Early atherosclerosis . . . what does it mean?

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The fact that the seeds of atherosclerosis are sown many decades before the manifestation of clinical end-points is undisputable. Even the description of atherogenesis as a ‘cradle to grave’ phenomenon underplays the importance of pre-natal programming and the intra-uterine environment. The evidence for familial clustering of coronary events has long been recognised, as has the correlation amongst relatives of various intermediate risk factors associated with atherosclerosis. A positive family history of cardiac events is known to be a strong independent risk factor for coronary artery disease with a parental history of myocardial infarction doubling an offspring’s chance of infarction. This risk is inversely related to the age of the parent at the time of their index event with early cardiac events being more familial than those occurring in later years.

Many risk factor scoring systems appear to sideline the significance of a family history. This is not a denial of the importance of this variable but rather a refection of the difficulties in reliably defining and quantifying this parameter in clinical practice.

Previous studies have investigated the influence of having affected family members on pre-clinical manifestations of disease and such influences are evident as early as 1 year of age. Autopsy studies have shown luminal narrowing in left and right coronary arteries in infants with a family history of coronary disease when compared with those with no such history. These findings are supported by Cuomo’s group reporting similar changes in carotid intima media thickness and endothelial function in a cohort of young adults.

In Cuomo’s current contribution the author suggests that studying cohorts of offspring from those with premature disease may help in the identification of major genes involved in the pathogenesis of atherosclerosis. Their second conclusion is that non-invasive techniques, such as the B-mode ultrasound imaging of the carotids described, may be utilized as a screening tool to direct early risk reduction in individuals with a positive family history.

The observation of vascular abnormalities in youngsters with a family history is of great interest but raises several issues worthy of further discussion. The first key question regards the significance of having a positive family history of cardiac events. It is obvious, but requires reiterating, that familial influences are not necessarily genetic. Shared environmental, and gene–environment interactions may be equally important and will vary depending on the population studied. In addition it is difficult to quantify the degree to which any specific individual’s risk is increased purely due to a positive family history in the absence of other known risk factors. A positive family history is a graded, if not continuous, variable. Cuomo reports that traditional risk factors do not account for all of the familial risk in this cohort but this is not quantified.

The second fundamental question raised is the extent to which arterial wall abnormalities detected in early life translate into later cardiovascular events. Carotid intima media thickness is thought to represent a measure of ‘total body atheroma burden’ and is...
used as a surrogate marker for coronary atheroma and coronary events in adults\textsuperscript{[9]}. Doubt has been cast on the role of carotid intima media thickness in screening adults as the addition of intima media thickness adds little to the predictive value of standard risk factors\textsuperscript{[10]}. However, this remains controversial and the American Heart Association recently endorsed the use of carotid intima media thickness in the assessment of subclinical atherosclerosis\textsuperscript{[11]}. However, childhood carotid intima media thickness has not been validated as a marker of outcome and whether one’s carotid intima media thickness at 5 years old has any influence over later (which may be 50–60 years later) morbidity and mortality is unknown. As such it does not, sadly, fulfil the criteria of an effective screening tool.

The third and perhaps most interesting question such studies raises is whether the adverse outcomes associated with a positive family history is mediated through the vessel wall abnormalities described. One cannot ignore the importance of a positive family history but our understanding of the mechanisms modulating its effect, or loci involved, is limited.

A study of young males with a history of myocardial infarction demonstrated familial clustering of risk factors and the presence of coronary artery disease. However the extent of coronary atheroma (number and severity of haemodynamically significant stenoses) did not differ between those with and without a family history of coronary disease implying the potential involvement of other mechanisms\textsuperscript{[12]}. In addition it has also been suggested that the heritability of carotid intima media thickness is minimal compared with other physiological parameters such as blood pressure. Perhaps the mechanisms of familial risk are mediated through the thrombogenesis and plaque instability axis rather than atheroma burden.

