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# Letters

## TO THE EDITOR

## "Do We Know What We Are Adding?"

Mina et al. (1) and their engendered comments (2), when assessing the benefits of radial artery access, have focused on radial artery bleeding when comparing access site to that of a femoral artery approach. More importantly than radial artery bleeding itself would be radial artery occlusion and thus the ability to potentially use the same site for further access if needed. Numerous studies have undeniably shown less bleeding with radial access over femoral access, but the true incidence of radial artery occlusion, much less the factors that are of most import in its occurrence and prevention, is not determined (3,4). Radial occlusion has been described anywhere from 5% to 9.5% after its use for diagnostic and interventional catheterization (3,4), partially dependent on when the assessment of patency has been made (early vs. late). The method of compression and the timing protocol in easing compression on the radial artery will no doubt effect patency rates (5).

Aggressive attempts to achieve patency of the radial artery following sheath removal should be made in the cath lab prior to the patient's departure from the suite. Compression time, when patency is not present at time of departure from the cath lab, should be kept to a minimal of 1.5 to 2 h maximal. Once patency is achieved, the time that a compression band is left in place should matter little.

In studies comparing radial versus femoral complications, occlusion of the artery at the access site should now be deemed important to report. This could even make the math "fuzzier." Then, efforts should be made to identify preventive factors and promote standards in clinical practice to reduce the incidence of this particular complication.

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Please note: Dr. Beckman has reported that he has no relationships relevant to the contents of this paper to disclose.

### REFERENCES

1. Mina GS, Gobrial GF, Modi K, Dominic P. Combined use of bivalirudin and radial access in acute coronary syndromes is not superior to the use of either one separately: meta-analysis of randomized controlled trials. J Am Coll Cardiol Intv 2016;9:1523–31.

2. Rao SV, Shah R. The fuzzy math of anticoagulation and access site: when 1 + 1 does not always equal 2. J Am Coll Cardiol Intv 2016;9:1532–4.

3. Slawin J, Kubler P, Szczepanski A, Piatek J, Stepkowski M, Reczuch K. Radial artery occlusion after percutaneous coronary interventions – an underestimated issue. Postepy Kardiol Interwencyjnej 2013;9:353–61.

4. Kotowycx MA, Dzavik V. Radial artery patency after transradial catheterization. Circ Cardiovasc Interv 2012;5:127–33.

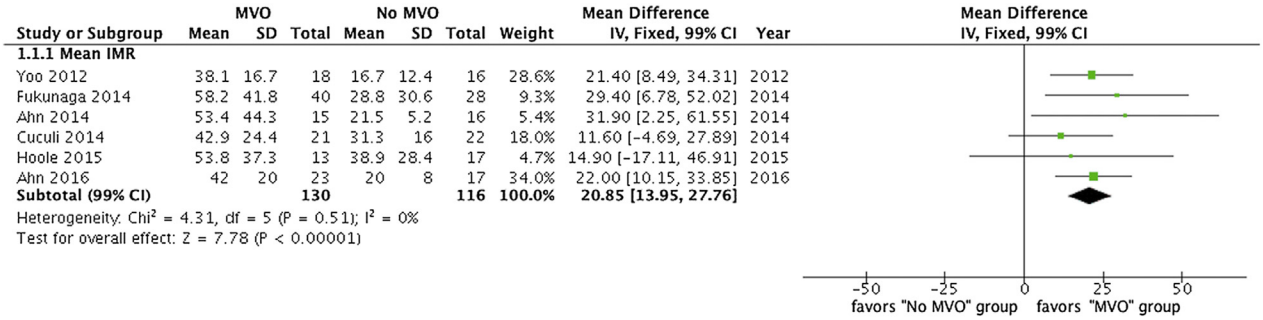
5. Pancholy SB, Patel TM. Effect of duration of hemostatic compression on radial artery occlusion after transradial access. Catheter Cardiovasc Interv 2012;79:78–81.

