Bond University

Research Repository

Why we might not need to stress about ruling out inducible myocardial ischemia

Bell, Katy J.L.; Semsarian, Christopher; Doust, Jenny

Published in:
Annals of Internal Medicine

DOI:
10.7326/M19-3731

Link to output in Bond University research repository.

Recommended citation(APA):
Bell, K. J. L., Semsarian, C., & Doust, J. (2020). Why we might not need to stress about ruling out inducible myocardial ischemia. *Annals of Internal Medicine*, *172*(3), 214-215. https://doi.org/10.7326/M19-3731

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

For more information, or if you believe that this document breaches copyright, please contact the Bond University research repository coordinator.

Download date: 29 Feb 2024

Why we might not need to stress about ruling out inducible myocardial ischaemia

Katy JL Bell[1], Christopher Semsarian[2,3,4], Jenny Doust[5],

In patients with symptoms of stable angina, cardiac stress testing and angiography have been recommended to evaluate for inducible myocardial ischaemia and obstructive coronary artery disease (CAD). In this issue of *Annals of Internal Medicine,* Walter et al investigate whether hs-cTn tests could be introduced as a new test in this diagnostic pathway. Because of their high sensitivity for detecting myocardial injury, negative hs-cTn tests are used to rule out acute coronary syndrome (ACS) in patients presenting with acute chest pain, allowing safe discharge home from the Emergency Department (their clinical utility for ruling in myocardial infarction is more uncertain(1)). The authors of the current study hypothesised that hs-cTn tests could be used in a similar way in patients with stable angina, such that a negative result would safely rule out inducible myocardial ischemia without the need for further tests. They tested this hypothesis in a well conducted diagnostic accuracy study of 1,896 consecutive patients who had been referred to a single treatment centre for stress testing using myocardial perfusion single-photon emission tomography/computer tomography (MPI-SPECT/CT). They measured hs-cTn using three different assays on blood samples taken before stress testing and processed by personnel blinded for clinical data. Adjudication of inducible myocardial ischemia was based on expert interpretation of MPI-SPECT/CT images for all 1,896 cases combined with information obtained from invasive coronary angiography and fractional flow reserve measurements in the 405 cases where this was available. The diagnostic accuracy of hs-cTn to identify inducible myocardial ischemia was found to be low, with no cut-off level that provided the predefined minimum negative predictive value and sensitivity of at least 90% (defined on the basis of acceptable risk of false-negatives as a safety threshold (2)). Patients with low pre-test probability (e.g. <20% risk judged by treating clinician, women without hypertension, or women without previous MI) came close to meeting these specified criteria for ruling out disease without further testing, but they tended to represent only a small proportion of the study population (7%, <1% and 8% respectively).

Under the current diagnostic pathway, patients with a positive stress test result are referred for an invasive coronary angiogram, and a decision made as to whether revascularization may be beneficial - particularly if the patient is already on maximal anti-angina medical therapy. However, approximately half of patients with angina and an abnormal stress test do not have obstructive CAD on angiography, with women more likely to have a negative angiogram than men(3). The cause of symptoms in these patients may be coronary microvascular dysfunction, conduit arterial vessel stiffness, and/or diffuse atherosclerosis of both the macro and microvasculature. Optimising risk factor management through lifestyle change and medical therapy are the mainstays of treatment for non-obstructive CAD(3, 4). Recent evidence from randomised trials questions whether revascularisation via percutaneous coronary intervention (PCI) is beneficial even for patients with obstructive CAD, including those who have moderate or severe ischaemia on stress testing(5). Randomised controlled trials in patients with stable obstructive CAD who are on optimal medical therapy have found no evidence that PCI reduces the risk of an ischaemic event(5-7), or that it reduces symptoms beyond that of a sham procedure(8). This raises the question of whether symptoms of stable CAD have been wrongly attributed to obstructive CAD found on tests, when the non-obstructive CAD causes outlined above may be the true culprits(4). The evidence for benefit from detection of obstructive CAD and subsequent revascularization is clear in patients with acute coronary syndromes, and in patients with severe stenosis of the left main coronary artery. There is also evidence that in selected patients with stable CAD on optimal medical therapy,

revascularisation via coronary artery bypass grafting (CABG) reduces the risk of myocardial infarction – perhaps reflecting treatment of atherosclerotic plaques throughout the diseased vessel rather than just a discrete lesion(4).

