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Atherosclerosis newsletter

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Issues 380 and 381 of *Atherosclerosis* contain several articles that describe the use of non-invasive methods for the assessment of manifest or emerging atherosclerotic cardiovascular diseases for differential diagnosis or prognosis.

Association of retinal microvascular density and complexity with incident coronary heart disease

The high mortality rate and huge disease burden of coronary heart disease (CHD) highlight the importance of its early detection and timely intervention. Currently, the assessment of coronary microvasculature with invasive coronary angiography is the gold standard for the diagnosis of CHD. While this shows a high degree of specificity and sensitivity in determining the presence and severity of CHD, it is not a suitable screening tool for CHD, due to technical challenges, complex procedures, and its invasiveness. To allow early detection and preventative healthcare, a noninvasive and cost-efficient diagnostic screening tool for CHD is warranted. Given the non-invasive nature of fundus photography and recent development in the quantification of retinal microvascular parameters with deep learning techniques, Fu et al. aimed to investigate the association between incident CHD and retinal microvascular parameters.

UK Biobanks participants with gradable fundus images and without a history of diagnosed CHD at recruitment were included in the analysis. A fully automated artificial intelligence system was used to extract quantitative measurements that represent the density and complexity of the retinal microvasculature, including fractal dimension (Df), number of vascular segments (NS), vascular skeleton density (VSD) and vascular area density (VAD).

A total of 57,947 participants (mean age 55.6 ± 8.1 years; 56% female) without history of diagnosed CHD were included. During a median follow-up of 11.0 years, 3211 incident CHD events occurred. In multivariable Cox proportional hazards models, decreasing Df, lower NS of arteries and venules were found, and reduced arterial VSD and venous VSD were related to an increased risk of incident CHD. A significant association between retinal microvascular parameters and incident CHD was observed.

The study supports the potential of the quantitative retinal structure measurements in predicting individuals with a high risk of incident CHD.

Bivariate relation of vascular health and blood pressure progression during childhood

Hypertension and obesity are main risk factors for the development of cardiovascular disease (CVD). Classical and lifestyle-related risk factors are linked to pre-atherosclerosis and endothelial dysfunction in children, which may lead to CV events later in life. An increased incidence of elevated blood pressure (BP) among children and adolescents has been shown in epidemiological surveys. Childhood hypertension has been shown to track into adulthood. Furthermore, childhood CV risk factors have been related to adult CV events. Previously published baseline results of Hauser et al. demonstrated that children with high BP and obesity had narrower central retinal arteriolar equivalents (CRAE) and a higher pulse wave velocity (PWV) compared to normal weight peers. In this study, the authors aimed to assess the association of retinal microvascular diameters and large artery pulse wave velocity (PWV) with progression of childhood BP.

In their prospective Basel cohort study, 1171 children aged 6–8 years were screened for BP, body mass index, retinal vessel diameters and PWV using standardized protocols. After 4 years, all parameters were assessed in 749 children using the same protocols.

Children with narrower CRAE and higher PWV at baseline developed higher systolic BP after 4 years. Children with increased systolic BP at baseline developed narrower CRAE and higher PWV at follow-up.

Retinal arteriolar diameter and PWV independently predicted progression of childhood BP, while initial BP was linked to development of micro- and macrovascular impairments, describing a bivariate temporal relationship between vascular health and BP. Childhood may present a window of opportunity for initiation of primary prevention strategies for the treatment of high BP to help prevent manifestation of CVD later in life.

Arterial stiffness but not carotid intima-media thickness progression precedes premature structural and functional cardiac damage in youth: A 7-year temporal and mediation longitudinal study

Arterial stiffness predicts future atherosclerotic cardiovascular disease (ASCVD) and causal ASCVD risk factors in the young and middle-aged population. The pathway through which arterial stiffness may exert its influence on cardiac structure and function in youth is unclear. Agbaje et al. examined the temporal causal path and mediation longitudinal associations of progression in arterial stiffness and carotid thickness with the risk of worsening structural and functional cardiac damage among adolescents and young adults.

