Αδενοσίνη: Φυσιολογία, φαρμακολογία και κλινικές εφαρμογές
Adenosine: Physiology, Pharmacology, and Clinical Applications

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Patras University Hospital, Patras, Rio, Greece.
I, Dimitrios Alexopoulos, have received honoraria for lecturing and research grants from:

Astra Zeneca
Boerenger Ingelheim
Menarini
General considerations

Coronary vasodilation

Myocardial protection

Adenosine and platelets
The potentially protective role of adenosine in ACS

• Adenosine is an endogenous purine nucleoside involved in many physiological processes, including:
  – Vasodilation
  – Cardioprotection
  – Modulation of inflammation
  – Inhibition of platelet function

• Adenosine is mainly formed by the breakdown of adenine nucleotides (ATP/ADP)
One of the most common reasons for using adenosine in the CV system:

vasodilation in the coronary microcirculation to produce hyperemia.

used for diagnostic and therapeutic effects for many years

widely adopted as the gold-standard method
Figure 2. The Cardiovascular Effects of Adenosine

Simplified diagram providing common sites for adenosine and adenoreceptor interaction in the cardiovascular system. AVN = atrioventricular node; SAN = sinoatrial node.
Adenosine and human physiology

- Adenosine has a short half-life in the circulation, because it is efficiently transported into cells,
- Under normal physiological conditions extracellular adenosine is present in nanomolar concentrations [Fredholm 2011]
  - Under ischaemic conditions or following massive tissue trauma extracellular adenosine concentrations can reach up to 30 μM

ADP, adenosine diphosphate; ATP, adenosine triphosphate.
Paroxysmal supraventricular tachycardia.

Therapeutically
Diagnostically

Pro-arrhythmic potential.

AF is well recognized
It is a rare occurrence in the catheter laboratory and in noninvasive assessments

Ventricular arrhythmias
as a consequence of adenosine-induced bradycardia
Safety concerns and side effects of adenosine.

Short lived. 
More prevalent with IV than with IC adenosine.

In the Adenoscan study in 81%. For 6 min flushing (36.5%) 
dyspnea (35.2%) 
chest pain (34.6%) 
gastrointestinal discomfort (14%) 
headache (11%) 
AV block / arrhythmias occurred in 7.6% / 3.3% 
Bronchospasm 0.1%

In 574 patients undergoing cardiac stress MRI. For 3 min 
chest pain and dyspnea 14% 
nausea and vomiting in 5%.

Contraindications

allergy to adenosine or severe asthma/COPD.

If chronic obstructive pulmonary disease severity is a major concern, then IC adenosine or an alternate agent can be used.

IC route

bradycardia/transient AV block

incidence varies from 0% (22) to 16% (41) with standard dosing.
Adenosine Interactions

Methylxanthines attenuate hyperemic response through blockade A2a receptors.

Caffeine competitively inhibit the A2a receptor/may attenuate hyperemic response.

Theophylline antagonizes adenosine and may need to be withheld.

Aminophylline and theophylline, may be used in situations where the effect of adenosine requires reversal.
General considerations

Coronary vasodilation

Myocardial protection

Adenosine and platelets
Adenosine exerts its predominant vasodilatory effect on coronary microvessels <150 μm in diameter.

Whether this is an endothelium-dependent process is unclear.

An intact endothelium is not necessary for an adenosine response in vitro.

However, work performed in humans in vivo has demonstrated that the vasodilator effect of adenosine in the forearm can be inhibited by a nitric oxide synthase inhibitor.
Effects of Adenosine on Human Coronary Arterial Circulation

Robert F. Wilson, MD, Keith Wyche, BS, Betsy V. Christensen, BSN, Steven Zimmer, MD, and David D. Laxson, MD

Adenosine is a potent vasodilator used extensively to study the coronary circulation of animals. Its use in humans, however, has been hampered by lack of knowledge about its effects on the human coronary circulation and by concern about its safety. We investigated in humans the effects of adenosine, administered by intracoronary bolus (2–16 μg), intracoronary infusion (10–240 μg/min), or intravenous infusion (35–140 μg/kg/min) on coronary and systemic hemodynamics and the electrocardiogram. Coronary blood flow velocity (CBFV) was measured with a 3F coronary Doppler catheter. The maximal CBFV was determined with intracoronary papaverine (4.5±0.2 · resting CBFV). In normal left coronary arteries (n=20), 16-μg boluses of adenosine caused coronary hyperemia similar to that caused by papaverine (4.6±0.7 · resting CBFV). In the right coronary artery (n=5), 12-μg boluses caused maximal hyperemia (4.4±1.0 · resting CBFV). Intracoronary boluses caused a small, brief decrease in arterial pressure (similar to that caused by papaverine) and no changes in heart rate or in the electrocardiogram. The duration of hyperemia was much shorter after adenosine than after papaverine administration. Intracoronary infusions of 80 μg/min or more into the left coronary artery (n=6) also caused maximal hyperemia (4.4±0.1 · resting CBFV), and doses up to 240 μg/min caused a minimal decrease in arterial pressure (−6±2 mm Hg) and no significant change in heart rate or in electrocardiographic variables. Intravenous infusions in normal patients (n=25) at 140 μg/kg/min caused coronary vasodilation similar to that caused by papaverine in 84% of patients (4.4±0.9 · resting CBFV). At submaximal infusion rates, however, CBFV often fluctuated widely. During the 140-μg/kg/min infusion, arterial pressure decreased 6±7 mm Hg, and heart rate increased 24±14 beats/min. One patient developed 1 cycle of 2:1 atrioventricular block, but otherwise, the electrocardiogram did not change. In eight patients with microvascular vasodilator dysfunction (ΔCBFV, <3.5 peak/resting velocity after a maximally vasodilating dose of intracoronary papaverine), the dose-response characteristics to intracoronary boluses and intravenous infusions of adenosine were similar to those found in normal patients. These studies suggest that maximal coronary vasodilation can be achieved safely with intracoronary adenosine administration and that intravenous infusions at a rate of 140 μg/kg/min cause near-maximal coronary hyperemia in most patients. (Circulation 1990;82:1595–1606)
FIGURE 1. Plot (from all patients) of the change in coronary blood flow velocity (ΔCBFV) after progressively greater doses of intracoronary adenosine. Larger doses caused more prolonged hyperemia.

