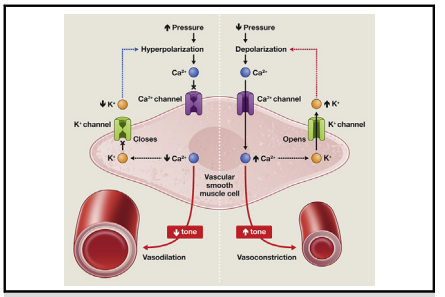
References

1. Aird WC. Phenotypic heterogeneity of the endothelium: I. Structure, function, and mechanisms. *Circ Res*. 2007;100:158-73.
2. Shah PJ, Gordon I, Fuller J, Seevanayagam S, Rosalion A, Tatoulis J, et al. Factors affecting saphenous vein graft patency: clinical and angiographic study in 1402 symptomatic patients operated on between 1977 and 1999. *J Thorac Cardiovasc Surg*. 2003;126:1972-7.
3. He GW. Arterial grafts for coronary surgery: vasospasm and patency rate. *J Thorac Cardiovasc Surg*. 2001;121:431-3.
4. Schachner T. Pharmacological inhibition of vein graft neointimal hyperplasia. *J Thorac Cardiovasc Surg*. 2006;131:1065-72.
5. Sun WT, Hou HT, Chen HX, Xue HM, Wang J, He GW, et al. Calcium-activated potassium channel family in coronary artery bypass grafts. *J Thorac Cardiovasc Surg*. 2021;161:e399-409.
6. Archer SL, Gragasin FS, Wu X, Wang S, McMurtry S, Kim DH, et al. Endothelium-derived hyperpolarizing factor in human internal mammary artery is 11,12-epoxyeicosatrienoic acid and causes relaxation by activating smooth muscle BK(Ca) channels. *Circulation*. 2003;107:769-76.
7. Bi D, Toyama K, Lemaître V, Takai J, Fan F, Jenkins DP, et al. The intermediate conductance calcium activated potassium channel K_{Ca} 3.1 regulates vascular smooth muscle cell proliferation via controlling calcium-dependent signaling. *J Biol Chem*. 2013;288:15843-53.

See Article page e399.

Commentary: Ions from eons: A hidden therapeutic potential of the resting potential?

Phillip S. Naimo, MD,[a,b,c] and
Igor E. Konstantinov, MD, PhD, FRACS[a,b,c,d]



Regulation of vascular tone via calcium-activated potassium channels.

CENTRAL MESSAGE

Large calcium-activated potassium channels may play an important role in vasodilation of the internal thoracic artery.

Calcium-activated potassium channels, particularly, large conductance potassium channels (BK_{Ca}), have been identified in virtually every type of smooth muscle. In blood vessels, they are involved in vascular tone regulation. In the uterus, BK_{Ca} channels participate in the control of myometrial cell membrane potentials.[1] In the airway, BK_{Ca} channels regulate the tone and contractility of bronchioles.[1] In gastrointestinal tract, BK_{Ca} channels are involved in the regulation of colonic motility.[1]

Potassium is one of the most common ions in living cells, and potassium channels are ubiquitous to all domains of life. The ion-channel superfamilies are thought to be as ancient as the last common ancestor of all organisms on earth.[2] Because of their wide distribution, potassium channels are thought to be one of the first ion channels to have evolved. The evolution of potassium channels has been traced back to the prokaryotic world.[3] Furthermore, small potassium channels have been found in viruses, which are some of the simplest potassium channels, and this has been suggested to predate the more complex channels seen in early bacteria. There have been both major (gene fusion and gene duplications) and minor (single-base mutations and deletions) genetic events that have led to the fascinating diversity of potassium channels that we see today.[3] Amazingly, the general molecular characteristics of the BK_{Ca} channels are evolutionarily conserved from worms to mammals.[1,4] A single mammalian gene may generate many variants of BK_{Ca} channels that may explain the variation in calcium sensitivity in blood vessels.

BK_{Ca} channels appear to play a crucial role in arterial smooth muscle tone by providing a negative feedback loop to regulate the degree of depolarization and

From the [a]Department of Cardiac Surgery, Royal Children's Hospital, [b]Department of Paediatrics, University of Melbourne, [c]Heart Research Group, Murdoch Children's Research Institute, and [d]Melbourne Children's Centre for Cardiovascular Genomics and Regenerative Medicine, Melbourne, Australia.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Nov 26, 2019; revisions received Nov 26, 2019; accepted for publication Dec 3, 2019; available ahead of print Dec 23, 2019.

Address for reprints: Igor E. Konstantinov, MD, PhD, FRACS, Royal Children's Hospital, Flemington Rd, Parkville, VIC 3052, Australia (E-mail: igor.konstantinov@rch.org.au).

