REVIEW ARTICLE

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

## Clinical Implications

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## Contents



## Abstract

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 antihypertensive agents is recommanded by numerous authorities. Among the noninvasive 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 risk 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 effects of long term treatment with ACE inhibitors, calcium channel antagonists and some β-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 favorable 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.

Large artery involvement is the major contributor to cardiovascular disease, which is the leading cause of mortality and morbidity in the industrialized countries. In patients with hypertension, morbidity and mortality are primarily related to arterial damage that may affect one or several organs: the kidney (nephroangiosclerosis), brain (stroke), heart (angina pectoris, myocardial infarction), etc. In hypertension, structural and functional properties of the arterial wall have been reported to be altered, even at early stages of the disease.[1-4]

Recently, the prognostic importance of arterial stiffness has been described in various populations, normotensive individuals and in patients with hypertension: it is an independent factor of target organ damage and a predictor of cardiovascular morbidity as well as cardiovascular and all-cause mortality.[21-24] Therefore, considering the potential implications of arterial assesment in the prevention of cardiovascular disease, the evaluation of the effect of antihypertensive agents on arterial stiffness is recommended by numerous authorities.[5] In fact, since the arterial wall constitutes the target site of all cardiovascular risk factor complications, it is important to assess the ability of antihypertensive treatment to reverse or improve arterial wall abnormalities.

The last decade has witnessed extraordinary advances in the methodological aspects of arterial measurements. One of the consequences of this remarkable development is the availability of devices, which not only allow evaluation of arterial stiffness but also its estimation at different sites on the arterial tree and assessment of other hemodynamic parameters. The growing interest in this field is not only reflected by the increasing number of publications during the last few years, but also by the number of ongoing studies. However, the drawback of this abundance in methodology and terminology described in the literature is that it makes the task of comparing results between studies and between research groups almost impossible. In fact, in a recent review,[6] 24 different indices for the description of arterial elastic properties have been identified, suggesting that such disparate methodology and terminology would cause even more problems. Therefore, in order to avoid any confusion, in this review, the effects of antihypertensive agents on arterial stiffness in large arteries will be discussed. According to a recent international consensus conference,[7] as a generic term, stiffness is preferable to any other, especially compliance which is more frequently used to describe adherence with therapy or advice, or adherence to protocol.

Whereas historically arteries have been described as simple conduits of blood, today the arterial system is described as a complex and heterogeneous system with major differences between the large arteries, the small arteries, the arterioles and the microcirculation. This review is focused on the effects of antihypertensive agents on the central (principally elastic) and the peripheral (principally muscular) large arteries.

Several methods can be employed to analyze the mechanical properties of the arterial wall. Most of them are complex or need sophisticated technical equipment which limits their application in clinical practice.[8-11] Among the noninvasive and simple methods to evaluate the segmental or regional arterial stiffness, pulse

wave velocity (PWV) measurement is widely used as an index of arterial elasticity and stiffness. This method is simple, accurate and reproducible, and thus can easily be applied in clinical trials.[12-15]

Since most of the studies have used this method to evaluate the arterial effect of the antihypertensive agents, this review is focused principally on the segmental stiffness as evaluated by PWV.

## 1. Pulse Wave Velocity (PWV) Measurement

The basic principle of PWV assessment is that the pressure pulse generated by ventricular ejection is propagated along the arterial tree at a speed determined by the geometric and elastic properties of the arterial wall.[16] PWV is calculated from measurements of the pulse transit time and the distance traveled by the pulse between two recording sites, according to the following formula: PWV (m/sec) = distance (m)/transit time (sec). For example, carotid-femoral PWV is calculated from the time delay between the recorded proximal (carotid) and distal (femoral) feet of the wave, and the superficially measured distance separating the respective transducers (fig. 1).

The time delay determination between the 'characteristic' points of the proximal and the distal waves can be performed according to several techniques which may be schematically divided into two major methods: the 'manual' measurements and the automatic determination.

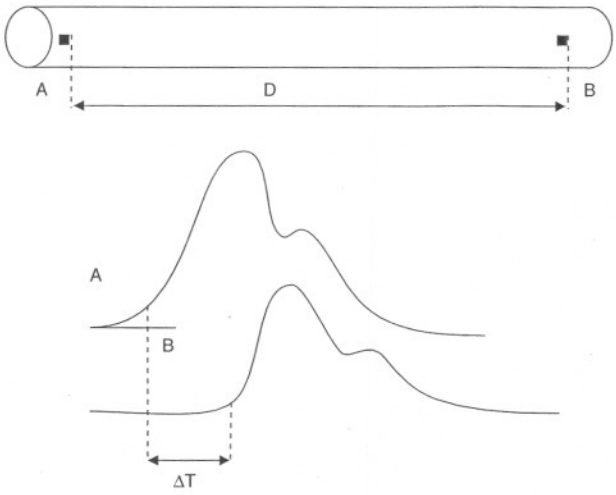


**Fig. 1.** Pulse wave velocity (PWV) measurement. **A** = wave recorded by the proximal transducer; **B** = wave recorded by the distal transducer; **D** = distance traveled by the wave; **ΔT** = time delay between the foot waves.

### 1.1 The Manual Method

The interval between the two characteristic points can be directly measured on the paper recording; this interval is then converted to time-delay after correction by the paper speed recording: time interval (time-delay) = interval/paper speed. This interval is usually measured for at least ten successive heart beats to cover at least one complete respiratory cycle, and the mean value is considered for PWV calculation.

### 1.2 Automatic Method – the Complior® Device

Among the several devices available for the automatic determination of PWV, the Complior® System (Artech-Medical, Pantin, France) is widely used. This system gives an automated measurement of PWV based upon dedicated mechanotransducers applied directly on the skin. Two arterial segments can be evaluated simultaneously, mainly the aortic trunk, and the upper or the lower limbs. The technical characteristics of this device have been described elsewhere in detail:[17] there was a good agreement between the manual method (gold standard) and the automatic device with a linear correlation coefficient between the two methods of r = 0.99 (automatic = 0.93, manual + 0.56 m/sec). The inter- and intra-observer repeatability coefficients of PWV measurements using these two methods were found to be ≥0.90, thus reflecting highly reproducible measurements.