1856 adolescents from the Avon Longitudinal Study of Parents and Children, UK birth cohort, (mean age 17.7 years) were followed up for 7 years. Vicorder-measured carotid-femoral pulse wave velocity (cfPWV) and ultrasound-measured carotid intima-media thickness (cIMT) were grouped in tertiles as low (reference), moderate, and high. Echocardiography-measured cardiac abnormalities are

left ventricular mass indexed for height$^{2.7}$ (LVMI$^{2.7}$) ≥51 g/m$^{2.7}$ as left ventricular hypertrophy (LVH); relative wall thickness (RWT) ≥44 as hiRWT; left ventricular diastolic (LVD) function E/A <1.5 as LVD dysfunction (LVDD); and left ventricular (LV) filling pressure E/e' ≥8 as hiLVFP. Data were analysed with generalized logit mixed-effect models, cross-lagged path, and mediation structural equation models adjusting for cardiometabolic and lifestyle factors.

Over follow-up, LVH prevalence increased from 3.6% to 7.2% and LVDD from 11.1 to 16.3%. High cfPWV progression was associated with worsening LVH in the total cohort, males, overweight/obese, and normotensive. High cfPWV progression was associated with worsening hiLVFP in the total cohort, females, and normal weight. Likewise, high cIMT progression was associated with worsening LVH in the total cohort, overweight/obese and elevated BP/hypertensive. Neither cfPWV nor cIMT progression was associated with worsening hiRWT in the total cohort. In cross-lagged models, higher baseline cfPWV was associated with future LVMI$^{2.7}$, RWT, LVDF, and LVFP. However, baseline LVMI2.7, RWT, LVDF, and LVFP were not associated with follow-up cfPWV. Baseline cIMT was not associated with follow-up cardiac indices and vice versa. Cumulative increased systolic blood pressure (34.3% mediation) and insulin resistance (15.1% mediation) mediated the direct associations of cumulative cfPWV with cumulative LVMI$^{2.7}$.

Arterial stiffness progression temporally preceded worsening structural and functional cardiac damage in youth with increased systolic blood pressure and insulin resistance partly mediating the relationships.

Association between telomere length and intima-media thickness of both common carotid arteries in patients with coronary heart disease: From the CORDIOPREV randomized controlled trial

Telomeres are repetitive nucleotide sequences (5'-TTAGGG-3')n at the end of chromosomes, which provide protection and maintenance of genetic material. In each cell division, telomere length (TL) is progressively shorten due to the absence of telomerase in most cells; thus, TL is considered a biomarker of cellular aging. Telomere attrition seems to be accelerated by various inflammatory and stress conditions, as well as by environmental factors (e.g. diet quality, physical activity, alcohol intake, smoking habits). A critical telomere length (TL) is associated with cardiovascular mortality. Dietary habits have been demonstrated to affect cardiovascular risk. However, it remains unclear how exactly TL determines the response to specific dietary approaches in the reduction of arterial injury. Ojeda-Rodriguez et al. aimed to evaluate whether TL was associated with progression of arterial injury (assessed by intima-media thickness of both common carotid arteries: IMT-CC), after long-term consumption of two healthy dietary models in patients with coronary heart disease (CHD).

From the 1002 CHD patients of the CORDIOPREV study, 903 completed IMT-CC and TL evaluation at baseline and were randomized to follow a Mediterranean diet or a low-fat diet for 5 years.

Patients at risk of short TL (TL < 20th percentile) presented an elevated IMT-CC, TL and IMT-CC showed an inverse association. Patients who consumed a Mediterranean diet, regardless of the risk of short TL, showed a significant decrease in IMT-CC, with a higher reduction in those patients with risk of short TL. TL, age, energy intake, use of statins and allocation into the Mediterranean diet (*vs* low-fat diet) were significant contributors to changes in IMT-CC.

Patients who had a reduced TL exhibited a greater decrease in IMT-CC after consuming a Mediterranean diet.

