Influences of adenosine receptor antagonism on vasodilator responses to adenosine and exercise in adenosine responders and nonresponders

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Martin, Elizabeth A., Wayne T. Nicholson, John H. Eisenach, Nisha Charkoudian, and Michael J. Joyner. Influences of adenosine receptor antagonism on vasodilator responses to adenosine and exercise in adenosine responders and nonresponders. J Appl Physiol 101: 1678–1684, 2006. First published August 31, 2006; doi:10.1152/japplphysiol.00546.2006. We previously demonstrated a bimodal distribution of vasodilator responsiveness to adenosine (Ado) infusion in human subjects, despite similar responses to exercise between subgroups [subjects responsive to Ado infusion (Ado responders) and subjects with blunted vasodilator responses to Ado infusion (Ado nonresponders)]. (Martin EA, Nicholson WT, Eisenach JH, Charkoudian N, and Joyner MJ. J Appl Physiol 101: 492–499, 2006). A component of this difference was attributed to a larger nitric oxide component of Ado-mediated vasodilation in responders. However, there may also be differences in Ado receptors between these subgroups. We hypothesized that Ado receptor antagonism would reduce vasodilator responsiveness to Ado and exercise only in Ado responders. To test this hypothesis, we compared forearm vasodilation induced by intra-arterial infusion of three doses of Ado to vasodilation during three workloads of forearm handgrip exercise before and after Ado receptor antagonism with aminophylline (Aph) in 19 subjects. In Ado responders, the change in forearm vascular conductance above baseline for the low, medium, and high doses of Ado, respectively, was 93 ± 16, 140 ± 14, 194 ± 18 before Aph and 27 ± 12, 71 ± 19, and 134 ± 34 ml·min⁻¹·100 mmHg⁻¹ after Aph (P < 0.05 for low and medium dose before vs. after Aph). For nonresponders, these values were 30 ± 5, 39 ± 6, and 78 ± 9 ml·min⁻¹·100 mmHg⁻¹ before Aph (P < 0.05 vs. responders), with no difference after Aph (P > 0.05). We found that Ado receptor blockade significantly inhibited exercise hyperemia only at high workloads in both responders and nonresponders (P < 0.05 before vs. after Aph). We conclude that there may be reduced Ado receptor responsiveness or sensitivity in nonresponders. Furthermore, Ado may play a limited role exercise hyperemia in both subgroups.

skeletal muscle; blood flow; vascular control; aminophylline; nitric oxide

EXERCISE HYPEREMIA OCCURS in large part due to the vasodilator actions of metabolites produced during muscle contraction, although the main contributors and their interactions remain uncertain (5, 17, 18). Adenosine (Ado) may be involved in exercise hyperemia, although the specific role of Ado in exercise hyperemia has been controversial for several decades.

We previously reported a bimodal distribution of vasodilator responsiveness to intra-arterial infusion of Ado, despite similar exercise blood flow responses at standard workloads, among human subjects (9). In about one-half of the subjects tested, intra-arterial infusion of Ado caused significant, dose-dependent, and repeatable increases in forearm vascular conductance (FVC). These subjects were identified as “Ado responders”; the remaining subjects demonstrated dramatically blunted vasodilator responsiveness to Ado and were identified as “Ado nonresponders.” Blockade of nitric oxide synthase (NOS) with N°-monomethyl-l-arginine (l-NMMA) resulted in a significant reduction in Ado-mediated vasodilation only in Ado responders. Furthermore, Ado responders demonstrated more robust vasodilator responses to isoproterenol and acetylcholine, suggesting that a portion of the difference in Ado vasodilator responsiveness is due to nitric oxide-mediated vasodilation, predominantly through a cGMP-mediated pathway. Besides the lack of difference in exercise-induced vasodilation, there was no difference in subject demographics, caffeine or methylxanthine use, or maximum FVC (reactive hyperemia) between these two subgroups of subjects.

Another possible contributor to this difference in Ado vasodilator responsiveness among our subjects is differences in Ado receptor function, density, or sensitivity between the Ado responders and nonresponders, as well as location of Ado receptors on the endothelial cells vs. those on the vascular smooth muscle cells, since different receptors are more or less sensitive to stimulation by endogenous Ado (produced during muscle contraction) or exogenous Ado (during intra-arterial Ado infusion). Previous studies using Ado receptor antagonism during exercise hyperemia have yielded conflicting results. Several studies in animals have failed to demonstrate a significant reduction of exercise hyperemia during Ado receptor antagonism (4, 6), whereas other animal (10, 13, 14, 20) and human studies (16) have demonstrated significant reduction of exercise hyperemia with blockade of Ado receptors.

