Digital reactive hyperemia (Endo-PAT 2000), a novel diagnostic test for the assessment of endothelial function

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Endothelium as a CVD risk factors transducer

Traditional Risk Factors

Non-Traditional Risk Factors

Genetic Predisposition

Unknown Factors

Local Factors (Shear)

Endothelial Dysfunction: “The Risk of the Risk Factors”

Vascular Contraction

Vascular Remodelling

Inflammation

Thrombosis

Plaque Rupture

Bonetti et al. ATVB 2003; 23:168
Four questions about endothelial function

• Can we measure it specifically and accurately

• Is it associated with CVD risk factors

• Is it associated with CVD
Quantitative coronary angiography

Intracoronary agonist infusion with quantitative coronary angiography

Advantages
- Direct quantification of endothelial function in the vascular bed of interest
- Allows for mapping dose-response relationships of endothelial agonists and antagonists
- Allows for examination of basal endothelial function (with NOS antagonist infusion)

Disadvantages
- Invasive
- Expensive
- Carries risks inherent with coronary artery catheterization
  (stroke, MI, infection, vascular injury)
Venous Occlusion Plethysmography

Brachial artery catheterization with venous occlusive plethysmography

Advantages
- More accessible circulation than coronary arteries
- Allows for mapping dose-response relationships of endothelial agonists and antagonists
- Allows for examination of basal endothelial function (with NOS antagonist infusion)

Disadvantages
- Invasive
- Risk of median nerve injury, infection, vascular injury
Brachial Flow Mediated Dilation

Brachial artery ultrasound with FMD

Advantages
  Noninvasive
  Safer and faster than either invasive method
  Reactivity correlates to endothelial dysfunction in coronary circulation
  Flow is a physiological stimulus for vasodilation unlike agonists such as acetylcholine

Disadvantages
  Poor resolution relative to arterial size
  Variability in measurements
  Highly operator-dependent
Endo PAT system overview

The Endo-PAT 2000
Peripheral arterial tone

PAT - Peripheral Arterial Tone

PAT Amplitude $= \Delta$ Arterial Pulsatile Volume

Only the Y-axis changes are utilized in calculating the PAT signal
Endo PAT probe

Functional Overview of PAT Probe

- Sensor Cap
- Proximal Annular Cuff
- Air tubes
- Electrical link

Both regions inflated to a sub-diastolic pressure:
1. Unloads arterial wall tension
2. Anti venous-pooling region
3. Better signal-to-noise ratio
Pressure-Volume Compliance Curve

Arterial Pressure vs. Volume compliance curve

- **Small volume change**
  - Pressure swing: 40 mmHg
  - External pressure: 70 mmHg

- **Large volume change**
  - Pressure swing: 40 mmHg

A
- **External pressure**: 0 mmHg

B
- **External pressure**: 70 mmHg

*Transmural pressure* (pressure inside artery - external pressure)
Example of finger PWA recording

Examination Protocol

- Study performed in a thermoneutral environment
- Overnight fasting
- Refrain from smoking, alcohol and caffeine on the day of the examination
PAT reactive hyperemia protocol

PAT Reactive Hyperemia Protocol

Cuff inflation
60mmHg > systole pressure

Baseline period
Occlusion
Test period

3 min
5 min
1 min
**PAT ratio**

Control Arm

Baseline period  Occlusion  Test period

Occluded Arm

\[
\text{PAT ratio} = \frac{A}{B} \times \frac{C}{D} \times \text{Baseline correction factor}
\]

Test/baseline ratio of tested arm  Test/baseline ratio of control arm
Correcting for baseline diameter

PAT Response Vs. Baseline Amplitude

PAT response vs baseline amplitude (10 pt av) n=310

$y = -0.438 \ln(x) + 4.0978$

$R^2 = 0.8256$

Average BL value

$\pm$ SEM
Systemic correction

Example of the Systemic Correction

The reactive hyperemia in the Occluded arm is cancelled by the systemic vasoconstriction as seen in the Control arm.
PAT Measurement with Reactive Hyperemia

- Contra-lateral arm serves as control
- Correction for baseline size
- PAT is highly sensitive - indicates effectiveness of occlusion
- No need for local or systemic pharmacological interventions
Results

Occluded period

Control arm

Result: 1.87
Endo-PAT 2000 Advantages

Non-invasive

• Easy to use, non user-dependent
• Automatic analysis
• Supports both clinical and research applications
• Reliable and reproducible
• FDA cleared and CE marked & CSA certified
Advantages of Endo-PAT2000 Vs. FMD

• Controls for systemic effects
• Normalizes for baseline amplitude
• Non user-dependent – technician operated & automated analysis
• Data archiving supports research applications
• Occlusion quality assessment
• Better reproducibility
CASE 1

M/ 53

HTN (+), DM (-), Smoking (-)

Endo-PAT index 2.364

FMD % Diameter-RH 7.3

% Diameter-NTG 12.2
CASE 1

FMD

Baseline

0.410 cm

Reactive hyperemia

0.440 cm : 7.3 % ↑

NTG

0.460 cm : 12.2 % ↑
CASE 2

M/ 44

HTN (+), DM (-), Smoking (+)

Endo-PAT index 2.00

FMD % Diameter-RH 4.1

% Diameter-NTG 4.1
CASE 2

FMD

Baseline 0.393 cm

Reactive hyperemia

0.409 cm : 4.1 % ↑

NTG

0.409 cm : 4.1 % ↑
Role of NO in Reactive Hyperemia

• Performed by Prof. Gerhard-Herman et al., Harvard Med School
• A prospective study of Reactive Hyperemia mechanism
• 21 normal patients before and after L-NAME (eNOS inhibitor)
• 20 control patients before and after saline
• PAT was used to measure endothelial response
Harvard Study - Results

The Effect of Nitric Oxide Inhibition on PWA Following Release of Occlusion

Increase in Pulse-Wave Amplitude (%)

PAT Vs. FMD

N=89

Linear regression evaluation of the relation between PAT hyperemia ratio and FMD of the brachial artery ($r = 0.55$, $P < .0001$).

PAT Vs. FMD

\[ p < 0.001 \text{ for trend} \]

Four questions about endothelial function

• Can we measure it specifically and accurately

• Is it associated with CVD risk factors

• Is it associated with CVD
PAT hyperemia and CV risk factors


Number of cardiac risk factors

PAT HYPEREMIA

R = 0.3, P = 0.02
CHD risk vs. Endo-PAT index

Relative risk

- $R = 0.375, \ P = 0.003$
- $R = 0.361, \ P = 0.004$

Endo-PAT index vs. Log Endo-PAT index

YUMC data 2005
Four questions about endothelial function

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PAT Hyperemic Response – Mayo Study
Compared to Coronary Response to Acetylcholine

Normal Endothelial Function

Baseline

Acetylcholine

PAT

Abnormal Endothelial Function

Bonetti PO et al. J Am Coll Cardiol 2004;44:2137-2141
PAT Hyperemic Response Compared to Coronary Response to Acetylcholine

N=94

(Abnormal if CBF<50%)

Endo-PAT2000
Sensitivity=80%
Specificity=85%

Bonetti PO et al. J Am Coll Cardiol 2004;44:2137-2141
PAT hyperemia and CAD

P=0.004


(Exercise Myocardial Perfusion Imaging)
Conclusion

• Reactive hyperemia PWA is a novel method to measure endothelial function

• It is easy to use and relatively objective

• The gold standard is still FMD: More clinical experience is needed with regards to clinical studies