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REPLY: Dr. Buxton questions the quantitative accuracy of estimates of myocardial perfusion obtained in our recent study (*1*) using PET and ^{15}O-labeled water because there was not a significant correlation between the double-product (the product of systolic blood pressure and heart rate, referred to by Dr. Buxton as the rate-pressure product) and myocardial perfusion.

While there is no question that myocardial perfusion is intimately related to myocardial oxygen consumption (MVO_2) (*2*), myocardial perfusion will only correlate to the double-product insofar as the double-product reflects MVO_2. Although some studies, as Dr. Buxton points out, have found a relationship between the double-product and myocardial blood flow when subjects are evaluated only at rest (*3,4*), the correlation is not strong and there is significant scatter around the line of regression. For instance, if the data from Volunteer 10, the subject with the highest levels of double-product and flow, (Table 4 in the article by Krivokapich et al., *4*) is eliminated, there would no longer be a statistically significant relationship between the double-product and myocardial perfusion estimated with PET using ^{13}N-ammonia. In fact, there are studies in the literature in which *no* correlation between the double-product and myocardial blood flow was found (*5*). In most studies in which such a correlation has been reported, the range of double-products observed was greater than the range observed in our study. The correlation improves greatly when a wider range of work levels is included in the data set, such as when patients are studied under conditions of exercise (*3,4,6,7*). When we calculate the correlation between the double-product and myocardial perfusion estimated with ^{15}O-water in 35 subjects studied at rest and after dobutamine, the correlation coefficient is 0.77 ($p < 0.001$).

Why isn't there a better correlation between the double-product and myocardial perfusion under the resting state? Aside from normal statistical variability over the low range of values encountered, the double-product takes into account only two (systemic) parameters that influence MVO_2. Important variables that are not accounted for include myocardial wall tension, the rate of tension development, and the inotropic status of the myocardium (independent of systemic hemodynamics), among other factors. Although MVO_2 can be estimated more accurately with more complicated formulas incorporating systemic hemodynamic measurements (*8*), as shown so elegantly by Suga et al. (*9*), accurate prediction of myocardial work, and thus of MVO_2, can be accomplished best with the left ventricular pressure-volume loop, a ventricular, not a systemic, measurement.

Dr. Buxton should be more concerned of the data he cites showing a significant relationship between myocardial perfusion in regions of normal myocardium and the double-product in patients with infarction or in patients with chronic coronary artery disease, since it would be anticipated that the remote normal regions in such patients would have a higher rate of myocardial work (and therefore of regional MVO_2 and accordingly, flow) to compensate for the dysfunctional myocardium.

The quantitative accuracy of estimates of myocardial perfusion with radiolabeled water has been validated extensively by us and by others over a wide range of flows and physiological and pathophysiological conditions. Estimates of perfusion with radiolabeled water correlate with directly measured perfusion in isolated hearts (*10*), and with radiolabeled microspheres in intact animals (*11–15*) even when different infusion protocols and methods for measurement of tissue water content are used. The approach also appears valid based on results of studies from three different institutions at which ^{15}O-water was used to estimate regional myocardial perfusion in human subjects (*13,15,16*). Nonetheless, direct validation in humans has not been previously documented. We have recently demonstrated that estimates of myocardial perfusion using PET and ^{15}O-water in humans at rest and after intravenous dipyridamole correlate with intracoronary Doppler flow velocity measurements (*17*), and, in a separate study, with estimates of regional myocardial perfusion made with PET and the partially extracted flow tracer, ^{62}Cu-PTSM (*18*).

Dr. Buxton's assertion that ^{13}N-ammonia may provide more accurate quantitative estimates of myocardial perfusion in humans is not supported by data currently in the literature. The studies by Krivokapich et al. (*4*) and by Hutchins et al. (*19*) using mathematical modeling of ^{13}N-ammonia data show that estimates in humans correlate with "expected" values. However, the approach of Krivokapich et al. uses an empirically defined relationship from dogs to decouple estimates of flow from extraction and the accuracy of this approach in humans has not been addressed. In addition, although the approach of Hutchins et al. appears mathematically more valid, to date there has been no experimental validation published in full.

