Assessment of Arterial Distensibility by Automatic Pulse Wave Velocity Measurement

Validation and Clinical Application Studies

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Abstract Pulse wave velocity is widely used as an index of arterial distensibility. The aim of this study was to evaluate the accuracy of a new automatic device to measure it and then to analyze the major determinants of pulse wave velocity by application of this device in a large population. We evaluated the accuracy of on-line and computerized measurement of pulse wave velocity using an algorithm based on the time-shifted and repeated linear correlation calculation between the initial rise in pressure waveforms compared with the reference method (manual calculation) in 56 subjects. The results, analyzed according to the recommendations of Bland and Altman, showed a mean difference of −0.20±0.45 m/s for the mean carotid-femoral pulse wave velocity values (reference method, 11.05±2.58 m/s; automatic device, 10.85±2.44 m/s). The interreproducibility and intrareproducibility of measurements by each method were analyzed with the use of the repeatability coefficient according to the British Standards Institution. The interobserver repeatability coefficient was 0.947 for the manual method and 0.890 for the automatic, and intraobserver repeatability coefficients were 0.938 and 0.935, respectively. We evaluated the major determinants of the carotid-femoral pulse wave velocity measured by the automatic method in a separate study performed in 418 subjects of both sexes without any cardiovascular treatment or complication (18 to 77 years of age; 98 to 222 mm Hg systolic and 62 to 130 mm Hg diastolic pressure). Multiple regression analysis between pulse wave velocity and clinical parameters (age, sex, weight, height, smoking, arterial blood pressure, heart rate) and biological plasma parameters (total cholesterol, high-density lipoprotein cholesterol, glycemia) showed that pulse wave velocity correlated positively and independently with age and systolic pressure (r^2=.47; P<.001) according to the equation Pulse Wave Velocity=0.07 Systolic Pressure (mm Hg)+0.09 Age (y)−4.3 (m/s). Similar results were obtained in the normotensive and hypertensive subgroups when analyzed separately. Pulse wave velocity can be easily and automatically determined. Its measurement is accurate and highly reproducible, and its major determinants are well established. It is of great interest to evaluate in large populations the therapeutic and epidemiological applications of an arterial parameter as evaluated by aortic pulse wave velocity. ***(Hypertension*. 1995;26:485-490.)**

Key Words • arteries • pulse • algorithms

The mechanical properties of the large arteries are important determinants of circulatory physiology in health and disease.[1,2] Elastic large arteries absorb energy during the systolic component of pulsatile flow and thereby reduce the cardiac work for a given cardiac output.[3] The study of large artery dynamics is inherently difficult because of the pulsatile nature of blood flow, the complex structure of the vessel wall, and the continually changing tone of the smooth muscle component. The measurement of pulse wave velocity (PWV), which is inversely related to arterial wall distensibility, offers a simple and potentially useful approach.[4,5] This concept has been formalized in a mathematical model, and the measurement of PWV as an arterial distensibility index is widely used. This PWV is calculated from measurements of pulse transit time and the distance traveled by the pulse between two recording sites. In contrast to pulse wave recording, which is simple and rapidly obtained, the manual determination of the pulse wave upstroke point reflection and the measurement of the time delay between the two waves are tedious and time consuming, thus considerably limiting the use of these procedures for a large clinical application. The aim of this study was to evaluate the accuracy of a new automatic device for measurement of PWV and then to analyze the major determinants of PWV by the application of this device to a large population.

Methods

Study Design

Study I: Validation and Reproducibility of Automatic PWV Measurements

The accuracy and reproducibility of the automatic measurement of PWV were evaluated by comparison with the manual calculation (gold standard) shown on a simultaneous recording of the same waveforms on a paper recorder at high speed (150 mm/s). PWV measurements with the use of the automatic device and manual method were performed simultaneously. In each subject two sequences of measurements were performed, and their mean was considered for analysis. All procedures were repeated by two observers (observer A and observer B) for analysis of the interobserver and intraobserver reproducibilities for the two methods.

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Study II: Clinical Application

After the validation study and to analyze the clinical and biological parameters that can modify PWV, we measured PWV using the automatic method in a large population (cross-sectional study) in which we evaluated clinical parameters (age, sex, weight, height, smoking, blood pressure, and heart rate) and some plasma biological cardiovascular risk factors (total cholesterol, high-density lipoprotein cholesterol, and glycemia). For these investigations a blood sample of approximately 5 mL was taken with the use of a dry tube after subjects had fasted overnight. Determination of plasma glucose and lipid parameters was performed with standard techniques; serum lipids were measured by a CX7 autoanalyzer (Beckman-Gagny) with enzymatic methods; high-density lipoprotein cholesterol was measured after precipitation of low- and very-low-density lipoproteins by the phosphotungstic acid $MgCl_2$ reagent.

