Referral bias: A difficult but important topic

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Consider the following hypothetical study designed to test the hypothesis that resting heart rate influences exercise performance. Resting heart rate would be assessed on two separate 1-minute rhythm strips after 5 minutes of quiet rest. To eliminate day-to-day variation, the measurements would be done on two separate occasions before two tests of exercise performance. Now assume that the measure of exercise performance was time for a full marathon and that the study group consisted of volunteers who participated in both the New York and Boston Marathons in a given calendar year. If there was a clear relationship between resting heart rate and marathon time in this study, would it be reasonable to extrapolate these results to the performance of other athletes, such as sprinters or weight lifters? Probably not, as the types of exercise are fundamentally different. Would the results be applicable to high school cross-country runners? Possibly not, given their youth. Would the results be applicable to the general population? Almost certainly not, given the vastly different training status of the general population, as well as the effects of confounders such as medications and sinus node dysfunction.

Although admittedly extreme, this hypothetical example demonstrates the difficulty of applying very carefully acquired data from one population of subjects to other populations. In many clinical cases, as in our hypothetical example, the difficulties are obvious. In other situations the difficulties are often more subtle. We intuitively tend to apply results from a published study to other patient populations without recognizing the inherent pitfalls in doing so. The study by Bourque et al¹ in this issue of the journal explores some of these issues at Duke University Medical Center. The authors sought to examine whether patients with left ventricular (LV) dysfunction and significant coronary artery disease (CAD) differed in important ways if they underwent cardiac

catheterization without single photon emission computed tomography (SPECT) perfusion imaging, SPECT perfusion imaging before catheterization, or SPECT perfusion imaging after catheterization. Not surprisingly, they found that there were important differences among the patient groups, depending on which of these three testing sequences was used. The authors conclude that these differences should be recognized when interpreting published data on myocardial perfusion imaging in patients with LV dysfunction and significant CAD.

Figure 1 is my own attempt to put this work in context. Each one of the four large circles on this Venn diagram represents a population of patients—those with LV dysfunction, those with CAD, those undergoing SPECT imaging, and those undergoing cardiac catheterization. Bourque et al¹ have attempted to study patients with both LV dysfunction and CAD who all underwent cardiac catheterization. Their study is therefore confined to the patients falling in the area within the bold lines. They have found important differences between the patients in sectors A, B1, and B2. This diagram is not drawn to scale to reflect the size of the groups. As reported by the authors, population A at Duke is about 10 times larger than population B1 and about 6 times larger than population B2.

This diagrammatic representation does demonstrate both the complexities of this issue and the limitations of the authors' analysis. Bourque et al¹ did not examine the characteristics at Duke of patients with LV dysfunction and CAD who underwent SPECT alone (area C). They also did not examine the characteristics of those patients with LV dysfunction without CAD who had catheterization alone (area D), SPECT alone (area F), or SPECT and catheterization (area E). Finally, this study does not examine the characteristics of those patients who have CAD without LV dysfunction, who may have undergone cardiac catheterization without SPECT (area G, exemplified by patients with unstable angina), SPECT alone (area J, exemplified by patients with mild reversible ischemia on SPECT), or both catheterization and SPECT (area H, exemplified by patients with markedly abnormal SPECT studies who then went on to cardiac catheterization).

The problem is even more complex if one considers other limitations of this diagram. The boundaries of the circles for both LV dysfunction and CAD may shift with slight changes in the definition based on ejection fraction

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Figure 1. Venn diagram showing four partially overlapping patient populations—those with CAD, those with LV dysfunction, those undergoing SPECT imaging, and those undergoing cardiac catheterization (*Cath*). Area A represents patients who underwent cardiac catheterization without SPECT; B1, patients who underwent SPECT before catheterization; and B2, patients who underwent SPECT after catheterization. Refer to text for further explanation.

or percent stenosis. The diagram does not consider the selection of patients for revascularization by either percutaneous coronary intervention or coronary artery bypass surgery, a very pertinent clinical issue. Finally, given the known large regional variations in diagnostic testing in different Medicare referral populations,^{2,3} the size of the circles representing patients undergoing catheterization and SPECT imaging should vary greatly from region to region in the country. This is clearly a very complex topic. Is it important that we try to understand it? I would argue strongly that the answer is yes.

