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<http://dx.doi.org/10.1016/j.jtcvs.2013.03.041>

Reply to the Editor:

We are grateful to Dr Catalana-Lopez for his continued comments regarding our work.

Although we do not want to prolong unnecessarily this correspondence, a couple of points are worthy of note in his response.

First, the suggestion of including observational evidence in the meta-analysis is flawed, and we found ourselves in this position. As Rosenbaum and Rubin,¹ the propensity score methods used by the authors can only address confounding when case mix adjustment is possible to the extent that the prescriber's decision to prescribe a treatment is otherwise ignorable. This is clearly not the case in our situation, in which the

observational studies describe a substantial latency (unmeasurable bias) associated with the decision to prescribe, which has been incorrectly interpreted as a risk associated with aprotinin.^{2,3} Thus, following Dr Catalana-Lopez's advice in this situation would actually compound the previous errors of interpretation that have led us to our difficulties with this agent.

Second, Dr Catalana-Lopez is simply incorrect when he suggests that network meta-analyses have the same status as observational studies. Network meta-analyses preserve the original randomization in trials, and provide fully conditional estimates of treatment effect. However, network meta-analyses require an additional assumption (of exchangeability; ie, that subjects share characteristics from the overall population and may, thus, appear in any of the trials). Thus, rather than fully giving up the protection of randomization, we may consider network meta-analyses to be quasi-randomized estimates.

Finally, with regard to potential conflicts of interest, they should be declared upfront and leave the reader to decide of their importance. These authors take conflicts of interest seriously and, as indicated by Dr Catalana-Lopez, have declared all possible conflicts in accordance with required journal requirements.

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GENDER DISPARITY MAY CONTRIBUTE TO THE QUASI PRESERVATION OF CARDIOPROTECTION BY REMOTE PRECONDITIONING WITH ISOFLURANE BUT NOT PROPOFOL IN CABG

To the Editor:

We read with great interest the article by Kottenberg and colleagues¹ published online in *The Journal of Thoracic and Cardiovascular Surgery* on March 1, 2013. They have done a series of impressive translational works to explore the underlying mechanisms of cardioprotection by remote ischemic preconditioning (RIPC) with isoflurane or propofol in patients undergoing coronary artery bypass grafting (CABG).¹⁻³ In their fundamental study published in *Acta Anaesthesiologica Scandinavica*,² they designed 2 independent substudies and found that isoflurane may be more effective in the preservation of cardioprotection by RIPC than propofol. Then, based on 2 consequently separated and independent studies,^{2,3} they believed that differential activation of signal transducer and activator of transcription 5 (STAT 5) phosphorylation may be the contributing factor.

Nevertheless, there remains inconclusive information about this interesting issue when looking into the fundamental study. In that study,² the male proportion may be even within the substudy (RIPC vs control with isoflurane; RIPC vs control with propofol); however, it may be uneven between the 2 substudies (isoflurane vs propofol, 89.7% vs 75.8%; mean difference, 14%).

Accumulating evidence from animal studies has supported gender-specific cardioprotection by ischemic

FIGURE 1. Meta-regression plot of male proportion (%) on standardized mean difference (SMD) of myocardial enzyme levels (coefficient, -0.022 ; $P = .098$). The area of each circle is inversely proportional to the variance of the SMD. Data taken from Zhou and colleagues.⁵

conditioning.⁴ Moreover, our recent study,⁵ including 10 randomized trials using the meta-regression method found an increased effect size (standardized mean difference) in postintervention myocardial enzyme levels of ischemic postconditioning by 0.22 per 10% increase in male proportion (Figure 1), indicating that a study with more male patients may result in a more pronounced effect than a study with fewer male patients. Hence, in their fundamental study, the authors cannot exclude the potential role of gender disparity in the quasi preservation of cardioprotection by RIPC with isoflurane, but not propofol, in CABG. At least, as the authors stated in the limitation section, both positive and negative controls are essential in one study, especially for the exploration of the role of STAT 5. The cardioprotective difference between isoflurane and propofol in the setting of RIPC needs further more rigorous studies.

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<http://dx.doi.org/10.1016/j.jtcvs.2013.04.035>

Reply to the Editor:

We thank Zhou and colleagues for their comments and interest in our recent work.^{1,2} We appreciate that they considered us to have done a series of impressive translational studies to explore the mechanisms of cardioprotection by remote ischemic preconditioning (RIPC) with isoflurane

or propofol in patients undergoing coronary artery bypass grafting (CABG) surgery.¹⁻³

Zhou and colleagues speculate that there might be an unrecognized effect of gender on the protection provided by RIPC and, thus, on our results. They underline this speculation by a meta-analysis including 10 randomized trials. However, these data are derived from studies related to ischemic postconditioning,⁴ rather than RIPC, and these 2 phenomena may be mechanistically different.⁵

In our studies, in contrast to others that have not addressed the impact of anesthetics,⁶ we showed that propofol interferes with the protection by RIPC, whereas the volatile anesthetic isoflurane² does not. Furthermore, the activation of signal transducer and activator of transcription 5 phosphorylation may be part of the mechanism by which RIPC exerts its cardioprotection during isoflurane anesthesia.^{1,3} Indeed, the gender distribution in our studies was not comparable in all subgroups.^{1,2} Certainly, therefore, effects provided by RIPC may be modified by gender, but this has not been studied. We agree that it would be worthwhile to examine whether there is a gender-specific effect of cardioprotection not only by ischemic postconditioning but also by RIPC. However, our studies were neither designed nor powered to examine a potential role of gender disparity. Therefore, we can neither exclude nor confirm gender effects on cardioprotection provided by RIPC.

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