Dyslipidemia, cardiovascular diseases, coronary heart diseases and carotid stiffness
Used studies and abstracts

1. D Liao, R P Sloan, W E Cascio, A R Folsom, A D Liese, G W Evans, J Cai and A R Sharrett. Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities Study. Diabetes Care December 1998 vol. 21 no. 12 2116-2122

Abstract
OBJECTIVE: To test at the population level whether people with multiple metabolic syndrome (MMS) disorders have reduced cardiac autonomic activity (CAA). RESEARCH DESIGN AND METHODS: We examined the association between the level of CAA and MMS disorders, at the degree of clustering and the segregate combination levels, using a random sample of 2,359 men and women aged 45-64 years from the biracial, population-based Atherosclerosis Risk in Communities (ARIC) Study. Supine resting 2-min beat-to-beat heart rate data were collected. High-frequency (HF) (0.15-0.35 Hz) and low-frequency (LF) (0.025-0.15 Hz) spectral powers, the ratio of LF to HF, and the SD of all normal R-R intervals (SDNN) were used as the conventional indices of heart rate variability (HRV) to measure CAA. The MMS disorders included hypertension, type 2 diabetes, and dyslipidemia. RESULTS: HRV indices were significantly lower in individuals with MMS disorders. The multivariable adjusted mean HF was 0.85 (beat/min)2 in subjects with all three MMS disorders, in contrast to 1.31 (beat/min)2 in subjects without any MMS disorder. At the segregated combination level, the

multivariable adjusted means +/- SEM of HF were 1.34 +/- 0.05, 1.16 +/- 0.05, 1.01 +/- 0.17, and 1.34 +/- 0.05 (beat/min)2, respectively, for subjects without any MMS disorder, with hypertension only, with diabetes only, and with dyslipidemia only, and the means +/- SEM of HF were 0.93 +/- 0.04, 0.70 +/- 0.15, and 1.20 +/- 0.05 (beat/min)2, respectively, for subjects with diabetes and hypertension, diabetes and dyslipidemia, and hypertension and dyslipidemia. An increase in fasting insulin of 1 SD was associated with 88% higher odds of having a lower HF. The pattern of associations was similar for LF and SDNN. CONCLUSIONS: These findings suggest that MMS disorders adversely affect cardiac autonomic control and a reduced cardiac autonomic control may contribute to the increased risk of subsequent cardiovascular events in individuals who exhibit MMS disorders.

2. Takazawa, Kenji; Tanaka, Nobuhiro; Fujita, Masami; Matsuoka, Osamu; Saiki, Tokuyu; Aikawa, Masaru; Tamura, Sinobu; Ibukiyama, Chiharu Assessment of Vasoactive Agents and Vascular Aging by the Second Derivative of Photoplethysmogram Waveform Hypertension: Volume 32(2)August 1998pp 365-370

Abstract:
To evaluate the clinical application of the second derivative of the fingertip photoplethysmogram waveform, we performed drug administration studies (study 1) and epidemiological studies (study 2). In study 1, ascending aortic pressure was recorded simultaneously with the fingertip photoplethysmogram and its second derivative in 39 patients with a mean +/- SD age of 54 +/- 11 years. The augmentation index was defined as the ratio of the height of the late systolic peak to that of the early systolic peak in the pulse. The second derivative consists of an a, b, c, and d wave in systole and an e wave in diastole. Ascending aortic pressure increased after injection of 2.5 [micro sign]g angiotensin from 126/74 to 160/91 mm Hg and decreased after 0.3 mg sublingual nitroglycerin to 111/73 mm Hg. The d/a, the ratio of the height of the d wave to that of the a wave, decreased after angiotensin from -0.40 +/- 0.13 to -0.62 +/- 0.19 and increased after nitroglycerin to -0.25 +/- 0.12 (P<0.001 and P<0.001, respectively). The negative d/a increased with increases in plethysmographic and ascending aortic augmentation indices (r=0.79, P<0.001, and r=0.80, P<0.001, respectively). The negative d/a reflects the late systolic pressure augmentation in the ascending aorta and may be useful for noninvasive evaluation of the effects of vasoactive agents. In study 2, the second derivative of the plethysmogram waveform was measured in a total of 600 subjects (50 men and 50 women in each decade from the 3rd to the 8th) in our health assessment center. The b/a ratio increased with age, and c/a, d/a, and e/a ratios decreased with age. Thus, the second derivative aging index was defined as b-c-d-e/a. The second derivative wave aging index (y) increased with age (x) (r=0.80, P<0.001, y=0.023x-1.515). The second derivative aging index was higher in 126 subjects with any history of diabetes mellitus, hypertension, hypercholesterolemia, and ischemic heart disease than in age-matched subjects without such a history (-0.06 +/- 0.36 versus -0.22 +/- 0.41, P<0.01). Women had a higher aging index than men (P<0.01). The b-c-d-e/a ratio may be useful for evaluation of vascular aging and for screening of arteriosclerotic disease. (Hypertension. 1998;32:365-370.)(C) 1998 American Heart Association, Inc.

