Anesthesiology 2009; 111:1177–9 

# *Postconditioning and Controlled Reperfusion*

## *The Nerve of It All*

IT is being recognized that reperfusion is not only the definitive treatment for tissues undergoing arterial occlusions but also a major contributor to postischemic injury. This "reperfusion injury" has been observed in most organ systems, including the heart, brain and spinal cord, kidney, and skeletal muscle. Among these organ systems, there is a remarkable similarity in mediators, cellular victims, and physiologic manifestations of reperfusion injury. Infarct size and the extent of apoptosis have both been reported to increase after onset of reperfusion,[1,2] suggesting that reperfusion may present a therapeutic window to mitigate tissue injury. Indeed, the existence of reperfusion injury has been demonstrated by indirect methods that are potentially therapeutic approaches, including drugs and mechanical interventions initiated before or at the onset of reperfusion.

Low-pressure or "gentle" reperfusion and postconditioning (also called *ischemic postconditioning*, but we have dropped the restrictive term *ischemic*) are two such mechanical interventions that have been shown to reduce reperfusion injury in heart and neural tissue. Since the initial report by Zhao *et al.* in 2003,[3] the question was raised early on whether postconditioning was an "old wine in an new bottle"[4] of mechanical interventions in which gentle or low-pressure reperfusion was the prototype. Although the term *postconditioning* was originally limited to the application of serial intervals of reperfusion and ischemia or reoxygenation and hypoxia, the moniker has been expanded to include many interventions applied at the onset of reperfusion, including drugs, hypothermia, and now low-flow or low-pressure reperfusion. Indeed, several reports have shown that low-pressure reperfusion reduced postischemic myocardial injury,[5,6] with one showing equivalence between low-pressure reperfusion and postconditioning in reducing irreversible injury and improving contractile recovery. In this issue of ANESTHESIOLOGY, Jiang *et al.*[7] compare two modalities of postconditioning: conventional "ischemic" postconditioning and low-pressure reperfusion, both applied at the onset of reperfusion after spinal cord ischemia was imposed by a balloon placed in the abdominal aorta distal to the renal arteries in the *in vivo* rabbit model. In this study, the authors induced 25 min of spinal cord ischemia in anesthetized rabbits by inflating an infrarenal balloon catheter. Ischemic postconditioning was achieved by serial 1-min inflations and 1-min deflations of the balloon at the onset of reperfusion repeated for five cycles, while low-pressure reperfusion was achieved by partial deflation of the balloon to achieve a measured perfusion pressure of 45–55 mmHg for the first 10 min of reperfusion. The interventions lasted for a total of 10 min. They reported that both "postconditioning interventions" equally improved neuromotor function (Tarlov score) and increased the number of intact motor neurons 28 days after treatment compared with a control group with rapid-onset reperfusion. In addition, the two postconditioning methods involved increased phosphorylation of the reperfusion injury survival kinase pathway components extracellular signal–regulated protein kinase (ERK1/2) and phosphatidylinositol 3-kinase 2 h after reperfusion/treatment; intrathecal injection of inhibitors of extracellular signal–regulated protein kinase and phosphatidylinositol 3-kinase abrogated phosphorylation of extracellular signal–regulated protein kinase and the downstream target of phosphatidylinositol 3-kinase, serine/threonine protein kinase protein kinase B (also known as Akt), morphologic salvage of motor neurons, and increased Tarlov motor scores. Hence, this study showed that neuroprotection by postconditioning is equivalent to that of low-pressure reperfusion after transient ischemia in spinal cord.

Now that the notion of equivalent tissue protection has been demonstrated for low-pressure reperfusion and postconditioning in both neural tissue and myocardium, it would be interesting to know whether the same physiologic and molecular mechanisms are engaged by the same triggers. The most obvious difference between the two maneuvers is transient periods of total ischemia in postconditioning, whereas low pressure presumes a continual blood flow that is lower than that required to fully meet energy demands. Hence, both methods may share some level of ischemia as a commonality. These periods of ischemia would maintain tissue acidosis and delay realkalinization. This "pH hypothesis" was introduced by Cohen *et al.*,[8] in which perfusion of isolated perfused rabbit hearts with an acidic buffer for the first 2 min of reperfusion reduced infarct size. Cardioprotection was abrogated by transient perfusion with alkalotic buffer, oxygen radical scavenger (N-2-mercaptopropionly glycine), protein kinase C inhibition (chelerythrine), or

This Editorial View accompanies the following article: Jiang X, Ai C, Shi E, Nakajima Y, Ma H: Neuroprotection against spinal cord ischemia–reperfusion injury induced by different ischemic postconditioning methods: Role of phosphatidylinositol 3-kinase–Akt and extracellular signal–regulated kinase. ANESTHESIOLOGY 2009; 111:1197–1205.

