

## Abstracts

### 1. Perspectives on systolic hypertension. The Framingham Study.

KANNEL WB, DAWBER TR, MCGEE DL

#### Abstract

Diastolic hypertension has been widely and justifiably accepted as a cause of cardiovascular mortality. However, it has also been accepted that the cardiovascular sequelae of hypertension derive chiefly from the diastolic component. Because systolic and diastolic pressure are usually highly correlated it is not easy to dissociate the effects of each. Statistical analysis suggests that systolic pressure is actually the more potent contributor to cardiovascular sequelae. Even isolated systolic pressure elevation is associated with an excess cardiovascular mortality. At low diastolic pressures (i.e., less than 95 mm Hg), risk rises with the level of systolic pressure. Also, isolated systolic hypertension is most ominous in the elderly, in whom it is highly prevalent. Isolated systolic hypertension was related to the occurrence of "direct" complications as well as to atherosclerotic sequelae. **It was also associated with excess mortality, taking into account rigid vessels as judged from pulse-wave recordings.** Trials to determine whether the treatment of isolated systolic hypertension is efficacious for avoiding its demonstrated excess cardiovascular morbidity and mortality are urgently needed.

(Circulation 1980 Jun 61:1179-1182)

## 2. Assessment of vasoactive agents and vascular aging by the second derivative of photoplethysmogram waveform.

TAKAZAWA K, TANAKA N, FUJITA M, MATSUOKA O, SAIKI T, AIKAWA M, TAMURA S, IBUKIYAMA C

### 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 $\pm$ SD age of 54 $\pm$ 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 microg 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 $\pm$ 0.13 to -0.62 $\pm$ 0.19 and increased after nitroglycerin to -0.25 $\pm$ 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 non-invasive 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 centre. 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 $\pm$ 0.36 versus -0.22 $\pm$ 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 Aug 32:365-70).

### **3. Photoplethysmographic assessment of pulse wave reflection. Blunted Response to Endothelium-Dependent Beta2 - Adrenergic Vasodilation in Type II Diabetes Mellitus**

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**OBJECTIVES:** We sought to determine whether a simple index of pressure wave reflection may be derived from the digital volume pulse (DVP) and used to examine endothelium-dependent vasodilation in patients with type II diabetes mellitus.

**BACKGROUND:** The DVP exhibits a characteristic notch or inflection point that can be expressed as percent maximal DVP amplitude ( $IP_{DVP}$ ). Nitrates lower  $IP_{DVP}$ , possibly by reducing pressure wave reflection. Response of  $IP_{DVP}$  to endothelium-dependent vasodilators may provide a measure of endothelial function.

**METHODS:** The DVP was recorded by photoplethysmography. Albuterol (salbutamol) and glyceryl trinitrate (GTN) were administered locally by brachial artery infusion or systemically. Aortic pulse wave transit time from the root of the subclavian artery to aortic bifurcation ( $T_{Ao}$ ) was measured by simultaneous Doppler velocimetry.

**RESULTS:** Brachial artery infusion of drugs producing a greater than threefold increase in forearm blood flow within the infused limb was without effect on  $IP_{DVP}$ , whereas systemic administration of albuterol and GTN produced dose-dependent reductions in  $IP_{DVP}$ . The time between the first and second peak of the DVP correlated with  $T_{Ao}$  ( $r = 0.75$ ,  $n = 20$ ,  $p < 0.0001$ ). The effects of albuterol but not GTN on  $IP_{DVP}$  were attenuated by  $N^G$ -monomethyl-L-arginine. The  $IP_{DVP}$  response to albuterol (400  $\mu$ g by inhalation) was blunted in patients with type II diabetes mellitus as compared with control subjects (fall  $5.9 \pm 1.8\%$  vs.  $11.8 \pm 1.8\%$ ,  $n = 20$ ,  $p < 0.02$ ), but that to GTN (500  $\mu$ g sublingually) was preserved (fall  $18.3 \pm 1.2\%$  vs.  $18.6 \pm 1.9\%$ ,  $p = 0.88$ ).

**CONCLUSIONS:** The  $IP_{DVP}$  is influenced by pressure wave reflection. The effects of albuterol on  $IP_{DVP}$  are mediated in part through the nitric oxide pathway and are impaired in patients with type II diabetes.

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#### 4. The influence of the peripheral reflection wave on left ventricular hypertrophy in patients with essential hypertension.

IKETANI T, IKETANI Y, TAKAZAWA K, YAMASHINA A

##### 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.

(Hypertens Res 2000 Sep 23:451-8)

## 5. Arterial stiffness and pulse contour analysis: an age old concept revisited

JOHN R COCKCROFT AND IAN B WILKINSON

‘In extreme old age, the arteries themselves, the grand instrument of the circulation, by the continual apposition of earth, become hard, and as it were bony, till, having lost the power of contracting themselves they can no longer propel the blood, even through the largest channels, in consequence of which death naturally ensues.’ ( John Wesley, 1703±1791)

Hardening of the arteries, and its relation to aging, is far from a new phenomenon. Indeed, the fact that arteries stiffen with age, and that such changes are associated with an increased incidence of major cardiovascular events, is now established beyond doubt [1±4]. However, the influence of arterial stiffening on the interaction between the heart and large vessels, and on atherosclerosis, is less well understood. Early researchers used pulse contour analysis of peripheral pressure waveforms to obtain information about arterial stiffness [5,6], but their results were mainly qualitative, and pulse contour analysis was largely abandoned by practicing clinicians in favour of conventional sphygmomanometry. With the increased longevity of modern societies and the recognition that arterial stiffness is an independent predictor of cardiovascular risk in selected populations, the factors underlying vascular stiffness have assumed major importance. In particular, there has been interest in the association between stiffness and cardiovascular risk factors, such as diabetes and hypertension in individuals without manifest atheroma [7]. It has become clear that arterial stiffness is not solely determined by structural elements within the vessel wall and distending pressure, but that there is also functional regulation by the sympathetic nervous system [8] and endothelial-derived NO[9]. This suggests that functional abnormalities, such as endothelial dysfunction, may underlie some of the large artery stiffening found in individuals with cardiovascular disease and risk factors, and thus may potentially be reversible [10]. Moreover, assessment of arterial stiffness in such individuals may aid risk stratification. It is against this background that several groups have focused on the development of simple reproducible methods to assess arterial stiffness in clinical practice [11].

In this issue of Clinical Science, Millasseau et al. [12], in a series of elegant studies, describe the use of pulse contour analysis to derive quantitative data concerning large arterial stiffness in the hope of providing new insights into ventricular vascular interaction. Using the established technique of photoplethysmography [13,14], they have devised a reproducible parameter termed ‘stiffness index’ by measuring the time delay between direct and reflected waves in the digital volume pulse [12]. Since this measure will be determined, to a large extent, by velocity of the arterial waveform in the aorta and large arteries, it is perhaps unsurprising that they were able to demonstrate a significant correlation between the stiffness index and carotid-femoral pulse wave velocity (PWV). In addition, both stiffness index and carotid-femoral PWV were, as expected, independently correlated with age and mean arterial pressure. Nevertheless, their results are important, as they suggest that stiffness index may be used as a valid

