INVITED COMMENTARY

Implication of Prognostically Significant Negative Results on Prone SPECT

Do we require the further refinements of modern technology applied to myocardial SPECT and, if so, for what? Everyday practice with gated myocardial SPECT without attenuation correction or prone acquisition yields excellent information for the diagnosis of obstructive coronary artery disease (CAD). To propagate a new technology through nuclear laboratories, what kind of study should one perform to prove the additional value of this new technology? We suggest that we badly need details of the prognostic significance, especially of normal or negative study results. In this context, the presentation on the prognostic implications of combined supine and prone myocardial SPECT by Hayes et al. (*1*) in this issue of *The Journal of Nuclear Medicine* was essential for the promotion of this prone acquisition technique. This is more than desirable because prognostic implications are critical for maintaining the cost-effectiveness of myocardial SPECT (*2*).

In several reports, the cost-effectiveness of the strategy of myocardial SPECT to coronary angiography was better, when the pretest likelihood of CAD was low to intermediate, than the strategies of exercise electrocardiography to angiography (*3*,*4*) or stress echocardiography to angiography (*2*). This finding was surprising at first because the reported cumulative diagnostic accuracy of stress echocardiography tended to be better than that of myocardial SPECT for the diagnosis of CAD (*5*). However, the different prognostic significances of false-negative studies on myocardial SPECT or stress echocardiography caused differences in terms of their cost-effectiveness (*2*). To maintain its superiority in cost-effectiveness, annual major adverse cardiac event rates of false-negative cases should have been 0.5%, which was reported repeatedly for false-negative cases on conventional myocardial SPECT (*2*).

Should the benign prognosis of negative results be proven, false-negative results having the same benign prognosis as true-negative results cannot be viewed as false. The excellent prognosis of negative cases obviates the need for intervention or further invasive studies to find prognostically insignificant coronary artery stenosis. Thus, newer expensive technology is not needed to decrease the false-negative rate and so to increase the present 85% sensitivity of conventional myocardial SPECT (*5*) in the diagnosis of CAD.

By the relatively inexpensive addition of prone acquisition, Hayes et al. (*1*) tried to reduce the false-positive rate (and increase specificity). However, when the false-positive rate is decreased, reflecting the well-known seesaw relationship between sensitivity and specificity, increasing the fraction of false-negative results (decreased sensitivity) should be a concern. Whether the patients belonging to the newly increased fraction of false-negative cases have an event-free prognosis becomes a problem. Receiver-operating-characteristic curve analysis might provide a partial escape from this seesaw phenomenon. However, our clinical experience warns that when one tries to decrease the false-positive rate without increasing the false-negative rate, posttest referral bias is also maximized—that is, no angiographic data tend to be available in equivocal cases. Without gold standard angiographic results, investigations into the exact diagnostic accuracy of a new technology for equivocal cases become obsolete.

Then, how can we be sure, without the data on diagnostic accuracy, that we are making the right decision by adopting a resource-demanding new technology in our nuclear laboratories? The most indispensable information is evidence of prognostic implication, which was well presented in the article of Hayes et al. with respect to additional prone acquisition (*1*). In terms of prognosis, patients with negative results on additional prone SPECT showed a benign future with a rate of annual major adverse cardiac events similar to that of those with negative results on conventional supine SPECT. Thus, we can be confident that negative results by prone acquisition also indicate event-free survival.

In this type of prognostic study, however, inherent sampling biases should be kept in mind when interpreting results. Patients who were revascularized within 60 d of myocardial SPECT studies were excluded as usual. This means that because a higher pretest likelihood of CAD would cause cardiologists to perform angiography or even angioplasty, these high-likelihood cases were excluded from the prognosis study cohort from the beginning. This exclusion would have tended to cause an overestimation of the benign prognostic implication of negative results, because negative cases with a high suggestion of CAD would have been referred to angiography laboratories. The lower event rate follows from the exclusion of higher

Received Jun. 2, 2003; revision accepted Jun. 13, 2003.

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risk negative cases. On the other hand, angiography and angioplasty would have been performed in patients having definitively positive results on supine-only or supine and prone protocols. The annual event rates of these positive cases would have been underestimated. Despite these inherent shortcomings of prognostic studies, the prognostic data of negative cases on supine and prone SPECT remain persuasive.

