Large Artery Dilation Produced by Converting Enzyme Inhibition in Hypertension: Therapeutic Aspects

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Large artery dilation is produced by angiotensin-converting enzyme inhibition in hypertensive subjects despite a significant blood pressure reduction. The resulting increase in arterial compliance may be due both to blood pressure decrease and to arterial smooth muscle relaxation. In healthy volunteers and in hypertensive subjects, dosages causing large artery dilation seem to be higher than those causing pure arteriolar dilation with resulting blood pressure reduction. Similar findings have been noted to obtain compliance enhancement. Such results may be important in considering antihypertensive therapy, particularly when remodeling of the cardiovascular system is considered in long-term treatment.

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Angiotensin II (AII) receptors are widely distributed throughout the vascular tree, and this pattern is observed from resistance arterioles to the aorta [1]. In particular, AII produces contractions in the aortic strip or rings as well as in isolated femoral, carotid, and coronary arteries [2–5]. From this simple finding, it is suggested that AII acts not only on vascular resistance (i.e., on the caliber of small arteries), but also on the function of large arteries.

It has been shown on the basis of both experimental and clinical data that angiotensin-converting enzyme (ACE) inhibition acts not only on blood flow and vascular resistance, but also on the capacitative function of the arterial system and therefore influences per se the viscoelastic properties of large arteries [6]. In the present report, we present our experience on the response of the hypertensive brachial and carotid arteries in humans and we compare dosages causing arterial dilation to dosages causing arteriolar dilation with resulting decrease in blood pressure. Before attempting to relate the principal findings associating the renin–angiotensin system, converting enzyme inhibition, and large arteries, some aspects describing the functional characteristics of large vessels in animals and humans are reviewed in detail.

PHYSIOLOGICAL FUNCTIONS OF LARGE ARTERIES

The arterial system has two distinct but interrelated functions: to deliver an adequate supply of blood to body tissues (conduit function) and to smooth the pulsations resulting from intermittent ventricular ejection (cushioning function) [7–9].

The function of arteries as conduits is characterized by steady (as opposed to oscillatory) components, i.e., mean arterial pressure (MAP) and flow (Q), and by their relationship in defining peripheral vascular resistance (VR):

$$VR = MAP/Q$$

The efficiency of conduit function depends on a wide caliber of the small arteries and the constancy of the steady component of the pressure wave, with

an almost imperceptible mean arterial pressure gradient between the ascending aorta and peripheral arteries. From the calculation of vascular resistance, important information is obtained on the caliber of small arteries, but not on the status of large arteries.

In contrast to the conduit function, the function of arteries as cushions (Windkessel function) is characterized by oscillatory components of flow and pressure and their frequency-dependent relationship (i.e., vascular impedance). The oscillatory component of blood pressure, which is clinically represented by pulse pressure, varies in amplitude between central and peripheral arteries and is determined by the geometric and viscoelastic properties of the vessels. The efficiency of the cushioning function is altered principally by stiffening of the vessel walls and alterations of the viscoelastic properties of arteries, resulting in a selective increase in pulse pressure, with no change in MAP.

Physiologically, large arteries offer little resistance to flow but are distensible and consequently are able to damp the pulsatile systolic output of the ventricle [7,8]. During left ventricular ejection, the aorta and its large branches become distended, due to their storage capacity. At aortic valve closure, the elastic aorta and its branches recoil, thereby sustaining the pressure head and rendering the blood flow to the periphery steadier than it would be otherwise. This characteristic buffering function is related to the viscoelastic properties of the arterial wall. Since the arteries are cylindrical, their physical properties are usually described in terms of compliance. This is done by increasing the distending pressure (P) inside the tube and measuring the concomitant change in radius (or in volume, V). The change in volume (dV) divided by the change in pressure (dP) (or arterial compliance) represents the slope (dV/dP) of the pressure–volume relationship and is used as a quantitative index to describe the storage capacity of the arterial system (**Figure 1**). Since the arterial wall is composed of a mixture of smooth muscle cells and connective tissue containing collagen and elastin fibers, the viscoelastic arterial wall gets stiffer as it is distended. Thus, the pressure–volume relationship is curvilinear and arterial compliance can only be defined at a given pressure. However, at this particular pressure, compliance is also influenced by the structure of the arterial wall and by the tone of arterial smooth muscle. In this review, the point to be discussed is: since ACE inhibition acts both on the level of blood pressure and on the structure and function of the arterial wall [6], it is possible that different dosages are required to obtain either blood pressure reduction alone (due to arteriolar dilation) or large artery dilation alone, or a combination of both. In this context, the present report relates the mechanisms involved in the changes of brachial and carotid arterial hemodynamics produced by ACE inhibition in normotensive and hypertensive subjects.