surrogate for aortic PWV. Since digital pulse contour analysis is simple, operator-independent and relatively inexpensive, it may be, as the authors suggest [12], suitable for use in large clinical studies. However, several relatively simple commercial systems are available to measure PWV directly. Thus any perceived benefit of the stiffness index must be weighed against the fact that it is an indirect measure, as the authors [12] themselves note; indeed path length is not measured directly, instead height is used as a surrogate. Such limitations may not be important, but it is becoming increasingly clear that small changes in PWV may still be physiologically meaningful [9]. Indeed, in humans, femoral PWV changes by only 5% per decade [2]. Therefore, although Millasseau et al. [12] report only a 'modest' change in stiffness index and PWV following administration of glyceryl trinitrate, the potential importance of such a change should not be underestimated. As the authors discuss [12], in addition to the stiffness index, other parameters have been shown to correlate with PWV, including central augmentation index (AIx), derived by from the radial artery waveform using a validated transfer function [15,16]. The timing of the start of wave reflection (TR) can also be derived from the ascending aortic waveform, and provides a surrogate of aortic PWV [17,18]. Interestingly, recent data [19], from the same cohort of patients with end-stage renal failure referred to by Millasseau et al. [12], demonstrates that central AIx and PWV are both independent predictors of mortality, despite the fact that the majority of subjects were receiving a wide variety of vaso active drugs [20]. Blood pressure varies throughout the arterial tree [21], and the normal amplification of pulse pressure towards the periphery depends on a number of factors, including age and mean pressure [22]. Interestingly, central rather than peripheral pulse pressure seems to predict mortality in patients with end-stage renal failure [23], and carotid intima-media thickness in healthy men [24]. Therefore, it appears that in order to fully assess the impact of disease processes and drugs on large arteries, perhaps both aortic PWV and AIx should be assessed, together with central blood pressure. There is no doubt that the assessment of arterial stiffness will make a major contribution to the improved management of cardiovascular disease in the clinical arena and should be included in all future large intervention studies. However, the choice of technique will be influenced by ease of use, cost and other less rationally chosen factors [25]. The race is on, and the technique of digital pulse contour analysis, as described by Millasseau et al. [12], is an important addition to the field. It is, however, robust outcome data that is likely to determine the eventual winner.

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## 6. Noninvasive Assessment of the Digital Volume Pulse Comparison With the Peripheral Pressure Pulse

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**Abstract**—The digital volume pulse can be recorded simply and noninvasively by photoplethysmography. The objective of the present study was to determine whether a generalized transfer function can be used to relate the digital volume pulse to the peripheral pressure pulse and, hence, to determine whether both volume and pressure pulse waveforms are influenced by the same mechanism. The digital volume pulse was recorded by photoplethysmography in 60 subjects (10 women, aged 24 to 80 years), including 20 subjects with previously diagnosed hypertension. Simultaneous recordings of the peripheral radial pulse and digital artery pulse were obtained by applanation tonometry and a servocontrolled pressure cuff (Finapres), respectively. In 20 normotensive subjects, measurements were obtained after the administration of nitroglycerin (NTG, 500 mg sublingually). Transfer functions obtained by Fourier analysis of the waveforms were similar in normotensive and hypertensive subjects. In normotensive subjects, transfer functions were similar before and after NTG. By use of a single generalized transfer function for all subjects, the radial and digital artery pressure waveforms could be predicted from the volume pulse with an average root mean square error of 4.462.0 and 4.361.9 mm Hg (mean±SD) for radial and digital artery waveforms, respectively, similar to the error between the 2 pressure waveforms (4.461.4 mm Hg). The peripheral pressure pulse is related to the digital volume pulse by a transfer function, which is not influenced by effects of hypertension or NTG. Effects of NTG on the volume pulse and pressure pulse are likely to be determined by a similar mechanism.

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## **7. Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients. A Longitudinal Study**

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Abstract-

Arterial stiffness may predict coronary heart 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, relative 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.

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Key Words: arterial stiffness, cardiovascular morbidity, cardiovascular mortality, coronary heart disease

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## **8. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure.**

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**BACKGROUND:** Aortic pulse wave velocity (PWV) is a predictor of mortality in patients with end-stage renal failure (ESRF). The PWV is partly dependent on blood pressure (BP), and a decrease in BP can attenuate the stiffness. Whether the changes in PWV in response to decreases in BP can predict mortality in ESRF patients has never been investigated. **METHODS AND RESULTS:** One hundred fifty ESRF patients (aged 52 $\pm$ 16 years) were monitored for 51 $\pm$ 38 months. From entry until the end of follow-up, the changes of PWV in response to decreased BP were measured ultrasonographically. BP was controlled by adjustment of "dry weight" and, when necessary, with ACE inhibitors, calcium antagonists, and/or beta-blockers, in combination if necessary. Fifty-nine deaths occurred, including 40 cardiovascular and 19 noncardiovascular events. Cox analyses demonstrated that independent of BP changes, the predictors of all-cause and cardiovascular mortality were as follows: absence of PWV decrease in response to BP decrease, increased left ventricular mass, age, and pre-existing cardiovascular disease. Survival was positively associated with ACE inhibitor use. After adjustment for all confounding factors, the risk ratio for the absence of PWV decrease was 2.59 (95% CI 1.51 to 4.43) for all-cause mortality and 2.35 (95% CI 1.23 to 4.41) for cardiovascular mortality. The risk ratio for ACE inhibitor use was 0.19 (95% CI 0.14 to 0.43) for all-cause mortality and 0.18 (95% CI 0.06 to 0.55) for cardiovascular mortality. **CONCLUSIONS:** These results indicate that in ESRF patients, the insensitivity of PWV to decreased BP is an independent predictor of mortality and that use of ACE inhibitors has a favourable effect on survival that is independent of BP changes.

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## 9. Determination of age-related increases in large artery stiffness by digital pulse contour analysis

MILLASSEAU SC, KELLY RP, RITTER JM AND CHOWIENCZYK PJ

### Abstract

The stiffness of the aorta can be determined by measuring carotid-femoral pulse wave velocity ( $PWV_{cf}$ ).  $PWV$  may also influence the contour of the peripheral pulse, suggesting that contour analysis might be used to assess large artery stiffness. An index of large artery stiffness ( $SI_{DVP}$ ) derived from the digital volume pulse (DVP) measured by transmission of IR light (photo-plethysmography) was examined.  $SI_{DVP}$  was obtained from subject height and from the time delay between direct and reflected waves in the DVP. The timing of these components of the DVP is determined by  $PWV$  in the aorta and large arteries.  $SI_{DVP}$  was, therefore, expected to provide a measure of stiffness similar to  $PWV$ .  $SI_{DVP}$  was compared with  $PWV_{cf}$  obtained by applanation tonometry in 87 asymptomatic subjects ( $21 \pm 68$  years; 29 women). The reproducibility of  $SI_{DVP}$  and  $PWV_{cf}$  and the response of  $SI_{DVP}$  to glyceryl trinitrate were assessed in sub-sets of subjects. The mean within-subject coefficient of variation of  $SI_{DVP}$ , for measurements at weekly intervals, was 9.6 %.  $SI_{DVP}$  was correlated with  $PWV_{cf}$  ( $r = 0.65$ ,  $P < 0.0001$ ).  $SI_{DVP}$  and  $PWV_{cf}$  were each independently correlated with age and mean arterial blood pressure (MAP) with similar regression coefficients:  $SI_{DVP} = 0.63 + 0.086 \times \text{age} + 0.042 \times \text{MAP}$  ( $r = 0.69$ ,  $P < 0.0001$ );  $PWV_{cf} = 0.76 + 0.080 \times \text{age} + 0.053 \times \text{MAP}$  ( $r = 0.71$ ,  $P < 0.0001$ ). Administration of glyceryl trinitrate (3, 30 and 300  $\mu\text{g}/\text{min}$  intravenous; each dose for 15 min) in nine healthy men produced similar changes in  $SI_{DVP}$  and  $PWV_{cf}$ . Thus contour analysis of the DVP provides a simple, reproducible, non-invasive measure of large artery stiffness.