## Index of Microvascular Resistance and Microvascular Obstruction in Patients With Acute Myocardial Infarction

Despite timely reperfusion by primary percutaneous coronary intervention (PPCI), microvascular obstruction (MVO) occurs in up to 50% of patients with ST-segment elevation myocardial infarction (STEMI) (1). Its presence is associated with adverse left ventricular remodeling and worse clinical outcomes (1), and there is currently no effective therapy for reducing its burden. MVO can be detected by cardiovascular magnetic resonance (CMR), but this can only be performed after PPCI, when it may be too late to implement potential therapies to minimize its deleterious effect.

In this regard, the index of microvascular resistance (IMR, defined as the product of the distal pressure and mean transit time of a saline bolus during maximum hyperemia using a dual temperature and pressure wire) has been introduced as a method for evaluating the coronary microvascular circulation at the time of PPCI. However, not all studies have consistently shown a significant difference in IMR between those with and without MVO and were likely due to being underpowered. Therefore, we conducted a meta-analysis to investigate the

**FIGURE 1** Forest Plot of IMR in Patients With and Without MVO by CMR




Forest plot of the 6 studies included and shows the weighted mean index of microvascular resistance (IMR) in those with and without microvascular obstruction (MVO) by cardiac magnetic resonance imaging (CMR). CI = confidence interval; IV = inverse variance.

role of IMR in detecting the presence of MVO at the time of PPCI in reperfused STEMI patients.

We searched MEDLINE and EMBASE databases up to June 2016. The inclusion criteria were those studies undertaking both IMR at the end of PPCI in STEMI patients and performing CMR to detect MVO. We only included studies reporting the mean IMR in patients with and without MVO. Further details of the studies included in this meta-analysis are available in the Online Appendix.

Six studies were included in the meta-analysis, comprising a total of 288 patients (2-7). Further details of the 6 included studies are available in the Online Appendix. MVO data by CMR was available for 246 patients. MVO was present in 130 of 246 patients (53%). The weighted mean IMR of the whole cohort was 38.6 ± 30.6 U (99% confidence interval [CI]: 33.5 to 43.6 U). The weighted mean IMR in the 130 patients with MVO was 49.1 ± 33.6 U (99% CI: 41.4 to 56.8 U), whereas it was 26.7 ± 21.5 U (99% CI: 21.6 to 32.0 U; $p < 0.0001$; heterogeneity; chi-square = 4.31; df = 5; $p = 0.51$; $I^2 = 0\%$) in 116 patients without MVO. The weighted mean difference in IMR between these 2 groups was 20.9 U (99% CI: 14.0 to 27.8 U; $I^2 = 0\%$; $p < 0.00001$; **Figure 1**).

This study suggests that patients with a weighted mean IMR of <32 U (upper limit of the 99% CI in the group without MVO) were far less likely to have MVO, whereas patients with a weighted mean IMR of >41 U (lower limit of the 99% CI in the group with MVO) were much more likely to have MVO. Interestingly, a median IMR value of >40 U was previously shown to be an independent predictor of death in a large study of 253 patients with STEMI (hazard ratio: 4.3; $p = 0.02$) after a median follow-up of 2.8 years (8). This IMR value was very close to the cutoff value we obtained from this meta-analysis using MVO by CMR as a surrogate.

Therefore, we would propose that when investigating a novel intervention for minimizing the burden of MVO, selecting patients with an IMR of >41 U may help to identify, at the time of PPCI, those very likely to have MVO and at risk of worse outcomes. This approach would identify those most likely to benefit from promising therapies such as an infusion of glycoprotein IIb/IIIa inhibitors and intracoronary thrombolysis. Furthermore, by only targeting those with an IMR of >41 U at the end of the PPCI procedure, those at lower risk of MVO (IMR ≤41U) will not be subjected to unnecessary risk of adverse events such as bleeding.

The main limitations of this study are patient-level data were not available to report on sensitivity and specificity of IMR to detect MVO. The SDs reported in some of these studies were quite wide and this highlights the heterogeneity present when measuring IMR. It is highly probable that the sensitivity and specificity of IMR to detect MVO would be affected as a result. However, our study is not suggesting that IMR measurement can dichotomize those with and without MVO, but is providing an approach to identify those at high risk of having MVO in the cardiac catheterization laboratory and could be targeted in future studies. The interval between PPCI and CMR was different in each study and could have affected the detection of MVO. MVO was assessed on late gadolinium enhancement performed between 10 and 15 min post contrast in the majority of the studies, but 1 study performed late gadolinium enhancement imaging between 5 and

10 min post-contrast (6) and may have led to a higher incidence of MVO in the latter.