The purpose of the present study, therefore, was to investigate the extent to which differences in Ado receptors may contribute to different Ado vasodilator responsiveness between Ado responders and nonresponders, by testing whether Ado receptor antagonism with aminophylline (Aph) would differentially affect vasodilator responsiveness to Ado or exercise in our subjects. We hypothesized, first, that there would again be a bimodal distribution of vasodilator responsiveness to Ado among our subjects. Second, we hypothesized that Ado receptor antagonism with aminophylline would blunt the responsiveness to Ado infusion only in the Ado responders, essentially making the Ado responders look like nonresponders in terms of their vasodilator...
responsiveness to Ado infusion. Finally, we hypothesized that exercise responses would be similar among all subjects and that Ado receptor antagonism would only affect exercise hyperemia in Ado responders.

**METHODS**

**Subjects**

All protocols and procedures were approved by the Institutional Review Board at Mayo Clinic. A total of 19 young healthy subjects (13 men and 6 women) participated in the study after giving written informed consent. All subjects were moderately active, nonsmokers, nonobese, normotensive, and not taking any medications other than oral contraceptives. Female subjects were not pregnant, as determined by a pregnancy test <24 h before the study. Female subjects were studied during the placebo phase of oral contraceptive use, or in the early follicular phase of their menstrual cycle, to minimize possible confounding influences of reproductive hormones on control of blood flow (1, 11). The subjects fasted overnight and refrained from caffeine use 48 h before the study and alcohol exercise 24 h before the study.

**General Methods**

**Arterial catheterization.** The brachial artery of the nondominant forearm was catheterized under aseptic conditions after local anesthesia (1% lidocaine). A standard 5-cm, 20-gauge Teflon catheter was inserted and connected to a three-port connector system for simultaneous measurements of arterial pressure and local administration of study drugs (2).

**Forearm blood flow and vascular conductance.** A 4-MHz pulsed Doppler probe (model 500V, Multigon Industries, Mt. Vernon, NY) was used to measure brachial artery mean blood velocity (MBV) with the probe securely fixed to the skin over the brachial artery proximal to the catheter insertion site as previously described (22). The probe insonation angle was 60°. A linear 7.0-MHz echo Doppler ultrasound probe (model 128XP, Acuson, Mountain View, CA) was placed in a holder securely fixed to the skin immediately proximal to the velocity probe to measure brachial artery diameter. Forearm blood flow (FBF) was calculated as:

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\text{FBF} = \frac{\text{MBV} \pi (\text{brachial artery diameter}/2)^2 \times 60},
\]

where units for FBF, MBV, and brachial artery diameter are milliliters per minute, centimeters per second, and centimeters, respectively, and 60 is used to convert units from milliliters per second to milliliters per minute. Other FVC values represent the change in FVC above baseline values. Baseline FBF and MAP reported represent 60-s averages during baseline. Other FVC values represent the change above baseline FVC values presented as 30-s averages taken during the last minute of each dose or workload.

**Data Acquisition and Analysis**

Data were collected and stored on computer at 250 Hz and analyzed off-line with signal processing software (WinDaq, DATAQ Instruments, Akron, OH). MAP was determined from the arterial pressure waveform. FVC is reported as the change in FVC above baseline values. Baseline FBF and MAP reported represent 60-s averages during baseline. Other FVC values represent the change above baseline FVC values presented as 30-s averages taken during the last minute of each dose or workload.

**Statistics**

All values are reported as means ± SE. Subject demographics were compared using a rank sum test, and gender was compared using Fisher’s exact test. Repeated-measures ANOVA was used to assess differences between treatment groups and levels. Two-sample t-test was used to compare pairs of group means over levels of a factor.
When significance was detected, Tukey’s post hoc test was used to identify individual differences and to adjust P values to account for multiple comparisons, to preserve an overall type I error rate of 0.05. Significance was set at P < 0.05.

