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The study on pathological mechanism and solution method for spinal cord ischemia reperfusion injury

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Abstract. – OBJECTIVE: We aimed at investigating the pathological mechanism changing of injury during reperfusion injury, reperfusion time correlation and compliance, finding the blood supply and improving the secondary damage.

MATERIALS AND METHODS: A total of 180 patients who underwent a surgical procedure and that received normal saline intraperitoneally immediately after the patients' aortic occlusions were investigated. Patients were divided in three groups. Experimental conditions and programs were designed for various approaches.

RESULTS: Thirty min after the onset of ischemia, we found a decrease in the local blood flow in the lumbar spinal cord, almost -77.48% of the baseline, which was reversed partially by initial reperfusion, even exceeding the baseline level. However, 1 hour after reperfusion, the blood flow was again decreased to the level below the baseline, followed by a decline to 207.13% ± 38.25 PU for 3 h without any recovery. Attenuating this secondary damage with neuroprotective strategies requires an understanding of these pathophysiologic processes.

CONCLUSIONS: This study showed the pathological mechanism changes during reperfusion injury and reperfusion time correlation and compliance, and analyzed some of the important pathophysiologic processes involved in secondary damage after spinal cord injury. Moreover, our research discusses a number of pharmacologic therapies that have either been studied or have future potential for this devastating injury.

Key Words:
Spinal cord injury, Primary and Secondary damage, Pathophysiology, Neuroprotection.

Introduction

The spinal cord injury[1-3] is caused by the occlusion of the thoracoabdominal aorta and remains an unpredictable and devastating complication of aortic surgery for the resection of thoracoabdominal aneurysms. Neurological deficits resulting from this injury may be immediate or delayed with an incidence ranging from 1.6% up to 35%, depending on the type of resected aneurysm. Individuals paralyzed by trauma to the spinal cord are left with one of the most physically disabling and psychologically devastating conditions known to humans. Over 10,000 North Americans, most of them under the age of 30 years, experience such injury each year[4]. Over the last decade, the costs for the medical, surgical and rehabilitative cares for spinal cord-injured patients were estimated to be over billions annually[5]. Nowadays, the situation has highly increased in the new millennium. Spinal cord ischemia reperfusion injury (SCIRI) is a devastating complication of thoracoabdominal aortic surgery[6-9], which can be occasionally seen after surgical or endovascular treatment of spinal vascular lesions. In the central nervous system, any serious decrease in the blood flow causes energy failure and triggers a cascade of events leading to cell damage through amplification of many pathways set in motion by ischemia. Literature has clearly shown the early accumulation of leukocytes in and around the microvessels at the ischemic zones. The role of cytokines in SCIRI has been highly investigated in many organs such as brain, heart, liver, and kidney. However, data about the role of these cytokines in the spinal cord, despite its vulnerability to IRI, are limited. Our analysis

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aimed at determining the early effects of systemic administration of correlated methods for spinal cord ischemia reperfusion injury. In addition, we discussed the pathological mechanism and solution for SCIRI, suggesting some proper programs for this research.

Patients and Methods

Patients

A total of 180 participants were studied for age, sex, and other influencing factors. The patients were randomly assigned to one of the three groups. All experimental procedures and protocols used in this investigation were in accordance with the Ethics Committee of our hospital. Group one (n = 60) underwent acute spinal cord injury, group two (n = 60) underwent slight spinal cord injury, and group three (n = 60) did not undergo spinal cord injury (Table I).

Experimental Preparation

After dividing the three groups of investigated patients, the experimental conditions and program were designed for various approaches. A total of 180 patients underwent a surgical procedure and patients who received normal saline intraperitoneally immediately after the patients' aortic occlusions were released. This observation lasted three years from 2003 to 2005; then, 180 hospital patients were divided into three groups for the research of spinal cord ischemia reperfusion injury experiment.