So how do we interpret the findings of the current study on hs-cTn, in light of the limited clinical utility of identifying inducible myocardial ischaemia and obstructive CAD? In the setting of imperfect reference standards, the concept of the 'Fair Umpire' may help to work out when a new test may be better than the existing test(9). The clinical consequences of the new test can be understood by applying a 'fair umpire' test to cases where the old and new tests disagree. In this case, we want to apply the fair umpire to people with a positive Hs-cTn result and negative stress test/angiogram, or with negative hs-cTn result and positive stress test/negative angiogram. The study presents data on an umpire test that we can use to assess the implications of the discordant test results in these people: prognosis/risk of adverse clinical outcomes. In both patients with and without inducible myocardial ischemia, higher hs-cTn concentrations were associated with a higher cumulative incidence of cardiovascular death, all-cause-death, and non-fatal AMI. From the Kaplan Meier curves presented, a positive result for inducible ischemia appeared to add to the prediction of revascularisation beyond hs-cTn level, likely reflecting the influence of this result on the decision for revascularisation (operators weren't blinded to results for inducible ischemia). For cardiovascular death and all-cause death, the curves show larger differences across hs-cTn quartiles than between inducible vs non-inducible ischaemia test results, suggesting that hs-cTn may in fact be a better prognostic test in patients with stable CAD than the existing stress test/angiogram reference standard. This prognostic ability is supported by the findings of a recently published study that included >240,000 patients without ACS, and found strong associations between troponin levels and mortality(10).

If identifying a coronary artery stenosis for revascularisation does not benefit the patient with stable CAD, but may cause them harm (through complications of PCI), then is it a diagnosis we actually want to make? Walter et al conclude that hs-cTn cannot safely exclude inducible myocardial ischemia, and by implication stable obstructive CAD, but the bigger question is whether that needs excluding in the first place. Rather, should the focus of testing in patients with stable CAD be on safely ruling out significant pathology such as left main artery disease (revascularisation likely to have net benefit), while preventing unnecessary invasive tests and interventions in the majority (likely to have net harm)? Whether hs-cTn has a role in such a triage process at this point remains unclear.

Affiliations:

[1]Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia;

[2]Agnes Ginges Centre for Molecular Cardiology Centenary Institute, The University of Sydney, Australia;
[3]Sydney Medical School Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia;

[4]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

[5]Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University

Funding Support:

KJLB is the recipient of a National Health and Medical Research Council (NHMRC) Investigator Grant (#1174523).

CS is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1154992).

References

1. Bell KJL, Doust J, Glasziou P, Cullen L, Harris IA, Smith L, et al. Recognizing the Potential for Overdiagnosis: Are High-Sensitivity Cardiac Troponin Assays an Example?Recognizing the Potential for Overdiagnosis. Annals of Internal Medicine. 2019;170(4):259-61.
2. Lord SJ, St John A, Bossuyt PMM, Sandberg S, Monaghan PJ, O'Kane M, et al. Setting clinical performance specifications to develop and evaluate biomarkers for clinical use. Annals of Clinical Biochemistry. 2019;56(5):527-35.
3. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL**.** Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation. 2017;135(11):1075-92.
4. Mitchell JD, Brown DL**.** Harmonizing the Paradigm With the Data in Stable Coronary Artery Disease: A Review and Viewpoint. J Am Heart Assoc. 2017;6(11).
5. Phend C;Pageshttps://www.medpagetoday.com/meetingcoverage/aha/83400 on Nov 29 2019.
6. Sedlis SP, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GBJ, et al. Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease. New England Journal of Medicine. 2015;373(20):1937-46.
7. Stergiopoulos K, Boden WE, Hartigan P, Möbius-Winkler S, Hambrecht R, Hueb W, et al. Percutaneous Coronary Intervention Outcomes in Patients With Stable Obstructive Coronary Artery Disease and Myocardial Ischemia: A Collaborative Meta-analysis of Contemporary Randomized Clinical Trials. JAMA Internal Medicine. 2014;174(2):240.
8. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. The Lancet. 2018;391(10115):31-40.
9. Glasziou P, Irwig L, Deeks JJ**.** When should a new test become the current reference standard? Ann Intern Med. 2008;149(11):816-22.
10. Kaura A, Panoulas V, Glampson B, Davies J, Mulla A, Woods K, et al. Association of troponin level and age with mortality in 250 000 patients: cohort study across five UK acute care centres. BMJ. 2019;367:l6055.