POTASSIUM (K⁺) CHANNELS in the endothelium and vascular smooth muscle are important to regulation of vascular tone (5, 8). The K⁺ channel, TREK-1, a member of the recently identified family of two-pore domain K⁺ channels, is highly expressed in vascular tissues. In particular, TREK-1 channels are abundant in the endothelium of cerebral vascular tissue (1–3). The substantial presence of TREK-1 channels in cerebrovascular endothelium may have important implications for regulation of cerebral vascular reactivity and regulation of cerebral blood flow under both normal and pathophysiological conditions. In a study described in their manuscript entitled, “Cerebrovascular responses in mice deficient in the potassium channel, TREK-1,” Namiranian et al. (7) developed a murine knockout of the TREK-1 channel to determine its role in regulation of cerebral vascular function. Although these authors hypothesized that TREK-1 is involved in control of arterial diameter, they did not find evidence to indicate that deletion of TREK-1 results in altered cerebrovascular function (7).

Because specific inhibitors of TREK-1 have not been identified, a TREK-1 murine knockout was developed to eliminate vasoactive signaling through this K⁺ channel; however, no significant differences were detected in vascular smooth muscle reactivity of cerebral arteries from TREK-1⁻/⁻ mice. This finding is in keeping with previous reports from TREK-1⁻/⁻ mice, in which responses to the NO donor, sodium nitroprusside, were not altered in cerebral or mesenteric arteries (1, 3). In contrast, the findings reported by Namiranian et al. (7) differ markedly from reports of significantly reduced endothelium-dependent vasodilation in TREK-1-deficient mice. Blondeau et al. (1) reported impaired dilation to ACh in mesenteric and basilar arteries of TREK-1⁻/⁻ mice. Although the exact reasons for these disparate findings remain unclear, it is important to note that Namiranian et al. (7) performed a comprehensive study that encompassed a very thorough and detailed characterization of cardiovascular regulatory mechanisms in TREK-1⁻/⁻ mice. These authors performed critical control experiments which verified that 1) TREK-1 deletion was complete in these mice, 2) TREK-1 deletion did not lead to compensatory upregulation of the activity of other two-pore domain K⁺ channels in the vasculature of these mice, and 3) TREK-1 deletion did not alter important central cardiovascular variables, including blood pressure and cardiac function. Thus, these authors were able to conclude that maintenance of normal cerebral arterial reactivity in TREK-1⁻/⁻ mice was not attributable to incomplete deletion of TREK-1 channel activity, nor were observations of cerebral arterial reactivity in TREK-1⁻/⁻ mice confounded by adaptations of cardiac function or blood pressure regulatory mechanisms.

Namiranian et al. (7) evaluated K⁺ currents in vascular smooth muscle cells isolated from cerebral arteries and did not observe phenotypic changes in cells from mice deficient in TREK-1 (7). They report evidence of activation of BKCa by polyunsaturated fatty acids (PUFA) in cerebral vascular smooth muscle from both TREK-1⁻/⁻ and wild-type mice but no apparent PUFA-induced activation of TREK-1 channels. In addition to their assessment of K⁺ channel activity in isolated vascular smooth muscle cells, Namiranian et al. (7) also reported that vasoconstriction to phenylephrine and vasodilation to MAHMA NONOate, a nitric oxide donor, did not differ between middle cerebral and basilar arteries from TREK-1⁻/⁻ mice and those from wild-type mice. These findings, in addition to previous reports (1, 3), reinforce the notion that although TREK-1 channels are expressed in cerebral vascular smooth muscle, their function is not critical to regulation of diameter in cerebral arteries.

Although Namiranian et al. (7) expected to find alterations of endothelium-dependent vasodilation, neither the responses of basilar arteries to ACh nor the responses of the middle cerebral arteries to ATP were altered by deletion of TREK-1. These results are in contrast to a previous study performed by Blondeau et al. (1), in which ACh-induced dilation of basilar arteries was significantly depressed in TREK-1⁻/⁻ mice. It does not appear that the discrepancies between these studies are related to strain differences since backcrossing of the TREK-1⁻/⁻ mice yielded mice similar to the C57BL6 strain used by Blondeau et al. (1), with no change in functional results. The phenotypic differences of the endothelium in these two murine models may be related to the strategy employed to achieve deletion of TREK-1. Namiranian et al. (7) substituted a cassette that included β-galactosidase and a neomycin resistance protein for exon 2, the second intron, and all of exon 3, whereas Heurteaux et al. (4) deleted only exon 3. The impact of these distinct targeting constructs on K⁺ channel function is thoroughly discussed by Namiranian et al. (7) in their article.

In the study performed by Blondeau et al. (1), the role of TREK-1 appeared minimal in regulation of carotid artery diameter compared with its role in regulation of basilar arterial tone (1), suggesting that the expression and function of these channels are heterogeneous in the vasculature. This heterogeneity of function may contribute to findings from both studies demonstrating that deletion of TREK-1 had no effect on blood pressure. Together, these results indicate that although TREK-1 is expressed in the endothelium and may even contribute to maintenance of vasomotor tone in some vascular
beds, the role of TREK-1 in regulation of total peripheral resistance is minimal.

TREK-1 is a potential target for the documented protective effects of polyunsaturated fatty acids (PUFA) in the cerebral circulation. The activation of TREK-1 by PUFA coupled with its relative abundance in the cerebral vasculature has prompted several investigations into its role in vasoactive signaling (1–3, 6, 7). Previous work by Garry et al. (3) has suggested that deletion of TREK-1 leads to loss of nitric oxide (NO) signaling; however, Namiranian et al. (7) found no evidence of altered signaling through either NO- or prostanoid-dependent mechanisms. The work of Namiranian et al. has produced several significant findings and raised important new questions. First, they have confirmed previous reports indicating that TREK-1 deletion does not alter vasoactive responses of cerebral vascular smooth muscle. Second, their work indicates that the role of TREK-1 in endothelial signaling likely involves mechanisms that are insensitive to inhibition of cyclooxygenase or nitric oxide synthase. Third, their work indicates that if TREK-1 channels are the targets of PUFA, these effects of PUFA must occur through endothelial TREK-1 channels, not channels in the vascular smooth muscle. Intuitively, it would seem that a vasoregulatory role should exist for a channel that is both highly expressed in the endothelium of cerebral vessels and responsive to vasoprotective PUFA. Thus, the findings of Namiranian et al. (7) underline the need to perform future studies in which the activity of TREK-1 channels is specifically evaluated in the endothelium. Without doubt, this constitutes a formidable task, but given the sound and comprehensive experimental approach described in their current article, Namiranian and colleagues are ready to accept this experimental challenge.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

REFERENCES