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## 10. Technical comparison of methods for measuring arterial compliance (stiffness)

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Background decreased arterial compliance is a significant predictor of cardiovascular disease. Systemic arterial compliance is principally determined by aortic compliance but its estimation using the 'area' method (Liu et al 1986) requires significant technical skill. Commercially available techniques that analyse the pulse pressure waveform are more practicable. Objectives To correlate arterial compliance measured by the 'area' and by commercial methods, and to assess the reproducibility of each technique. Methods Fifteen males with known coronary disease and 15 young healthy volunteers were recruited. Repeat measures were performed randomly and sequentially by the same operator: large and small artery compliance (C1 and C2) ('CR2000 TradeMark '), augmentation index (AI), central pulse wave velocity (PWV) and central pulse pressure (CPP) ('Sphygmacor TradeMark '), stiffness index (SI) ('Pulse Trace TM '), and the 'area' method. Reproducibility was assessed by coefficient of variation (CV), and correlations by linear regression. Results The CV's for C1, C2, AI, PWV, CPP, SI and the area method were 11.3%, 15.6%, 22.4%, 10.5%, 25.3%, 17.8% and 19.3% respectively. All techniques except SI correlated significantly with the 'area' method ( $r^2=0.20$  to  $0.38$ ,  $p<0.05$ ). AI, SI, C2 and central PWV were all correlated with each other ( $r^2=0.42$  to  $0.64$ ,  $p<0.01$ ). Conclusions All commercial methods showed good reproducibility but were weakly associated with an estimate of central aortic compliance. Other properties of the circulation, such as peripheral wave reflectance, may therefore also contribute to AI, C2, PWV and SI. The discriminatory value of these measures for the development of cardiovascular disease merits further examination.

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## **11. First Experience With Salbutamol - Induced Changes In The Photoplethysmographic Digital Volume Pulse**

ALEKSANDRAS LAUCEVICIUS, LIGITA RYLISKYTE, ZANETA PETRUIONIENE, MILDA KOVAITE, NERIJUS MISONIS

Summary. Photoplethysmographic digital volume pulse analysis provides an additional possibility to evaluate arterial stiffness and to analyse the reflected pulse waves from the lower part of the body. Systemic effect of beta2-adrenergic agonist salbutamol is partially mediated through the L-arginine-NO pathway. Attenuation of photoplethysmographic digital volume pulse parameters under salbutamol inhalation could be a means of evaluating vasomotor endothelial dysfunction in cardiovascular patients. The aim of the present study was to estimate the digital volume pulse parameters after the inhalation of salbutamol in patients with arterial hypertension, coronary heart disease and to compare them with the results obtained in healthy adults. Normal response of digital volume pulse to salbutamol in healthy subjects was a decreased height of the inflection point (IP) and the prolongation of peak - to -peak time (PPT). In groups of patients with arterial hypertension and coronary heart disease the typical response was attenuation in the drop of the height of the inflection point and the corresponding minimal or absent prolongation of the PPT interval. The blunted response of photoplethysmographic digital volume pulse parameters to inhaled salbutamol in hypertensive and coronary patients could suggest a disturbed endothelial vasomotor function in these patients.

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## 12. Oxidative stress could precede endothelial dysfunction and insulin resistance in Indian Mauritians with impaired glucose metabolism

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### Abstract

**Aims/hypothesis.** To measure oxidative stress, endothelial dysfunction and insulin resistance in Indian Mauritians at different stages of development of Type II (non-insulin-dependent) diabetes mellitus.

**Methods.** Plasma total 8-epi-PGF<sub>2a</sub>, an indicator of oxidative stress, was determined in age-matched subjects with normal glucose metabolism (n=39), impaired glucose tolerance (n=14), newly diagnosed diabetes (n=8) and established diabetes (n=14). Plasma glucose and insulin were measured at baseline and 2 h following an oral glucose tolerance test. Endothelial function was assessed by non-invasive digital pulse wave photoplethysmography.

**Results.** Plasma 8-epi- PGF<sub>2a</sub> increased in subjects with impaired glucose tolerance ( $p < 0.05$ ) compared with control subjects, and was even higher in newly diagnosed diabetic patients ( $p < 0.01$ ) and established ( $p < 0.01$ ) diabetic patients. A tendency towards reduced endothelial function in subjects with impaired glucose tolerance became significant in patients with newly diagnosed and established diabetes ( $p < 0.01$ ), and was correlated with 8-epi- PGF<sub>2a</sub> ( $r = 0.36$ ,  $p < 0.01$ ). Insulin resistance (homeostasis model assessment) did not change in subjects with impaired glucose tolerance compared with control subjects, but increased in newly diagnosed ( $p < 0.01$ ) and established ( $p < 0.001$ ) diabetic subjects: The 8-epi- PGF<sub>2a</sub> was correlated with fasting glucose ( $r = 0.50$ ,  $p < 0.001$ ), triglycerides ( $r = 0.40$ ,  $p < 0.001$ ) and insulin resistance ( $r = 0.35$ ,  $p < 0.001$ ).

**Conclusion/interpretation.** Oxidant stress is an early event in the evolution of Type II diabetes and could precede the development of endothelial dysfunction and insulin resistance. (**Diabetologia (2001) 44: 706-712**)

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### 13. Beside digital plethysmography detects endothelial dysfunction in recent onset angina.

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**Background:** Endothelial dysfunction (ED) may be an early marker of ischaemic heart disease (IHD), but current assays are time-consuming and laborious limiting them to chronic IHD. Consequently, the degree of ED in very recent onset angina is not known. We assessed a 10-minute test in patients attending a Rapid Access Chest Pain Clinic where patients are assessed within 48 hours of new symptoms.

**Method:** Consecutive chest pain patients (54 noncardiac controls and 46 IHD) had digital volume pulse plethysmograms before and after 400 µg inhaled salbutamol. The inflection point (IP) from the first derivative of the waveform and its change from baseline (IP-response) were calculated. The pulse wave response to salbutamol is dependent on nitric oxide synthase can be inhibited with L-NMMA. Ischaemic heart disease diagnosis was based on history and Bruce protocol exercise electrocardiography. Multiple regression was used to control for age, mean blood pressure (BP) and smoking status.

**Findings:** IP-response is lower in patients with new angina than those with noncardiac chest pain. This is independent of age, smoking status and mean BP (table).

	IHD(n=46mean±SD)	Noncardiac(n=54mean±SD)	p-value
IP-response %	4.8 (160)	18 (22)	0.03
Age	65 (10)	55 (9.4)	0.06
Smoking/day	1.0 (3.1)	5.5 (1.2)	0.09
Mean BP	102 (12)	94 (10)	0.1
Cholesterol	6.1 (1.2)	5.8 (1.3)	0.3
Duke's Score	-7.1 (6.8)	7.8 (4.0)	<0.0001

IP-response = percentage change in pulse wave inflection point from baseline after salbutamol inhalation; Duke's Score = ischaemia scoring system based on Bruce exercise protocol; IHD = ischaemic heart disease.

**Discussion:** IP-response is a rapid bedside test that identifies endothelial dysfunction early in the course of ischaemic heart disease. It may be useful as a diagnostic marker of IHD and identifies the need for early initiation of interventions aimed at improving endothelial dysfunction in this group of patients.

## **14. Clinical Evaluation of a Noninvasive, Widely Applicable Method for Assessing Endothelial Function**

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

**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 N<sup>G</sup>-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 ( $-9.8 \pm 5.5\%$  vs  $-4.7 \pm 2.7\%$ ;  $P=0.02$ ). 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.

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## 15. Rapid non-invasive analysis of vascular function in pre-eclampsia

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**Background:** Photoplethysmography, the measurement of infra-red light transmission through the finger pulp provides a rapid method for deriving the digital volume pulse (DVP). We have previously shown that indices relating to pressure wave reflection (RI) and large artery stiffness (SI) can be obtained from the DVP<sup>1</sup>. Both RI and SI are reduced in normal pregnancy.

