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Editorial

Adrenomedullin and endothelin-1: Promising biomarkers of endothelial function, but not ready for prime time

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Endothelial dysfunction appears to be the final common pathway in the development of coronary atherosclerosis and ultimately flow-limiting stenoses. Key mediators of endothelial function include the vasodilators nitric oxide (NO) and adrenomedullin (ADM) and the vasoconstrictor endothelin-1 (ET-1), bioactive peptides secreted by the endothelium whose complex interplay regulates vascular integrity. NO—the most potent vasodilator in humans—inhibits platelet adhesion and aggregation, smooth muscle cell proliferation, and leukocyte recruitment, and thereby reduces the propensity for vasoconstriction, thrombosis, cellular proliferation, and inflammation throughout the vessel wall [1]. Notably, ADM-mediated vasodilation occurs through enhanced calcium signaling leading to increased NO synthesis, thus making ADM a surrogate marker of NO [2]. In contrast to these vasodilators, ET-1 is the most powerful vasoconstrictor in humans and exerts mitogenic and pro-inflammatory effects in the vessel wall [3]. In the era of precision medicine, these biomarkers of endothelial function carry the potential to further risk stratify and prognosticate patients with cardiovascular disease non-invasively. Lower ADM and higher plasma ET-1 concentrations have both been previously reported to be associated with major adverse cardiovascular events (MACE) in patients with stable coronary artery disease, though these data are limited to a few studies [4,5].

In the current issue of the *International Journal of Cardiology*, Theuerle et al. contribute important new data to this underexplored domain [6]. The investigators performed a prospective, single-center study primarily evaluating the association of plasma ADM and ET-1 levels with invasive indices of epicardial and microvascular coronary function (i.e. flow) and tone as well as long-term clinical outcomes in 32 consecutive patients with stable angina and/or a positive stress test undergoing coronary angiography (≤1-vessel obstructive disease) over a median follow-up of 8.8 years (interquartile range 7.9–9.2). Specifically, in an angiographically normal or near normal (<20% diameter stenosis) coronary artery, they measured 1) coronary flow reserve (CFR), which reflects the function of the entire coronary tree, 2) the index of microcirculatory resistance (IMR), which focuses solely on the function of the microvasculature, and 3) coronary flow mediated dilation (cFMD), which estimates epicardial vasomotor tone. After multivariate adjustment, ET-1 was positively correlated with IMR and ADM was positively correlated with cFMD; a modest, nonsignificant correlation between ADM and CFR was also observed. The rate of MACE (unstable angina, myocardial infarction [MI], stroke, congestive heart failure, and all-cause mortality) was 50%, with a total of 22 adverse events (45% of which were hard endpoints—MI, stroke and mortality). The median time to first MACE was 3.1 years. Patients free of MACE had significantly increased cFMD and a nonsignificant trend toward elevated ADM levels. There was no significant association between ET-1 and MACE.

Theuerle and colleagues should be congratulated for their excellent work. The authors prospectively conducted a fairly comprehensive physiologic analysis of the entire coronary circulation in consecutive stable angina patients with multiple risk factors of cardiovascular disease, resulting in an enriched, generalizable cohort with limited selection bias. They also collected long-term outcome data with nearly complete (94%) follow-up, leading to a MACE rate of 50% that conferred reasonable statistical power. Additionally, the current work is quite novel, as there is limited (ET-1) to no (ADM) published data examining the association of these biomarkers with invasive indices of coronary physiology [7]. Nevertheless, this study must be viewed in the context of its small sample size. Namely, the conclusions drawn from the data should be tempered and considered hypothesis generating. For example, the authors conclude that ADM primarily exerts its effects in the epicardial conduit while ET-1 predominantly regulates the microcirculation. However, several studies support the more plausible hypothesis that ADM and ET-1 are biologically active throughout the coronary tree [8,9].

Other notable limitations include methodological flaws that diminish the overall robustness of the study. First, fractional flow reserve (FFR)—the gold standard index for evaluating epicardial

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coronary function—was not measured; the investigators did measure CFR and cFMD, but the former incorporates the microvasculature and the latter quantifies vascular tone rather than flow. In the present study, physiologic measurements were performed in an angiographically normal or near normal vessel, and so we would have expected FFR values to be well above the validated ischemic threshold of 0.80 similar to how the reported IMR values (15.6 ± 5.9) were well below the ischemic cutoff of 25. Non-ischemic FFR and IMR values in minimally diseased coronary arteries have been shown to have major prognostic implications in other cardiovascular disease populations [10]. Second, the authors curiously did not apply standard Cox proportional hazards models to adjust for confounding demographic and cardiovascular risk factors in the outcomes analyses. Hence, it is unknown whether cFMD (or any other covariates) were independent predictors of MACE in this study. Finally, adherence to evidence-based, guideline-endorsed medical therapy was not reported; medication nonadherence may have contributed to the observed outcomes and thus is an important unmeasured confounder.

Notwithstanding these limitations, the current study offers intriguing insights into the possible role of ADM and ET-1 in predicting impaired coronary artery function and MACE in patients with stable angina. Larger studies are necessary to validate these data and derive biomarker thresholds, which will then require external validation to establish clinical viability. Furthermore, replicating the present study in a higher risk acute coronary syndrome population (i.e. larger derangement in coronary physiologic measurements and higher MACE rate) would be interesting, as it could provide greater statistical power to assess the impact of ADM and ET-1 on hard endpoints over a shorter time period. Thus, although ADM and ET-1 are not ready for prime time, the work by Theuerle et al. herein reinforces the promise of these biomarkers and paves the way forward for future investigation.

Disclosures

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