HYPERHOMOCYSTEINEMIA EXERTS AN ADDITIVE EFFECT ON ENDOTHELIAL DYSFUNCTION IN THE FOREARM OF ESSENTIAL HYPERTENSIVE PATIENTS

A. Virdis, S. Taddei*, L. Ghiadoni, H. Cardinal, S. Favilla, P. Duranti, G. Salvetti, A. Magagna, A. Salvetti*. Department of Internal Medicine, University of Pisa, Italy

To evaluate the possible relationship between hyper(H)homocysteinemia (HCY) and endothelial function in the forearm of essential hypertensive patients (EH), we studied in 28 normotensive subjects (NS, age: 50.2±10.8 years; blood pressure (BP): 124.0±7.4/80.2±3.5 mmHg, HCY:12.5±7.8 μmol/L) and 55 EH (age: 49.1±8.6 years; BP: 147.4±9.2/99.6±4.0 mmHg, HCY: 14.6±9.1 μmol/L) the forearm blood flow changes (FBF, strain-gauge venous plethysmography) induced by intrabrachial acetylcholine (ACH: 0.15, 0.45, 1.5, 4.5, 15 μg/100 ml/min), an END-dependent agonist, and sodium nitroprusside (SNP: 1, 2, 4 μg/100 ml/min), an END-independent agonist. We divided EH in two groups according to HCY plasma levels (HPLC method): normal HCY (<15: 10.4±2.2 μmol/L, N-HCY, n=39, BP: 147.3±9.7/99.2±3.3 mmHg), and high HCY (>15: 25.0±7.2 μmol/L, H-HCY, n=16; 48.5±10.6 years; BP: 148.3±8.4/100.2±4 mmHg); (p<0.01 vs N-HCY). EH showed a reduced (*p<0.01) VD to ACH (FBF%: 35±26, 90±49, 161±68, 251±63, 339±83), as compared to NS (FBF %: 41±21, 147±42, 252±58, 421±73*, 593±83*), while VD to SNP was similar in both groups. H-HCY EH showed a further reduced VD to ACH (FBF%: 14±14, 52±34, 121±45, 168±53*, 244±58*) as compared to N-HCY EH (FBF%: 8±9, 46±33, 145±39, 272±42, 379±67; *p<0.05), while VD to SNP was similar in both groups. In EH, HCY showed a significant inverse correlation with maximal response to ACH (r=-0.51, p<0.001), while no relation was observed with SNP (r=0.25, p=N.S.). Moreover, on multivariate analysis including total cholesterol, HDL and LDL cholesterol, glucose, age, systolic and diastolic BP, only HCY influenced (p<0.001) max VD to ACH.

In conclusion, this study suggests that in the forearm microcirculation, essential hypertension and H-HCY exert an additive effect in inducing endothelial dysfunction.

Key Words: Endothelium; homocysteine; nitric oxide; hypertension

ARE ABNORMAL HOMOCYSTEINE LEVELS IN ESSENTIAL HYPERTENSION RELATED TO PROGNOSIS AND ENDOTHELIAL DYSFUNCTION?

E. Edmunds, S.C. Martin, A.F. Jones, A.D. Blann, D.G. Böevers, G.Y.H. Lip. Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham. B18 7QH, UK

Elevated homocysteine levels are associated with venous and arterial thromboses and an adverse prognosis. We hypothesized that this may be due to increased thrombogenesis as a result of direct damage to the vascular endothelium. To investigate this hypothesis further venous blood was obtained from 83 patients with essential hypertension (43 male; mean age 54±15.9) and from 25 healthy controls (13 male; mean age 56±11.8). Homocysteine (HPLC) and von Willebrand factor (vWF, a marker of endothelial dysfunction) (ELISA) were measured in citrated plasma.

<table>
<thead>
<tr>
<th>Homocysteine</th>
<th>Hypertensives</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>median [IQR]</td>
<td>11.6 [9.0–16.7]</td>
<td>9.2 [7.5–11.8]</td>
<td>0.0001</td>
</tr>
<tr>
<td>VWF mean (sd)</td>
<td>114 (30)</td>
<td>98 (29)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

These patients were followed-up for a mean of 44.6 months (range 1–66). 17 subjects (22%) experienced a cardiovascular event (myocardial infarction, stroke or cardiovascular death). These individuals were older (mean age 65.1 vs 51.3 p=0.0002) and had hypertension for longer (15.6 vs 73 months p=0.018). They had no significant elevation in homocysteine (13.9 vs 11.4 μmol/L, p=0.07) or vWF (124 vs 112 iU/dL, p=0.014) levels.

