The heart rate response to regadenoson in patients with atrial fibrillation

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BACKGROUND

Regadenoson is the most widely used pharmacologic stress agent for myocardial perfusion imaging (MPI) in the United States.[1] By selectively activating the adenosine A2A receptor, regadenoson induces hyperemia in the coronary bed which is the basis for its use with MPI. However, we and others have noted that regadenoson, and other activators of the A2A receptors, also induces a rise in heart rate that has been attributed to the activation of the autonomic nervous system.[2] We demonstrated that patients with diabetes mellitus and/or metabolic syndrome, who are more likely to have cardiac autonomic dysfunction, have a lower heart rate response (HRR) than those without these conditions.[2,3] In addition, we showed that the HRR associates with other markers of autonomic dysfunction in patients with diabetes mellitus.[4] Importantly, there is now a substantial body of evidence in cohorts that span the risk-spectrum, and from multiple laboratories that demonstrate the prognostic value of HRR independent of MPI findings, thereby improving risk stratification.[4–13]

Autonomic innervation of the heart is not uniform. Different structures in the heart including the sinus and atrioventricular nodes receive different types and densities of autonomic fibers and these distributions can vary between individuals and even in the same person over a lifetime.[14] Unlike in normal sinus rhythm, where the heart rate is driven by autonomic impulses to the sinus node, the heart rate in atrial fibrillation is dominated by autonomic activity to the atrioventricular node. It is currently not known whether (1) the heart rate increases with regadenoson in patients with atrial fibrillation, and (2) if the HRR provides prognostic information similar to that provided in those with normal sinus rhythm. In addition to the direct value that this data provides to the care of patients with atrial fibrillation, it will shed light on the importance of the differential autonomic innervation of the heart on regadenoson-induced HRR.

METHODS AND RESULTS

We identified 43 patients who had atrial fibrillation at the time of MPI from a cohort of 1400 patients who underwent regadenoson MPI for clinical indications at the University of Alabama at Birmingham and the Kirklin Clinic from July 2008 to January 2010. The cohort has been previously described.[1] This group was then paired 2:1 with 86 controls that were in sinus rhythm at the time of MPI and did not have a history of atrial fibrillation. The controls and the study group were matched for age, gender, diabetes and end-stage renal disease status, and perfusion deficit size on MPI.

The baseline characteristics and medication intake at time of MPI of both groups are shown in Tables 1 and 2, respectively. Findings on MPI can be found on Table 3 and hemodynamic changes are shown in Table 4. There was no statistically significant difference between the groups with respect to baseline characteristics, medication intake, perfusion defect size, or left ventricular ejection fraction (LVEF). The atrial fibrillation group had a higher baseline heart rate and higher peak heart rate compared to the control group. The HRR

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to regadenoson was calculated as the peak heart rate minus the baseline heart rate, divided by the baseline heart and multiplied by 100 to obtain a percent value [HRR = (peak HR – baseline HR) x100/baseline HR] as previously described.[2,5] The HRR was not different between the 2 groups (Figure 1). There was a moderate reduction in systolic and diastolic BP in both groups with administration of regadenoson. However, the reduction did not differ between the groups. Furthermore, the proportion of patients with a positive SBP (23% vs 20%, $P = 0.7$) and DBP (21% vs 16%, $P = 0.6$) responses were not different in patients with atrial fibrillation and controls, respectively. Importantly, the proportion of patients with a positive BP response were not different based on the presence of a blunted HRR (<10%) in patients with atrial fibrillation ($P > 0.9$ for SBP and DBP) and controls ($P > 0.9$ for SBP and 0.4 for DBP).

The cohort was followed up for a mean of 43 ± 17 months. During this time, 35% of the patients died (44% atrial fibrillation, 30% control, $P = 0.1$). On Kaplan-Meier analysis, a blunted HRR (<10%) was associated with worse survival in the control group but not in the atrial fibrillation group (Figure 2). Cox regression analysis demonstrated a 3-fold increased risk of mortality for blunted HRR in the control group (hazard ratio 3.4 95% confidence interval 1.4-8.2, $P = 0.005$). In the atrial fibrillation group, the association with mortality was not statistically significant (1.7, 0.7-4.7, $P = 0.3$).

