Effect of the Angiotensinogen M235T Polymorphism on Human Coronary Vascular Endothelial Function

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Introduction: A missense substitution in exon 2 of the angiotensin gene (T704-C) encoding threonine instead of methionine at position 235 (M235T) may influence the risk of coronary disease. We hypothesized that the polymorphism is associated with coronary vascular endothelial dysfunction.

Methods: Angiotensinogen M235T genotyping was performed in 118 Caucasian patients with mild coronary atherosclerosis (<50% stenosis) or angiographically smooth coronary arteries undergoing cardiac catheterization. Changes in coronary vascular resistance (SCVR) and epicardial artery diameter (SAD) were measured as indices of microvascular and epicardial coronary vasodilator capacity during administration of intra-coronary acetylsalicylic acid (ACH, 15 mg/ml), and sodium nitroprusside (SNP, 25 mg/ml), to test endothelium-dependent and -independent coronary vascular function, respectively.

Results: 235T allele frequency was 0.40. Coronary microvascular dilation with ACH was reduced in TT compared to MT+TT patients (SCVR: +36±9% vs +42±8%, p = 0.04), whereas responses to SNP were similar in both groups (SCVR: -48±7% vs -54±12%, p = 0.35). In the epicardial coronary circulation, a net vasodilator response with ACh was observed in TT individuals, compared with a net vasodilator response in MM+MT subjects (+2.2±2.3% vs +2.1±1.0%, p = 0.003). Epicardial responses to SNP were similar in TT and MM+MT genotypes groups (+23±6% vs +21±4%, p = 0.73). This impaired microvascular and epicardial coronary endothelial function observed in TT patients was independent of conventional risk factors (age, gender, smoking, hyperlipidemia, diabetes, hypertension) for endothelial dysfunction by multivariate analysis (SCVR: p = 0.02 and SAD: p = 0.03).

Conclusions: Individuals homozygous for the angiotensinogen 235T allele have impaired endothelium-dependent coronary artery vasodilator compared with MM+MT subjects. This finding provides mechanistic insight into the increased association between the 235T allele and hypertension, atherosclerosis, and myocardial infarction observed in several epidemiologic studies.

1128-86 Endothelial Dysfunction Following Radial Artery Cannulization

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Background: There is an increasing tendency to use arterial conduits, including the radial artery (RA), for coronary artery bypass surgery. At the same time, invasive cardiologists are increasingly using the RA as a conduit for cardiac catheterization. The purpose of this study was to assess endothelial function following RA cannulization. Methods: 20 patients scheduled to undergo diagnostic catheterization via the radial approach underwent non-invasive evaluation of endothelial function. RA diameter was measured at baseline, then at 30 and 90 seconds following reactive hyperemia (endothelial dependent), and following administration of nitroglycerin (endothelial independent). These measurements were obtained prior to catheterization, within 24 hours, at one week, and at one month following catheterization. Results: Endothelial function in the RA was evidenced 24 hours after catheterization regardless of the catheterization technique. Endothelial function measured at 1 week and 1 month in the radial artery was significantly improved over 24 hour values for nitro at 30 seconds (p = 0.023 and p = 0.016, respectively), and cuff at 90 seconds (p = 0.045 and p = 0.028, respectively). Nonsignificant improvements in endothelial function were evident at the remaining interventions between 1 week and 1 month.

Conclusion: RA catheterization results in endothelial dysfunction following catheterization and may have implications for its use as an arterial conduit in coronary artery bypass surgery.

1128-87 Effect of Xanthine Oxidase Inhibition on Endothelial Function in Smokers

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Background: Cigarette smoking causes endothelial dysfunction, possibly due to oxidant stress. One proposed mechanism has been generation of oxidant species by the enzyme xanthine oxidase (XO). We tested the hypotheses that XO impairs endothelial function in

POSTER SESSION

1128-85 Prothrombotic Mutations Are Associated With Increased Cardiovascular Events in Postmenopausal Women Receiving Hormone Replacement Therapy

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Recent studies have suggested that hormone replacement therapy (HRT) in postmenopausal women (PMW) may be associated with an increased cardiovascular risk. Recent reports suggest that the prothrombotic variant 20210G to A is associated with an increased risk of events in hypertensive PMW with a previous myocardial infarction. To these end 50 PMW with documented vascular event underwent prospective evaluation of antithrombin III, protein C, free and total protein S, activated protein C resistance, fibrinogen, factor VIII:C and homocysteines levels. In all the presence of antiphospholipid antibodies was investigated by kaolin clotting time (KCT), diluted Russell's viper venom time (DRVT) and by measurement of anticardiolipin antibodies IgG and IgM (ACA-M). Prevalence of factor V Leiden, prothrombin variant G20210A and homozygosity for thermolabile variant C677T of the metilenetetrahydrofolate reductase (MTHFR) were evaluated and compared with those of 50 normal matched controls. Antithrombin III and protein C were normal in all cases. One patient (2%) showed free protein S deficiency and 3 patients (6%) had activated protein C resistance. Homocysteine levels above 15 μmol, were found in 3 patients (6%). Antithrombin III levels were found in 36 patients (72%). Among women receiving HRT 87% had combined inherited and acquired prothrombotic factors (CR = 0.73, 96% CI = 0.5-0.85643) while no combined prothrombotic factors were found in control PMW receiving HRT. In conclusion vascular events in women receiving HRT are associated with a high prevalence of combined inherited and acquired prothrombotic factors. Therefore screening for prothrombotic factors may be of help in identify those women at increased risk for cardiovascular events with HRT.

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Effect of HRT, Tibolone or DHEAS on Endothelial Function in Postmenopausal Women With Increased Cardiovascular Risk

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Menopause is associated with an increased cardiovascular risk and with a decrease in endothelial function. Hormone replacement therapy (HRT) improves endothelial function in postmenopausal women (PMW). New alternative treatments for menopausal women have been suggested among these Tibolone (T) and dehydroepiandrosterone sulfate (DHEAS) have been suggested to have cardioprotective effects. Although in vitro animal studies have suggested that T and DHEAS improve endothelial function, their effect in humans has never been tested. Aim of the present study was to compare the effects of HRT, DHEAS and T on endothelium-dependent and -independent coronary artery vasodilation compared with MM+MT subjects (+2.2±2.3% vs +2.1±1.0%, p = 0.003). Epicardial responses to SNP were similar in TT and MM+MT genotype groups (+23±6% vs +21±4%, p = 0.73). This impaired microvascular and epicardial coronary endothelial function observed in TT patients was independent of conventional risk factors (age, gender, smoking, hyperlipidemia, diabetes, hypertension) for endothelial dysfunction by multivariate analysis (SCVR: p = 0.02 and SAD: p = 0.03).

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