RESULTS

Subjects

Group mean age, body mass index (BMI), and FAV were 28 ± 2 yr, 23.6 ± 0.6 kg/m², and 1,080 ± 62 ml, respectively, for all subjects. Based on criteria outlined below and the approach used in our prior study (9), subjects who had demonstrating robust vasodilator responses to both Ado infusion and handgrip exercise were identified as Ado “responders” and those that had blunted vasodilator responsiveness to Ado infusion, compared with their vasodilator responsiveness to handgrip exercise, as Ado “nonresponders.” Ado nonresponders were defined as subjects in whom the FVC during each exercise workload was twice the FVC during each Ado dose. Group mean age, BMI, and FAV were 29 ± 2 yr, 22.6 ± 0.4 kg/m², and 1,005 ± 67 ml, respectively, for Ado responders (n = 9; 7 men, 2 women) and were 27 ± 3 yr, 24.9 ± 1.2 kg/m², and 1,182 ± 108 ml, respectively, for nonresponders (n = 10; 7 men, 3 women). There was no statistical difference in subject demographics, including caffeine use or exercise training, between Ado responders and nonresponders (P > 0.05).

Baseline Values

Overall group averages (n = 19) for baseline FVC during the first Ado trial (Ado) and first exercise trial (exercise) were 47 ± 6 and 45 ± 4 ml·min⁻¹·100 mmHg⁻¹, respectively. After Ado receptor antagonism for the Ado trial (Ado + Aph) and exercise trial (exercise + Aph), FVC was increased (71 ± 8 and 67 ± 7 ml·min⁻¹·100 mmHg⁻¹, respectively; P < 0.05 vs. baseline). Baseline MAP was 90 ± 2, 92 ± 2, 94 ± 2, and 96 ± 2 mmHg during the Ado, exercise, Ado + Aph, and exercise + Aph trials, respectively. These effects of Aph on baseline FVC and MAP have been previously reported for this dose of Aph (7), and they may result from the effects of Aph as a phosphodiesterase inhibitor, as well as an Ado receptor antagonist, which likely results in increased baseline cAMP levels in the vascular smooth muscle, and consequent increases in FVC.

However, these effects of Aph did not differ between Ado responders and nonresponders (P > 0.05). Overall baseline FVC averages during each Ado dose and exercise trial (exercise) were 47 ± 6 and 45 ± 4 ml·min⁻¹·100 mmHg⁻¹, respectively, for all subjects. After Ado receptor antagonism for the Ado trial (Ado + Aph) and exercise trial (exercise + Aph), these values were 71 ± 8 and 67 ± 7 ml·min⁻¹·100 mmHg⁻¹, respectively (P > 0.05 among trials). Baseline MAP was 90 ± 2, 92 ± 2, 94 ± 2, and 96 ± 2 mmHg during the Ado, exercise, Ado + Aph, and exercise + Aph trials, respectively.

Adenosine vs. Exercise Vasodilator Response

Nine subjects showed robust vasodilator responses to both Ado infusion and handgrip exercise, and they were, hence, categorized as Ado responders. The other ten subjects showed blunted vasodilator responses to Ado infusion compared with vasodilator responses to handgrip exercise (FVC during each exercise workload was more than twice the FVC during the corresponding dose of Ado), and they were, hence, categorized as Ado nonresponders. Table 1 shows individual change in FVC above baseline values for each Ado dose and exercise workload for all Ado responders and nonresponders.

As shown in Fig. 2, for the low, medium, and high doses of Ado, respectively, the change in FVC above baseline before Aph infusion for the 9 Ado responders was 93 ± 16, 140 ± 10, and 194 ± 18 ml·min⁻¹·100 mmHg⁻¹, and for the 10 nonresponders it was 30 ± 5, 39 ± 6, and 78 ± 9 ml·min⁻¹·100 mmHg⁻¹.
mmHg⁻¹ (P < 0.05 at each dose for Ado responders vs. nonresponders).

As shown in Fig. 3, for the low, medium, and high handgrip exercise workloads, respectively, the change in FVC above baseline before Aph infusion for the Ado responders was 68 ± 12, 142 ± 16, and 204 ± 23 ml·min⁻¹·100 mmHg⁻¹ for the nonresponders was 73 ± 11, 139 ± 11, and 204 ± 12 ml·min⁻¹·100 mmHg⁻¹ (P > 0.05 at the each workload for Ado responders vs. nonresponders).

