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Review Article

Effects of pharmacological intervention on arterial stiffness using pulse wave velocity measurement

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Abstract

Arterial stiffness is an independent and powerful marker of all-cause mortality and cardiovascular morbidity and mortality. Pharmacological studies have shown that it is feasible to improve arterial stiffness or to slow its progression with a number of lifestyle modifications or pharmacological agents including antihypertensive, statins, nitrates, and others. Therapeutic improvement of arterial stiffness has been reported to be associated with an improvement of cardiovascular prognosis. Assessment of pharmacological treatment on arterial stiffness needs to include several important aspects in order to avoid inadequate conclusions. Among these parameters: 1) *the arterial site*: effects of treatment may differ according to the arterial site with differences between radial (muscular) and carotid (elastic) artery; 2) *the duration of treatment*: long-term treatment is usually needed to assess the arterial effect; and 3) *the dose of drug used is also of major importance*: the dose-effect relationship varies for the same drug, whether the blood pressure reduction or the arterial effect is considered. In general, high doses are usually needed for the arterial wall property modification. This review is focused on the effects of major pharmacological treatment on arterial stiffness because it has been considered recently as the "gold standard"; effects on other arterial hemodynamic parameters such as central blood pressure are not reviewed.

Keywords: Compliance; large artery; antihypertensive therapy; hypocholesterolemia, statins.

Introduction

Arterial functional and structural alterations have been described at early stages of several cardiovascular diseases. Such vascular abnormalities have been reported even before the clinical manifestation of the so-called "classic cardiovascular risk factors".[1,2] Recently, there has been growing recognition that the disease of interest is based on the arterial wall properties.[3] Therefore, several non-invasive methods have been introduced to assess particular aspects or parameters of the arterial wall structure and function.[4] Among these methods, measurement of arterial stiffness using pulse wave velocity (PWV) and measurement of the central blood pressure (BP) are the most popular. Because most of the pharmacological and non-pharmacological interventional studies have used PWV to assess the arterial effects and because PWV has been widely used for a long time and has been recognized recently as the "gold standard" measurement of arterial stiffness, we focused this review on arterial stiffness.[4–6]

Arterial Stiffness — PWV

Prognostic values of increased arterial stiffness have been described in various populations as a powerful independent factor of target organ damage (brain, heart, kidney) and an independent predictor of cardiovascular morbidity as well as cardiovascular and all-cause mortality.[7–16] Moreover, arterial stiffness has been reported as an independent predictor of cardiovascular disease progression even in patients free of cardiovascular diseases and/or medications.[17] Table 1 summarizes the longitudinal studies reporting the PWV predictive value.[6]

Assessment of arterial stiffness using PWV measurements is a simple and reproducible method. Principles of this method have been described in detail elsewhere.[5] To sum up, the left ventricular contraction and ejection generates a pulse wave that propagates throughout the arterial wall at a finite speed or velocity; theoretically, the higher the velocity, the stiffer the artery. However, several experimen-

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Table 1
Longitudinal studies reporting the PWV predictive value

Measurement Site	Study	Events	Follow-up (yrs)	Type of Patients (no.)	Reference
Aortic PWV	Blacher	CV mortality	6.0	ESRD (241)	7
	Laurent	CV mortality	9.3	Hypertension (1,980)	10
	Meaume	CV mortality	2.5	Elderly (>70) (141)	13
	Shoji	CV mortality	5.2	ESRD (265)	46
	Boutouyrie	CHD events	5.7	Hypertension (1,045)	8
	Cruickshank	All-cause mortality	10.7	IGT (571)	9
	Laurent	Fatal strokes	7.9	Hypertension (1,715)	11
	Sutton-Tyrrell	CV mortality and events	4.6	Elderly (2,488)	14
	Shokawa	CV mortality	10	General population (492)	16
	Willum-Hansen	CV mortality	9.4	General population (1,678)	15
	Mattace-Raso	CV mt, CHD	4.1	Elderly (2,835)	12

CHD, coronary heart disease; CV, cardiovascular; ESRD, end-stage renal disease; IGT, impaired glucose tolerance; Mt, mortality; PWV, pulse wave velocity.

