

## Pharmacologic Stress Testing in Patients With Bronchoconstrictive Disease

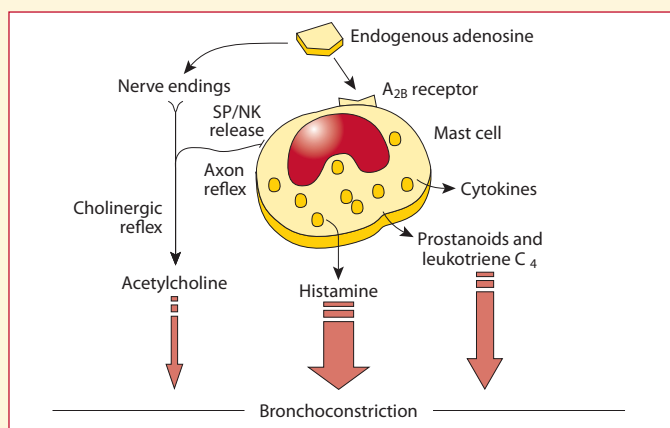
### ADENOSINE RECEPTORS AND BRONCHOCONSTRICTION

The bronchoconstrictive effect of endogenous adenosine (EA) has been recognized since 1983,<sup>1</sup> and the response to adenosine in the form of inhaled adenosine monophosphate (AMP) is commonly used as a noninvasive test to assess the severity of asthma.<sup>2</sup> While the mechanism underlying the bronchoconstrictive effect of EA remains unclear, it probably involves both direct stimulation of airway smooth muscle contraction and activation of mast cells in the lungs.<sup>2</sup>

The mechanisms by which EA causes bronchoconstriction are actually thought to occur in two bodily systems—the nervous system and the cellular immune system. In the former, acetylcholine acts on the muscarinic acetylcholine receptor, causing smooth muscle contraction and bronchoconstriction. In the cellular immune system, EA activates the  $A_{2B}$  receptor, causing mast cells to release mediators that cause bronchoconstriction.<sup>3</sup> Though both mechanisms are thought to be implicated, mast cell-derived inflammatory mediators are considered to have a greater effect than the effect of neural pathway activation<sup>4</sup> (Figure 1).

The physiological effects of adenosine are mediated by 4 types of receptors located in various tissues throughout the body—the adenosine  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$  receptors.<sup>5</sup> A large number of in vitro and preclinical studies support a role for the  $A_1$  and  $A_{2B}$  receptors in EA-mediated bronchoconstriction (Table 1).<sup>2</sup> Airway smooth muscle cells from the lungs of asthmatic subjects contain more adenosine  $A_1$  receptors compared with that of healthy subjects,<sup>6</sup> and EA-stimulated contraction of lung tissue appears to be mediated by the  $A_1$  receptor.<sup>7</sup> An indirect bronchoconstrictive effect of EA is believed to involve activation of the  $A_{2B}$  receptors on mast cells in the lungs.<sup>8</sup> Adenosine-stimulated mast cell degranulation leads to the release of histamine and various inflammatory cytokines, which in turn induce bronchoconstriction.<sup>9-13</sup>

**Figure 1. Proposed Mechanisms of Endogenous Adenosine Bronchoconstriction in Asthma and COPD<sup>4</sup>**



Adapted from Polosa R.

**Table 1. Adenosine Receptor-Mediated Bronchoconstriction<sup>2</sup>**

$A_1$ RECEPTOR	$A_{2B}$ RECEPTOR
<ul style="list-style-type: none"> <li>Expressed in bronchial smooth muscle and epithelial cells</li> <li>Direct effect on airway smooth muscle cell contraction</li> </ul>	<ul style="list-style-type: none"> <li>Expressed in bronchial smooth muscle and epithelial cells and mast cells</li> <li>Indirect stimulation of bronchoconstriction                             <ul style="list-style-type: none"> <li>Mast cell degranulation</li> <li>Histamine release</li> <li>Inflammatory cytokine release</li> </ul> </li> </ul>

