diac fibers that links the septal crossing of descending and ascending segments. Some of this is recognized, as they indicate that the final model is conjectural and based on the examiners' experience with dissection slide reading. Despite this, they see the helical patterns and thus add another coiled observation to cardiac anatomy.

We agree that function is related to the muscular formation of the wrapped tube, and we also recognize that joining of form and function can produce departure between the anatomist and pathologist that observe only the nonfunctional structure, and the physiologist and surgeon that must link function with underlying form. Our recent report of sonomicrometer verification of the functional components along the band, that correlate with magnetic resonance imaging studies of contraction, indicates we must take a new look into the form/function relationship, based on spatial orientation of the ventricular muscular band.[6]

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Alternate explanation of the hypothermic prolonged induction of heat shock protein

To the Editor:

Motoyoshi and associates[1] are to be congratulated for their provocative article, titled "Establishment of a Local Cooling Model Against Spinal Cord Ischemia Representing Prolonged Induction of Heat Shock Protein." Their method seems reliable as a model to study heat shock protein (Hsp) problems unrelated to temperature, but it seems less reliable as a method to study spinal cord protection from which temperature cannot be unlinked. The explanation of how and why Hsp was induced consistently, in our opinion, is inadequate.

We do not contest that modest hypothermia exerts protective effects.[2] However, to claim that it is better not to do anything before ischemia to maximize the beneficial effects of ischemic stress before inducing hypothermia is contradictory to conventional hypothermic and/or pharmacologic protection concepts/approaches.

Systemic hypothermia induced by surface cooling in rabbits was used in studies of spinal cord protection. We found that esophageal temperature measured 3 cm above the gastroesophageal junction before aortic clamping correlated with that of the spinal cord, within 0.1°C to 0.2°C, and therefore was usable as a surrogate site, but rectal temperature was not usable. An esophageal temperature of 29.4°C ± 0.07°C allowed full functional recovery within 5.5 hours of reperfusion after 60 minutes of ischemia in all rabbits, which yielded 6 to 6.2 minutes of ischemic protection for each 1°C, decreased by surface cooling after eucapnic ventilation, equivalent to pH-stat perfusion hypothermia, and rewarmed over a 90-minute period to 34°C to 35°C; however, only 0.5°C higher hypothermia uniformly failed.[3,4] The proposed cooling method that results in spinal cord temperature with variability as large as 2°C is unacceptable for investigation or clinical use. Because it lacks other surrogate sites, without measuring actual spinal cord temperature, the exact role or degree of hypothermia required to achieve the reported effect could not be elucidated.

As illustrated in their Figure 1, the model was one of ischemia at 37°C to 36°C during the first 5 minutes and at 35°C to 33°C during the last 10 of the 15 minutes. *Fifteen* minutes of ischemia could theoretically be protective at 35.8°C induced by surface cooling.

Use of a normothermic group seems inappropriate to support their contention that local cooling is the key element. Instead, rabbits surface-cooled systemically to 36.1°C to 36.3°C before ischemia should have been used. Two rewarming rates should have been studied: a relatively fast rate, using conventional total body rewarming sources, and a rate similar to that of the locally cooled spinal cord. Although the authors did not mention how quickly the animals were rewarmed, in our opinion this information is needed to justify their conclusion, for the rate of rewarming could be the definitive and advantageous feature of local hypothermia.

Whether ischemia-injured neurons die by apoptosis or necrosis depends on the extent of depletion of high-energy~P[5]; apoptosis-necrosis is a continuum,[6] necrosis occurring when depletion is maximal, but in either situation sustained Hsp70 synthesis cannot be supported, as in their normothermic rabbits.

Hsp70 is produced under stressful conditions for protection. If reduced stress was the mechanism of the prolonged induction of Hsp70, as the authors explain, the immunoreactivity should decrease, not increase. In our opinion, timely hypothermia spared enough high-energy~P to preserve the metabolic machinery that enabled continuing synthesis of sufficient Hsp70 for 2 days, but not enough to restore normal function immediately after reperfusion. Two days later, normal function was restored and the presence of Hsp70 was no longer required, thus disappearing by 7 days; apoptosis was averted, as in their hypothermic group.