Other methods using pulse wave analysis or PWV measurements to assess arterial stiffness are now available: the Sphygmocor® system (PWV Co., Sydney, Australia), the CVProfilor™ device (Hypertension Diagnostics Inc., Minneapolis, USA) and the Wall Track System (Pie Medical, Maastricht, The Netherlands).

## 2. PWV Alterations in Clinical Conditions and Prognosis

### 2.1 Correlation Between PWV and Cardiovascular Risk Factors

Several studies performed in various populations showed significant correlations or powerful interactions between PWV and cardiovascular risk factors such as age, hypertension, diabetes mellitus and smoking.[18]

There is a positive linear correlation between PWV and arterial blood pressure or age. Higher PWV and stiffness index were observed in patients with borderline, white-coat or sustained hypertension than in age-matched normotensive individuals. Elevated PWV and increased arterial stiffness are not only related to the stretching effect of elevated blood pressure but also to early changes and abnormalities in the arterial wall in hypertension.[18]

Increased PWV was repeatedly observed in patients with type 1 or 2 diabetes mellitus, and PWV was proposed as an early indicator of atherosclerosis in patients with diabetes mellitus and in individuals with a positive family history of diabetes mellitus.[18] The pathophysiologic mechanisms involved in the association between arterial stiffness and type 1 or 2 diabetes mellitus remain, however, unclear and need more specific, large-scale studies.

Relations between arterial stiffness and the other cardiovascular risk factors remain unclear. In fact, whereas some studies reported positive relationships between arterial stiffness and dyslipidemia or smoking, others described controversial results.

A recent study has evaluated the relationships between three different methods of assessing arterial compliance and risk markers such as age, serum creatinine levels, high density lipoprotein-cholesterol levels, and the use of tobacco. These determinants of cardiovascular outcome were found to be clearly associated with simple compliance indicators such as PWV.[19,20]

### 2.2 PWV As a Marker of Cardiovascular Disease

In addition, aortic PWV was shown to be strongly associated with the presence and extent of atherosclerosis and constitutes a forceful marker and predictor of cardiovascular risk in normotensive and hypertensive patients.[21,22] Aortic PWV has also been shown to be an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension[23] and in those with end-stage renal failure (ESRF).[24]

### 2.3 Aortic Stiffness Attenuation and Cardiovascular Morbidity and Mortality

The impact of aortic stiffness attenuation on survival was recently studied in patients in ESRF: results indicate that in these patients, the use of an antihypertensive treatment by ACE inhibitors has a favorable effect on survival that is independent of reduction in blood pressure.[25]

Thus, in addition to blood pressure reduction, the main goal of the drug treatment in patients with hypertension should include decreasing cardiovascular morbidity and mortality by reducing aortic stiffness.

## 3. Methodological Aspects

The following are some of the important methodological aspects which must be taken into consideration when evaluating the arterial effects of an antihypertensive agent:

(i) the study design (nonblind, single-blind or randomized, double-blind)

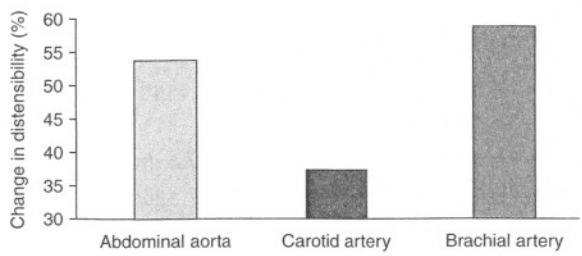


**Fig. 2.** Relative change in distensibility after antihypertensive treatment in 3 arterial territories: abdominal aorta, carotid artery and brachial artery. A significant site effect was noticed. (Reproduced from Topouchian et al.,[34] with permission).

(ii) the arterial site at which measurements are performed. Since arterial hypertension may affect different vascular beds in a different manner (fig. 2), it is important to consider the arterial effects of antihypertensive agents according to the arterial site being evaluated.

(iii) the mechanism of action of the antihypertensive agent used and also the dosage and duration of treatment. It is likely that the response of large arteries to antihypertensive agents differ according to the mechanism of action of each particular agent. Since different mechanisms may be involved in the possible improvement of the structural and functional properties of the arterial wall, the arterial effects of the antihypertensive agents have to be considered in the short term but also, and principally, in the long term treatment. Finally, since the arterial effect of an antihypertensive agent may not be necessarily related to its antihypertensive effect, several dosages have to be analyzed.

## 4. Antihypertensive Agents and Arterial Stiffness - Effect on PWV

### 4.1 Nonblind and Single-Blind Studies

Table I shows nonblind and single-blind studies which have evaluated the arterial effects of antihypertensive agents using PWV measurement.

#### *4.1.1 Short Term Treatment*

Results of short term treatment (<28 days) showed no significant effect on aortic PWV with vasodilators such as cadralazine or dihydralazine, whereas decreased brachial-radial PWV has been reported with nicorandil. Lower aortic PWV (higher distensibility) has been observed in one study with calcium channel antagonist (nitrendipine) and in one study with an ACE inhibitor (perindopril).

