

## The Rocky Road from Bench to Bedside

### $\beta$ -blockers and Anesthetic Postconditioning

VOLATILE anesthetics have been shown to exhibit excellent cardioprotection when given temporarily as preconditioning agents hours<sup>1</sup> or longer<sup>2</sup> before myocardial ischemia/reperfusion or as postconditioning agents<sup>3</sup> immediately on myocardial reperfusion, as demonstrated once more by Lange *et al.*<sup>4</sup> in this issue of ANESTHESIOLOGY. These findings are certainly true for animal experiments, but their translation into clinical practice, unfortunately, remains more challenging than anticipated<sup>5,6</sup> for a variety of possible reasons,<sup>7</sup> and the improvement in outcome is sometimes more subtle and not as evident at first.<sup>8,9</sup>

To test a seemingly straightforward hypothesis—cardiac postconditioning by temporary desflurane exposure causes its protective effect by  $\beta$ -adrenergic stimulation—Lange *et al.*<sup>4</sup> used an established *in vivo* animal model and administered the  $\beta_1$ -blocker esmolol or the  $\beta_2$ -blocker ICI 118,551 alone or together with desflurane for 30 min following reperfusion after sustained myocardial ischemia. Either of the two antagonists abolished the cardioprotective effect of desflurane as assessed by infarct size measurements. The authors concluded that postconditioning with desflurane is indeed mediated by  $\beta$ -adrenergic stimulation. This was supported by additional findings in their study that blockade of certain intracellular signaling pathways known to be downstream of  $\beta$ -activation also abolished desflurane postconditioning.

So far, so good. The scientist in us is probably pleased to have one more piece of evidence that—at least in rabbits—desflurane given on myocardial reperfusion is beneficial for the heart and to have identified another pathway how this may actually be mediated inside the cell. As clinicians, however, we naturally wonder if any of these results may have any bearing on how to anesthetize patients at risk for myocardial ischemia, which and how much anesthetic to choose, and what other drugs to give or to avoid when we encounter myocardial ischemia/reperfusion in our patients. One valid, yet incomplete, interpretation of the current animal study could be that  $\beta$ -blockers— $\beta_1$  or  $\beta_2$ —are best to be

avoided in this context because they abolish the cardioprotective effect of desflurane given on reperfusion.

The truly interesting point of this study,<sup>4</sup> however, is a different one. The authors also studied the effect of sustained  $\beta_1$ -blockade on reperfusion by administering esmolol during the entire reperfusion period, in either the absence or the presence of the anesthetic given on initial reperfusion. Interestingly, in contrast to shorter  $\beta_1$ -blockade, the sustained  $\beta_1$ -blockade not only failed to abolish the beneficial effect of desflurane, but it turned out to be as protective as desflurane postconditioning itself. These additional findings introduce a whole new level of complexity to the study. Although short-term  $\beta$ -blockade—if one focuses strictly on the current study—appears to be neutral at best or actually counterproductive in the presence of desflurane, sustained  $\beta$ -blockade, in contrast, appears to be beneficial. This benefit outweighs the negative effect on desflurane postconditioning, which—according to the authors—could be attributed to the energy-sparing effect of  $\beta_1$ -blockade, mainly by heart rate reduction.

When taken together, these differential findings strongly suggest a biphasic role of  $\beta$ -blockade on reperfusion; the present study, however, does not provide any evidence as to what duration of  $\beta$ -blockade may possibly still be detrimental and what duration may already be beneficial. The same could be said about the effect of  $\beta$ -activation on reperfusion, in this case by desflurane: how much and how long would it be beneficial and when would this change to the contrary? What was probably planned as a simple and straightforward study trying to provide some more mechanistic insights on the interesting phenomenon of anesthetic postconditioning now opens the door to a multitude of unanswered questions. Apart from the optimal duration of  $\beta$ -activation *versus*  $\beta$ -blockade on myocardial reperfusion, one wonders if the current results are specific for desflurane only, an anesthetic known to have sympathomimetic effects<sup>10</sup> compared to other anesthetics. Is the effect of desflurane on the heart in this *in vivo* model direct or indirect? Would short-term catecholamine administration be as beneficial as desflurane? Would the cardioprotective effect of sustained  $\beta$ -blockade on reperfusion actually lead to an overall improved outcome? One only has to notice the significantly decreased blood pressures in the sustained esmolol groups provided in table 1<sup>4</sup> to be immediately reminded of the vivid discussion triggered by the results from the POISE trial published only a few months ago.<sup>11</sup>

The current study by Lange and colleagues<sup>4</sup> represents another example for the challenges we inevitably face when trying to extract and translate findings from basic

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science research into patient care. The amount of new and unanswered questions suddenly multiplies, and the road from bench to bedside appears rockier than ever. Does this mean we should give up? By no means; in our attempt to understand nature, we have no choice but to break things down into smaller, digestible pieces that can be scientifically evaluated but carry the natural shortcoming of providing only a very limited aspect of the whole. Just like in a complicated puzzle, the art is to identify and study the neighboring pieces next and slowly expand our insight.

In this sense, Lange *et al.*<sup>4</sup> may be commended for not having restricted their experiments to short-term  $\beta$ -blockade only, and they and others may certainly be encouraged to further investigate the interesting biphasic effects of  $\beta$ -activation and  $\beta$ -blockade on attenuating ischemia/reperfusion injury. Sometimes, it takes nothing less than a rocky road to reach the summit.

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