**Objective:** The aim of this study was to investigate whether RI and SI are abnormal in pre-eclampsia.

**Methodology:** Women with pre-eclampsia, diagnosed according to the ISSHP definition were studied shortly after admission and were not on anti-hypertensive medication. Women with essential hypertension and diabetes were excluded. Healthy normotensive pregnant women were studied in the ante-natal clinic as controls (similar age, ethnicity and gestation)

**Results:** Subject characteristics (means  $\pm$  SD) and mean ( $\pm$ SE) values of heart rate (HR), blood pressure (BP), RI and SI are tabulated:

	Age	Gestation	HR (bpm)	BP (mmHg)	RI (%)	SI (m/s)
Healthy (n=20)	29 $\pm$ 6.5	34 $\pm$ 3.7	90 $\pm$ 2.1	121 $\pm$ 4.5 / 69 $\pm$ 2.2	28.2 $\pm$ 2.3	6.2 $\pm$ 0.2
Pre-eclampsia (n=10)	28 $\pm$ 6.0	36 $\pm$ 4.2	84 $\pm$ 5.0	151 $\pm$ 3.1 / 99 $\pm$ 4.6**	47.8 $\pm$ 3.7**	7.9 $\pm$ 0.7*

\*P<0.01, \*\*P<0.0001 (compared the healthy pregnant women).

**Discussion and Conclusions:** These results show that both RI and SI are increased in pre-eclampsia with minimal overlap compared to normal pregnant women. The increase in RI is likely to result from an increase in tone of small arteries from which the majority of pressure wave reflection occurs. The increase in SI may result from increased stiffness of the aorta and large arteries. Both effects may contribute to adverse haemodynamic consequences of pre-eclampsia. Prospective evaluation of these indices may be helpful in identifying early circulatory changes caused by pre-eclampsia, and women at increased risk who can be targeted for intervention.

**References:** 1. Chowienczyk PJ, Kelly R, MacCallum H, Millasseau SC, Andersson T, Gosling RG, Ritter JM, Anggard EE. Photoplethysmographic assessment of pulse wave reflection: Blunted response to endothelium-dependent beta<sub>2</sub>-adrenergic vasodilation in type II diabetes mellitus. J Am Coll Cardiol 1999; 34:2007-2014

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## 16. Comparison of central aortic augmentation index obtained from radial and carotid tonometry

SC MILLASSEAU. PRESENTED AT THE BHS 2002

Aortic augmentation index (AIx), an indirect measure of arterial stiffness and pressure wave reflection is usually obtained by application of a transfer function to the pressure pulse recorded at the radial or carotid arteries by applanation tonometry. The accuracy of the transfer function approach for obtaining values of aortic systolic and diastolic blood pressures has been validated. AIx, however, depends upon higher frequency components of the pressure waveform and the accuracy of a transfer function to determine AIx has been questioned. We examined the agreement between AIx obtained from a transfer function applied to the radial artery (AIx-TFR) and AIx obtained from a transfer function applied to the carotid artery (AIx-TFC). We also examined the relation between augmentation indices derived from the radial and carotid arteries with no transfer function applied (AIx-R and AIx-C) and those derived from the transformed waveforms. Two groups of subjects were studied: young healthy normotensive subjects (23-45 years, n=10) and older subjects (47-69 years, n=8) with coronary artery disease (CAD). Subjects were studied in a temperature controlled laboratory after 10 min resting supine. Carotid and radial pressure waveforms were determined by arterial tonometry using a Millar tonometer and Sphygmocor PWA device (AtCor Medical, Australia). Six successive measurements were obtained from each artery at 3 min intervals by an observer with more than 1 year's experience of arterial tonometry. Measurements for which automated quality control measures were not optimal were repeated. Augmentation indices were derived from radial and carotid waveforms using the software SCOR-2000 version 6.31 (AtCor Medical, Australia). Repeatability of AIx was similar to that obtained by other investigators with within subject standard deviations of 9.1 for AIx-R, 9.9 for AIx-C, 9.1 for AIx-TFR and 6.6% for AIx-TFC. All AIx were significantly greater in patients with CAD compared with young control men ( $32.5 \pm 4\%$  (range: 14% to 49%) vs.  $2.0 \pm 2\%$  (range: -8% to 15%) for AIx-TFR in CAD and controls respectively (mean  $\pm$  SE)). In men with CAD, AIx-TFR was closely correlated with AIx-TFC ( $R=0.91$ ,  $P<0.005$ ). The SD of the difference from the Bland-Altman summary statistic (AIx-TFR - AIx-TFC) was 7.3%. In control subjects, the correlation was weak ( $R=0.386$ ,  $P=0.27$ , SD of the difference: 10.1%). In both groups AIx-R and AIx-C were closely correlated with AIx-TFR and AIx-TFC ( $R=0.88$ ,  $P<0.0001$  for AIx-R vs. AIx-TFR;  $R=0.98$ ,  $P<0.0001$  for AIx-C vs. AIx-TFC). The poor correlation between AIx-TFR and AIx-TFC in healthy subjects suggests that the transfer function for the radial or carotid waveforms or both is inaccurate in these subjects. The results do not question the use of a transfer function to obtain central aortic systolic and diastolic blood pressure. The close correlation between AIx-R and AIx-TFR raises the possibility that similar information to "central aortic augmentation index" may be obtained from the radial waveform without resort to a transfer function.

## **17. Comparison of central pulse pressure and augmentation index derived from analyses of carotid and radial artery waveforms**

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**Background:** Pulse pressure provides a surrogate marker of arterial stiffness and is an independent risk factor of cardiovascular disease. However peripheral pulse pressure does not reliably predict central pulse pressure. Analysis of peripheral artery waveforms using a generalised transfer function to evaluate central pulse pressure (CPP) and central augmentation index (CAI) is a simple technique but has recently been criticised.

**Objectives:** To compare CPP and CAI assessed using carotid and radial artery pulse pressure waveforms. **Methods:** Fifteen males with known coronary disease and 15 young healthy volunteers were studied. Measures of CPP and CAI were performed using applanation tonometry of the right carotid artery (SPT-301, Millar instruments) and of the right radial artery using a generalised transfer function (SphygmaCor). Brachial blood pressure was recorded to permit calibration of the carotid arterial pressure contours using mean and diastolic blood pressure. Comparisons were made using linear regression and paired t-tests. **Results:** CPP and CAI were both significantly correlated using the two techniques ( $r=0.75$ ,  $p<0.001$  and  $r=0.84$ ,  $p<0.001$  respectively). However, radial CAI was significantly higher (14.8%,  $p<0.001$  without heart rate correction, and 6.2%,  $p=0.003$  with heart rate correction) than carotid CAI. Carotid CPP was higher (10.2mmHg,  $p<0.001$ ) than radial CPP and exhibited proportional bias ( $p=0.02$ ).

**Conclusions:** Carotid and radial-derived measures of CPP and CAI were strongly associated. However, CPP is lower and CAI higher using analysis of radial artery waveforms with a generalised transfer function. Caution should be employed when comparing results obtained using methods based upon analysis of peripheral and central waveforms.

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## 18. Pulse wave analysis

MICHAEL F. O'ROURKE, ALFREDO PAUCA & XIONG-JING JIANG

### Introduction

Since the information which the pulse affords is of so great importance, and so often consulted, surely it must be to our advantage to appreciate fully all it tells us, and to draw from it every detail that it is capable of imparting' F.A. Mahomed 1872 [1].

