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Letters

TO THE EDITOR

Adenosine-Dependent Vasodilation and the Quest for "Maximal" Hyperemia

Does Flow Provide an Answer?

With great interest, we read the work of Adjedj and colleagues (1), demonstrating the dose-response curve of intracoronary adenosine for hyperemia, expressed in terms of coronary flow velocity. The authors should be congratulated for this elegant study, which by focusing on the flow response to adenosine has important incremental value over previous studies on the subject. Nonetheless, some considerations may require further attention.

First, the authors studied unobstructed coronary vessels only. Although, as explained by the authors, only in these vessels an adequate dose-response curve of adenosine for flow velocity can be obtained, it is important to realize that vasoreactivity in the distal microvasculature is altered in the presence of epicardial stenosis due to altered tone regulation and remodeling of the microcirculation (2). Hence, the present findings apply to unobstructed coronary vessels and cannot be unequivocally extrapolated to stenosed vessels. Nonetheless, the extrapolation to the fractional flow reserve (FFR) framework is hypothesis-generating. Because the expected difference between the minimal and observed FFR is smaller than the variability of the FFR measurement itself for adenosine doses above 40 μg, the authors document that low-dose adenosine administration does not lead to relevant ambiguities in FFR assessment. This finding importantly strengthens the conclusions derived from clinical studies that were previously scrutinized for using low(er)-dose adenosine administration (3,4).

Second, in contrast to many interventional practices, the authors decided not to flush the dead space after administration of adenosine, and estimate a 15% difference in administered adenosine versus the actual dose reaching the coronary ostium. However, a 6-F guiding catheter as used by the authors has over 2 ml worth of dead space. With administration of the documented dose of adenosine in 8 ml (1), a 2-ml dead space means 25% of the administered dose will not reach the coronary ostium: of the proposed 160- to 200-μg and 60- to 100-μg doses for the left coronary artery and right coronary artery, respectively, only 120 to 150 μg and 45 to 75 μg reached the coronary ostium. This does not invalidate the study results, but stresses the notably low doses of intracoronary adenosine required to exhaust adenosine-dependent vasodilation, and suggests that the proposed doses should not be firmly extrapolated to the clinical setting.

Finally, it is important to realize that neither this study, nor most of the preceding studies using FFR as the endpoint, assess the achievement of maximal hyperemia. Despite using this terminology, all of these studies merely investigate the amount of adenosine required to exhaust adenosine-dependent vasodilation. It is well-known that many vasoconstrictors interfere with the complete abolishment of vasomotor tone required to achieve "maximal" hyperemia (5). The prevailing balance between adenosine-dependent and non-adenosine-dependent vasoconstriction determines at what dose and to what extent adenosine is able to dilate the coronary resistance vessels. This balance will be different in each patient, which makes the identification of a single dose of adenosine to optimize adenosine-induced vasodilation an impossible task.

Notwithstanding the aforementioned considerations, the present study (1) is the first to provide adenosine dosing advice based on the vasodilatory response of the unobstructed coronary circulation to intracoronary adenosine. More importantly, rest assured: it documents the appropriateness of intracoronary adenosine administration for invasive physiological assessment even at low doses of around 40 μg of adenosine.

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Please note: Dr. van de Hoef has served as a speaker for Philips-Volcano Corporation, St. Jude Medical, and Boston Scientific. Dr. Escaned has served as a speaker for Boston Scientific, Philips-Volcano Corporation, and St. Jude Medical. Dr. Piek has served as a speaker for Philips-Volcano Corporation.

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3-Year Outcomes of the OLIVE Registry, a Prospective Multicenter Study of Patients With Critical Limb Ischemia

We read with much interest the recent paper and editorial by Iida et al. (1) and Menard (2), respectively, in *JACC: Cardiovascular Interventions* assessing the mid-term outcomes after endovascular therapy in a prospective multicenter (A Prospective, Multi-Center, Three Year Follow-Up Study on Endovascular Treatment for Infra-Inguinal Vessel in Patients With Critical Limb Ischemia [OLIVE]) registry in 314 patients with chronic limb ischemia (CLI). At 3 years, amputation-free survival, freedom from major adverse limb events, and wound-free survival rates were 55.2%, 84.0%, and 49.6%, respectively. Wound recurrence rate was at 3 years was 43.9%. After multivariable analysis, age (hazard ratio [HR]: 1.43, $p = 0.001$), body mass index 18.5 (HR: 2.17, $p = 0.001$), dialysis (HR: 2.91, $p < 0.001$), and Rutherford 6 (HR: 1.64, $p = 0.047$) were identified as predictors of 3-year major amputation or death. Statin use (HR: 0.28, $p = 0.02$), Rutherford 6 (HR: 2.40, $p = 0.02$), straight-line flow to the foot (HR: 0.27, $p = 0.001$), and heart failure (HR: 1.96, $p = 0.04$) were identified as 3-year major adverse limb event predictors. Finally, CLI due to isolated, below-the-knee lesion was a wound recurrence predictor (HR: 4.28, $p = 0.001$). Three-year survival, freedom from major amputation, and reintervention rates were 63.0%, 87.9%, and 43.2%, respectively.

The authors should be commended for writing this important and timely paper, especially as the research in CLI has reoriented towards optimizing long-term patient outcomes. Long-term patient outcomes beyond limb salvage are critical because large registry studies in peripheral artery disease have shown that suboptimal medical management increases the risk of cardiovascular death, stroke, and myocardial infarction by up to 7-fold at 3 years (3). In this regard, it is striking that in the OLIVE registry, despite a very high incidence of established vascular disease (100%) and cardiovascular disease (21% to 46%), only 26% are on statin therapy, 40% on clopidogrel, and/or 50% on cliostazol. Additionally, there are no data presented on whether the statin use or blood pressure control had been optimized and reached the targets set by the TransAtlantic Inter-Society Consensus (TASC) II guidelines (4). However, the authors should be congratulated for reporting on the degree of optimal medical therapy in their patient subset. In fact, most of the recent prospective studies have focused primarily on endovascular device use/techniques to optimize limb outcomes and have not quantified whether patients received guideline-based optimal medical therapy before or after endovascular intervention (1).

These observations suggest a persistent deficit in the quality of medical care in CLI and have profound implications. First, population-based interventions that improve medical therapy for CLI may have a large impact both on amputation-free survival and reducing the risk of cardiovascular mortality and myocardial infarction. Second, the addition of an optimal medical treatment metric in the assessment of endovascular and/or surgical interventions on CLI will allow for uniform comparisons between different treatment strategies. Furthermore, it is known that the costs of inpatient care in the year before amputation in patients with CLI is more than $20,000 per patient. This cost varies by 2-fold across hospital referral regions in the United States; much of this difference in cost is driven by the use of revascularization treatments and not related to patient or amputation care. Additionally, there is little evidence that higher spending on vascular care (primarily endovascular care) in the year prior lowers amputation rates. The quality of baseline medical therapy will be important in assessing and comparing the overall quality and cost of vascular care provided by institutions and individual providers (5). This is axiomatic in light of the environment in