EFFECTS OF OXIDISED LDL ON NITRIC OXIDE AND ENDOTHELIN-1 PRODUCTION IN HUMAN MICROVASCULAR ENDOTHELIUM: ROLE OF THROMBOXANE A2 RECEPTOR

Valter Lubrano*, Simona Baldi°, Ele Ferrannini°, Antonio L’Abbate# and Andrea Natali°

*C.N.R. Institute of Clinical Physiology, °Department of Internal Medicine, University of Pisa, #Scuola Superiore S. Anna, Pisa, Italy,

Abstract 4.EAS07.000173

LDL particles modulate the release of NO and endothelin-1 by the endothelium. To what extent these effects depend on LDL concentration and degree of oxidation and eventually what is the role of tromboxane A2 receptor is unknown.

HMEC-1 were exposed for 24-h to a) 3 concentrations (50, 100 and 200 µg/ml) of either native, low- or medium-oxidised LDL, b) 8-epi-PGF2α (F2–IP, 10⁻¹¹, 10⁻¹⁰, 10⁻⁹, and 10⁻⁸ M) either alone or with TXA₂ receptor blocker SQ 29.548 (10⁻⁶ M), c) native, low- and medium-oxidised LDL either alone or with SQ 29.548 (10⁻⁶ M). In all experiments intracellular eNOS, and NO₂/NO₃, endothelin-1 and interleukin-6 concentration in the medium were measured.

Both native and oxidised LDL induced a NO₂/NO₃ accumulation with dose and degree of oxidation acting synergistically; eNOS was stimulated only by oxidised LDL. F₂–IP, NO₂/NO₃ and eNOS with SQ 29.548 completely preventing these effects but only partially the effect of LDL. IL-6 was also synergistically stimulated by LDL dose and degree of oxidation but not by direct exposure to F₂–IP nor was affected by SQ 29.548. Both native and oxidised LDL stimulated endothelin-1 production independently of dose or degree of oxidation. F₂–IP had a modest stimulatory effect while the effect of SQ 29.548 was evident only with oxidised LDL.

In HMEC-1 LDL dose and degree of oxidation synergistically stimulate NO and IL-6 production and the effect on NO is largely mediated through the TXA₂ receptor. LDL simultaneously facilitate endothelin-1 production independently of the dose and degree of oxidation.