On the Relativity of Dipyridamole and Dobutamine Flows

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Myocardial perfusion imaging with pharmacologic vasodilator stress has become an integral component of assessing the risk for future major adverse cardiac events (MACE). The addition of quantitative flows in ml/min/g to standard perfusion imaging has further refined the accuracy of predicting major adverse cardiovascular events.¹ The level of flow increase during pharmacologic stress largely defines the degree of risk: a normal flow response indicates low risk whereas moderate to severe attenuations of the flow response signify increasing levels of cardiac risk.¹ Pharmacologic stress typically employs vasodilators like adenosine, dipyridamole, and, most commonly, the adenosine receptor agonist regadenoson, agents that raise coronary blood flow via maximum vascular smooth muscle relaxation. When use of adenosine-related vasodilators is contraindicated, the sympathomimetic amine dobutamine serves as alternative stressor. Unlike adenosine-related agents that raise coronary flow independent of cardiac work, dobutamine increases cardiac work and thus myocardial oxygen consumption (MVO₂) which prompts a commensurate metabolism-mediated rise in coronary flow in order to meet the myocardium's increased O₂ and substrate needs.

Flow responses to dobutamine stimulation have been measured in the past with radiotracers of

myocardial blood flow like O-15 water or N-13 ammonia and PET.^{2–4} No such measurements with PET and Rubidium-82 (Rb-82) have been reported as yet, even though it is the very radiotracer that it is now most widely employed with cardiac PET in the clinical setting. Because its physical and imaging properties differ from those of O-15 water and N-13 ammonia, quantitative estimates of flow responses to dobutamine stimulation with Rb-82 would be informative and clinically useful.

In the current issue of the journal, Pelletier-Galarneau *et al.*⁵ are first to report such Rb-82 PET measurements in a group of 156 patients, all of whom had been referred for evaluation of suspected or known coronary artery disease to the University of Ottawa Heart Institute from 2006 to 2016. All had undergone Rb-82 PET rest and dobutamine perfusion imaging combined with quantitative flow measurements. Median global flows at rest were 0.84 ml/min/g and were similar in four subgroups of patients, that is, (a) patients with less than 3 and (b) patients with more than 3 risk factors but without coronary artery disease; (c) patients with prior revascularization but no prior myocardial infarction; and (d) patients with prior myocardial infarction. Dobutamine stress followed the standard ASNC protocol⁶ with 10 µg/kg/min increments in the rate of dobutamine infusion, up to a maximum of 50 µg/kg/min or until 85% of the maximum predicted heart rate had been achieved. Dobutamine raised heart rate by 61% and the rate pressure product (RPP) by 80%. Flow responses to dobutamine varied between patients (as seen in Figure 2), depending to some extent on presence or absence of coronary artery disease and on its extent and severity. For the entire patient cohort, median dobutamine-stimulated flows were 2.36 ml/min/g with a median flow reserve of 2.75. As expected, median dobutamine-stimulated flows and flow reserves were higher in the subgroups of patients with risk-factor only and lower in patients with known coronary artery disease.

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Estimates of the flow response to dobutamine in the current study compare well with responses obtained with N-13 ammonia and O-15 water and PET.^{2-4,7} The 2.9-fold flow increase observed in patients with risk factors only is well within the range of previously reported 2.9-fold to 3.4-fold increases in normal volunteers.^{1-4,8} Like in these earlier investigations, dobutamine raised heart rate and RPP and thus MVO_2 that were associated with flow increases for meeting higher O_2 and substrate demands. The dobutamine-driven 1.8-fold increase in RPP in the current study also falls within the range of 1.6-fold to 2.9-fold increases reported in earlier investigations.^{2-4,8} Less certain is however, whether the flow response fully and quantitatively matches the dobutamine-stimulated increase in cardiac work. In one study for example, a 2.7-fold increase in RPP was matched by a 3.0-fold increase in myocardial blood flow,² whereas in another study, the flow response plateaued already at lower dobutamine doses (20 $\mu\text{g}/\text{min}/\text{kg}$) without additional significant increases at higher dobutamine doses despite further increases in RPP.⁷ Similarly, as the authors emphasize, dobutamine at a dose of only 20 $\mu\text{g}/\text{min}/\text{kg}$ maximally reduces the coronary resistance to flow. Intracoronary pressure measurements revealed no further reductions in myocardial resistance to flow when dobutamine doses were raised beyond 20 $\mu\text{g}/\text{min}/\text{kg}$ and RPP further increased.⁹ Whether and how the coronary circulation accommodates additional increases in coronary flow with further dobutamine and/or atropine induced increases in heart rate and RPP awaits clarification. Yet, it is important to note that possible further flow increases encounter ever higher opposing resistive forces as for example related to further shortening of time-averaged period of diastole, when myocardial flow is highest, or higher extravascular resistive forces imposed by higher systolic and diastolic left ventricular pressures.¹⁰ Importantly, within the context of the current study, an apparent disparity between dobutamine-induced increases in flow and in cardiac work suggests that levels of flow responses to dobutamine cannot be fully appreciated or be predicted by corresponding RPP increases.

An interesting aspect of the current study is the comparison of flow responses to dobutamine with those to dipyridamole, determined in a second group of 156 patients. Patients were carefully selected from a pool of 12,000 patients with clinical rest and dipyridamole stress Rb-82 PET perfusion and quantitative flow studies, for matching the dobutamine patient group in terms of age, sex, body mass index, metabolic state, risk factors, and coronary artery disease. Median values of global flows at rest were 0.69 ml/min/g and 1.66 ml/min/g for dipyridamole flows. Consistent with the findings in the dobutamine patient group, dipyridamole flows were

highest in patients with risk factors only but were attenuated in patients with coronary artery disease. Remarkably, median global dipyridamole flows and flow reserves were 30% and 17% lower than dobutamine flows and flow reserves in the dobutamine patient group, so that the authors concluded that “the results of the study suggest that dobutamine produces higher MBF compared to dipyridamole in a representative population referred to nuclear cardiology laboratories.”

