that ATGs have a protective effect upon IRI by direct blocking adhesion molecules or diminution of production of these molecules by leukocyte depletion. This experimental study suggests that preoperative therapy with ATGs may limit the IRI resulting in an advantageous effect on primary non-function and improved long-term allongraft survival.

### L-Arginine and Antioxidative Vitamin Treatment

The study of NANOBAHVILI *et. al.*, [16] clearly indicates that alterations in production of NO and oxygen free radicals are important in the development of IRI. As compared with treatment with L-arginine or antioxidative vitamins alone, a combination of both compounds was the best treatment against IRI, as expressed by protection against microvessel constriction, abolition of microvascular plugging, increase in NO production over the basal level, and higher blood flow.

### Prostaglandins (PGE)

Currently prostaglandins are not used routinely in the treatment of limb ischemia, Rowlands et al. study suggest that PGE could have a role in the therapeutic management of skeletal muscle ischemia-reperfusion injury improving blood flow. [2]

## Conclusion

In conclusion, our data demonstrate that are many possible therapies for ischemic reperfusion injury, but most of them are still not used in practical scenarios because of it small samples studies, or *in vitro* techniques or the clinical trials are still not concluded. Although significant work remains to be done. These data highlight the potential of innumerable studies in the area, and provide an important foundation to suggest further investments at this kind of treatment to prevent morbidity (and possible mortality) that can result from ischemic reperfusion injury.

## References

1. Riccio, M., Pangrazi, P.P., Campodonico, A., Scalise, A., Marchesini, A., Talevi, D., Carboni, A., Bertani, C., Bertani, A., Mazzanti, L. Combined use of WEB2170 and HBO therapy can reduce ischemia and reperfusion injury to the skeletal muscle in a rabbit model. *Microsurgery*, 2007, 27(1): 43-47.
2. Rowlands, T.E., Gough, M.J., Homer-Vanniasinkam, S. Do prostaglandins have a salutary role in skeletal muscle ischaemia-reperfusion injury? *European Journal of Vascular and Endovascular Surgery*, 1999, 18(5): 439-444.
3. Beiras-Fernandez, A., Chappell, D., Hammer, C., Thein, E. Influence of polyclonal anti-thymocyte globulins upon ischemia-reperfusion injury in a non-human primate model. *Transplant Immunology*, 2006, 15(4): 273-279.
4. Chen, X.K., Rathbone, C.R., Walters, T.J. Treatment of tourniquet-induced ischemia reperfusion injury with muscle progenitor cells. *Journal of Surgical Research*, 2011, 170(1): e65-e73.
5. Bozok, Ş., İlhan, G., Yılmaz, Y., Dökümcü, Z., Tumkaya, L., Karamustafa, H., Karakisi, S.O., Ergene, Ş., Ener, E. Protective effects of hyperbaric oxygen and iloprost on ischemia/reperfusion-induced lung injury in a rabbit model. *European Journal of Medical Research*, 2012, 17 (1):

6. Bir, S.C., Pattillo, C.B., Pardue, S., Kolluru, G.K., Shen, X., Giordano, T., Kevil, C.G. Nitrite anion therapy protects against chronic ischemic tissue injury in db/db diabetic mice in a NO/VEGF-dependent manner. *Diabetes*, 2014, 63(1): 272-281.
7. Duehrkop, C., Banz, Y., Spirig, R., Miescher, S., Nolte, M.W., Spycher, M., Smith, R.A.G., Sacks, S.H., Rieben, R. C1 Esterase Inhibitor Reduces Lower Extremity Ischemia/Reperfusion Injury and Associated Lung Damage. *PLoS ONE*, 2013, 8(8): e72059.
8. Djoric, P., Zeleskov-Djoric, J., Stanislavljevic, D.M., Markovic, Z.D., Zivkovic, V., Vuletic, M., Djuric, D., Jakovljevic, V. Distal venous arterialization and reperfusion injury: Focus on oxidative status (2012) *European Surgical Research*, 2012, 48(4): 200-207.
9. Chen, X.K., Rathbone, C.R., Walters, T.J. Treatment of tourniquet-induced ischemia reperfusion injury with muscle progenitor cells (2011) *Journal of Surgical Research*, 2011, 170(1): e65-e73.
10. Goga, L., Pushpakumar, S.B., Perez-Abadia, G., Olson, P., Anderson, G., Soni, C.V., Barker, J.H., Maldonado, C. A novel liposome-based therapy to reduce complement-mediated injury in revascularized tissues. *Journal of Surgical Research*, 2011, 165(1): e51-e57.
11. Boutros, C., Zegdi, R., Lila, N., Cambillau, M., Fornes, P., Carpentier, A., Fabini, J.N. Carbon Monoxide Can Prevent Acute Lung Injury Observed After Ischemia Reperfusion of the Lower Extremities. *Journal of Surgical Research*, 2007, 143(2): 437-442.
12. Cowled, P.A., Khanna, A., Laws, P.E., Field, J.B.F., Varelias, A., Fitridge, R.A. Statins Inhibit Neutrophil Infiltration in Skeletal Muscle Reperfusion Injury. *Journal of Surgical Research*, 2007, 141(2): 267-276.
13. Gera, L., Varga, R., Török, L., Kaszaki, J., Szabó, A., Nagy, K., Boros, M. Beneficial Effects of Phosphatidylcholine During Hindlimb Reperfusion. *Journal of Surgical Research*, 2007, 139(1): 45-50.
14. Conrad, M.F., Albadawi, H., Stone, D.H., Crawford, R.S., Entabi, F., Watkins, M.T. Local Administration of the Poly ADP-Ribose Polymerase (PARP) Inhibitor, PJ34 During Hindlimb Ischemia Modulates Skeletal Muscle Reperfusion Injury. *Journal of Surgical Research*, 2006, 135(2): 233-237.
15. Kauvar, D.S., Baer, D.G., Dubick, M.A., Walters, T.J. Effect of Fluid Resuscitation on Acute Skeletal Muscle Ischemia-Reperfusion Injury after Hemorrhagic Shock in Rats. *Journal of the American College of Surgeons*, 2006, 202(6): 888-896.
16. Nanobashvili, J., Neumayer, C., Fuegl, A., Punz, A., Blumer, R., Mittlböck, M., Prager, M., Polterauer, P., Dobrucki, L.W., Huk, I., Malinski, T. Combined L-arginine and antioxidative vitamin treatment mollifies ischemia-reperfusion injury of skeletal muscle (2004) *Journal of Vascular Surgery*, 2004, 39(4): 868-877.
17. P. W. Henderson, N. Jimenez, J. Ruffino et al., "Therapeutic delivery of hydrogen sulfide for salvage of ischemic skeletal muscle after the onset of critical ischemia," *Journal of Vascular Surgery*, 2011, 53(3): 785-791.
18. Bosco, G., Yang, Z.-J., Nandi, J., Wang, J., Chen, C., Camporesi, E.M. Effects of hyperbaric oxygen on glucose, lactate, glycerol and anti-oxidant enzymes in the skeletal muscle of rats during ischaemia and reperfusion (2007) *Clinical and Experimental Pharmacology and Physiology*, 2007, 34(1-2): 70-76.

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