

Heart rate response during vasodilator stress myocardial perfusion imaging: Mechanisms and implications

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Myocardial perfusion imaging (MPI) using adenosine, dipyridamole, or regadenoson (a selective A_{2A} receptor agonist) is an established method for detecting coronary artery disease (CAD) and risk stratification.¹ In high-risk populations, as in those with diabetes mellitus (DM) or chronic kidney disease, MPI has been shown to be a powerful predictor of risk, but nevertheless, patients with normal myocardial perfusion are at higher risk than those without DM or chronic kidney disease.^{2,3} Thus, there continues to be a need to extract more useful prognostic data from stress MPI especially in high-risk populations.

A blunted heart rate (HR) response to exercise stress has been known to be an independent predictor of poor outcome and is used clinically in conjunction with other prognostic variables such as perfusion defects, left ventricular (LV) ejection fraction (EF) and volumes, exercise time, and symptoms during exercise to derive an overall assessment of risk in a particular patient.⁴ In patients undergoing stress testing, for one reason or another, with adenosine or regadenoson (and dipyridamole, which acts indirectly by increasing interstitial levels of endogenous adenosine), there is a modest increase in HR and a modest decrease in blood pressure (BP). The increase in HR has been traditionally attributed to a reflex response to the vasodilatory effect on the systemic circulation and the resultant increase in

sympathetic discharge.^{5,6} The true mechanism of HR increase, however, is more complicated and involves direct stimulation of the sympathetic nervous system.⁷ The administration of adenosine as a bolus, as done for the interruption of supra-ventricular tachycardias, has a negative chronotropic effect on the atrio-ventricular node via stimulation of the A₁ receptor. This is in contradistinction to its effect on the A_{2A} receptor when given as an infusion in stress MPI studies where it induces an increase in HR.^{5,8} The development of selective A_{2A} receptor agonists (such as regadenoson) has allowed for the dissection of the effects of adenosine on the multiple receptors. A well-done pivotal study in rats by Dhalla et al⁷ that used regadenoson in combination with a selective A_{2A} receptor antagonist, B-blocker, a ganglionic blocker (to block the sympathetic nervous system), and a direct vasodilator (nitroprusside) demonstrated the dissociation of tachycardia and hypotension (secondary to peripheral vasodilation) responses to regadenoson. This and other data (reviewed in Ref. ⁹) confirm that A_{2A} receptor agonists cause a direct stimulation of the autonomic nervous system, which results in sinus tachycardia independent of the baroreflex mechanism. Thus, the change in HR in response to A_{2A} receptor agonists can be used to evaluate autonomic function.

In order to evaluate the HR response to adenosine and regadenoson in relation to DM (since there is a high prevalence of autonomic dysfunction in patients with DM), we used data from the ADenoscan Versus RegAdenoson Comparative Evaluation for Myocardial Perfusion Imaging (ADVANCE MPI 1 and 2) Trials.^{9,10} The ADVANCE MPI Trials^{11,12} are randomized multicenter phase 3 trials that demonstrated the non-inferiority of regadenoson to adenosine in detecting reversible defects by comparing the strength of agreement between sequential adenosine-regadenoson and adenosine-adenosine images. The HR and BP were measured at baseline and at predetermined intervals extending to 45 minutes after the administration of adenosine or regadenoson. In the 2,000 patients with known DM status (643 with DM, 1357 non-DM, 15 unknown DM status) there was a blunted HR response (maximal percent change of HR from baseline) in those

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with DM ($29.42 \pm .64$ vs $36.08 \pm .54\%$, $P < .001$).⁹ A larger proportion of patients with a HR response in the lower vs upper tertile had DM (40% vs 22%, $P < .001$). This relationship was present irrespective of age, gender, myocardial perfusion abnormalities, LV function, use of beta-blockers, and renal function, and was dissociated from the BP response.⁹ Similarly, patients with the metabolic syndrome had a lower HR response than those without it ($32.43 \pm .52$ vs $36.15 \pm .71\%$, $P < .001$), and there was a stepwise decrease in the HR response for increasing features of the metabolic syndrome and for increasing blood sugar levels on the morning of the MPI even in patients not known to have DM (Figure 1).¹⁰ Decreasing renal function was also linearly related to decreasing HR response (Figure 2). In a multivariate model, DM status, metabolic syndrome status and renal function were all independently associated with the HR response after controlling for age, gender, LV function, BP, baseline HR, and beta-blocker use.¹⁰ Although these associations were similar irrespective of whether patients received adenosine or regadenoson, the HR increased to a greater extent with regadenoson than with adenosine. Thus, non-DM patients had a 31% increase in their HR with adenosine compared to 39% with regadenoson and the corresponding numbers for DM patients were 26% and 31%.

