Ischemic Preconditioning and Spinal Cord Function Monitoring in the Descending Thoracic Aorta Approach

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Summary

Objectives: To evaluate the effectiveness of acute ischemic preconditioning (IP), based on somatosensory evoked potentials (SSEP) monitoring, as a method of spinal cord protection and to asses SSEP importance in spinal cord neuromonitoring.

Methods: Twenty-eight dogs were submitted to spinal cord ischemic injury attained by descending thoracic aorta cross-clamping. In the C45 group, the aortic cross-clamping time was 45 min (n=7); in the IP45 group, the dogs were submitted to IP before the aortic cross-clamping for 45 min (n=7). In the C60 group, the dogs were submitted to 60 min of aortic cross-clamping (n=7), as in the IP60 group that was previously submitted to IP. The IP cycles were determined based on SSEP changes.

Results: Tarlov scores of the IP groups were significantly better than those of the controls (p = 0.005). Paraplegia was observed in 3 dogs from C45 and in 6 from C60 group, although all dogs from IP45 group were neurologically normal, as 4 dogs from IP60. There was a significant correlation between SSEP recovery time until one hour of aortic reperfusion and the neurological status (p = 0.011), showing sensitivity of 75% and specificity of 83%.

Conclusion: Repetitive acute IP based on SSEP is a protection factor during spinal cord ischemia, decreasing paraplegia incidence. SSEP monitoring seems to be a good neurological injury assessment method during surgical procedures that involve spinal cord ischemia.

Key words: Ischemic preconditioning; spinal cord; aortic aneurysm; evoked potencial.

Introduction

Paraplegia is a severe complication of the surgical approach to descending thoracic aorta aneurysms, being in the majority of the cases, an irreversible deficit, caused by a spinal cord ischemic injury during the process of aneurysm correction[1]. The main risk factors associated to paraplegia are those related to the patient's individual anatomy, the anesthetic care necessary during the procedure and the surgical technique used.

The high sensitivity of the evoked potentials to the interruption of the spinal cord perfusion allowed its recording to become an effective and rapid evaluation method of distal aortic perfusion and spinal cord viability during the surgical correction of aortic aneurysms[2,3]. Changes observed in these potentials that can suggest spinal cord ischemia allow an immediate intervention on the part of the surgeon in an attempt to correct the factors responsible for their occurrence[2,4-6].

In parallel, several maneuvers have been proposed in an effort to minimize the risk of spinal ischemia during the correction of thoracic and abdominal aorta aneurysms, although with controversial results. These maneuvers include pharmacological interventions[7,8,9], decrease of aortic cross-clamping time[10], reduction of the distance between the vascular clamps[10], systemic[11] or regional[12] hypothermia, systemic hyperthermia[13,14], reimplantation of the intercostal and lumbar arteries[9,15], CSF drainage[9,15,16], and perfusion of the distal aorta at the last cross-clamping[1,9].

Based on the description of the beneficial effects of the ischemic pre-conditioning (IP) regarding the myocardium[17], several authors have studied the influence of such procedure on other organs and systems[18]. Studies have shown an apparent efficacy of IP in protecting against spinal cord ischemia, with the benefit being obtained mainly when the procedure is performed 1 or 2 days before a prolonged ischemic injury[19-21]. On the other hand, the acute IP of the spinal cord, potentially more likely to be incorporated to clinical practice, has shown controversial results[22-26], especially due to a failure in the adequate control of ischemia and reperfusion time, necessary to achieve its effect.

This study aims at evaluating the influence of somatosensory evoked potential (SSEP) monitoring on the use of immediate IP as a spinal cord protection method in dogs, and the use of this monitoring method in the early detection of spinal cord ischemic impairment due to prolonged aortic cross-clamping.

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Métodos

Twenty-eight male and female mixed-breed dogs, weighing between 15 and 25 kg, obtained at the City Pound of the city of São Paulo, Brazil, were used in the study. The experiments were carried out according to the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Academy of Sciences, Washington, D. C. 1996) and the Ethical Principles of Animal Experimentation of the Brazilian College of Animal Experimentation (COBEA).

The animals were divided in 4 groups, with the objective of comparing the effects of IP in four different times of spinal cord ischemia induction:

• Group I – Control I (C45): aortic occlusion for 45 minutes;

• Group II – Pre-conditioning I (IP45): Three cycles of IP, followed by 45 minutes of aortic occlusion;

• Group III – Control II (C60): aortic occlusion for 60 minutes.

• Group IV– Pre-conditioning II (IP60): Three cycles of IP, followed by 60 minutes of aortic occlusion.

