Impact of intravenous nitrates on platelet reactivity in patients with stable coronary disease who receive dual antiplatelet therapy and undergo coronary angioplasty

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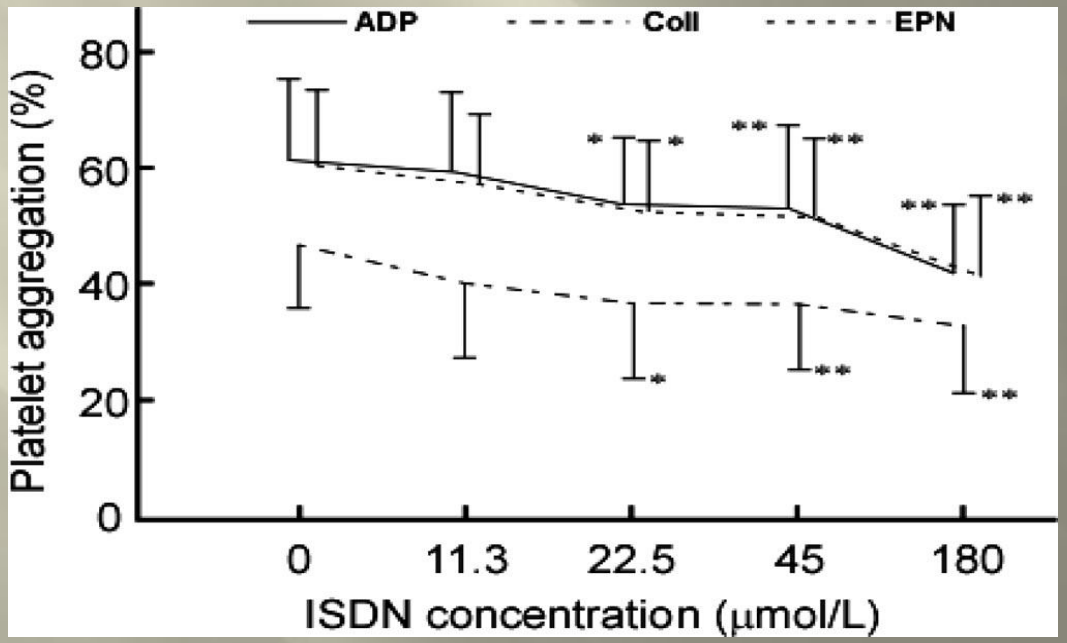
Background I

- ✓ Organic nitrates are used in patients with acute coronary syndromes, stable angina and congestive heart failure for symptomatic relief.
- ✓ The mechanism of action of these drugs is traditionally believed to lie in their arterial vasodilation and venodilation effects, resulting in an improvement of coronary artery blood supply and/or reduction of cardiac workload in the treatment of coronary artery disease and congestive heart failure.

Zhou et al. Cardiology in Review 2010;18: 198–203

Background II

- Zhou et al showed that isosorbide dinitrate inhibited platelet aggregation (measured by LTA) induced by adenosine diphosphatase, epinephrine, and collagen both in vitro and in vivo in patients with CAD.



Zhou et al. Chin J Cardiol 1995;11:97 – 98

Background III

- ✓ On the other hand, a recent study by Price et al suggests that long-term therapy with nitrates correlates with high platelet reactivity. Despite the increased residual reactivity in patients treated with nitrates, there was no association between nitrate use and HRPR.

Table 2
Relations between clinical characteristics and residual platelet reactivity in the study population

Characteristic	Mean Residual Platelet Reactivity (PRU)		p Value
	Characteristic Present	Characteristic Absent	
Concomitant medications			
β Blocker	209 ± 75	194 ± 84	0.091
Calcium channel blocker	209 ± 74	203 ± 80	0.519
Angiotensin-converting enzyme inhibitor	198 ± 79	209 ± 78	0.168
Angiotensin receptor blocker	213 ± 79	201 ± 78	0.190
Nitrates	223 ± 70	200 ± 80	0.018
Proton-pump inhibitor	218 ± 79	198 ± 78	0.020
Statin	204 ± 79	204 ± 72	0.986
Lipophilic statin	204 ± 78	205 ± 79	0.937
Hormone replacement therapy	243 ± 84	203 ± 78	0.139
Body mass index >25 kg/m2	204 ± 77	202 ± 83	0.840
Creatinine clearance < 60 ml/min	215 ± 79	201 ± 77	0.107
Current smoker	168 ± 82	208 ± 77	0.006
Aspirin nonresponsive	215 ± 90	203 ± 77	0.334

Table 3
Relations between clinical characteristics and high residual platelet reactivity (HRPR)

