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We here summarize some articles, recently published in *Atherosclerosis,* that investigated different methods for the measurement of cardiovascular functions towards their analytical or clinical performance.

The relationship between cardiorespiratory fitness, cardiovascular risk factors and atherosclerosis

Cardiorespiratory fitness (CRF) refers to the ability of the cardiopulmonary system to supply oxygen to skeletal muscles during exercise. Regular physical activity optimizes these systems by physiologic means that not only decrease cardiovascular risk factors but also independently affect mortality. Importantly, CRF is an integrative measure of the effects of its upstream risk factors including physical activity and genetics.

In this review, Chu et al. summarize the main methods that are frequently used to estimate CRF. Findings from the major studies on CRF are cited, which demonstrate a beneficial effect on prevalent cardiovascular risk factor burden, subclinical atherosclerosis, and incident adverse outcomes including death, myocardial infarction, stroke, and cancer. The authors conclude by suggesting the incorporation of CRF into clinical decision-making given the prognostic information it provides.

The impact of pre-procedure heart rate on adverse clinical outcomes in patients undergoing percutaneous coronary intervention: Results from a 2-year follow-up of the GLOBAL LEADERS trial

The prognostic impact of pre-procedure heart rate (PHR) following percutaneous coronary intervention (PCI) has not yet been fully investigated. In this *post-hoc* analysis, Wang et al. aimed to assess the impact of PHR on medium-term outcomes among patients undergoing PCI, enrolled in the "all-comers" GLOBAL LEADERS trial.

The primary endpoint (composite of all-cause death or new Q-wave myocardial infarction [MI]) and key secondary safety endpoint (bleeding according to Bleeding Academic Research Consortium [BARC] type 3 or 5) were assessed at 2 years. PHR was available in 15,855 patients, and when evaluated as a continuous variable and following adjustment using multivariate Cox regression, it significantly correlated with the primary endpoint. Using dichotomous cut-off criteria, a PHR >67 bpm was associated with increased all-cause mortality and more frequent new Q-wave MI. No significant association was found between PHR and BARC 3 or 5 bleeding. There was no interaction with the primary or secondary endpoint when high and low PHR was analyzed according to different antiplatelet strategies.

Elevated PHR was an independent predictor of all-cause mortality at 2 years following PCI in the "all-comer" GLOBAL LEADERS trial. Ticagrelor monotherapy *versus* standard dual antiplatelet therapy did not improve the bad ischemic prognosis of PHR.

Carotid intima-media thickness and subclinical left heart dysfunction in the general population

Although carotid intima-media thickness (IMT) is an established marker of atherosclerosis and carries independent risk for cardiovascular disease, its possible association with subclinical cardiac dysfunction has not been extensively evaluated. Left ventricular global longitudinal strain (LVGLS) and peak left atrial longitudinal systolic strain (PALS) can detect subclinical left heart dysfunction. Nakanishi et al. aimed to investigate the association between carotid IMT and subclinical left heart dysfunction in a sample of the general population without overt cardiac disease.

They examined 1161 participants who underwent extensive cardiovascular examination. Ultrasonography of common carotid artery was performed for the measurement of maximal carotid IMT. LVGLS and PALS were assessed by 2-dimensional speckle-tracking echocardiography.

The prevalence of abnormal LVGLS and PALS was greatest in the upper quartile of carotid IMT. In multivariable analyses, carotid IMT was associated with abnormal LVGLS as well as PALS independent of traditional cardiovascular risk factors, echocardiographic parameters including left ventricular (LV) ejection fraction, LV mass index and diastolic dysfunction, and pertinent laboratory parameters. The independent association between carotid IMT and PALS persisted even after adjustment for LVGLS.

Participants with increased IMT had significantly impaired LV and left atrium (LA) function in an unselected community-based cohort. This association may be involved in the higher incidence of cardiovascular disease in individuals with increased carotid IMT.

Comparison of different ankle-brachial indices in the prediction of overall and cardiovascular mortality

Low ankle-brachial index (ABI) calculated using systolic blood pressure (SBP) (ABIsbp) is associated with an increased overall and cardiovascular (CV) mortality in different populations, such as patients with chronic kidney disease, hemodialysis, ischemia heart disease, diabetes, and atrial fibrillation. However, there is no study assessing ABI calculated using mean artery pressure (MAP) (ABImap) and diastolic blood pressure (DBP) (ABIdbp) in predicting mortality. Hsu et al. aimed to evaluate whether ABImap and ABIdbp are useful parameters in the prediction of overall and CV mortality. In addition, this study was aimed to identify the best cutoff values of ABImap and ABIdbp in the prediction of peripheral artery disease (PAD).