One hour before each experiment, under anesthesia, stimulation electrodes were placed on the right posterior tibial nerve and recording electrodes were placed in the epidural space, between T12 and L1. These electrodes were used to determine SSEP before, during and after the induction of the spinal cord ischemia by the occlusion of the descending thoracic aorta.

The dogs were anesthetized with endovenous sodium pentobarbital (30 mg/kg) and submitted to orotracheal intubation and ventilated in a pressure-controlled ventilation (PCV) apparatus, maintaining a volume of 12ml/kg and an optimal respiratory frequency to maintain the pressure of carbon dioxide between 35 and 45 mmHg and oxygen saturation of 100%.

The body temperature of the animals was monitored by a rectal thermometer, and a continuous electrocardiogram recording was also performed. The mean arterial pressure (MAP) was monitored by an invasive procedure, through two catheters introduced into the right carotid artery (proximal MAP) and one of the femoral arteries (distal MAP).

A left posterolateral thoracotomy was performed in the fourth intercostal space to approach the descending thoracic aorta. After systemic heparinization with 100 U/kg, spinal cord ischemia was induced through the occlusion of the descending thoracic aorta, attained with the placement of a vascular clamp 1 cm below the left subclavian artery emergence.

The IP was performed based on SSEP alterations. When a decrease of 40% in the amplitude of SSEP (ischemia time) was observed, after the initial aortic cross-clamping, the clamp was removed until the SSEP presented the same initial amplitude of N1 (reperfusion time). Two more IP cycles were performed, with the same ischemia and reperfusion times determined in the first cycle. After the IP, the dogs were submitted to prolonged aortic cross-clamping for the periods established for each study group.

After the induction of spinal cord ischemia through prolonged aortic cross-clamping, the SSEP recovery time was evaluated. The potential was considered to be recovered when it presented, up to one hour after the reperfusion of the aortic segment, at least 90% of the SSEP amplitude observed before the ischemia.

The animals were observed for a period of 72 hrs after the induction of spinal cord ischemia, being submitted to the evaluation of sensitive-motor recovery of back paws and tail, according to the method of Tarlov:

• 0: Spastic paralysis of the back paws;

• 1: Perceptible tonus in the back paws;

• 2: Movements in the back paws, but the dog cannot sit and is statically unstable;

• 3: Capable of standing and sitting, but with difficulty;

• 4: Full motor recovery.

The animals were classified according to the resulting neurological score: animals with neurological scores 0 and 1 were considered to be paraplegic, those with score 2 or 3 were considered paraparetic and those with score 4 were considered to be normal.

The physiological data are presented as mean ± standard deviation. The neurological results and SSEP recovery times were expressed as medians and percentiles. The overall differences between the groups, when the physiological variables considered, were analyzed by one-way analysis of variance, followed by Bonferroni t test. The differences in the neurological results and SSEP recovery times between the groups were analyzed by Kruskal-Wallis test and Friedman's non-parametric analysis of variance, complemented by Dunn's test. Spearman's correlation test was used to analyze the existence of correlation between SSEP recovery times and the neurological results. A p value < 0.05 was considered to be statistically significant, and the statistical analyses were carried out by the software programs SPSS for Windows, version 13.0 (SPSS Inc, Chicago, USA) and Graphpad Prism 4.2 (Graphpad Inc., USA).

Results

There was no significant statistical difference among the four groups regarding weight, rectal temperature, hemoglobin, hematocrit, and blood gasometry during the experiments. Additionally, there were no significant differences regarding proximal and distal mean arterial pressure before, during and after the aortic cross-clamping.

During the IP periods, the ischemic induction times based on the SSEP alterations were similar between the 2 groups. The mean times of N1 decrease, in minutes, for a value ≤60% of the original value, were 2.6 ± 0.5 and de 4.4 ± 2.4 for the IP45 and IP60 groups, respectively. The mean recovery times of N1 in minutes after the reperfusion during IP were 7.5 ± 1.6 and 5.6 ± 2.6 for the IP45 and IP60 groups, respectively.

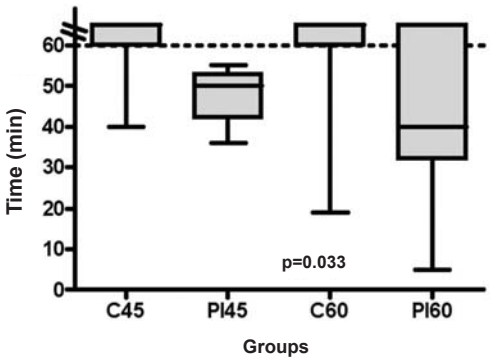
The results of the neurological assessment performed 72 hrs after the procedure are shown in Table 1. Paraplegia was observed in 3 dogs from Group C45 (Tarlov score = 0), paraparesis in 1 dog (Tarlov = 3) and 3 dogs had a normal evolution in this group. In the IP45 group, the 7 dogs had a

full neurological recovery (Tarlov = 4). In the C60 group, 6 dogs were paraplegic and 1 dog was paraparetic (Tarlov score = 2). In the IP60 group, 2 dogs presented Tarlov score = 0 and 1 dog presented Tarlov score = 1, with the three being considered paraplegic. Four dogs presented Tarlov score = 4, being considered normal. The statistical analysis showed that there was a significant influence of spinal cord ischemia time in relation to the occurrence of paraplegia (p=0.0015). In parallel, the results observed in the groups submitted to IP show the significant influence of this factor on the prevention of neurological deficits occurrence (p=0.0051).

