Supplementary Material

Supplementary Methods

Experimental protocol schematics

Experiment 1

12 study participants

Baseline MBFR

Control (n=6) Insulin-dextrose (n=6)

Commence insulin-dextrose (1.5mU/kg/min insulin + 25% dextrose)

Repeat MBFR at 30, 60, and 120 minutes

Experiments 2 and 3

22 healthy participants  MetS participants  T2DM participants

Insulin Dose Group (mU/kg/minute)

n=7  n=8  n=7  n=7

0.5mU  3.0mU  1.5mU

Baseline MBFR

Commence insulin-dextrose

MBFR at 60 minutes
Experiment 4

- **ST-elevation MI**
  - Emergent PCI
  - **Baseline MCE**
  - Insulin 1.5mU/kg/min + 25% Dextrose
    - Repeat MCE at 30, 60, 120 mins
    - Discontinue Insulin, wean Dextrose
  - Guideline-directed therapy (control)
    - Repeat MCE at 30, 60, 120 mins
Recruitment flow diagrams

Experiment 1

14 volunteers screened

1 had previous reaction to ultrasound contrast

13 underwent randomization

6 assigned to normal saline

6 completed controls

7 assigned to insulin-dextrose

1 developed bronchospasm to adenosine

6 completed insulin-dextrose infusion

Experiments 2 and 3

34 volunteers screened

1 abnormal exercise stress echo

6 Type 2 diabetes

5 Metabolic syndrome

22 healthy participants underwent randomization

7 assigned to 3.5mU/kg/min insulin-dextrose

7 assigned to 0.5mU/kg/min insulin-dextrose

8 assigned to 3.0mU/kg/min insulin-dextrose

18 received 1.5mU/kg/min insulin-dextrose

18 completed 1.5mU/kg/min insulin-dextrose

7 completed 0.5mU/kg/min insulin-dextrose

8 completed 3.0mU/kg/min insulin-dextrose
Experiment 4

23 patients eligible for randomization

1 declined participation
1 insufficient intravenous access

21 underwent randomization

10 assigned to insulin-dextrose
11 assigned to control

1 corrupted echo data

10 insulin-dextrose patients included in analysis
10 controls included in analysis
List of regular medications taken by participants at time of enrolment

Experiment 1: None

Experiment 2:
0.5mU/kg/minute insulin group: 1 Aspirin, 2 Statin
1.5mU/kg/minute insulin group: 1 Aspirin, 1 Statin, 1 Angiotensin Receptor Blocker or ACE Inhibitor
3.0mU/kg/minute insulin group: 1 Statin.

Experiment 3:
Metabolic Syndrome group: 1 Aspirin, 1 Statin, 2 Angiotensin Receptor Blocker or ACE Inhibitor
Type-2 diabetes mellitus group: 2 Aspirin, 2 Statin, 2 Angiotensin Receptor Blocker or ACE Inhibitor, 4 Metformin, 1 Gliclazide, 3 Gliptin, 1 Empagliflozin, 1 long acting insulin
Adenosine / dipyridamole protocols

Dipyridamole was infused at 0.56mg/kg over 4 minutes to achieve hyperemia. Peak hyperemia occurs between 6 minutes and 10 minutes after commencing infusion.¹

Adenosine was infused at 140mcg/kg/min over a total of 6 minutes. Peak hyperemia occurs from 3 minutes after commencing infusion.
Metabolic Syndrome definition (International Diabetes Federation criteria 2005)  

Central Obesity (defined as waist circumference >94cm in males, >80cm in females)

plus any two of the following four:
- Raised triglycerides (>150mg/dL)
- Reduced HDL cholesterol (<40mg/dL in males, <50mg/dL in females)
- Raised blood pressure (systolic BP > 130 or diastolic BP >85 mmHg or treatment of previously diagnosed hypertension)
- Raised fasting plasma glucose (Fasting plasma glucose > 100mg/dL or 5.6mmol/L)
Supplementary Tables and Figures