Statistical Analysis

All statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). The difference in TMEM between metastatic and non-metastatic patients was evaluated via using the Wilcoxon signed-rank (matched pairs) test. The statistical significance of differences between two experiment groups or among three experiment groups was determined by Mann-Whitney test, Student's *t*-test, x^2-test or One-way ANOVA, as appropriate. Tukey's HSD (honestly significant difference) test was used in conjunction with an ANOVA to find means that are significantly different from each other. Correlation analysis was also performed by using Spearman rank correlation coefficient test or Pearson product-moment correlation, as appropriate. Statistical significance was set at $p < 0.05$.

Results

The Model of Spinal Cord Injury

As some injuries to the spinal cord occur, the osteoligamentous spinal column fails under a variety of loading conditions, including flexion, extension, axial load, rotation and distraction. These forces impart the primary mechanical insult to the spinal cord, which, in its mildest form, causes a cord concussion with brief transient neurologic deficits, whilst in its most severe forms causes complete and permanent paralysis. Whereas the former represents local axonal depolarization and transient dysfunction, the latter represents a primary axonal and neuronal injury followed by spreading of secondary tissue damage that expands from the injury epicenter. The schematic and detailed explanation of primary and secondary damage after spinal cord injury is shown in Figure 1. An ordered procedure offers the mechanical forces imparted to the spinal cord.

The mechanical forces imparted to the spinal cord at the time of injury cause immediate tissue disruption[6]. The cooperation of the six procedures acts as a systematic administration; this primary injury rarely transects the spinal cord but rather leaves an intact rim of tissue. This adjacent tissue that survives to the primary injury, is vulnerable to acute pathophysiologic processes that quickly follow. Neuroprotective interventions aim to minimize the destructive effects of these processes. Therefore, the primary and secondary damage after spinal cord injury play an important role in the mechanism of injury.

Table I. Information of groups for age and sex.

Groups	Age (mean ± SD)	Sex (male/female)
Group 1	48.7 ± 11.2 (N = 60)	1.2
Group 2	50.2 ± 10.1 (N = 60)	1.7
Group 3	47.8 ± 12.3 (N = 60)	1.3

