Childhood origins of endothelial dysfunction

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MINI-SYMPOSIUM

Endothelial dysfunction is present in children and young adults exposed to conventional risk factors including hypercholesterolaemia, a family history of hypertension, and active and passive smoking. Indeed, conventional risk factors “cluster” in certain individuals, and clear relations emerge between the risk factor “burden” and the degree of endothelial dysfunction. This has particular relevance for the rapidly expanding population of overweight and obese children with mild hypertension, dyslipidaemia, insulin resistance, and low grade inflammation. Indeed, obese children have impaired FMD and increased vascular stiffness, which may in part be mediated by leptin.

The role of inflammation in driving the atherogenic process has been shown in numerous large adult cohorts. A link between inflammation, endothelial dysfunction, and structural arterial disease emerges remarkably early. A small study of 79 “healthy” 10 year old children demonstrated an association between mild elevation of C reactive protein and impaired FMD as well as carotid intimal thickening. Pro-inflammatory influences commonly operating in childhood include obesity and exposure to infectious pathogens.

Abbreviations: ALSPAC, Avon longitudinal study of parents and children; EPC, endothelial progenitor cell; FMD, flow mediated dilation; NO, nitric oxide
found that mild childhood respiratory infection is associated with, at least partially reversible, endothelial dysfunction, consistent with experimental data describing accelerated atherosclerosis after specific infections and associations between infectious pathogen burden and inflammation, endothelial dysfunction, and clinical coronary artery disease. Thus, low grade chronic infection may play a more significant role in the initiation and progression of early, preclinical disease than in the destabilisation of advanced disease.

There has been considerable debate about the potential for prenatal “programming” of long term cardiovascular risk. We and others have demonstrated a relation between birthweight, a measure of fetal well being, and endothelial function by the end of the first decade of life. Recent provocative data from our institution suggest that the critical window for metabolic and vascular programming occurs during the very early postnatal period, suggesting great potential for long term cardiovascular benefits from appropriate early postnatal nutritional modification.

The strong familial and genetic contribution to atherogenesis has long been recognised. Characterisation of early functional and structural vascular disease facilitates evaluation of the genetic contribution by minimising the confounding impact of long term exposure to the complex risk factor burden characteristic of older western populations. We examined the relation between the Glu298Asp polymorphism of the endothelial nitric oxide synthase gene and FMD and found that although there was no relation between the polymorphism and endothelial function in the whole cohort, the 298Asp allele appeared to predispose to endothelial dysfunction in smokers. This effect was attenuated by increased ω-3 fatty acid concentrations, indicating the potential for genetic variation and specific environmental factors to influence the vascular phenotype from an early stage. Large cohorts will be required to answer questions addressing the potential interactions between specific genes and environmental modifiers with sufficient statistical power. We have recently completed measurements of FMD and vascular stiffness in a well characterised cohort of 8000 10 year old children who were recruited prospectively and followed up from pregnancy in the Avon longitudinal study of parents and children (ALSPAC). This study will provide a unique opportunity to explore in detail the impact of genetic and environmental factors and their interactions at this early stage of life, and examine how these factors drive the atherosclerotic process through puberty and into adult life.

**RESTORATION AND PROTECTION OF ENDOTHELIAL FUNCTION REVERSIBILITY**

Endothelial dysfunction is directly relevant to the risk and progression of atherosclerosis. Pharmaceutical intervention with statins and angiotensin converting enzyme (ACE) inhibitors can improve endothelial function and modify progression to clinical disease. However, such measures are currently only considered appropriate for young subjects at very high risk. Several studies have now demonstrated improvement in endothelial function with exercise training and nutritional supplementation with L-arginine, niacin, and n-3 fatty acids. In endothelial function with exercise training and nutritional supplementation with L-arginine, niacin, and n-3 fatty acids. In

The management of subjects both with and at risk of clinical atherosclerosis has been improved dramatically over recent decades by treatments such as statins and stents. However, the population burden of atherosclerotic disease may be increasing as a consequence of the deteriorating risk profile of the young population. We now have non-invasive techniques that are accurate, reproducible, reflect the biology of the vascular wall, link to long term prognosis, and respond to appropriate interventions which can be used to quantify progression of vascular disease in early life. These measures are ideal for use as surrogate end points in clinical studies, since the low clinical morbidity and mortality from this disease in the young precludes the use of clinical events as a primary outcome measure. This provides us with a valuable opportunity to study the early evolution of atherosclerosis and should assist in the design of effective risk reduction strategies in the young.

**REFERENCES**


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Left ventricular non-compaction diagnosed by real time three dimensional echocardiography

A 65 year old man was admitted with syncope. An ECG in the emergency department revealed ventricular tachycardia with haemodynamic compromise necessitating electrical cardioversion. Serum electrolytes and post-cardioversion ECG were normal. Two dimensional transthoracic echocardiography showed moderate concentric left ventricular hypertrophy with normal systolic function (panels A, B). Cardiac catheterisation showed no evidence of obstructive coronary artery disease. The left ventriculogram was peculiar with a double wall appearance to the left ventricular free wall (panel C). A cardiac biopsy was performed at the same time, which showed normal histology. Having identified the abnormal left ventriculogram, the patient underwent real time three dimensional echocardiography (RT3DE) to study the left ventricle in detail (panels D, E). This revealed severe trabeculation of the left ventricular wall, particularly in the apical–lateral segments. Contrast enhanced RT3DE (panels F, G) demonstrated large amounts of filling defects, consistent with extensive trabeculation in the same area. These findings were consistent with non-compaction of the left ventricle (NCLV). The patient was commenced on a β-blocker and an angiotensin converting enzyme inhibitor, and a cardiac defibrillator was implanted.

This is the first case to report the value of three dimensional echocardiography in the diagnosis of NCLV, an unusual cause of malignant ventricular tachycardia that may be underdiagnosed on two dimensional echocardiography. Moreover, RT3DE allows assessment of any left ventricular dyssynchrony causing heart failure, a recognised complication of NCLV, which helps in planning treatment such as biventricular pacing. These make RT3DE a single superior investigation modality for both the diagnosis and assessment of treatment of LVNC.