A STUDY BY Clark et al in this issue of the Journal compares postoperative core temperatures in patients having conventional cardiopulmonary bypass surgery and off-pump coronary artery grafting. Core temperatures exceeding 38°C were twice as common in the conventional bypass patients; their peak temperatures were 38.5°C ± 0.4°C versus 37.9°C ± 0.5°C, and the area under the curve for temperatures above 38°C was 1.6°C · hours versus 0.4°C · hours. Each of these differences was statistically significant. These results raise 3 questions that will be discussed in turn.

ARE THE RESULTS BELIEVABLE?

The study by Clark et al is a retrospective analysis of patients enrolled in a previous study. Specifically, patients who had conventional bypass grafting were enrolled in a study of off-pump bypass, but were subsequently converted, for technical reasons, to on-pump surgery at 32°C to 34°C. There were thus only 9 patients in this group as opposed to 32 who had off-pump surgery.

As might be expected from a nonrandomized design, there were several differences among the populations. For example, all patients having cardiopulmonary bypass were men, whereas only half were in the off-pump group. And, as another consequence of the design, patients having conventional surgery were sicker and required significantly more coronary grafts.

The authors attempted to compensate for lack of randomization by performing a multivariate analysis that included gender, the number of coronary grafts, and other potential confounding factors. Multivariate analysis is at best a partial substitute for randomization because unanticipated factors, or factors that were not measured, can contribute subtle, or not so subtle, distortions. And, of course, the analysis cannot possibly compensate for factors that were not included. In this case, for example, surgery took an hour longer in the 9 patients undergoing conventional on-pump operations. Duration of surgery should thus have been included in the analysis.

The results of Clark et al are based on a retrospective, nonrandomized study. Furthermore, one group was small and the 2 populations are demonstrably nonhomogenous. Nonetheless, it seems unlikely that any of these factors substantially altered the results. Bias is another potential problem in nonrandomized and unblinded trials; fortunately, the major variable in this study (core temperature) is an objective measurement that was presumably recorded accurately. It would no doubt be possible, although perhaps difficult, to find patients willing to be assigned to conventional or off-pump bypass. This would have been the optimal approach because it would have eliminated selection bias and presumably the other inhomogeneities in this study. But it is also unlikely that doing so would alter this study’s primary conclusions.

WHAT MECHANISMS MIGHT CONTRIBUTE TO POSTOPERATIVE HYPERTHERMIA?

Core temperature is defined as the average temperature of the highly perfused central tissues of the body. In practice, the core consists of the trunk and head and represents roughly half the body mass. Core temperature is not the highest temperature in the body; temperature of the liver, for example, normally exceeds core temperature by about 1°C. Core temperature in humans normally averages about 37°C. However, there is a superimposed 1°C circadian variation; the menstrual cycle superimposes an additional 0.5°C variation. Consequently, temperatures ranging from 36°C to 38°C are considered relatively normal.

The distinction between hyperthermia and fever is important. Hyperthermia is defined by a core temperature that, for any reason, exceeds the upper bounds of the normal range (ie, 38°C). Hyperthermia can be passive (ie, resulting from an excessively warm, humid environment) or active (eg, exercise-
induced heat stroke or malignant hyperthermia). But by far, the most common cause of hyperthermia is fever. Fever differs from other causes of hyperthermia in being a pyrogen-mediated, regulated increase in body temperature. Common pyrogens include interferon, tumor necrosis factor, and interleukin-6.

Core hyperthermia, no matter what the cause, must result from reduced environmental heat loss, increased metabolic heat production, or constraint of metabolic heat to the core thermal compartment. Humans have little if any capacity for non-shivering thermoregulatory hypermetabolism. The rising phase of fever is thus inevitably accompanied by arteriovenous shunt vasoconstriction, which constrains metabolic heat to the core thermal compartment.

Postoperative hyperthermia is common after major noncardiac surgery, with a typical temperature elevation being 1.5°C peaking 11 hours after surgery. Postoperative hyperthermia is associated with increased plasma interleukin-6 and arteriovenous shunt vasoconstriction, indicating that it is a febrile response rather than passive hyperthermia. (There is no basis for the common attribution of postoperative fever to “atelectasis.”) Cardiac surgery, even more than general surgery, is associated with release of inflammatory mediators, and mediator release is especially pronounced after conventional on-pump bypass. It is thus reasonable to conclude that the hyperthermia observed by Clark et al was indeed fever and further that it was mediated by systemic release of inflammatory cytokines, all of which are pyrogenic.

