Arterial elasticity: asset or liability?

That inflammatory polyarthritis and cardiovascular disease are closely related is now undoubted. Even with myocardial infarction and congestive heart failure as surrogates of molecular change, there is a significantly higher frequency of cardiovascular disease in RA compared with age- and sex-matched control individuals [1, 2]. The late John Cosh, in his time the only rheumatologist to hold a joint appointment with cardiology, followed his cohort of 100 patients with RA, recruited upon his appointment, for over 25 yrs to provide prospective confirmation that between one-third and one-half of all RA-related deaths are directly attributable to cardiovascular disease [3]. This was in a cohort of patients not specifically selected for vasculitic features, might have caused this proportion to climb even higher. Collaboration with other disciplines has continued, to the benefit of rheumatology. A striking recent collaboration is the joint funding by the Arthritis Research Campaign and the British Heart Foundation of the Trial of Atorvastatin in the primary prevention of Cardiovascular Endpoints in Rheumatoid Arthritis (TRACE-RA) study which can only bring ‘added value’ to each of these important national charities. The British Society for Rheumatology, created by the successful amalgamation of two rival bodies, might yet be subsumed into a British Society of Inflammology!

All these conditions are treated by drugs and much ink has also been spilled on the implications on the vascular system of successful drug treatment for arthritis. Most attention has been directed towards the coxib controversy, probably because the market for NSAIIDs is so large and lucrative. Few would doubt the harmful effect from certain coxibs though any harmful effect from rival, more antiquated NSAIIDs may have gone unnoticed because it was not looked for. In contrast, the effect of glucocorticoids is less studied with divided opinions on whether they do or do not aggravate vascular damage [4]. This may reflect a problem in endpoints. Certain evidence for steroid-induced carotid plaque and arterial incompressibility is persuasive [5]. The effect of the route of glucocorticoid administration (including intra-articular and intramuscular) and the precise steroid used (e.g. whether fluorinated or not) tends not to be considered. Whether gold standards in treatment such as methotrexate [6] and anti-tumour necrosis factor therapy protect against vascular disease is likely to emerge from appropriate registers in due course. The possible protective effect of statins is also being researched.

A variety of methods are available for the assessment and imaging of vascular disease, with varying degrees of sensitivity. Central atherosclerosis is often measured with high-resolution carotid ultrasound for the presence of plaque, though the extent of carotid artery intima–media thickness (CIMT) conveys different, though possibly just as important, information. B-mode ultrasound is a safe, reliable and non-invasive method of measuring CIMT [7]. The combined thickness of the intima and media can be measured in various sections of the carotid artery, although the common carotid artery appears to be the most reproducible and accurate area to assess [8]. This is usually measured 1 cm below the bifurcation of the common carotid in order to accurately reassess the same area. The internal carotid is technically more difficult to assess but appears to correlate more closely with major atherosclerosis risk factors and pre-existing cardiovascular disease [8].

An increase in CIMT has been shown to correlate with cardiovascular risk factors such as smoking, high cholesterol and hypertension [7]. It has also been shown to be an independent predictor for subsequent myocardial infarction and stroke [9]. In addition, various studies have shown an increase in CIMT in inflammatory joint conditions such as RA and psoriatic arthritis [10, 11], along with other inflammatory conditions such as Behcet’s disease and Takayasu’s arteritis [12, 13]. There is emerging evidence that smoking influences CIMT in RA and that treatment with anti-tumour necrosis factors may have a beneficial effect on CIMT measurements [14, 15]. This suggests that these treatments may reduce cardiovascular risk. In the future, CIMT measurements could be used to assess cardiovascular risk of patients with rheumatic disease, although it is largely a research tool at present.

There may also be further confounding factors. CIMT is corrected for age, gender and blood pressure when used in studies on rheumatic diseases. Previous drug history is clearly relevant both for cardiovascular disease and other comorbidities as well as any previous disease-modifying drug interventions for inflammatory arthritis.