**Table I.** Changes in pulse wave velocity observed in open or single-blind studies evaluating the effects of antihypertensive agents with hypertension

| Reference | Agent | Short term treatment <28 days | | Long term treatment ≥28 days | |
|---|---|---|---|---|---|
| | | aorta | arm/leg | aorta | arm/leg |
| **Vasodilators & equivalent** | | | | | |
| Bouthier et al.[35] | Cadralazine | Unchanged | | | |
| Levenson et al.[36] | Nicorandil | | ↓ | | |
| Benetos et al.[37] | Dihydralazine | Unchanged | | | |
| **β-blockers** | | | | | |
| De Cesaris et al.[38] | Atenolol | | | | Unchanged |
| Asmar et al.[39] | Bisoprolol | | | ↓ | |
| De Cesaris et al.[40] | Metoprolol | | | | Unchanged |
| **Calcium channel antagonists** | | | | | |
| Bouthier et al.[35] | Nitrendipine | ↓ | | | |
| De Cesaris et al.[38] | Nicardipine | | | | ↓ |
| Tedeschi et al.[41] | Nitrendipine | | | ↓ | |
| Benetos et al.[42] | Nicardipine | | | ↓ | |
| **ACE inhibitors** | | | | | |
| Asmar et al.[43,44] | Perindopril | | | | ↓ |
| Benetos et al.[37] | Perindopril | ↓ | | | |
| Benetos et al.[42] | Ramipril | | | ↓ | Unchanged |
| De Cesaris et al.[40] | Lisinopril | | | | ↓ |
| Benetos et al.[45] | Perindopril | | | ↓ | |
| **Diuretics** | | | | | |
| Laurent et al.[46] | Canrenoic acid | | | | Unchanged |
| | Indapamide | | | | Unchanged |
| Safar et al.[47] | Indapamide | | | | Unchanged |

#### *4.1.2 Long Term Treatment*

During long term treatment (≥28 days) most of the β-blockers (except bisoprolol) showed no significant modification in arterial stiffness at the level of the limbs. For calcium channel antagonists, nicardipine induced a decrease in aortic and brachial-radial PWV. Most of the studies with ACE inhibitors reported a significant decrease in PWV measured at the aortic and the arm levels. Diuretics did not show any significant changes in PWV.

Therefore, according to these results, diuretics, vasodilators (except nicorandil) and β-blockers (except bisoprolol) did not significantly modify PWV. Calcium channel antagonists and principally ACE inhibitors induced significant improvement of PWV at the aortic and the brachial levels.

### 4.2 Double-Blind Studies

Double-blind studies which have evaluated the effects of antihypertensive agents based on arterial stiffness using PWV measurements are presented in table II.

#### *4.2.1 Short Term Treatment*

Few studies have used a short term treatment period; most of them included ACE inhibitors and reported improvement of arm and aortic PWV from pretreatment values.

#### *4.2.2 Long Term Treatment*

During long term treatment, ACE inhibitors induced a constant increase in arterial distensibility (decrease in aortic PWV), and there was a lesser improvement in PWV at the aortic and limb levels with calcium channel antagonists. Diuretics showed limited effects on PWV at the aortic and limb levels and β-blockers exhibited variable effects according to the drug used.

#### *4.2.3 Meta-Analysis*

Recently, Delerme et al.[26] performed a meta-analysis on individual data from several pharmacological studies conducted between 1987 and 1994 using similar methodology. Only controlled, randomized, double-blind, parallel-group trials analyzing the effect of various antihypertensive agents or placebo on carotid-femoral PWV either during short term (<28 days) or long term (≥28 days) periods, were selected.

The results showed that in short and long term trials, antihypertensive agents reduced PWV in comparison to placebo independently of blood pressure reduction and after adjustment on baseline parameters. The pressure-independent decrease in PWV was more important with long term than with short term treatment. This improvement in aortic PWV was significantly more pronounced after treatment with ACE inhibitors than after treatment with calcium channel antagonists in short term studies. In long term studies, improvement in PWV was greater after treatment with an ACE inhibitor, β-blocker or a diuretic than after calcium channel antagonists but this difference did not attain statistical significance (fig. 3). However, it is important to emphasize that limited agents were included in each antihypertensive class. Thus, β-blockers included mostly bisoprolol which has been shown to exhibit highly significant changes in PWV compared with other β-blockers. Therefore, more studies performed

**Table II.** Changes in pulse wave velocity observed in double-blind studies evaluating the effects of antihypertensive agents with hypertension

| Reference | Agent | Short term treatment < 28 days | | Long term treatment ≥28 days | |
|---|---|---|---|---|---|
| | | aorta | arm/leg | aorta | arm/leg |
| **Vasodilators** | | | | | |
| Lacolley et al.[48] | Cadralazine | Unchanged | | | |
| **β-blockers** | | | | | |
| Kelly et al.[49] | Dilevalol | | | ↓ | ↓ |
| | Atenolol | | | ↓ | ↓ |
| Asmar et al.[50] | Bisoprolol | | | ↓ | ↓/≡ |
| Barenbrock et al.[51] | Metoprolol | | | Unchanged (carotid) | |
| Simon et al.[52] | Metoprolol | | | | Unchanged |
| Savolainen et al.[53] | Atenolol | | | Improvement (MRI) | |
| Kahonen et al.[54] | Propranolol | ↓ (normotensive) | | | |
| **Calcium channel antagonists** | | | | | |
| Pancera et al.[55] | Lacidipine | | | | ↓ |
| | Nifedipine | | | | ↓ |
| Asmar et al.[56] | Nitrendipine | | | ↓ | Unchanged |
| Asmar et al.[57] | Felodipine | | | ↓ | ↓ |
| Simon et al.[52] | Isradipine | | | | ↓ |
| Pannier et al.[58] | Lacidipine | Unchanged | | | |
| Kahonen et al.[54] | Verapamil | ↓ (normotensive) | | | |
| Topouchian et al.[34] | Verapamil | | | ↓ | |
| **ACE Inhibitors** | | | | | |
| Lacolley et al.[48] | Captopril | ↓ | | | |
| Asmar et al.[59] | Trandolapril | ↓ | | | |
| Asmar et al.[60] | Lisinopril | ↓ | ↓ | | |
| Barenbrock et al.[51] | Lisinopril | | | Distensibility™ ↑ (carotid) | |
| Kool et al.[61] | Perindopril | | | Distensibility™ ↑ (carotid) | |
| Savolainen et al.[53] | Cilazapril | | | Improvement (MRI) | |
| Benetos et al.[62] | Perindopril | | | ↓ | |
| Kahonen et al.[54] | Captopril | ↓ (normotensive) | | | |
| Topouchian et al.[63] | Quinapril | ↓ | ↓ | | |
| Topouchian et al.[34] | Trandolapril | | | ↓ | |
| **Diuretics** | | | | | |
| Asmar et al.[57] | Hydrochlorothiazide (HCTZ) | | | Unchanged | Unchanged |
| Kool et al.[61] | Amiloride + HCTZ | | | Unchanged (carotid) | |
| Benetos et al.[62] | Amiloride + HCTZ | | | ↓ | |

**MRI** = magnetic resonance imaging; ↓ indicates a decrease from pretreatment values, ↑ indicates an increase from pretreatment values; ≡ indicates no change from pretreatment values

in larger patient populations are needed before extrapolating the results observed with one specific antihypertensive agent to other agents of its class and hastily concluding a 'class-effect'.