In the study by Mathur et al reported in this issue of the *Journal*¹³ an increase in HR by less than 20% in response to dipyridamole was considered blunted, and this was present in 64% of the entire population (2,890 out of 4,484 patients). Therefore, caution must be

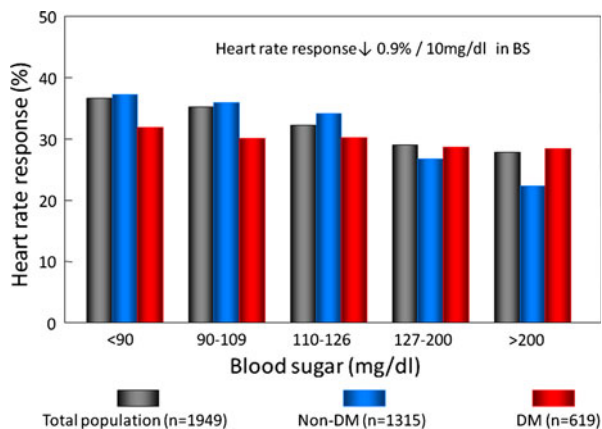


Figure 1. The heart rate response to adenosine or regadenoson in the ADVANCE MPI trials in patients according to their blood sugar level on the day of the vasodilator stress myocardial perfusion imaging. There is a stepwise decrease in the heart rate response with increasing blood sugar levels both in patients with diabetes mellitus (DM) and in those without DM (non-DM) ($P < .001$). Figure modified from Ref.¹⁰

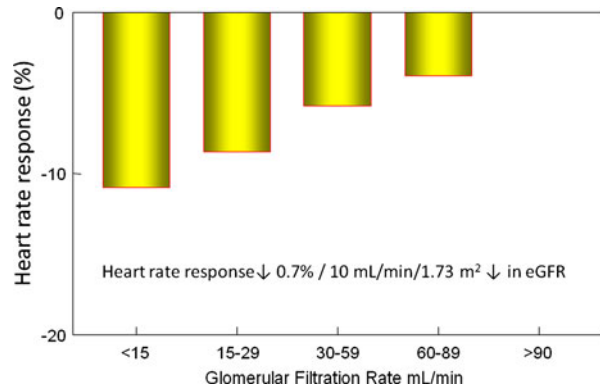


Figure 2. There is a stepwise association between the heart rate response to adenosine or regadenoson in relation to decreasing estimated glomerular filtration rate. The heart rate response for each category of renal function is compared to the reference value of patients with estimated glomerular filtration rate >90 , who had an average heart rate response of 38.1%. Figure based on data from Ref.⁹

exercised in the utilization of data from these multiple agents since they have different pharmacokinetic properties although they all act by stimulating the adenosine receptors. Further studies are definitely needed to characterize ideal cutoffs tailored for each reagent.

Since cardiac autonomic dysfunction has been linked to increased cardiovascular risk,¹⁴ the evaluation of the HR response to these vasodilators can be prognostically useful. The relation between autonomic dysfunction and outcome is supposedly due to an increase in sudden death due to arrhythmias. Imaging using I-123 metaiodobenzylguanidine (MIBG), a non-metabolized norepinephrine analogue, has been used to aid in the diagnosis of cardiac autonomic denervation and has been shown to be prognostically useful in DM and heart failure patients.^{15,16} Indeed, in dogs, the induction of sustained ventricular tachycardia after myocardial infarction has been shown to be associated with a larger area of myocardial perfusion-innervation mismatch as assessed by [13N]-ammonia and [11C]-epinephrine positron emission tomography.¹⁷ Abidov et al were the first to report on the prognostic significance of the HR change after adenosine infusion.¹⁸ In their study, the hemodynamic response of 3,444 patients who underwent adenosine MPI was assessed. After $2.0 \pm .8$ years, 6.5% of the population experienced cardiac death, and a blunted HR response (defined as low peak/rest HR) was an independent predictor of poor outcome after controlling for clinical and perfusion variables. The size of the perfusion abnormality (summed stress score) and the HR response added incremental prognostic information for the prediction of cardiac deaths.¹⁸ In another study, a low HR response to dipyridamole has been associated with all-cause