Subjects

Study I

Fifty-six normotensive and untreated hypertensive subjects participated in this study (27 women and 29 men; age, 55±13 years [±1 SD]; weight, 76±15 kg; height, 168±9 cm). In each subject carotid-femoral PWV was measured simultaneously with the automatic and manual methods. Two successive sequences of measurements were performed by the same observer in each subject in the supine position after at least 15 minutes of rest; their mean was considered for statistical analysis. All procedures were repeated by two different observers for analysis of interobserver and intraobserver reproducibilities.

Study II

Four hundred and eighteen subjects of both sexes without any cardiovascular treatment or complication participated in this study (age, 46±12 years [±1 SD]; range, 18 to 77 years). Their arterial blood pressure values measured by a mercury sphygmomanometer ranged from 98 to 222 mm Hg systolic and from 62 to 130 mm Hg diastolic. A carotid-femoral PWV measurement was performed in all subjects; the mean value of 10 consecutive measurements in each subject was considered for analysis.

PWV Measurement

Principles

The pressure pulse generated by ventricular ejection is propagated throughout the arterial tree at a speed determined by the elastic and geometric properties of the arterial wall and the blood density. Since fluid is contained in a system of elastic conduits, energy propagation occurs predominantly along the arterial wall and not through the incompressible blood.[5] The material properties of the arterial wall, its thickness, and the lumen diameter thus become the major determinants of PWV. This concept has been formalized in a mathematical model[6] in which PWV is given by the Moens-Korteweg equation, $PWV=\sqrt{Eh/2\rho R}$, or by the Bramwell-Hill equation, $PWV=\sqrt{\Delta P \cdot V/\Delta V \cdot \rho}$, where E is Young's modulus of the arterial wall; h is wall thickness; R is arterial radius; ρ is blood density; and ΔV and ΔP are changes in volume and pressure, respectively.

PWV is calculated from measurements of pulse transit time and the distance traveled by the pulse between two recording sites: PWV=Distance (meters)/Transit Time (seconds). Different signals can be used for measurement of PWV (Doppler, pressure, diameter); the most commonly used is the pressure signal recorded by a pressure-sensitive transducer.[5,7] In this study we used the TY-306 pressure transducer (Fukuda Co); this transducer has a large frequency bandwidth from less than 0.1 Hz to more than 100 Hz, which largely covers the principal frequency harmonics of the pressure wave at different heart rates and thus allows its application for PWV measurement.

Manual Calculation of PWV

For the manual determination of PWV two different pressure waves obtained at two sites (at the base of the neck for the common carotid artery and over the right femoral artery) were recorded simultaneously on a paper recorder at high speed (150 mm/s).

Transit time was determined from the time delay between the two corresponding foot waves: the proximal (A) and the distal (B) pulse waveforms. The foot of the wave is identified as the beginning of the initial upstroke. When this point could not be identified precisely, a tangent was drawn to the last part of the preceding wave and to the upstroke of the next wave, and the foot wave was taken as the intersection point of these two lines. The distance traveled by the pulse wave was obtained from superficial measurements of the distance between the two transducers (A and B). PWV was calculated on the mean basis of 10 consecutive pressure waveforms to cover a complete respiratory cycle.

