Arterial stiffness, Microalbuminuria and Endothelial Dysfunction in CAD

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Arterial stiffness is increasingly recognized as a potent and independent predictor of adverse cardiovascular outcomes. It is known to be caused by the aging process and many disease states such as diabetes, atherosclerosis, and chronic renal disease. Increased thickness of the intima-media and endothelial dysfunction underlie its mechanism. Although considered as a contributing factor in the mechanism of arterial stiffness, arterial thickness itself is an independent predictor of cardiovascular events.

Microalbuminuria and Arterial stiffness

Microalbuminuria is also known as a strong, independent predictor of cardiovascular events and deaths, and an indicator of endothelial dysfunction or developing atherosclerosis. Cottone et al reported recently that the positive and independent correlation between PWV and AER in untreated nondiabetic essential hypertensives with normal renal function. Aortic distensibility and microalbuminuria have been related with cardiovascular prognosis.

Aortic Pulse Wave Velocity and Cardiovascular Disease

Arterial stiffness has been known as a major contributory factor to cardiovascular (CV) morbidity and mortality in patients with hypertension. Pulse wave velocity (PWV) is widely used for a surrogate measurement of large artery damage. We prospectively enrolled 326 consecutive patients undergoing coronary angiography and measured PWV invasively for the assessment of suspected CAD. PWV was higher in patients with CAD than those without CAD(12.5 _ 5.1 vs 10.2 _ 3.1 m/s, p _ 0.001). In multivariate logistic regression analysis, after entering for age, diabetes and other CV risk factors, PWV remained the significant independent variable for CAD(p = 0.050). When the severity of CAD was expressed as one-, two- or three-vessel disease, PWV was a significantly associated with the severity of CAD (p _ 0.001). For prospective study, we measured direct Intra-arterial aorto-femoral PWV at baseline in 1,004 patients with chest pain. Among these patients, 497 (237 male) were enrolled in the study. Tertiles were defined as follows: tertile 1, $\leq$9.20 m/sec; tertile 2, 9.21 to 12.49 m/sec; and tertile 3, $\geq$12.50 m/sec. The impact of aPWV on newly developed CV events, CAD, stroke, and congestive heart failure was evaluated. the mean duration of follow-up was 31.31 $\pm$ 15.25 months. A higher aPWV was associated with new CV events (odds ratio, 2.18 for tertile 3 *v* tertile 1; 95% confidence interval [CI], 1.32 to 3.60) and new CAD (odds ratio, 1.87 for tertile 3 *v* tertile 1; 95% CI, 1.10 to 3.18) in univariate analysis. In multivariate analysis, aPWV was associated with new CV events (odds ratio, 2.05 for tertile 3 *v* tertile 1; 95% CI, 1.18 to 3.55) and new CAD (odds ratio, 1.86 for tertile 3 *v* tertile 1; 95% CI, 1.03 to 3.35). Aortic pulse-wave velocity was not associated with either new stroke (P = .096) or congestive heart failure (P = .63). PWV is

an independent risk factor for future CV events and CAD in patients with chest pain.