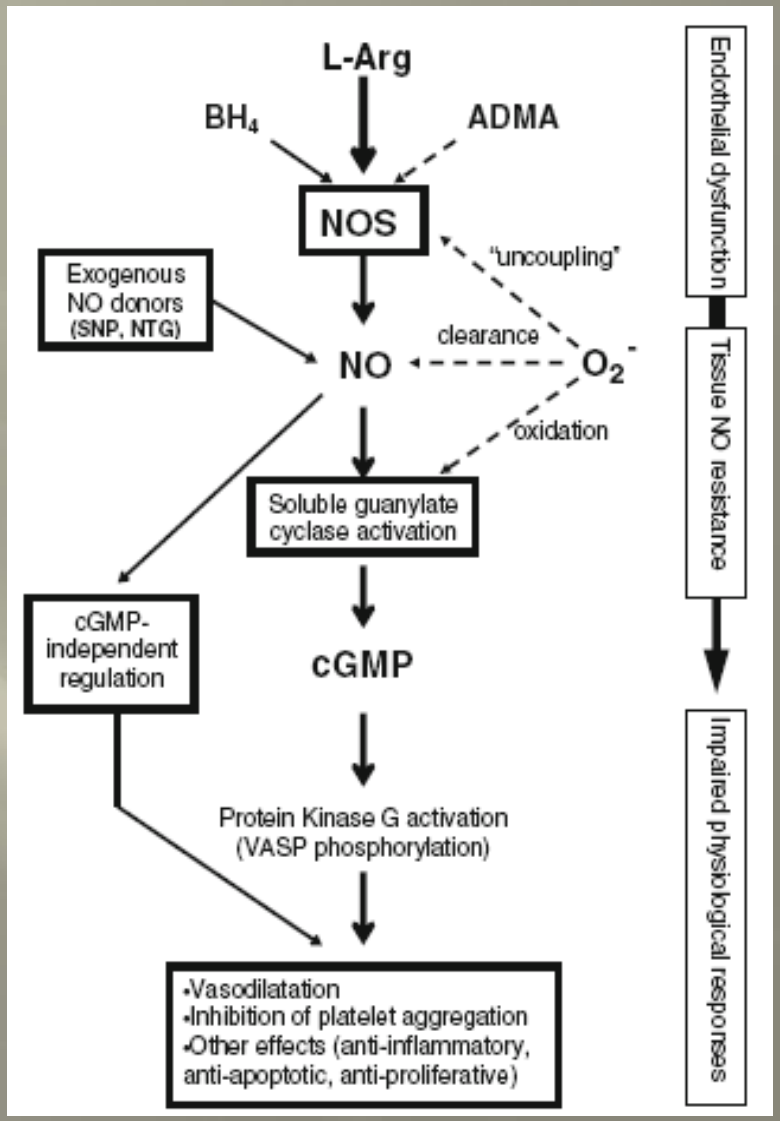
Characteristic	Rate of HRPR		p Value
	Characteristic Present	Characteristic Absent	
Men	32.3%	47.5%	0.012
Non-Caucasian ethnicity	55.6%	33.4%	0.008
Diabetes mellitus	42.5%	32.0%	0.044
β-Blocker use	38.6%	28.8%	0.065
Nitrate use	41.3%	34.1%	0.242
Proton-pump inhibitor use	42.1%	32.3%	0.061
Current smoker	19.4%	37.0%	0.049

Price et al. Am J Cardiol 2009;103:1339 –1343

- Nitrates stimulate endogenous endothelial NO by releasing NO in vivo that can activate platelet guanylyl cyclase, leading to an increase of platelet cGMP.

- As a result, an agonist-induced calcium flux is suppressed, which in turn leads to a reduction of fibrinogen binding to the platelet glycoprotein IIb/IIIa receptor.

- As fibrinogen binding is essential for bridging platelet aggregation, its inhibition results in an inhibition of platelet function.



Rajendran et al. Cardiovasc Drugs Ther 2008;22:193–203

Methods I

- ✓ Prospective, randomized, single-center, single-blind, investigator-initiated study
- ✓ Patients with stable coronary disease will be randomized in a 1:1 ratio to receive intravenous nitrates (0.01 – 0.2mgr/min) or placebo for 1 hour, 24 hours after coronary angioplasty
- ✓ Platelet reactivity will be assessed with the Verify Now assay and Multiplate analyzer:

A. Before (iv) administration
B. Immediately after (iv) administration
C. 24 hours after (iv) administration

Methods II

Inclusion criteria

- age 18-75 years
- patients with stable coronary disease who receive dual antiplatelet therapy and undergo coronary angioplasty
- written informed consent

Exclusion criteria

- pregnancy
- major periprocedural complications
- PLT<100.000
- Ht<30% or Ht>50%
- IIB/IIIA inhibitors
- SBP<90mmHg
- HOCM
- Chronic use of nitrates
- Glaucoma

Primary end point

Final PRU and AU*min value difference between patients who receive nitrates vs placebo

- Thank you

✓The potentially beneficial effects of nitrates could be negated by the development of tolerance and the generation of deleterious oxidative stress causing endothelial dysfunction during continuous nitrate administration.

✓Mechanisms contributing to this phenomenon may be a nitrate-induced stimulation of vascular (mitochondrial) superoxide and/or peroxynitrite production and the ensuing inhibition of ALDH-2, leading to impaired biotransformation of GTN.