### 4.3 Large-Population Clinical Studies

In order to analyze whether long term antihypertensive treatment can fully reverse arterial alterations in treated patients with hypertension who have normalized diastolic blood pressure, carotid-femoral PWV was measured in normotensive individuals, patients with untreated hypertension and in a cohort of patients with treated hypertension.[2] The treated patients with hypertension were classified as being 'well controlled with antihypertensive treatment' (irrespective of which drug was being used) if their diastolic blood pressure was <90mm Hg during the 3 months preceding the study. During the study, 37% of the patients were receiving monotherapy, 32% dual therapy and 31% triple or multiple therapy. Agents representing all antihypertensive classes were used without any significant preponderance of any one class over the others. The results showed that when compared with patients with untreated hypertension, patients with treated hypertension and well-controlled diastolic blood pressure had significantly lower blood pressure and aortic PWV according to age (fig. 4). However, although diastolic blood pressure in patients with well controlled hypertension was not significantly different from that of normotensive individuals, the aortic PWV of the patients with controlled hypertension increased faster with age than that in normotensive individuals.

#### *4.3.1 Role of Controlled Blood Pressure*

To analyze the role of controlling systolic blood pressure on PWV, treated patients in this study[2] were divided into two subgroups: subgroup A where both diastolic and systolic blood pressures were controlled (<140/90mm Hg); and subgroup B where only diastolic blood pressure was controlled (<90mm Hg) but not systolic blood pressure (>140mm Hg). The results showed higher PWV in subgroup B, and despite the diastolic blood pressure normalization, some patients continued to present PWV values outside the normotensive normogram. These results suggest that the exclusive choice of diastolic blood pressure for the study of vascular complications in hypertension may not be adequate, and that long term antihypertensive treatment may not always be associated with a reversal of arterial alterations.

### 4.4 The Complior® Study

The Complior Study,[27] performed in 69 centers from 19 countries and concerning more than 2000 patients, was the first study aimed at assessing the feasibility of using PWV as an end-

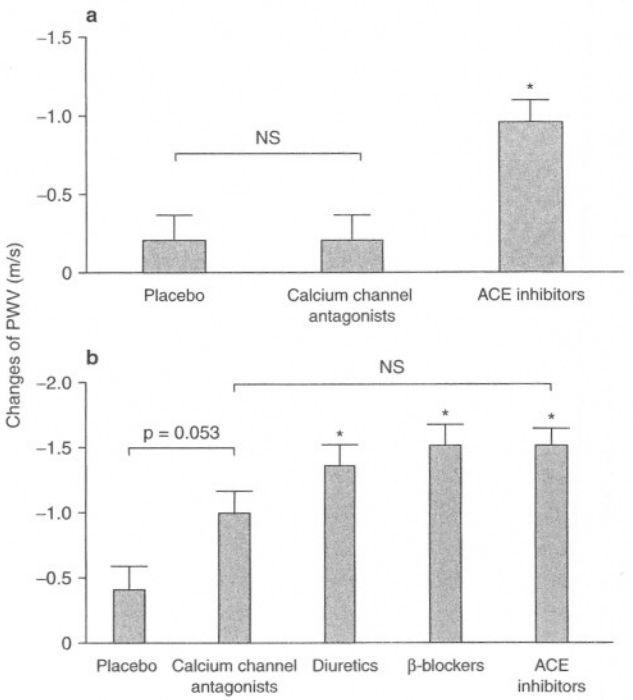


**Fig. 3.** Changes in carotid-femoral PWV [adjusted for blood pressure reduction and baseline values]. (**a**) Short term drug administration (<28 days) and (**b**) Long term drug administration (≥28 days). **NS** = non significant; **PWV** = pulse wave velocity; * $p < 0.05$ vs placebo (Reproduced from Delerme et al.,[26] with permission).

point in a large-scale intervention trial. The major finding of this study was that the evaluation of arterial effects of long term treatment with antihypertensive agents was feasible using an automatic device for measuring aortic PWV measurements, the Complior® system, provided some methodological aspects were considered.

This study[27] evaluated the ability of an antihypertensive therapy based on ACE inhibition to improve the arterial abnormalities observed in hypertension. Patients were treated for six months, starting with an ACE inhibitor (perindopril) and a diuretic (indapamide) was added on if blood pressure was uncontrolled with monotherapy. Arterial stiffness was assessed at inclusion, and at two and six months after treatment, by carotid-femoral PWV measurements.

#### *4.4.1 Limits of the Method*

Measurement of PWV allows an overall assessment of the arterial wall which is related to the arterial geometry and wall function; it does not provide information about the precise underlying mechanisms or specific factors that may be involved in the pathogenesis of arterial abnormalities or changes. In fact, changes

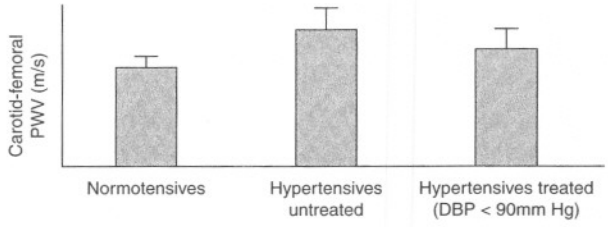


**Fig. 4.** Carotid-femoral pulse wave velocity (PWV) in normotensive individuals, in patients with untreated hypertension and in treated patients with well-controlled hypertension (reproduced from Asmar et al.,[2] with permission). **DBP** = diastolic blood pressure.

in PWV may be due to changes either in structural parameters such as the arterial wall thickness, the internal diameter or, to changes in functional parameters such as changes in blood pressure.

