

Dear Editor in Chief,

RE: Radial artery access site complications during cardiac procedures, clinical implications and potential solutions: the role of nitric oxide (Manuscript NO:50559)

Thank you for your and the reviewers' comments on our article, we are grateful for the constructive comments and we have responded to them in full in the revised manuscript. We appreciate the opportunity to re-submit the manuscript for publication pending changes. We hope our responses and revisions are acceptable to yourself and the reviewers.

Please find our detailed responses to the reviewers' comments below, the comments from the reviewers are presented in bold, while our responses are in regular font. All the Editor's marked comments on the manuscript have also been addressed.

Sincerely,

Emma M Coghill

Reviewer 1

RQ1 Generally well-written if long review

AR1 We thank the reviewer for this comment. We have shortened the review by removing the cannulation protocol which we did not think added much to the article (Under **Radial artery cannulation** heading).

RQ2 The review emphasizes NO donors for spasmolytics, but the most effective agent is verapamil

AR2 Thank you for this comment, we have highlighted that verapamil is an effective agent whether used alone or in combination with nitroglycerin (pg 9 ln 1-2 pg 9 ln 6-9). However, it is worth noting that there is a risk of systemic side-effects with verapamil, including bradycardia (pg 9 ln 9-13) and that this agent does not carry the additional benefit of anti-platelet activity to help prevent thrombosis during the procedure.

RQ3 Radial artery cannulation - "Puncture access is usually around 1-2 cm above the cross striation of the patient's right palm" - consider using a bony marker

AR3 Thank you for this comment, we have removed the description of the cannulation procedure as both reviewers suggested that the manuscript be shortened and we felt that details of the cannulation procedure were superfluous, given the expertise of the anticipated audience. (Under **Radial artery cannulation** heading)

RQ4 "A single-wall anterior puncture is performed" - this misstates the state of the field where probably 40% perform the technique with a double wall puncture

AR4 Thank you for this comment. As noted above, we have removed the description of the cannulation procedure as both reviewers suggested that the manuscript be shortened. (Under **Radial artery cannulation** heading)

RQ5 Suggest referencing the Greek study indicating that moderate sedation reduces the incidence of spasm - JACC Cardiovasc Interv. 2013 Mar;6(3):267-73.

AR5 Thank you for this useful reference. We had mentioned "In selected cases, sedatives such as short acting benzodiazepines can be used (or at least offered to patients)" (pg 8 In 16-19) and we have now added this reference.

RQ6 The manuscript offers the tantalizing prospect of adding coatings to the sheath to locally deliver NO, which makes a lot of sense, but are there any examples of this in other fields?

AR6 Thank you for this comment. There are other examples and we have added the following text to the manuscript 'A 2017 study examined the release of NO from vascular catheters to prevent bacterial infection using a NO donor^[47]. Results showed inhibition of bacterial adhesion without any cytotoxic effects towards mammalian cells. Another study investigated the release of NO from a coronary stent using a NO donor^[48]. Results showed the promising positive effect of NO as a releasing agent to suppress or prevent restenosis and thrombosis. Authors proposed further investigations using other NO carriers or donors to further improve NO release pattern.' (pg 11 In 20-27). The following references were added:

49. Pant J, Goudie MJ, Chaji SM, Johnson BW, Handa H. Nitric oxide releasing vascular catheters for eradicating bacterial infection. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. Wiley Online Library; 2018;106(8):2849–57. [PMID: 29266734 DOI: 10.1002/jbm.b.34065]
50. Elnaggar MA, Seo SH, Gobaa S, Lim KS, Bae I-H, Jeong MH, et al. Nitric Oxide Releasing Coronary Stent: A New Approach Using Layer-by-Layer Coating and Liposomal Encapsulation. *Small*. Wiley Online Library; 2016;12(43):6012–23. [PMID: 27623489 DOI: 10.1002/smll.201600337]

RQ7 What is the safety of zeolites and MOFs in the circulation?