Low adherence to the Mediterranean diet is associated with increased prevalence and number of atherosclerotic plaques in the ILERVAS cohort

Subclinical atherosclerotic disease (SAD), defined as signs of atherosclerotic cardiovascular disease (ACD) at early stages, is commonly revealed by the presence of atherosclerotic plaque(s) in the carotid, aortic, or iliofemoral territories. Accumulating evidence suggests that healthy dietary patterns, particularly adherence to the Mediterranean Diet (MDiet), are protective against CVD and the development of atherosclerotic plaques (AP). Current research on the association between dietary patterns and subclinical atherosclerotic disease (SAD) is still limited, and published results are inconsistent and with small population sizes. Rojo-López et al. aimed to evaluate the association between MDiet and SAD in a large cohort of Mediterranean individuals.

This cross-sectional study included 8116 subjects from the ILERVAS cohort. The presence of AP was assessed by ultrasound examination. Adherence to MDiet was assessed using the 14-item Mediterranean Diet Adherence Score (MEDAS). Inclusion criteria were subjects with at least one cardiovascular risk factor. Exclusion criteria were a clinical history of diabetes, chronic kidney disease, or a prior cardiovascular event. Bivariable and multivariable models were performed.

Compared with subjects without SAD, those with SAD were older and had a higher frequency of smoking habit, hypertension, dyslipidemia, HbA1c and waist circumference. The adjusted multivariable analysis showed that a higher MEDAS was associated with a lower risk of AP. Furthermore, moderate or high adherence to MDiet was associated with a lower number of AP compared with a low MDiet adherence. In both models, female sex was associated with a lower risk of AP.

These findings point to a potentially protective role of MDiet for SAD in a Mediterranean population with low-to-moderate cardiovascular risk.

The correlation between medial pattern of intracranial arterial calcification and white matter hyperintensities

Intracranial arterial calcification (IAC) is found to be an independent risk factor for stroke. Apart from its association with intracranial large artery atherosclerosis, IAC may also correlate to cerebral small vessel disease (CSVD), of which white matter hyperintensities (WMH) is one of the common types on neuroimaging. However, current studies about the impact of IAC on WMH are controversial. In this study, Du et al. investigated the association between IAC pattern (intimal IAC and medial IAC) and the presence and burden of WMH.

Consecutive acute stroke patients were included. IAC pattern was categorized as intimal or medial on plain brain CT. The number of cerebral arteries involved by IAC for each patient was recorded. IAC severity was defined as focal or diffuse. On brain MRI, the burden of WMH was visually graded and classified as absent mild, moderate and severe. Multiple logistic regression was performed to examine the relationship between IAC and WMH.

Among 265 patients, intimal IAC was detected in 54.7% patients and medial IAC in 48.5% patients. Diffuse IAC was present in 27.9% patients, all of which were medial. WMH was found in 75.5% patients, including 39.6% patients with mild WMH, 26.0% with moderate WMH, and 9.8% with severe WMH. The severity of medial IAC was correlated with WMH occurrence. Chi-square linear trend suggested the number of arteries involved by medial IAC and the severity of medial IAC were correlated with WMH burden. Multiple ordinal logistic regression demonstrated a positive correlation of WMH burden with the number of arteries involved by medial IAC and the severity of medial IAC.

Medial IAC was correlated with WMH. The dose-effect relationship between medial IAC and WMH suggested underlying shared mechanisms of intracranial large artery disease and small vessel disease.

Computed tomography perfusion and angiography in patients with chronic total occlusion undergoing percutaneous coronary intervention

Chronic total occlusions (CTO) are observed in approximately 20% of patients referred for invasive coronary angiography. Myocardial perfusion imaging (MPI) and anatomical imaging with coronary computed tomography angiography (CCTA) can play an important role in the preprocedural planning of a CTO percutaneous coronary intervention (PCI). Kwiecinski et al. aimed to establish the feasibility of a novel dynamic computed tomography perfusion (CTP) analysis for the assessment of myocardial perfusion before and after a successful recanalization of CTO in patients undergoing CCTA as part of a standard preprocedural workup.

In a prospective observational study, symptomatic patients underwent dynamic CTP on a dual-source CT scanner before and 3 months after successful CTO PCI.

Twenty-seven patients completed the study (63 ± 8 years old, 78% male). Following successful CTO PCI, there was a significant reduction in the ischemic burden, and improvement in myocardial blood flow resulting in an increase in the relative flow reserve.