One fact that we should also note in the study of Hayes et al. (*1*) is the risk-adjusted data. The proportion of male sex was larger and the prescan likelihood was higher in the supine and prone group, but the annual event rates were lower in this group. In a subgroup of moderately to severely abnormal findings, annual event rates were also lower. Nevertheless, risk-adjusted event rates of the moderately to severely abnormal subgroup of supine and prone protocol became higher after adjusting for other risks, and risk-adjusted event rates of the subgroup of supine-only protocol became lower. Of course, in the normal subgroup of both scan protocols, risk adjustment influenced event rates, so that the event rate of the supine and prone protocol is reduced. Probably, risk adjustment differentially affected the annual event rates of normal, mildly abnormal, and moderately to severely abnormal groups, because the differences between the supine-only and the supine and prone groups are eliminated after risk adjustment (*1*). Prognostically speaking, and in terms of cost-effectiveness, additional prone imaging is justified.

Despite the posttest referral bias, the diagnostic performance of prone SPECT has been the subject of continued study. Segall and Davis investigated the diagnostic performances in ^{201}Tl SPECT with exercise stress and reported an improved overall specificity with a minimal loss of sensitivity (59%–82% and 79%–75%, respectively) for prone SPECT (*6*). In their study, most of the improvement resulted from improvements in the diagnosis of the right coronary artery (RCA). Kiat et al. also reported a high specificity of about 90%, although they did not directly compare supine and prone SPECT images (*7*). Increases in inferior wall counts and consequent improvements of diagnostic performance were also observed with ^{99m}Tc agents (*8*). Lisbona et al. analyzed only the RCA lesions of 82 patients in dipyridamole-stressed ^{99m}Tc-sestamibi SPECT and reported that the specificity was improved from 58% to 79% in prone SPECT, whereas the sensitivity remained at 74% (*9*). However, later studies paid more attention to limitations in the diagnostic performance of prone SPECT. Schoss and Gorten observed high false-positive rates in the anterior wall and apex by prone SPECT, although overall diagnostic performance was better than that of supine SPECT (*10*). Dogruca et al. even reported that the overall accuracy of prone SPECT at the inferior wall was no different from that of supine SPECT. In their study, specificity improvements were only obtained by sacrificing diagnostic sensitivity (*11*).

Now, we are at a branching point; are we going to adopt this technique in our laboratories? What about attenuation correction? Which is more costly? In the study of Hayes et al. (*1*), one fifth of the patients received a second acquisition, and 20% more camera time was consumed, which equates to processing 20% fewer patients. For attenuation correction, no loss of patient throughput is expected, but we need to pay the transmission source regularly. Which is more costly? Before considering the cost side, we should ask the question: Does attenuation correction perform as well as prone SPECT?

Attenuation correction is another technical solution for the attenuation artifact. Several methods using external line sources have been developed for attenuation correction and are now commercially available. Theoretically, attenuation correction is a better solution, which can resolve both the inferior and the anterior wall artifact (breast attenuation). However, available data on the efficacy of attenuation correction are conflicting. Although attenuation correction resulted in an improved diagnostic performance in some studies (*12–14*), other authors observed the improvements in specificity only at the sacrifice of sensitivity (*15–17*). The current consensus on attenuation correction is that it can be a supplementary and complementary tool but it is not a complete substitute for conventional study (*18–20*). We need to know the prognostic implication of negative results on attenuation-corrected myocardial SPECT.

In conclusion, prone SPECT can be used as a supplementary tool for conventional supine SPECT to improve diagnostic specificity at the inferior wall. Prone acquisition is not a new technology but is a burdensome technique for patients and laboratories. The prognostic significance of negative results on this additional prone SPECT warrants event-free survival. Until attenuation correction technology for gated myocardial SPECT becomes available and produces robust results, we might use additional prone acquisition. On the basis of the findings of additional prone SPECT, the need for further invasive studies could be decided. On the assumption that cost-effectiveness studies achieve prognostic performances similar to those of Hayes et al. (*1*), they are warranted in individual laboratories. The decision to use supine and prone SPECT is probably best made by individual institutes on the basis of their own experiences.

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