In conclusion, IMR at the time of PPCI can identify those patients with MVO, allowing the implementation of treatment to minimize this complication. We provide weighted mean IMR values in patients with MVO (49 ± 33 U) and without MVO (27 ± 22 U), information that may be used to estimate sample sizes when planning future studies to assess the efficacy of novel therapies for reducing its burden.

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## REFERENCES

**1.** van Kranenburg M, Magro M, Thiele H, et al. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. J Am Coll Cardiol Img 2014;7:930–9.

**2.** Yoo SH, Yoo TK, Lim HS, Kim MY, Koh JH. Index of microcirculatory resistance as predictor for microvascular functional recovery in patients with anterior myocardial infarction. J Korean Med Sci 2012;27:1044–50.

**3.** Ahn SG, Lee SH, Lee JH, et al. Efficacy of combination treatment with intracoronary abciximab and aspiration thrombectomy on myocardial perfusion in patients with ST-segment elevation myocardial infarction undergoing primary coronary stenting. Yonsei Med J 2014;55:606–16.

**4.** Cuculi F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1894–904.

**5.** Fukunaga M, Fujii K, Kawasaki D, et al. Thermodilution-derived coronary blood flow pattern immediately after coronary intervention as a predictor of microcirculatory damage and midterm clinical outcomes in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2014;7:149–55.

**6.** Hoole SP, Jaworski C, Brown AJ, et al. Serial assessment of the index of microcirculatory resistance during primary percutaneous coronary intervention comparing manual aspiration catheter thrombectomy with balloon angioplasty (IMPACT study): a randomised controlled pilot study. Open Heart 2015;2:e000238.

**7.** Ahn SG, Hung OY, Lee JW, et al. Combination of the thermodilution-derived index of microcirculatory resistance and coronary flow reserve is highly predictive of microvascular obstruction on cardiac magnetic resonance imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2016;9:793–801.

**8.** Fearon WF, Low AF, Yong AS, et al. Prognostic value of the index of microcirculatory resistance measured after primary percutaneous coronary intervention. Circulation 2013;127:2436–41.

**APPENDIX** For an expanded Methods section, please see the online version of this article.

# Antithrombotic Therapy and Vascular Access Site

## Comparing Effect Sizes, Not Only p Values

In a recent paper, Mina et al. (1) presented an interesting meta-analysis of 8 randomized trials evaluating the safety and the efficacy of antithrombotic therapy according to the type of vascular access and vice versa. The investigators concluded that bivalirudin reduced the risk for major bleeding in patients who underwent femoral access but was ineffective in case of radial access. Analogously, radial access reduced the risk for bleeding among patients who received unfractionated heparin, but not bivalirudin.

However, the investigators did not formally assess the presence of treatment heterogeneity through interaction testing. As shown in **Figure 1**, although bivalirudin versus heparin significantly reduced the risk for major bleeding in patients with femoral access (odds ratio [OR]: 0.51; 95% confidence interval [CI]: 0.46 to 0.60) compared with radial access (OR: 0.75; 95% CI: 0.45 to 1.26), the test for interaction was not significant (p for interaction = 0.155). However, radial versus femoral access significantly reduced the risk for major bleeding in patients who received unfractionated heparin (OR: 0.57; 95% CI: 0.43 to 0.77), but not in those who received bivalirudin (OR: 0.96; 95% CI: 0.65 to 1.41), and, importantly, the test for interaction was significant (p interaction = 0.035). Therefore, a more nuanced interpretation would be that bivalirudin reduces the risk of major bleeding irrespective of the type of access, whilst radial access reduces the risk for major bleeding predominantly among patients receiving unfractionated heparin. Although apparently puzzling, this result is easily explained by the fact that bivalirudin decreases the risk for both access- and non-access-site bleeding, and therefore, its safety profile is not determined exclusively by the type of vascular access (2). Of course, radial access is only able to reduce access-site bleeding.