3. Toshiaki OTSUKA , Tomoyuki KAWADA , Masao KATSUMATA ,Chikao IBUKI , and Yoshiki KUSAMA Independent Determinants of Second Derivative of the Finger Photoplethysmogram among Various Cardiovascular Risk Factors in Middle-Aged Men Hypertens Res 2007; 30: 1211–1218)

Abstract
The second derivative of the finger photoplethysmogram (SDPTG) has been used as a non-invasive examination for arterial stiffness. The present study sought to elucidate independent determinants of the SDPTG among various cardiovascular risk factors in middle-aged Japanese men. The SDPTG was obtained from the cuticle of the left-hand forefinger in 973 male workers (mean age: 446 years) during a medical checkup at a company. The SDPTG indices (b/a and d/a) were calculated from the height of the wave components. Multiple logistic regression analyses revealed that the independent determinants of an increased b/a (highest quartile of the b/a) were age (odds ratio [OR]: 1.12 per 1-year increase, 95% confidence interval [CI]: 1.09–1.15), hypertension (OR: 1.65, 95% CI: 1.03–2.65), dyslipidemia (OR: 1.51, 95% CI: 1.09–2.09), impaired fasting glucose/diabetes mellitus (OR: 2.43, 95% CI: 1.16–5.07), and a lack of regular exercise (OR: 2.00, 95% CI: 1.29–3.08). Similarly, independent determinants of a

decreased d/a (lowest quartile of the d/a) were age (OR: 1.11 per 1-year increase, 95% CI: 1.08–1.14), hypertension (OR: 3.44, 95% CI: 2.20–5.38), and alcohol intake 6 or 7 days per week (OR: 2.70, 95% CI: 1.80–4.06). No independent association was observed between the SDPTG indices and blood leukocyte count or serum C-reactive protein levels. In conclusion, the SDPTG indices reflect arterial properties affected by several cardiovascular risk factors in middle-aged Japanese men. The association between inflammation and the SDPTG should be evaluated in further studies.

4. Toshiaki Otsuka, , Tomoyuki Kawada, Masao Katsumata, and Chikao Ibuki, Utility of Second Derivative of the Finger Photoplethysmogram for the Estimation of the Risk of Coronary Heart Disease in the General Population Circ J 2006; 70: 304 – 310

Abstract
Background Increased arterial stiffness has been shown to be associated with coronary heart disease (CHD). However, it remains unclear as to whether the second derivative of the finger photoplethysmogram (SDPTG), a non-invasive method for the assessment of arterial stiffness, is useful for the estimation of risk of CHD in the general population. Methods and Results The SDPTG in 211 subjects (age: 63±15 years, range: 21-91 years, 93 males) was recorded without apparent atherosclerotic disorders from a community. The relationship between the SDPTG indices (b/a and d/a) and coronary risk factors (n=211) or the Framingham risk score (n=158, age: 60±12 years, range: 30-74 years, 63 males) were analyzed. The SDPTG indices significantly correlated with the Framingham risk score in both genders (b/a; rmale =0.43, rfemale =0.54 and d/a; rmale =-0.38, rfemale =-0.58), as well as several coronary risk factors. In the receiver operating characteristics curve analyses, the b/a discriminated high-risk subjects for CHD, who were in the highest quintile of the Framingham risk score in each gender, with a sensitivity and specificity of 0.85 and 0.58 in males and 0.83 and 0.72 in females, respectively. Conclusions These results suggest that the SDPTG is useful for the estimation of risk of CHD in the general population. (Circ J 2006; 70: 304 - 310)