Effect of Aph Infusion on Ado Responsiveness

As shown in Fig. 2, Ado receptor blockade significantly blunted Ado responsiveness in Ado responders at the low and medium doses (P < 0.05 Ado vs. Ado+Aph), and blunted Ado responsiveness at the high dose in Ado responders, although this was not statistically significant (P > 0.05 Ado vs. Ado+Aph). Ado responsiveness was not blunted by Aph at any dose in nonresponders (P > 0.05 Ado vs. Ado+Aph). For the low, medium, and high Ado doses, respectively, the change in FVC above baseline (ml·min⁻¹·100 mmHg⁻¹) after Aph infusion was 27 ± 12, 71 ± 19, and 134 ± 34 ml·min⁻¹·100 mmHg⁻¹ for the Ado responders and was 22 ± 7, 31 ± 10, and 53 ± 16 ml·min⁻¹·100 mmHg⁻¹ for the nonresponders. After blockade, the FVC values at each dose were not significantly different between responders and nonresponders (P > 0.05 at the each dose for Ado responders vs. nonresponders), although there was a trend for FVC values to remain higher in Ado responders (P = 0.08, and 0.06 for the medium and high doses of Ado+Aph, respectively, in Ado responders vs. nonresponders).

Effect of Aph Infusion on Exercise Hyperemia

As shown in Fig. 3, Ado receptor blockade significantly blunted exercise hyperemia only at the high workload in both Ado responders and nonresponders (P < 0.05 at the high workload for exercise vs. exercise+Aph for both Ado responders and nonresponders), although the ~15% blockade could be considered limited. For the low, medium, and high handgrip exercise workloads, respectively, the change in FVC above baseline (ml·min⁻¹·100 mmHg⁻¹) after Aph infusion was 75 ± 14, 140 ± 20, and 178 ± 17 ml·min⁻¹·100 mmHg⁻¹ for the Ado responders and for the nonresponders was 73 ± 6, 131 ± 9, 178 ± 11 ml·min⁻¹·100 mmHg⁻¹ for the nonresponders. The FVC values at each workload were not significantly different between responders and nonresponders (P > 0.05 at each workload for Ado responders vs. nonresponders).

**DISCUSSION**

The main finding of the present study was that Ado receptor antagonism significantly blunted Ado-mediated vasodilation at low and medium infusion doses of Ado in Ado responders but that it failed to blunt vasodilation at any Ado dose in nonresponders. Essentially, Aph infusion made Ado responders behave similarly to nonresponders in terms of vasodilator responses to brachial artery infusions of Ado, although responders did have higher mean FVC changes at each Ado dose. Furthermore, Aph infusion blunted exercise hyperemia ~15% only at high workloads in both Ado responders and nonresponders.

Our finding of a bimodal distribution of vasodilator responsiveness to Ado is consistent with findings from a previous study in our laboratory (9), in which 15 subjects demonstrated robust vasodilator responsiveness to Ado infusion and 12 subjects demonstrated blunted Ado responsiveness. As in the earlier study, both subgroups in the present study showed similar vasodilator responses to handgrip exercise. This chosen method for studying the role of Ado in exercise hyperemia, as well as the method for categorizing Ado responders and nonresponders, is discussed below. In the previous study, a portion

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**Fig. 2.** Change (Δ) in FVC above baseline for the low, medium, and high doses of Ado for Ado-responders (n = 9) and nonresponders (n = 10) before and after Aph infusion. Values are means ± SE. *P < 0.05 for each dose before vs. after Aph infusion in Ado responders and at each dose for Ado responders vs. nonresponders before Aph. †P < 0.05 for low and medium Ado doses before vs. after Aph infusion in Ado responders.

**Fig. 3.** ΔFVC above baseline for the low, medium, and high handgrip exercise workloads for Ado responders (n = 9) and nonresponders (n = 10) before and after Aph infusion. Values are means ± SE. *P < 0.05 for high workload before vs. after Aph infusion for Ado responders. †P < 0.05 for high workload before vs. after Aph infusion for nonresponders.
of the difference in Ado responsiveness between subgroups was attributed to a difference in the nitric oxide component of Ado-mediated vasodilation (Ado responders had significant blunting of Ado-mediated vasodilation after NOS blockade with L-NMMA) (9).

Our finding that Aph infusion blunted Ado-mediated vasodilation only at low and medium doses in Ado responders is consistent with a study by van Ginneken et al. (23), in which the effect of 0.28 μmol·min⁻¹·dl⁻¹ or ~180 μg·min⁻¹·dl⁻¹ theophylline (another Ado receptor antagonist) was only significant at a low dose of Ado (6 nmol·min⁻¹·dl⁻¹ or ~1.6 μg·min⁻¹·dl⁻¹) but not at a high dose (20 nmol·min⁻¹·dl⁻¹ or ~5.35 μg·min⁻¹·dl⁻¹). This suggests that there may be competitive inhibition for the Ado receptors between the Ado and the Ado receptor antagonists, such that as more Ado becomes available (at higher infusion doses of Ado), the binding of the Ado receptor blockers to the Ado receptors becomes reduced.