Tables showing absolute MBF values in experiments 1 to 3

Experiment 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (mins)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Rest</td>
<td>5.51±2.05</td>
<td>3.23±1.85</td>
<td>2.98±0.86</td>
<td>3.49±0.94</td>
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<tr>
<td></td>
<td>Hyperemia</td>
<td>11.34±5.77</td>
<td>7.94±3.89</td>
<td>6.76±1.25</td>
<td>7.19±1.66</td>
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<tr>
<td>ID</td>
<td>Rest</td>
<td>4.36±3.08</td>
<td>3.89±1.63</td>
<td>3.52±1.40</td>
<td>4.07±1.28</td>
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<tr>
<td></td>
<td>Hyperemia</td>
<td>10.96±7.95</td>
<td>10.22±4.62</td>
<td>12.18±4.38</td>
<td>12.76±5.37</td>
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Values are mean±SD MBF (dB^2/s)

Experiment 2

<table>
<thead>
<tr>
<th>Insulin Dose</th>
<th>Time (mins)</th>
<th>0</th>
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</thead>
<tbody>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>Rest</td>
<td>2.62±1.84</td>
<td>3.65±1.63</td>
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<tr>
<td></td>
<td>Hyperemia</td>
<td>4.83±2.42</td>
<td>6.70±2.24</td>
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<tr>
<td>1.5</td>
<td>Rest</td>
<td>1.78±0.86</td>
<td>2.18±1.04</td>
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<tr>
<td></td>
<td>Hyperemia</td>
<td>4.18±1.93</td>
<td>5.75±2.34</td>
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<tr>
<td>3.0</td>
<td>Rest</td>
<td>2.34±1.79</td>
<td>3.39±1.82</td>
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<tr>
<td></td>
<td>Hyperemia</td>
<td>4.40±3.84</td>
<td>5.96±2.84</td>
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</table>

Values are mean±SD MBF (dB^2/s)

Experiment 3

<table>
<thead>
<tr>
<th>Diabetic State</th>
<th>Time (mins)</th>
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</tr>
<tr>
<td>Healthy*</td>
<td>Rest</td>
<td>1.78±0.86</td>
<td>2.18±1.04</td>
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<tr>
<td></td>
<td>Hyperemia</td>
<td>4.18±1.93</td>
<td>5.75±2.34</td>
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<td>MetS</td>
<td>Rest</td>
<td>2.47±0.39</td>
<td>3.08±1.27</td>
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<td>Hyperemia</td>
<td>4.74±1.14</td>
<td>8.07±2.71</td>
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<td>T2DM</td>
<td>Rest</td>
<td>4.03±1.78</td>
<td>3.61±3.41</td>
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<td>Hyperemia</td>
<td>6.13±2.91</td>
<td>5.52±4.47</td>
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*same data set as 1.5 dose group in Experiment 2

Values are mean±SD MBF (dB^2/s)
Table showing blood glucose and blood insulin levels in experiment 4 STEMI study patients who received insulin-dextrose infusion

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol)</td>
<td>7.9±2.6</td>
<td>7.9±0.7</td>
<td>7.9±0.9</td>
<td>8.4±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>62±53</td>
<td>340±276</td>
<td>361±285</td>
<td>493±361</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are mean±SD

**Experiment 4 Regional and Global MBF's (dB²/s)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (mins)</th>
<th>p value*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Control</td>
<td>Global MBF</td>
<td>6.64±5.20</td>
</tr>
<tr>
<td></td>
<td>Remote MBF</td>
<td>7.00±5.70</td>
</tr>
<tr>
<td></td>
<td>Ischemic MBF</td>
<td>7.71±9.42</td>
</tr>
<tr>
<td>ID</td>
<td>Global MBF</td>
<td>5.18±4.11</td>
</tr>
<tr>
<td></td>
<td>Remote MBF</td>
<td>4.59±3.49</td>
</tr>
<tr>
<td></td>
<td>Ischemic MBF</td>
<td>7.87±13.9</td>
</tr>
</tbody>
</table>

*Mixed linear model longitudinal time series.
Numerical values are mean±SD.
References