DISCUSSION

This study provides important information on the HRR to regadenoson in patients with atrial fibrillation. We show for the first time that the heart rate increases in response to regadenoson even when patients are in atrial fibrillation. The study demonstrates that the HRR was not statistically different between a group of patients in atrial fibrillation and a control group in sinus rhythm at time of MPI. This suggests that regadenoson-induced autonomic activation is not restricted to the sinus node but also influences other cardiac structures including the atrioventricular node. Initially it was postulated that the HRR to regadenoson was a result of a baroreceptor reflex to hypotension induced by regadenoson. However a pivotal study by Dhalla et al. demonstrated that there is direct activation of the autonomic system mediated by the A2A receptor, independent of BP response.[15] In this study, increases in HR in rats were induced even with small doses of regadenoson when no hypotension was present and persisted long after hypotension resolved. In contrast, nitroprusside which is a pure vasodilator had an increase in HR that was directly proportionally to the degree of hypotension.

A major interest in the HRR to regadenoson stems from the incremental prognostic information it provides. The use of non-perfusion variables, such as the HRR to regadenoson, to augment risk stratification has increased importance with vasodilator compared to exercise MPI due to the loss of important prognostic information provided by the exercise portion of the stress test such as exercise capacity, heart rate recovery, blood pressure response, symptomatic and ECG response to exercise.[16] In this context, multiple studies have demonstrated that the HRR provides incremental prognostic information to the perfusion pattern and LVEF on MPI and other baseline characteristics.[4–13] For example, in a study of 1,156 patients who underwent regadenoson MPI, we demonstrated that a HRR in the lowest (<17%) compared to the highest (>43%) quartile was independently associated with a five-fold increased risk of mortality after adjusting for age, gender, diabetes mellitus, renal disease, and MPI findings.[5] More recently, a multicenter positron emission tomography registry of 2,398 patients confirmed the independent association of HRR with

Table 1. Baseline patient characteristics

	Atrial fibrillation	Control	*p*
Age	69 ± 9	69 ± 10	0.8
Diabetes	21 (49%)	42 (49%)	>0.9
End-stage renal disease	8 (19%)	16 (19%)	>0.9
Male gender	31 (72%)	62 (72%)	>0.9
Caucasian race	33 (81%)	55 (66%)	0.1
Hypertension	36 (84%)	76 (88%)	0.6
Dyslipidemia	27 (63%)	60 (70%)	0.4
Prior myocardial infarction	13 (30%)	20 (23%)	0.4
Prior percutaneous coronary intervention	15 (35%)	20 (24%)	0.2
Prior coronary artery bypass graft	14 (33%)	28 (33%)	>0.9

Table 2. Prescribed medications at baseline

	Atrial fibrillation	Control	*p*
Aspirin	25 (58%)	48 (56%)	0.9
Beta-blocker	33 (77%)	60 (70%)	0.5
ACE- inhibitor/angiotensin receptor blocker	28 (65%)	55 (64%)	>0.9
Calcium channel blocker	16 (37%)	23 (27%)	0.2
Statin	25 (58%)	48 (56%)	0.9
Insulin	6 (14%)	22 (26%)	0.2

Table 3. Myocardial perfusion findings (standard deviation)

	Atrial fibrillation	Control	*p*
LV ejection fraction (%)	49 ± 17	54 ± 18	0.2
Perfusion deficit size (%)	18 ± 17	18 ± 17	>0.9
Ischemia (%LV)	7 ± 9	9 ± 11	0.2

LV left ventricle

Table 4. Hemodynamic response to regadenoson (standard deviation)

	Atrial fibrillation	Control	*p*
Baseline heart rate	82 ± 15	71 ± 15	<0.001
Peak heart rate	100 ± 18	89 ± 17	0.001
Heart rate response (%)	23 ± 20	27 ± 17	0.3
Baseline systolic blood pressure	130 ± 20	136 ± 25	0.1
Peak systolic blood pressure	123 ± 22	123 ± 24	>0.9
Systolic blood pressure response (%)	−5 ± 12	−9 ± 12	0.09
Baseline diastolic blood pressure	75 ± 11	73 ± 14	0.4
Peak diastolic blood pressure	70 ± 11	67 ± 15	0.1
Diastolic blood pressure response (%)	−5 ± 18	−9 ± 15	0.2

outcomes after accounting for traditional PET findings.[10] In this context, our finding that a blunted HRR to regadenoson is not associated with mortality in patients with atrial fibrillation is novel.