Other studies (7, 21) also showed blunting of Ado-mediated vasodilation with Aph infusion (at doses ranging from 50 to 1,000 μg·min⁻¹·dl⁻¹), but the highest Ado infusion doses tested in those studies were 5–10 μg·min⁻¹·dl⁻¹. Additionally, the failure of Aph to blunt Ado vasodilator responsiveness at any Ado infusion doses in Ado nonresponders suggests that this subgroup of subjects may have altered density, structure, or function of their vasodilating Ado receptors or that the location of the Ado receptors sensitive to endogenous or exogenous Ado may be different between subgroups, as discussed below. If this is the case, then perhaps the factors that limit a robust vasodilator response to exogenous Ado may also limit the impact of Aph on this response.

Several previous studies conducted in animals demonstrated blunting of exercise hyperemia by blocking Ado receptors (10, 13, 14, 20), whereas others failed to show any effect of Ado receptor antagonist on exercise hyperemia (4, 6). Several different animal species and Ado receptor antagonists were used in those studies, as well as different methods of stimulating muscle contraction or exercise. Unlike animal studies, only one group of human studies (16) has investigated the effect of Ado receptor antagonism on exercise hyperemia in skeletal muscle. In those studies, theophylline blunted exercise hyperemia by 20% in human subjects performing one-legged dynamic knee extension at ~50% of peak power output (16).

The results of the present study are consistent with the idea that Ado receptor antagonism can blunt exercise hyperemia; however, in our subjects, this effect occurred only at high workloads of handgrip exercise in the forearm and resulted in 15% blockade (P = 0.04 in both subgroups), which is similar to that found in the study by Radegran et al. (16). The significant blunting of exercise hyperemia by amp in both Ado responders and nonresponders was unexpected. Because the vasodilator responsiveness to Ado and exercise was similar in Ado responders, but not in nonresponders, we suspected that Ado would contribute more to exercise hyperemia in Ado responders. We, therefore, hypothesized that Aph would only blunt exercise hyperemia in Ado responders. However, the results of this study suggest that 1) Ado has a limited contribution to exercise hyperemia at high workloads in both Ado responders and nonresponders; 2) other vasodilating mechanisms may contribute more significantly to exercise hyperemia at lower workloads, making it less likely that Ado receptor antagonism would have an effect; and 3) Ado contributes more to exercise hyperemia, although the role is still limited, at higher workloads when blood flow and metabolism are less well matched and skeletal muscle is relatively "underperfused" (19). Finally, Aph has a number of nonspecific effects that are not due to its action on Ado receptors and it is possible that these effects are what caused the blunting of exercise hyperemia in both the Ado responders and nonresponders at the highest workloads.

**Experimental Considerations**

We chose Ado doses and workloads from previous studies in our laboratory (9), which resulted in identification of Ado responders and nonresponders. In previous and ongoing studies (unpublished), the use of these Ado doses has consistently resulted in a bimodal distribution of Ado vasodilator responsiveness in subjects, whereas the exercise workloads chosen result in similar vasodilator responses in all subjects. Although this is an indirect method of investigating the role of Ado in exercise hyperemia, we believe that it sheds new light on a controversial topic that has resulted in conflicting results and conclusions over several decades. We believe that categorizing subjects as Ado nonresponders if the change in FVC above baseline during exercise was twice as much as change in FVC above baseline during respective Ado doses is justified in that it has consistently resulted in a statistically significant bimodal distribution among our subjects, with about one-half of all subjects tested in each subgroup.

We did analyze the data using more stringent cutoff values, but found similar results. With a 25% cutoff value, only two subjects are categorized as Ado nonresponders and demonstrate no blockade of Ado- or exercise-induced vasodilation with Aph infusion. Also in agreement with the data obtained with the 50% cutoff value, the Ado responders identified by a 25% cutoff value demonstrate Aph-induced blockade of Ado-mediated vasodilation at the low and medium Ado doses (no blockade at the high Ado dose) and blockade of exercise hyperemia only at high workload only. With a 10% cutoff value, no subjects fit the criteria to be categorized as Ado nonresponders.