The correlation of the maximal change in coronary blood flow velocity after adenosine or papaverine was 0.99 (SEM ± 0.46) and resting velocity. Adenosine

FIGURE 3. Plot (from all patients) of the change in coronary blood flow velocity (ΔCBFV) after an intracoronary bolus of adenosine (16 μg) or papaverine (maximally vasodilating dose, 10±2 mg). Both agents caused a marked increase in coronary blood flow velocity, but the response to adenosine was much shorter than that elicited by papaverine.
**Figure 4.** Bar graph of change in coronary blood flow velocity (ΔCBFV) during intravenous adenosine infusion and after intracoronary papaverine.
# IV vs IC Pharmacologic Hyperemic agents

<table>
<thead>
<tr>
<th></th>
<th>Adenosine</th>
<th>Adenosine</th>
<th>Papaverine</th>
<th>NTP</th>
<th>Regadenoson</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>IV</td>
<td>IC</td>
<td>IC</td>
<td>IC</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>140 mcg/kg/min</td>
<td>30 – 60 LCA</td>
<td>15 mg LCA</td>
<td>50 – 100 mcg</td>
<td>0.4 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 – 36 RCA</td>
<td>10 mg RCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half Life</strong></td>
<td>1 – 2 min</td>
<td>30 – 60 sec</td>
<td>2 min</td>
<td>1 – 2 min</td>
<td>2 – 4 min (up to 30 min)</td>
</tr>
<tr>
<td><strong>Time to Max Hyperemia</strong></td>
<td>&lt; 1 – 2 min</td>
<td>5 – 10 sec</td>
<td>20 – 60 sec</td>
<td>10 – 20 sec</td>
<td>1 – 4 min</td>
</tr>
<tr>
<td><strong>Advantage</strong></td>
<td><strong>GOLD STANDARDS</strong></td>
<td>Short action</td>
<td>Short action</td>
<td>Short action</td>
<td>IV bolus</td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>↓BP, chest burning</td>
<td>AV Block, ↓BP</td>
<td>Torsades, ↓BP</td>
<td>↓BP</td>
<td>↑HR, ?redose, long action</td>
</tr>
</tbody>
</table>
High Intracoronary Dose FFR

Resting state      Maximum hyperaemia (IV adenosine)
Steady-State is not the lowest FFR

Tarkin, Davies et al
Circ Cardio Interv, 2013 epub
Resting state      Maximum hyperaemia (IV adenosine)
General considerations

Coronary vasodilation

Myocardial protection

Adenosine and platelets
Adenosine Inhibits Mechanisms Involved in Reperfusion Injury

- Reperfusion
  - Platelets: A_2A, TxA_2, PAF, Ang II, NE, ET-1
  - Leukocytes: A_2A
  - Calcium: A_1, A_3
  - Oxygen: A_1, A_3, Oxygen Free Radicals

- Platelet Aggregation: A_2A, No Reflow
- Vasoconstriction: A_2A
- MPO Proteases
- Adherence to Endothelium: No Reflow
- Cellular Calcium Overload
- Adenosine: A_2A, A_2A/2B, Angiogenesis, Vasculogenesis