5. R. Kelly, MB, FRACP, C. Hayward, MB, BSc, A. Avolio, PhD, and M. O'Rourke, MD, FACC Noninvasive Determination of Age-Related Changes in the Human Arterial Pulse Circulation Vol 80, No 6, December 1989 p.1652-1659

Abstract
Arterial pressure waves were recorded noninvasively from the carotid, radial, femoral, or all three of these arteries of 1,005 normal subjects, aged 2-91 years, using a new transcutaneous tonometer containing a high fidelity Millar micromanometer. Waves were ensemble-averaged into age-decade groups. Characteristic changes were noted with increasing age. In all sites, pulse amplitude increased with advancing age (carotid, 91.3%; radial 67.5%; femoral, 50.1% from first to eighth decade), diastolic decay steepened, and diastolic waves became less prominent. In the carotid pulse, there was, in youth, a second peak on the downstroke of the waves in late systole. After the third decade, this second peak rose with age to merge with and dominate the initial rise. In the radial pulse, a late systolic wave was also apparent, but this occurred later; with age, this second peak rose but not above the initial rise in early systole, even at the eighth decade. In the femoral artery, there was a single systolic wave at all ages. Aging changes in the arterial pulse are explicable on the basis of both an increase in arterial stiffness with increased pulse-wave velocity and progressively earlier wave reflection. These two factors may be separated and effects of the latter measured from pressure wave-contour analysis using an "augmentation index," determined by a computer algorithm developed from invasive pressure and flow data. Changes in peak pressure in the central (carotid) artery show increasing cardiac afterload with increasing age in a normal population; this can account for the cardiac hypertrophy that occurs with advancing age (even as other organs atrophy) and the predisposition to cardiac failure in the elderly. Identification of mechanisms responsible offers a new approach to reduction of left ventricular afterload. (Circulation 1989;80:1652-1659)

6. Ito H, Nakasuga K, Ohshima A, Sakai Y, Maruyama T, Kaji Y, Harada M, Jingu S, Sakamoto M.. Excess accumulation of body fat is related to dyslipidemia in normal-weight subjects. Int J Obes Relat Metab Disord. 2004 Feb; 28(2):242-7.

Abstract:
OBJECTIVE: To assess the relationship of fat mass (FM) and its distribution to hypertension and dyslipidemia in normal-weight Japanese individuals.
DESIGN: Cross-sectional study.
SUBJECTS: Apparently healthy Japanese subjects with a body mass index (BMI) between 20 and 23.5 kg/m2 (265 males and 741 females, age 21–69 y).
MEASUREMENTS: BMI, waist circumference (WC), waist-hip ratio (WHR), systolic and diastolic blood pressure, serum levels of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) were measured. Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula. Percentage fat mass (%FM) and trunk fat mass–leg fat mass ratio (FMtrunk/FMlegs) were obtained by dual-energy X-ray absorptiometry.
RESULTS: WC, WHR, %FM and FMtrunk/FMlegs were significantly correlated with TC, LDL-C, HDL-C and TG with the tendency of FMtrunk/FMlegs to show the strongest correlations. For %FM and FMtrunk/FMlegs in both sexes, odds ratios (ORs) of the third tertiles with respect to the first tertiles increased for LDL-C elevation, TG elevation and dyslipidemia. In males, ORs of the third tertiles of WC were significantly high for LDL-C elevation and dyslipidemia whereas those of WHR were high for TG elevation and dyslipidemia. ORs of the third tertiles of WC and WHR were significantly high for TG elevation in females. BMI was not associated with the risk of abnormal lipid levels. ORs for hypertension showed significant increases in none of the variables of obesity.
CONCLUSIONS: Excess accumulation of FM, especially to the upper body, was related to dyslipidemia in normal-weight subjects. Simple anthropometric variables, WC and WHR, may be useful for screening and management of dyslipidemia in these subjects.