AR 7 We thank the reviewer for this question, this is a very good point and currently the toxicity of these agents is unknown in this setting. We have added the following to the manuscript. 'However, cytotoxicity of these compounds is yet to be examined in the cardiac setting' (pg 11 ln 1-2)

RQ8 The manuscript could do well by focusing on just the area of spasm rather than painstakingly reviewing all of radial access technique and complications

AR8 We thank you for this comment. With the benefit of hindsight, we concur that the original manuscript was too broad in scope and have taken the reviewer's advice relating to this concern. We have reduced the text on non-spasm complications (pg 7/8 under **Other complications** heading) but have retained Table 1 for context.

Reviewer 2

RQ9 A recent meta-analysis concluded that verapamil 5 mg, with or without nitroglycerin, was the most effective and frequently used spasmolytic agent (Kwok CS, Rashid M, Fraser D, Nolan J, Mamas M. Intra-arterial vasodilators to prevent radial artery spasm: a systematic review and pooled analysis of clinical studies. Cardiovasc Revasc Med. 2015;16:484–490. doi: 10.1016/j.carrev.2015.08.008)

AR9 Thank you for this useful review. We have used this to highlight verapamil as the preferred option and further described its effects (pg 9).

41. Kwok CS, Rashid M, Fraser D, Nolan J, Mamas M. Intra-arterial vasodilators to prevent radial artery spasm: a systematic review and pooled analysis of clinical studies. Cardiovascular Revascularization Medicine. Elsevier; 2015;16(8):484–90. [PMID: 26365608 DOI: 10.1016/j.carrev.2015.08.008]

RQ10 The bibliographic data are not recent and moreover not complete.

AR10 We thank you for this comment. We have added the following more recent references

15. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. Circulation: Cardiovascular

Interventions. Am Heart Assoc; 2018;11(9):e000035. [PMID: 30354598 DOI: 10.1161/HCV.0000000000000035]

16. Elfandi A, Safirstein JG. Transradial PCI and same day discharge. Current treatment options in cardiovascular medicine. Springer; 2018;20(2):10. [PMID: 29478204 DOI: 10.1007/s11936-018-0605-3]
17. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. The Lancet. Elsevier; 2015;385(9986):2465–76. [PMID: 25791214 DOI: 10.1016/S0140-6736(15)60292-6]
18. Basavarajaiah S, Brown A, Naganuma T, Gajendragadkar P, McCormick L, West N. Should technical and anatomical difficulties discourage operators from embarking on transradial access for percutaneous coronary intervention. J Invasive Cardiol. 2018;30:341–7. [PMID: 30012888 DOI: N/A]
22. Backman SB. Radial artery spasm: Should we worry? Can J Anaesth. 2017;64(12):1165–8. [PMID: 28822090 DOI: 10.1007/s12630-017-0946-5]

RQ11 The data about the spasm of RA is not complete

AR11 We thank the reviewer for this comment, we have added the following references to update our information on spasm.

18. Basavarajaiah S, Brown A, Naganuma T, Gajendragadkar P, McCormick L, West N. Should technical and anatomical difficulties discourage operators from embarking on transradial access for percutaneous coronary intervention. J Invasive Cardiol. 2018;30:341–7. [PMID: 30012888 DOI: N/A]
19. Backman SB. Radial artery spasm: Should we worry? Can J Anaesth. 2017;64(12):1165–8. [PMID: 28822090 DOI: 10.1007/s12630-017-0946-5]

RQ12 Data on other possible complications is also few.

We thank you for this comment. The main complication we wanted to highlight is spasm, so we only included a short piece on other potential complications. Reviewer 1 suggested that we remove all details of non-spasm complications and reduce the overall length of the manuscript – as a compromise we have retained Table 1, but reduced some of the text describing non-spasm complications as these are not the focus of the manuscript

RQ13 I suggest reviewing recent literature, for example: Peter J. Maso et al AHA SCIENTIFIC STATEMENT An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome A Scientific Statement From the American Heart Association. Circ Cardiovasc Interv. 2018;11:e000035. DOI: 10.1161/HCV.0000000000000035 I suggest to review the article based on the most recent literature.

AR13 We thank you for the literature recommendation and have found it useful to update the review. Not only have we added this reference to support our statements, we also added the ones mentioned previously.

15. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. Circulation: Cardiovascular Interventions. Am Heart Assoc; 2018;11(9):e000035. [PMID: 30354598 DOI: 10.1161/HCV.0000000000000035]