Adapted with permission from Laurent S, Crockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Eur Heart J 2006;27:2588–605.[6]

tal studies have shown that PWV is also related to the arterial wall structure, function, geometry, and endothelium.[5] Therefore, because this method is complex, theories around it have been considered simplistic or inaccurate. Nevertheless, most recently it has been considered the "gold standard" measurement of regional arterial stiffness alone. Nowadays, numerous devices are available allowing automatic measurements of PWV,[4] and it is important to note here that PWV represents a regional measurement of arterial stiffness over an arterial segment. Other methods are available to measure either local or systemic stiffness. In contrast to systemic arterial stiffness that can only be estimated from models, regional and local arterial stiffness can be measured directly. Additionally, some limitations of PWV measurements have to be mentioned, such as a number of other hemodynamic parameters. PWV is a pressure-dependant parameter. PWV represents a global estimation of regional arterial stiffness but does not give any specific information on arterial geometry.

PWV — A Pharmacological Tool

Several characteristics are required in order to consider a technique as a pharmacological tool. In fact, the technique has to be:

a. Non-invasive in order to allow the repeatability of its evaluation
b. Accurate, which requires its clinical validation
c. Reproducible, which requires assessment of its intra- and interobservers' variability[18–20]

Automatic measurements of PWV have been reported as simple, non-invasive, accurate, and reproducible, therefore fulfilling the criteria to be considered as a sensitive pharmacological tool. As mentioned before, other methods dedicated to the evaluation of systemic, regional, or local arterial stiffness, and also central pressure and augmentation index, are now available and have been reported to be suitable as pharmacological tools.

Basic Pharmacological Aspects

To better understand the effects of pharmacological intervention on arterial stiffness, several fundamental points need to be highlighted:

- The arterial site: Atherosclerosis and arterial wall alterations are systemic, but some arterial areas are particularly affected related to the underlying disease. Therefore, arterial abnormalities and their progression may vary in different arterial beds. Moreover, because arteries are heterogenous with major differences between central (elastic) and peripheral (muscular) large arteries, assessment of the pharmacological treatment has to consider the arterial site.[21]
- Duration of treatment: Since several mechanisms may be involved in the arterial stiffness improvement under treatment, assessment of arterial stiffness must distinguish between the acute or short-term treatment (less than 4 weeks) and the longer-term treatment (>4 weeks). Long-term studies should be preferred because acute effects may not predict chronic efficacy.[21,22]
- Drug doses: Because several pathophysiological parameters may be involved in the arterial stiffness improvement, assessment of drug efficacy needs to consider the dose/effect relationship. In fact, the arterial dose/effect relationship may differ from other properties of the drug such as the dose/effect of its antihypertensive effects or its cholesterol-lowering effects, for example. In general, high doses of statins or antihypertensive drugs are needed to observe the effect on the arterial wall.[21,22]