The superficial measurement of the distance traveled by the pulse wave between the carotid and femoral arteries constitutes the major error in PWV determination. In fact, the noninvasive superficial measurement of the arterial pathway allows only an estimate of the true distance; accurate measurements of this distance are obtained only by inva sive procedures. However, if the distance error is important for the determination of PWV absolute value, it represents only a relative limitation in studies where analyses are based on within patient comparison.

#### *4.4.2 Results*

The results showed significant decreases from baseline in blood pressure and PWV (table III) in patients with essential hypertension after long term treatment based on ACE inhibition, which are in agreement with data previously reported in sections 4.1 and 4.2. Collectively, these data show that ACE inhibition improves the properties of large arteries in controlled studies performed in limited numbers of patients to date.

Despite a significant correlation between changes in blood pressure and PWV in these trials, less than 10% of the observed arterial effects were related to blood pressure reduction. Moreover, individual analysis showed that improvement in PWV was not always concomitant with blood pressure reduction, and vice versa.

### 4.5 Specific Populations

#### *4.5.1 Patients in End-Stage Renal Failure*

Epidemiological and clinical studies have shown that increased aortic stiffness, determined by the measurement of aortic PWV is a major contributor to the mortality in patients with ESRF.[24] In clinical studies in patients with ESRF, ACE inhibitors and calcium channel antagonists were shown to decrease aortic PWV in response to blood pressure reduction.[28,29]

To determine the impact of the aortic stiffening response to sustained decreased blood pressure on all-cause and cardiovascular mortality, a recent prospective study was conducted on a cohort of patients with ESRF (mean 51 ± 38 months of follow up).[25] The results indicate that independent of blood pressure changes, survival was substantially better for those in whom aortic PWV declined in response to decreased blood pressure (fig. 5). In addition, this study indicates that arterial stiffness is not only a risk factor contributing to the development of cardiovascular disease but also a marker of established, more advanced, less reversible arterial changes: in patients with ESRF, the insensitivity of PWV to decreased blood pressure was an independent predictor of mortality. In agreement with previous data,[30] results of this study suggested that antihypertensive treatment *per se*, has a favorable effect on the arterial wall. The use of ACE inhibitors has a favorable effect on survival that is independent of blood pressure changes. A specifically designed, prospective, trial is needed to confirm these data.

### 4.6 Genetic Factors

Genetic background can influence the vulnerability of the arterial wall to risk factors such as hypertension: for a similar degree of risk, arterial stiffening may be more or less pronounced as a function of genetic factors. The renin-angiotensin-

**Table III.** The Complior® study.[27] Treatment effects (ACE inhibitor and ACE inhibitor plus diuretic) on blood pressure and PWV. Mean values and changes from baseline (M0), during (2 months; M2) and at the end of the study (6 months; M6) [reproduced from Asmar et al.,[27] with permission]

| Variables | M0 | M2 | M6 | Δ(M2-M0) | p-Values | Δ(M6-M0) | p-Values |
|---|---|---|---|---|---|---|---|
| Systolic BP (mm Hg) | 158 ± 15 | 139 ± 16 | 134 ± 13 | –20 ± 17 | <0.001 | –24 ± 17 | <0.001 |
| Diastolic BP (mm Hg) | 98 ± 7 | 86 ± 9 | 84 ± 8 | –12 ± 10 | <0.001 | –14 ± 10 | <0.001 |
| Mean BP (mm Hg) | 118 ± 8 | 103 ± 10 | 100 ± 9 | –15 ± 11 | <0.001 | –18 ± 11 | <0.001 |
| Pulse Pressure (mm Hg) | 59 ± 15 | 52 ± 12 | 50 ± 10 | –7 ± 14 | <0.001 | –9 ± 15 | <0.001 |
| Heart Rate (bpm) | 75 ± 10 | 75 ± 9 | 75 ± 10 | –0.4 ± 10 | NS | –0.3 ± 10 | NS |
| PWV (m/sec) | 11.6 ± 2.6 | 10.7 ± 2.2 | 10.5 ± 2.1 | –0.9 ± 1.4 | <0.001 | –1.1 ± 1.4 | <0.001 |

**BP** = blood pressure; **NS** = not significnat; **PWV** = pulse wave velocity; Δ indicates the magnitude of change between time points.

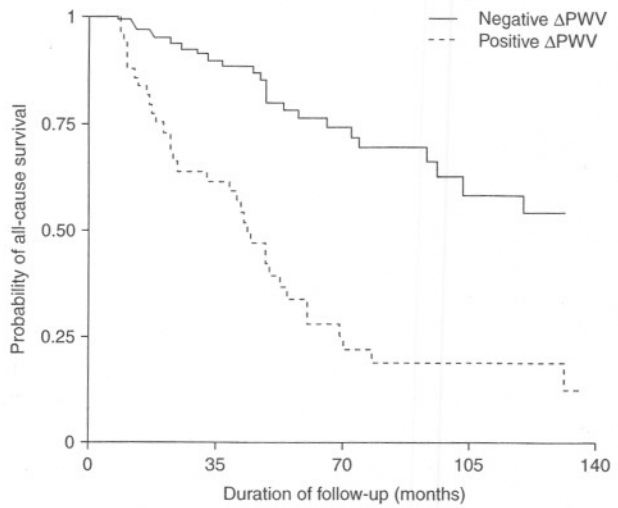


**Fig. 5.** Probability of all-cause survival according to change in pulse wave velocity (ΔPWV) under antihypertensive therapy. Comparison on the basis of PWV changes between responders (**negative ΔPWV** = decrease in PWV) and non-responders (**positive ΔPWV** = absence of PWV decrease) in treated patients with end-stage renal failure was highly significant. (Reproduced from Guérin et al.,[25] with permission).

aldosterone system plays an important role in large artery structure and blood pressure homeostasis.

