Regulation of Human Coronary Vascular Tone: Further Evidence Must Be Sought Before Ruling Out the Direct Role of ATP-Sensitive Potassium Channels in Regulation of Coronary Vasculature

To the Editor:

The study by Kakkar et al in Circulation Research established that spontaneous coronary vasospasm in ATP-sensitive potassium channels (K<sup>ATP</sup>) mutant mice arises from a smooth-muscle extrinsic process.1 We congratulate the investigators for successfully accomplishing such meticulous research. The concluding hypothesis, which points toward a multiorgan involvement or a paracrine cross-talk effect of neuronal or endothelial K<sup>ATP</sup> channels to vascular smooth muscle (VSM) in the event of coronary vasospasm, is very novel and appealing. The elucidated finding, which negates a direct role of VSM K<sup>ATP</sup> channels in tone regulation of coronary vasculature, is very striking as a direct implication of the VSM K<sup>ATP</sup> ATP channels is well established in extracoronary vasculatures.2-4 We recommend a scrupulous exploration into the matter before any direct, or indirect, conclusions can be made.

In our study on isolated human left internal mammary artery (LIMA),5 we proved that acidosis induces relaxation of the vessel through direct involvement of VSM. In the next phase of the study, we were able to block the effect by exposing the artery to Glibenclamide, a potent blocker of K<sup>ATP</sup> ATP channels, hence establishing a role for K<sup>ATP</sup> ATP channels in the acidosis-induced relaxation of vessels. The human LIMAs used in our study were denuded of endothelial tissue, thus ruling out any potential cross-talk by endothelial K<sup>ATP</sup> ATP channels. Also, in our study, the vessels were derived from patients undergoing coronary artery bypass grafting and were used after a washout interval that ensured they were not under any residual hormonal influences at the time of the experiment. Therefore, we convincingly illustrated that the relaxation of human LIMA during acidosis is a direct function of VSM K<sup>ATP</sup> channels.5 Although the conflicting results between our study and Kakkar et al<sup>1</sup> can be explained simply on the basis of a differential behavior of coronary and extracoronary vasculature, one must keep in consideration the use of different experimental models (rodents and humans) in the 2 studies.

Interestingly, this is not the first time that human and rodent models have differed in the characterization of VSM. Our research group conducted several studies on the effects of acidosis on spontaneously hypertensive and Wistar Kyoto rat aorta and discovered that intracellular acidosis is associated with contraction in both of these strains. The same experiment under perfectly replicated experimental conditions when performed on human VSM yielded entirely opposite results, i.e., instead of contraction, the human VSM underwent relaxation when exposed to a low pH.3 What makes the disparity in the 2 models more substantial is the evidence in literature that acidosis had induced contraction of VSM in other rodent models as well.6 A direct implication of VSM K<sup>ATP</sup> ATP channels has been elucidated in control of vasculature tone in an isolated study by Wang et al on rodent vasculature as well. Therefore, we cannot disregard the fact that the study was on mesenteric vasculature and the results cannot be generalized to coronary vasculature.3

The justification of these discrepancies often observed in animal experimental models is complex and can be partially explained on the basis of contrasting genetic makeup, differences in membrane permeability, and possibly divergent cellular control mechanisms apart from other confounding factors.7 K<sup>ATP</sup> ATP channels have a complex functionality at the tissue level in humans. The functions that have been elucidated so far include vascular tone regulation; regulation of smooth muscles of the bladder, GI tract, and airways; and cardio-protection through the mechanism of ischemic preconditioning of the heart apart from their long-known involvement in insulin secretion in the pancreatic β-cells.8 The conclusive hypothesis of Kakkar et al is definitely valid for rodent coronary vasculature, but the proposition will become unjustified if the drawn conclusions are generalized to human coronary vasculature. A strong possibility exists that arterial tone regulation through K<sup>ATP</sup> ATP channels in mammals has evolved over thousands of years and presently is constituted by an intricate interplay between neuronal, endothelial, and VSM K<sup>ATP</sup> ATP channels. The study by Kakkar et al is surely a milestone in the endeavor to understand the complex functionality of K<sup>ATP</sup> ATP channels in human arterial tone regulation. However, until the picture becomes more vivid, adoption of a cautious approach when deriving any further implications remains the best option.

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