7. IKETANI T, IKETANI Y, TAKAZAWA K, YAMASHINA A. The influence of the peripheral reflection wave on left ventricular hypertrophy in patients with essential hypertension. Hypertens Res 2000 Sep 23:451-8

Abstract
The objective of this study was to clarify the relationship between afterload, which consists mainly of the vascular reflection wave, and left ventricular hypertrophy in patients with untreated essential hypertension using the fingertip photoplethysmogram (PTG) and second derivative wave (SDPTG) methods, the simplest and most convenient tools for pulse wave analysis. The augmentation index (AI) is defined as the ratio of the height of the late systolic peak, augmented by the peripheral reflection wave, to that of the early systolic peak caused mainly by left ventricular ejection in the pulse. Increased AI of the PTG and negative d/a, obtained by multiplying the ratio of the late re-decreasing wave (d wave) to the initial positive wave (a wave) of the SDPTG by -1, have the same meaning as increased ascending aortic AI. The left brachial artery blood pressure was measured in 60 patients. The PTG and SDPTG of the right second finger were recorded by a digital photoplethysmograph. The left ventricular mass index (LVMI) was investigated by ultrasonography. Subjects were assigned to one of two groups: a low AI (AI of PTG<1.6; group 1) or a high AI (AI of PTG> or =1.6; group 2) group. LVMI was significantly higher in group 2 than in group 1. In the study group as a whole, the LVMI was positively correlated with both the AI of PTG (r=0.60, p<0.0001) and negative d/a (r=0.63, p<0.0001). An increase in the LVMI was seen in subjects with an augmented late systolic component in the waveform. It was concluded that an increase in the peripheral reflection wave on the left ventricle is one of the important factors causing cardiac hypertrophy in patients with hypertension.

8. PIERRE BOUTOUYRIE, ANNE ISABELLE TROPEANO, ROLAND ASMAR, ISABELLE GAUTIER, ATHANASE BENETOS, PATRICK LACOLLEY, STEPHANE LAURENT. Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients. A Longitudinal Study. Hypertension. 2002;39:10-15

Abstract:
Arterial stiffness may predict coronary heart disease beyond classic risk factors. In a longitudinal study, we assessed the predictive value of arterial stiffness on coronary heart disease in patients with essential hypertension and without known clinical cardiovascular disease. Aortic stiffness was determined from carotid-femoral pulse wave velocity at baseline in 1045 hypertensives. The risk assessment of coronary heart disease was made by calculating the Framingham risk score according to the categories of gender, age, blood pressure, cholesterol, diabetes, and smoking. Mean age at entry was 51 years, and mean follow-up was 5.7 years. Coronary events (fatal and nonfatal myocardial infarction, coronary revascularization, and angina pectoris) and all cardiovascular events served as outcome variables in Cox proportional-hazard regression models. Fifty-three coronary events and 97 total cardiovascular events occurred. In univariate analysis, the relative risk of follow-up coronary event or any cardiovascular event increased with increasing level of pulse wave velocity; for 1 SD, ie, 3.5 m/s, relatives risks were 1.42 (95% confidence interval [CI], 1.10 to 1.82; P<0.01) and 1.41 (95% CI, 1.17 to 1.70; P<0.001), respectively. Framingham score significantly predicted the occurrence of coronary and all cardiovascular events in this population (P<0.01 and P<0.0001, respectively). In multivariate analysis, pulse wave velocity remained significantly associated with the occurrence of coronary event after adjustment either of Framingham score (for 3.5 m/s: relative risk, 1.34; 95% CI, 1.01 to 1.79; P=0.039) or classic risk factors (for 3.5 m/s: relative risk, 1.39; 95% CI, 1.08 to 1.79; P=0.01). Parallel results were observed for all cardiovascular events. This study provides the first direct evidence in a longitudinal study that aortic stiffness is an independent predictor of primary coronary events in patients with essential hypertension.

