Upsala J Med Sci 93: 127–129, 1988

Hypoxia and Reoxygenation—Two Mechanisms for Tissue Injury in Ischemia and Shock

Ulf Haglund*

Department of Surgery, Lund University, Malmö General Hospital, Malmö, Sweden

The role of impaired oxygen delivery and hypoxia for the development of tissue injury in shock and ischemia has been studied extensively during the last years. It is well accepted that total ischemia and severely restricted oxygen delivery may cause tissue injury. However, it is probably less well known that reoxygenation, following a period of oxygen deficit, may induce tissue injury by itself. This will be discussed in the following and the development of intestinal tissue injury has been chosen as an example, mainly because reperfusion-reoxygenation injury was first demonstrated in this organ (2).

Shock and ischemia induce a characteristic injury of the small intestinal mucosa. This injury starts as a subepithelial space at the tip of the villi and may extend to a total destruction of the villi. The development of this tissue injury is dependent on the severity of the ischemia and its duration (1). Addition of small amounts of oxygen by intraluminal perfusion of oxygenated saline may prevent intestinal mucosal injury following periods of ischemia (3). The mechanism of development of tissue hypoxia during shock and partial ischemia in the small intestinal mucosa is rather complicated. This tissue has a high capacity to increase oxygen extraction by increasing arteriovenous oxygen difference, and oxygen consumption is not depressed until very low levels of intestinal blood flow supply (4). The vascular arrangement in the intestinal villi, providing the prerequisite for a countercurrent exchange system, explains why the tissue pO_2 is very low at the tip of the villi also during normal circulation. At low perfusion pressures the efficacy of the countercurrent exchanger will be much increased and the tip of the villi might become anoxic during hypotension despite a fairly normal blood flow supply (for further details see Haglund et al) (5).

Recently, Granger and co-workers (2) discovered that part of the intestinal tissue injury occurs also following reperfusion of the ischemic intestine.

*Appointed professor of Surgery, Uppsala University, by January 1, 1988.

These authors demonstrated that the intestinal vascular permeability was increased following ischemia and reperfusion, and this increase was much less if animals were treated with superoxide dismutase (SOD), a free oxygen radical scavenger, during ischemia or pretreated with allopurinol, an inhibitor of xanthine oxidase (2,11). It was then postulated that the main generation of oxygen free radicals following ischemia reperfusion was caused by xanthine dehydrogenase to xanthine oxidase conversion and accumulation of hypoxanthine during ischemia (2). At reoxygenation, xanthine oxidase facilitates the conversion of hypoxanthine to uric acid with the formation of superoxide anion. Later, the experiments performed by Granger and co-workers, in which the intestinal vascular permeability was chosen as the endpoint, were confirmed in studies where intestinal mucosal morphology was studied (4,12,13).

In these latter studies it was demonstrated that tissue injury, developing during the hypoxic period, was exacerbated during reperfusion. The prevention of this aggravation by SOD and allopurinol provides good indirect evidence for a free radical-mediated mechanism. More direct evidence for such a mechanism was obtained in experiments where the ultraweak light emission from the small intestine was recorded. Light specific for oxygen free radicals was induced by infusion of the xanthine oxidase and hypoxanthine to the small intestine (9) as well as at reperfusion following ischemia (10).

The relative importance of the hypoxic injury as related to reperfusion injury is dependent on the severity and the duration of ischemia. Preliminary data indicate that in the extracorporeally perfused kidney, the time interval (the window) during which the free radical-mediated mechanism for tissue injury is of importance as a exacerbating factor - causing injury in addition to that caused by hypoxia itself - is approximately 1 hour in warm och 24 hours in cold ischemia (7). As a comparison following rabbit ear frostbite the window for radical-mediated injury is approximately 1 minute (8). For the intestine available data indicate that following total ischemia, as seen clinically in intestinal strangulation, the reperfursion component of the small intestinal injury is insignificant (6). Partial ischemia with blood flow reduction to less than 50 per cent of control does not cause detectable injury. Neither is reperfusion following such mild ischemia followed by detectable injury. Between these two extremes, i.e. partial ischemia reducing intestinal blood flow to more than 50 per cent of control, available data clearly demonstrate an important reperfusion component of the mucosal injury seen following ischemia of various duration (6). During shock intestinal ischemia of this latter severity is what can be expected. Reperfusion injury is therefore likely to be a pathophysiological mechanism of the intestinal mucosal injury seen in shock,

as well as of the late consequences of such injury complicating shock (5).

