Peripheral Arterial Disease and Subsequent Cardiovascular Mortality
A Strong and Consistent Association

Michael H. Criqui, MD, MPH

In this issue of Circulation, Davey Smith and colleagues report the association of intermittent claudication with subsequent mortality among more than 18,000 men in the Whitehall Study. Intermittent claudication was assessed by self-administration of the brief and simple London School of Hygiene and Tropical Medicine questionnaire, better known as the Rose Questionnaire after its author. This questionnaire is the epidemiological standard for assessment of angina, infarction pain, and intermittent claudication.

The Whitehall Study confirms earlier reports of a doubling of mortality and a significant reduction of life expectancy in subjects with symptoms of peripheral arterial disease (PAD). Most of this increase in mortality is due to cardiovascular disease. A population-based study from our institution confirmed that Rose claudication, called probable claudication in the Whitehall Study, doubled the risk of mortality. However, we also assessed large-vessel PAD at baseline with highly valid and reliable non-invasive tests (i.e., flow velocity by Doppler ultrasound and segmental blood pressure ratios). We had earlier published an analysis showing a high specificity value and high positive and negative predictive values of Rose claudication for large-vessel PAD but a low sensitivity value. Because of misclassification due mostly to this low sensitivity, we anticipated that large-vessel PAD measured noninvasively would show a better association with mortality; indeed, the relative risk of 1.9 in our study for Rose claudication was nearly quadrupled to 7.5 when large-vessel PAD measured noninvasively was used to predict subsequent mortality. After adjustment for other risk factors and exclusion of prevalent disease at baseline, the relative risk of large-vessel PAD for mortality was 4.5.

Interestingly, after exclusion of subjects with baseline ischemia in the Whitehall Study, the association of “possible” claudication (or exercise calf pain that could disappear while walking) with mortality was stronger than the association for probable claudication. We had earlier reported that defining claudication as any exercise calf pain not present at rest (i.e., possible or probable claudication) doubled the sensitivity for large-vessel PAD, albeit at the expense of some loss of specificity and positive predictive value, and, interestingly, doubled the relative risk of claudication for subsequent mortality.

It appears that there is a new lesson to be learned and an old lesson to be emphasized from these new analyses. The new lesson is that, as the Whitehall investigators note, the atypical or possible claudication group “contains many genuine cases.” This may not surprise clinicians who have long recognized that some of their patients with angiographically documented large-vessel PAD can “walk through” their pain, but it is perhaps more surprising that in the two population studies that have considered this issue, possible claudication is a category with such validity that the prediction of mortality is actually improved by its inclusion as “real” claudication. Interestingly, this is concordant with a recently published study in older men and women indicating that the risk of coronary heart disease mortality for those reporting any chest pain on exertion was higher than that for those whose symptoms met the Rose criteria for angina. Thus, similar to the results for possible claudication above, inclusion of “atypical” exertional chest pain in the angina group improved the prediction for subsequent mortality. On a cautionary note, the Rose questionnaire is a short, standardized assessment, and in a more extensive interview the clinician might be able to classify true claudication (or angina) with greater accuracy, but clinicians must be aware that claudication and angina may be atypical.

The old lesson to be emphasized is that large-vessel PAD has a remarkable ability, whether defined somewhat crudely by claudication or sharply by non-invasive testing, to predict subsequent cardiovascular mortality, independent of both other cardiovascular risk factors and prevalent disease at baseline. In addition, large-vessel PAD has been shown to be one of the strongest independent predictors of subsequent mortality in both post–myocardial infarction
patients\(^1\) and post–coronary artery bypass patients.\(^2\) It has been recommended that patients being considered for large-vessel PAD surgery have coronary angiography first and bypass surgery when appropriate because of the otherwise poor postoperative survival,\(^3\) although recent evidence suggests preoperative electrocardiographical monitoring for ischemia in large-vessel PAD patients may delineate the high-risk group.\(^4\)

Notably, the predictive power of claudication for mortality was comparable to that of angina in the Whitehall Study, and the predictive power of noninvasively measured PAD for mortality in the PAD study from our institution\(^8\) rivaled that for exercise electrocardiography in published reports.\(^9\)

The Whitehall investigators conclude that the Rose Questionnaire for claudication “can identify a group . . . whose increased risk of death may be partially preventable.” We concur but also strongly reiterate what we said in 1985, that “men and women at high risk of impending mortality might be identifiable by noninvasive PAD testing, and . . . such testing may alert us to subjects who require additional evaluation or . . . intervention.”\(^8\) The potential value of noninvasive testing may be augmented when tests for isolated small-vessel PAD are included. Isolated small-vessel PAD is unrelated to claudication,\(^9\) is not associated with traditional cardiovascular risk factors,\(^10\) and by definition cannot be present concurrently with large-vessel PAD. New data suggest isolated small-vessel PAD is independently predictive of subsequent cardiovascular morbidity and mortality.\(^11\)

References

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M H Criqui

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