Forman MB et al; Cardiovasc Drug Reviews 2006;24:116-47
## Adenosine in Peri-reperfusion Period Preclinical Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Ischemic time (min)</th>
<th>Reperfusion period (h)</th>
<th>Dose and route of administration</th>
<th>Infusion time (min)</th>
<th>Infarct size reduction</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olafsson et al. (114)</td>
<td>Dog</td>
<td>90</td>
<td>24</td>
<td>3.75 mg/min intracoronary</td>
<td>60</td>
<td>Yes</td>
<td>75</td>
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<tr>
<td>Velasco et al. (153)</td>
<td>Dog</td>
<td>40</td>
<td>72</td>
<td>3.75 mg/min intracoronary</td>
<td>60</td>
<td>Yes</td>
<td>63</td>
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<tr>
<td>Forman et al. (57)</td>
<td>Dog</td>
<td>120</td>
<td>24</td>
<td>3.75 mg/min intracoronary</td>
<td>60</td>
<td>Yes</td>
<td>75</td>
</tr>
<tr>
<td>Babbitt et al. (10)</td>
<td>Dog</td>
<td>180</td>
<td>72</td>
<td>3.75 mg/min intracoronary</td>
<td>60</td>
<td>No</td>
<td>0</td>
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<tr>
<td>Pitarys et al. (121)</td>
<td>Dog</td>
<td>90</td>
<td>72</td>
<td>140 μg/kg/min intracoronary</td>
<td>150</td>
<td>Yes</td>
<td>50</td>
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<tr>
<td>Budde et al. (20)</td>
<td>Dog</td>
<td>60</td>
<td>6, 24, 48</td>
<td>140 μg/kg/min intravenous</td>
<td>120*</td>
<td>Yes</td>
<td>50</td>
</tr>
<tr>
<td>Zhao et al. (168)</td>
<td>Dog</td>
<td>60</td>
<td>6</td>
<td>140 μg/kg/min into left atrium</td>
<td>120</td>
<td>Yes</td>
<td>50</td>
</tr>
<tr>
<td>Norton et al. (113)</td>
<td>Rabbit</td>
<td>30</td>
<td>48</td>
<td>0.1, 0.3, 0.55 mg/min intravenous</td>
<td>60</td>
<td>Yes</td>
<td>40</td>
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<tr>
<td>Norton et al. (112)</td>
<td>Rabbit</td>
<td>30</td>
<td>48</td>
<td>0.1, 0.01, 0.001 mg/min intravenous</td>
<td>60</td>
<td>Yes</td>
<td>53</td>
</tr>
</tbody>
</table>
AMISTAD-II
Randomized, placebo-controlled, double blind, 2118 anterior STEMI

BUT: Combined clinical endpoint not significantly different
AMISTAD-II
Post hoc analysis

Early reperfusion (<3.2 h)  Late reperfusion (>3.2 h)

Kloner RA et al; Eur Heart J 2006;27(20): 2400-5
Adenosine 2 x 120 µg i.c. after thrombus aspiration

ST-segment resolution

<table>
<thead>
<tr>
<th></th>
<th>Adenosine (N=226)</th>
<th>Placebo (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70%</td>
<td>12,2</td>
<td>19,6</td>
</tr>
<tr>
<td>30-70%</td>
<td>12,4</td>
<td>21,2</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>68,3</td>
<td>66,3</td>
</tr>
</tbody>
</table>

Myocardial Blush

<table>
<thead>
<tr>
<th></th>
<th>Adenosine (N=226)</th>
<th>Placebo (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30,8</td>
<td>29,8</td>
</tr>
<tr>
<td>2</td>
<td>40,6</td>
<td>34,9</td>
</tr>
<tr>
<td>0 or 1</td>
<td>28,6</td>
<td>35,3</td>
</tr>
</tbody>
</table>

Adenosine 4 mg i.c. just before reperfusion

MRI day 2-3: Primary Endpoints

\[ P = 0.52 \]

\[ P = 0.07 \]

Desmet W et al, Eur Heart J 2011;32(7):867-77
REOPEN-AMI: A Prospective, Randomized Trial of Intracoronary Adenosine and Nitroprusside in Patients with ST-Segment Elevation Myocardial Infarction

Giampaolo Niccoli, MD, PhD, FESC
Catholic University, Rome, Italy
**ST-segment resolution**

<table>
<thead>
<tr>
<th></th>
<th>STR &gt;70%</th>
<th>STR 30-70%</th>
<th>STR &lt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>23.7</td>
<td>25.0</td>
<td>51.3</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>21.2</td>
<td>25.0</td>
<td>53.8</td>
</tr>
<tr>
<td>Adenosine</td>
<td>21.2</td>
<td>7.5</td>
<td>71.3</td>
</tr>
</tbody>
</table>

Adenosine vs Saline $p = 0.009$
Nitroprusside vs Saline $p = 0.75$
Meta-analysis of 7 randomised trials in patients with STEMI

IC adenosine: improvement in ST segment resolution
no increase in adverse events,

no significant effect upon death or heart failure.

Singh M, et al.

