In Reply:

The authors sincerely thank Dr. Roth for his letter regarding their recent article and are happy to respond to his comments and anecdotes.

The problematic of chest wall compliance is of interest and is not new. In 1989, Pizov et al. demonstrated in a canine model that reducing chest wall compliance by external chest compression induced an increase in the deltalnd component of the systolic pressure variation, suggesting a decrease in the venous return. More recently, Mesquida et al. found an increase in pulse pressure variations and stroke volume variations after reduction in chest wall compliance induced by chest and abdominal binders in an experimental study. As suggested by Dr. Roth, decrease in chest wall compliance may be due to truncal rigidity. This situation may be related to a lack of sedation (which contraindicates the use of dynamic indices) or may be provoked by high doses of opioids (an uncommon practice actually even in cardiac surgery). In contrast, a decrease in chest wall compliance secondary to abdominal hypertension is a common situation in an operating room (laparoscopy) or an intensive care unit. As highlighted in the article, abdominal hypertension may lead to an increase in pulse pressure variations in this setting.

To our knowledge, the ability of dynamic index to predict fluid responsiveness in the specific obese population has not yet been tested. The possible impact of obesity should be more complex than stated by Dr. Roth. Indeed, a direct effect of the fat distribution in obese patients is a reduction in the respiratory system compliance due to the reduction in lung and chest wall compliance. As mentioned previously, decrease in chest wall compliance will induce an increase in pulse pressure variations. In contrast, during decreased lung compliance, airway pressure transmission is reduced such that the cyclic changes in intrathoracic pressure could be attenuated even in case of marked changes in alveolar pressure. Thus, Monnet et al. demonstrated that the predictive value of pulse pressure variations is related to lung compliance. The clinical impact of these hypothetic mechanisms, which is probably low, except for morbid obese patients, remains to be demonstrated.

We do not agree with Dr. Roth when he claims that administering neuromuscular blockade may result in a lower volume infusion. This affirmation is not supported by any publication. The impact of neuromuscular blockade administered in anesthetized patients without pathological decrease in chest wall compliance on dynamic index has never been demonstrated. Furthermore, most of the patients included in validation studies of dynamic index in intensive care unit were not paralyzed.

On the contrary, we totally agree with Dr. Roth that stroke volume variations and its surrogates should not be the endpoint of therapy. As clearly mentioned in the article, the dynamic index must be considered as useful tools to predict an increase in stroke volume after volume expansion. But they clearly cannot help to answer the following question: Does my patient need an increase in stroke volume?

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Pharyngeal Cooling, Brain Temperature Reduction and a Neglect of History

To the Editor:

Takeda et al. are to be congratulated for carrying out a series of experiments in monkeys and man in developing and evaluating a minimally invasive technique to selectively lower brain temperature. There are, however, a number of questions concerning the methodology and experimental design, which should be mentioned.

It should be noted that 10 monkeys were involved in this study, five of which were subjected to 30 min of cooling after cardiac arrest and resuscitation, whereas the remaining five served as the controls and arrested, resuscitated but not
cooled for 30 min. Because pharyngeal cooling was the principal variable, would it not have been more appropriate to include a third arm to this animal study to carry out anesthesia, no cardiac arrest and resuscitation but use pharyngeal cooling for 30 min. This would give a control with the brain being cooled without arrest and further test the efficacy of cooling in the normal brain.

The article noted the use of laser Doppler flowmetry for monitoring cerebral blood flow with the cerebral blood flow more pronounced in the pharyngeal cooling group than in the control. In absolute terms, namely mmHg/100 qbrain/min what flows were calculated? Were upper and lower limits of autoregulation of cerebral blood flow also determined before arrest and after resuscitation?

The small decreases in tympanic membrane temperature in the clinical cases may in part be due to the measurement error inherent in the tympanic membrane technique, but is also possibly due to the inadequate thermal exchange using a flow rate of 500 ml/min with water entering at 5°C. With the monkey weighing on the average of 8.9 kg, the brain having a weight of about 0.36 kg, and accepting a cerebral blood flow of 50 ml/100g/brain/min, the caloric interchange was adequate to achieve the decrease noted. However, with the human brain weighing at an average of 1,200 grams, the blood volume going into the brain is in the order of approximately 5–6 l/min, making the caloric gradients on the negative side when 500 ml/min perfusate at 5°C was employed. This writer is familiar with this problem in that he participated in experiments related to direct cooling of the spinal cords of Rhesus monkeys and found that a normal saline perfusate bathing the cord at a flow rate of 100 ml/min entering between 2° and 5°C was able to reduce intrinsic spinal cord temperatures to 10°C within 20 min. In the human spinal cord, because of its larger mass and vascularity, flow rates of 1.0 l/min with perfusate at 2.0°C–5.0°C was needed to overcome the higher caloric gradient to reach 10°C in the spinal cord.

This writer feels that with the apparent demonstration of minimal side effects resulting from this technology, and the ability to lower brain temperature while keeping body core at or near normothermia, the authors should design and carry out another subhuman primate study that would determine the lowest temperature levels in brain, which might be achieved with this technique without impinging seriously on body core temperatures.

No mention was made as to the clinical background of the three patients treated with pharyngeal hypothermia. How long before pharyngeal cooling were the patients in the intensive care unit and what were their Glasgow Coma Scale levels?