J Thorac Cardiovasc Surg 2021;161:e412-3
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.12.020

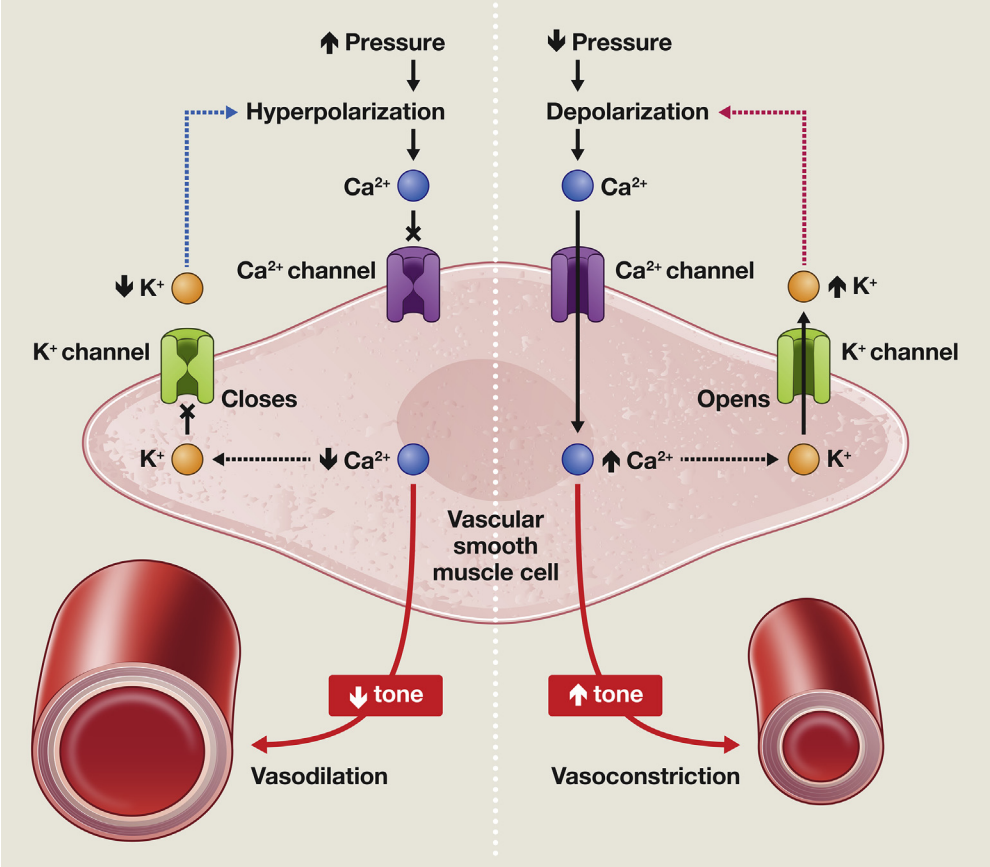


FIGURE 1. Regulation of vascular tone and restoration of cellular resting potential via calcium-activated potassium channels. A decrease in blood pressure causes the cell to depolarize. This opens calcium channels flow into the smooth muscle cell. The increase in intracellular calcium causes vasoconstriction and activates potassium channels, which opens and allows potassium to leave the smooth muscle cell. The potassium efflux has a negative effect on depolarization and restores the cell's resting potential. An increase in blood pressure causes the cell to hyperpolarize. This closes calcium channels and, thus, lowers intracellular calcium. A reduction in intracellular calcium causes vasodilation and closure of potassium channels. Keeping potassium inside the cell causes the hyperpolarized cell to return to it resting potential.

hyperpolarization.[5] Small arteries exist in a partially contracted state from which they can either constrict further or dilate depending on the end-organ demand for blood.[5] Although several pathways are responsible for the contraction or relaxation of vascular smooth muscle, increases in intracellular calcium that occur during cell depolarization increase vascular tone and open the BK_{Ca} channels to restore the cell's resting potential (Figure 1).[5] Conversely, a reduction in intracellular calcium that occurs during cell hyperpolarization decreases vascular tone and closes BK_{Ca} channels to, again, restore the cell's resting potential.[5]

The study by Sun and colleagues[6] in this issue of the *Journal* has demonstrated a remarkable difference in the BK_{Ca} subtypes within the internal thoracic artery and saphenous vein, pointing at a potential therapeutic target to treat internal thoracic artery spasm. They demonstrated a greater proportion of BK_{Ca} channels within the internal thoracic artery, which may explain the greater variability in vasodilatory properties of the vessel.[6] Although systemic therapy may wreak havoc on the whole body, given the widespread distribution of these channels, a targeted therapy at the time of surgery may prove to be potentially beneficial.

References

1. Contreras GF, Castillo K, Enrique N, Carrasquel-Ursulaez W, Castillo JP, Milesi V, et al. A BK (Slo1) channel journey from molecule to physiology. *Channels*. 2013;7:442-58.
2. Moran Y, Barzilai MG, Liebeskind BJ, Zakon HH. Evolution of voltage-gated ion channels at the emergence of Metazoa. *J Exp Biol*. 2015;218:515-25.
3. Thiel G, Moroni A, Blanc G, Van Etten JL. Potassium ion channels: could they have evolved from viruses? *Plant Physiol*. 2013;162:1215-24.
4. Moulton G, Attwood T, Parry-Smith D, Packer J. Phylogenomic analysis and evolution of the potassium channel gene family. *Receptors Channels*. 2003;9:363-77.
5. Nelson MT, Quayle JM. Physiological roles and properties of potassium channels in arterial smooth muscle. *Am J Physiol*. 1995;268:C799-822.
6. Sun WT, Hou HT, Chen HX, Xue HM, Wang J, He GW, et al. Calcium-activated potassium channel family in coronary artery bypass grafts. *J Thorac Cardiovasc Surg*. 2020;161. 2021;e399-409.