There were no significant correlations between homocysteine or vWF.

Conclusion: Essential hypertension is associated with raised plasma homocysteine levels but there did not appear to be a significant relationship to endothelial damage (vWF) or prognosis.

Key Words: Hypertension; homocysteine; von Willebrand factor

BLUNTED REACTIVE HYPERAEMIA AND REDUCED t-PA RELEASE IN HYPERTENSIVE AND Atherosclerotic Men

G. Dell’Omo, L. Ferrini, F. De Negri, F. Carmassi, R. Pedrinelli, M. Marianni*. Dipartimento Cardio-Toracico & Medicina Interna, Università di Pisa, Italy

Background: Endothelial dysfunction increases atherosclerotic risk, but the reasons of this association are unclear. An interesting hypothesis postulates a direct relationship between defective endothelial-mediated vasomotion and reduced local release of tissue plasminogen activator (t-PA), the key fibrinolytic control mechanism in man. However, the concept, based upon data obtained by infusing pharmacological concentrations of endothelial-mediated vasodilators, needs testing under more physiological conditions. For this reason, we evaluated t-PA release (REL) during reactive hyperaemia (RH), a physiological local vasodilator response mediated by endothelial-derived compounds produced in response to ischemia.

Methods: Forearm blood flow (FBF, strain-gauge plethysmography), arterial (A) and venous (V) t-PA and plasminogen activator inhibitor (PAI)-1 antigen concentrations (ELISA) to derive REL (V-A × FBF), were measured in the right forearm of 7 uncomplicated males (CON, 42±9 yrs, total cholesterol: 190±40 mg/dl) and 6 older (60±8 yrs), hypercholesterolemic (260±15 mg/dl) male patients with atherosclerotic vascular disease (ATH), i.e. a group at high risk for endothelial dysfunction. Data were measured before

© 2000 by the American Journal of Hypertension, Ltd. Published by Elsevier Science, Inc.
and 1, 5, 10 minutes after release of a 10-min cuff inflation at the midpoint between systolic and diastolic values.

**Results:** (Means±SD or Medians&Range): Baseline (A) t-PA was higher in ATH than CON (18.6±6.2 vs 9.4±2.4 ng/ml, p<0.01). 1 min after cuff release, FBF (from 3.2±1.6 to 18.4±3 ml/min × dl⁻¹, p<0.001) and t-PA REL [from 1.4 (−7.4/8.3) to 49 (−38/195) ng/ml × min⁻¹ (p<0.02)] increased in CON, while minor FBF increases (from 2.9±0.7 to 4.7±1.3 ml/min × dl⁻¹, p<0.02) without changes in t-PA REL [from 0.4 (−30/10) to 6.3 (−44/54) ng/ml × min⁻¹] characterised ATH. PAI-1 REL did not change.

**Conclusions:** Blunted RH, a likely expression of dysfunctional endothelial-mediated vasomotion, is associated with reduced t-PA release in hypertensive and atherosclerotic men, possibly as a consequence of lesser production of endothelial derived metabolic products, although defective endothelial-mediated vasomotion, is associated with reduced t-PA release in hypertensive and atherosclerotic men, possibly as a consequence of lesser production of endothelial derived metabolic products, although defective endothelial-mediated vasomotion may perhaps explain the atherothrombotic tendency in presence of a dysfunctional endothelial-mediated vasomotion.

Key Words: Tissue plasminogen activator; endothelium; hypertension; reactive hyperemia

**ENDOTHELIAL FUNCTION IN LARGE AND SMALL ARTERIES IS CLOSELY CORRELATED IN HUMAN HYPERTENSION**

J.B. Park, F. Charbonneau, E.L. Schiffrin*. Clinical Research Institute of Montreal, Montreal, Quebec, Canada