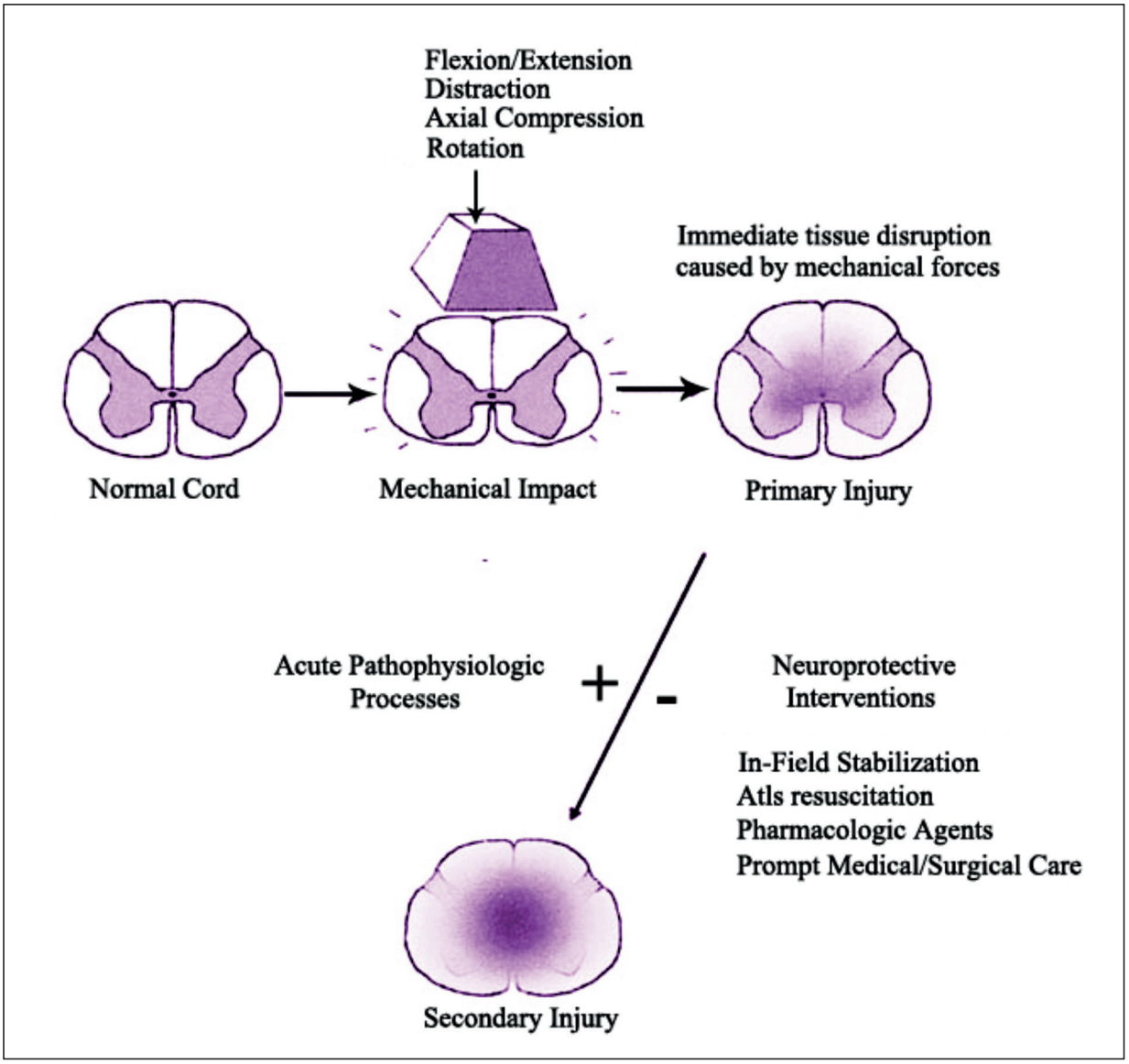

Figure 1. Schematic of primary and secondary damage after spinal cord injury.

The dynamic variation of spinal cord blood perfusion is shown in Table II. The baseline value of spinal cord blood perfusion is 303.5 ± 45.76 PU, the initial SCBP value of ischemia drops rapidly, and the pure ischemia for 10 min drops to 38.66 ± 17.92 PU of the SCBP value; the correlated percentage is -73.98% comparing to the baseline value. Thirty min after the onset of ischemia, we found a decrease in the local blood flow in the lumbar spinal cord, almost -77.48% of the baseline, which was reversed partially by initial reperfusion, even exceeding the baseline level. However, 1 hour after reperfusion, the local blood flow returned to baseline levels, and finally dropped to 207.13% ± 46.14 PU for 3 hours, without any recovery.

Histopathologic Evaluation

The features consistent with neuronal injury included eosinophilic cytoplasm, vacuolization, and pyknotic appearance loss of nuclear structure (Figure 2). Cells that contained Nissl substance in the cytoplasm, loose chromatin, and prominent nucleoli, were considered viable. The viability index was calculated as the number of clearly viable neurons divided by the total neuronal count

Table II. The value of lumbar spinal cord blood flow of spinal cord ischemia perfusion.

Time	SCBP (PU)	Percentage of the baseline
Baseline	303.5 ± 45.76 (30)	–
I 10 min	38.66 ± 17.92 (5)	-73.98%
I 30 min	42.19 ± 13.86 (5)	-77.48%
P 10 min	427.09 ± 88.37 (4)**	37.17%
P 30 min	326.92 ± 71.33 (4)$^{\Delta}$	18.05%
P 50 min	249.57 ± 72 (4)*	-17.84%
P 60 min	244.31 ± 29.17 (4)**	-19.27%
P 90 min	246.35 ± 52.29 (4)*	-20.57%
P 120 min	239.87 ± 53.18 (4)*	-22.87%
P 180 min	207.13% ± 46.14 (3)*	-33.91%

Note: PU: the unit of blood perfusion, Baseline: baseline value before ischemia, I: ischemia, P: reperfusion, compare to baseline value: *$p < 0.05$, **$p < 0.01$, $^{\Delta}p > 0.05$.

within the anterior horn of each section for each animal. In the analysis of the tissue (Figure 2), the red arrows suggest exhibiting inflammatory cell accumulation, destruction and vacuolization of the gray matter, pyknosis of neurons, and capillary proliferation.