Automatic Measurement of PWV

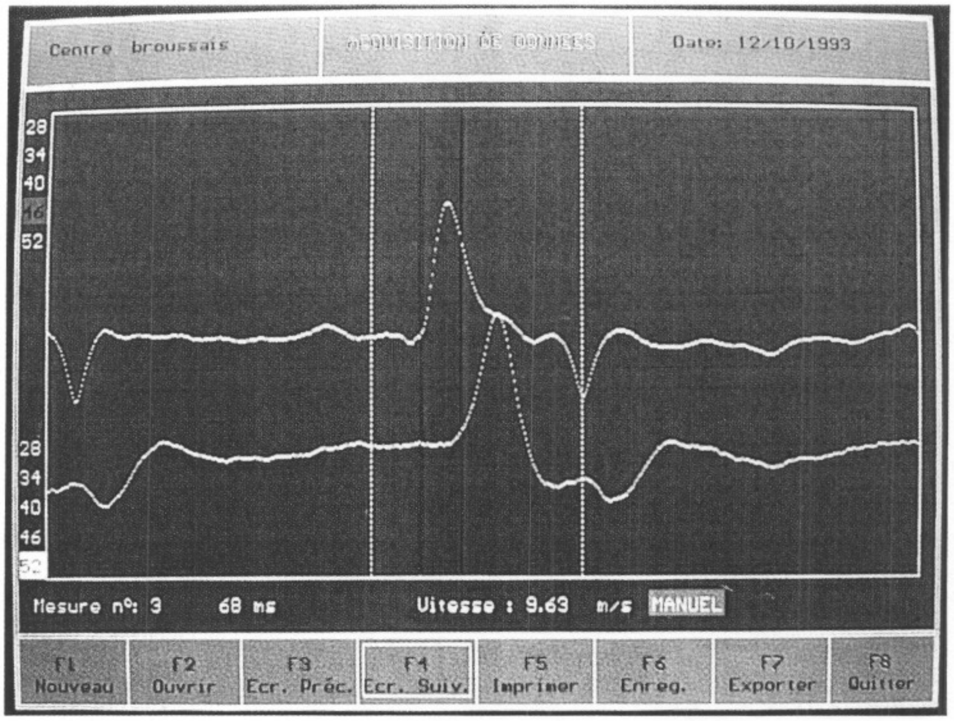
For automatic measurement of PWV, pressure waveforms are digitized at different rates according to the distance between the recording sites; the sampling acquisition frequency is 500 Hz for carotid-femoral PWV and 800 Hz for carotid-radial PWV and all others. The two pressure waveforms are stored in a recirculating memory buffer, half of which is displayed at any given time. Preprocessing analyses automatically adjust the gain of each waveform for an equality of the two signals. A maximum of 588 data points per waveform are displayed at any given time; ie, the display will cover a time period from 0.735 to 1.47 seconds. This is sufficient to always capture at least one complete cardiac pressure upstroke.

When the operator observes a pulse waveform of sufficient quality on the computer screen, digitization is suspended and calculation of the time delay between the two pressure upstrokes is initiated (Fig 1). The first operation performed is the removal of spikes that may be present in the pulse waveform because these will interfere with later processing. This is done by using a moving average digital filtering algorithm. The leading pulse waveform is then digitally differentiated, and the time at which the peak value occurs is determined. This will occur (in a normal cardiac pulse cycle) near the center of the upstroke. An interval corresponding to 90 data points is then subtracted from this time, and a second digital differentiation is performed on the distal pressure waveform, starting from that point and moving through a total of 180 data points. Two vertical lines are drawn on the computer display to indicate the positions of the maximal rate of change of the pressure waveforms.

The delay between the two pulse waves is determined by performing a correlation between the data of the two waveforms. Hence, waveform data are transferred into the correlation array from a point 100 milliseconds before the first line position and up to 50 milliseconds after the second line. This ensures that the correlation is performed on the initial rise of the pulse until just after the true pulse peak. The correlation algorithm is then performed, the distal pressure upstroke is time-shifted by subtracting one sample period, and the correlation coefficient is again calculated. The procedure is repeated until the amount of data point shift for best fit is calculated. The correlated waveforms are then displayed in their shifted positions, and the calculated pulse delay is printed.

Statistical Analysis

Statistical analysis was performed with STATVIEW SE 1.03 software (Abacus Concepts Inc) on a Macintosh computer. Values are given as mean±SD. The relationship between variables was evaluated by linear regression. The *t* test was used for comparison of differences between measurements. Two-sided *P* values were used.


Centre broussais

Date: 12/10/1993

Mesure n°: 3 68 ms

Vitesse : 9.63 m/s MANUEL

FIG 1. Traces show automatic measurement of pulse wave velocity. The upper wave is obtained from the proximal recording site (carotid) and the lower from the distal site (femoral). Vertical discontinuous lines indicate the calculation interval, and vertical continuous red lines indicate the possibility of manual and visual control. Values on the left-hand side indicate the gain of each pressure wave.

When two series of paired measurements were compared, the results were analyzed in two steps according to the recommendations of Bland and Altman.[8] First, the correlation between measurement values (equation of the linear relationship, correlation coefficient r, and P value) was investigated. This first step was used to gauge the degree of agreement between the two series of measurements. Second, the relative (positive or negative) differences within each pair of measures (Di) were plotted against the mean of the pair to make sure that no obvious relation appeared between the estimated value (mean) and Di. The lack of agreement between the two measurements was estimated by the mean difference Di and the SD of the differences.

