Preclinical Studies for the Treatment of Blast-related Injuries

Pressure, Hemodynamics, and Metabolism Changes within the Spinal Cord after Injury

Traumatic spinal cord injury (SCI) triggers many perturbations within the injured cord, such as decreased perfusion, reduced tissue oxygenation, increased hydrostatic pressure, and disrupted bioenergetics. The temporo-spatial characteristics of these responses within the injured cord are not well documented. Researchers at the University of British Columbia (Vancouver, British Columbia) utilized a Yucatan mini-pig model of thoracic vertebra 10 contusion/compression SCI to characterize intraparenchymal hemodynamic (e.g., blood flow, oxygenation and hydrostatic pressure) and metabolic changes within the spinal cord for one week post-injury (*Streijger et al. 2017*). They demonstrated that traumatic SCI results in an expanded area of ischemia/hypoxia as evidenced in changes of spinal cord blood flow (SCBF), diminished oxygenation, and elevated hydrostatic pressure (Figure 1). They also reported an imbalance between SCBF and tissue metabolism that resulted in metabolic stress (Figure 2). The physiological perturbations were sustained out to seven days post-injury and extending away from the injury site. These findings indicate that the post-injury changes tended to continue and sometimes worsen over days two through seven, even at measurement sites farther away from the injury. This suggests that the current clinical practice of hemodynamically supporting patients out to seven days post-injury may fail to address persistent ischemia within the injured cord.

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REFERENCES:

Streijger, F., So, K., Manouchehri, N., Tigchelaar, S., Lee, J. H. T., Okon, E. B., Shortt, K., Kim, S. E., McInnes, K., Cripton, P., and Kwon, B. K. 2017. "Changes in Pressure, Hemodynamics, and Metabolism within the Spinal Cord During the First 7 Days after Injury Using a Porcine Model." J Neurotrauma 34 (24):3336-3350. doi: 10.1089/neu.2017.5034.

These preclinical findings using a large animal model have identified potential deficiencies in the current clinical practice and could change the paradigm of how physicians manage SCI patients.

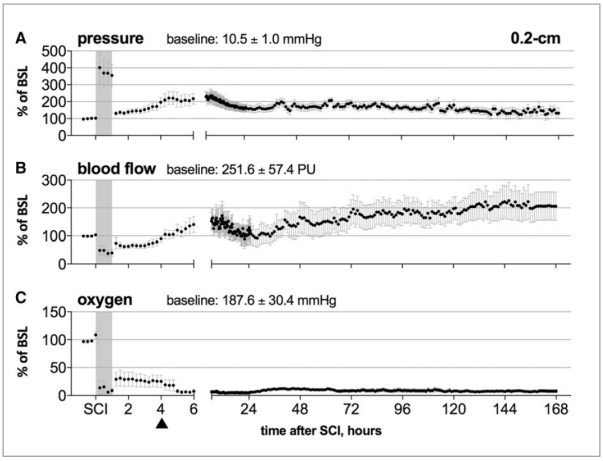

FIGURE 1: Dynamic changes (%Δ) of blood flow, partial pressure of oxygen and pressure in the penumbra (0.2 cm) of the traumatic SCI site. The percentage change (%Δ) is calculated using an average of 60 min of baseline before SCI. (A) Intraparenchymal spinal cord pressure, (B) SCBF, (C) and PaPO2 responses before, during and after 1-hour spinal cord contusion/compression (gray shading). SCI resulted in a promote increase in cord pressure and a loss of SCBF with a critical reduction in PaPO2. Following decompression, spinal cord pressure decreased sharply; however, it increased again within hours and remained consistently elevated for days. Within hour so decompression, SCBF restore to within baseline levels and continue to increase up to 200 percent above baseline levels by Day seven. Decompression only partially restored PaPO2 and through the seven-day monitoring period seemed entirely unaffected. The dashed line at the four-hour post-SCI mark (▲) represents the discontinuation of anesthesia and ventilation at the end of the surgical procedure. BSL, baseline; SCI, spinal cord injury. (Figure from Streijger et al. (2017) used with permission from the authors)

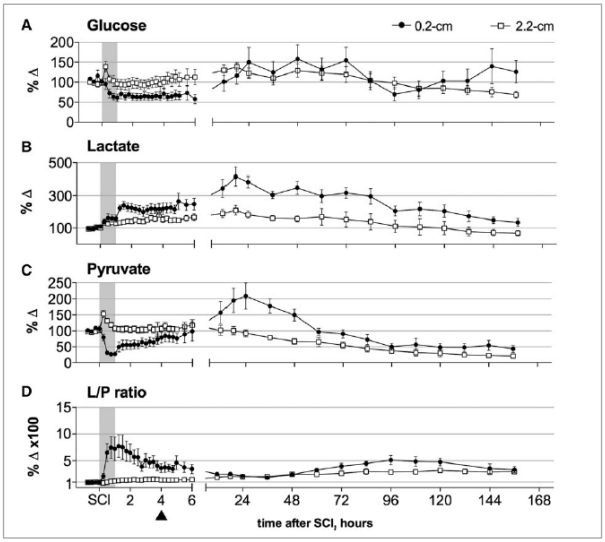

FIGURE 2: Microdialysis measurements of intraparenchymal glucose, lactate, and pyruvate (%D) in response to SCI at 0.2 and 2.2 cm from injury. The percentage change (%Δ) is calculated using the average of measurements obtained through 60 minutes of baseline recordings just prior to the SCI. (A) Glucose, (B) lactate, (C) pyruvate, and (D) lactate to pyruvate (L/P) ratio responses before, during, and after 1-hour spinal cord contusion/compression (gray shading). At the 0.2-centimeter position (●), glucose values decreased significantly upon SCI, and subsequently returned to baseline by Day one. Within minutes after SCI, we observed an increase in lactate, a decrease in pyruvate, and a resulting increase in L/P ratio. After decompression, glucose, pyruvate and lactate increased while L/P ratio declined to 200 percent above baseline at 24 hours. Thereafter, both lactate and pyruvate levels decreased again, although pyruvate fell proportionately more, resulting in a subsequent rise in L/P ratio till the end of the experiment (500 percent above baseline). At the 2.2-centimeter position (□), a slight increase in glucose levels was observed within the first 24 hours after SCI; however, levels retuned to baseline thereafter. Within hours after SCI, researchers observed a slow but steady rise in lactate while pyruvate levels remained unchanged, producing an increase in L/P ratio. After 24 hours, researchers observed a drop in lactate and a simultaneous and disproportionately greater drop in pyruvate, resulting in a continuous increase in L/P ratio to 500 percent above baseline at Day seven. The dashed line at the four-hour post-SCI mark (▲) represents the discontinuation of anesthesia and ventilation at the end of the surgical procedure. BSL, baseline; SCI, spinal cord injury. (Figure from Streijger et al. (2017) used with permission from the authors)