Table 33  Recommendations for specific percutaneous coronary intervention devices and pharmacotherapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.</td>
<td>I</td>
<td>A</td>
<td>15, 28</td>
</tr>
<tr>
<td>DES&lt;sup&gt;d&lt;/sup&gt; are recommended for reduction of restenosis/re-occlusion, if no contraindication to extended DAPT.</td>
<td>I</td>
<td>A</td>
<td>45, 46, 55, 215</td>
</tr>
<tr>
<td>Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolization of debris and prevent MI.</td>
<td>I</td>
<td>B</td>
<td>171, 213</td>
</tr>
<tr>
<td>Rotablation is recommended for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.</td>
<td>I</td>
<td>C</td>
<td>—</td>
</tr>
<tr>
<td>Manual catheter thrombus aspiration should be considered during PCI of the culprit lesion in STEMI.</td>
<td>IIa</td>
<td>A</td>
<td>204–208</td>
</tr>
<tr>
<td>For PCI of unstable lesions, i.v. abciximab should be considered for pharmacological treatment of no-reflow.</td>
<td>IIa</td>
<td>B</td>
<td>55, 209, 212</td>
</tr>
<tr>
<td>Drug-eluting balloons&lt;sup&gt;d&lt;/sup&gt; should be considered for the treatment of in-stent restenosis after prior BMS.</td>
<td>IIa</td>
<td>B</td>
<td>174, 175</td>
</tr>
<tr>
<td>Proximal embolic protection may be considered for preparation before PCI of SVG disease.</td>
<td>IIb</td>
<td>B</td>
<td>214</td>
</tr>
<tr>
<td>For PCI of unstable lesions, intracoronary or i.v. adenosine may be considered for pharmacological treatment of no-reflow.</td>
<td>IIb</td>
<td>B</td>
<td>209</td>
</tr>
<tr>
<td>Tornus catheter may be used for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting.</td>
<td>IIb</td>
<td>C</td>
<td>—</td>
</tr>
<tr>
<td>Cutting or scoring balloons may be considered for dilatation of in-stent restenosis, to avoid slipping-induced vessel trauma of adjacent segments.</td>
<td>IIb</td>
<td>C</td>
<td>—</td>
</tr>
<tr>
<td>IVUS-guided stent implantation may be considered for unprotected left main PCI.</td>
<td>IIb</td>
<td>C</td>
<td>—</td>
</tr>
<tr>
<td>Mesh-based protection may be considered for PCI of highly thrombotic or SVG lesions.</td>
<td>IIb</td>
<td>C</td>
<td>—</td>
</tr>
<tr>
<td>For PCI of unstable lesions, intracoronary nitroprusside or other vasodilators may be considered for pharmacological treatment of no-reflow.</td>
<td>IIb</td>
<td>C</td>
<td>—</td>
</tr>
</tbody>
</table>
Pre- and post-conditioning.

partly mediated by endogenous adenosine.

Pre: activation of A1 and A3 receptor subtypes.

Post: activation of A2a and A3 receptor subtypes.
Individual (left) and average (right) values of ST-segment shifts on the surface ECG at the end of the first, second, and third balloon inflations in control and adenosine-treated patients.


ClinicalTrials.gov NCT01148147

Giuseppe De Luca, MD, PhD
Aggregate Professor of Cardiology
Chief Interventional Cardiology
Eastern Piedmont University
Novara
Primary End-point

- Adenosine
- Placebo

Troponin I > 3 times ULN (%)

- Adenosine: 67.7%
- Placebo: 70%

p = 0.69

PREVENT-ICARUS
Ischemic Postconditioning During Primary Percutaneous Coronary Intervention Clinical Perspective

by Joo-Yong Hahn, Young Bin Song, Eun Kyoung Kim, Cheol Woong Yu, Jang-Whan Bae, Woo-Young Chung, Seung-Hyuk Choi, Jin-Ho Choi, Jang-Ho Bae, Kyung Joo An, Jong-Seon Park, Ju Hyeon Oh, Sang-Wook Kim, Jin-Yong Hwang, Jae Kean Ryu, Hun Sik Park, Do-Sun Lim, and Hyeon-Cheol Gwon

Circulation
Volume 128(17):1889-1896
October 22, 2013
ECG data according to treatment group.

General considerations

Coronary vasodilation

Myocardial protection

Adenosine and platelets
Ticagrelor inhibits adenosine uptake via the nucleoside transporter ENT-1

*Ticagrelor bound to ENT-1.
ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPD, adenosine monophosphate deaminase; ATP, adenosine triphosphate; ENT-1, equilibrative nucleoside transporter-1; IMP, inosine monophosphate.
Why investigate an interaction between ticagrelor and adenosine?

- PLATO is the only study that has shown a significant CV mortality benefit of an oral antiplatelet agent compared with an active control.

- Preclinical data show that ticagrelor can inhibit cellular adenosine uptake [Van Giezen 2012].

- Studies have demonstrated that dyspnoea is more common with ticagrelor than with clopidogrel [Cannon 2007; Storey 2011; Wallentin 2009].

- Dyspnoea is a known effect of adenosine [Adenocard US PI 2013; Burki 2005].
Ticagrelor augments blood flow in the canine LAD artery after exogenous adenosine infusion

Adenosine 15 μg/kg/min

Adenosine 30 μg/kg/min

*p<0.05 versus control, unequal variance t test.

LAD, left anterior descending.

Please note: a vehicle is a substance of no therapeutic value used to convey an active medicine for administration. In this case the vehicle is saline.

Effect of ticagrelor on adenosine-induced coronary blood flow in humans

- Study objective: To determine if a clinically relevant dose of ticagrelor can augment adenosine-induced physiological responses, coronary blood flow velocity and dyspnoea.

Healthy male subjects aged 18–40 years old (n=40)

Ticagrelor (180 mg, single dose)  Placebo (single dose)

Placebo (single dose)  Ticagrelor (180 mg, single dose)

Visit 1  6–21 day washout

Visit 2  4–21 days

Follow-up visit
Clinical assessment of potential augmentation of adenosine-induced effects

[Pre-dosing adenosine ladder]
- Placebo (single dose)
- Ticagrelor (180 mg, single dose)

2 hours

[Post-dosing adenosine ladder]
- Adenosine receptor inhibitor (theophylline 5 mg/kg i.v. over 20 minutes)

10 minutes

[Post-dosing adenosine ladder in the presence of theophylline]

Adenosine ladder (µg/kg/min)

Baseline 0

0 50 80 110 140

Ticagrelor augments adenosine-induced CBFV


CBFV, coronary blood flow velocity.
Theophylline blocks ticagrelor-related increases in adenosine-induced CBFV

CBFV, coronary blood flow velocity.
Theophylline blocks the ticagrelor-related increase in adenosine-induced dyspnoea

*Scored using the Modified Borg Scale, from 0 (no sensation of dyspnoea) to 10 (maximum sensation of dyspnoea).

