Blunted Response of Myocardial Perfusion to Dipyridamole in Older Adults (Revisited)

TO THE EDITOR: In 1991, Senneff et al. published an article in *The Journal of Nuclear Medicine* demonstrating that myocardial perfusion response to dipyridamole in older adults was blunted when compared to young adults (*1*). After analysis of the data in this article, I wrote a letter to the editor questioning the accuracy of the quantitative flow measurements reported (*2*). The basis of this criticism was the absence of a relationship between the estimated resting myocardial blood flow (MBF) and the rate pressure product (RPP). In contrast, a number of studies using both invasive methods and PET had found a significant relationship between these parameters (*2*). In reply, the authors argued (*3*) that the lack of correlation between estimated MBF and the RPP was due to the influence of other factors, such as wall tension, rate of tension development and inotropic status and the limited range of rate pressure products in the population studied.

A recent study by Herrero et al. (*4*) examined the effects of errors in the timing of the input function on estimates of MBF. The authors studied 30 volunteers; the flow data for 24 of these were taken from the 26 volunteers analyzed in the previous study of Senneff et al. (*1*). They found that the previous analysis was flawed by time discrepancies between the input function and the tissue time-activity curves, which introduced large errors into their flow estimates. For the 30 baseline studies, the corrected MBF decreased from 1.28 ± 0.28 to 0.98 ± 0.27 ml/g/min. After dipyridamole, corrected flow values decreased from 3.60 ± 1.4 to 3.24 ± 1.26 ml/g/min.

The demonstration that the quantitative flow data published previously (*1*) were seriously flawed raises important questions regarding that study's conclusions. The first is whether the revised blood flow values (*4*) affect the conclusions of the study of Senneff et al. (*1*), which demonstrated normal resting MBF but blunted response to dipyridamole in older adults. This issue is of importance for the correct interpretation of quantitative blood flow studies in older patients with coronary artery disease (CAD).

The second question is whether the authors now find a significant relationship between the RPP and baseline MBF. Bergmann et al. (*3*) attributed the lack of a correlation between MBF and RPP to the relatively small range of RPP and the contributions of other variables affecting MVO_2. Senneff et al. (*1*) studied 26 patients with RPPs ranging from 4730 to 11782, a range of 2.5, and found no correlation between MBF and RPP ($r = 0.178$, $p = 0.38$). In comparison, Czernin et al. (*5*) studied 40 patients with a similar range of RPP's, and found a strong correlation ($r = 0.72$, $p < 0.0001$). Numerous invasive studies have found similar relationships over limited ranges of RPP's; in addition to the studies cited previously (*2*), Klocke (*6*), using the He-desaturation technique, found a significant relationship between MBF and RPP in 25 patients without CAD ($MBF = 0.62 \times 10^{-4} \cdot RPP + 0.16$; $r = 0.56$, $p < 0.005$). Data taken from Chen et al. (*7*) using ^{133}Xe clearance in 10 normal volunteers also show a correlation between MBF and RPP ($MBF = 0.48 \times 10^{-4} \cdot RPP + 0.18$; $r = 0.84$, $p < 0.0025$). Thus, while a limited range of blood flows and small patient groups may lead to a poor correlation between MBF and RPP, this is not an adequate explanation for the lack of correlation found by Senneff et al. (*1*), since numerous studies with similar patient numbers and range of RPP found strong correlations. In contrast, Bergmann et al. (*3*) cite a study by Ganz et al. (*8*) as demonstrating no correlation between the RPP and MBF, while in fact, that study measured coronary sinus blood flow, not MBF per gram of heart, thereby introducing the significant additional variable of heart weight. Although the use of more refined hemodynamic indices would be expected to give better correlations to MBF (*6,7*), it is clear that the RPP should correlate well with MBF. In the absence of such a relationship, grave doubts must still remain as to the quantitative accuracy of MBF measurements.

The study of Senneff et al. (*1*) addresses an important clinical issue with implications for the interpretation of quantitative flow data in older patients. The data provided in their more recent publication (*4*) appear to confirm the contention that the original data were seriously flawed. A correction or retraction of the original paper (*1*) would thus appear fitting in order to set the scientific record straight.