#### *4.6.1 Role of the Genetic Factors of the Renin-Angiotensin System*

Increasing evidence from human genetic studies show that the ACE genotype is an independent risk factor for myocardial infarction and for cardiac and arterial hypertrophy.[31] The recent identification of angiotensin II $(AT)_1$-receptor gene adenine/cytosine polymorphism suggests that $AT_1$-receptors are involved in arterial alterations. Clear conclusions about the influence of the ACE Insertion/Deletion (I/D) gene polymorphisms on aortic stiffness cannot be drawn; in fact, because of the low incidence of the II genotype, wider studies are needed to define this issue.

Elsewhere, the assessment of the role of $AT_1$ receptor ($AGTR_1A1166C$) gene polymorphisms on PWV in cross-sectional studies has shown that in patients with hypertension, the presence of the $AT_1C$ allele was associated with increased aortic stiffness in both genders, independent of blood pressure levels.[33] Thus, $AT_1$-receptor gene polymorphism may be a particularly important risk marker for arterial stiffness, and could modulate the effects of hypertension and those of the antihypertensive treatment.

#### *4.6.2 Role of the Aldosterone Synthase Gene Polymorphisms*

The role of two variations of the aldosterone synthase gene (CYP11B2), one located in the promoter of the gene $T^{-344}C$, and the other in the seventh exon, the T4986C (Val/Ala), has been evaluated on plasma levels of renin and aldosterone, blood pressure, and arterial stiffness in patients with essential hypertension.[32] The presence of the -344C allele was associated with elevated levels of plasma aldosterone and PWV. No association was found between the T4986C polymorphism and PWV. These differences were not associated with variations in blood pressure levels. Aldosterone synthase polymorphism (CYP11B2 -344C or -344T) is thus also involved in arterial stiffness regulation.

#### *4.6.3 Genetic Factors and Antihypertensive Agents*

Essential hypertension is a multifactorial and heterogeneous disease. This heterogeneity influences the response to the antihypertensive agents as suggested previously. A1166-->C gene polymorphism of the $AT_1$ receptor may influence the antihypertensive agents' effect on blood pressure and large arteries. One study showed that in patients carrying the C allele, blood pressure reduction and regression of arterial stiffness were more pronounced with ACE inhibitors than with calcium channel antagonists, whereas the inverse tendency was observed in AA homozygotes (table IV).[33] These results need to be confirmed in wider studies, but suggest that determination of genetic polymorphisms may be of interest in order to identify high risk patients and in the selection of antihypertensive therapy.

## 5. Conclusion

Structural and functional properties of the arterial wall have been reported to be altered in hypertension, even at early stages

**Table IV.** Impact of the adenine1166 to cytosine (A1166-->C) gene polymorphism of the angiotensin ($AT_1$) receptor on hemodynamic parameters before and after treatment with perindopril or nitrendipine (reproduced from Benetos et al.,[33] with permission)

| Parameter | $AT_1$ receptor genotype | | | | Interaction p-values (ANOVA) |
|---|---|---|---|---|---|
| | AA baseline | end-point | AC + CC baseline | end-point | |
| **Perindopril** | | | | | |
| SBP (mm Hg) | 155 ± 3 | 146 ± 3** | 159 ± 6 | 140 ± 3*** | <0.05 |
| DBP (mm Hg) | 92 ± 2 | 87 ± 2* | 96 ± 3 | 85 ± 2*** | <0.05 |
| MBP (mm Hg) | 114 ± 2 | 108 ± 2** | 117 ± 4 | 103 ± 3*** | <0.05 |
| HR (bpm) | 66 ± 2 | 70 ± 2 | 67 ± 2 | 69 ± 4 | NS |
| PWV (m/sec) | 12.5 ± 0.4 | 11.5 ± 0.3** | 14.4 ± 1.0 | 11.5 ± 0.7*** | <0.001† |
| **Nitrendipine** | | | | | |
| SBP (mm Hg) | 158 ± 3 | 140 ± 3*** | 158 ± 2 | 146 ± 2** | NS |
| DBP (mm Hg) | 96 ± 2 | 87 ± 2** | 96 ± 2 | 89 ± 1** | NS |
| MBP (mm Hg) | 119 ± 2 | 106 ± 2*** | 117 ± 2 | 109 ± 2** | NS |
| HR (bpm) | 69 ± 2 | 70 ± 1 | 71 ± 3 | 75 ± 3 | NS |
| PWV (m/sec) | 12.2 ± 0.6 | 10.8 ± 0.6** | 13.9 ± 0.8 | 13.9 ± 0.9 | <0.01‡ |

**DBP** = diastolic blood pressure; **HR** = heart rate; **MBP** = mean blood pressure; **NS** = not significant; **PWV** = pulse wave velocity; **SBP** = systolic blood pressure; * $p < 0.05$, ** $p < 0.01$, *** $p < .001$ *vs* pretreatment values; † $p < 0.02$, ‡ $p < 0.01$ after adjustement for age and changes in mean blood pressure.

of the disease. Morbidity and mortality associated to hypertension are primarily related to arterial damages that may affect one or several organs. Thus, in addition to their effects on blood pressure, evaluation of the arterial effect of antihypertensive agents is recommended. Aortic PWV is a well recognized marker of cardiovascular ri sk and pharmacological studies have shown its improvement with antihypertensive treatment. This improvement in PWV was reported to be independent from blood pressure reduction, more pronounced after long-term treatment than after short-term administration and could be influenced by the genetic background. Clinical studies, generally performed in a small number of patients, suggest that ACE inhibitors, calcium channel antagonists and some β-blockers are equally effective in reducing arterial stiffness in long term treatment.