Differential Effect of Ticagrelor Versus Prasugrel on Coronary Blood Flow Velocity in Patients With Non-ST-Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention
An Exploratory Study

Dimitrios Alexopoulos, MD, FACC, FESC; Athanasios Moulias, MD; Nikolaos Koutsogiannis, MD; Ioanna Xanthopoulou, MD; Apostolos Kakkavas, MD; Eleni Mavronasiou, MD; Periklis Davlouros, MD; George Hahalis, MD

Background—Prasugrel and ticagrelor provide a superior anti-ischemic action than clopidogrel, with some of ticagrelor’s benefits possibly attributed to adenosine-mediated mechanisms. We aimed to compare the effect of maintenance dose of ticagrelor versus prasugrel on coronary blood flow velocity (CBFV) during increasing doses of intravenously administered adenosine.

Methods and Results—In a prospective, single-center, single-blind, crossover study, 56 patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention were randomized to receive either ticagrelor 90 mg BID or prasugrel 10 mg OD with a 15-day treatment period. At the end of each treatment period, CBFV by transthoracic Doppler echocardiography was assessed at baseline and under incremental doses (50 μg/kg per minute, 80 μg/kg per minute, 110 μg/kg per minute, and 140 μg/kg per minute) of adenosine infusion. Maximal CBFV area under the curve was higher for ticagrelor-treated than for prasugrel-treated patients, with a least squares mean difference of 7.16 (95% confidence interval, 2.61–11.7; P=0.003). Maximal CBFV/baseline CBFV ratio was higher with ticagrelor than prasugrel at 50, 80, and 110 μg/kg per minute but not at 140 μg/kg per minute adenosine infusion rate, with mean difference (95% confidence interval) of 0.17 (0.08–0.26; P<0.001), 0.21 (0.02–0.41; P=0.03), 0.24 (0.01–0.47; P=0.04), and 0.14 (−0.12 to 0.4; P=0.3), respectively.

Conclusions—In patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention, ticagrelor augments CBFV to a greater extent than prasugrel when incremental doses of adenosine are administered. Although exploratory, these results may represent a pleiotropic action of ticagrelor, possibly contributing to its beneficial effects in such patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01642966 (Circ Cardiovasc Interv. 2013;6:00-00.)

Key Words: acute coronary syndrome ■ adenosine ■ P2Y12 receptor ■ prasugrel ■ ticagrelor
NonSTEACS, PCI treated patient
- Eligible for the study
- Baseline LAD CBFV adequately recorded
- Informed consent

Study procedure at Visit 1 and 2

10 min Resting Period
- Compliance with treatment assessment
- MACES, adverse events and bleeding events documentation
- BP, HR
- LAD bCBFV

5 min Recovery periods between the infusions
Adverse events monitoring throughout the procedure
Example of transthoracic Doppler echocardiography images in a single patient

LAD baseline (A) and maximal at 110μg/kg/min adenosine infusion rate (B) CBFV recorded at Day 15 while under prasugrel. Same patient’s images of baseline (C) and maximal at 110μg/kg/min adenosine infusion rate CBFV (D) on Day 30, while under ticagrelor. The respective ratios of maximal CBFV/baseline CBFV are shown (B, D).
Ticagrelor increases adenosine-induced CBFV in NSTE-ACS patients relative to prasugrel

*Significantly higher ratio of LAD maxCBFV/bCBFV for ticagrelor vs. prasugrel.
Ticagrelor, but not prasugrel active metabolite, delays adenosine degradation

Extension of adenosine half-life after addition of 7.1 μM to human whole blood in the presence of DMSO, prasugrel-AM, ticagrelor or dipyridamole

A significant 3.4-fold increase at 1 μM exposure of ticagrelor

Residual adenosine concentrations in whole blood 1 min after addition of 7.1 μmol/L adenosine, in the presence of a concentration range of dipyridamole or ticagrelor

**Ticagrelor inhibits human platelet aggregation via adenosine in addition to P2Y\textsubscript{12} antagonism**

- In whole blood, adenosine contributed an additional antiplatelet effect when in combination with ticagrelor but not prasugrel-AM.

![Graph showing platelet aggregation in whole blood](image)

- Residual collagen-induced platelet aggregation in whole blood, in the presence of added compounds alone or in combination.
  - Adenosine 7.1 μmol/L,
  - Dipyridamole 14 μmol/L,
  - Ticagrelor 14 μmol/L,
  - Prasugrel-AM 14 μmol/L
  - ZM241385 14 μmol/L

Adeno, adenosine; AM, active metabolite; ZM241385, selective A\textsubscript{2A} antagonist.

TICAGRELOR Adenosine Mediated Effects
Inhibition of platelet aggregation via adenosine

- *In vitro*, ticagrelor unmasked the inhibitory effect of exogenous adenosine on platelet aggregation in whole blood from healthy volunteers and patients with inherited severe P2Y12 deficiency.

