Editorial Commentary

Advancing coronary artery bypass grafting: the fasudil-nitroglycerin cocktail as a potential antispastic solution

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Coronary artery disease accounts for >7 million deaths per year worldwide with >800,000 coronary artery bypass grafting (CABG) procedures performed annually (1). The three main conduits used for myocardial revascularization are the internal thoracic artery (ITA), radial artery (RA), and saphenous vein (SV) (2). Vasospasm occurs during harvesting in a high proportion of grafts that may have both immediate and long term adverse effects (3,4). A variety of antispastic drugs studied have either dilator or anti-constrictor actions. The elegant study by Ding *et al.* describes the effects of diltiazem, nitroglycerin, urapidil and nicorandil on the ITA, RA and SV both *in vitro* and *in vivo* (5). *In vivo*, the effects of vasodilators on RA free flow and hemodynamic were measured while, *in vitro*, organ bath studies were performed on the effect of vasodilators in isolated ring preparations of the ITA, RA and SV. *In vitro*, maximal relaxations with urapidil, nitroglycerin and nicorandil were significantly greater in all vessels than with diltiazem. All three conduits showed similar relaxation with nitroglycerin or with diltiazem, but the relaxation with urapidil in RA was greater than that in the ITA and SV, and RA and SV showed greater relaxation with nicorandil than ITA. *In vivo*, urapidil and nitroglycerin significantly increased RA blood flow, where potency was greater than diltiazem. It was concluded that nitroglycerin causes a significantly greater relaxation than nicorandil, urapidil and diltiazem in all three graft vessels tested; nitroglycerin, nicorandil and urapidil were more effective in preventing RA spasm than diltiazem. An important point made by the authors was that "… isolated vessels may not completely reflect events *in vivo*", a situation that may question the validity of certain 'bench to bedside", translational, studies. The suggestion that the Rho-kinase inhibitor, fasudil, may be useful in the treatment of coronary artery surgery was made 20 years ago where fasudil prevented spasm and improved myocardial ischemia suggesting that this compound may be useful to treat intractable and otherwise fatal coronary spasm resistant to intensive conventional vasodilator therapy after CABG (6,7).

A more recent study compared the antispastic effect of the commonly used vasodilator, papaverine, with the Rho-kinase inhibitor, fasudil, on free flow following intraluminal injection in the isolated ITA (8). Fasudil exhibited a very potent vasodilatory effect compared with conventional papaverine.

The authors conclude that the increased graft free flow suggests that fasudil is a useful graft dilating agent and provide an example of histology showing the increased

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luminal diameter of the ITA after fasudil injection compared with control ITA.

The current article by Hou *et al.* takes a novel approach by investigating the combined effect of fasudil and nitroglycerin in arterial grafts (9). The development of the fasudil cocktail solution offers a potential therapeutic strategy for preventing and treating spasm in arterial grafts during CABG. The study provides mechanistic insights into the vasorelaxant effect of fasudil, emphasizing the downregulation of ROCK2 protein expression. This contributes to the understanding of the molecular pathways involved in the observed effects.

Isolated rings of ITA obtained from patients undergoing CABG were used to study the cumulative concentration-relaxation curves for fasudil precontracted with KCl or U46619. The inhibitory effects of fasudil alone or in combination with nitroglycerin on ROCK2 protein was also measured in ITA tissue extracts by Western blot analysis. The relaxation to fasudil in the ITA was similar in rings precontracted with either KCl or U46619. Whereas fasudil pretreatment significantly depressed contractions induced by both KCl and U46619, fasudil in combination with nitroglycerin produced a more effective, more rapid and sustained relaxation than either fasudil or nitroglycerin alone. Western blots showed that fasudil caused a decrease in ROCK2 protein content. Based on these results the authors suggest that the potent antispastic effect of this cocktail solution of fasudil and nitroglycerin may provide a new method of reducing spasm in arterial conduits used in CABG. Apart from patient demographics, statements on ethics and consent, the methods section provides little information regarding the condition of vessels used in this study except that, "discarded ITA segments were collected and cut into rings 3 mm in length in Krebs solution". In studies conducted in isolated organ baths, the endothelium plays a pivotal role in regulating vascular tone and reactivity and produces vasodilatory factors, such as nitric oxide (NO), which contribute to the relaxation of vascular smooth muscles (10). When assessing the effects of fasudil on isolated vessels, it is crucial to consider its interactions with the endothelium. Conversely, fasudil might also have direct effects on vascular smooth muscle, independent of endothelial influence. Furthermore, it is known that fasudil causes vasodilation through both endothelium-dependent and -independent mechanisms (11,12). For instance, it has been demonstrated that fasudil influences human basal vascular tone and that endothelium-dependent NO release mediates a substantial amount of fasudil-induced vasodilation (11). However, as the review by Raja states that fasudil may be useful in conditions where endothelial function is impaired, such as pulmonary arterial hypertension, based on emerging evidence from both animal and human studies suggesting that it can promote vasodilation independent of the endothelium (12). Moreover, by blocking ROCK, fasudil could also directly inhibit smooth muscle contraction, contributing to vasorelaxation, even in the absence of a functional endothelium (10). Therefore, understanding the fasudil effect in relation to the endothelial capacity of isolated vessels is crucial for unravelling its mechanisms of action. This knowledge is vital for its potential application in conditions where vascular dysfunction or spasm is a significant factor. However, in the study of Hou *et al.*, there is a lack of information regarding the endothelial status of the vessels (9). It is essential to assess both endothelium-dependent and independent vasorelaxation in the ITA rings. In addition, it may be particularly important to consider the form of harvesting used by the surgeons performing CABG. While the ITA is generally harvested with its pedicle of perivascular fat (PVF) intact, in many cases the ITA is 'skeletonized', where the PVF is removed (13,14), a procedure that may affect spasm when compared with pedicled ITA. Furthermore, *in vitro*, organ bath studies have shown a vasodilatory effect of human ITA PVF that involves calcium-dependent potassium channels (15). An extensive list of storage solutions and antispastic agents are used on conduits at harvesting during CABG, ranging from papaverine, nitroglycerine, and sodium nitroprusside to NO donors, iloprost and fasudil. Application of such antispastic agents include wrapping in soaked swabs, immersion in solution, topical spray and intraluminal administration (16).