The repeatability of the measurements by each method was investigated through a calculation of the repeatability coefficient (RC) as defined by the British Standards Institution,[9] ie, according to the formula $RC^2=\Sigma\, Di^2/N$, where N is the sample size and Di the difference between two measurements in a pair. This coefficient is the SD of the estimated difference between two repeated measurements performed by the same observer for intraobserver reproducibility and by two observers for interobserver reproducibility. The 95% confidence interval of the expected difference was calculated as ±1.96 RC. Repeated measurements are expected to differ by more than the confidence interval with a probability of only 5%.

A simple regression test was performed for analysis of the linear correlations between two parameters, and a multiple regression test was used for analysis of the multiple, simple, and partial correlations between more than two parameters. The significance level was set at a value of .05.

Results

Validation of the PWV Automatic Measurement

The comparison between the mean values of PWV measured by the manual method (gold standard) and the automatic device (COMPLIOR Colson) showed a mean difference of 0.20 ± 0.45 m/s (range, -0.65 to $+1.26$ m/s), with slightly lower values obtained by the automatic device (manual, 11.05 ± 2.58; automatic, 10.85 ± 2.44; $P<.05$).

Fig 2, top, shows the linear correlation between the mean values of PWV obtained by the two methods ($r=.99$, $P<.001$; Automatic=0.93 Manual+0.56 m/s). Fig 2, bottom, shows the plot of the individual difference observed between the PWV values calculated by the two methods according to the average of PWV calculated as (Automatic+Manual)/2.

Repeatability of PWV Measurements

The repeatability of PWV measurements performed by each method (manual and automatic) was evaluated through calculation of the SD of the repeated measurements and calculation of the RC (see "Statistical Analysis").

For intraobserver repeatability the mean values of PWV measurements performed at times 1 and 2 were, for the manual method, 11.13 ± 2.77 and 11.03 ± 2.54 m/s, respectively, and for the automatic method, 10.96 ± 2.69 and 10.77 ± 2.39 m/s. The RC values were 0.938 and 0.935 for manual and automatic, respectively. No significant difference was observed for intraobserver repeatability between the two methods.

For interobserver repeatability the mean values of two sequences of PWV measurements performed by observers A and B were, for the manual method, 11.13 ± 2.77 and 10.98 ± 2.54 m/s, respectively, and for the automatic method, 10.96 ± 2.69 and 10.80 ± 2.39 m/s. The RC values were 0.947 and 0.890 for manual and automatic, respectively. No significant difference was noted for interobserver repeatability between the two methods.