CTP emerges as a robust and safe method for MPI in CTO patients. The single imaging session assessment of both coronary anatomy and perfusion with CT lends itself to precise disease phenotyping in the challenging population of CTO patients.

Improving detection of obstructive coronary artery disease with an artificial intelligence-enabled electrocardiogram algorithm

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in developed countries. To evaluate the risk of CAD, the traditional approach involves assessing patient's symptoms, traditional cardiovascular risk factors (CVRFs), and a 12-lead electrocardiogram (ECG). However, currently, there are no established criteria for interpreting an ECG to diagnose CAD. Using large databanks of ECG as input, artificial intelligence (AI) algorithms have been able to detect ECG patterns otherwise unrecognizable by the human eye that can indicate cardiac diseases. In this context, Lee et al. aimed to develop an AI-enabled ECG model to assist in identifying patients with CAD.

They included in the study patients who underwent coronary angiography (CAG) at a single center between 2017 and 2019. Preprocedural 12-lead ECG performed within 24 h was obtained. Obstructive CAD was defined as a ≥50% diameter stenosis. Using age, gender and ECG data, the authors developed stacking models with both deep learning and machine learning. Then they compared the performance of their models with CVRFs and with cardiologists' ECG interpretation. Additionally, they validated their model on an external cohort from a different hospital.

4951 patients (67% men, mean age 65.5 ± 12.5 years) were included. Based on CAG, obstructive CAD was confirmed in 2637 patients (53.2%). The AI model demonstrated comparable performance to CVRFs in predicting CAD, with an AUC of 0.70 compared to 0.71. The sensitivity and specificity of the AI model were 0.75 and 0.54, respectively, while those of CVRFs were 0.67 and 0.63. Compared to cardiologists, the AI model showed better performance with an F1 score of 0.68 *vs* 0.41. The external validation showed generally consistent diagnostic findings, although there was a slightly lower level of agreement observed in the external cohort. Incorporating ECG and CVRFs improved the AUC to 0.72.

This study suggests that an AI-enabled ECG model can assist in identifying patients with obstructive CAD, with diagnostic performance similar to that of the traditional approach based on CVRFs.

Effects of activity levels on aortic calcification in hyperlipidemic mice as measured by microPETmicroCT

Cardiovascular calcification, especially coronary artery calcification (CAC), is associated with risk for adverse cardiovascular events and mortality, and often coexists with osteoporosis, whereas physical activity is associated with lower risk for cardiovascular events and mortality. A study shows that exercise intensity, but not exercise volume, is associated with changes in CAC. Prevalence of cardiovascular disease and risk factors were lower with low and moderate volumes of exercise but not benefited by higher doses of exercise. In this study, Hon et al. compared the effects of low- and high-speed exercise regimens on quantitative cardiovascular and skeletal bone parameters in mice with underlying calcific atherosclerosis.

Female hyperlipidemic (*Apoe*$^{-/-}$) mice with baseline aortic calcification were subjected to high-speed (18.5 m/min), low-speed (12.5 m/min), or no treadmill exercise for 9 weeks. ^{18}F–NaF microPET/CT images were acquired at weeks 0 and 9, and echocardiography was performed at week 9.

In controls, aortic calcium content and density increased significantly. Exercise regimens did not alter the time-dependent increase in content, but the increase in mean density was blunted. Interestingly, the low-speed regimen significantly reduced ^{18}F–NaF uptake, a marker of surface area. Left ventricular (LV) systolic function was lower while LV diameter was greater in the low-speed group compared with controls or the high-speed group. In the low-speed group, vertebral bone density by CT decreased significantly, contrary to expectations. Male hyperlipidemic (*Apoe*$^{-/-}$) mice were fed a Western diet and ubjected to low-speed or no exercise followed by imaging at weeks 0 and 9. In males, exercise did not alter the time-dependent increase in aortic calcification. Exercise did not affect ^{18}F–NaF uptake or bone mineral density, but it blunted the diet-induced LV hypertrophy seen in controls.

These results suggest that in mice exercise has differential effects on aortic calcification, cardiac function, and skeletal bone mineral density.