Aph was chosen on the basis of availability. Aph is a higher molecular weight version of the other commonly used Ado receptor antagonist, theophylline (Aph has an added salt), but exerts similar effects. Both of these two Ado receptor antagonists are nonspecific (they antagonize all 4 Ado receptor isoforms: A1, A2A, A2B, and A3) and exert other biological effects, such as inhibiting phosphodiesterase (21). However, more specific antagonists of Ado receptor subtypes are not yet available for use in humans.

The Aph dose was chosen on the basis of previous studies in humans (7, 21). Our goal was to significantly block Ado receptors, so we chose a dose that has resulted in significant Ado receptor blockade in the majority of subjects tested. We chose not to infuse a higher dose of Aph, because Leuenberger et al. (7) showed after infusing Aph at incremental doses (from 25, 50, 100, and 200 μg·min⁻¹·100 ml forearm tissue⁻¹) for 10 min at each dose until they observed attenuation of Ado-induced increases in FBF, that the infusion rate of Aph that achieved ~40% attenuation of Ado-induced increases in FBF was 50 μg·min⁻¹·100 ml⁻¹ in one subject, 100
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µg·min⁻¹·100 ml⁻¹ in three subjects, and 200 µg·min⁻¹·100 ml⁻¹ in four subjects. Given these results, which showed that the 200-µg·min⁻¹·100 ml⁻¹ dose caused the most consistent attenuation of Ado-induced increases in FBF, we chose this dose for our study. Furthermore, we infused Aph for 20 min at rest before infusing Ado, giving the drug adequate time to block the Ado receptors. Therefore, we believe that this dose was adequate in our studies.

However, this dose did significantly increase baseline FVC, which was an unwanted and possibly confounding effect. This baseline shift was consistent in all subjects, and it has been previously demonstrated (7). A possible explanation for this baseline shift is that Aph is a phosphodiesterase inhibitor, as well as an Ado receptor antagonist, which likely resulted in increased baseline cAMP levels in the vascular smooth muscle, and consequent increases in FVC. Therefore, data were presented as the change in FVC above baseline to account for this shift. However, there was another reason we chose not to increase the dose of Aph: to avoid further confounding effects of augmentation of baseline FBF.

It could be argued that delivery of exogenously infused Ado into the interstitial space may be limited if there is a significant endothelial barrier to exogenous Ado. This argument would suggest that the infused Ado increased FVC mostly by stimulating Ado receptors located on the endothelial cells and not the abluminal receptors located on the vascular smooth muscle cells, i.e., those receptors likely stimulated by endogenous release of Ado during muscle contraction, due to this lack of delivery of the exogenous Ado into the interstitial space. However, Mo and Ballard (12) have shown that interstitial concentrations of Ado increased when sufficient Ado was infused arterially into dog skeletal muscle (12). The Ado infusion doses used in this study are likely large enough to account for much of the vasodilator response we observed during the Ado infusion trials, since the resting interstitial concentration of Ado in human skeletal muscle is very low (8). Nonetheless, this argument may suggest that the difference between Ado responders and nonresponders may be related to a difference in the number of functioning Ado receptors on the endothelial cells, rather than the structure, function, or density of Ado receptors.

Finally, our subjects refrained from caffeine use 48 h before the study. This was done to prevent confounding effects of methylxanthine antagonism of Ado receptors during the study. We also considered possible differences in caffeine use among subjects, which could contribute to variable responses to Ado, but after querying all subjects about caffeine use, we found no difference between Ado responders and nonresponders, eliminating the possibility that sensitivity or tolerance to Ado infusion could be related to excessive caffeine use in either subgroup of subjects.

In summary, we investigated the potential role of Ado in exercise hyperemia by comparing Ado-mediated vasodilation with vasodilation during voluntary forearm contractions in human subjects before and after Ado receptor antagonism with Aph. We report a bimodal distribution of Ado vasodilator responsiveness in the human forearm, and we show that this vasodilation is inhibited significantly at low and moderate infusion doses of Ado and only in subjects who respond robustly to Ado infusion. This observation suggests that differences in function or density of Ado receptors or location of Ado receptors more or less sensitive to endogenous or exogenous Ado may contribute to differences in Ado responsiveness between subgroups. Furthermore, exercise hyperemia was only blunted at high workloads in both Ado responders and nonresponders, suggesting that Ado is not obligatory for exercise hyperemia at low to moderate workloads and that it makes a limited contribution during heavier exercise. Finally, our data raise the possibility that genetic differences in some element of the Ado signaling pathway might exist in humans and perhaps explain the variable vasodilator responses to Ado that we have observed.

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