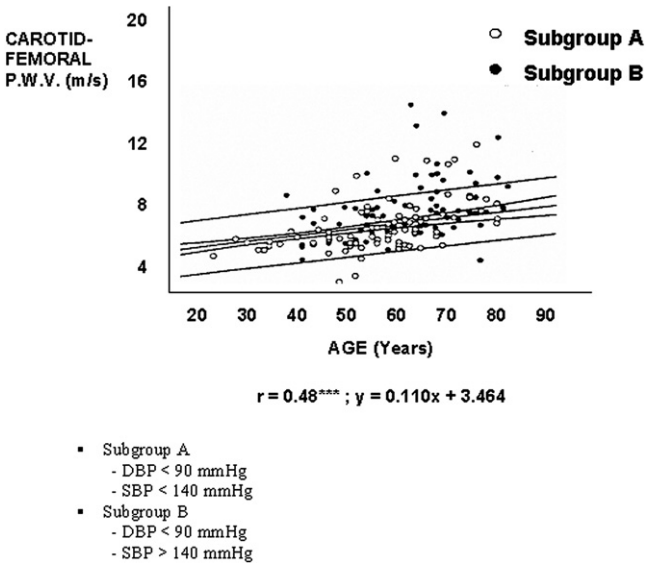

Figure 1. Carotid-femoral pulse wave velocity (PWV) meter/second (m/s): relationship with age in well-controlled hypertensive treated subjects plotted on the normotensive normogram and its individual and mean 95% confidence limits. DBP, diastolic blood pressure; SBP, systolic blood pressure. Adapted with permission from Asmar R, Benetos A, London GM, Hugue C, Weiss Y, Topouchian J, et al. Blood Pressure 1995;4:48–54.[23]

Can The Arterial Stiffness Be Improved?

Whether the arterial wall abnormalities can be reversed under treatment (reversible phenomena) or once these arterial damages are clinically apparent as an irreversible phenomena was a debate subject for a long time. Nowadays, a large number of publications and reviews have reported possible changes in arterial stiffness after various non-pharmacological or pharmacological interventions.[6,21–23] Most of these studies analyzed arterial stiffness changes after pharmacological treatment of the co-existing cardiovascular risk factors or diseases. It is important to notice here that arterial stiffness improvement is often, but not always, associated or only partly related to the corresponding cardiovascular risk changes such as BP reduction or cholesterol lowering level, etc. Figure 1 shows PWV changes in treated hypertensive patients with normalized BP. Results showed that it is possible to normalize arterial stiffness in some treated and normalized patients, but a number of patients maintain stiffer arteries (abnormal high PWV) despite the BP normalization.[23] It is of importance to notice that most of these patients with stiffer arteries were over 70 years of age; therefore, normalization of arterial stiffness may be more difficult to achieve in elderly patients or after a long period of disease history.

Is Improvement Of Arterial Stiffness Similar In All Arterial Trees?

Since arterial abnormalities affect in different manners the arterial sites according to the underlying disease, and since the impact of a given pharmacological drug may differ on the various compounds of the arterial wall (elastin, collagen, muscle) according to its pharmacokinetics, it is logical to assume that the arterial effect of a given drug administered at a given dose and period of time may differ according to the arterial site whether we are considering more elastic (aorta, carotid) or more muscular (radial) or mixed (brachial, femoral) arteries.[24] Moreover, even if a given drug acts on various pathophysiological mechanisms with a "systemic" effect, the degree of the observed arterial stiffness effect is usually different in the different arterial regions. Consequently, it is of importance to focus on which arterial site is assessed for stiffness. Figure 2 shows an example of such diverging arterial effects — of the same

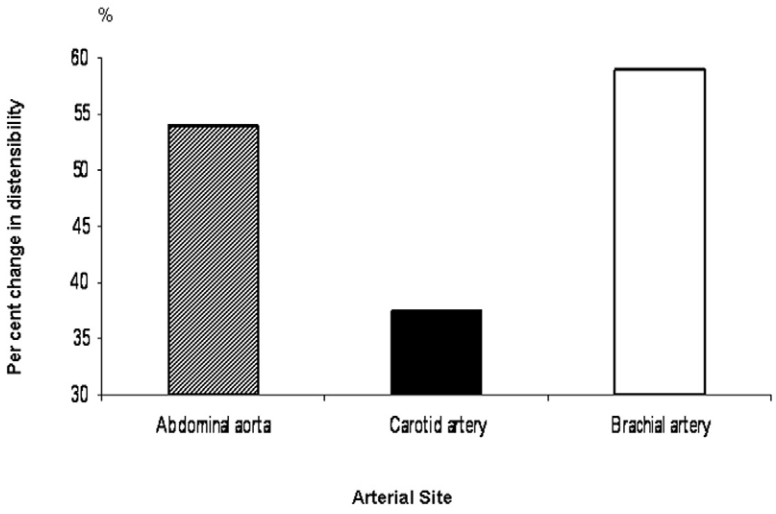

Figure 2. Relative change in arterial distensibility after antihypertensive treatment in 3 arterial sites: abdominal aorta, carotid artery, and brachial artery. Significant site effect was observed. Adapted with permission from Topouchian J, Asmar R, Sayegh F, Rudnicki A, Benetos A, Bacri AM, et al. Stroke 1999;30:1056–64.[24]

