Atherosclerosis, neoatherosclerosis, and vascular disease

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Geoffrey Rose (1926–1993) pioneered the concept that, to reduce the burden of disease, improving the population distribution of a risk factor was preferable to interventions that target high-risk individuals.1 This strategy has become commonplace today and the basis of many guidelines.2–4 To strengthen this approach, the European Society of Cardiology has thus established the Geoffrey Rose Lecture on prevention at their annual congress. One of the recent awardees was Veronique L. Roger from the Mayo Clinic in Rochester, Minnesota USA. In her Clinical Review ‘Cardiovascular diseases in populations: secular trends and contemporary challenges’5, she reflects on this concept and examines if temporal trends in the burden of cardiovascular disease, in particular myocardial infarction and heart failure, support that hypothesis.

Patients with coronary artery disease and myocardial infarction, still the most important form of cardiovascular disease,6 are commonly treated with balloon angioplasty and stents or bypass surgery, depending on the coronary anatomy and the SYNTAX score, and on the decision reached in the HeartTeam.7,8 Despite the reduction in late thrombotic events with newer generation drug-eluting stents,9 late stent failure remains a concern following stent placement. This issue continues with a Clinical Review manuscript entitled ‘Neoatherosclerosis: overview of histopathological findings and implications for intravascular imaging assessment’ by Michael Joner from CVPath Institute Inc. in Gaithersburg, Maryland USA.10 In-stent neoatherosclerosis has emerged as an important contributing factor to late vascular complications including very late stent thrombosis and late in-stent restenosis. Histologically, neoatherosclerosis is characterized by accumulation of lipid-laden foamy macrophages within the neointima with or without necrotic core formation and/or calcification. The development of neoatherosclerosis may occur in months to years following stent placement, whereas atherosclerosis in native coronary arteries develops over decades. Pathological and clinical imaging studies have demonstrated that neoatherosclerosis occurs more frequently and at an earlier time point in drug-eluting stents as compared with bare metal stents, but increases over time in both types. The mechanisms of rapidly developing neoatherosclerosis remain unknown; however, endothelial dysfunction and reduced integrity may contribute. In-stent plaque rupture probably accounts for most thrombotic events associated with neoatherosclerosis, but also may be involved in in-stent restenosis. Future studies should assess the impact of iterations in stent technology and risk factor modification on disease progression. Similarly, refinements in imaging techniques are also warranted to permit more reliable detection of neoatherosclerosis.

In the first FAST TRACK manuscript, ‘The association between in-stent neoatherosclerosis and native coronary artery disease progression: a long-term angiographic and optical coherence tomography cohort study’11, Lorenz Räber and colleagues from Bern University Hospital in Switzerland continue on this subject as they investigated the relationship between in-stent neoatherosclerosis and native atherosclerosis progression of untreated coronary segments. In-stent neoatherosclerosis was assessed among 88 patients included in the SIRTAX-LATE OCT study with 88 lesions available for optical coherence tomography (OCT) analysis12. 5 years after sirolimus-eluting or paclitaxel-eluting stent implantation. Neoatherosclerosis was defined as the presence of fibroatheroma or fibrocalcific plaques within the neointima of stented segments with a longitudinal extension of >1 mm. Atherosclerosis progression in untreated native coronary segments was evaluated by serial quantitative coronary angiography (QCA). The key clinical endpoint was non-target lesion revascularization throughout 5 years. In-stent neoatherosclerosis was observed in 16% of lesions, with 11% of plaques being fibroatheromas and 5% fibrocalcific. A total of 704 non-target lesion segments were serially evaluated by QCA. Between baseline and 5-year follow-up, the reduction in minimal lumen diameter was more pronounced in patients with neoatherosclerosis as compared with those without it. Similarly, non-target lesion revascularization had to be performed in three-quarters of patients with neoatherosclerosis, but in less than half of those without it. The authors conclude that in-stent neoatherosclerosis is more common among patients with angiographic and clinical evidence of native atherosclerosis progression, suggesting similar pathophysiological mechanisms. This issue is also discussed in a comprehensive Editorial by Michael Joner from the CVPath Institute Inc. in Gaithersburg, Maryland USA.13