Treatment of high blood pressure aims principally to reduce blood pressure. This decrease in blood pressure is generally associated with a reduction in cardiovascular risk. However, despite the reduction in blood pressure in treated patients, cardiovascular morbidity and mortality remains higher than that in normotensive individuals. One of the hypothesis to explain this observation might be an unchanged arterial stiffness. In favor of this hypothesis, the data obtained in high risk patients with ESRF show that the insensitivity of PWV to decreased blood pressure is an independent predictor of mortality. The correlation between antihypertensive treatment-induced reversion of arterial stiffness and decreased cardiovascular morbidity and mortality need to be confirmed in populations of patients with lower cardiovascular risk.

## References


1. Isnard R, Pannier B, Laurent S, et al. Pulsatile diameter and elastic modulus of the aortic arch in essential hypertension: a noninvasive study. J Am Coll Cardiol 1989; 13: 399-405
2. Asmar R, Benetos A, London G, et al. Aortic distensibility in normotensive untreated and treated hypertensive patients. Blood Press 1995; 4: 48-54
3. O'Rourke M. Mechanical principles in arterial disease. Hypertension 1995; 26: 2-9
4. World Health Organization. International Society of Hypertension guidelines for the management of hypertension. Guidelines subcommittee. J Hypertens 1999; 17: 151-83
5. Frohlich ED, Tarazi RC, Dustan HP. Re-examination of the hemodynamics of hypertension. Am J Med Sci 1969; 257: 9-23
6. Lehmann ED. Terminology for the definition of arterial elastic properties. Path Biol 1999; 47: 656-4
7. Asmar R, Avolio A, Benetos A, et al. Clinical applications of arterial stiffness. A summary report of the first international consensus conference. Circulation. In press
8. Kannel WB. Blood pressure as a cardiovascular risk factor. Prevention and treatment. JAMA 1996; 275: 1571-6
9. Hoeks APG, Brands PJ, Smeets GAM, et al. Assessment of the distensibility of superficial arteries. Ultrasound Med Biol 1990; 16: 121-8
10. Tardy Y, Meister JJ, Perret F, et al. Assessment of the elastic behaviour of peripheral arteries from a non-invasive measurement of theirs diameter-pressure curves. Clin Phys Meas 1991; 12: 39-54
11. Kawasaki T, Sasayama S, Yagi SI, et al. Non-invasive assessment of the age related changes in stiffness of the human arteries. Cardiovasc Res 1987; 21: 678-87
12. Asmar R, Brunel PC, Pannier BM, et al. Arterial distensibility and ambulatory blood pressure monitoring in essential hypertension. Am J Cardiol 1988; 61: 1066-70
13. Lehman ED, Parker JR, Hopkins KD, et al. Validation and reproductibility of pressure-corrected aortic distensibility measurements using pulse-wave velocity Doppler ultrasound. J Biomed Eng 1993; 15: 221-8
14. Lehmann ED. Pulse wave velocity as a marker of vascular disease. Lancet 1996; 348: 744
15. Asmar RG, Topouchian JA, Benetos A, et al. Non-invasive evaluation of arterial abnormalities in hypertensive patients. J Hypertens 1997; 15 Suppl. 2: S99-107
16. Nichols WW, O'Rourke MF. McDonald's blood flow in arteries: theoretical, experimental and clinical principles. 3rd ed. London: Edward Arnold, 1990
17. Asmar R, Benetos A, Topouchian J, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995; 26: 485-90
18. Asmar R. Arterial stiffness and pulse wave velocity. Clinical applications. Elsevier 1999 Amsterdam:
19. Weber M. The measurement of arterial properties in hypertension [editorial]. Am J Hypertens 2001; 14: 183-5
20. Asmar R, Rudnichi A, Blacher J, et al. Pulse pressure and aortic pulse wave are markers of cardiovascular risk in hypertensive populations. Am J Hypertens 2001; 14: 91-7
21. Blacher J, Asmar R, Djane S, et al. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999; 33: 1111-7
22. Van Popele N, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis. The Rotterdam Study. Stroke 2001; 32: 454-60
23. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37: 1236-41
24. Blacher J, Guérin AP, Pannier B, et al. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999; 99: 2434-9
25. Guérin AP, Blacher J, Pannier B, et al. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001; 103: 987-2
26. Delerme S, Boutouyrie P, Laloux B, et al. Aortic stiffness is reduced beyond blood pressure lowering by short- and long term antihypertensive treatment: a meta-analysis of individual data in 294 patients. Hypertension 1998; 32: 789
27. Asmar R, Topouchian J, Pannier B, et al., on behalf of the scientific, quality control, coordination and investigation committees of the Complior Study. Pulse wave velocity as endpoint in large scale intervention trial. The Complior Study. J Hypertens 2001; 19: 1-6
28. Asmar RG, Pannier B, Santoni JP, et al. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. Circulation 1988; 78: 941-50
29. London GM, Marchais SJ, Guérin AP, et al. Salt and water retention and calcium blockade in uremia. Circulation 1990; 82: 105-3
30. Salem MM, Bower J. Hypertension in the hemodialysis population: any relation to one-year survival? Am J Kidney Dis 1996; 28: 737-40
31. Cambien F, Poirier O, Lecerf L, et al. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. Nature 1992; 359: 641-4
32. Pojoga L, Gautier S, Blanc H, et al. Genetic determination of plasma aldosterone levels in essential hypertension. Am J Hypertens 1998; 11: 856-60
33. Benetos A, Gavtier S, Ricard S, et al. Influence of angiotensin-converting enzyme and angiotensin II type I receptor gene polymorphisms on aortic stiffness in normotensive and hypertensive patients. Cirulcation 1996; 94: 698-703
34. Topouchian J, Asmar R, Sayegh F, et al. Changes in arterial structure and function under trandolapril-verapamil combination in hypertension. Stroke 1999; 30: 1056-64
35. Bouthier JD, De Luca N, Safar ME, et al. Cardiac hypertrophy and arterial distensibility in essential hypertension. Am Heart J 1985; 109: 1345-52
36. Levenson J, Bouthier J, Chau NP, et al. Effects of nicorandil on arterial and venous vessels of the forearm in systemic hypertension. Am J Cardiol 1989; 63: 40J-3J