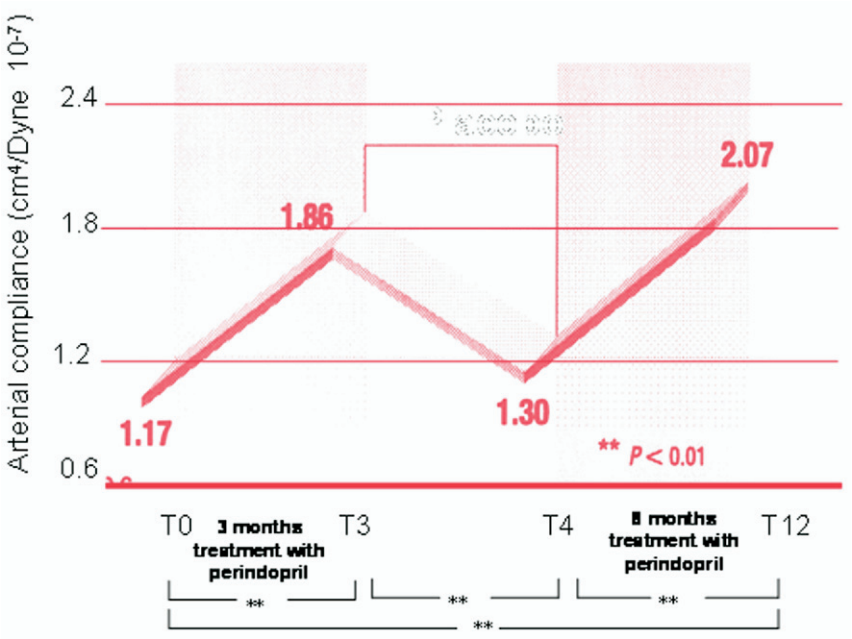

Figure 3. Effects of perindopril on arterial compliance. Mean values are shown at baseline (T0), after 3 months of treatment with perindopril 4 to 8 mg/OD (T3), after 1 month of perindopril withdrawal and its replacement by placebo (T4), and after 1 year of treatment with perindopril (T12). Adapted with permission from Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, Levy BI, et al. Circulation 1988;78:941–50[25] and Asmar R, Journo HJ, Lacolley PJ, Santoni JP, Billaud E, Levy BI, et al. J Hypertens 1988;6(suppl 3):S33–9.[26]

antihypertensive drugs observed in the same patients — according to the arterial site.[21,24]

Which Treatment Duration And What Doses Have To Be Used To Assess Arterial Stiffness?