Amongst the parameters of vascular change distressingly is sometimes quoted, presumably because it is easily visualized, which may or may not be synonymous with the more frequently described arterial stiffness, usually accepted to be impaired, though often measured by different methods. There is sometimes a lack of clarity as to whether this is a primary phenomenon of rheumatic disease or a secondary consequence of cardiovascular disease once present. A consensus would accept, however, that arterial stiffness is increased in most chronic inflammatory diseases [16] including not only post-menopausal females with RA [17] but also in adolescents and young adults with SLE [18]. Sometimes this may be site specific [19], and in RA it can be reduced by atorvastatin, particularly in patients with the most severe disease [20]. Arterial stiffness can also be enhanced in vasculitis, including both Takayasu’s arteritis and giant cell arteritis [21, 22].

One of the determinants of ‘stiffness’, not always dissected out, is likely to be elasticity. By implication this reflects collagen structure which, in the case of arterial wall is likely to be predominantly inherited though it is conceivable that once arterial disease occurs stiffness, of which elasticity is likely to be only one component, will become impaired. However, there is circumstantial evidence from inherited abnormalities of connective tissue that the distribution of elasticity may vary along the length of a blood vessel, not least as a consequence of anatomical mechanical tethering that would appertain to some sites of bifurcation and which might be influenced considerably by non-vascular factors such as bony foramina and ligamentous bands that dictate the course of the blood vessels, tethering them safely where appropriate. Dynamic imaging of blood flow in major vessels lends support to this argument. Even in the absence of pathology, linear flow may be interrupted by variation in angle of the vessel wall, producing eddies before these dynamic variations are further influenced by local pathology.

Further lessons may come from this sometimes neglected area of inherited collagen structure since the final outcome of any acquired disease is likely to depend as much upon the seed as the soil. When rare inherited diseases such as Ehlers-Danlos syndrome and Marfan syndrome are used as models, eponymous clinical classification sometimes detracts from a more functional classification that would logically be directed at the particular type of collagen present and the way this might have been modified.
genetically. Relations between collagens are complex but it seems likely that collagen types I, III, V and VI are those most likely to determine vascular elasticity. In turn, the potential gene involvement is legion even before local mechanical modification is taken into account. Some collagens may be key players. Abundance of collagen III, for example, confers particular delicacy, even fragility [23] and this may be more relevant than the mutation to collagen V, normally felt to herald traits I and II in the classical nosology for Ehlers-Danlos syndrome. Moreover, attitudes to inherited abnormalities are changing. Overlay between eponymous syndromes, previously felt to be discrete, is seen increasingly as is overlap with the mild benign joint familial hypermobility syndrome, which if simply regarded as one extreme of a graded trait in observable collagen laxity throughout the population, might affect some 10% of individuals even though the majority of these would probably be asymptomatic.

Interaction between rheumatologists and neurologists is also providing new insights. Traditionally, in Marfan syndrome, blood vessel walls dissect with the aortic ring and aortic valve of prime importance in the heart. In Ehlers-Danlos syndrome, particularly the type IV vascular variant, bursting (possibly of a micro-aneurysm) leads to haemorrhage, valvular involvement in the heart being less pronounced and more likely to affect valves other than aortic. However, these classifications are breaking down our own clinical observations suggesting an apparent increased propensity to dissect, irrespective of the disease present, though, in part, this impression is from the study of patients reaching rehabilitation wards who may represent a selected group.

For all of these arguments, arterial elasticity and its accurate imaging surely deserves more attention than it has hitherto received. In the case of inherited abnormalities, serial elasticity assessment (possibly through the surrogate of distensibility) in peripheral vessels might predict those unfortunate individuals who carry a particular risk of serious cerebrovascular event, which with prophylactic drug therapy for Marfan syndrome on the horizon would be of extreme significance for this relatively small group of patients. The extent to which the inherited elasticity, also behaving largely as a graded trait in the population, might influence acquired vascular disease such as atheroma, also merits study perhaps with the hypothesis that increased elasticity might protect, not just because of any hypotensive advantage this also invariably confers. The extent to which inherited elasticity might also influence the propensity for vascular disease, once inflammatory arthritis is present, also deserves greater consideration with the hypothesis that here also a modest degree of hyper-elasticity may be an asset rather than a liability.

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**References**


