assessed the *late* remote ischemic preconditioning (RIPC) in 22 children who underwent cardiac surgery with cardiopulmonary bypass. The authors concluded that “late remote ischemic preconditioning did not provide clinically relevant cardioprotection to children undergoing cardiopulmonary bypass.” A few comments seem to be appropriate. It appears that at least 5 children in their RIPC group had cyanotic heart disease (Taussig-Bing anomaly, tricuspid atresia, and tetralogy of Fallot). Inasmuch as the 2 groups in this study appear comparable, the children with cyanotic heart disease have chronic hypoxia before surgery. Is it possible to further precondition the patients with chronic hypoxia by brief intermittent episodes of limb ischemia induced before surgery? This question remains to be answered.

My colleagues and I² have previously demonstrated in a randomized controlled trial a clinically relevant beneficial effect of the RIPC in children who underwent preconditioning immediately before surgery. Pavione and colleagues used the same RIPC stimulus to assess a *late* phase of protection. We^{3,4} have previously demonstrated that the RIPC modifies gene expression both early and late in human blood and in the myocardium of the experimental animals. Furthermore, it appears that intraoperative ischemia-reperfusion itself induces an early myocardial gene expression in the children undergoing heart surgery.⁵ Thus, both intermittent preoperative (ie, RIPC) and prolonged intraoperative ischemia-reperfusion induce changes at the genomic level. One would expect that chronic hypoxia of the cyanotic heart disease does the same. Do these genomic changes translate into proteomic response? This is yet unknown. Our recent, yet unpublished, randomized controlled trial performed in 40 children undergoing surgery for tetralogy of Fallot indicated that the myocardial phosphorylated protein signaling is already activated in children with chronic hypoxia. Thus, regardless of whether the

RIPC-induced activation of gene expression translates into proteomic response or not, its clinical effect may be lost in children with cyanotic heart disease.

I commend Pavione and colleagues on their interesting study and look forward to seeing whether the RIPC will find a clinical application in children undergoing heart surgery. Time will show. At the meantime, the researchers should be cautioned against including patients with chronic hypoxia into the trials inasmuch as chronic hypoxia may mask the effects of the ischemic preconditioning.

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Reply to the Editor:

We thank Dr Konstantinov¹ for his interesting comments on our article.²

We do not, however, believe that the presence of patients with cyanotic heart disease in the group undergoing remote ischemic preconditioning (RIPC) in our study may have masked the effects of the ischemic stimulus, because there were actually 9 patients with cyanotic heart defects in the RIPC group (75%) and 6 in the control group (60%; $P = .65$). In addition, preoperative oxygen saturations were similar in the RIPC and control groups (mean $\pm$ SD, $89\% \pm 11\%$ vs $89\% \pm 7\%$, respectively; $P = .84$). We emphasize that studies performed in adults undergoing coronary artery bypass surgery³ and in infants with ventricular septal defect,⁴ in which cases chronic hypoxia would not be a confounding factor, also failed to demonstrate any clinically significant effect of RIPC. Moreover, the usefulness of RIPC would be most important in patients at high risk of postoperative complications, such as those included in our study. Nevertheless, many infants with complex congenital heart disease have some degree of preoperative cyanosis. Considering that RIPC is an innocuous, inexpensive, and simple procedure, we hoped that it would decrease inflammation and postoperative morbidity. Unfortunately, we did not observe these effects. It thus seems evident that RIPC with brief periods of limb occlusion, as currently performed, lacks clinical applicability in patients undergoing heart surgery with cardiopulmonary bypass.

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TRANSCATHETER AORTIC VALVE IMPLANTATION: CLINICAL EVIDENCE VERSUS CLINICAL PRACTICE

To the Editor:

Enthusiasm and use of transcatheter aortic valve implantation (TAVI) have grown exponentially since the first TAVI procedure was performed a decade ago. Critics of this relatively novel technique, however, argue that clinical practice has far outpaced robust clinical evidence. The recent summary by Agnihotri¹ provides a broad overview of the recent consensus statement approved by a dozen professional societies, including the American Association for Thoracic Surgery. Agnihotri¹ correctly emphasizes the subjectivity of the patient selection process for TAVI and a number of postprocedural complications such as stroke, requirement for permanent

pacemaker, vascular injury, and severe aortic regurgitation, all of which are significantly more likely to occur than after conventional surgical aortic valve replacement (AVR). Agnihotri¹ also stated, "There is limited information regarding durability beyond 5 years in registry data." One should also point out there are no published comparative data between TAVI and surgical AVR beyond 5 years in the current literature.

From an evidence-based perspective, level I evidence has only been presented from 2 randomized controlled trials. The better known of these, the PARTNER (Placement of Aortic Transcatheter Valve) trial financed by Edwards Lifesciences (Irvine, Calif), involved patients who were either deemed to be at "high surgical risk" (cohort A) or "inoperable" (cohort B).^{2,3} Recently, Van Brabandt and colleagues⁴ highlighted the significant ethical, scientific, and industry-related challenges to the PARTNER trial related to publication bias, lack of data transparency, unbalanced patient characteristics, and incompletely declared conflicts of interest.⁴ The lesser known STACCATO trial, which was not cited by Agnihotri¹ or the consensus statement, included patients who were considered to have "low surgical risk." This trial was prematurely terminated by a data safety monitoring board after unexpectedly poor results for patients in the TAVI arm.⁵ The chief investigator of the STACCATO trial stated that TAVI should not be considered in patients who are at a low surgical risk because of the excellent and established outcomes offered by surgical AVR.

In summary, patients with severe aortic stenosis should be considered in three subgroups, according to their surgical risk with conventional AVR, as illustrated in Figure 1. Results from randomized, controlled trials suggest that "inoperable" patients may benefit from TAVI in terms of mortality and symptomatic outcomes, although at the cost of increased stroke risk. The evidence for "high surgical risk" patients is limited by short-term follow-up, and existing data suggest a higher risk of stroke or transient ischemic attack than that associated with conventional AVR without any significant all-cause mortality benefit. With respect to "low surgical risk" patients, the STACCATO trial has shown that TAVI should not be offered to these patients in the current clinical setting. Finally, there is a fourth recognized subgroup of patients who are considered to be at too high a risk for any form of interventional treatment.^{2,3}

In the future, the development of novel devices should also be complemented by the development of standardized, stringent patient selection processes to allow meaningful comparison of outcomes between institutions. On the basis of the available evidence, the use of TAVI for eligible surgical candidates should only be considered within clinical trials or registries.⁶

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FIGURE 1. Spectrum of patients with severe aortic stenosis according to surgical risk for conventional aortic valve replacement (AVR). TAVI, Transcatheter aortic valve implantation.