Two cohort populations were enrolled. The first population comprised 379 patients (106 patients with angiography-proved peripheral artery disease (PAD) and 273 relative normal patients) to evaluate the best cutoff values of ABImap and ABIdbp for prediction of PAD. The second population included 941 patients undergoing echocardiographic examinations to assess the ability of different ABIs in predicting mortality. ABIs were measured using an ABI-form device.

The best cutoff values of ABImap and ABIdbp for prediction of PAD were 0.92 and 0.88, respectively. In the second population, median follow-up to mortality was 93 months. There were 87 cardiovascular and 228 overall deaths. In a direct comparison of 6 multivariable models, the basic model (consisting of significant variables in the univariable analysis) plus ABImap <0.92 had the highest predictive value for overall and cardiovascular mortality.

These results suggest that calculation of ABI using MAP except SBP might provide extra benefit in survival prediction.

Distance measurement for pulse wave velocity estimation in pediatric age: Comparison with intra-arterial path length

Central pulse wave velocity (PWV) is a marker of arterial stiffness, and consequently a strong predictor of cardiovascular outcome, and is calculated by dividing the pulse wave travel distance by the transit time. To date, there is no consensus as to the ideal distance measurement in children. Reusz et al. aimed to identify a more reliable method to assess the distance measurement in the pediatric age.

Carotid-femoral PWV was measured by applanation tonometry in 988 healthy children aged 6.5–19.9 years. Two different surface distances were assessed: the subtraction method, representing the distance from the suprasternal notch to the femoral artery minus the distance from the carotid artery to the suprasternal notch, and the direct method, consisting of 80% of the distance from the

carotid artery to the femoral artery. Both these methods were compared with the actual path length determined by magnetic resonance imaging (MRI) in 31 children.

Subtraction and direct methods were significantly correlated in patients aged <14 years and the corresponding PWV values showed a good agreement. In children aged ≥14 years, a significant difference between the two methods was found: subtraction - direct distance = -45 ± 28 mm, with a significant difference in the resulting PWV values = -0.57 ± 0.35 m/s. This result was confirmed by MRI, showing a 10% overestimation in distance measurement by the direct method in subjects aged ≥14 years, resulting in a significantly higher PWV.

These data suggest that the use of the "subtractive" method is recommended in children since it shows greater reliability that the direct method.

Effects of dipeptidyl peptidase 4 inhibition on inflammation in atherosclerosis: A 18F-fluorodeoxyglucose study of a mouse model of atherosclerosis and type 2 diabetes

Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists have been shown to prevent progression of atherosclerosis and cardiovascular complications in patients with type 2 diabetes mellitus (T2DM), but the underlying mechanisms are incompletely understood. Virta et al. evaluated the effects of the DPP-4 inhibitor linagliptin on atherosclerotic plaque and hepatic inflammation using histology and 2-deoxy-2-[^{18}F]-fluoro-d-glucose (^{18}F-FDG), a positron emission tomography tracer of inflammation, in a mouse model of hypercholesterolemia and type 2 diabetes.

Igf2/Ldlr$^{-/-}$*Apob*$^{100/100}$ mice were fed a high-fat diet (HFD) for 8 weeks and then randomly allocated to receive HFD, or HFD with linagliptin for 12 additional weeks. Five mice fed a chow diet were studied as control. At the end of the study, glucose tolerance, aortic and liver uptake of ^{18}F-FDG, and histology were studied.

Mice in the linagliptin and HFD groups had similar fasting glucose concentrations, but linagliptin improved glucose tolerance. Aortas of linagliptin and HFD groups showed advanced atherosclerotic plaques with no difference in the mean intima-to-media ratio or number of macrophages in the plaques. Autoradiography showed similar ^{18}F-FDG uptake by atherosclerotic plaques in linagliptin and HFD groups. In the liver, linagliptin reduced the histologic inflammation score but had no effect on ^{18}F-FDG uptake. Compared with chow diet, uptake of 18F-FDG was similar in the aorta, but higher in the liver after HFD.

Linagliptin therapy improved glucose tolerance and reduced hepatic inflammation but had no effect on plaque burden or atherosclerotic inflammation in atherosclerotic mice with type 2 diabetes.