It is now possible to generate the ascending aortic pressure wave from the arterial pressure pulse, recorded non-invasively by applanation tonometry in the radial or carotid artery. This represents a blend of nineteenth century sphygmography with cuff sphygmomanometry, and is made possible by introduction of high fidelity tonometers, by characterization of arterial hydraulic properties in the upper limb and neck, and through application of mathematical engineering techniques in modern computer systems. This review will consider historical development, theoretic background, present status and future potential, as well as comparing this technique with radial and carotid tonometry alone, and with analysis of flow pulse and volume pulse waveforms as determined by Doppler or photoplethysmographic techniques.

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[1] Mahomed FA. The physiology and clinical use of the sphygmograph. Med Times Gazette 1872; 1: 62.

## **19. Vascular Compliance and Cardiovascular Disease A Risk Factor or a Marker?**

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STANLEY M. FINKELSTEIN, ALAN J. BANK, DENNIS J. MORGAN,  
AND JAY N. COHN

Pathophysiologic changes in the blood vessels are associated with a wide variety of cardiovascular events, but our ability to assess vascular structure and function are limited. Although arteriography provides some information regarding intimal pathology, it provides little information about the structure of the arterial wall or its physiology. A reduction in arterial compliance has long been regarded as a potentially useful indicator of the presence of arterial disease.<sup>1</sup> Changes in the arterial wall leading to reductions in arterial compliance may precede the onset of clinically apparent disease, and may identify individuals at risk before disease onset (symptoms due to disease are, in general, late manifestations of alterations in organ function). The ability to predict alterations in vascular structure and function before the onset of clinical diseases such as atherosclerosis, hypertension, and diabetes mellitus has potential advantages. Whether reduced vascular compliance precedes the development of cardiovascular disease (i.e., is a risk factor) or is the consequence of established cardiovascular disease (i.e., a marker) is a matter of debate. To qualify as a risk factor the presence of a condition must increase the probability of disease compared to those without the condition (implying stronger causality). Recent studies have suggested that the ascending aorta of the aortic trunk in Chinese has a larger diameter and thinner media than that in Australians and population differences such as these may be genetically determined.<sup>2</sup> Studies have suggested that the angiotensin II type 1 receptor (AT1) gene is involved in the development of aortic stiffness.<sup>3</sup> A conceptual example where abnormalities in vascular compliance might be both a risk factor and a marker is hypertension. Hypertension may alter arterial wall tone and structure increasing blood pressure, which results in a decrease in compliance (i.e., the decrease in compliance is a marker for hypertension). Alternatively, when sclerotic changes occur in vessels arising from diseases that may or may not increase blood pressure, decreased compliance becomes a risk factor for the development of hypertension. In the following discussions, it should be kept in mind that there is both morphologic (structural) and functional heterogeneity in the different vascular beds. Also, there is no accepted “gold standard” methodology for estimating vascular compliance, so comparison of results obtained with differing methodologies is difficult if not impossible.

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## 20. Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease

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**Abstract** - The number of non-invasive techniques available for the assessment of the cardiovascular system is quite limited. A need exists for simplified methods of determining or suggesting the presence of existing disease and predicting its development in asymptomatic individuals. One such technique which has been suggested to be of value for this purpose is the pulse wave as determined by oscillometry. Oscillometric methods have achieved a certain amount of popularity among European physicians. However, in the United States these techniques have not been accepted as useful tools in assessing the cardiovascular system. An example of the general attitude toward oscillometry may be found in a standard textbook: "To the experienced observer the oscillometer gives little information which cannot be detected by simple palpation of the arteries and the observance of postural color changes. The mechanism by which the normal pulse wave is developed has been studied in moderate detail, but interest in this subject has been primarily exhibited by physiologists rather than clinicians. Data regarding the usefulness of the study of the peripheral pulse wave are limited. In spite of the pessimism which had been previously expressed recent studies of oscillography using the lower extremities have suggested that this method of clinical investigation may have some usefulness in determining which subjects have obstructive peripheral arterial disease. Certain clinical studies have been carried out in the United States by Henry Lax M.D., who continued his earlier investigations begun in Europe. Together with his associates he succeeded in developing a reliable non-invasive method of determining the pulse wave in the upper extremity } Using a narrow cuff applied to a finger he was able to show that pulse wave patterns provided by this method closely resembled those obtained directly by an intra-arterial needle. The pulse wave pattern was also demonstrated to be reproducible in the same subject. The instrument which he developed was termed a Vasculograph and the recordings obtained, Vasculograms. Lax and his associates studied the pulse wave patterns found in normal subjects. They also compared the tracings observed in subjects with hypertension, arteriosclerotic disease and diabetes mellitus. Although a number of variables were measured, Lax et al concluded that the appearance of the dicrotic notch was the single most important feature of the peripheral pulse wave. Using as the criterion of abnormality the disappearance of an incisura on the downward descent of the pulse tracing they were able to make certain observations: e.g., out of 40 young adults 38 had "normal" tracings, i.e. a definite incisura was observed. In 24 subjects, with "hypertensive vascular disease" none had normal tracings. In a study of healthy ) young people (ages 11-29) only eight per cent had abnormal tracings. However, 62 per cent of 162 diabetic subjects of the same age distribution had abnormal tracings. The smoking of cigarettes and cooling of the extremity prior to the time of obtaining the vasculograms reduced the amplitude of the pulse wave but did not change its configuration. The explanation for the appearance of

the dicrotic notch in the peripheral pulse wave has usually been attributed to closure of the aortic valve, with a rebound in the blood pressure due to the continued elastic recoil of the arterial tree. Peripheral factors including the tone of the smaller vessels in which the muscular layer plays a major role in blood vessel tone have been shown to exert an important role in the appearance of the dicrotic notch. Peripheral vasoconstriction induced by intravascular injection of adrenalin may cause the incisura to disappear. This observation is possibly inconsistent with the previously noted apparent negative effect of tobacco smoking on the pulse wave pattern. In the absence of aortic valvular disease or congestive heart failure with inadequate emptying of the left ventricle it appears reasonable to consider the configuration of the dicrotic notch as largely a function of arterial wall elasticity and muscular tension in the walls of the smaller arteries and arterioles in the periphery. In the absence of peripheral vasoconstriction the persistence of a normal incisura may thus be a good measure of maintenance of the normal elasticity observed in the young. The loss of elasticity of the arterial bed with age presumably reflects changes in the quality or quantity of elastin in the vascular wall. Conflicting reports regarding the changes in the elastin content of the aorta with age have been published. Some reports suggest that elastin does decrease with age, however, other reports suggest no essential change in elastin content according to age or sex. The loss of elasticity of the vascular bed with age may, however, be related to changes in the make-up of elastin since it is reported that the elastin of older persons contains more calcium (elastocalcinosis). The authors postulate that the increased binding of calcium to elastin is a prerequisite to the development of atherosclerosis. Calcium is deposited chiefly in the region of the elastic fibers. Medial calcification was found in only four per cent of subjects under the age of 20; in .58 per cent by the age of 40; and in 100 per cent of Subjects over the age of 50.<sup>10</sup> The authors observed that the calcium concentration in dry elastin increased from 0.4 to 0.7 per cent before age 20 to 4.7 to 6.9 per cent over age 40.

Lax's data suggest a relationship between disappearance of the dicrotic notch and the presence of existing vascular disease. However, he suggested the desirability that the method be tested again using a cross section of the general population. He believed that the method also had value for the prediction of the development of vascular disease in the apparently healthy population. Accordingly, he made available a vasculograph so that tracings could be made on members of the Framingham Study population. The Heart Disease Epidemiology Study ("Framingham Study") was established by the National Heart Institute in 1949 in Framingham, Massachusetts. It has investigated the natural history of coronary heart disease and other atherosclerotic diseases in 5,127 adults age 30-59 free of disease at entry into the study. These subjects have been examined periodically at two-year intervals. Observations regarding the life habits and personal characteristics as well as the development of disease have been made since the establishment of the study in 1949. Although the National Heart and Lung Institute is still making observations with respect to mortality and morbidity from death certificates and hospital records in the remaining subjects, the responsibility for the clinical evaluation of the subjects has now been undertaken by the Boston University Medical Center-Framingham Study. The present report represents our experience comparing the finger vasculography readings with disease diagnosed at the same examination.