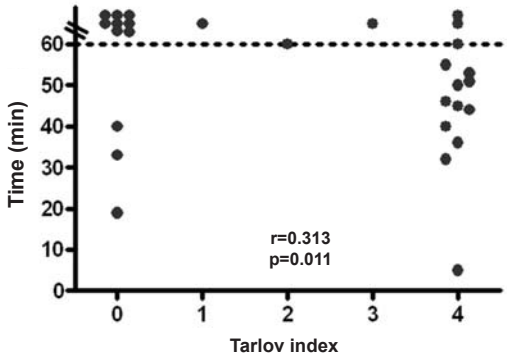
Table 1 - Number of animals classified by Tarlov Index 72 hrs after the aortic cross-clamping (Friedman's non-parametric analysis: p = 0.0015 for time of ischemia and p = 0.0051 for the presence of ischemic pre-conditioning - IP)

	C45	PI45	C60	PI60
Tarlov 0	3	0	6	2
Tarlov 1	0	0	0	1
Tarlov 2	0	0	1	0
Tarlov 3	1	0	0	0
Tarlov 4	3	7	0	4

Graphic 1 shows that most of the animals in both control groups did not present recovery of at least 90% of the SSEP range within one hour after the aortic reperfusion. On the other hand, all dogs from the IP45 group and most of the dogs from the IP60 group presented normalization of this parameter within the studied period (p=0.033). Overall, the dogs that recovered SSEP up to 1 hour of reperfusion after the critical ischemic injury presented fewer postoperative neurological deficits. On the other hand, dogs that did not recover the SSEP in up to one hour of reperfusion had a higher chance of presenting neurological deficits 72 hours after the surgery (Graphic 2). The correlation between time of SSEP recovery and the postoperative neurological state was statistically significant according to Spearman's test, which showed a correlation index r=0.313 (95%CI -0.621 to -0.079) and p value = 0.011.



Graphic 1 - *Time of somatosensory evoked potential (SSEP) recovery in each of the groups studied. Values presented as medians and quartiles, p obtained by Kruskal-Wallis test. C= Control; IP= Ischemic preconditioning.*



Graphic 2 - *Association between the somatosensory evoked potential recovery up to 1 hour of post-critical ischemia reperfusion with the Index in Tarlov scale. Values obtained by Spearman's correlation test.*

The absence of complete recovery of SSEP after the 60-minute reperfusion in the four groups studied showed a sensitivity of 0.75 (95%CI 0.48 to 0.93) and specificity of 0.83 (95%CI 0.52 to 0.98) in predicting the occurrence of neurological deficit (Tarlov ≤ 3). The predictive value of this test was 0.86 (95%CI 0.57 to 0.98) the negative predictive value was 0.71 (95%CI 0.42 to 0.92).

Discussion

The present study shows that the acute IP of the spinal cord is responsible for the increase of the tolerance to ischemia, when the times of ischemia and reperfusion used are based on the monitoring of the spinal cord function. It is na important step to add the acute IP as a neuroprotective strategy in thoracic and abdominal aorta surgeries as well as spinal cord surgeries that involve some degree of ischemia.

IP is a process where the sublethal ischemic stress increases tissue tolerance to the subsequent ischemic injury. This process involves cell protection mechanisms that include a phase of early protection as well as a late one[18]. Although some authors have previously demonstrated the late protection phase of IP[19-22,27], the acute effects of immediate IP have been controversial. Some studies have shown a significant impact of previous periods of ischemic induction some minutes before the prolonged occlusion of the aorta, in the prevention of spinal cord injury[24,26]. On the other hand, other authors have failed in demonstrating the same effect with the use of ischemic periods and shorter intervals in animals of the same species[23,25].

At the IP induction, determining the ideal duration of the times of ischemia and reperfusion is one of the main factors related to the success of the procedure. In the case of the spinal cord, as the residual blood flow can vary among different species of animals and individually, within the same species[28], it becomes necessary to adequately monitor the spinal cord function and its viability, during the ischemia as well as the reperfusion periods.

The determination of SSEP provides important diagnostic information related to the functional state of the spinal cord[3].

