FFR

Hyperemia and Standardization

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Hyperemic Stimuli

Why ?
How ?
FAQ !

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Why?

1. General concept of stress test (as opposed to “rest test”)
2. Standardized measurements (as opposed to “moving target”)
3. Rest vs hyperemia = window towards the microvasculature
4. All clinical outcome data are based on hyperemic data (FFR)
General concept of stress test
Mild Aortic Stenosis

- Rest
  - CO 4.8 L/min
  - \( \Delta P = 17 \text{ mm Hg} \)

- Dobutamine
  - 40 µg/kg/min
  - CO 8.1 L/min
  - \( \Delta P = 21 \text{ mm Hg} \)
General concept of stress test

Diabetes

Oral Glucose Tolerance Test:
75 g of sugar to be drunk within 5 minutes

<table>
<thead>
<tr>
<th>Mg/dL</th>
<th>Normal</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>2 hours</td>
<td>100</td>
<td>&gt;200</td>
</tr>
<tr>
<td>4 Hours</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

Cardiovascular Center Aalst
General concept of stress test
The Wind Tunnel
Why?

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The Control of Resting Myocardial Blood Flow

The "resting state" in biology is wishful thinking of biologists

"Rest" is almost never "steady state"

Adapted from D.J.G.M. Duncker
The Control of Resting Myocardial Blood Flow
Why?

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Hyperemia
A window towards the microvasculature

Resting gradient is similar but the hyperemic gradient is very different

Largely due to a difference in microvascular function
Risk factors:

- Dyslipidemia
- Family history of CAD
- Hypertension
- Obesity

Clinical presentation

- NSTEMI
- LVH on angiography
Hyperemia
A window towards the microvasculature

Large resting gradient which does not increase during hyperemia

Suggests microvascular dysfunction
Why?

1. General concept of stress test (as opposed to “rest test”)
2. Standardized measurements (as opposed to “moving target”)
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4. All clinical outcome data are based on hyperemic data (FFR)
How?

“Keep it Simple and Standardized”

The KISS principle
Maximal Vasodilation

**Epicardial**
- Conductance
- Arteries > 550 µ

**Microvasculature**
- Resistance
- Arteries < 550 µ

*Vasospasm*  
*Autoregulation*
Maximal Vasodilation

1. Nitrates ➔ Epicardial arteries

2. Adenosine ➔ Microvasculature

- **IV**: 140 µg/kg/min
- **IC**: 100 – 200 µg in bolus
Maximal Vasodilation

1. Nitrates ➔ Epicardial arteries

2. Adenosine ➔ Microvasculature

3. Papaverine
   - inhibition of phosphodiesterase ➔ cyclic adenosine MP ↑

4. Regadenoson
   - precursor of adenosine

5. Apadenoson
   - precursor of adenosine

6. Binodenoson
   - precursor of adenosine

7. Nitroprusside
   - NO pathways direct non-selective vasodilator

8. Nicorandil
   - ↑ guanylate cyclase to increase formation of cyclic GMP

9. Dopamine
   - $\beta_1$-agonist ➔ ↑ $O_2$ consumption ➔ adenosine ↑

10. Exercise
    - Adren stimulation ➔ ↑ $O_2$ consumption ➔ Adenosine ↑

11. Coronary occlusion
    - Ischemia ➔ release of adenosine
Adenosine: Mechanisms of Action

**Target organs**
- Coronary arteriolar smooth muscle cells
- Renal arteries (organ level)
- Peripheral and central nervous system
- Myocardium
- Cardiac Conduction system
- Respiratory tract
- Fibroblast, Adipocytes, Immune System

**Receptors (A_1, A_{2A}, A_{2B}, A_3)**
- A_{2A}
- A_1
- A_1 A_{2A}
- A_3
- A_1
- A_2B

ADO 40 µg bolus in Renal Artery

ADO 40 µg bolus in LAD

Half Life = 4 to 10 s
Maximal Vasodilation

1. Nitrates $\rightarrow$ Epicardial arteries

2. Adenosine $\rightarrow$ Microvasculature

- IV: 140 µg/kg/min
- IC: 100 – 200 µg in bolus
Adenosine IV
Specificities of IV Adenosine (140 µg/kg/min)