- Ticagrelor increases the inhibitory effect of exogenous adenosine on platelet aggregation.

- Evidence of an additional antiplatelet mechanism by ticagrelor, mediated by the induced increase of adenosine levels.

Ticagrelor increases adenosine plasma concentration in medium to high-risk n-STEMI ACS patients

Comparisons of adenosine plasma concentration (APC) in the ticagrelor, clopidogrel, at 6 hrs after loading dose, and control group

*: p<0.01 Ticagrelor group versus control or clopidogrel

Bonello et al, JACC 2014;63:872-7
Coronary Flow Reserve With a Turbo

A Warning for the Use of Adenosine as a Provocative Test in Patients Receiving Ticagrelor?

Paolo Voci, MD, PhD, Francesco Pizzuto, MD
Rome, Italy

The paper by Bonello et al. (1), published in this issue of the Journal, is the first human study investigating the effect of ticagrelor on adenosine plasma concentration in patients with acute coronary syndrome.

Ticagrelor is a new antiplatelet drug directly blocking P2Y12-adenosine diphosphate (ADP) receptors, which show a better clinical profile compared to clopidogrel in patients with acute coronary syndrome (2). As for other popular drugs, a “pleiotropic” non-platelet-directed property has been suggested to explain the favorable clinical results.
Adenosine Plasma Concentration Increase by Ticagrelor in Patients With Acute Coronary Syndrome
No Cause for Fear in Clinical Practice

We read with great interest the work by Bonello et al. (1). The authors are to be commended for a very elegant study of acute coronary syndrome (ACS) patients demonstrating an increase in adenosine plasma concentration (APC) by ticagrelor compared to clopidogrel through inhibition of adenosine uptake by red blood cells and supporting the hypothesis of significant off-target properties of ticagrelor. Although not specifically addressed in the present study, increases in APC may represent an additional antiplatelet mechanism for ticagrelor (2). More importantly, findings by Bonello et al. (1) provide a causative, missing link for the differential effects of ticagrelor versus those of prasugrel on coronary blood flow velocity (CBFV) during increasing doses of intravenously administered adenosine, as reported by our group in 56 ACS patients (3). Although the APC increase was described in blood samples obtained 6 hours post-antiplatelet loading, one could hypothesize a variability of adenosine levels with time of ticagrelor or dipyridamole, respectively (2). In the case of ticagrelor, the suggested 4- to 5-fold dose reduction of adenosine (ie, <50 μg/kg/min) would result in 35% to 45% of maximal CBFV seen at peak hyperemia (3,5). Voci and Pizzuto (4) warn against the use of adenosine as a provocative test in ticagrelor-treated patients, which in our opinion, is not supported by available evidence. At peak hyperemia, mean arterial pressure, heart rate, and double product did not differ between ticagrelor- and prasugrel-treated patients (3). Adenosine-induced dyspnea is indeed significantly augmented with ticagrelor on board, although it is self-limited and of questionable clinical relevance. Moreover, the asymptomatic, transient, second-degree atrioventricular block that does not need medical treatment observed infrequently during adenosine infusions may be slightly more common in subjects taking ticagrelor (3,5).

We believe that the increased APC described in patients with ACS given ticagrelor should not raise any evidence-based concern by clinicians.

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Once again, I thank Dr. Taegtmeyer for his interest in our work.

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REFERENCE


Ticagrelor’s Adenosine-Mediated Effect and the Accuracy of Fractional Flow Reserve

We read with great interest the paper by Wittfeldt et al. (1), which demonstrated that the novel adenosine diphosphate receptor P2Y12 antagonist, ticagrelor, augments the adenosine-induced
Because ticagrelor has been shown to enhance adenosine-induced vasodilatation, the degree of hyperemia obtained with adenosine infusion may be greater than that obtained in patients taking clopidogrel. **This would lead to a lower FFR** and a more accurate reflection of the true functional significance of a coronary lesion.

The increasing use of ticagrelor in the future may also allow for the **routine use of intracoronary adenosine**, because it has previously been shown to be less reliable and more problematic than intravenous infusion (6). If this is the case, the adoption of this more simplified method may translate into an increased utilization of FFR as a valuable investigative procedure with subsequent improved patient outcomes and cost-effectiveness.
Differential effect of ticagrelor vs thienopyridine loading on fractional flow reserve: Possible implications for clinical practice
Dimitrios Alexopoulos, MD, Ioanna Xanthopoulou, MD, Grigorios Tsigkas, MD, Nikolaos Koutsogiannis MD, Athena Hassapi, MD, Dionyssios Ktenas, MD, Christos Schortsanitis, Periklis Davlouros, MD.
AHA Scientific Sessions 2014, Chicago, 15-19 Nov
ADENOSINE DEPENDENT AND INDEPENDENT MECHANISMS LEADING TO PLEIOTROPIC EFFECTS

**Beneficial effects**
- Plaque stabilization
- Increased adenosine-induced coronary blood flow
- Improved endothelial function
- Inhibition of ADP-induced vascular muscle cells contraction

**Adverse effects**
- Dyspnoea
- Increased uric acid
- Increased creatinine
- Increased ventricular pauses

**Ticagrelor**

**P2Y12 receptors**
- in vascular smooth muscles
- in coronary atherosclerotic plaques
- platelet inhibition through ATP release from RBC and subsequent degradation to adenosine
- Reuptake in RBC
CONCLUSIONS

• Adenosine has a critical role in the noninvasive and invasive assessment of myocardial perfusion.