REFERENCES

1. Senneff MJ, Geltman EM, Bergmann SR, Hartman J. Noninvasive delineation of the effects of moderate aging on myocardial perfusion. *J Nucl Med* 1991;32:2037–2042.
2. Buxton DB. Blunted response of myocardial perfusion to dipyridamole in older adults [Letter]. *J Nucl Med* 1992;33:1425–1426.
3. Bergmann SR, Senneff MJ, Geltman EM. Blunted responses of myocardial perfusion to dipyridamole in older adults. *J Nucl Med* 1992;33:1426–1427.
4. Herrero P, Hartman JJ, Senneff MJ, Bergmann SR. Effects of time discrepancies between imput and myocardial time-activity curves on estimates of regional myocardial perfusion. *J Nucl Med* 1994;35:558–566.
5. Czernin J, Müller P, Chan S, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993;88:62–69.
6. Klocke FJ. Measurements of coronary blood flow and degree of stenosis: current clinical implications and continuing uncertainties. *J Am Coll Cardiol* 1983;1:31–41.
7. Chen PH, Nichols AB, Weiss MB, Sciacca RR, Walter PD, Cannon PJ. Left ventricular myocardial blood flow in multivessel coronary artery disease. *Circulation* 1982;66:537–547.
8. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan JC. Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971;44:181–195.

Denis B. Buxton
UCLA School of Medicine
Los Angeles, California

REPLY: Dr. Buxton continues to question the accuracy of estimates of regional myocardial perfusion made with ^{15}O-water and PET. The basis of Dr. Buxton's concern is the absence of a relationship between the double product (the product of systolic pressure and heart rate which Dr. Buxton refers to as the RPP and MBF at rest. Dr. Buxton has raised this issue previously (*1*), and we would suggest that he "revisit" our response (*2*) as well as the thoughts of others (*3–7*) about why the double product is a poor descriptor of myocardial oxygen consumption. Dr. Buxton should look at recent data from his own institution (*8*) in which MBF estimated with ^{13}N-ammonia did not correlate under resting conditions with the double product. Data from Table 2 (and Fig.

1C) from Krivokapich et al. (*8*) show that under resting circumstances the relationship between the double product and myocardial perfusion is poor ($y_{\text{double product}} = 1124x_{\text{myocardial blood flow}} + 6563$; $r = 0.215$, $p = 0.552$). There is no question that, in the absence of hypoxia or certain drugs, MBF and myocardial oxygen consumption are related, but the double product and myocardial oxygen consumption are only poorly correlated when measurements are made at rest over a limited range of heart rate and blood pressure.

Dr. Buxton cites several works in which a correlation between the double product and myocardial perfusion were observed. As we have previously discussed (*2*), in almost all of the studies Dr. Buxton cites, the relationships were demonstrated when subjects were studied during interventions to increase the double product (i.e., pharmacologically or with exercise) and in almost all cases, levels of the double product were higher than those observed under resting circumstances in our study. As mentioned previously (*2*), when wide ranges of the double product are evaluated, correlations with myocardial perfusion estimated with $H_2{}^{15}O$ do exist. One would not expect a correlation between the double product and myocardial perfusion after dipyridamole since dipyridamole dissociates flow from oxygen consumption, as corroborated by studies from Dr. Buxton's institution (*9*).

As Dr. Buxton well knows, ^{15}O-water has been used extensively, not only by us (*10,11*), but by numerous other researchers (*12–14*), including investigators at UCLA (*15*). In every circumstance, flow estimated with ^{15}O-water has correlated extremely closely with flow estimated with radiolabeled microspheres in experimental animals over a wide range of flows (*10,11,13–15*). We (*16–18*) and others (*19,20*) have also demonstrated that flow estimated with ^{15}O-water correlates with coronary flow velocity reserve and coronary flow estimated with intracoronary Doppler flow techniques and angiographic assessments in human subjects. In addition, in humans, estimates of flow with ^{15}O-water correlate with flow estimated with extracted flow tracers (*21–23*). Accordingly, there should be absolutely no question that estimates of regional myocardial perfusion made with ^{15}O-water and PET are accurate and reliable.