Accepted for publication August 28, 2009. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article. Dr. Vinten-Johansen has two patent applications pending related to postconditioning for myocardial protection.

activation of adenosine triphosphate–sensitive potassium channels (5-hydroxydecanoate). Similar results have been reported by others.[9] Tissue acidosis maintains the mitochondrial permeability transition pore in a closed state, and inhibits sodium–hydrogen exchanger and the linked calcium influx and accumulation *via* the sodium–calcium antiporter. Both tissue acidosis and lower calcium inhibit mitochondrial permeability transition pore opening. In addition, the periods of ischemia would increase the generation and release of adenosine and other G-protein receptor agonist autacoids found to be involved in postconditioning.[10,11] The brief periods of reperfusion would limit the delivery of oxygen to that sufficient for generating signaling reactive oxygen species,[12] but insufficient to generate cytotoxic amounts of reactive oxygen species.[13] Because blood flow and oxygen delivery in low-pressure reperfusion would be inadequate to meet tissue demands in an autoregulating vascular bed, one could hypothesize that low-pressure reperfusion may (1) maintain tissue acidosis and delay realkalinization, (2) limit the delivery of oxygen to the tissues which would favor generation of signaling reactive oxygen species and limit cytotoxic reactive oxygen species, and (3) release adenosine and other cardioprotective autacoids. In short, low-pressure reperfusion may create the same cardioprotective tissue environment as achieved by postconditioning. However, the mechanisms that trigger and mediate the tissue protection of low-pressure reperfusion, as well as the endpoints, all remain to be identified. In addition, in view of the article published by Skyschally *et al.*,[14] it is not clear that the reperfusion injury survival kinase pathway correlates with myocardial salvage in larger animal models of ischemia–reperfusion.

If low-pressure (low-flow) perfusion achieves similar tissue protection as postconditioning, either method may be used, albeit by different methods used in different settings. Low-pressure perfusion may be achieved by partial inflation of an intravascular balloon as used by Jiang *et al.*[7] in this issue of ANESTHESIOLOGY, but some measure of blood pressure or flow must be used to avoid pressures that are too high or too low to induce protection.[15] Low-pressure postconditioning may also be implemented for a strategic duration of time by a perfusion system. This may be most appropriate for a surgical approach in which direct cannulation of the artery is readily accessible, but may also be used for percutaneous approaches where access to the arterial supply to the target organ can be achieved by intravascular catheter. Again, the use of low-pressure postconditioning requires some measure of distal intravascular pressure and/or blood flow by which to control the pump. Some measure of the adequacy of pressure and blood flow assessed by means of intravascular pressure or a marker substance (*i.e.*, lactate) may be helpful in adjusting those parameters to induce a "postconditioned" state. Conventional postconditioning, on the other hand, may be implemented by serial deflations and inflations of an intravascular balloon as used in early preclinical and clinical studies, and also by vascular perfusion pumps in which alternating total ischemia and full blood flow may be achieved. Alternatively, similar pulses of perfusion and occlusion may be imposed by surface occlusion of vessel during surgery. In this case, some knowledge of adequacy of blood flow would be necessary to avoid either overperfusion or underperfusion of the target tissue.

The article by Jiang *et al.*[7] adds to the growing body of data demonstrating that organs undergoing ischemia and reperfusion have an innate capacity to protect themselves. These innate mechanisms have limited potential, however, and are often overwhelmed by ischemia–reperfusion. The result is that the tissue succumbs to irreversible injury, and the degree of salvage gained by reperfusion therapy is less than that intended, and certainly less than is potentially achievable. However, mechanical modifications of reperfusion alone, in the absence of pharmacologic agents, may augment these self-same innate protective mechanisms, thereby salvaging tissue and preserving function of that organ. Neural tissue is added to the list of organs and cell types that are protected by controlled reperfusion, including ischemic postconditioning and low-pressure postconditioning. Drugs may be used to mimic or enhance the effects of the mechanical interventions, or to enhance the overall level of tissue protection to salvage more tissue from irreversible injury. The algorithms used for ischemic postconditioning and the pressure and flow characteristics used for controlled low-flow postconditioning require fine-tuning to achieve the optimal degree of salvage. In addition, industry will find new opportunities in the development of catheters, pumps, and devices that implement controlled reperfusion and that measure biochemical markers, which may implement optimal reperfusion therapeutics to a host of tissues that undergo ischemia. One implication of increased tissue salvage with a reperfusion therapy (*i.e.*, postconditioning) is that ischemic time is no longer the predominant determinant of injury; reperfusion is an important contributor. If so, the physician can be less threatened and less preoccupied by limiting the ischemic time, and more focused on modifying reperfusion to gain the most tissue salvage. However, whether postconditioning by any means converts a 4-h injury profile (infarct size, dysfunction, apoptosis) into a 1-h injury profile and whether the ischemic time–injury curve is clinically extended are interesting questions that remain to be answered.

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