

Peer Review File

Article Information: <https://dx.doi.org/10.21037/jtd-23-1953>

Reviewer A

Comment:

Well-reasoned criticism of a flawed study by Hou et al. The writing needs significant refinement to meet publication standards. For instance, in the excerpt below, the second sentence contradicts the first, hindering clarity and conciseness.

54 “When assessing the effects of fasudil on isolated vessels, it is crucial to consider its 55 interactions with the endothelium. Conversely, fasudil might also have direct effects on 56 vascular smooth muscle, independent of endothelial influence.”

Reply:

We thank this reviewer for describing our Editorial as a “Well-reasoned criticism” and appearing to agree that the study by Hou et al is “flawed”. Presumably the comment regarding “The writing needs significant refinement to meet publication standards” is related to the journal format rather than style of presentation.

Moreover, this reviewer makes the comment, “In the excerpt below, the second sentence contradicts the first, hindering clarity and conciseness” – relating to “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.”

There are many situations in which vasoactive substances have been described as being both endothelium-dependent and non-endothelium-dependent (too numerous to list). Furthermore, it is known that fasudil causes vasodilation through both endothelium-dependent and -independent mechanisms (12,3). 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 (1). However, as the review by Raja states that fasudil may be useful in conditions where endothelial function is impaired, such as pulmonary arterial hypertension, emerging evidence from both animal and human studies suggests that it can promote vasodilation independent of endothelium (2). Moreover, as discussed in the manuscript by blocking ROCK, fasudil could also directly inhibit smooth muscle contraction, contributing to vasorelaxation, even in the absence of a functional endothelium (3).

References:

1. 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(1):H541-H547. doi:10.1152/ajpheart.00770.2006
2. Raja SG. Evaluation of clinical efficacy of fasudil for the treatment of pulmonary arterial hypertension. *Recent Pat*

Cardiovasc Drug Discov. 2012;7(2):100-4).

3. 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 Oct;788:226–33.

Changes in the text:

We have modified our text according to Reviewer's comment (see Page 3, line 24, Page 4, line 1-6).

Therefore, we have added two new more references (see Page 7-8, references 11, 12).

Reviewer B

Comment:

I am very proud to review the manuscript which commenting on the article in Ann Thorac Surg, entitled "Antispastic effect of fasudil and cocktail of fasudil and nitroglycerin in internal thoracic artery (ITA)." Overall, I agree that this comment article will appear in Journal of Thoracic Disease.

All cardiac surgeons recognize that spasm in ITA grafts results in serious sequelae. Therefore, as the authors stressed, the ways to prevent ITA spasm are interesting topics. As the authors also suggested, the study reported by Hou et al. is attractive for cardiac surgeons. They reported fasudil, especially in combination with nitroglycerine, has potent relaxant properties on ITA segments exposed to a variety of vasoconstrictor-induced contractions.

Fasudil is a Rho-kinase inhibitor which has been used for the prevention of cerebral vasospasm related to intracranial hemorrhage in neurosurgery. Also in cardiology, it has been increasingly highlighted to attenuates coronary artery spasm. Fasudil is an alternative choice when the spasm is refractory to standard treatments, including calcium channel blockers as the first-line and long-acting nitrates or nicorandil as the second-line medications. Although the authors commented the perspectives of fasudil, they should include the above roles of fasudil in treatment of coronary artery spasm.

Also, to the best of my knowledge, the following study is the first clinical study demonstrating that fasudil is highly effective in dilating ITA with resultant increase in ITA graft free flow.

G. Watanabe, Y. Noda, T. Takagi, et al. Fasudil is a superior vasodilator for the internal thoracic artery in coronary surgery Ann Thorac Surg, 96 (2013), pp. 543-547

The authors should discuss the history of studies investigating fasudil in cardiac surgery.

Reply 1:

We thank to reviewer for her/his helpful comment. It is reassuring that this reviewer states "I agree that this comment article will appear in Journal of Thoracic Disease".

One comment from the reviewer is "Although the authors commented the perspectives of fasudil, they should include the above roles of fasudil in treatment of coronary artery spasm." The suggestion that fasudil may be

useful in the treatment of coronary artery spasm was made over 20 years ago (1). We could include a reference to this study (and others), although this may be difficult given the Journal's word limit for Editorials.

This reviewer makes the point "Also, to the best of my knowledge, the following study is the first clinical study demonstrating that fasudil is highly effective in dilating ITA with resultant increase in ITA graft free flow - G. Watanabe, Y. Noda, T. Takagi, et al. Fasudil is a superior vasodilator for the internal thoracic artery in coronary surgery *Ann Thorac Surg*, 96 (2013), pp. 543-547." In fact we cite this publication early in our Editorial (Reference 6) – perhaps the reviewer missed this. Interestingly, this group subsequently showed fasudil to be an effective vasodilator in other CABG conduits, the right gastroepiploic artery (2) and radial artery (3). Again, word count restriction limits our ability to include such discussion in our editorial.

Regarding the comment "The authors should discuss the history of studies investigating fasudil in cardiac surgery".

This suggestion was made over 20 years ago (1) where the authors showed that "Fasudil successfully resolved the spasm and improved myocardial ischemia in all patients without any systemic adverse effects" concluding "the treatment with fasudil may be useful to treat intractable and otherwise fatal coronary spasm resistant to intensive conventional vasodilator therapy after CABG". A similar suggestion was made 2 year later by Inokuchi K et al (4).

We have added a short section to our revised manuscript. Again, word count restrictions prevent any detailed discussion on this aspect of fasudil and cardiac surgery *per se*.

In our Editorial we also remind those using isolated vessel segments in organ bath studies the importance of considering the role of the endothelium and PVAT when attempting to examine the effect of vasoactive compounds in vitro.

References:

1. Masumoto A. et al., Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation*. 2002;105(13):1545-7.)
2. Watanabe G, Yamaguchi S, Tomita S, Nishida Y. Fasudil Is an Effective Graft Vasodilator for Gastroepiploic Artery in Coronary Artery Bypass Grafting. *Innovations (Phila)*. 2015;10(4):268-72)
3. Watanabe G, Yamaguchi S, Takagi T, Tomita S, Tuan PM. Potent vasodilatory effect of fasudil on radial artery graft in coronary artery bypass operations. *Ann Thorac Surg*. 2014;97(3):845-50)
4. Inokuchi K 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(3):275-7)

Changes in the text:

We have modified our text according to Reviewers' comments (see Page 2, line17-20). Therefore, we have added two new more references (see Page7, references 6-7).