1. Preferred route when a pressure pull back is needed

2. Induces a brief increase in systemic pressure followed by a decrease in systemic pressure by 10-20%

3. Is almost uniformly accompanied by a burning sensation

4. Fluctuation of the \( P_d/P_a \) ratio are observed in some cases

5. A-V blocks are relatively frequent, always transient
Adenosine IV
“Classic Appearance”

Adenosine IV 140 µg/kg/min

STOP
Adenosine IV

“Humped Appearance”
Adenosine IV: Femoral or Hand vein?
Time to “Smart Minimum”

Cumulative distribution (%)

- 84% within 2 minutes
- 75% within 99 seconds
- 50% within 74 seconds
- 25% within 54 seconds

Time to smart minimum FFR (seconds)

- 159 seconds
- 89 seconds
- 51 seconds

Nils P Johnson et al JACC Interv 2015 In Press
Repeatability of FFR ("Smart Minimum")

- **Fractional flow reserve (FFR):**
  - $r^2 = 98.2\%$
  - Coefficient of variation 2.5%

- **Coronary pressure (Pd):**
  - $r^2 = 83.1\%$
  - Coefficient of variation 9.9%

- **Heart rate (HR):**
  - $r^2 = 60.3\%$
  - Coefficient of variation 11.9%

- **Aortic pressure (Pa):**
  - $r^2 = 67.3\%$
  - Coefficient of variation 9.8%
FAQ

Useful to increase the dose of IV ado > 140 µg/kg/min ?

NO
Is it Useful to increase the dose of IV ado > 140 µg/kg/min?
Is it Useful to increase the dose of IV ado > 140 µg/kg/min?

- 12 patients
- Increasing dosages of ATP intravenously (from 0 to 280 µg/kg/min)
Adenosine IC
IC Adenosine: reproducible but shortlasting
Dose-Response Curve of IC Adenosine

Left coronary artery

Right coronary artery

200 µg

100 µg

Adjej J, Toth G et al. 2015
Hemodynamic Effect of IC Adenosine

Left coronary artery

Right coronary artery

Time to return to baseline (s)

Duration of the hyperemic plateau (s)

Changes in Blood pressure (%)

Changes in heart rate (%)

Intracoronary adenosine dose (µg)
Effect on Blood Flow Velocity (% of Max) of Various Stimuli

Adjedj J, Toth G et al. 2015
Specificities of IC Adenosine (100-200 µg)

1. Can be used in the vast majority of lesions
2. Short half live
3. Rare AV blocks, always transient
4. Extremely reproducible: do it twice (or more!)
## Cost of Adenosine

<table>
<thead>
<tr>
<th>Adenosine Product</th>
<th>Countries Provided</th>
<th>Concentration</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocor, Sanofi</td>
<td>Belgique, Bulgarie, Danemark, Royaume Uni, Hongrie, Irlande, Pays-Bas, Portugal</td>
<td>3 mg/ml (2ml)</td>
<td>6-16 €</td>
</tr>
<tr>
<td>Krenosin, Sanofi</td>
<td>France, Italie, Suisse</td>
<td>3 mg/ml (2 ml)</td>
<td>6-16 €</td>
</tr>
<tr>
<td>Adenoscan, Sanofi</td>
<td>France, Allemagne, Italie, Japon, Portugal, Espagne, USA, Royaume Uni Allemagne</td>
<td>3 mg / ml (10 ml)</td>
<td>30-50 €</td>
</tr>
<tr>
<td>Adenosin, Life Medical</td>
<td></td>
<td>5 mg/ml (10 ml)</td>
<td>26 €</td>
</tr>
<tr>
<td>Adenosin Injection, USP</td>
<td>Canada</td>
<td>3 mg/l (2 ml)</td>
<td>11 C$</td>
</tr>
</tbody>
</table>

Adenosine prepared by your own pharmacy:
- IV ± 8 € / seringue
- IC ± 0.30 € / bolus

*Courtesy of Nicolas Amabile, MD, Jan 2015*
Quality of the Pressure Recordings

- Recording of 12 beats steady state at rest
- Very short (1-2 s) injections of adenosine
- Total recording of 45-60 s
Rest or Hyperemia?
When $P_d/P_a$ at rest $> 0.90$, hyperemia?