In conclusion ischemia/hypoxia as well as oxygen delivery at reperfusion may cause tissue injury. The relative importance of these two mechanisms is mainly depending on the extent but also on the duration of ischemia.

REFERENCES

1. Chiu C.-J., McArdle, A.H., Bown, R., Scott, H.J. & Gurd, F.N.: Intestinal mucosal lesion in low-flow states. Arch Surg 101:478-483, 1970.
2. Granger, D.N., Rutili, G. & McCord, J.M.: Superoxide radicals in feline intestinal ischemia. Gastroenterology 81:22-29, 1981.
3. Haglund, U., Abe, I., Åhrén, C., Braide, I. & Lundgren, O.: The intestinal mucosal lesions in shock: 1. Studies on the pathogenesis. Eur Surg Res 8:435-447, 1976.
4. Haglund, U., Morris, J.B. & Bulkely, G.B.: Hemodynamic characterization of the isolated (denervated) parabiotically perfused rat jejunum. Acta Physiol Scand, in press.
5. Haglund, U., Jodal, M. & Lundgren, O.: The small bowel in arterial hypotension and shock. In: Physiology of the Intestinal Circulation (ed. A.P. Shepherd & D.N. Granger) pp 305-319, Raven Press, New York, 1984.
6. Haglund, U., Bulkley, G.B. & Granger, N.: On the pathophysiology of intestinal ischemic injury, Acta Chir Scand 153:321-324, 1987.
7. Hoshino, T., Warren, R., Maley, W.R., Bulkley, G.B. & Williams, M.: A quantitative evaluation of the proportion of free radical-mediated reperfusion injury follwing periods of warm, cold, and combined warm and cold ischemia in kidneys. Abstract. Fourth World Congress for Microcirculation, Program and Abstracts, 224 (213), 1987.
8. Manson, P.N., Jesudass, R., Bulkley, G.B., Marzella, L., Im, M.J. & Narayan, K.: The quantitative importance of free radical-mediated reperfusion injury in frostbite. Abstract. Fourth World Congress for Microcirculation, Program and Abstracts, 226 (214), 1987.
9. Morris, J.B., Haglund, U.H., Bulkley, G.B., Hall, T.S., Paky, A., Gurtner, G.H., Cadenas, E. & Sies, H.: Direct demonstration of oxygen free radical generation from a living, intact organ (the feline intestine). Surg Forum 37:123-125, 1986.
10. Morris, J.B., Haglund, U.H. & Bulkley, G.B.: The direct, real-time demonstration of oxygen free radical generation at reperfusion following ischemia in the living, intact, rat small intestine. Abstract. Gastroenterology 92:1541, 1987.
11. Parks, D.A., Bulkley, G.B., Granger, D.N., Hamilton,S.R. & McCord, J.M.: Ischemic injury in the cat small intestine: Role of superoxide radicals. Gastroenterology 82:9-15, 1982.
12. Schoenberg, M., Muhl, E., Sellin, D., Younes, M., Schildberg, F.W. & Haglund, U.: Posthypotensive generation of superoxide free radicals - possible role in the pathogenesis of the intestinal mucosal damage. Acta Chir Scand 150:301-309, 1984.
13. Schoenberg, M.H., Fredholm, B., Haglund, U., Jung, H., Sellin, D., Younes, M. & Schildberg, F.W.: Studies on the oxygen radical mechanism involved in the small intestinal reperfusion damage. Acta Physiol Scand 124:581-589, 1985.