The ability of this test procedure to predict disease will be the subject of a future report.

**(Angiology 1973, Vol24, p244-255)**

## **21. Vasoactive Drugs Influence Aortic Augmentation Index Independently of Pulse-Wave Velocity in Healthy Men**

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**Abstract**—Aortic augmentation index, a measure of central systolic blood pressure augmentation arising mainly from pressure-wave reflection, increases with vascular aging. The augmentation index is influenced by aortic pulse-wave velocity (related to aortic stiffness) and by the site and extent of wave reflection. To clarify the relative influence of pulse-wave velocity and wave reflection on the augmentation index, we studied the association between augmentation index, pulse-wave velocity, and age and examined the effects of vasoactive drugs to determine whether altering vascular tone has differential effects on pulse-wave velocity and the augmentation index. We made simultaneous measurements of the augmentation index and carotid-to-femoral pulse-wave velocity in 50 asymptomatic men aged 19 to 74 years at baseline and, in a subset, during the administration of nitroglycerin, angiotensin II, and saline vehicle. The aortic augmentation index was obtained by radial tonometry (Sphygmocor device, PWV Medical) with the use of an inbuilt radial to aortic transfer function. In multiple regression analysis, the aortic augmentation index was independently correlated only with age ( $R^2=0.58$ ,  $P<0.0001$ ). Nitroglycerin (3 to 300 mg/min IV) reduced the aortic augmentation index from 4.862.3% to 211.965.3% ( $n=510$ ,  $P=0.002$ ). Angiotensin II (75 to 300 ng/min IV) increased the aortic augmentation index from 9.362.4% to 18.362.9% ( $n=512$ ,  $P=0.001$ ). These drugs had small effects on aortic pulse-wave velocity, producing mean changes from baseline of, 1 m/s (each  $P>0.05$ ). In healthy men, vasoactive drugs may change aortic augmentation index independently from aortic pulse-wave velocity.

(Hypertension. 2001;37:1429-1433.)



## 22. Aortic Pulse-Wave Velocity and Its Relationship to Mortality in Diabetes and Glucose Intolerance An Integrated Index of Vascular Function?

KENNEDY CRUICKSHANK, MB, MD; LISA RISTE, PHD; SIMON G. ANDERSON, PHD; JOHN S. WRIGHT, PHD; GRAHAM DUNN, PHD; RAY G. GOSLING, PHD

**Background**—Arterial distensibility measures, generally from pulse-wave velocity (PWV), are widely used with little knowledge of relationships to patient outcome. We tested whether aortic PWV predicts cardiovascular and all-cause mortality in type 2 diabetes and glucose-tolerance–tested (GTT) multiethnic population samples.

**Methods and Results**—Participants were randomly sampled from (1) a type 2 diabetes outpatient clinic and (2) primary care population registers, from which nondiabetic control subjects were given a GTT. Brachial blood pressures and Doppler-derived aortic PWV were measured. Mortality data over 10 years' follow-up were obtained. At any level of systolic blood pressure (SBP), aortic PWV was greater in subjects with diabetes than in controls. Mortality risk doubled in subjects with diabetes (hazard ratio 2.34, 95% CI 1.5 to 3.74) and in those with glucose intolerance (2.12, 95% CI 1.11 to 4.0) compared with controls. For all groups combined, age, sex, and SBP predicted mortality; the addition of PWV independently predicted all-cause and cardiovascular mortality (hazard ratio 1.08, 95% CI 1.03 to 1.14 for each 1 m/s increase) but displaced SBP. Glucose tolerance status and smoking were other independent contributors, with African-Caribbeans experiencing reduced mortality risk (hazard ratio 0.41, 95% CI 0.25 to 0.69).

**Conclusions**—Aortic PWV is a powerful independent predictor of mortality in both diabetes and GTT population samples.

In displacing SBP as a prognostic factor, aortic PWV is probably further along the causal pathway for arterial disease and may represent a useful integrated index of vascular status and hence cardiovascular risk.

(*Circulation*. 2002;106:2085-2090.)

## **23. Aortic Pulse Wave Velocity Predicts Cardiovascular Mortality in Subjects >70 Years of Age**

S. MEAUME, A. BENETOS, O.F. HENRY, A. RUDNICH, M.E. SAFAR

**Abstract**—Aortic pulse wave velocity (PWV) is a significant and independent predictor of cardiovascular mortality in subjects with essential hypertension and in patients with end-stage renal disease. Its contribution to cardiovascular risk in subjects 70 to 100 years old has never been tested. A cohort of 141 subjects (mean<sub>SD</sub> age, 87.1<sub>6.6</sub> years) was studied in 3 geriatrics departments in a Paris suburb. Together with sphygmomanometric blood pressure measurements, aortic PWV was measured with a validated automatic device. During the 30-month follow-up, 56 patients died (27 from cardiovascular events). Logistic regressions indicated that age (P<sub>0.005</sub>) and a loss of autonomy (P<sub>0.01</sub>) were the best predictors of overall mortality. For cardiovascular mortality, aortic PWV was the major risk predictor (P<sub>0.016</sub>). The odds ratio was 1.19 (95% confidence interval, 1.03 to 1.37). Antihypertensive drug treatment and blood pressure, including systolic and pulse pressure, had no additive role. In subjects 70 to 100 years old, aortic PWV is a strong, independent predictor of cardiovascular death, whereas systolic or pulse pressure was not. This prospective result will need to be confirmed in an intervention trial.

(*Arterioscler Thromb Vasc Biol.* 2001;21:2046-2050.)

## **24. Analysis of endothelium-dependent vasodilation by use of the radial artery pulse wave obtained by applanation tonometry.**

LIND L, PETTERSSON K, JOHANSSON K.

**OBJECTIVES:** To evaluate applanation tonometry as a method to obtain arterial pulse waves suitable for pulse wave analysis of the height of the diastolic inflection point (IP), and to use this technique to study endothelium-mediated vasodilation by evaluation of the contribution of nitric oxide (NO) to the reduction in the height of the IP induced by beta2-adrenergic stimulation. **METHODS:** The radial artery pulse waveform was recorded by applanation tonometry in young healthy subjects before and after interventions both locally in the forearm and systemically by different vasodilators and vasoconstrictors, and vasodilatation was analysed as a change in the height of the IP. The mechanism behind the reduction in the height of the IP induced by terbutaline was investigated by systemic interventions with both N(G)-monomethyl-L-arginine (L-NMMA) and noradrenaline (NA). **RESULTS:** Applanation tonometry was a convenient method to obtain radial artery pulse waves of good quality. The reduction in IP was substantially more pronounced when vasodilators were given systemically than when given locally in the forearm, indicating that the effect was obtained through an effect on peripheral pulse wave reflection. Systemically given L-NMMA, but not NA, increased the IP ( $P<0.05$ ). Systemically given L-NMMA also caused a more pronounced attenuation than NA of the reduction in IP following terbutaline injection ( $P<0.05$ ). **CONCLUSION:** Changes in IP following beta2-adrenergic stimulation appears to be a measurement of pulse wave reflection mainly governed by NO. Applanation tonometry and pulse wave analysis is a minimally invasive method suitable to assess endothelium-dependent vasodilation in large-scale studies.

