In general, there are different surgical ways to deal with this challenging subset of patients. In this context we have to be aware that conventional surgery can be performed with excellent results. Therefore, catheter-based techniques have to be compared with the ‘old fashioned’ conventional way of surgery. This does not mean that new approaches should not be pushed further.

Again, we congratulate Lentini and co-workers for their good results and valuable discussion [1].

References


Letter to the Editor

Rho-kinase, the forgotten link?

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I congratulate Shackcloth and co-workers for their article on receptor-dependent and independent vasoconstriction in the human radial artery [1]. I find of interest their work on the role of Rho-kinase on radial artery graft spasm following coronary artery bypass grafting.

Ca2+ sensitisation of the contractile apparatus by altering the level of myosin light chain (MLC20) phosphorylation is now a well-established mechanism by which agonists can increase the force of contraction in smooth muscle cells without necessarily increasing the cytosolic concentration of Ca2+. This phosphorylation is regulated by Ca2+-calmodulin activated myosin light chain kinase (MLCK) and myosin phosphatase (MLCP) [2].

The Ca2+ sensitisation effect of activation of G-protein coupled receptors (e.g. muscarinic, α1-adrenergic, endothelin, thromboxane A2, etc.) is mimicked in permeabilised smooth muscles, by GTPγS, a nonhydrolysable GTP analogue. These findings indicate the role of a G-protein in Ca2+ sensitisation. A critical protein in the process appears to be the monomeric G-protein Rho A, which can be activated by guanine-nucleotide exchange factors following receptor stimulation. Rho A is a member of the Rho subgroup within the Ras superfamily of low molecular weight monomeric GTP-binding proteins [3].

G-protein-mediated Ca2+ sensitisation can be abolished by pharmacologically blocking Rho-kinase. Two Rho-kinase inhibitors (HA 1077 and Y27632) have been shown to prevent MLC20 phosphorylation.

HA 1077 (fasudil), has been shown to act as a vasodilator in vivo and in vitro. HA 1077 totally abolishes GTPγS inhibition of myosin phosphatase activity and consequent enhancement of MLC20 phosphorylation. In vivo, fasudil has been shown to be effective in preventing acetylcholine-induced coronary artery spasm and resultant myocardial ischaemia in patients with vasospastic angina [4].

HA 1077 and Y27632 (the inhibitor of Rho-kinase used in Shackcloth’s manuscript) are profound relaxants of contractions evoked by the thromboxane A2 mimetic U46619 in human internal mammary artery. Y27632 also abolishes contraction evoked by endothelin-1 and significantly reduces resting tone in the absence of a vasoconstrictor [5].

There is growing evidence that the Rho/Rho-kinase-mediated pathway plays an important role in various cellular functions, not only in vascular smooth muscle contraction but also in actin cytoskeleton organization, cell adhesion and motility, cytokinesis, and gene expressions, all of which may be involved in the pathogenesis of atherosclerosis. Animal experiments have demonstrated that long-term inhibition of Rho-kinase inhibits the development of coronary arteriosclerotic lesions and even causes regression of coronary vascular lesions in vivo [4].

In summary, Shackcloth’s manuscript gives further evidence of the value of Rho-kinase inhibition in cardiovascular surgery. Further clinical research in the field is to be encouraged in order to expand the use of these agents.

References


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