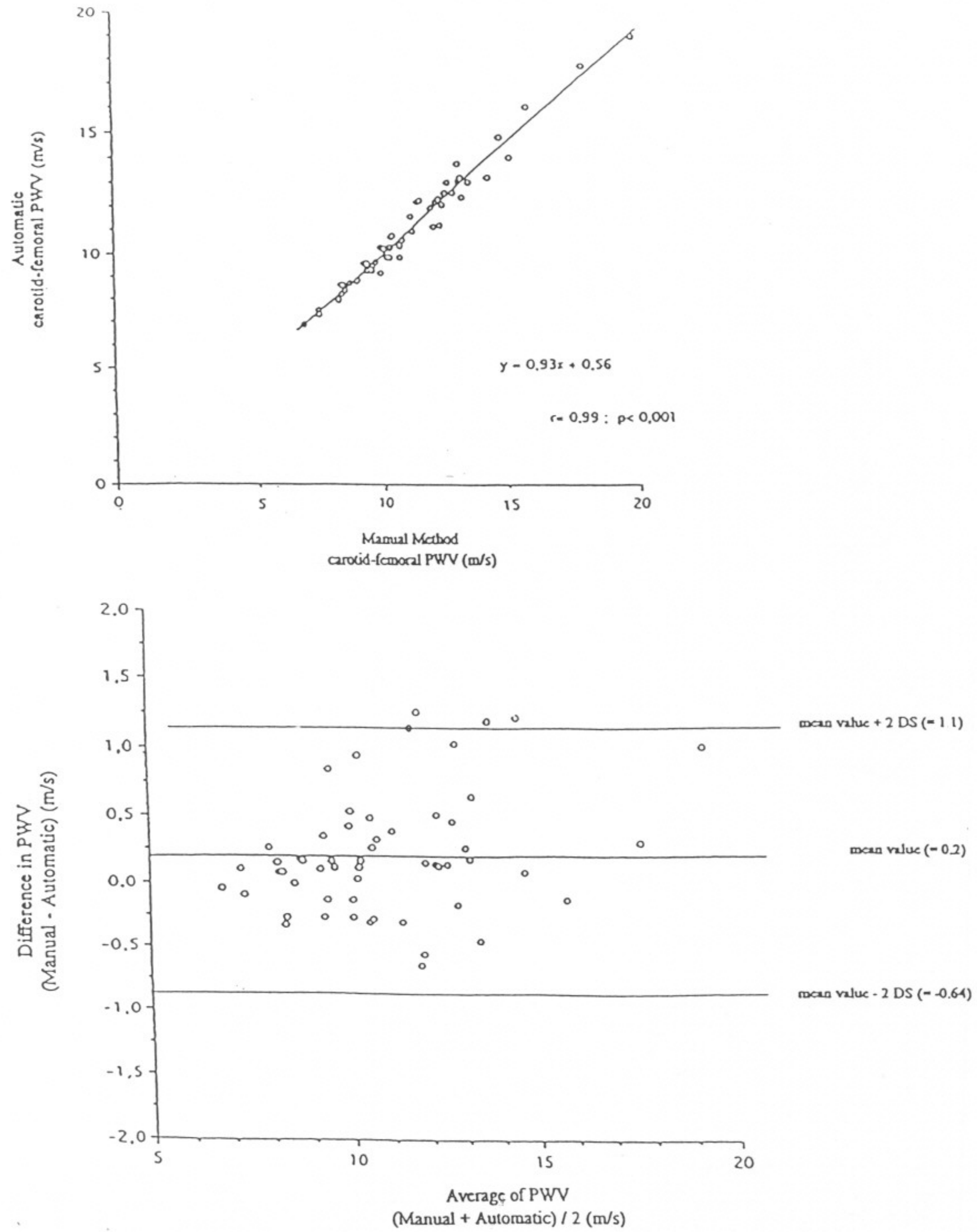


FIG 2. Top, Scatterplot shows linear correlation between the mean values of pulse wave velocity (PWV) measured by manual and automatic methods. Bottom, Scatterplot shows individual differences observed between PWV values obtained by the two methods according to the mean level of PWV calculated as (Manual+Automatic)/2.

Clinical Application: PWV Determinants

The multiple regression analysis between carotid-femoral PWV and clinical parameters and biological cardiovascular risk factors showed that the two major determinants of PWV are age ($P<.001$) and systolic pressure ($P<.001$), which correlate positively with PWV. These relations can be expressed by the formula PWV=0.07×Systolic Pressure (mm Hg)+0.09×Age (y)−4.3 (m/s). No other major determinant of PWV was found in this study.

To analyze the role of the other factors[10-12] and lower the weight of blood pressure in this model, we studied the determinants of PWV in two separate subgroups: normotensive subjects (n=178, blood pressure ≤140/90 mm Hg) and hypertensive subjects (n=240, blood pressure >140/90 mm Hg). Similar results were observed (for normotensive subjects: PWV=0.06×Systolic Pressure [mm Hg]+0.09×Age [y]−2.3 [m/s]; for hypertensive subjects: PWV=0.06×Systolic Pressure [mm Hg]+0.09×Age [y]−2.7 [m/s]).

Discussion

We designed this study to analyze the validity, accuracy, and repeatability of an automatic, noninvasive method for measurement of PWV and then to evaluate the clinical application of this method to a large population by analyzing some of the clinical parameters and biological plasma cardiovascular risk factors as PWV determinants.

We chose to measure carotid-femoral PWV to evaluate aortic distensibility for several reasons: first, because pressure waveforms can be easily recorded on these two sites; second, because the distance between these two sites is large enough to allow an accurate calculation of the time interval between the two waves (initial rise upstroke) recorded simultaneously on a paper recorder at relatively high speed (150 mm/s); and third, because carotid-femoral PWV reflects arterial wall elasticity, which is widely related to the aorta.