Traditionally, both the ITA and RA are harvested as pedicled conduits, with PVF intact. Paradoxically, the PVF is removed using conventional SV harvesting (17), a procedure causing a high proportion of grafts to go into spasm.

The anti-contractile effects of PVF, first reported by Soltis and Cassis (18), has been demonstrated *in vitro* using isolated ring preparations of the ITA (15), RA (19) and SV (20) from patients undergoing CABG. These experimental studies suggest that the PVF surrounding bypass conduits may play a beneficial role in graft performance in patients following bypass surgery (21). The question arises, is the use of antispastic agents necessary when spasm is reduced or prevented if alternative surgical harvesting techniques are used? There are conflicting views regarding the ITA

with the general consensus being that skeletonization not only increases the available length of this conduit but that it may also increase graft flow and conduit diameter (13,14). As previously described, the SV is conventionally harvested with PVF removed, a procedure that causes a high proportion of grafts to go into spasm and that is overcome using 'manual', high-pressure, intraluminal saline distension (22). Like the RA and ITA, antispastic agents, such as papaverine and nitroglycerin, are used on the SV to reduce spasm at harvesting (5). Of particular relevance to the SV, the most commonly used conduit for CABG, is that using the no-touch technique of harvesting, where SV PVF remains intact, a graft is achieved with patency that is comparable to the ITA at up to 16 years (23).

Mechanisms underlying the improved patency of no-touch SV grafts are multifactorial, ranging from reduced vascular damage, preservation of normal vessel architecture and mechanical properties of the PVF (24,25) to the potential role of adipocyte-derived relaxing factors (21). Although there is strong evidence that PVF-derived factors play a role in improved SV graft patency, the effects of skeletonization on the ITA and RA grafts is less convincing. Given the various antispastic agents and cocktails used on conduits in CABG patients, preservation of PVF may offer a simple additional option for reducing spasm, particularly for the SV. Collectively, details concerning the status of the utilized vessels are of utmost importance. Therefore, it is imperative to explicitly state and examine the presence and functionality of both the endothelium and PVF in all bypass conduits.

While the results of this current study by Hou *et al.* (9) are valuable and contribute significantly to the literature, certain aspects require attention. The study focuses specifically on ITA, and the application of the results to other graft materials frequently utilized in CABG, namely the SV, remains uncertain. The focus of the study restricts its wider relevance to diverse clinical situations. Moreover, this study provides mechanistic insights into the vasorelaxant effect of fasudil, emphasizing the downregulation of ROCK2 protein expression, thus contributing to the understanding of the molecular pathways involved in the observed effects. The study appropriately acknowledges its limitations, such as the small patient population and the need for *in vivo* tests. However, it would be beneficial to discuss potential biases or confounding factors that might affect the interpretation of results. For example, there is no comparison of the fasudil-nitroglycerin cocktail with existing standard treatments for arterial graft spasm during CABG. Without such a reference point, it is not possible to assess the true efficacy and superiority of the proposed cocktail solution.

In conclusion, the study offers promising insights into the potential antispastic effects of the fasudil-nitroglycerin cocktail in the ITA. However, there remains a considerable amount of work required to determine the impact of similar cocktail solutions such as those of Hou *et al.* (9). Given that the authors have acknowledged various limitations, such as the small sample size, and disparities between *in vitro* and *in vivo* conditions, it is crucial to take these factors into account. Subsequent research endeavours should focus on addressing these limitations to ascertain the clinical feasibility and applicability of this innovative approach in CABG.

