Journal of the American Society of Hypertension 1(2) (2007) 104–112

Review Article

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

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Manuscript received and accepted January 19, 2007

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-

Conflict of interest: none.

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1933-1711/07/$ – see front matter
doi:10.1016/j.jash.2007.01.007

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]