• Role for preconditioning? Therapeutic efficacy in patients with no-reflow?

• Important role in diagnosis and treatment of arrhythmias.
CONCLUSIONS

- Side effects: frequent, seldom troublesome and transient.
- Platelet function is inhibited by adenosine
- Responsible for dual mode of action/pleiotropic actions of ticagrelor.
Ticagrelor Increases Adenosine Plasma Concentration in Patients With an Acute Coronary Syndrome

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Objectives
This study aimed to investigate the impact of ticagrelor on adenosine plasma concentration (APC) in acute coronary syndrome (ACS) patients.

Background
Ticagrelor is a direct-acting P2Y₁₂-adenosine diphosphate receptor blocker. The clinical benefit of ticagrelor compared with clopidogrel in ACS patients suggests that the drug has non-platelet-directed properties. Animal and in vitro models suggested that the "pleiotropic" properties of ticagrelor may be related to an interaction with adenosine metabolism.

Methods
We prospectively randomized 60 ACS patients to receive ticagrelor or clopidogrel. The APC was measured by liquid chromatography. To assess the mechanism of APC variation, we measured adenosine deaminase concentration, adenosine uptake by red blood cells, and cyclic adenosine monophosphate production by cells overexpressing adenosine receptors. The P2Y₁₂-adenosine diphosphate receptor blockade was assessed by the vasodilator-stimulated phosphoprotein index.

Results
Patients receiving ticagrelor had significantly higher APC than patients receiving clopidogrel (1.5 μM [interquartile range: 0.98 to 1.7 μM] vs. 0.68 μM [interquartile range: 0.49 to 0.78 μM]; p < 0.01). The APC was not correlated with vasodilator-stimulated phosphoprotein (p = 0.16). Serum-containing ticagrelor inhibited adenosine uptake by red blood cells compared with clopidogrel or controls (p < 0.01 for both comparisons). Adenosine deaminase activity was similar in serum of patients receiving clopidogrel or ticagrelor (p = 0.1). Ticagrelor and clopidogrel had no direct impact on adenosine receptors (p = not significant).

Conclusions
Ticagrelor increases APC in ACS patients compared with clopidogrel by inhibiting adenosine uptake by red blood cells. (J Am Coll Cardiol 2014;63:872–7) © 2014 by the American College of Cardiology Foundation
Arrhythmias. Adenosine has proarrhythmic potential. AF is well recognized (81) and in some reports is the most common arrhythmia (2.7% after IV administration) (81). Adenosine is thought to provoke AF through shortening of the atrial action potential duration. Its incidence varies depending on the population being studied. For example, in patients with known conductive system disease undergoing electrophysiological assessment, the incidence of AF was 12%. However, it is a rare occurrence in the catheter laboratory and in noninvasive assessments (82). In a retrospective dataset of 1,948 patients undergoing adenosine stress myocardial perfusion studies, the incidence of AF was 0.41% (83). AF was usually preceded by either increasing atrial ectopy or significant bradycardia. When AF occurs, it is usually well tolerated unless associated with an accessory pathway, where it may produce unstable arrhythmias requiring direct current cardioversion (84).

Ventricular arrhythmias have also been reported with adenosine. This is usually as a consequence of adenosine-induced bradycardia and is more likely to occur in patients with a propensity for bradycardia-related arrhythmias such as those with prolonged QTc interval (85).
Study Flow-Chart

471 STEMI patients were assessed for eligibility

123 patients did not meet angiographic eligibility criteria
- 12 did not undergo PCI
- 97 had TIMI flow 2-3 did not provide written informed consent
- 4 had culprit lesion non-identified
- 5 had culprit lesion in a by-pass graft
- 6 had stent thrombosis
- 6 had left main disease
- 3 had acute CABG

108 patients did not meet clinical or ECG eligibility criteria
- 13 had a diagnosis other than STEMI
- 7 did not provide written informed consent
- 5 died before entry into the cath-lab
- 12 had a previous STEMI in the same territory
- 16 had cardiogenic shock
- 5 had contraindications to contrast agent
- 13 had contraindications to study medications
- 12 had severe renal failure
- 25 had left bundle block, frequent ventricular ectopy, paced rhythm, or pre-excitation

240 STEMI patients (TIMI flow 0-1) were randomly assigned to a treatment group

80 were assigned to TA+saline
(2 ml of heparinized saline as fast bolus followed by 33 ml of heparinized saline in 2 min as slow bolus)
- drug through the guiding catheter due to TA failure
- N=7
- N=73

80 were assigned to TA+Adenosine
(120 mcg as fast bolus followed by 2 mg in 33 ml of saline in 2 min as slow bolus)
- drug through the guiding catheter due to TA failure
- N=8
- N=72

80 were assigned to TA+Nitroprusside
(60 mcg as fast bolus followed by 100 mcg in 33 ml of 5% glucose in 2 min as slow bolus)
- drug through the guiding catheter due to TA failure
- N=9
- N=71

All patients received a weight adjusted bolus and infusion of abciximab for 12 h
A1 receptors: myocardial depressant effect with negative chronotropic and dromotropic effects. Inhibition of atrioventricular (AV) node conduction and prolongation of the refractory period via inhibition of cAMP-mediated calcium influx and enhances potassium conduction (14) (Fig. 2).

