**10:45**

**ROLE OF ENDOTHELIUM IN ESSENTIAL HYPERTENSION: EFFECT OF ANTIHYPERTENSIVE TREATMENT ON ENDOTHELIUM-DEPENDENT VASCULAR RELAXATION**

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We have shown that endothelium-dependent vasodilation is impaired in hypertensive patients. To investigate the role of this endothelial dysfunction in essential hypertension, we studied the forearm vasculature response to intra-arterial infusion of the endothelium-dependent dilator acetylcholine (Ach), and the direct smooth muscle dilator sodium nitroprusside (SNP) in 14 patients (age 55±11 years; 11 male). Patients were studied while normotensive (mean blood pressure [BP] 93±9 mmHg) (half on treatment and half with drugs stopped 5 half-lives before the study), and while hypertensive (mean BP 118±7 mmHg) (after withdrawal of medications for ≥ 2 weeks). The sequence of studies was randomized, such that 7 patients were normotensive for > 2 months before the initial study. Forearm blood flow responses (ml/min/100 ml) were:

| Ach (mcg/min) | basal | 7.5 | 15 | 30 | |
|---|---|---|---|---|---|
| Off treatment | 3.3±1.2 | 3.4±1.4 | 4.3±1.5 | 6.7±3.5 | |
| On treatment | 2.9±1.7 | 3.1±1.9 | 3.5±2.1 | 6.9±4.2 | p=NS |
| SNP (mcg/min) | basal | 0.8 | 1.6 | 3.2 | |
| Off treatment | 3.4±1.3 | 5.8±2.5 | 8.6±2.3 | 10.4±3.2 | |
| On treatment | 3.2±2.0 | 5.8±2.2 | 7.5±2.7 | 10.8±4.1 | p=NS |

Both off and on treatment, the response to Ach was blunted (p<0.0001) but that to SNP was normal, compared to a group of 18 normotensive controls. Thus, the abnormal endothelium-dependent vascular relaxation observed in patients with essential hypertension is not improved when BP is normalized with treatment. These findings suggest that such endothelial dysfunction either plays a primary causal role in the hypertensive process or, if secondary, becomes irreversible once this process is established.

**11:00**

**THE EFFECT OF DIETARY SODIUM ON THE PRESSOR AND ENDOCRINE ACTION OF ENDOTHELIN.**

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Endothelin (ET) is an endothelial-derived peptide which when infused at pharmacologic concentrations increases mean arterial pressure (MAP), systemic and renal vascular resistances, decreases cardiac output and may activate the renin-angiotensin-aldosterone system (RAAS). As the RAAS and pressor effects of vasoconstrictor are modulated by dietary sodium, this study was designed to investigate the hypothesis that changes in dietary sodium modulates the vascular as well as endocrine response to ET in vivo. We studied the endocrine and cardiovascular responses of ET at pathophysiologic concentrations (ET-1, 5ng/kg/min, IV) for 60 min. in anesthetized dogs, following diets of 300 mEq/d (High $Na^+$, n=6) or 10 mEq/d (Low $Na^+$, n=6) for 5 days. Plasma ET was determined by a newly developed radioimmunoassay to ET-1(Amersham, UK). Plasma samples were obtained and stored at -20 degrees C until time of assay. Plasma was extracted with C-8 Bond Elut cartridges with a recovery of 86%. Intra- and interassay variability are 6% and 9% respectively.

| | High $Na^+$ diet | | Low $Na^+$ diet | |
|---|---|---|---|---|
| | Baseline | ET infusion | Baseline | ET infusion |
| ET(pg/ml) | 14.5±0.5 | 49.9±5.4* | 22.1±2.5† | 43.1±4.6* |
| Renin (ng/ml/hr) | 0.8±0.3 | 0.3±0.1 | 5.7±2.0† | 3.5±1.3 |
| Aldosterone(ng/ml) | 6.3±1.5 | 8.5±1.7 | 40±6.9† | 65±15.4* |

Exogenous ET resulted in a greater pressor response in the High $Na^+$(Δ MAP, 33±9 mmHg) vs. Low $Na^+$ (Δ MAP, 10±4 mmHg) group (p<0.05). The current studies demonstrate that dietary sodium modulates plasma ET concentrations. These studies also demonstrate the important role of dietary sodium on the pressor response as well as endocrine to pathophysiologic concentrations of ET, independent of baseline plasma ET concentrations and the activations of the RAAS.

**11:15**

**ENDOTHELIN LEVELS IN HYPERTENSIVE PATIENTS FOLLOWING CARDIAC TRANSPLANTATION**

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Endothelin, a recently discovered vasoactive peptide which produces sustained vasoconstriction in most vascular beds, is increased in acute myocardial infarction, cardiogenic shock and possibly essential hypertension. However, it has not been reported in patients with hypertension following cardiac transplantation. To evaluate the effect of endothelin, 18 patients with a mean interval of 32.6 months following cardiac transplantation were studied. Groups were defined by diastolic blood pressures. Group I contained four patients with a diastolic blood pressure (DAP) between 85-100 mm/Hg, Group II, eight patients with a DAP between 100-115 mm/Hg and Group III contained six patients with a DAP > 115 mm/Hg. The mean endothelin level in picograms (pg) for Group I was 8.7 pg/ml. This value was elevated over controls of 5.1 pg/ml in healthy non-hypertensive patients. The mean endothelin levels in Group II of 11.4 pg/ml and 15.9 pg/ml in Group III were significantly different than controls ($p < 0.001$). In Groups I, II and III there were significant increases in endothelin values as the mean arterial pressure increased (R=0.966). Our findings indicate a stepwise increase in endothelin levels associated with hypertension post cardiac transplantation. Further investigation is warranted to determine whether endothelin is involved in the etiology of hypertension or serves as a marker for the hypertensive state.

**11:30**

**INCREASED ENDOTHELIN AT REST AND DURING EXERCISE IN OLDER HYPERTENSIVE MEN**

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The purpose of this study was to determine if circulating levels of endothelin (ET), an endothelium-derived peptide with potent vasoconstrictor properties, are altered at rest or during exercise in older men with hypertension (HTN). Six men with NO HTN, identified by negative history and screening office blood pressure (BP) 138±5/89±2 mmHg (mean±SE), were compared to 14 older men with HTN, all on medication. Exercise consisted of graded cycle ergometry performed to exhaustion. All anti-HTN medications were discontinued one week prior to exercise testing. There were no differences between groups (NO HTN vs. HTN) for age (60±2 vs. 61±2 yrs), weight (95±6 vs. 88±2 kg), resting heart rate (78±5 vs. 69±3), exercise heart rate (163±6 vs. 149±4), exercise workload (150±16 vs. 136±6 watts), or oxygen uptake (22.4±2.2 vs. 19.7±0.7 mL/kg/min). Pre-exercise resting and peak exercise BP (mmHg) and ET (pg/mL) levels are summarized below:

| | | Systolic BP | Diastolic BP | ET |
|---|---|---|---|---|
| NO HTN | Rest | 145±6 | 94±3 | 11.6±0.8 |
| HTN | Rest | 164±6 | 98±3 | 15.4±0.5* |
| NO HTN | Exercise | 218±10 | 98±3 | 13.1±2.0 |
| HTN | Exercise | 225±8 | 102±2 | 18.8±0.8*† |

* p<0.005 HTN vs. NO HTN.
† p<0.005 Exercise vs. Rest ET.

CONCLUSIONS: 1) ET levels at rest and exercise are elevated in older men with HTN, suggesting a potential pathophysiologic role for ET in HTN. 2) ET increases modestly but significantly in older men with HTN during maximal exercise.