The proposed strategy is applicable to only short ischemic periods. Ischemic periods lasting long enough to exhaust the high-energy~P store before implementation of systemic or local hypothermia commensurate to the ischemic time will induce a degree of metabolic machinery derangement that could not be protected by the then scarcely available Hsp70, resulting in irreversible injury as either apoptosis or necrosis. To protect the spinal cord during such long ischemic times necessitates implementation of hypothermic and/or pharmacologic preischemic protective means. The question is not how the hypothermia was induced, but whether it was timely and

commensurate with the duration of ischemia. In our opinion, lasting Hsp production would occur with a *barely effective degree of preischemic systemic hypothermia* as part of the protective mechanism. If the ischemic duration is short, or the protective strategy results in effective sparing of enough high-energy~P to sustain normal function until aerobic metabolism is reestablished after reperfusion, production of Hsp is not induced. We believe that is what happened in the study by Kumar and associates,[7] who described 10 minutes of ischemia at 30°C in the gerbil brain, although the authors' interpretation was different.

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Reply to the Editor:

We read with interest the letter by Miyamoto and Miyamoto concerning our article about the method of establishment of local spinal cord cooling and interpretation of heat shock protein (Hsp) induction. The authors proposed that as much as 2°C might be inappropriate for investigation of the hypothermic effect on brain ischemia. Some reports have shown the importance of strict management of temperature.[1] However, we were satisfied in our early period with the utility of this model, in which a cold pack was attached to the lumbar region of the animals, because we had aimed to establish a *simple, local cooling model* against spinal cord ischemia. Preliminary study had provided us the spinal cord temperature, which was significantly lower than those of two other sites (rectal and esophageal [the latter data were not shown]), which meant regional hypothermia was established.[2] Other types of local cooling in animal models have been reported, but few series of studies have been performed. One reason may be that those previous models are complicated to reproduce. We may need to apply a few tips for the establishment of a refined model in which the temperature of the spinal cord can be managed minutely. We did not report preischemic or postischemic hypothermia in this study; therefore, that type of research might be expected.

The authors also insisted that spinal cord ischemia for 15 minutes would not occur under an esophageal temperature of *35.8°C.* Inappropriate comparison of spinal cord temperatures using different models should not be performed because the ischemic effect depends on small differences in temperature.[1] Many investigations of brain ischemia have informed us that no absolute critical temperature has been identified that could avoid an ischemic insult *through all ischemic models.* We could not find any comments in the previous reports that ambient preischemic hypothermia could preserve high-energy~P to support continuous Hsp synthesis in spinal cord motor neurons, as Miyamoto and Miyamoto explained. Furthermore, our study provided the effect of intraischemic hypothermia, not preischemic hypothermia.

Miyamoto and Miyamoto also commented that apoptosis and necrosis are continuum reactions unrelated to Hsp synthesis. There have been some reports describing the relations between apoptosis/necrosis and Hsp induction.[3,4] Some kinds of Hsp families have been reported to inhibit apoptosis/necrosis.[5] Less than 10 minutes of ischemia was reported to result in Hsp induction. One study reported that neuronal ischemia for even 6 minutes was enough to promote Hsp induction.[6] Ten minutes of normothermic spinal cord ischemia also induced sustained Hsp72 synthesis, which resembled 15 minutes of ischemia under mild hypothermia using the same transient ischemic model.[7] The 10 minutes of ischemia did not cause neuronal damage; moreover, this ischemic period seemed to protect against the following ischemic insult, known as *preconditioning.* There should be a topical correlation with Hsp induction and neuronal damage that might lead to cell death.

The rewarming condition, which was thought to be constant in our animals, was not considered in our report. Rewarming conditions have not been studied in most investigations of neuronal ischemia. However, it would be interesting to research whether various rewarming durations would alter the degrees of spinal cord ischemic insult in our model, as Miyamoto and Miyamoto have already suggested.

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