Variations in the range and latency of the N1 wave of SSEP in comparison to basal values are crucial for the diagnosis of ischemic injury to the spinal cord. The deterioration of the N1 range is indicative of decrease in the nervous transmission of the posterior and lateral sensory columns, indicating that the spinal cord perfusion is compromised[3,10]. During the process of ischemia, we can also observe the progressive deterioration of the other SSEP waves, which reappear in reverse order after reperfusion[29]. According to the spinal cord vascular anatomy, different types of SSEP responses can be identified and used to indicate the necessity of prophylactic measures to minimize the spinal cord ischemia[3].

It is known that SSEP monitoring as well as of the motor evoked potential can yield false-negative results, i.e., the responses of these potentials do not show alterations during the surgical procedure, although the spinal cord is under ischemia[30,31]. Several studies have shown that the false-negative results have a similar incidence with the two types of evoked potentials[31,32].

In this experimental model, we used the decrease of SSEP N1 range to define the periods of ischemia and reperfusion during IP. This choice was based on its sensitivity to regional hypoperfusion and the fact that the prolonged spinal cord ischemia could result in a complete loss of this potential. The times of disappearance of N3 and N4 waves at SSEP could also define adequate periods to induce ischemic tolerance, as proposed by Matsumoto et al[33] N1 and N2 waves seem to be pre-synaptic, whereas N3 and N4 seem to be post-synaptic[29].

Observing the difficulty in obtaining neuroprotection by IP in some previous studies, one can speculate that the ischemia and reperfusion times during IP were not adequate, as these times were not individualized, but pre-established. Cheng et al[29] showed that the last waves of SSEP are more sensitive to ischemia and disappear concomitantly with a decrease of N1 range more than 6 minutes after the induction of spinal cord ischemia in rabbits. Using animals from this same species, Haan et al[34], Sader et al[23] and Ueno et al[25] did not show induction of spinal cord ischemic tolerance with periods of short-term sub-lethal ischemia, whereas Matsumoto et al[33], Munyao et al[21] and Sakuray et al[35] obtained success with longer IP periods.

On the other hand, the SSEP response to spinal cord ischemia induction seems to be earlier in dogs[10], which justifies the use of shorter periods of aortic occlusion during the IP cycles in the present study.

Studies on the mechanisms of acute IP are limited, but some studies show a role in the increase of spinal cord blood flow[19,25]. Ueno et al[25] speculated that this effect can occur due to the attenuation of the post-ischemic capillary anti-reflux mechanism and by direct vasodilation action. In parallel, Fan et al[19] demonstrated that positive alterations in the spinal cord blood flow were associated with descending concentrations of norepinephrine and activation of the receptor of adenosine A1, some minutes after the IP induction in rabbits. However, further studies are necessary to clarify the biochemical mechanisms of spinal cord acute IP.

On the other hand, although several mechanisms have been proposed to explain the late protection observed at IP[18], it is likely that alterations in the genic expression of protective proteins have an important role in nervous system[36]. Recent studies have demonstrated the presence of higher levels of heat shock protein 24 hrs or more after spinal cord IP and this fact was associated with the acquisition of tolerance to the subsequent lethal ischemia[13,14,20,33,35]. There is a hypothesis that during the response to cellular stress, the elevation of heat shock protein response can allow denaturated proteins to re-obtain their conformations and facilitate the synthesis of new proteins.

The recovery of the SSEP wave range after the end of the aortic reperfusion has been correlated with the postoperative neurological result in experimental and clinical studies[36]. In the present study, the attainment of elevated levels of sensitivity and specificity for the correlation between time of SSEP recovery and postoperative spinal cord function impairment corroborates the increased clinical use of this method in the follow-up of patients submitted to prolonged aortic occlusion. This observation is probably caused by a lesser acute impairment of the spinal cord sensory and motor pathways, resulting in the non-impairment of the functional condition.

The present study had some limitations. The follow-up time of the animals was short, which might have hindered the observation of a late neurological injury. Observations by Abraham et al[22] showed that there can be a late worsening of the level of spinal cord impairment after the IP induction in rats, which can manifest within a 7-day period, when accompanied by significant spinal cord injury. Additionally, no anatomopathological studies of the spinal cord were carried out as well as no possible mechanisms involved with acute IP were evaluated, as the focus was on the choice of the best IP times based on SSEP.

The results of this experimental study showed that acute IP, based on SSEP monitoring, is a neurological protection factor to spinal cord ischemic injury, induced by the prolonged cross-clamping of the descending thoracic aorta. Additionally, it was also observed that the determination of SSEP is a good method of neurological monitoring and evaluation of the clinical prognosis of procedures that involve spinal cord ischemia induction.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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