A proposed mechanism for the prognostic information provided by the HRR is related to the stimulation of the sympathetic nervous system by A2A activation.[15] Therefore, HRR is an easily obtained gage of the autonomic nervous system. Since it is widely acknowledged that autonomic dysfunction is associated with worse cardiovascular outcomes,[17–19] the addition of HRR to prognostic models is expected to improve risk stratification. Indeed, in a study of 2000 patients with normal perfusion on MPI, the addition of HRR to traditional risk stratification models resulted in net reclassification improvement in mortality of 18% and cardiovascular events of 22%.[7] The lack of association of HRR with outcomes in atrial fibrillation may be a reflection of the differential innervation of the sinus and

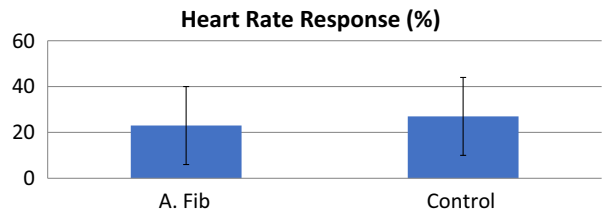

Figure 1. Heart rate response to regadenoson (mean +/− standard deviation). *A. Fib*, atrial fibrillation.

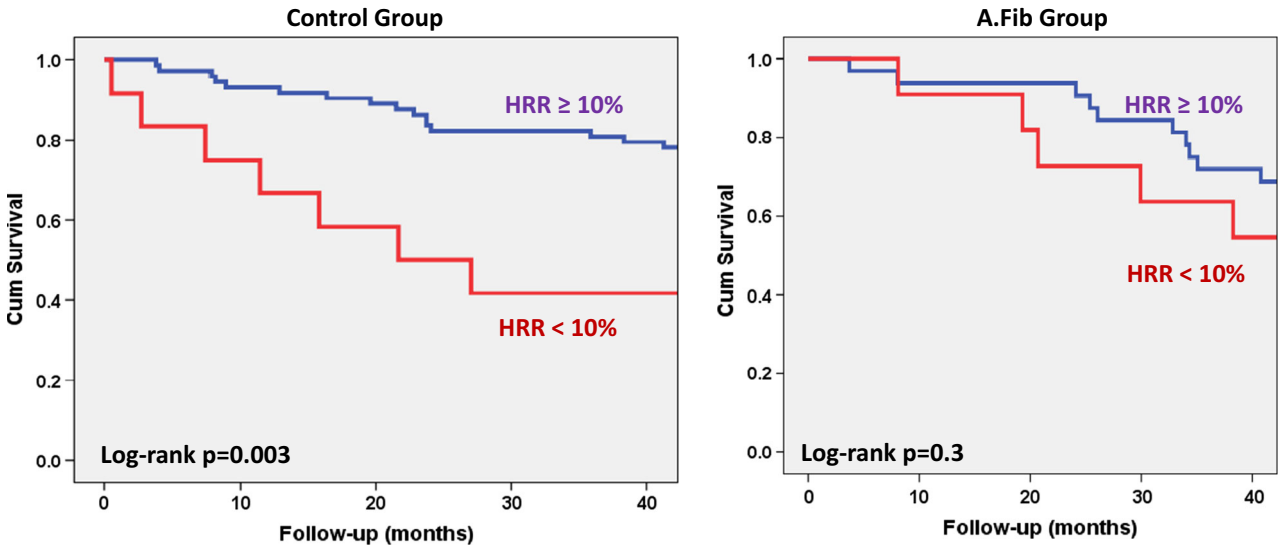

Figure 2. Kaplan-Meier analysis of heart rate response and survival in patients with A. Fib vs Controls. *A. Fib*, atrial fibrillation; *HRR*, heart rate response.

atrioventricular nodes by autonomic fibers.[14] Further, it is possible that activation of Adenosine A1 receptors which delays conduction in the atrioventricular node may have opposed the effects of regadenoson on A2A receptors on the sympathetic drive that enhances conduction in the node thereby confounding the association of HRR with autonomic innervation. Further studies on the effects of regadenoson on the sinus and atrioventricular nodes will help elucidate these mechanisms further.

A major limitation of this study is its retrospective nature, small size, and derivation from a single center. Future large, prospective, multicenter studies are needed to corroborate the results. Also, evaluations that incorporate and control for location of MPI perfusion deficit may prove beneficial. Perfusion deficits in the territory of the RCA are known to have direct effects on the AV nodal conduction and HR, which could confound results if not accounted for.

NEW KNOWLEDGE GAINED

This study is the first to show that patients in atrial fibrillation have an increased HRR to regadenoson similar to that seen in patients with sinus rhythm. However, the association of HRR with mortality was limited to patients in sinus rhythm and was not demonstrated in those with atrial fibrillation. Understanding the mechanism behind the difference in outcomes based on cardiac rhythm and the specific way the autonomic system is activated by regadenoson in these subsets of patients will help in further risk stratifying patients undergoing vasodilator stress tests.

Disclosures

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