Plasma endothelin and adrenomedullin are associated with coronary conduit and microvascular function

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☐ I have no disclosures
Endothelin (ET-1) and adrenomedullin (ADM) are potent vasoactive peptides.

ET-1 is a vasoconstrictor and an elevated level is associated with cardiovascular disease (CVD) (Schneider et al., 2000).

ADM is a vasorelaxant and may result in protection from atherosclerosis in experimental studies.
Endothelin

- ET is an endothelium-derived, 21-amino acid peptide with potent vasoconstrictor activity.
- After binding to its receptors on vascular smooth muscle, ET acts directly on voltage-dependent membrane ion channels (Yanagisawa et al., 1988).
- ET has a physiological role in regulation of vascular tone (Haynes and Webb, 1994).
- It may play an important part in the pathophysiology of atherosclerosis (Lerman et al., 1995, Burnett, 1997).
- An increased level of ET in patients with atherosclerosis may contribute to the alteration in vascular tone and remodelling.
Adrenomedullin

- ADM is a 52-amino acid potent vasorelaxant peptide that elicits a long lasting hypotensive effect (Kitamura et al., 1993).
- Endothelial and smooth muscle cells have been shown to produce ADM (Sugo et al., 1994) dilating vessels and competing with ET (Isumi et al., 1998).
- ADM infusion into the coronary arteries enhances CBF and dilates the coronary arteries, via an increase in nitric oxide production (Ueda et al., 2005), activation of K(+) channels (Terata et al., 2000) and activation of adenosine receptors (Sabates et al., 1997).
- ADM promotes endothelial cell proliferation and migration and elicits vascular regeneration (Miyashita et al., 2003).
Aims

- We sought to determine the relationship of ET-1 and ADM with coronary conduit and microvascular resistance.
Methods

- Stable patients with chest pain syndromes having clinically indicated coronary angiography were recruited (n=32).
- Plasma ET-1 and ADM level were measured by radioimmunoassay.
- Coronary artery measures were assessed by QCA and coronary pressure guidewire.
cFMD was defined as percentage increase in coronary diameter during maximal hyperaemia as assessed by (QCA).

\[
cFMD = \left[ \frac{\text{hyperaemic diameter} - \text{baseline diameter}}{\text{baseline diameter}} \right] \times 100
\]
CFR is defined as the ratio of maximum blood flow achieved by hyperaemic stimuli and calculated as resting $T_{mn}$ / hyperaemic $T_{mn}$

IMR is defined as $P_d \times T_{mn}$ at maximum hyperaemia, which is the time required for the indicator (3 mL normal saline of room temperature) to travel from the injection site (the tip of the guiding catheter) to the distal sensor.
Pearson’s correlation and linear regression analysis were used to determine the relationship between plasma biomarkers and coronary measures.
Results

- Mean age was 66 ± 9 year-old with 69% male
- The sample included patients with
  - hypertension (75%)
  - dyslipidaemia (84%)
  - diabetes (34%)
  - current smokers (13%)
  - prior coronary artery disease (66%)
- Mean body mass index (BMI) was 33 ± 6 kg/m².
## Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adrenomedullin</th>
<th>Endothelin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Flow Reserve</td>
<td>$r=0.50$ ($p=0.04$)</td>
<td>ns</td>
</tr>
<tr>
<td>Index of Microcirculatory Resistance (units)</td>
<td>ns</td>
<td>$r=0.57$ ($p&lt;0.01$)</td>
</tr>
<tr>
<td>Coronary Flow Mediated Dilatation (%)</td>
<td>$r=0.62$ ($p=0.01$)</td>
<td>ns</td>
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</table>
For each 1 pmol/L increase in ET-1, IMR increased by 7 units (95% CI 2.8, 10.5; p<0.01).

For each 1 pmol/L increase in ADM, CFR increased by 0.20 (95% CI 0.01, 0.40; p=0.04) and

For each 1 pmol/L increase in ADM, cFMD increased by 0.92% (95% CI 0.29, 1.55; p=0.01).
After adjustment for age, gender, mean blood pressure, hypertension, diabetes, dyslipidaemia, BMI, and serum glucose and cholesterol, the relationship between ADM and CFR was no longer significant, however, the association between ET-1 and IMR and between ADM and cFMD remained significant.

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<tr>
<td>Index of Microcirculatory Resistance (units)</td>
<td>ns</td>
<td>β=5.7 (p=0.01) (1.4, 10.0)</td>
</tr>
<tr>
<td>Coronary Flow Mediated Dilatation (%)</td>
<td>β=0.79 (p&lt;0.01) (0.45, 1.13)</td>
<td>ns</td>
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Higher adrenomedullin was associated with larger coronary FMD, but had no association with IMR.

Higher endothelin-1 was associated with higher IMR, but had no association with coronary FMD.

ADM and ET-1 may have different effects on coronary conduit and microvascular function in stable patients with chest pain syndromes.

These vasoactive factors may therefore play a role in regulating the coronary circulation in disease states and might be used as a therapeutic target.

- Long term (6 months) treatment with ET-A receptors antagonist improves coronary blood flow but not CFR or vessel diameter, in patients with chest pain but no obstructive coronary artery disease.
- This work supports the role of endogenous endothelin system in the regulation of endothelial function in early atherosclerosis.
- ET-A receptor blockade improves coronary microvascular function.
**Clinical implication**

- Van Guilder et al, Hypertension, 2007, 50 (2), 403-409
- ET-1 increases with age, however, it can be reduced with regular aerobic exercise

- We have also shown in our lab that ET-1 was increased
  - age (10 years) \( \beta = 0.16 \) (0.08, 0.23) \( p<0.01 \)
  - DMII \( \beta = 0.21 \) (0.04, 0.37) \( p=0.01 \)
  - CVD risk score (1%) \( \beta = 0.02 \) (0.01, 0.03) \( p<0.01 \)
  - SBP (10mmHg) \( \beta = 0.07 \) (0.02, 0.11) \( p<0.01 \)
  - Creatinine (10 umol/L) \( \beta = 0.13 \) (0.10, 0.15)
Nakamura et al. 1997, Circulation
- Infusion of ADM into human forearm increased FBF in the control group (healthy individuals) but not to the same level in CHF group indicating impaired NO production.

- Infusing ADM into healthy individuals forearm increased FBF at a plasma level similar to those found in heart failure, indicating that endogenous ADM in heart failure increased to reduce vascular resistance.
Kobayashi, Am. H. J, 1996

ADM increased in AMI and continue over 3 weeks follow up compared to control
Clinical implication

- Nakayama et al, Peptides, 1999
  - Hypoxia induced increase of ADM by 5 folds in cultured coronary arteries

  - In vitro study demonstrated that coronary arteries dilate in response to infusion of ADM
Clinical implication

  - ADM correlated with MBP and PWV (tonometry)

- Nishida et al. Peptides, 2008
  - Increased ADM might be used as a predictor of CVD events (121 patients, CVD risk factors, 3.5 years FU)

- Kita et al. Hypertension Research, 2010
  - Infusion of ADM decreased PWV and BP, and increased FBF, HR and CO
In our lab ADM inversely related with

- Smoking $\beta = -1.13$ (-2.25, -0.01) ($p=0.05$)
- Triglyceride (1mmol/L) $\beta = -0.95$ (-1.74, -0.17) ($p=0.02$)

Clinical implication
Funding and Grants

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