- Several mechanisms can be involved in the possible improvement of arterial stiffness under treatment. These mechanisms differ completely whether assessment is performed after acute administration or long-term administration of a given drug. After *acute administration* of, eg, an antihypertensive drug, improvement of arterial stiffness is principally related to functional or mechanical mechanisms such as reduction of distension pressure, reduction of smooth muscle tone, enhancement of endothelial functions; whereas after *longer-term treatment*, additional mechanisms may be involved, eg, changes of the arterial geometry and structure compounds such as reduction of fibrosis, increase of elastin/collagen ratio, remodelling of the arterial wall, etc.[21,22] Therefore, experts agree that assessment of arterial stiffness using a long-term treatment period should be preferred because of the underlying pathophysiological mechanisms and because acute effects may not predict long-term efficacy. Few studies have been performed in order to evaluate in the clinic the necessary duration of treatment for the establishment of functional and structural changes. We showed that withdrawal of converting enzyme inhibitor after 3 months of treatment in hypertensive patients was associated with an increase of arterial stiffness almost to the baseline level (Figure 3), whereas 12 months of treatment was associated with a significant improvement of the arterial properties.[25,26] Similar results have been reported after 6 months of treatment with continuing improvement of arterial stiffness between 3 and 6 months.[27] For that reason, assessment of arterial stiffness is preferable after at least 3 months or even 6 months of treatment.[21,22]
- In the absence of specific pharmacological agents to improve the arterial wall properties, most of the drugs that have been evaluated for their arterial effects are those used for cardiovascular risk factors or disease treatment such as antihypertensive, hypocholesterolemic agents, etc. So it is important to analyze the dose/effect curves of these drugs on the arterial stiffness independently from those curves observed for BP reduction or cholesterol-lowering level. In this regard, we showed a clear dissociation between antihypertensive and arterial effects of converting enzyme inhibitors with evidence that the effect on the arterial wall properties was obtained with a higher dose than that required for BP reduction in patients treated for hypertension[28,29] (Figure 4). More recently, most of the studies evaluating the effects of statins on the arterial wall showed significant improvement of arterial stiffness using principally high doses of statins. These observations are of importance because unlike our initial thinking that arterial stiffness may be improved using long-term administration of low doses, because of the tissue effects, results from pharmacological studies clearly showed that high doses are often needed to observe improvement in arterial stiffness. These findings have been recently confirmed by large clinical

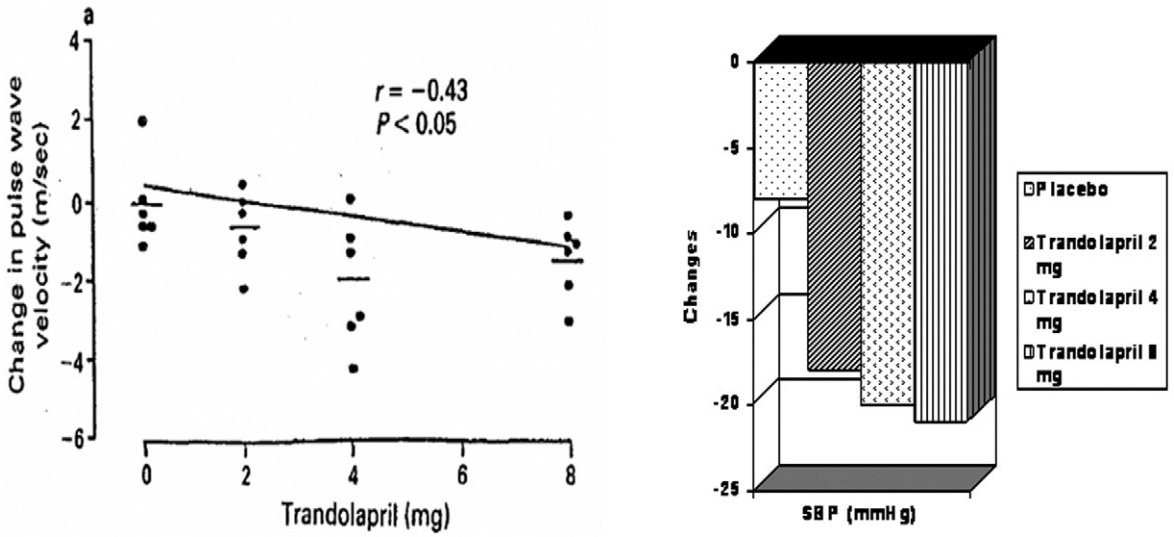

Figure 4. Dose/effect relationships of an angiotensin-converting enzyme inhibitor (trandolapril) on carotid-femoral pulse wave velocity (left panel) and systolic blood pressure (right panel). Dissociation between the arterial and antihypertensive effects was observed. Adapted with permission from Asmar R, Benetos A, Darne B, Pauly N, Safar M. J Hum Hypertens 1992;6:381–5.[28]

studies performed in patients at high cardiovascular risk independently from their effects on BP or cholesterol levels. In fact, positive results of these studies have been observed with high doses of converting enzyme inhibitors[30–32] or statins.[33,34]