From the beginning of our work with ^{15}O-water, we have pointed out that the effect of time discrepancies in the measured input function and the true input function need to be considered (*10,24,25*). In our study in which a blunted flow response to dipyridamole in older subjects was demonstrated (*26*), data were corrected for time discrepancies as stated in the methods section. The minor differences that Dr. Buxton cites were caused by changes in the program used to calculate the timing differences. In our recent study (*25*), we used a curve-fitting program which was not used previously. A paired comparison of data from the 24 subjects evaluated in the study by Senneff et al. (*26*) that were subsequently reanalyzed by Herrero et al. (*25*) indicates that there is no statistical difference between the flows at rest (1.15 ± 0.29 compared with 0.99 ± 0.27 ml/g/min), after dipyridamole (3.56 ± 1.42 compared with 3.55 ± 1.28 ml/g/min) or myocardial perfusion reserve (3.40 ± 1.58 compared with 3.94 ± 2.10), respectively (p = ns for all three comparisons). Age-based data for the 30 subjects evaluated in Herrero et al. (*25*) are summarized in Table 1.

Although Czernin et al. (*9*) found that there was no statistically significant decrement in hyperemic flow after dipyridamole in older adults using flow estimated with ^{13}N-ammonia (3.0 ± 0.76 ml/g/min in subjects <50 yr of age compared with 2.66 ± 0.58 ml/g/min in subjects >50 yr of age), a study by Uren et al., published in abstract form (*27*), corroborates our findings. Thus, contrary to Dr. Buxton's assertions, the data in the Senneff, Geltman, and Bergmann (*26*) were not "seriously flawed." In fact, the expanded data shown above corroborate our previous findings. Accordingly, we stand by the results of our original data demonstrating that older subjects have a diminished flow response to dipyridamole.

TABLE 1
Age-Based Differences in Perfusion Response

Subjects	Myocardial perfusion		Myocardial perfusion reserve
	Rest	After dipyridamole	
Younger (n = 11)	0.90 ± 0.29	3.89 ± 1.31	4.63 ± 2.00
Older (n = 19)	1.02 ± 0.26	2.91 ± 1.16*	3.09 ± 1.83*

*$p < 0.042$ compared with younger subjects.

Finally, we suggest that Dr. Buxton be more careful in raising issues of scientific integrity. In the words of Charles Caleb Colton:

> "The greatest friend of truth is Time, her greatest enemy is Prejudice, and her constant companion is Humility."

REFERENCES

1. Buxton DB. Blunted response of myocardial perfusion to dipyridamole in older adults [Letter]. *J Nucl Med* 1992;33:1425–1426.
2. Bergmann SR, Senneff MJ, Geltman EM. Blunted response of myocardial perfusion to dipyridamole in older adults [Reply]. *J Nucl Med* 1992;33: 1426–1427.
3. Kocke FJ, Ellis AK. Control of coronary blood flow. *Ann Rev Med* 1980; 31:489–508.
4. Klocke FJ. Measurements of coronary blood flow and degree of stenosis: current clinical implications and continuing uncertainties. *J Am Coll Cardiol* 1983;1:31–41.
5. Chen PH, Nichols AB, Weiss MB, Sciacca RR, Walter PD, Cannon PJ. Left ventricular myocardial blood flow in multivessel coronary artery disease. *Circulation* 1982;66:537–547.
6. Baller D, Schenk H, Strauer BE, Hellige G. Comparison of myocardial oxygen consumption indices in man. *Clin Cardiol* 1980;3:116–122.
7. Suga H, Hisano R, Hirata S, et al. Mechanism of higher oxygen consumption rate: pressure vs. volume-loaded heart. *Am J Physiol* 1982;242:H942–H948.
8. Krivokapich J, Huang S-C, Schelbert HR. Assessment of the effects of dobutamine on myocardial blood flow and oxidative metabolism in normal human subjects using nitrogen-13 ammonia and carbon-11 acetate. *Am J Cardiol* 1993;71:1351–1356.
9. Czernin J, Müller P, Chan S, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993;88:62–69.
10. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography. *J Am Coll Cardiol* 1989;14:639–652.
11. Bergmann SR. Quantification of myocardial perfusion with positron emission tomography. In: Bergmann SR, Sobel BE, eds. *Positron emission tomography of the heart.* Mount Kisco, NY: Futura Publishing, Inc; 1992: 97–127.
12. Iida H, Kanno I, Takahashi A, et al. Measurement of absolute myocardial blood flow with $H_2{}^{15}O$ and dynamic positron-emission tomography. *Circulation* 1988;78:104–115.
13. Araujo LI, Lammertsma AA, Rhodes CG, et al. Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. *Circulation* 1991;83:875–885.
14. Bol A, Melin JA, Vanoverschelde J-L, et al. Direct comparison of [^{13}N]ammonia and [^{15}O]water estimates of perfusion with quantification of regional myocardial blood flow by microspheres. *Circulation* 1993;87:512–525.
15. Huang SC, Schwaiger M, Carson RE, et al. Quantitative measurement of myocardial blood flow with oxygen-15 water and positron computed tomog-