Structure and function of blood vessels vary along the vascular tree, and alterations in hypertension are also different. The aim of this study is to determine whether noninvasive measurement of endothelial function in conduit arteries reflects that of subcutaneous resistance arteries measured in vitro. Ten male hypertensive patients (age: 49±2 years) were studied. Flow-mediated dilation (FMD) during reactive hyperemia (endothelium-dependent) and sublingual nitroglycerin (NTG)-induced dilation (endothelium-independent) were assessed in brachial arteries by ultrasound. Structure and acetylcholine (10⁻⁷ to 10⁻⁵ mol/L)-and sodium nitroprusside (SNP; 10⁻⁸ to 10⁻⁵ mol/L)-induced vasorelaxation were measured in gluteal subcutaneous resistance arteries in vitro, using a pressurized myograph. Dilatory responses in brachial arteries were compared to those in resistance arteries. Brachial artery FMD and NTG-induced dilation were 8.3±1.5 and 18.4±1.2%, respectively. In subcutaneous resistance arteries, the media/lumen ratio was 8.9±0.5%, and the maximal acetylcholine- and SNP-responses were 75±4 and 86±2%, respectively. FMD was strongly correlated with maximum acetylcholine responses (adjusted r²; 0.76, p<0.001, statistic power with alpha=0.05; >0.90), and weakly correlated with media/lumen ratio in resistance arteries (adjusted r²; 0.34, p=0.058). By multivariate analysis, FMD predicted resistance artery endothelial function independently of age, body mass index, and blood lipid status. In conclusion, endothelial dilatory responses are similar in small and large arteries in hypertensive patients. FMD in the brachial artery is a powerful predictor of endothelial function in human resistance arteries, but not of their structure.

Key Words: Flow-mediated dilation; acetylcholine-induced relaxation; brachial artery; resistance artery

**INFLUENCE OF LOW DOSE ASPIRIN AND SIMVASTATIN ON BLOOD PRESSURE, FLOW-DEPENDENT VASODILATATION, TONUS AND ELASTICITY OF BRACHIAL ARTERY IN HYPERTENSIVE NONHYPERLIPIDEMIC SUBJECTS**

J.R. Viskoper, E. Magen, A. Feldman, R. Priluk, A. Last, A. London, D. Michaeli, A. Altshuler. WHO collaborative center for prevention of CVD, Barzilai Hospital, Ben Gurion University of Negev, Israel

It is still uncertain whether improvement of endothelial function by HMG-CoA reductase inhibitors may assist to better blood pressure control in hypertensive patients. This study aimed to examine the effects of coadministration of low dose Aspirin and Simvastatin on blood pressure, on endothelial function, tonus and elasticity of brachial artery in non-hyperlipidemic, treated hypertensive subjects.

23 non-hyperlipidemic (LDL = 106.4±16.3 mg/dl) subjects (M:14, F:9) with treated arterial hypertension, (BP syst 148.4±9.0 mm/Hg, BP diast 82.4±7.7 mm/Hg) 21 to 70 years of age (mean 54±12) were randomized to two groups to receive in addition to their antihypertensive medications: Group A: Aspirin 75mg per day for 8 weeks, Group B: The same + Simvastatin 10mg/day for the first 4 weeks. Using high resolution ultrasound, brachial artery diameter was measured at rest and during reactive hyperemia (RH) after 4.5 min. of pressure 250 mm/Hg on forearm, (with flow increase causing endothelial-dependent dilation.) Flow mediated dilation (FMD) was calculated. Brachial artery tonus and elasticity were measured by analyzing pulsatile variations and brachial artery pulse contour, using pulse echo ultrasound (Device the Ultrasound brain Vessel Scanner. Inta Medics Ltd. Israel). In the group B we observed a significant reduction of both systolic (17,8±4.7, mm/Hg, p<0.001) and diastolic (6,0±2.8, mm/Hg, p<0.05) blood pressure, improvement of FMD (ΔFMD2) 17.2±6.3, %, p<0.001) and tonus (T1/T2 147.3±14.8%, p<0.001) of brachial artery after one month, while discontinuation of simvastatin there was elevation of systolic (ΔSBP3.2 8.9±3.6, 1 mm/Hg, p<0.05) and diastolic (ΔDBP3.2 4.1±2.9, mm/Hg, p<0.05) blood pressure and deterioration of FMD (ΔFMD3.2 13.3±5.9%, p<0.001).

In the group A no significant changes in any parameter was seen along the two months. Brachial artery elasticity was not changed in both groups. Simvastatin 10mg/d improves (while aspirin 75 mg/d does not) endothelial dysfunction in non-hyperlipidemic hypertensive subjects and may assist to better blood pressure control.

Key Words: Aspirin; simvastatin; endothelial; brachial artery; tonus