**(Clin Physiol & Func Im, 2003; 23:50-57)**

## **25.Assessment of endothelial function using peripheral waveform analysis: a clinical application.**

HAYWARD CS, KRAIDLY M, WEBB CM, COLLINS P.

**OBJECTIVES:** The study was done to determine whether radial artery applanation tonometry can be used as a noninvasive method of assessing global endothelial function. **BACKGROUND;** It is known that beta(2)-receptor stimulation results in endothelial release of nitric oxide. Furthermore, for over a century glyceryl trinitrate (GTN) has been known to markedly affect the arterial pressure waveform, even in the absence of significant blood pressure (BP) changes. Therefore, it was hypothesized that the change in the peripheral pressure waveform, as measured using tonometry and quantified using the augmentation index (AIx) and in response to Salbutamol (Salb), would allow assessment of global endothelial function. **METHODS:** The study contained three parts. In the first study, Salb (400 microg) was administered to 11 healthy subjects via inhalation after either intravenous N-omega-nitro-monomethyl-L-arginine (L-NMMA) (3 mg/kg over 5 min) or control solution (normal saline) in the supine, rested, fasted condition. The BP, heart rate and waveform responses were recorded each 5 min following Salb for 20 min. Next, GTN was given and responses recorded 5 min later. In the second study, both the reproducibility of Salb and the GTN responses were assessed in 9 subjects studied twice on separate days. In the third study, the Salb and GTN responses of 12 subjects with angiographic coronary artery disease (CAD) were compared with 10 age-matched control subjects with no atherosclerotic risk factors. **RESULTS:** After control infusion, AIx decreased following Salb, from 50.8 +/- 4.3% to 44.8 +/- 4.2%, a change of -11.8 +/- 3.7%,  $p < 0.01$ . After L-NMMA, AIx did not significantly change following Salb (54.2 +/- 5.1% vs. 52.9 +/- 5.3%, -2.0 +/- 3.1%). The GTN-induced decreases in AIx were similar after either infusion (35.1 +/- 3.3% vs. 36.5 +/- 3.3%). Reproducibility of Salb-induced changes in AIx between studies performed on separate days was good ( $r = 0.80$ ,  $p < 0.01$ ). Salb-induced changes in AIx in CAD patients were significantly less compared to control subjects (-2.4 +/- 1.9% vs. -13.2 +/- 2.4%, respectively,  $p < 0.002$ ). The GTN-induced changes were not significantly different (-27.6 +/- 4.2 vs. -38.9 +/- 4.4%,  $p = 0.07$ ). **CONCLUSIONS:** The peripheral arterial pressure waveform is sensitive to beta(2)-stimulation. Changes are related to nitric oxide release, are reproducible and can distinguish between clinical subject groups. Arterial waveform changes following Salb may thus provide a noninvasive method of measuring "global" arterial endothelial function.

**(J Am Coll Cardiol 2002; 40:521-528)**

## 26. Aortic stiffness as a risk factor for recurrent acute coronary events in patients with ischaemic heart disease

C. STEFANADIS, J. DERNELLIS, E. TSIAMIS, C. STRATOS, L. DIAMANTOPOULOS, A. MICHAELIDES AND P. TOUTOUZAS

### Abstract

**Aims** Aortic elasticity is an important determinant of left ventricular performance and coronary blood flow. Moreover, it has been shown that aortic elastic properties deteriorate in patients with coronary artery disease. However, the predictive role of aortic elasticity in the occurrence of coronary events, has not been addressed so far. Therefore, we set out to test prospectively the hypothesis that invasive as well as non-invasive measures of aortic elastic properties, assessed at rest from pressure–diameter relationships, could predict the development of recurrent coronary events.

**Methods and Results** Clinical variables and measures of aortic function were assessed in 54 normotensive patients with coronary artery disease. The aortic pressure–diameter relationship was derived invasively with a high-fidelity Y shaped catheter (developed in our Institution) for aortic diameter measurements, simultaneously with a Millar catheter for aortic pressure measurements. Aortic root distensibility was assessed by non-invasive techniques. During an average of 3 years follow-up, 12 of 54 patients either developed unstable angina (n=8) or acute myocardial infarction (n=4). By multivariate Cox model analysis, aortic stiffness was the strongest predictor of progression to any end-point (relative risk: 3.24, CI: 1.79 to 5.83; P=0.000). When aortic stiffness was not considered, aortic distensibility was the only independent predictor for acute coronary syndromes (relative risk: 0.37 CI: 0.21 to 0.65; P=0.000).

**Conclusion** In patients with coronary artery disease, aortic elastic properties are powerful and independent risk factors for recurrent acute coronary events.

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## **27. Lack of effect of oral vitamin C on blood pressure, oxidative stress and endothelial function in Type II diabetes**

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### **ABSTRACT**

Type II diabetes is characterized by increased oxidative stress, endothelial dysfunction and hypertension. We investigated whether short-term treatment with oral vitamin C reduces oxidative stress and improves endothelial function and blood pressure in subjects with Type II diabetes. Subjects (n=35) received vitamin C (1.5 g daily in three doses) or matching placebo for 3 weeks in a randomized, double-blind, parallel-group design. Plasma concentrations of 8-epiprostaglandin F<sub>2a</sub> (8-epi-PGF<sub>2a</sub>), a non-enzymically derived oxidation product of arachidonic acid, were used as a marker of oxidative stress. Endothelial function was assessed by measuring forearm blood flow responses to brachial artery infusion of the endothelium-dependent vasodilator acetylcholine (with nitroprusside as an endothelium-independent control) and by the pulse wave responses to systemic albuterol (endothelium-dependent vasodilator) and glyceryl trinitrate (endothelium-independent vasodilator). Plasma concentrations of vitamin C increased from 58<sup>36</sup> to 122<sup>310</sup> μmol/l after vitamin C, but 8-epi-PGF<sub>2a</sub> levels (baseline, 95<sup>34</sup> pg/l ; after treatment, 99<sup>35</sup> pg/l), blood pressure (baseline, 141<sup>35</sup>/80<sup>32</sup> mmHg; after treatment, 141<sup>35</sup>/81<sup>33</sup> mmHg) and endothelial function, as assessed by the systemic vasodilator response to albuterol and by the forearm blood flow response to acetylcholine, were not significantly different from baseline or placebo. Thus treatment with vitamin C (1.5 g daily) for 3 weeks does not significantly improve oxidative stress, blood pressure or endothelial function in patients with Type II diabetes.

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## **28. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement.**

**YAMASHINA A, TOMIYAMA H, TAKEDA K, TSUDA H, ARAI T, HIROSE K, KOJI Y, HORI S, YAMAMOTO Y.**

The present study was conducted to evaluate the validity and reproducibility of noninvasive brachial-ankle pulse wave velocity (baPWV) measurements and to examine the alteration of baPWV in patients with coronary artery disease (CAD). Simultaneous recordings of baPWV by a simple, noninvasive method and aortic pulse wave velocity (PWV) using a catheter tip with pressure manometer were performed in 41 patients with CAD, vasospastic angina, or cardiomyopathy. In 32 subjects (15 controls and 17 patients with CAD), baPWV was recorded independently by two observers in a random manner. In 55 subjects (14 controls and 41 patients with CAD), baPWV was recorded twice by a single observer on different days. baPWV were compared among 172 patients with CAD (aged 62  $\pm$  8 years); 655 age-matched patients without CAD but with hypertension, diabetes mellitus, or dyslipidemia; and 595 age-matched healthy subjects without these risk factors. baPWV correlated well with aortic PWV ( $r=0.87$ ,  $p<0.01$ ). Pearson's correlation coefficients of interobserver and intraobserver reproducibility were  $r=0.98$  and  $r=0.87$ , respectively. The corresponding coefficients of variation were 8.4% and 10.0%. baPWV were significantly higher in CAD patients than in non-CAD patients with risk factors, for both genders ( $p<0.01$ ). In addition, baPWV were higher in non-CAD patients with risk factors than in healthy subjects without risk factors. Thus, the validity and reproducibility of baPWV measurements are considerably high, and this method seems to be an acceptable marker reflecting vascular damages. baPWV measured by this simple, noninvasive method is suitable for screening vascular damages in a large population.