Elsewhere studies have shown that improvement of arterial stiffness using a given drug may be independent or only partly related to its effect on other parameters such as BP reduction.[21] In fact, we showed in one long-term angiotensin-converting enzyme (ACE) inhibitor study that improvement of arterial stiffness was observed even in patients defined as non-responders for their BP reduction.[35] Similar data have been reported in subanalysis of other studies.[36]

Effects of Pharmacological Intervention on Arterial Stiffness

Several pharmacological treatments have been shown to reduce arterial stiffness. Most of these studies included antihypertensive treatment such as diuretics, beta-blockers, ACE inhibitors, AT1 angiotensin II receptor blockers, and calcium-channel antagonists. Few studies have evaluated hypolipidemic agents such as statins and very few have assessed various agents such as thiazolidinediones, sildenafil, aldosterone antagonists, and advanced glycation end-product breakers. Thus, we focused this review on the most used classes: antihypertensive and statin agents.

Effect of Antihypertensive Agents on Arterial Stiffness

Table 2 shows the effects of the different antihypertensive classes on PWV administered in a double-blind fashion either during a short-term period (<28 days) or a longer-term (≥28 days) period.[21,37–40]

Few studies have been performed using a *short-term* period of treatment. Results showed that central and peripheral stiffness are improved principally with ACE inhibitors and angiotensin II receptor blockers (fewer studies), whereas aortic stiffness has been described to remain unchanged in most studies after acute administration of other drugs.

During *longer-term* treatment, studies have shown improvement of central and peripheral arterial stiffness with ACE inhibitors. Beta-blockers exhibited variable results according to the drug used; heart rate reduction does not explain the reduction of arterial stiffness but contributes partly to the lack of changes in central BP. Results with calcium-channel blockers are more complex to evaluate. At the aortic level, all calcium-channel blockers show a significant reduction of arterial stiffness together with BP reduc-

Table 2
Pulse wave velocity and antihypertensive drugs

	Short-Term Treatment <28 Days		Long-Term Treatment ≥28 Days	
	Aorta	Arm/Leg	Aorta	Arm/Leg
Beta-blockers	↘/≡	NA	↘/≡	↘/≡
Diuretics	NA	NA	≡/↘	≡
Calcium antagonists	≡	NA	↘	↘/≡
ACE-inhibitors	↘	↘	↘	↘
ARBs	↘	↘	≡/↘	NA
Vasodilators	≡	NA	NA	NA

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NA, not available.

Table 3
Effects of statins on arterial stiffness

Patients	Statin	Dose mg/day	Short-Term ≤3 months		Long-Term >3 months	
			Car/Ao	Arm/Leg	Car/Ao	Arm/Leg
HCT	Simva	10–20	NA	NA	↓	↓
HCT	Simva	40	NA	NA	NA	↔/↓
HCT	Simva	40–80	NA	NA	↔	↓
HCT	Simva	20–40	↔	↔	NA	NA
HT + HCT	Atorva	10	↓	NA	NA	NA
HCT	Atorva	20	NA	NA	↓	NA
ISH/NCT	Atorva	80	↓	↓	NA	NA
HCT	Prava	20	NA	NA	↓	NA
HCT	Ceriva	.3	NA	NA	↓	NA
	Prava	20			↔	
Diabetes + ESRD	Fluva	20	NA	NA	↓	↓

Ao, aorta; Car, carotid; ESRD, end-stage renal disease; HCT, hypercholesterolemic; HT, hypertensive; NCT, normocholesterolemic; NA, not available.

Adapted with permission from Rajzer M, Klocek M, Kawecka-Jaszcz K. Am J Hypertens 2003;16:439–44.[40]

tion. At the peripheral level, arterial stiffness improvement was less evident. Diuretics showed no significant effects.