Endothelial Dysfunction and Spasm in Coronary Myocardial Bridge

The longstanding compression-relaxation effects of myocardial bridging(MB) may produce endothelial dysfunction by direct stress on the endothelium. We tested the hypothesis that myocardial bridging induces endothelial dysfunction and subsequently increases the risk of coronary spasm and investigated the symptomatic response to medication in patients with documented myocardial bridging and coronary spasm. In 81 patients with myocardial bridging (44 men; mean age 57.2 years) and 195 control patients without bridging and atherosclerotic lesions confirmed by angiography (97 men; mean age 58.4 years), spasm provocation testing was done by incremental acetylcholine infusion into the left coronary artery. Spasm was documented in 62 of 81 patients with bridging and in 31 of 195 controls ($p < 0.001$). A focal spasm was limited to the bridging segments compared with controls ($p < 0.001$). The results of this study showed that myocardial bridging increased the risk of coronary spasm by endothelial dysfunction in the bridging segment. We also studied 128 patients (54.7±10.9 yr, 42 men) with typical angiographic systolic milking effects having greater than a 30 % reduction in diameter of the coronary artery during systole after intracoronary nitrate (NTG, 200 μg) infusion. There were 231 control patients without overt coronary artery disease including MB (54.1±13.2 yr, 111 men). Endothelial function was estimated by incremental acetylcholine infusion (Ach: 20, 50 and 100 μg/min) into the left coronary ostium. Assessments using intracoronary ultrasound (ICUS) were obtained in 74/128 patients with MB and 81/231 controls.
The mean vasoconstrictive response to maximal Ach was more pronounced at the bridging segments than at matched segments in the controls (-71.9±24.4 vs. -30.3±22.6, $p = 0.009$). Coronary vasoconstriction (> 50 %) to Ach was seen more frequently in the MB group than in controls (114/128 (89.8 %) vs. 81/231 (35.1) %, $p = 0.007$). There was no significant correlation between the severity of MB and vasoconstriction in response to Ach. As determined by ICUS, there was a typical half-moon phenomenon in 71/74 (95.9 %) cases of the MB group, but not in controls ($p<0.001$). The plaques at the bridging segments were absent in 67/74 (90.5 %) and mild in 7/74 (9.5 %) cases, as compared with those of matched segments of the LAD in controls (plaque burden 5.91±1.37 % vs. 24.71±24.21 %, $p = 0.002$). Despite the prominent relationship between the MB and endothelial dysfunction, the bridging segments are spared from atherosclerotic plaque formation.

Plasma Adiponectin, Hypertension, Vasospam and Pulse Wave Velocity

To characterize the relationships among plasma adiponectin,essential hypertension, left ventricular diastolic function and left ventricular hypertrophy, we measured Plasma adiponectin concentration in 275 patients (138 women and 137 men) by radioimmunoassay, The plasma adiponectin concentration of the hypertensive group was significantly lower than that of the non-hypertensive group (9.9 $\pm$ 9.8 ug/ml vs. 12.9 $\pm$ 9.5 ug/ml, $p = 0.019$). PWV in the hypertensive group was 12.0 $\pm$ 3.9 m/s compared with 9.3 $\pm$ 2.8 m/s in the normotensive group ($p < 0.001$). LVMI in the hypertensive group was 135.1 $\pm$ 35.4 g/m2

compared with 100.5 ± 18.7 g/m2 in the normotensive group ($p < 0.001$). E/A ratio (0.8 ± 0.3 vs. 1.1 ± 0.4, $p = 0.041$) was lower in the hypertensive group. DT (200.0 ± 61.2 ms vs. 177.3 ± 40.8 ms, $p = 0.048$) and IVRT (106.9 ± 25.4 vs. 91.3 ± 27.6 ms, $p = 0.243$) were higher in the hypertensive group. Plasma adiponectin showed an inverse correlation with LVMI ($r = -0.525$; $p < 0.001$) and PWV ($r = -0.557$; p _ 0.001), IVRT ($r = -0.485$; $p = 0.008$), and showed a positive correlation with E/A ratio ($r = 0.359$; $p < 0.001$). Multiple regression analyses showed that PWV and plasma adiponectin were able to explain the 73.3% of LVMI variability ($r = 0.856$; $p < 0.001$). *We found* a decrease in plasma adiponectin concentration is associated with the progression of left ventricular hypertrophy with diastolic dysfunction.

Wemeasured plasma adiponectin concentrations in the vasospastic angina pectoris (VAP) group (n=101) were compared with
those of the acute coronary syndrome (ACS) group (n=117), the stable angina pectoris group (n=108), and the normal coronary group (n=81). Plasma adiponectin concentrations in VAP and ACS were significantly lower than that of the normal coronary group (6.6±5.4 vs 5.2±4.0 vs 9.0±6.2 g/ml, p<0.001, respectively). Multivariate analysis indicated that plasma adiponectin (odds ratio (OR) 0.735, 95% confidence interval (CI) 0.621–0.855, p=0.011), smoking (OR 2.012, 95% CI 1.210–3.880, p=0.020), and age (OR 0.976, 95% CI 0.957–0.997, p=0.022) correlated independently with the development of VAP. Our results suggest that a decrease in plasma adiponectin concentration might be associated with the development of VAP.