It is also likely that fever was exaggerated in patients having conventional cardiac surgery because the bypass circuit injures platelets and leukocytes, which promotes release of pyrogenic substances. However, a limitation of Clark’s study, imposed by its retrospective design, is that neither cytokine concentrations nor arteriovenous shunt vasoconstriction, which constrains metabolic heat to the core thermal compartment.

An additional factor to consider is that the release of pyrogenic inflammatory factors presumably depends on the duration of surgery, hence the concern that the authors failed to include duration of surgery in their multivariate analysis. That said, it seems unlikely that doing so would substantially change the conclusion that hyperthermia after cardiac surgery is fever mediated by pyrogen release and that fever is greater in patients having conventional on-pump bypass.

**IS THE MAGNITUDE OF THE HYPERTHERMIA CLINICALLY IMPORTANT?**

Hypothermia provides unquestioned protection against brain and myocardial ischemia in animals. In fact, a 2°C reduction in tissue temperature provides greater protection against ischemia than any known drug. The difficulty has been proving comparable benefit in humans. Only 2 randomized trials have shown benefit from therapeutic hypothermia in humans, both in patients recovering from cardiac arrest. In contrast, no convincing benefit was observed in large studies of traumatic brain injury, aneurysm repair, or acute myocardial infarction. None of these studies was perfect, though, and it remains possible that distinct benefits of hypothermia will yet be identified in humans. A recent book details temperature regulation, temperature dependence of ischemia, and therapeutic hypothermia.

To the extent that hypothermia is protective against tissue ischemia, it would be unsurprising if hyperthermia proved harmful. And there is, in fact, some animal evidence that hyperthermia is detrimental to the ischemic brain. Studies in humans similarly suggest detriment in humans, but all are observational or uncontrolled. Typically, they conclude that the outcome of stroke is worse in hyperthermic patients. The trouble with such studies, of course, is that larger strokes are associated with more tissue injury, presumably a greater release of pyrogenic factors, and therefore higher core temperatures. As might be expected, outcomes are worse in patients with larger strokes, but this hardly proves that the hyperthermia was causal. The effect of mild hyperthermia on cerebral ischemia continues to be an area of active investigation.

The rationale for Clark’s evaluation of postoperative temperatures appears to be largely based on previous work from the same group, which, according to the authors, showed “a significant correlation between delayed hyperthermia and decreased neurocognitive function.” It is thus worth considering the limitations and conclusions of that study. The work was a nonrandomized comparison between 65 patients who were rewarmed slowly from hypothermic bypass and 100 patients who were rewarmed rapidly. Neurocognitive outcomes did not differ significantly by univariate analysis and were only barely significant with multivariate analysis ($p = 0.047$). That there was any difference at all is hard to attribute to a temperature effect because the rewarming rates were virtually identical ($0.56°C/h$ vs $0.49°C/h$) and the maximum temperatures differed only slightly ($38.2°C ± 0.7°C$ vs $37.8°C ± 1.3°C$). A formal randomized trial of sufficient size will thus be required before the authors’ conclusion that “this study confirms our hypothesis that a slower rewarming rate with lower peak temperatures results in significantly better cognitive performance after cardiac surgery” can be accepted. This is especially the case because the same group reports that cognitive outcomes are similar after normothermic ($35.1°C ± 1.3°C$) and hypothermic ($30.4°C ± 1.4°C$) bypass, a result that is consistent with most other studies. And, in any case, it would be risky to extrapolate from outcomes related to rewarming rate on bypass to hyperthermia observed 4 to 14 hours after surgery.

Per protocol, Clark et al’s patients were given 500 mg of acetaminophen when the core temperature reached 38°C; this threshold was reached in all but 1 of the 9 patients undergoing conventional bypass but only half of the 32 patients undergoing off-pump procedures. It is possible that the temperature difference between the 2 groups would have been greater had acetaminophen been avoided, but even high doses of acetaminophen ($3,900$ mg/d) only trivially reduced stroke-induced hypothermia. Even in carefully controlled animal studies, temperature differences of only $0.6°C$, as observed by Clark et al, have never been shown to influence brain protection. It thus seems unlikely that such temperature differences will prove important in humans, especially because fever did not start until about 4 hours after surgery.
SUMMARY

The study of Clark et al suffers from a retrospective design that resulted in 1 group being more than 3 times the size of the other. More importantly, the groups were not entirely homogeneous. The results nonetheless confirm that hyperthermia is common after cardiac surgery and suggest that hyperthermia is a regulated fever that is exaggerated in patients having conventional on-pump bypass.

Peak temperatures, although, differed by only 0.6°C. There is currently no evidence, even in animals, that such small temperature differences influence outcomes from brain ischemia. The choice between conventional on-pump bypass and off-pump coronary artery grafting should thus be based on factors other than anticipated postoperative fever.

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REFERENCES