Dr. Buxton also raises several issues regarding perceived limitations associated with the use of ^{15}O-water. Although currently available tomographs are capable of achieving raw resolution of between 5 and 8 mm (FWHM), in almost all studies, the reconstructed resolution is generally from 9 to 13 mm. Positron energy (and thus range) will have little effect with this level of resolution in non-gated studies of the heart. In addition, the human dosimetry for ^{15}O-water is much more favorable than that of ^{13}N-ammonia, and although the number of "usable" counts is less with ^{15}O-water because of its free diffusability, the quantitative quality of the data is quite adequate for estimation of perfusion. In addition, ^{15}O-water does not degrade to metabolites in blood as does ^{13}N-ammonia and its kinetics in the heart are not linked

to metabolism. Since the approaches of Krivokapich et al. (*4*) and of Hutchins et al. (*19*) for measuring myocardial perfusion with ^{13}N-ammonia use kinetic data from the first several minutes after administration of tracers (contrary to what is used for "qualitative" imaging), these approaches also require tomographic units that are capable of faithfully recording the high count rates achieved (more difficult on tomographs with bismuth germanate detectors than on those with cesium fluoride detectors such as the scanner used in our study), and issues of randoms correction, deadtime, and spillover of radioactivity from blood to myocardium will be similar for ^{15}O-water as for ^{13}N-ammonia.

Finally, Dr. Buxton is concerned about the coefficient of variation in regional perfusion estimates made with ^{15}O-water. We believe these are largely due to the large regions of interest that we use for assessing perfusion. Smaller values have been published by Araujo et al. (*15*) and by Iida et al. (*16*) in results of their studies measuring regional myocardial perfusion in humans with PET and ^{15}O-water. We observe a coefficient of variation for ^{15}O-water similar to that for the extracted flow tracer, ^{62}Cu-PTSM (*18*). Although Dr. Buxton cites data regarding the coefficient of variation for studies with ^{13}N-ammonia, these data have not been published in the literature and we obviously cannot comment on personal communications.

In summary we believe that, at the present time, estimation of myocardial perfusion with ^{15}O-water is the most accurate and well-validated approach for measuring myocardial perfusion in experimental animals and human subjects. Although estimation of regional myocardial perfusion with ^{15}O-water is technically demanding and requires meticulous data collection and analysis as well as tomographs capable of faithfully recording high-count rates with high temporal resolution, we stand by the quantitative accuracy of the approach and believe that the conclusion drawn from our study, i.e., that older subjects exhibit a diminution in the hyperemic response to the standard dose of dipyridamole, is valid.

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Marrow Scintigraphic Changes After Hormonal Therapy

TO THE EDITOR: We have read with interest the paper of Berna et al. (*1*) in which they reported the marrow scintigraphic changes that they observed after hormonal therapy using ^{99m}Tc-antigranulocyte monoclonal antibody BW250/183 (AGMab) in two patients with bone metastases from prostate carcinoma. In this letter, we would like to report on our previously published experience with marrow scintigraphy in such patients (n = 11) using ^{99m}Tc-labeled nano-sized human serum albumin colloids in comparison to conventional bone scans using phosphonates (*2,3*).

In six patients, bone scans and marrow scintigraphy yielded identical findings (one status quo, two regressions, three progressions of disease). On the other hand, in five patients, marrow scintigraphy and bone scan findings diverged or disagreed. In these patients, and with regard to the ultimate evolution of the disease, marrow scintigraphy could be deemed superior to bone scans. Indeed, marrow scintigraphy showed clear progression of the metastatic process in two patients (who finally died of their cancers), whereas the bone scans remained unchanged. In two other patients, bone scans suggested disease regression but with unchanged underlying marrow scintigraphic lesions and with later