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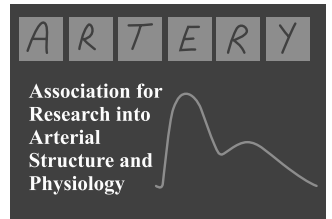
### **02.02: SHORT-TERM DAILY ADMINISTRATION OF L-ARGININE IMPROVES ENDOTHELIAL FUNCTION AND ARTERIAL STIFFNESS IN HEALTHY SMOKERS**

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## Abstracts of ARTERY 6, Athens, Greece, 22-23 September 2006

### Oral Presentations

#### Free Communications (Young Investigators)

##### 02.01

#### SIMVASTATIN PREVENTS ACUTE INFLAMMATION-INDUCED AORTIC STIFFENING IN HEALTHY VOLUNTEERS.

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**Objective:** Impairment of endothelial function following typhoid vaccine can be prevented with HMG CoA reductase inhibitors (statins). Whether statins can protect against large artery stiffening is unclear. We hypothesised that an acute inflammatory stimulus (typhoid vaccine) would induce endothelial dysfunction and arterial stiffening and that pre-treatment with simvastatin would attenuate this effect.

**Methods:** We studied 50 healthy volunteers (mean age  $26 \pm 5$  years). Aortic pulse wave velocity (aPWV) was derived using sequential carotid/femoral waveform recordings. Endothelial function we assessed using flow-mediated dilatation (FMD). Following baseline readings, subjects were randomised to take 40 mg simvastatin or placebo for 14 days. Haemodynamic readings were then repeated prior to and 8 hours following intramuscular injection *Salmonella typhi* 0.025 mg.

**Results:** Treatment with simvastatin caused a -19% reduction in total cholesterol and -30% reduction in LDL (both  $P < 0.001$ ). Following vaccination there was a significant increase in aPWV at 8 hours in the placebo group ( $5.80 \pm 0.87$  vs  $6.21 \pm 0.96$  m/s;  $p = 0.002$ ) when compared to the simvastatin group ( $5.74 \pm 0.72$  vs  $5.73 \pm 0.77$  m/s;  $p = 0.9$ ). There was a significant 30% reduction of FMD following vaccine in the placebo group ( $6.77 \pm 4.09$  versus  $5.20 \pm 2.83$ ;  $P = 0.028$ ). White cell count and neutrophils were significantly increased at 7hrs post vaccination in both groups (both,  $P < 0.05$ ).

**Conclusions:** We have demonstrated that acute inflammation increases large artery stiffness, and this process can be prevented by pre-treatment with simvastatin therefore statins appear to play a vasculo-protective role against inflammatory stimuli.

##### 02.02

#### SHORT-TERM DAILY ADMINISTRATION OF L-ARGININE IMPROVES ENDOTHELIAL FUNCTION AND ARTERIAL STIFFNESS IN HEALTHY SMOKERS

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**Background:** L-arginine, being the substrate for endothelial nitric oxide synthase, is essential for normal endothelial function. Endothelial dysfunction is accompanied by increased arterial stiffness. Aim of the study was to investigate in healthy smokers the effect of a short-term daily L-arginine administration on vascular function.

**Methods:** We studied the effect of a 3-day oral administration of L-arginine in 12 healthy smokers (aged  $24 \pm 3$  yrs) on 3 occasions (day 0: baseline measurements, day 1 and day 3). The study was carried out on two separate arms, one with L-arginine (7 g tid) and one with placebo according to a randomized, placebo-controlled, double-blind, cross-over design. All

measurements were performed one hour after L-arginine or placebo intake. Endothelial function was evaluated with flow-mediated dilatation (FMD) of the brachial artery. Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as a measure of wave reflections

**Results:** Compared to placebo, L-arginine led to a progressive increase of FMD (by 1.74%,  $p = \text{NS}$  at day 1 and by 1.96%,  $p < 0.05$  at day 3), indicating a favorable effect on endothelial function. Moreover, L-arginine intake led to a progressive decrease of PWV (by 0.32 m/s at day 1 and by 0.36 m/s at day 3, both  $p < 0.01$ ) and of AIx (by 5.1%,  $p < 0.01$  at day 1 and by 9.3%,  $p < 0.001$  at day 3), indicating a decrease in aortic stiffness and wave reflections.

**Conclusion:** Short-term daily administration of L-arginine, improves arterial performance in healthy smokers. These findings provide further insights into the cardiovascular profile of this molecule.

##### 02.03

#### AORTIC STIFFNESS AND WAVE REFLECTIONS ARE INCREASED IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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**Background:** Patients with COPD are at greater cardiovascular risk, even after allowing for confounding risk factors such as smoking. Arterial stiffness is an independent predictor of cardiovascular events. We have therefore assessed arterial stiffness in patients with COPD.

**Methods:** Patients with COPD ( $n = 75$ ), 42 male were studied when clinically stable, together with 42 age and gender matched healthy smokers (HS). The degree of airways obstruction was assessed using spirometry. Circulating IL-6 and TNF $\alpha$  soluble receptors (sr) I&II in all subjects and arterialised capillary pO<sub>2</sub> in patients were measured. Augmentation index (AIx) and Aortic pulse wave velocity (APWV) were determined as measures of wave reflections and aortic stiffness respectively using the Sphygmocor system.

**Results:** Patients, median (range) age 66 (45-86) years exhibited airways obstruction across a wide spectrum of severity. Mean arterial pressure (MAP) was similar in patients and HS, while AIx, APWV, peripheral pulse pressure, and circulating inflammatory mediators were all higher in patients than HS (see table). In patients, APWV was related to age ( $r = 0.63$ ,  $p < 0.0001$ ), IL-6 ( $r = 0.31$ ,  $p < 0.01$ ), TNF $\alpha$  srI ( $r = 0.27$ ,  $p < 0.05$ ), airways obstruction ( $r = 0.43$ ,  $p < 0.01$ ) and inversely related to pO<sub>2</sub> ( $r = -0.34$ ,  $p < 0.01$ ).

|                 | AIx            | APWV (m/s)     | Pulse pressure (mmHg) | IL-6 (pg/ml)    |
|-----------------|----------------|----------------|-----------------------|-----------------|
| Patients        | $30.1 \pm 8.2$ | $11.4 \pm 2.7$ | $62.5 \pm 15.9$       | $2.11 \pm 1.84$ |
| Healthy smokers | $25.9 \pm 6.2$ | $8.95 \pm 1.7$ | $56.5 \pm 11.5$       | $1.29 \pm 1.58$ |
| P value         | 0.002          | $p < 0.0001$   | 0.02                  | $p < 0.0001$    |

**Conclusions:** Aortic stiffness and wave reflections are increased in patients with COPD. Aortic stiffness is related to the severity of airways obstruction, systemic inflammation and hypoxia. This may explain the increased risk of cardiovascular disease in this population.