Therefore, during long-term treatment, diuretics showed no significant effects, beta-blockers exhibited variable results according to the used agent, a constant improvement of arterial stiffness was observed with ACE inhibitors, and less marked improvement was reported with angiotensin II receptor blockers and calcium-channel blockers.

Effects of Statins on Arterial Stiffness

There are multiple mechanisms by which statins may improve arterial stiffness: functional changes, matrix proteins including collagen and elastin, structural arterial remodelling, improvement of endothelial function, and reduction of vascular inflammation, etc. As for the antihypertensive agents, the effects of statins on arterial wall appear to be dependent on the dose and duration of treatment.[37,41–43] If results are interpreted according to the patient population, the dose, and the duration of treatment, a plausible pattern is evident. Only 1 study compared the effects of different statins on arterial stiffness; the results showed higher efficacy using fluvastatin versus provastatin and simvastatin.[42] This has to be confirmed by further studies in large populations with various doses and durations of treatment.

A recent review of statins and arterial stiffness was performed by Kingwell.[41] Table 3 summarizes most of the statin studies on arterial stiffness. Evidence indicates that long-duration treatment reduces arterial stiffness in both hypercholesterolemic and normolipidemic patients at high cardiovascular risk. Such effects can occur at a shorter-term period using intensive lipid-lowering therapy but became more established with lower-dose therapy after 6 months of treatment.

Is Arterial Stiffness Improvement Associated With A Better Prognosis?

Few studies have analyzed the effect of arterial stiffness improvement and its association with an improvement of cardiovascular morbidity and mortality. In a longitudinal study, Guerin et al[44] assessed the impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Their results clearly indicated that arterial stiffness attenuation in response to BP lowering using ACE inhibitors had a beneficial and BP-independent impact on the survival of this population. Several issues remain to be addressed here. The study of Guerin et al[44] was performed in patients with renal failure. No similar data are available in patients with hypertension or at low or moderate cardiovascular risk. Similarly, whether the reduction in central pulse pressure (wave reflection) is associated with a concomitant reduction in hard end points remains to be demonstrated. Some indirect arguments have been suggested by the results of the REASON Study[36] where only the perindopril/indapamide combination significantly reduced wave reflection and central BP. The CAFÉ (Conduit Arterty Function Evaluation) Study, an ancillary study of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Study,[33,45] showed that the reduction in central BP was higher in the amlodipine + perindopril group than in the atenolol + thiazide group. Therefore, whether therapeutic strategy aiming at normalizing arterial stiffness may be more effective in preventing cardiovascular events needs to be assessed in a specific long-term and large-scale therapeutic trial.

Future Perspectives

Evaluation of regional arterial stiffness using PWV measurement has been recently recognized as the "gold stan-

dard" measurement of arterial stiffness. Other methods to evaluate systemic or local arterial stiffness, including central BP, are available and allow various arterial parameters to be measured in order to evaluate the arterial wall properties. Studies have highlighted the importance of arterial stiffness for assessing cardiovascular risk and for predicting cardiovascular outcomes. Therefore, measurement of arterial stiffness may avoid misclassification of cardiovascular risk in an individual. In fact, the predictive value of PWV for primary coronary heart disease events in hypertensive patients was more marked for patients considered at low risk from their Framingham risk score than for patients at higher risk, indicating that such low-risk population benefited the most from PWV assessment.[8] Current guidelines on hypertension and risk management do not consider arterial stiffness as target organ damage, but evidence is now available demonstrating the clinical value of arterial stiffness; consequently, inclusion of arterial stiffness in the future guidelines may be suitable. Better targeting the existing pharmacological agents and development of specific agents to enhance arterial wall properties may also be very useful in the management of cardiovascular diseases. Whether such a strategy aimed at normalizing arterial stiffness may be effective in preventing cardiovascular events needs to be assessed in a specific therapeutic trial.[46]

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