mortality in 1,087 patients with normal myocardial perfusion followed for 8 years even after adjustment for multiple factors.¹⁹ Since sudden cardiac death is a major cause of mortality in end-stage renal disease (ESRD),²⁰ and the HR response to adenosine showed a strong relationship to renal function,^{9,10} we examined the prognostic significance of this parameter in ESRD patients.²¹ In a well characterized cohort of ESRD patients awaiting renal transplantation who underwent screening adenosine MPI followed by invasive coronary angiography, the HR response was lower than a control population and a blunted HR response in this population was a strong independent predictor of death²¹ (Figure 3). This association was independent of LVEF, presence and extent of CAD by angiography and size of perfusion abnormality by MPI. A blunted HR response in this study was a stronger predictor of all-cause mortality than perfusion abnormalities by MPI or angiographic presence of CAD.²¹

The study by Mathur et al adds to an expanding body of evidence that suggests that HR response to vasodilators is just as important as HR response during exercise and should be included in future studies of risk assessment. Ideally, the role of blunted HR response in predicting sudden death rather than all-cause mortality or composite end points should be studied, although the adjudication of whether death is sudden or non-sudden is

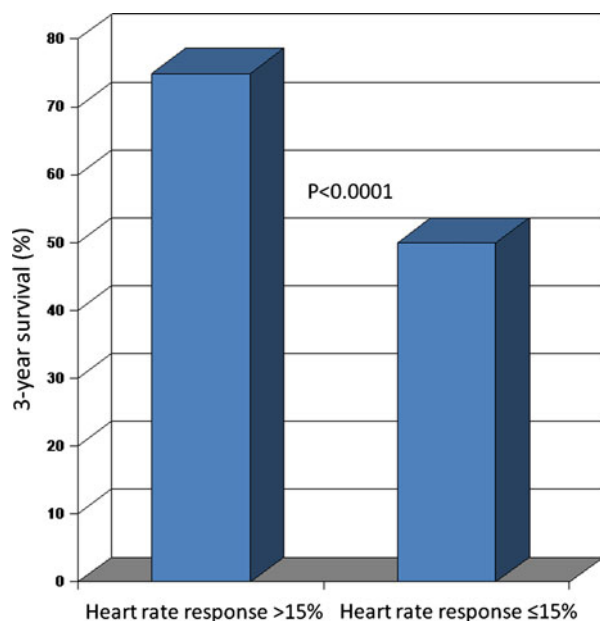


Figure 3. Survival at 3-years is significantly lower in patients with end-stage renal disease with a blunted heart rate response to adenosine (% change in heart rate $\leq 15\%$) as compared to those with higher heart rate response. Figure based on data from Ref. ²¹

even more difficult than whether death is cardiac or non-cardiac. The Duke investigators have examined the predictors of sudden death using the largest database available and have carefully crafted the criteria of defining sudden death.^{22,23}

Impressively, a blunted HR response to dipyridamole in the Mathur study was independently associated with increased cardiac death even after controlling for myocardial perfusion, LVEF, age, abnormal electrocardiogram and a history of DM, myocardial infarction, and heart failure. The HR response was thus predictive of cardiac death in subgroups of patients with low, intermediate, and high summed stress score and whether or not patients were receiving beta-blocker therapy. As pointed out in their article, and as anticipated based on the data from ADVANCE MPI, more patients with DM had a blunted HR response to dipyridamole. The authors correctly point out that a blunted HR response is prognostically useful in diabetics and that DM patients with a blunted HR response had a higher event rate than non-DM patients with a blunted response. Interestingly, however, a blunted HR response predicted cardiac death just as well in non-DM patients and patients without DM with a blunted HR response had an annualized cardiac death rate of $>3\%$, which is numerically higher than DM patients with a higher HR response. Future studies should examine the relationship between HR response and other direct measures of autonomic function including the perfusion-denervation mismatch pattern. It remains to be determined whether the HR response could be modified by life style changes or medications and whether such a modification results in a directional change in patient outcome. Finally, the relationship of HR response as a continuum and outcome and the particular cutoff point in an individual patient that defines a poor outcome need to be defined.

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