## Blunted Response of Myocardial Perfusion to Dipyridamole in Older Adults

**TO THE EDITOR:** I read with interest the recent article by Senneff and co-workers (*1*) demonstrating a blunted response of myocardial perfusion to dipyridamole in older adults when compared to young adults. However, inspection of Table 1 of that article, which contains data on hemodynamics and myocardial blood flow (MBF) in the individual subjects, raises questions with regard to the quantitative accuracy of the tomographic method used for estimation of myocardial blood flow. It is well known that hemodynamics represent a major determinant of myocardial blood flow, and that the rate-pressure product (RPP), the product of systolic blood pressure and heart rate, correlates closely with myocardial blood flow (*2–4*). While most studies have investigated the relationship between MBF and RPP over a wide range of hemodynamic conditions, finding correlation coefficients of approximately 0.9, the relationship also holds over limited ranges of conditions. Data taken from the study of Holmberg and coworkers (*2*), which measured myocardial blood flow invasively by thermodilution catheter, demonstrate a significant relationship between RPP and MBF (MBF ($ml.min^{-1}.g^{-1}$) = $0.6 \times 10^{-4}$.RPP + 0.15; r = 0.88, $p < 0.01$) at rest in seven control subjects over a range of RPP from 6,200–13,800. The data of Nelson and coworkers (*4*) demonstrate that MBF correlated with RPP even when only static work experiments in 10 volunteers with a very limited range of RPP (10,910–15,710) were considered (MBF = $0.7 \times 10^{-4}$.RPP + 0.13; r = 0.60, $p < 0.025$). Data from the study of Krivokapich et al. (*5*) in 11 normal volunteers studied noninvasively with PET using $^{13}NH_3$ show a significant relationship between resting MBF and RPP (MBF = $2.6 \times 10^{-4}$.RPP-1.34; r = 0.71, $p < 0.02$). In normal remote myocardium of 18 patients with acute myocardial infarctions studied at rest with PET and $^{13}NH_3$, MBF was found to correlate significantly with RPP (MBF = $0.9 \times 10^{-4}$.RPP − 0.1; r = 0.74, $p < 0.001$) (*6*). A significant relationship between MBF and RPP was also demonstrated at rest in normal remote myocardium of 15 patients with chronic coronary artery disease using PET and $^{13}NH_3$ (*7*). Finally, in 39 volunteers, aged 19–86, studied at rest with PET and $^{13}NH_3$, with RPPs from 5,000 to 12,000, the relationship between MBF and RPP was: MBF = $1.0 \times 10^{-4}$.RPP + 0.1; r = 0.68, $p < 0.001$ (Czernin J, *personal communication*).

In contrast, it is apparent from Table 1 that large variations were found in resting myocardial perfusion which did not correlate with differences in myocardial workload, as assessed by the RPP. For example, in subjects P693 and P729, resting blood flows of 1.09 and 2.14 ml/g/min respectively were found, despite a higher RPP in subject P693 (11,782 versus 10,660). A plot of resting MBF as a function of the RPP from the data contained in Table 1 does not show any significant relationship between these two parameters (Fig. 1), despite a similar range of RPPs to those in the studies cited above. Significant relationships were also absent when the two subgroups (young and old volunteers) were analyzed separately. For the older volunteers, the relationship was MBF = $0.8 \times 10^{-4}$. RPP + 0.5 (r = 0.44, p = 0.1), while for younger volunteers the relationship was actually negative (MBF = $1.8 - 0.8 \times 10^{-4}$. RPP; r = 0.4, p = 0.24). Thus, while the mean values for resting blood flow found by Senneff et al. are in the range expected from the literature, the absence of any relationship between MBF and RPP must call into great doubt the accuracy of the individual values.

As a freely diffusible tracer, $H_2{}^{15}O$ has theoretical advantages over flow tracers such as $^{13}NH_3$ and $^{82}Rb$, for which the extraction fraction is less than 100% and flow dependent. While a good correlation between PET MBF with $H_2{}^{15}O$ and microsphere MBF was found in dogs (*8*), quantification of MBF in humans is technically more difficult. Count statistics are limited by dosimetric considerations, and the larger diameter of the whole-body PET scanner used in human studies relative to the neurological scanner used for canine studies also decreases count recovery. Photon attenuation is also much greater in humans than in dogs. In addition, the poorer resolution of the reconstructed human images (at FWHM 13.5 mm versus 12 mm for canine studies) will also have a negative effect on estimation of recovery coefficients and spillover fractions. Because of these technical difficulties, it is important to find a way to assess more directly the accuracy of flow estimates in humans. In the absence of invasive measurements of MBF, correlation of MBF to the RPP provides an appropriate method of assessing accuracy of MBF estimation. The increased technical complexity of imaging with $H_2{}^{15}O$ due to labeling of both blood and myocardium appear to limit the accuracy of estimates of human MBF in the study of Sennef et al. (*1*). This is also reflected by the large coefficient of variation found in individual estimates of blood flow in the young volunteers, 35% ± 10% in resting studies and 29% ± 16% after dipyridamole (*8*). For comparison, the coefficients of variation obtained with $^{13}NH_3$ and PET, analyzing similar volume regions of interest in 20 normal volunteers, were 19% and 9% at rest and with dipyridamole respectively (Chan SY, *personal communication*).

In conclusion, while population estimates of MBF in normal volunteers at rest are in the expected range, the absence of the expected association between MBF and the RPP strongly suggests that individual estimates of MBF in resting volunteers reported (*1*) cannot be considered quantitative. Estimates of regional MBF using this methodology will suffer from even greater uncertainty.

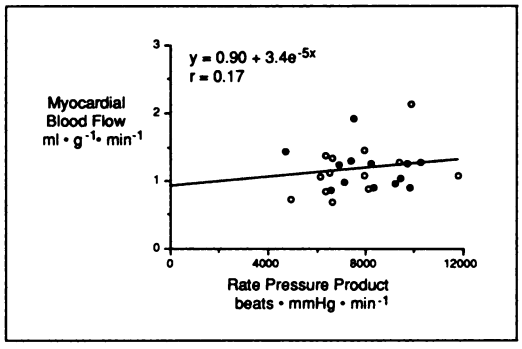


**FIGURE 1.** Relationship between estimated myocardial blood flow and the rate pressure product in young (●) and old (○) volunteers. Data taken from Table 1 (*1*).

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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