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References

1. World Health Organization. 2021. Cardiovascular diseases (CVDs). Available online: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Dimeling G, Bakaeen L, Khatri J, et al. CABG: When, why, and how? Cleve Clin J Med 2021;88:295-303.
3. Novaković A, Gojković-Bukarica L, Beleslin-Cokić B, et al. Differential antivasoconstrictor effects of levcromakalim and rilmakalim on the isolated human mammary artery and saphenous vein. J Pharmacol Sci 2003;92:108-14.
4. Gaudino M, Antoniades C, Benedetto U, et al. Mechanisms, Consequences, and Prevention of Coronary Graft Failure. Circulation 2017;136:1749-64.
5. Ding R, Feng W, Li H, et al. A comparative study on in vitro and in vivo effects of topical vasodilators in human internal mammary, radial artery and great saphenous vein. Eur J Cardiothorac Surg 2008;34:536-41.
6. Masumoto A, Mohri M, Shimokawa H, et al. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation 2002;105:1545-7.
7. Inokuchi K, Ito A, Fukumoto Y, et al. Usefulness of fasudil, a Rho-kinase inhibitor, to treat intractable severe coronary spasm after coronary artery bypass surgery. J Cardiovasc Pharmacol 2004;44:275-7.
8. Watanabe G, Noda Y, Takagi T, et al. Fasudil is a superior vasodilator for the internal thoracic artery in coronary surgery. Ann Thorac Surg 2013;96:543-7.
9. Hou HT, Wang ZQ, Wang J, et al. Antispastic Effect of Fasudil and Cocktail of Fasudil and Nitroglycerin in Internal Thoracic Artery. Ann Thorac Surg 2023;115:1152-61.
10. Chen YC, Yuan TY, Zhang HF, et al. Fasudil evokes vasodilatation of rat mesenteric vascular bed via Ca(2+) channels and Rho/ROCK pathway. Eur J Pharmacol 2016;788:226-33.
11. Büssemaker E, Pistrosch F, Förster S, et al. Rho kinase contributes to basal vascular tone in humans: role of endothelium-derived nitric oxide. Am J Physiol Heart Circ Physiol 2007;293:H541-7.
12. Raja SG. Evaluation of clinical efficacy of fasudil for the treatment of pulmonary arterial hypertension. Recent Pat Cardiovasc Drug Discov 2012;7:100-4.
13. Kusu-Orkar TE, Kermali M, Masharani K, et al. Skeletonized or Pedicled Harvesting of Left Internal Mammary Artery: A Systematic Review and Meta-analysis. Semin Thorac Cardiovasc Surg 2021;33:10-8.
14. Shafiq A, Maniya MT, Duhan S, et al. Skeletonized versus Pedicled harvesting of internal mammary artery: A systematic review and Meta-analysis. Curr Probl Cardiol 2024;49:102160.
15. Malinowski M, Deja MA, Janusiewicz P, et al. Mechanisms of vasodilatatory effect of perivascular tissue of human internal thoracic artery. J Physiol Pharmacol 2013;64:309-16.
16. He GW, Taggart DP. Spasm in Arterial Grafts in Coronary Artery Bypass Grafting Surgery. Ann Thorac Surg 2016;101:1222-9.
17. Favaloro RG. Saphenous vein graft in the surgical treatment of coronary artery disease. Operative technique. J Thorac Cardiovasc Surg 1969;58:178-85.
18. Soltis EE, Cassis LA. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. Clin Exp Hypertens A 1991;13:277-96.
19. Kociszewska K, Deja MA, Malinowski M, et al. Vasorelaxing properties of the perivascular tissue of the human radial artery. Eur J Cardiothorac Surg 2022;61:1423-9.
20. Ozen G, Topal G, Gomez I, et al. Control of human vascular tone by prostanoids derived from perivascular adipose tissue. Prostaglandins Other Lipid Mediat 2013;107:13-7.
21. Fernández-Alfonso MS, Gil-Ortega M, Aranguez I, et al. Role of PVAT in coronary atherosclerosis and vein graft patency: friend or foe? Br J Pharmacol 2017;174:3561-72.
22. Tsui JC, Dashwood MR. Recent strategies to reduce vein graft occlusion: a need to limit the effect of vascular damage. Eur J Vasc Endovasc Surg 2002;23:202-8.
23. Samano N, Geijer H, Liden M, et al. The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: A randomized trial. J Thorac Cardiovasc Surg 2015;150:880-8.
24. Dashwood MR, Tsui JC. "No-touch" saphenous vein harvesting improves graft performance in patients undergoing coronary artery bypass surgery: a journey from bedside to bench. Vascul Pharmacol 2013;58:240-50.
25. Samano N, Souza D, Pinheiro BB, et al. Twenty-Five Years of No-Touch Saphenous Vein Harvesting for Coronary Artery Bypass Grafting: Structural Observations and Impact on Graft Performance. Braz J Cardiovasc Surg 2020;35:91-9.

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