$P_d/P_a = 0.96$

FFR = 0.62
Conclusive Remarks

1. Hyperemia is mandatory to “interrogate” a lesion properly

2. Can be obtained very easily, safely, cheaply, ...

3. Provided it is standardized in each laboratory
FAQ

✓ When $P_d/P_a$ at rest > 0.90, do we have to induce hyperemia?
✓ When $P_d/P_a$ at rest < 0.80, do we have to induce hyperemia?
✓ Useful to increase the dose of IV ado > 140 µg/kg/min?
✓ Useful to increase the dose of IC ado > 200 µg (bolus)?
✓ Is the burning sensation related to ischemia?
✓ Are some patients resistant to Adenosine?
✓ Can Papaverine be used instead of Adenosine?
✓ Is hyperemia expensive?
✓ What to do with radial procedures?
✓ Interference with some medications?
✓ Is adenosine contraindicated in patients with lung disease?
FAQ

When $P_d/P_a$ at rest > 0.90, do we have to induce hyperemia?

YES

$P_d/P_a = 0.96$

FFR = 0.62
FAQ

When Pd/Pa at rest < 0.80, do we have to induce hyperemia?
When $P_d/P_a$ at rest < 0.80, do we have to induce hyperemia?
FAQ

Useful to increase the dose of IV ado > 140 µg/kg/min?

NO
Increasing the dose above 140 µg/kg/min decreases systematic BP and increases the thoracic pain.
FAQ

Useful to increase the dose of IC ado > 200 µg (bolus) ?

720 µg decreases $P_d/P_a$ a bit further w/o any decrease in BP, any increase in HR and no heart blocks ????

De Luca et al JACC Interv 2011
Is the burning sensation related to ischemia?

NO

Adenosine is an algesic substance which stimulates the same nerves than those responsible for angina ... which is also due to the local release of adenosine during ischemia.

Sylven C. Cardiovasc Drugs Ther 1993;7:745
FAQ

Are some patients resistant to Adenosine?

NO,

Resistance to exogenous Adenosine does not exist
FAQ

Can Papaverine be used instead of Adenosine?
Papaverine IC
16 mg IC in LCA  12 mg IC in RCA
Papaverine IC
16 mg IC in LCA   12 mg IC in RCA
Papaverine IC
16 mg IC in LCA  12 mg IC in RCA
Papaverine IC
16 mg IC in LCA   12 mg IC in RCA
Is hyperemia expensive?

... NOT REALLY:

0.12 € / bolus of 100 µg IC;  0.24 € / bolus of 200 µg

1.34 € / syringe needed for approx 15 minutes of IV administration
FAQ

What to do with radial procedures?

IC BOLUS

IV adenosine INFUSION

IV Regadenosone BOLUS
FAQ

Some medications interfere with Adenosine

- Beta-blockers
- Alpha-blockers
- Caffeine
- Ticagrelor
- ACE-inhibitors
Effect of Caffeine on FFR

Before Caffeine: 0.76
After Caffeine: 0.75

Aqel RA et al Am J Cardiol. 2004
Beta-Adrenergic Blockade and Myocardial Flow

Changes in Myocardial Blood Flow

- Carvedilol
- Metoprolol

Rest
- Hyperemia

Effect of α-Blockers on Diameter and FFR

Phentolamine

Pre Post

MCL (mm)

P=NS

Pre Post

FFR

P=0.03

Pre Post

P=0.0001

Pre Post

P=NS

E. Barbato et al EHJ 2004
FAQ

Is adenosine contraindicated in all patients with lung disease?

NO

1. Adenosine is strictly contraindicated in asthma
2. Adenosine is NOT contraindicated in COPD
Regadenoson IV peripheral
**Regadenoson ( = Rapiscan ® )**

Regadenoson as single peripheral i.v. bolus 400 µg

- maximum hyperemia within 60 sec and lasting for at least 30 seconds (sufficient for pull-back recording)

- can be safely repeated after 10 min

- hyperemia completely comparable to i.v. adenosine

- ideal in radial procedures or ad-hoc FFR

*Van Nunen et al EuroIntervention. 2014*
Regadenoson vs Adenosine (N=100)

- Mean Difference 0.00 ± 0.01

Van Nunen et al EuroIntervention. 2014