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## **29. Increased arterial wall stiffness limits flow volume in the lower extremities in type 2 diabetic patients.**

SUZUKI E, KASHIWAGI A, NISHIO A ET AL

**OBJECTIVE:** To document an association between arterial wall stiffness and reduced flow volume in the lower-extremity arteries of diabetic patients. **RESEARCH DESIGN AND METHODS:** We recruited 60 consecutive type 2 diabetic patients who had no history or symptoms of peripheral arterial disease (PAD) in the lower extremities and normal ankle/brachial systolic blood pressure index at the time of the study (non-PAD group) and 20 age-matched nondiabetic subjects (control group). We used an automatic device to measure pulse wave velocity (PWV) in the lower extremities as an index of arterial wall stiffness. At the popliteal artery, we evaluated flow volume and the resistive index as an index of arterial resistance to blood flow using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging. **RESULTS:** Consistent with previous reports, we confirmed that the non-PAD group had an abnormally higher PWV compared with that of the control group ( $P < 0.001$ ). To further demonstrate decreased flow volume and abnormal flow pattern at the popliteal artery in patients with a higher degree of arterial wall stiffness, we assigned the 60 non-PAD patients to tertiles based on their levels of PWV. In the highest group, magnetic resonance angiograms of the calf and foot arteries showed decreased intravascular signal intensity, indicating the decreased arterial inflow in those arteries. The highest group was also characterized by the lowest late diastolic and total flow volumes as well as the highest resistive index among the groups. From stepwise multiple regression analysis, PWV and autonomic function were identified as independent determinants for late diastolic flow volume ( $r(2) = 0.300$ ;  $P < 0.001$ ). **CONCLUSIONS:** Arterial wall stiffness was associated with reduced arterial flow volume in the lower extremities of diabetic patients.

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### **30. Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular Mortality in Hypertensive Patients**

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**Abstract**—Although various studies reported that pulse pressure, an indirect index of arterial stiffening, was an independent risk factor for mortality, a direct relationship between arterial stiffness and all-cause and cardiovascular mortality remained to be established in patients with essential hypertension. A cohort of 1980 essential hypertensive patients who attended the outpatient hypertension clinic of Broussais Hospital between 1980 and 1996 and who had a measurement of arterial stiffness was studied. At entry, aortic stiffness was assessed from the measurement of carotid-femoral pulse-wave velocity (PWV). A logistic regression model was used to estimate the relative risk of all-cause and cardiovascular deaths. Selection of classic risk factors for adjustment of PWV was based on their influence on mortality in this cohort in univariate analysis. Mean age at entry was 50.613 years (mean±SD). During an average follow-up of 112.653 months, 107 fatal events occurred. Among them, 46 were of cardiovascular origin. PWV was significantly associated with all-cause and cardiovascular mortality in a univariate model of logistic regression analysis (odds ratio for 5 m/s PWV was 2.14 [95% confidence interval, 1.71 to 2.67, P,0.0001] and 2.35 [95% confidence interval, 1.76 to 3.14, P,0.0001], respectively). In multivariate models of logistic regression analysis, PWV was significantly associated with all-cause and cardiovascular mortality, independent of previous cardiovascular diseases, age, and diabetes. By contrast, pulse pressure was not significantly and independently associated to mortality. This study provides the first direct evidence that aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension.

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## **31.Effect of Antihypertensive Agents on Arterial Stiffness as Evaluated by Pulse Wave Velocity.**

ROLAND ASMAR

Structural and functional properties of the arterial wall have been reported to be altered in hypertension, even at early stages of the disease. Morbidity and mortality associated with hypertension are primarily related to arterial damage that may affect one or several organs. Considering the potential implications of arterial assessment in the prevention of cardiovascular disease, evaluation of the arterial effects of anti-hypertensive agents is recommended by numerous authorities. Among the non-invasive and simple methods to evaluate large arteries, pulse wave velocity (PWV) measurement is widely used as an index of regional arterial stiffness. This method is related to the arterial geometry and wall function, simple and reproducible, and thus, can easily be applied in clinical trials.

Several studies performed in various populations showed significant powerful interactions between PWV and cardiovascular risk factors. In addition, aortic PWV was shown to be a forceful marker and predictor of cardiovascular in normotensive individuals and patients with hypertension. Furthermore, aortic PWV was shown to be an independent predictor of all cause mortality in patients with essential hypertension.

In comparison with placebo, clinical studies have shown that in short and long term trials, Antihypertensive agents improved arterial stiffness (as evidenced by a reduction in PWV ) independently of blood pressure reduction. The decrease of PWV was more pronounced with long term treatment than with short term treatment. Whether Antihypertensive agents differ in their arterial effects independently of blood pressure changes remains unclear. Pharmacological studies, generally performed in small numbers of patients, indicate that the long term effects of long term treatment with ACE inhibitors, calcium channel antagonists and some  $\beta$ -blockers on arterial stiffness are generally similar. The effectiveness of an Antihypertensive agent in reducing arterial stiffness may also be influenced by the genetic background of the patient.

Recently, the Complior? Study has shown the feasibility to assess arterial stiffness in clinical trials involving large populations using an automatic device for measuring PWV. Long term treatment with an ACE inhibitor, perindopril was associated with a decrease in blood pressure and aortic PWV in patients with essential hypertension. In high risk patients with end stage renal failure ACE inhibitors effectively decreased arterial stiffness and had a favourable effect on survival which was independent of changes in blood pressure. The correlation between reversion of arterial stiffness and decrease in cardiovascular morbidity and mortality needs to be confirmed in populations of patients with lower cardiovascular risk.

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## **32. Arterial Stiffness and cardiovascular risk factors in a population based study,**

AMAR J, RUIDAVETS JB, CHAMONTIN B ET AL.

**OBJECTIVE:** To determine the relationships between pulse wave velocity (PWV), an estimate of arterial distensibility and cardiovascular risk factors.  
**DESIGN:** This cross-sectional population-based study was carried out from 1995 to 1997 to investigate these relationships.

**POPULATION AND METHODS:** Some 993 subjects, aged 35-64 years (52.7% men), living in the south-west of France, were randomly selected from electoral rolls and participated in a cross-sectional study. Medical examinations were performed by specially trained medical staff. Carotid-femoral PWV was measured using a semiautomatic device (Complior, Garges les Gonesse, France). The relationships between PWV and risk factors were assessed, first in subjects not treated with hypolipidaemic, antidiabetic and antihypertensive drugs and then in treated subjects. In subjects not treated for cardiovascular risk factors, age, gender, systolic blood pressure (SBP) and heart rate ( $P < 0.001$ ) were the variables significantly associated with PWV. In treated patients, age ( $P < 0.01$ ), SBP ( $P < 0.001$ ), heart rate ( $P < 0.001$ ), apolipoprotein B ( $P < 0.05$ ) and the number of treated cardiovascular risk factors ( $P < 0.05$ ) were positively correlated with PWV.

**CONCLUSION:** This study shows that, in a sample of subjects at high risk, the cumulative influence of risk factors, even treated, is an independent determinant of arterial stiffness. These results suggest that PWV may be used as a relevant tool to assess the influence of cardiovascular risk factors on aortic stiffness in high-risk patients.

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