The histopathologic evaluations were performed by a pathologist blinded to the study groups and clinical information[10-12]. Histopathologic sections were evaluated both by qualitative and quantitative methods in order to maximize scientific accuracy. Histologic damage was scored qualitatively, using a previously defined system, explaining the pathology mechanism for spinal cord ischemia reperfusion injury.

Discussion

Pathophysiological Changes of SCIR

With a series of ischemia following spinal cord ischemia injury pathophysiological changes, the spinal cord injury was amplified. Because of changes in SCBF as well as pathological changes of spinal cord tissue reactions, we monitored closely the local blood flow in L1-2-segmental spinal cord with ischemic injury. The experimental results showed that ischemia for 30 min and 4 h of reperfusion spinal cord, delayed hypoperfusion. According to the results of pathological examinations[13], we confirmed that blood supply was restored at 30 min

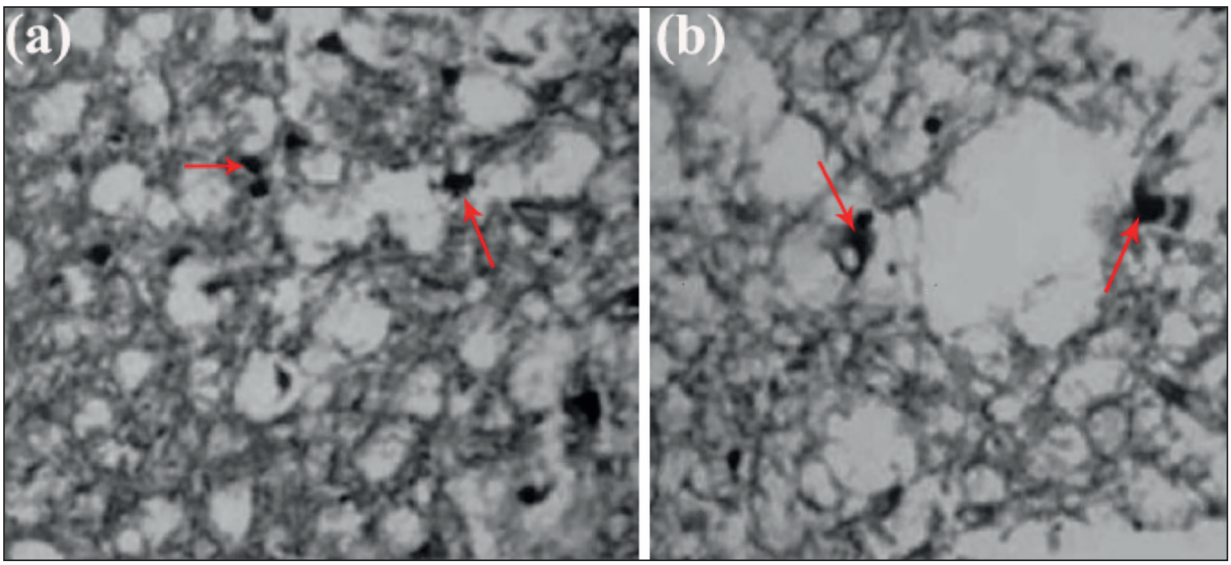

Figure 2. Histopathologic observation of anterior horn of lumbar spinal cord segments procured hours after reperfusion at ***(a)*** 1 hour, ***(b)*** 3 hours.