The observation of higher dobutamine than dipyridamole flows differs from earlier comparison studies with 25% to 40% higher dipyridamole than dobutamine flows.^{3,4} The authors refer to a third comparison study in young healthy volunteers with opposite findings where dobutamine flows were 36% higher than dipyridamole flows.¹¹ In that study, dobutamine administration was supplemented by sequential small doses of atropine until reaching 85% of the maximum predicted heart rate. Remarkably, the study reports a dobutamine flow reserve of 8.8, which would appear to be excessively high, even in young normal volunteers. Such level of flow reserve would substantially exceed the 5-fold flow increase during strenuous physical exercise, an increase that does not fully match the 6-fold increase in MVO_2 .¹² Furthermore, the observation of higher dobutamine than dipyridamole flows would also argue against the known somewhat lower diagnostic sensitivity of dobutamine stress for detecting obstructive epicardial coronary disease, a shortfall that has been attributed partly to lesser flow increases achieved with dobutamine than with adenosine-related vasodilators.^{13,14}

This then raises the question whether an overestimation of dobutamine flows or an underestimation of dipyridamole flows might account for the findings in the current study. There is little if any reason to ascribe the higher dobutamine flows to higher dobutamine doses as mentioned by the authors in comparison to earlier studies (50 $\mu\text{g}/\text{min}/\text{kg}$ versus 40 $\mu\text{g}/\text{min}/\text{kg}$) because as mentioned above even lower doses (20 $\mu\text{g}/\text{min}/\text{kg}$) already maximally reduce coronary resistance to flow and produce maximum flows.^{2-4,7} Possible methodologic explanations for overestimating dobutamine flows exists. They include under-sampling of the arterial radiotracer input function, though unlikely in this study, or, conversely, a partial volume related ‘overestimation’ of the myocardial radiotracer tissue response (i.e., the myocardial radiotracer activity concentration). According to the partial volume effect, PET-derived radiotracer tissue activity concentrations equal the true tissue activity concentrations only if the size of the imaged object equals at least twice the spatial resolution of the imaging device, so that for smaller imaged objects, the PET-observed (‘recovered’) tissue activity concentration under-estimates the true tissue activity concentration.

The degree of underestimation, defined by the ‘recovery coefficient’, depends in a nonlinear fashion on the size of the imaged object. For cardiac PET, the ‘recovery coefficient’ depends thus on the time-averaged myocardial wall thickness and that can be used to up-correct the observed to the true activity concentration. During dobutamine stress, the time-averaged myocardial wall thickness increases because of higher heart rates (i.e., the fraction of time the left ventricle is in systole increases) and because of an actual increase in systolic wall thickness, due to the inotropic effect of dobutamine. Therefore, if the observed tissue activity concentrations were up-corrected with the same recovery coefficient used for correction of the rest images, it would result in an overestimation of the true dobutamine myocardial activity concentrations and, thus, of the actual dobutamine flow. While some software analysis packages employ a fixed recovery coefficient for partial volume corrections of observed myocardial activity concentrations, the analysis program for PET flow measurements in the current study did in fact adjust for changes in the time-averaged left ventricular wall thickness.¹⁵ This is corroborated by the reported higher recovery coefficients for dobutamine stress than for rest images and confirms that appropriate adjustments for the increase in wall thickness were made. Therefore, a method-related overestimation of dobutamine flows appears to be an unlikely explanation for the higher dobutamine stress flows.

Is it therefore possible that global myocardial blood flows in the dipyridamole patient group were underestimated? What if dipyridamole were less effective than adenosine, used in the earlier comparison studies, in raising myocardial blood flow? No evidence exists to support of this possibility; hyperemic dipyridamole flows fully equal hyperemic flows stimulated by adenosine or regadenoson.¹ There are additional reasons to believe that an underestimation might indeed be possible. For example, in the subgroup of patients with <3 risk factors but no coronary artery disease and hence the likely most normal patients, myocardial blood flows at rest were on average 20% lower than those in the dipyridamole group despite comparable levels of RPP and thus of cardiac work. This statistically significant difference is not fully or convincingly explained in the study. Further, flows at rest in the dipyridamole patient group are also lower than those reported from the authors’ laboratory for normal volunteers and for patients with suspected or documented coronary artery disease.^{15,16} Furthermore, while fully acknowledging possible differences between study populations, dipyridamole-stimulated flows in the current study are on average about 16% lower than values reported previously from the investigators’ laboratory for a large group

of patients with a broad spectrum of cardiovascular risk factors and disease.¹⁶ The authors are aware of the lower flows in the dipyridamole group and entertain the possibility of a bias in patient selection. For example, did the very criteria used for the assigning patients to dobutamine rather dipyridamole stress introduce a bias? If such bias in patient selection existed, it would weaken a major conclusion of the study, that dobutamine produces higher flow responses than dipyridamole and would limit the generalizability of comparison findings. Yet, it should be emphasized that in difference to earlier comparison studies, the conclusions of current study are based on findings in a large and real-world patient population, which is one of its major strengths. Even so the possibility of an intrinsic bias cannot be discounted entirely, the current findings are important because they are first to demonstrate that flow responses to dobutamine can accurately be measured with Rb-82 PET. The Rb-82 PET measured flow responses are consistent with those determined with other radiotracers of myocardial blood flow and PET. Together with threshold values of normal established in the study, the current findings set a much needed standard for the use of Rb-82 PET for estimating flow responses to dobutamine stimulation in the clinical setting.

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