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Abstracts: Communications

26

INFLUENCE OF GENETIC RISK FACTORS FOR CARDIOVASCULAR DISEASE ON HUMAN LONGEVITY

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Longevity is influenced by enviromental as well as genetic factors, which are involved in determining an individual's susceptibility to vascular disease. Several variants of genes involved in haemostasis and blood pressure regulation have been associated with the evolution of cardiovascular disease. Aim of this study is to evaluate the allele frequency and genotype distribution of polymorphisms in genes involved in renin angiotensin system [I/D angiotensin converting enzyme (ACE) gene polymorphism and A/C angiotensin II type 1 receptor (AT1R) variant], P-selectin gene (Thr715Pro polymorphysm) and in genes codifying for homocysteine metabolism enzymes [C677T and A1298C 5,10-methylenetetrahydrofolate reductase (MTHFR) mutation, 844INS68 cystathionine beta-synthase (CBS) insertion variant]. We investigated 61 healthy Italians over the age of ninety (mean age 92.9±3.2, range 90-106 years) and 66 healthy controls (mean age 37.9±10.4, range 25-55 years) from the same geographical area. For mutation detection, DNA was amplified by PCR using specific oligonucleotides and RFLP and VNTR analysis were performed. Hardy-Weinberg equilibrium was observed in ultranonagenarians and control subjects for all the polymorphisms analysed. The frequencies of the D ACE allele and of 715Pro P-selectin allele in ultranonagenarians were significantly higher than in young individuals ($p=0.01$ and $p<0.05$, respectively). Moreover, the genotype distribution of I/D ACE and P-selectin polymorhisms in ultranonagenarians was different in comparison to that in the younger group ($p=0.001$ and $p<0.05$, respectively). 1298CC ($p=0.018$) and 1298AC ($p=0.048$) MTHFR genotypes turned out to be risk factors for the attainment of the extreme old age; the 677TT MTHFR genotype has been found to be associated with longevity, even not in a statistical signficant manner ($p=0.062$). No association between CBS and AT1R polimorphisms and longevity has been found. These results suggest that common genetic determinants such as ACE, P-selectin and MTHFR polymorphisms are able to affect human longevity.

27

COMPLEMENT RECEPTOR 1 AND ATHEROSCLEROSIS: A PRELIMINARY STUDY

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Various research suggests a role for immunity with the involvement of Complement (C) in the pathogenesis of Atherosclerosis (ATS). From this perspective the involvement of complement receptors, and in particular CR1, could be an interesting hypothesis. CR1 is a glycoprotein expressed on the surface of several cell types. It binds C3b-coated particles and is involved in the inactivation of C3b itself. In the case of erythrocytes it plays a role in the clearance of Immunocomplexes (IC), preventing the damage caused by complement activation. Our attention was focused on erythrocyte CR1, which is the most widely represented in the human body. Blood samples from 27 young healthy donors (mean age 29.3 years), and 27 elderly (mean age 84.5 years) were collected and submitted to a quantitative analysis of CR1 by immunobloting as well as a quantitative evaluation by flow cytometry. The populations were evaluated under a clinical-anamnestic point of view. Three different CR1 isoforms were detected: A (190 kD); B (220 kD); C (160 kD). Young donors showed a distribution of CR1 isoforms similar to that reported in literature (A 81.5%; AB 18.5%) while elderly subjects evidenced an increased expression of B isoform (A 55.2%; AB 37%; B and C 3.7% each). At flow cytometry the mean percentage of CR1-positive erythrocytes from young donors was 33.9%, whereas it reduced to 19.7% in the elderly.Elderly subjects expressing B were on average older, with less frequent cerebrovascular disease. This could be related to the observation of a lower incidence of ATS-related disease in the families of the B-expressing young subjects. The low number of cases does not allow the role of CR1 in ATS to be defined, nevertheless, it provides indications for further investigations.

28

B-MODE IMAGING AND INTIMA MEDIA THICKNESS: ANALOG VS DIGITAL TECHNOLOGIES

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New advances in B-mode imaging technologies have led to increased image quality for detecting minute changes of IMT and plaques. The new digital systems with multiple frequency probes and increased micro-processing speeds, now generate images comparable to those of their analog predecessors. To assess whether digital systems have reproducibility values comparable to pure analog systems, a study comparing a Biosound 2000II (analog) and a Esaote AU4 (digital) was performed. Twenty-two subjects with varying degrees of IMT on the far wall of the Common Carotid Artery were chosen. Common Carotid Intima-Media Thickness (CC-IMT) was determined in each patient with both analog and digital system and replicated within two weeks. The images were recorded for off-line measurements and CC-IMT was measured by appropriate software (Eurequa, France). The intra-method agreement was high with the Biosound system (mean absolute differences = 0.027±0.020 mm; repeatability coefficient = 0.067 mm). AU4 system provided the highest reproducibility (mean absolute differences = 0.012±0.01 mm; repeatability coefficient = 0.033 mm). When analog and digital processing were compared, the mean difference was 0.018 mm, with good agreement between the two systems (mean relative difference -0.011 and repeatability coefficient 0.047 mm). These results suggest that the digital system is a reliable technology for clinical and epidemiological trials.

29

Effect of different calcium antagonists on smooth muscle cell migration and proliferation.

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Proliferation of smooth muscle cells (SMC) is an early event in atherogenesis. Since calcium ion is essential for cell growth, Calcium Antagonists (CA) are potential antiatherosclerotic agents. We investigated different classes of calcium channel blocker: Lacidipine and Lercanidipine among L-type and Mibefradil among T-type. Lercanidipine and its enantiomers inhibited the replication and migration of arterial myocytes in concentrations ranging from 10 to 50 μM. The antiproliferative effect of Lercanidipine, evaluated as cell number, was dose dependent, with a potency similar to that of Lacidipine. The new CA Mibefradil was more potent than dihydropyridines in inhibiting SMC proliferation and migration in a concentration-dependent manner (IC_{50} 1 μM). Lacidipine, Lercanidipine and Mibefradil inhibited DNA synthesis in foetal calf serum stimulated SMC in a concentration dependent manner. These results suggest that the tested drugs act in the early-middle G_1 phase of the cell cycle. Mibefradil (IC_{50} 1 μM) was more potent than Lacidipine (IC_{50} 15 μM) and Lercanidipine (IC_{50} 17 μM) in decreasing [^{3}H]-thymidine incorporation.

To rule out the role of calcium channels in the antiatherosclerotic properties of tested drugs we must consider that high concentration of L-type calcium antagonists block other types of ion channel, thus the effects reported in growing cultures may not be related to specific blockade of calcium influx via L-type channels. Besides, Lercanidipine enantiomers have a different potency in binding L-type calcium channels, however, they are able to inhibit SMC proliferation and migration at the same concentrations. Mibefradil, at used concentration, bind selectively T-type calcium channels, suggesting that T-channels blockade may be directly involved in the reported effects of Mibefradil on SMC. According with these observation we can hypothesize a possible role of T-type calcium channels in the pathogenesis of atherosclerosis.