## PHARMACOLOGIC STRESS TESTING AND BRONCHOCONSTRICTION

### VASODILATOR AND $\beta_1$ -RECEPTOR STIMULATOR PHARMACOLOGIC STRESS AGENTS

Of the 4 known adenosine receptor subtypes, the  $A_1$  and  $A_2$  adenosine receptors mediate the known cardiovascular effects of adenosine, and activation of the  $A_{2A}$  receptor stimulates coronary vasodilation.<sup>5,14</sup> Vasodilatory pharmacologic stress agents either directly or indirectly activate the  $A_{2A}$  receptors in the coronary arteries to increase blood flow and induce hyperemia that can be detected by radionuclide myocardial perfusion imaging (MPI).<sup>15</sup> Vasodilatory stress agents also activate other adenosine receptor types (though to varying degrees), including those thought to mediate bronchoconstriction. This explains why there are warnings or contraindications in the prescribing information for these agents regarding use in people with suspected bronchoconstrictive disease, asthma, or chronic obstructive pulmonary disease (COPD).

Though dobutamine (which stimulates cardiac beta-adrenergic receptors) is not indicated for use in stress testing, it increases heart rate, blood pressure, and myocardial contractility, and does not cause bronchospasm.<sup>15,16</sup> It does not have the same pharmacologic effect as vasodilator agents because the mechanism of action is not through the adenosine receptors. Dobutamine does not stimulate coronary blood flow to the same extent as vasodilator pharmacologic stress agents and is not considered to be ideal for use in radionuclide MPI.<sup>17</sup> Additionally, the protocol for dobutamine is complex, with a high risk for side effects (75% of patients).<sup>15,17</sup> For these reasons, guidelines recommend the use of dobutamine only in patients who are unable to exercise and for whom vasodilator pharmacologic stress agents are contraindicated.<sup>15,17</sup>

### SELECTIVE AND NONSELECTIVE PHARMACOLOGIC STRESS AGENTS

The available vasodilatory pharmacologic stress agents can be categorized as selective or nonselective adenosine receptor agonists. Nonselective agents are thought to activate all adenosine receptors without specifically targeting any one receptor.

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## IDENTIFYING AND MANAGING AT-RISK PATIENTS

Assessment of a patient's potential bronchoconstrictive reactions is crucial when referring for or administering pharmacologic stress. During the screening process, the clinician should determine the patient's history of bronchoconstrictive disease and whether it is diagnosed as COPD (generally disease with permanent or temporary narrowing of small bronchi, in which forced expiratory flow is slowed<sup>18</sup>) or asthma (widespread narrowing of the airways—varying over short periods of time—due in varying degrees to contraction [spasm] of smooth muscle, edema of mucosa, and mucus in the bronchi and bronchioles<sup>18</sup>). Beyond diagnosis, it is important to note whether the patient is using medication, such as an inhaler, to control their bronchoconstrictive disease. Your best clinical judgment should be utilized in managing instances where a patient arrives in the lab with active wheezing. For instance, patients with a history of airway obstruction who meet certain criteria may be pretreated with 2 inhalations of a short-acting  $\beta_2$ -adrenergic agonist 5 to 10 minutes before pharmacologic stress is administered, as described in studies published both by Reyes and Ananthasubramaniam.<sup>19,20</sup>

For patients with severe or persistent adverse reactions (including bronchoconstriction) associated with pharmacologic stress, aminophylline may be administered in doses ranging from 50 mg to 250 mg by intravenous injection to attenuate these effects.<sup>15</sup> All adenosine receptor agonists may potentially cause bronchoconstriction and respiratory compromise, so appropriate bronchodilator therapy and resuscitative measures should always be available prior to administration.

## CONCLUSIONS

Vasodilatory pharmacologic stress agents either directly or indirectly activate the  $A_{2A}$  receptors in the coronary arteries to increase blood flow and induce hyperemia that can be detected by radionuclide myocardial perfusion imaging (MPI). Vasodilatory stress agents also activate other adenosine receptor types to varying degrees, including those thought to mediate bronchoconstriction. It is important to follow the contraindications and warnings in the prescribing information for these agents regarding use in people with suspected bronchoconstrictive disease, asthma or chronic obstructive pulmonary disease (COPD).