The importance of referral bias has long been recognized. Its impact on the diagnosis of CAD is well established. Almost 20 years ago, the Cedars-Sinai group reported on the declining specificity of radionuclide ventriculography,⁴ which reflected the changing patterns of referral to cardiac catheterization after radionuclide ventriculography. Despite the importance of this phenomenon, most studies on the diagnosis of CAD test performance try to ignore it, and very few studies try to eliminate it or adjust for it. The latest American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines on radionuclide imaging list 50 published studies on exercise and vasodilator stress SPECT imaging for detecting CAD that did not correct for referral bias, compared with only 5 that did.⁵

Bourque et al¹ focus on the use of SPECT imaging for viability. Although the nuclear cardiology community generally accepts the validity of the many published studies showing improvement in patients with LV dysfunction and myocardial viability by SPECT imaging who subsequently undergo revascularization, physicians treating patients with LV dysfunction and heart failure are far more skeptical. They are reluctant to apply these results based on generally small numbers of selected patients to larger unselected groups, whom they believe may be different. The American College of Cardiology/American Heart Association guidelines for the management of congestive heart failure gave only a class IIa recommendation to “non-invasive imaging to detect ischemia and viability in patients with known coronary disease and no angina who are being considered for revascularization.”⁶ A recent study from the Mayo Clinic found that less than 15% of patients with congestive heart failure and large areas of ischemia on SPECT imaging subsequently underwent revascularization,⁷ reflecting not only the presence of comorbidities and poor target vessels, but also the skepticism of the heart failure specialists, interventionists, and cardiac surgeons that patient outcomes would be improved by revascularization. Bourque et al have shown that patients with dysfunction and CAD who underwent SPECT imaging and cardiac catheterization were different in several ways from those who did not undergo SPECT. The results of revascularization in these two groups of patients may therefore not be identical. The findings of Bourque et al therefore provide some support for the reluctance of heart failure specialists to accept the nuclear cardiology literature. Hopefully, the applicability of the nuclear cardiology literature to current clinical practice will be clarified by the ongoing Surgical Treatment in Ischemic Heart Failure (STICH) trial, which should establish the benefit of revascularization in patients with LV dysfunction.

Bourque et al¹ have made an important contribution to the literature on this topic. We need far more studies like this to better understand this complex issue. In the meantime, evidence-based physicians should recognize the impact of referral bias and be cautious in their extrapolation of published data to other patient populations.

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References

1. Bourque JM, Velazquez EJ, Borges-Neto S, et al. Clinical characteristics and referral pattern of patients with left ventricular dys-

- function and significant coronary artery disease undergoing radionuclide imaging. *J Nucl Cardiol* 2004;11.
2. Wennberg JE, Birkmeyer JD, Birkmeyer NJO, et al. The Dartmouth atlas of cardiovascular health care. Chicago: AHA Press; 1999.
 3. Beller GA. President's page: geographic variations in delivery of cardiovascular care: an issue of great importance to cardiovascular specialists. *J Am Coll Cardiol* 2000;36:652-5.
 4. Rozanski A, Diamond GA, Berman D, et al. The declining specificity of exercise radionuclide ventriculography. *N Engl J Med* 1983;309:518-22.
 5. Klocke FJ, Baird MG, Bateman TM, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Review the 1995 Guidelines for the Clinical Use of Radionuclide Imaging). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/radio/rni_fulltext.pdf. 2003. Accessed February 14, 2004.
 6. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm. 2001. Accessed February 14, 2004.
 7. Miller WL, Tointon SK, Hodge DO, et al. Long-term outcome and the use of revascularization in patients with heart failure, suspected ischemic heart disease and large reversible myocardial perfusion defects. *Am Heart J* 2002;143:904-9.

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