A major concern with this article is the lack of thoroughness in the bibliographic review. The area of experimental and therapeutic hypothermia is indeed rich with extraordinary information waiting for the patient investigator to mine it. Interestingly, from a historic perspective, 47 yr ago, Brown et al. produced a striking brain-body temperature gradient in canines by naso-oral perfusion and head immersion using cold saline as the hypothermic medium. Within 20–38 min (median time, 32 min), intracerebral temperatures less than 20°C were reached with right atrial temperatures stabilizing between 30° and 33°C. Termination of perfusion allowed for rewarming of the brain from the warmer body core without eye injuries or neurological deficits.

In 1973, Albin et al. reported on differential brain cooling using cephalic immersion similar to the method reported by Brown et al. in six canines and five Rhesus monkeys. In both species, a brain target temperature of 30°–31°C was reached in less than 15 min, with the core temperature at or near normothermia. In two monkeys, cerebral blood flow was measured using Xe 133 injected through a catheter placed in the common carotid artery after ligation of the external carotid, with a marked decrease in cerebral blood flow occurring from preperfusion levels on reaching 30°C in the brain. No behavioral or neurological deficits were noted in these two monkeys after 6 weeks of observation.

Another more recent publication not cited in the report of Takeda et al., was published in 2011 by Abu-Chebl et al., in which they described yet another technique to produce pharyngeal and brain cooling. They achieved this by the insertion of nasal catheters that spray a perfluorocarbon-oxygen mixture into the nasopharynx to achieve cooling. This technique was used in a safety and feasibility study of intubated brain-injured patients for whom temperature reduction was indicated. The aim of reducing core temperatures by 1.0°C within 1 h was met in 14 of the 15 cases, with hypertension occurring in one patient leading to discontinuation of therapy. The authors noted that there were no nasal complications with this modality.

This writer is forced to add that in spite of the very sophisticated information technology we have today, science did exist earlier than the 21st century. Winston Churchill once noted, “The farther backward you can look, the farther forward you are likely to see.”

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In Reply: We thank Albin for his interest in and for important comments regarding our article.1

His first comment regarding the experimental design was to have another control group of animals that are anesthetized but not arrested. In our study, we used Japanese monkeys to avoid the effects of carotid rete by which many experimental animals can selectively decrease brain temperature with panting. Because we have to reduce the number of animals for compliance with the 3R principles, we examined the effect of pharyngeal cooling in one anesthetized animal. The results were shown in figure 5.

The next comment was related to the unit of cerebral blood flow (CBF) and the residual CBF during cardiac arrest. It has been reported that laser Doppler flowmetry does not measure absolute CBF; rather, it accurately measures relative changes in absolute CBF.2 In our article, therefore, we presented CBF with percent changes of its preischemic value. At the end of cardiac arrest, all animals showed ventricular fibrillation, and CBF was decreased to 7 ± 4% and 5 ± 3% of the preischemia level in the treated and control groups, respectively. It is unlikely that the 2% difference in CBF indicated a significant difference in blood flow reduction during cardiac arrest. It is more likely that decrease in blood flow exceeded the level at which accurate measurement can be performed by Doppler flowmetry.

The comment about the flow rate of perfusate is an important issue. In our study, the flow rate of perfusate was 500 mL/min in both the monkey and patients regardless of body weight (8.2 ± 2.1 kg vs. 47.3 ± 12.4 kg) and cuff volume (size 2, 40 mL vs. size 4, 115 mL). Because core brain temperature in the anesthetized monkey and tympanic temperatures in patients were similarly decreased by 0.9ºC and 0.6º ± 0.1ºC, respectively, during 30 min of pharyngeal cooling, we assumed that the flow rate of 500 mL/min exceeded the optimum flow rate for monkeys. However, we need to evaluate the optimum flow rate in each cuff size in the future.

We demonstrated that pharyngeal cooling can rapidly and selectively decrease brain temperature. However, because 20% of cardiac output circulates in the brain in normal conditions, it seems that a long duration of brain cooling eventually decreases whole body temperature. Therefore, we would like to use pharyngeal cooling during the acute phase of brain ischemia, especially during cardiac arrest. After recovery of spontaneous circulation, pharyngeal cooling would be replaced by another cooling technique that decreases whole body temperature. For the induction of whole body cooling, intravenous infusion of cold saline is recommended.3 For maintaining a stable temperature at 32º–34ºC for 24 h, an endovascular cooling system or a gel-coated pad cooling system has been reported to be reliable.4 Brown et al.5 reported the effects of nasal cooling in an animal study in 1964. To date, several researchers have successfully shown decrease in brain temperature with a nasal or nasopharyngeal cooling technique, with different approaches.6 To the best of my knowledge, various effects of nasal or nasopharyngeal cooling on tympanic temperature in humans were measured in seven studies, including our study.7–12 We cited two of these reports. Our study is the first study in which a pharyngeal cooling cuff was used in humans. Because we should avoid subcutaneous emphysema or edema due to direct contact of cold air or fluid in the nasal and pharyngeal regions, we made a pharyngeal cooling cuff that is similar in shape to the supraglottic airway device. The shape was carefully decided by three-dimensional contrast-enhanced computed tomography images and cadaver dissections to fit the pharynx and carotid arteries. The channel in the cooling cuff was designed by thermal fluid analysis to increase the efficacy of cooling.

Albin suggested increasing the bibliographic review in the article. We agree with his suggestion because we can realize what we need to do by learning from previous works. However, our article focused on clinical application of the pharyngeal cooling technique. Therefore, we cited articles in which results of clinical trials were presented.

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