37. Benetos A, Santoni JP, Safar ME. Vascular effects of intravenous infusion of the angiotensin converting enzyme inhibitor perindoprilat. J Hypertens 1990; 8: 819-26
38. De Cesaris R, Ranieri G, Filitti V, et al. Large artery compliance in essential hypertension. Effect of calcium antagonism and β-blocking. Am J Hypertens 1992; 5: 624-8
39. Asmar R, Hugues C, Pannier B, et al. Duration of action of bisoprolol after cessation of a 4 week treatment and its influence on pulse wave velocity and aortic diameter: a pilot study in hypertensive patients. Eur Heart J 1987; 8: 115-20
40. De Cesaris R, Ranieri G, Filitti V, et al. Forearm arterial distensibility in patients with hypertension: comparative effects of long term ACE inhibition and β-blocking. Clin Pharmacol Ther 1993; 53: 360-7
41. Tedeschi C, Guarini P, Giodano G, et al. Effects of nicardipine on intimal-medial thickness and arterial distensibility in hypertensive patients. Int Angiol 1993; 12: 344-7
42. Benetos A, Asmar R, Vasmant D, et al. Long lasting arterial effects of the ACE-inhibitor ramipril. J Hum Hypertens 1991; 5: 363-8
43. Asmar R, Journo HJ, Lacolley PJ, et al. Treatment for one year with perindopril: effect on cardiac mass and arterial compliance in essential hypertension. J Hypertens 1988; 6 Suppl. 3: S33-9
44. Asmar R, Pannier B, Santoni JP, et al. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. Circulation 1988; 78: 941-50
45. Benetos A, Cambien F, Gautier S, et al. Influence of the angiotensin II type 1 receptor gene polymorphism on the effects of perindopril and nitrendipine on arterial stiffness in hypertensive individuals. Hypertension 1996; 28: 1081-4
46. Laurent S, Lacolley PM, Cuche JL, et al. Influence of diuretics on brachial artery diameter and distensibility in hypertensive patients. Fundam Clin Pharmacol 1990; 4: 685-93
47. Safar M, Laurent S, Safavian A, et al. Sodium and large arteries in hypertension: Effects of indapamide. Am J Med 1988; 84 Suppl. 1B: 15-29
48. Lacolley PJ, Laurent ST, Billaud EB, et al. Carotid arterial hemodynamics in hypertension: acute administration of captopril or cadralazine. Cardiovas Drug Ther 1989; 3: 859-63
49. Kelly R, Daley J, Avolio A, et al. Arterial dilation and reduced wave reflection. Hypertension 1989; 14: 14-21
50. Asmar R, Kerihuel JC, Girerd XJ, et al. Effect of bisoprolol on blood pressure and arterial hemodynamics in systemic hypertension. Am J Cardiol 1991; 68: 61-4
51. Barenbrock M, Speicker C, Hoeks APG, et al. Effect of lisinopril and metoprolol on arterial distensibility. Hypertension 1994; 23 Suppl. I: I161-3
52. Simon A, Merli I, Del Pino M, et al. Vasoselective and drug-specific effects of isradipine on large arterial vessels in hypertensive patients compared to metoprolol. Arzneimittel Forschung 1994; 44: 305-9
53. Savolainen A, Keto P, Poutanen VP, et al. Effects of angiotensin-converting enzyme inhibition versus β–adrenergic blockade on aortic stiffness in essential hypertension. J Cardiovasc Pharmacol 1996; 27: 99-104
54. Kahonen M, Ylitalo R, Koobi T, et al. Influence of captopril, propranolol, and verapamil on arterial pulse wave velocity and other cardiovascular parameters in healthy volunteers. Int J Clin Pharmacol Ther 1998; 36: 483-9
55. Pancera P, Arosio E, Arcaro G, et al. Haemodynamic parameters in hypertensive patients: changes induced by lacidipine and nifedipine. J Hypertens 1989; 7 Suppl. 6: S284-5
56. Asmar R, Benetos A, Brahimi M, et al. Arterial and antihypertensive effects of nitrendipine: a double-blind comparison versus placebo. J Cardiovasc Pharmacol 1992; 20: 858-63
57. Asmar R, Benetos A, Chaouche-Teyara K, et al. Comparison of effects of felodipine versus hydro-chlorothiazide on arterial diameter and pulse wave velocity in essential hypertension. Am J Cardiol 1993; 72: 794-808
58. Pannier BM, Lafeche AB, Girerd X, et al. Arterial stiffness and wave reflections following acute calcium blockade in essential hypertension. Am J Hypertens 1994; 7: 168-76
59. Asmar R, Benetos A, Darne BM, et al. Converting enzyme inhibition: dissociation between antihypertensive and arterial effects. J Hum Hypertens 1992; 6: 381-5
60. Asmar R, Iannascoli F, Benetos A, et al. Dose optimization study of arterial changes associated with angiotensin converting enzyme inhibition in hypertension. J Hypertens 1992; 10 Suppl. 5: S13-9
61. Kool MJ, Lustermans FA, Breed JG, et al. The influence of perindopril and the diuretic combination amiloride + hydrochlorothiazide on the vessel wall properties of large arteries in hypertensive patients. J Hypertens 1995; 13: 839-48
62. Benetos A, Lafleche A, Asmar R, et al. Arterial stiffness, hydrochlorothiazide and converting enzyme inhibition in essential hypertension. J Hum Hypertens 1996; 10: 77-82
63. Topouchian J, Brisac AM, Pannier B, et al. Assessment of the acute arterial effects of converting enzyme inhibition in essential hypertension: a double-blind, comparative and crossover study. J Hum Hypertens 1998; 12: 181-7

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