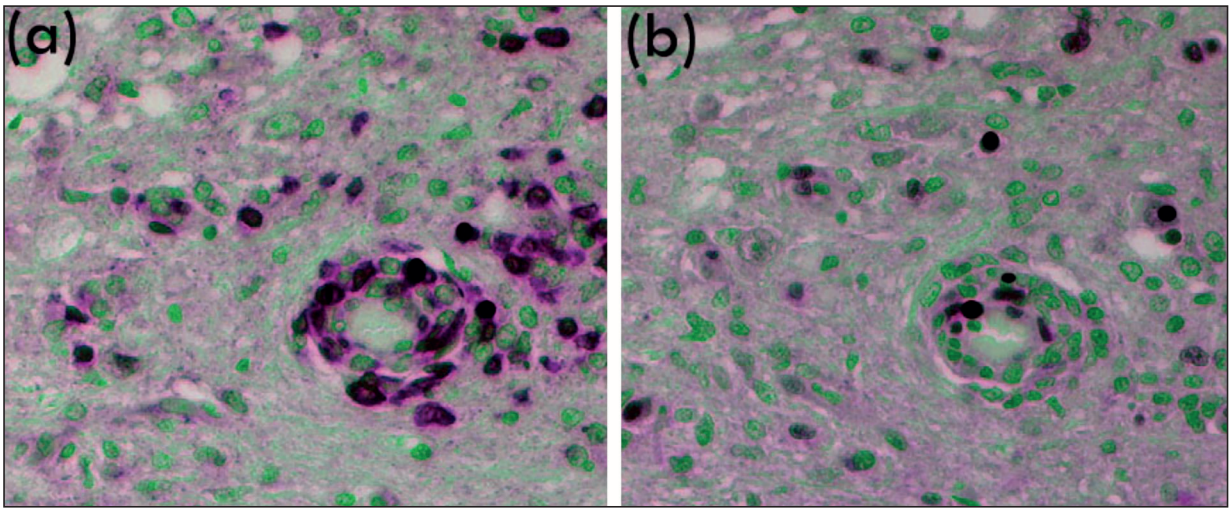

Figure 3. Lymphocytic infiltrates tissue changes observed in the spinal cord of patients 3 days following transient aortic cross-clamp and ligation of four pairs of intercostal arteries.

after ischemic attack, and after 4 hours of reperfusion, pathological and progressive increase in blood supply would result in secondary injuries to the spinal cord.

Some changes of detailed information are shown in Figure 3. The spinal cord of patients was observed three days following transient aortic cross-clamp and ligation of four pairs of intercostal arteries.

As dorsal, intermediate, and ventral horns were affected; the lesions did not change in severity from cranial to caudal within the affected segments. Degenerative changes in surviving neurons were characterized by central chromatolysis. Lymphocytic perivascular infiltrates were observed within the affected grey matter that extended into the surrounding neuropil. Immunohistochemical staining showed that these lymphocytes were CD3+ (Figure 3).

Further study showed that the local SCBF changes are correlated with the pathologic examination results. Ischemia-induced ultrastructural changes in spinal cord anterior horn cells after reperfusion are more evident than ischemic injuries; with the lapse of reperfusion time, spinal cord ventral horn cells appear in swelling-shape with vague nuclear structure, increased cohesion of intracytoplasmic vacuoles and mitochondria. Hypoxia, thickening of capillary endothelium, and matrix compact cavity, are confirmed in the ischemia-reperfusion (I/R) of spinal cord spinal cord.

Conclusions

We showed that pathological mechanism changes during reperfusion injury and reperfusion time correlation and compliance. I/R microcirculation is regarded as the pathology of reperfusion injuries to spinal cord and that of focal ischemia injury, where the blood circulation is hard to be improved through the spinal cord itself. This means that it is hard to restore the blood supply and improve the secondary damage. 30 min after the onset of ischemia, we found a decrease in the local blood flow in the lumbar spinal cord, almost -77.48% of the baseline, which was reversed partially by initial reperfusion, even exceeding the baseline level. However, 1 hour after reperfusion, the blood flow was again decreased to the level below the baseline, followed by a decline to 207.13% ± 38.25 PU for 3 h without any recovery. Under the normal conditions, a variety of substances secreted by endothelin are involved in the regulation of vascular tone, so as to maintain the blood flow and prevent the thrombosis[14,15]. Hemodynamic changes, during reperfusion after ischemia, result in injuries to endothelial cells in arteries and microvessel, leading to the morphological and functional changes, further resulting in a decrease in the vasodilatation ability and blockage in capillaries.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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