raphy: an assessment of potential and problems. *J Nucl Med* 1985;26:616–625.
16. Shelton ME, Senneff MJ, Ludbrook PA, Sobel BE, Bergmann SR. Concordance of nutritive myocardial perfusion reserve and flow velocity reserve in conductance vessels in patients with chest pain with angiographically normal coronary arteries. *J Nucl Med* 1993;34:717–722.
17. Miller DD, Donohue TJ, Kern MJ, Mechem CJ, Hartman JJ, Bergmann SR. Concordance of oxygen-15 water PET myocardial perfusion with poststenotic intracoronary Doppler blood flow [Abstract]. *J Nucl Med* 1994;35: 23P.
18. Miller DD, Donohue TJ, Kern MJ, et al. Initial characterization of the relationship of quantitative myocardial perfusion assessed with PET to distal coronary Doppler volumetric blood flow in human subjects [Abstract]. *Circulation* 1994;90:I-447.
19. Merlet P, Mazoyer B, Hittinger L, et al. Assessment of coronary reserve in man: comparison between positron emission tomography with oxygen-15-labeled water and intracoronary Doppler technique. *J Nucl Med* 1993;34: 1899–1904.
20. De Bruyne B, Baudhuin T, Melin JA, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation* 1994;89:1013–1022.
21. Bergmann SR, Herrero P, Anderson CJ, Welch MJ, Green MA. Measurement of regional myocardial perfusion in human subjects using copper-62-PTSM [Abstract]. *J Nucl Med* 1992;33(suppl):837P.
22. Senda M, Nishizawa S, Yonekura Y, et al. A new subtraction method for obtaining myocardial perfusion images with oxygen-15 water and positron emission tomography. *Ann Nucl Med* 1988;2:101–106.
23. Nitzsche E, Choi Y, Czernin J, Hoh C, Huang S-C, Schelbert H. Comparison of O-15 water and N-13 ammonia PET measurements of myocardial blood flow in humans [Abstract]. *Circulation* 1993;88:I-274.
24. Herrero P, Markham J, Bergmann SR. Quantitation of myocardial blood flow with $H_2{}^{15}O$ and positron emission tomography: assessment and error analysis of a mathematical approach. *J Comp Assist Tomogr* 1989;13:862–873.
25. Herrero P, Hartman JJ, Senneff MJ, Bergmann SR. Effects of time discrepancies between input and myocardial time-activity curves on estimates of regional myocardial perfusion with PET. *J Nucl Med* 1994;35:558–566.
26. Senneff MJ, Geltman EM, Bergmann SR. Noninvasive delineation of the effects of moderate aging on myocardial perfusion. *J Nucl Med* 1991;32: 2037–2042.
27. Uren NG, Camici PG, Wijns W, et al. The effect of aging on coronary flow reserve in man [Abstract]. *Circulation* 1993;88:I-171.

Steven R. Bergmann
Pilar Herrero
Edward M. Geltman
Cardiovascular Division
Washington University School of Medicine
St. Louis, Missouri