Only after these questions have been answered are we able to address the final issue — What can, or should, be done if these arterial wall changes are detected in childhood? Effective risk reduction therapies are now impacting on the prevalence of cardiovascular events. In most primary prevention guidelines an arbitrary risk is deemed necessary to justify specific intervention such as statin therapy. The European Society guidelines quote an absolute Coronary Heart Disease risk of greater than 20% over the next 10 years or a risk expected to exceed 20% if projected to the age of 60 years\textsuperscript{[13]}. Although we empirically feel such ‘vascular abnormalities’ detected early in life require our most aggressive efforts to ameliorate risk it is important to establish where these individuals lie in the ‘Primary Prevention Pyramid’ before embarking on decades of drug therapy.

Another inherent difficulty in reducing risk in individuals with a positive family history is managing those with a personal or family history of early events but few traditional risk factors. Unfortunately, these individuals have a less modifiable risk factor profile. Those who are particularly at risk (from their genetic legacy) may be those who are most ‘resistant’ to the benefits of primary prevention (unless mediated through, for example, an obvious lipid abnormality). Until there is a clearer understanding of these issues it is difficult to share the author’s enthusiasm that ‘ultrasonographic carotid evaluation could provide a valuable method for selecting those young subjects who will attain the greatest benefit from aggressive primary prevention’. It is also difficult to endorse the development of similar non-invasive imaging techniques as clinical tools\textsuperscript{[14]}. Advocating a ‘primary prevention’ lifestyle should be our routine prescription to all-comers and does not necessitate resorting to additional screening techniques.

Unfortunately it is naïve to hope that such studies will easily offer up the ‘answer’ to atherosclerosis. A more realistic model is of a genetic architecture involving many genetic loci each having polymorphic alleles, which in themselves contribute little effect. There are, for example, over 200 genes involved in the regulation of simple lipid metabolism; only one aspect of the atherosclerotic disease process. These complexities are compounded by population variances, the principles of age-specific genetic effects, epistasis and gene–environment interactions. Indeed previous studies on the influence of a family history on carotid intima media thickness in older adults have been negative\textsuperscript{[15]} suggesting that an early genetic predisposition is either swamped by later environmental factors or that different genes are important at different points in the disease process.

As we often find the observations described in Cuomo’s study leave the field wide open with the unknowns greatly outweighing that which is known. Neither the molecular biologist, genetic epidemiologist, the paediatrician nor the adult cardiologist can attempt to address these issues alone.

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References


Intracoronary brachytherapy for restenosis: an efficient technique in the struggle for survival?

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In the last few years intracoronary radiation has emerged as an effective antirestenotic therapy in percutaneous interventional cardiology.

Radiation, by damaging the DNA of the nucleus, inhibits cell proliferation non-selectively, mostly during mitosis and the G2 phase of the cell cycle[11]. Intravascular radiation, at sufficient doses to the arterial wall, can inhibit proliferation of smooth muscle cells and fibroblasts in the media and adventitia, in response to an arterial injury and additionally, by preventing adventitial fibrosis, it avoids negative arterial remodelling[2,3]. This was shown to be highly effective in experimental animal models, both with gamma and beta sources and doses of 10–30 Gy targeted at the tunica media[4,5].

In the last 5 years, several randomized clinical trials and registries have been published[6–13], using different brachytherapy (meaning, a short distance between the source and target) systems[3]. The gamma sources (mainly with iridium-192) were the first to be used. They are more penetrating, allowing a more homogeneous distribution between superficial and deep layers of the arterial wall, but are potentially more harmful to neighbouring tissues. The handling of the sources is more complicated for all personnel, requires a 25-mm lead screen and evacuation of the laboratory during the dwell time for treatment, of around 30 min. The solid beta sources (yttrium-90, strontium/yttrium-90, phosphorous-32) penetrate in tissue only a few millimetres, allow a more localized treatment in several sites, and the handling of the source and radioprotection measures are much simpler. The need for centring of the beta source within the arterial lumen is still controversial and one solution is the use of liquid beta sources (rhenium-188 and 186) injected into the angioplasty balloon catheter. Radioactive stents (phosphorous-32) have also been used and although conceptually very attractive the clinical results have been disappointing mainly