Chronic inflammation not only plays an important role in atherosclerosis,14 but also appears to be involved in aortic stenosis.15 Of note, psoriasis, a chronic inflammatory disease, is associated with increased risk of cardiovascular disease including atherosclerosis.16 As the pathogenesis of aortic stenosis also features an inflammatory component, Usman Khalid and colleagues from the Gentofte Hospital in Copenhagen, Denmark investigated the risk of this valvular...
condition in patients with psoriasis in their paper entitled ‘Increased risk of aortic valve stenosis in patients with psoriasis: a nationwide cohort study’. The study comprised the entire Danish population aged 18 years or older, followed until diagnosis of aortic stenosis or death. The authors found that among 5 107 624 subjects, 58 747 had mild and 11 918 patients severe psoriasis. The overall incidence rates for aortic stenosis were 8.09, 16.07, and 20.08 per 10 000 person-years for the reference population, mild psoriasis, and severe psoriasis, respectively. After full adjustment of the data, the risk of aortic stenosis was markedly increased in patients with mild (risk ratio 1.22) and particularly severe psoriasis (risk ratio 1.61). The authors conclude that in a nationwide cohort, psoriasis was associated with a disease severity-dependent increased risk of aortic stenosis. The mechanisms underlying this novel finding require further study, an aspect that is also discussed in an accompanying Editorial by Joel M. Gelfand from the University of Pennsylvania in Philadelphia, USA.

Vascular disease affects not only the coronary circulation, but also large arteries such as the aorta. Some of them are genetic in nature and need special attention. In the second FAST TRACK ‘Marfan Sartan: a randomized, double blind, placebo-controlled trial’ by Guillaume Jondeau from the Hopital Bichat in Paris, France the authors focused on this patient group and aimed to determine if inhibition of the angiotensin receptor by losartan prevents aortic dilatation in humans with Marfan syndrome as is suggested by mouse models. They randomized in a multicentre, placebo-controlled trial 303 patients with Marfan syndrome to either losartan or placebo with a median follow up of 3.5 years. The two groups were similar at baseline, 86% receiving beta-blocker therapy. Patients on losartan had a slight, but significant decrease in blood pressure. The evolution of aortic diameter at the level of the sinuses of Valsalva was not modified by losartan, with a mean increase of 0.44 mm/year and 0.51 mm/year in those receiving placebo. During the study period, aortic surgery was performed in 28 patients, i.e. 15 on losartan and 13 on placebo. There were very few deaths, occurring in only three patients, none on losartan and three on placebo. The authors conclude that losartan was able to decrease blood pressure in patients with Marfan syndrome, but unable to limit aortic dilatation during a 3-year period. Beta-blocker therapy alone should therefore remain the standard of care in these patients. This paper is accompanied by an Editorial by Julie De Backer from the University Hospital Ghent Belgium.

Osteopontin is a multifunctional cytokine critically involved in coronary artery disease and cardiac fibrosis. However, the underlying mechanisms are unresolved. In the fourth Basic Science paper entitled ‘Osteopontin is indispensable for AP1-mediated angiotensin II-related miR-21 transcription during cardiac fibrosis’, Thomas Thum and colleagues from the Hannover Medical School in Germany noted that non-coding RNAs are powerful regulators of gene expression and thus might mediate this process. In this study, osteopontin and miR-21 were significantly increased in cardiac biopsies of patients with myocardial fibrosis. In wild-type, but not osteopontin knockout mice, angiotensin II infusion via osmotic minipumps led to specific miRNA regulations, with miR-21 being strongly induced. This was associated with enhanced cardiac collagen content, myofibroblast, ERK–MAP kinase, as well as AKT signalling pathway activation and reduced expression of Phosphatase and Tensin Homologue as well as SMAD7 in wild-type, but not osteopontin knockout mice. In contrast, cardiotoxic adeno-associated virus 9-mediated overexpression of osteopontin in vivo further enhanced cardiac fibrosis. In vitro, angiotensin II induced expression of miR-21 in wild-type cardiac fibroblasts, while miR-21 levels were unchanged in osteopontin knockout fibroblasts. As pri-miR-21 was also increased by angiotensin II, the authors studied potentially involved upstream regulators; electrophotoretic mobility shift and chromatin immunoprecipitation analyses confirmed activation of the miR-21 upstream transcription factor AP-1 by angiotensin II. Recombinant osteopontin activated miR-21 and the phosphoinositide 3-kinase pathway and enhanced fibrosis. Locked nucleic acid-mediated miR-21 silencing ameliorated cardiac fibrosis development in vivo. The authors conclude that in cardiac fibrosis related to angiotensin II, miR-21 is transcriptionally activated and targets Phosphatase and Tensin Homologue as well as SMAD7, resulting in increased fibroblast survival. Osteopontin knockout animals were protected from miR-21 increase and fibrosis development due to impaired AP-1 activation and fibroblast activation. This paper is put into perspective by an Editorial by Gianluigi Condorelli from the University of Milan in Rozzano, Italy.

The editors hope that this issue of the European Heart Journal will be of interest to its readers.

References


