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Editorial

Role of adenosine in the treatment of cardiovascular diseases: Focus on hyperemia

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Adenosine is a well-known purine nucleoside with a wide range of cellular and molecular functions; it is primarily generated by breakdown of adenosine 5′ triphosphate (ATP) catalyzed by ectonucleoside triphosphate diphosphohydrolase and 5′ ectonucleotidase [1], and is rapidly transported into vascular endothelial cells. It is a multifunctional molecule, involved in neuromodulation, inflammatory responses, coagulation and erythropoiesis, among other functions. The increasing use of adenosine in both diagnostic and interventional cardiology has occurred because it's widely available and relatively inexpensive, and it produces stable and reproducible effects. Adenosine is also an antiarrhythmic, and may be proarrhythmic, as this molecule has potent depressant effects at the sinoatrial and atrioventricular nodes, inducing transient sinus bradycardia and atrioventricular block. Furthermore, adenosine may cause atrial fibrillation, premature ventricular beats, brief episodes of non-sustained ventricular tachycardia (VT) and torsades de pointes VT. Therefore, it is already known that adenosine plays an important role in the cardiovascular system [2]. The main reason to use adenosine in the cardiovascular system is to generate vasodilation in the coronary microcirculation to produce hyperemia. To modify microcirculatory function for diagnostic and therapeutic effects, adenosine is a gold-standard diagnostic tool diagnosing ischemia [3].

Adenosine binds to four evolutionarily-conserved receptor subtypes: A1, A2a, A2b and A3, with A2a and A2b subtypes being extensively expressed in the cardiovascular system. A1 receptors generally have inhibitory functions, where activation of cardiac A1 receptors has a myocardial depressant effect linked to negative chronotropic effects, as well as an inhibitory effect on atrioventricular node conduction, enhancing potassium conduction. Activation of A2a receptors by adenosine for stress testing and hyperemia is linked to augmentation of myocardial blood flow [3]. Adenosine and its analogues have been used successfully in the treatment of cardiovascular diseases owing to their capacity to modulate the A2 adenosine receptors, principally the A2a and A2b subtypes that are the extensively expressed in the cardiovascular system, because the modulation of these receptors using A2 adenosine receptor agonists or antagonists regulates blood pressure, heart rate, heart rate variability and cardiovascular toxicity during normoxia and hypoxia conditions [4]. In the Table 1, we included the effects of A2 adenosine receptor regulators on cardiovascular disease. Selective A2a receptor agonists are recognized as a new class of coronary vasodilators used in stress perfusion imaging with radiotracers, with adenosine as the current agent of choice for pharmacologic stress testing. Selective A2a receptor agonists have been considered new promising drugs developed as vasodilators for the diagnosis of coronary artery disease used in the myocardial perfusion imaging stress test [5]. Because the half-time of adenosine is brief, both desired and unwanted effects are generally short lived, and these unwanted effects occus principally with the IV rather than with IC route administration. According to literature the common side-effects include flushing (36.5%), dyspnea (35.2%), chest pain (34.6%) gastrointestinal discomfort (14%) and headache (11%); these side-effects were more common in females, younger patients, and those with higher body mass indexes. Although side effects are frequently reported, they are seldom troublesome and, because of the short half-life of the drug, they are transient [4].

According to the literature, fractional flow reserve (FFR) is currently indicated as a first line strategy for functional assessment of intermediate coronary stenoses. Recently, researchers have found progressive increases in the duration of hyperemia after administration of increasing doses of intracoronary adenosine for the assessment of FFR [6]. According to these authors, the potential advantages of high-dose adenosine are that it allows more prolonged hyperemia and more accurate and reliable measurements of FFR. This preliminary study brings innovations to the diagnosis; however, it requires in-depth the study in order to identify the effects in the medium and long term, before routine use is implemented.

Adenosine was administered safely via both the intracoronary and intraventricular routes and it reliably induced near-maximal coronary

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Table 1
Effects of A2 adenosine receptor regulators on cardiovascular disease.

Adenosine agonist or antagonist	Main finding	References
CPCA	Decreased blood pressure and heart rate in artificially ventilated male Sprague–Dawley rats which was abrogated in the presence of adenosine A2 receptor agonist	[7]
CPCA	Produced a dose-dependent decrease of heart rate and blood pressure in rats, while pre-administration of MDL-12,330, an adenylate cyclase inhibitor, attenuated the cardiovascular responses of CPCA.	[8]
CGS-21680 (CGS)	Elevated heart rate from in sheep	[9]
ZM-241385	Increased mean arterial pressure without altering heart rate during normoxia in fetal sheep	[10]

Note: CPCA: 50 (N cyclopropyl) carboxamidoadenosine; ZM-241385: 4 (2 [7 Amino 2 (2 furyl)[1,2,4]triazolo[2,3 a][1,3,5]triazin 5 ylamino]ethyl)phenol; CGS-21680 (CGS): 4 [2 [[6 Amino 9 (N ethyl β D ribofuranuronamidosyl) 9H purin 2 yl] amino]ethyl]benzenepropanoic acid hydrochloride.

hyperemia in most patients with little effect on systemic blood pressure, and exerts its predominant vasodilatory effect on coronary microvessels <150 μm diameter. During hyperemia, total resistance decreased across the coronary circulation by 70%; however, the resistance decreased 86% and 98% in the arteriolar and venular compartments, respectively, resulting in minimal alteration of capillary hydrostatic pressure such that the capillaries offer the most resistance to coronary blood flow during hyperemia. Adenosine exerts a vasodilatory effect on coronary microvessels via several methods of administration, with the intracoronary and intravenous routes used most often.

The intravenous (IV) route is the most common method used to attain hyperemia in noninvasive stress testing. In the context of obtaining maximal hyperemia in the catheter laboratory, the intracoronary (IC) and IV routes are also used. The IC administration of Ado is thought to be simple and quick; its peak occurs <10 s after administration and its duration is approximately 20 s. For this reason, the IC route is not used in cases in which a longer period of steady-state hyperemia is necessary. Furthermore, data suggest that higher doses of adenosine can be used to achieve maximal hyperemia, and a higher bolus of 100–150 μg adenosine is need to ensure an adequate hyperemic response [3]. There are controversial opinions regarding which route is more effective to produce maximal hyperemia. According to some, the IV route of appears to provide greater efficacy for achieving maximal hyperemia than that of conventional IC with the added advantage that FFR pullback and more complex physiological assessments can be made [3]. Therefore, adenosine plays critical roles in both invasive and noninvasive assessments of myocardial perfusion as well as possessing therapeutic efficacy and having an important role in diagnosis and treatment of arrhythmias.

Based on this evidence, adenosine and its analogues can be used to modify microcirculatory function and increase peak hyperemia for assessment of FFR.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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