A2A receptor activation also produces anti-inflammatory effects and acts as a major target of caffeine.

A2B receptors are found on human mast cells and are thought to produce mast cell degranulation and bronchial constriction (15). A3 receptors are
A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II).

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Abstract

OBJECTIVES:
The purpose of this research was to determine the effect of intravenous adenosine on clinical outcomes and infarct size in ST-segment elevation myocardial infarction (STEMI) patients undergoing reperfusion therapy.

BACKGROUND:
Previous small studies suggest that adenosine may reduce the size of an evolving infarction.

METHODS:
Patients (n = 2,118) with evolving anterior STEMI receiving thrombolysis or primary angioplasty were randomized to a 3-h infusion of either adenosine 50 or 70 microg/kg/min or of placebo. The primary end point was new congestive heart failure (CHF) beginning >24 h after randomization, or the first re-hospitalization for CHF, or death from any cause within six months. Infarct size was measured in a subset of 243 patients by technetium-99m sestamibi tomography.

RESULTS:
There was no difference in the primary end point between placebo (17.9%) and either the pooled adenosine dose groups (16.3%) or, separately, the 50-microg/kg/min dose and 70-microg/kg/min groups (16.5% vs. 16.1%, respectively, p = 0.43). The pooled adenosine group trended toward a smaller median infarct size compared with the placebo group, 17% versus 27% (p = 0.074). A dose-response relationship with final median infarct size was seen: 11% at the high dose (p = 0.023 vs. placebo) and 23% at the low dose (p = NS vs. placebo). Infarct size and occurrence of a primary end point were significantly related (p < 0.001).

CONCLUSIONS:
Clinical outcomes in patients with STEMI undergoing reperfusion therapy were not significantly improved with adenosine, although infarct size was reduced with the 70-microg/kg/min adenosine infusion, a finding that correlated with fewer adverse clinical events. A larger study limited to the 70-microg/kg/min dose is, therefore, warranted.
Pre- and post-conditioning. partly mediated by endogenous adenosine. activation of A1 and A3 receptors by adenosine

In a small study of 30 patients undergoing PCI, Leesar et al. (67) demonstrated that a 10-min IV adenosine infusion (dose of 2 mg/min) administered before the PCI pre-conditioned the myocardium (67).

However, among stable elective patients undergoing PCI, the randomized administration of 120 mg and 180 mg of adenosine into the right and left coronary arteries, respectively, was not associated with a reduction of periprocedural myocardial infarction, Thrombolysis In Myocardial Infarction frame count, or in-hospital death (68).
Post-conditioning

Several small studies on acute STEMI patient groups have shown a cardioprotective effect of post-conditioning (70).

Hahn et al. (71), using a protocol that consisted of 4 cycles of 1 min of balloon inflation followed by 1 min of balloon deflation within 1 min of reflow after coronary stent deployment, demonstrated that patients in the post-conditioning group were found to have 36% smaller infarctions as determined by serum creatine kinase release during the first 72 h of reperfusion and lower peak creatine kinase.

However, POST trial in 700 patients undergoing primary PCI demonstrated that ischemic post-conditioning with 4 cycles of 1 min of balloon inflation after restoration of coronary blood flow was not associated with improved myocardial reperfusion.
Adenosine

A ubiquitous extracellular signaling molecule with essential functions in human physiology.

Provides the backbone for basic energy transfer through its adenosine triphosphate (ATP) and adenosine diphosphate interactions

Role in cell signaling,

- Induces vasodilation in most vascular beds
- Regulates activity in the sympathetic nervous system
- Has antithrombotic properties
- Reduces blood pressure and heart rate

Adenosine and its derivatives have therapeutic effects in most organ systems.
Preclinical investigations of ticagrelor’s adenosine mode of action

- Ticagrelor dose-dependently inhibits adenosine uptake in human erythrocytes [Van Giezen 2012]
  - Approximately 10 times less potent than the model adenosine transport inhibitor dipyridamole [Gresele 1986; Van Giezen 2012]

- Ticagrelor significantly augments endogenous adenosine-induced coronary artery blood flow versus control following a 1-minute occlusion in a canine model [Van Giezen 2012]

*p<0.05 versus control.

Please note: a vehicle is a substance of no therapeutic value used to convey an active medicine for administration. In this case the vehicle is saline.

Dipyridamole, a commonly used vasoactive medication exerts its effects through inhibition of adenosine deaminase.

Adenosine levels can rise rapidly in ischemic tissue due to adenosine kinase inhibition

Adenosine can be synthesized de novo during purine biosynthesis or accumulate as a result of ATP breakdown.

Intracellular adenosine concentrations increase when there is a mismatch between ATP synthesis and use as in ischemia or hypoxia.
Adenosine binds with 4 receptor subtypes that are ubiquitously expressed: A1, A2A, A2B, and A3.


Adenosine has highest affinity for the A1 and A2a receptors.

Activation of A2A and A2B adenosine receptors produces potent vasodilation of most vascular beds including the coronary circulation, resulting in an increase in myocardial blood flow.