9. IAN B. WILKINSON, IAN R. HALL, HELEN MACCALLUM, ISLA S. MACKENZIE, CARMEL M. MCENIERY, BART J. VAN DER AREND, YAE-EUN SHU, LAURA S.MACKAY, DAVID J. WEBB, JOHN R. COCKCROFT. Clinical Evaluation of a Noninvasive, Widely Applicable Method for Assessing Endothelial Function. Arterioscler Thromb Vasc Biol. 2002;22:147-152

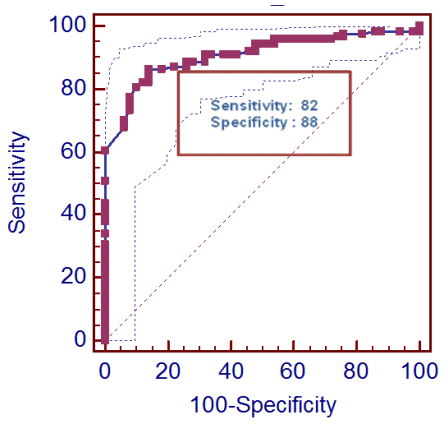
Abstract:
Current methods for assessing vasomotor endothelial function are impractical for use in large studies. We tested the hypothesis that pulse-wave analysis (PWA) combined with provocative pharmacological testing might provide an alternative method. Radial artery waveforms were recorded and augmentation index (AIx) was calculated from derived aortic waveforms. Thirteen subjects received sublingual nitroglycerin (NTG), inhaled albuterol, or placebo. Twelve subjects received NTG, albuterol, and placebo separately during an infusion of NG-monomethyl-L-arginine (LNMMA) or norepinephrine. Twenty-seven hypercholesterolemic subjects and 27 controls received NTG followed by albuterol. Endothelial function was assessed by PWA and forearm blood flow in 27 subjects. Albuterol and NTG both significantly and repeatably reduced AIx (P<0.001). Only the response to albuterol was inhibited by LNMMA (-9.8±5.5% vs -4.7±2.7%; P=0.02). Baseline AIx was higher in the hypercholesterolemic subjects, who exhibited a reduced response to albuterol (P=0.02) but not to NTG when compared with matched controls. The responses to albuterol and acetylcholine were correlated (r=0.5, P=0.02). Consistent with an endothelium-dependent effect, the response to albuterol was substantially inhibited by LNMMA. Importantly, the response to albuterol was reduced in subjects with hypercholesterolemia and was correlated to that of intra-arterial acetylcholine. This methodology provides a simple, repeatable, noninvasive means of assessing endothelial function in vivo.

10. C. STEFANADIS, J. DERNELLIS, E. TSIAMIS, C. STRATOS, L.DIAMANTOPOULOS, A. MICHAELIDES AND P. TOUTOUZAS. Aortic stiffness as a risk factor for recurrent acute coronary events in patients with ischemic. heart disease. Hippokration Hospital, Department of Cardiology, University of Athens,Greece. Revised 15 June 1999; accepted 16 June 1999. Available online 25 March 2002.