The validation of the automatic measurement of PWV by comparison with the manual method shows a significant linear correlation between the mean values of PWV measured by each of these methods. This highly significant correlation coefficient reflects the good agreement between the two PWV measurement methods. The analysis of the difference between the two methods showed a slightly lower value obtained by the automatic device (−0.20±0.45) that was not related to clinical parameters such as age, weight, and height. This difference is minor to consider in clinical practice because it is practically insignificant in terms of absolute values (less than 2% for a mean PWV value of approximately 11 m/s) and because the agreement between the two methods is high, with a linear correlation coefficient of $r=.99$. In addition, it is important to note that this difference is very low compared with the PWV modification observed after drug administration, which usually reaches 10%.

Our results indicate that the intraobserver and interobserver RC values of the automatic PWV measurement showed high reproducibility, which allows its application for longitudinal clinical studies, provided that they are done by an experienced investigator.

The clinical application of this method in a large population for analysis of PWV determinants showed that age and systolic pressure strongly correlate with PWV. In fact, the most important factor contributing to increased PWV in human populations is age because of increased arterial stiffness caused by medial calcification and loss of elasticity. Reports conflict regarding the effects of age-related development of atherosclerosis on arterial distensibility as evaluated by PWV. Some studies[7,12] suggest that the increase in PWV could be an early indicator of atherosclerosis development (as diabetes); other studies show no significant difference in PWV with age in subjects predisposed to a high risk of atherosclerosis, such as familial hypercholesterolemia. However, there has been a qualitative association between the process of atherosclerosis and arterial "rigidity"; PWV studies indicate that hypertension contributes more than atherosclerosis to increased arterial stiffening with age.[5,7,11]

In addition to the role of age, PWV also depends on blood pressure level: the higher the pressure, the faster the speed of wave travel. In fact, since PWV is related to wall elasticity, it becomes directly related to distending pressure. However, varying correlation coefficients have been reported between PWV and systolic, diastolic, and mean blood pressures.[5] These variations are probably attributable to the inherent variability in both PWV and blood pressure within and across individual subjects. In our study multiregression analysis showed that systolic pressure was correlated with PWV. This can be explained by the determinants of systolic pressure; in fact, one of the major factors influencing systolic pressure is arterial distensibility, as it can be evaluated by PWV.[4]

In our study sex, weight, tobacco consumption, plasma glucose, cholesterol, and high-density lipoprotein cholesterol did not significantly influence PWV. There are conflicting reports on the relationship of some of these factors with the stiffening of large arteries in humans. Reduced arterial compliance in nonoccluded arteries has been demonstrated in patients with coronary artery disease and in patients with diabetes mellitus.[12,13] Other studies have shown no significant differences in PWV with age in subjects with a high risk of atherosclerosis, such as familial hypercholesterolemia, or in populations with different prevalences of atherosclerosis, such as Western and Asian populations. Furthermore, studies of large groups of Chinese and German populations have failed to demonstrate any association between PWV and total plasma cholesterol.[5,7,10] However, in such investigations the different fractions of lipoproteins were not widely evaluated. More recently, in analyses of the relationship between lipid fractions and aortic PWV, Relf et al,[11] London et al,[14] and Asmar et al[15] found a weak negative correlation between high-density lipoprotein cholesterol and aortic PWV but no significant correlation with total plasma cholesterol. In the present study we observed no significant relationship between PWV and different lipoprotein fractions. These apparently conflicting reports can be explained by the differences between the analyzed populations. In the previous studies they were healthy men,[11] patients with end-stage renal failure,[14] or treated hypertensive patients,[15] whereas in the present study they were normotensive and untreated hypertensive subjects.

Conclusion

Large artery damage is a major contributing factor to the elevated cardiovascular morbidity and mortality observed in cardiovascular risk factors such as hypertension. Reduced arterial distensibility contributes to a disproportionate increase in systolic pressure and an increase in arterial pulsatility, which has been shown to be associated with an increase in cardiovascular morbidity and mortality. Quantitative information on the large arteries may be easily obtained by determination of PWV. This method enables one to evaluate indirectly arterial distensibility and stiffness.[5,7]

Recent progress in noninvasive techniques enables a simple automatic measurement of PWV that provides a real on-line measurement of this parameter. The validation study of this technique compared with manual calculation (the gold standard) shows that the two methods are highly correlated and have high interobserver and intraobserver reproducibilities. The analysis of the determinants of aortic PWV in a large population showed that the two major determinants of PWV are age and systolic pressure, as expressed in the formula $\text{PWV}=0.07\times\text{Systolic Pressure (mm Hg)}+0.09\times\text{Age (y)}-4.3$ (m/s). Whether these correlations will remain unchanged or will be modified by antihypertensive treatment still needs to be clarified by large therapeutic and epidemiological studies.

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