Astract:
Background Aortic elastic properties, important determinants of left ventricular function and coronary blood flow, are compromised in hypertension. The aim of this study was to determine aortic function in hypertensive patients and in normal subjects before and after administration of diltiazem, a calcium antagonist widely used in the treatment of essential hypertension.
Methods and Results The aortic pressure-diameter relation was obtained before and after diltiazem administration in 15 hypertensives and 15 control normotensives. Instantaneous diameter of the thoracic aorta was acquired with a high-fidelity intravascular catheter developed in our institution and previously validated. Instantaneous aortic pressure was measured simultaneously and at the same aortic level with a catheter-tip micromanometer. Energy loss due to the viscosity of aortic wall was measured from the area of the loop. Aortic distensibility was calculated using the formula 2x(pulsatile change in aortic diameter)/([diastolic aortic diameter]x[aortic pulse pressure]). At baseline, aortic distensibility was lower and energy loss was greater in hypertensives than in normotensives (distensibility: 1.4±0.3 versus 3.5±0.7 cm2 · dyne-1 · 10-6, respectively, P<.001; energy loss: 14.1±3.3 versus 8.2±2.2 mm · mm Hg, respectively, P<.001). After diltiazem administration, aortic distensibility was increased, whereas energy loss was decreased in both hypertensives (peak response: distensibility, 2.0±0.4 cm2 · dyne-1 · 10-6, P<.001; energy loss, 9.3±1.6 mm · mm Hg, P<.001) and normotensives (peak response: distensibility, 5.2±0.5 cm2 · dyne-1 · 10-6, P<.001; energy loss, 5.0±1.2 mm · mm Hg, P<.001).
Conclusions Aortic elastic properties are compromised and energy loss due to aortic wall viscosity is increased in hypertensives compared with normotensives. Function of the aorta is improved in both hypertensive and normotensive subjects after the administration of diltiazem

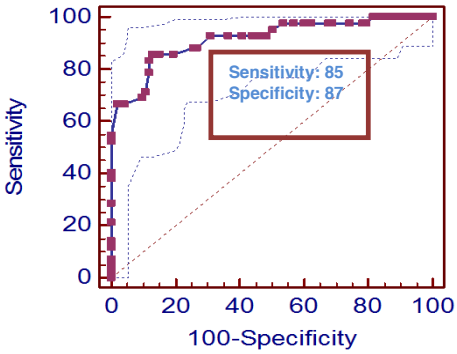
According to the above clinical investigations including 5340 subjects diagnosed for dyslipidemia, heart disease screening, coronary heart diseases and carotid stiffness and control group
9 indicators were identified:
b/a:
-d/a:
SDNN:
HRV Total power:
LF/HF:
Fat mass:
Stiffness Index
Reflection Index /Augmentation Index

Comparison of the Roc curves dyslipidemia



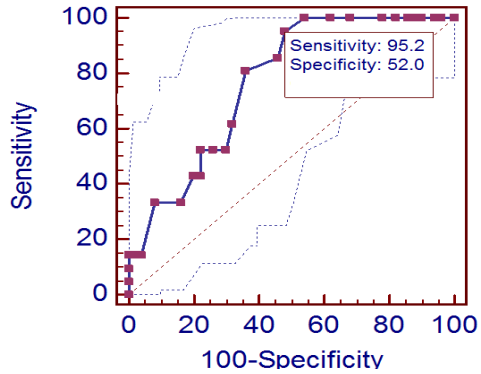
ROC curve		
Variable	cholesterol variable regression	
Classification variable	diagnosis	
Sample size		174
Positive group :	diagnosis = 1	124
Negative group :	diagnosis = 0	50
Disease prevalence (%)	71.3	
Area under the ROC curve (AUC)	0.908	
Standard Error [a]	0.022	
95% Confidence Interval [b]	0.855 to 0.947	
z statistic	18.561	
Significance level P (Area=0.5)	<0.0001	

Comparison of the Roc curves cardiovascular diseases



ROC curve		
Variable	Test_1	
Classification variable	diagnosis	
Sample size		1635
Positive group :	diagnosis = 1	867
Negative group :	diagnosis = 0	768
Disease prevalence (%)	31.1	
Area under the ROC curve (AUC)	0.915	
Standard Error [a]	0.0282	
95% Confidence Interval [b]	0.855 to 0.956	
z statistic	14.715	
Significance level P (Area=0.5)	<0.0001	

Comparison of the Roc curves carotid stiffness



ROC curve		
Variable	Test_1	
Classification variable	diagnosis	
Sample size		289
Positive group :	diagnosis = 1	156
Negative group :	diagnosis = 0	133
Disease prevalence (%)	29.6	
Area under the ROC curve (AUC)	0.768	
Standard Error [a]	0.0554	
95% Confidence Interval [b]	0.652 to 0.860	
z statistic	4.834	
Significance level P (Area=0.5)	<0.0001	