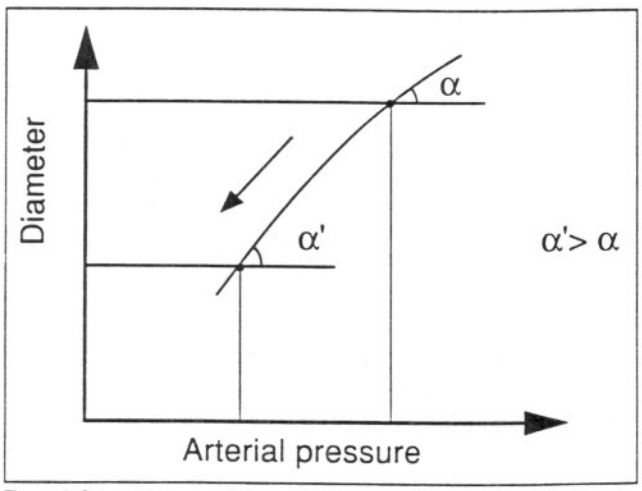

Figure 1. Schematic representation of the pressure (P) volume (V) relationship in a given large artery (see text).

HEMODYNAMIC MECHANISMS RELATED TO LARGE ARTERY DILATION

Hemodynamic abnormalities in untreated hypertensive subjects are not limited to arterioles but involve also large arteries with a resulting decrease in arterial compliance [9,10]. In the last few years, available echocardiographic and Doppler methods have been developed to permit noninvasive investigation of in situ large arteries [11–13], enabling the evaluation of the inner diameter and the cross-sectional area of the thoracic aorta and of straight superficial arteries, such as the brachial and the common carotid arteries. Since the overall pressure–volume relationship of a given large artery is still impossible to determine in humans, adequate models have been developed and validated for the determination of forearm and systemic compliance [7,8,10].

When a given antihypertensive drug acts on the large arteries, the decrease in the distending pressure may influence per se the geometry of the arterial vessel, resulting in a passive decrease in arterial diameter (D) and volume (V), and a change in arterial compliance (dV/dP). Thus, if an antihypertensive agent acts specifically on the arterial wall independently of the change in transmural pressure, one or several of the following particularities should be observed: an increase in arterial diameter despite the occurrence of blood pressure reduction or a change in compliance unrelated to the level of blood pressure.

Following drug treatment, the modifications in the caliber of large arteries may be influenced not only by the changes in the distending pressure, but

also by several nonspecific mechanisms, principal of which are the myogenic and the flow-dilating responses [7–10]. The former relates to the Bayliss hypothesis based on the intrinsic tendency of vascular smooth muscle to shorten in response to stretch and, conversely, to relax in response to decreased stretch or wall tension. The latter relates to the observation that high flow per se may be responsible for arterial dilation through an active mechanism that is partly endothelium-dependent through the release of vasoactive substances [14–16]. For instance, in clinical situations, the increase in brachial artery diameter produced by ACE inhibition has been shown to be associated with an increase in blood flow velocity, and it has been suggested that the increase in velocity (due to forearm arteriolar dilation) contributed to modulate the diameter enhancement [17,18]. Thus, it appears clear that, following ACE inhibition, the drug-induced arterial smooth muscle relaxation may be due both to direct and indirect mechanisms.

DOSE–RESPONSE CURVES FOR THE CHANGES IN BRACHIAL AND CAROTID ARTERIAL DIAMETER FOLLOWING ACE INHIBITION

In healthy volunteers maintained on a sodium diet ad libitum, acute increasing doses of the ACE inhibitor perindopril were given orally in a double-blind study versus placebo [19]. Although no change in systemic blood pressure occurred, the drug had a preferential vasodilating effect on the arterioles of the brachial and the carotid circulation at the lower doses. In contrast, changes in brachial and carotid arterial diameter required doses higher by 2–3-fold (**Figure 2**). With ramipril, only one dose was given, but the dilation occurred only at the site of the brachial artery and not at the carotid artery [20] (**Figure 3**). Since, in these experiments, ACE

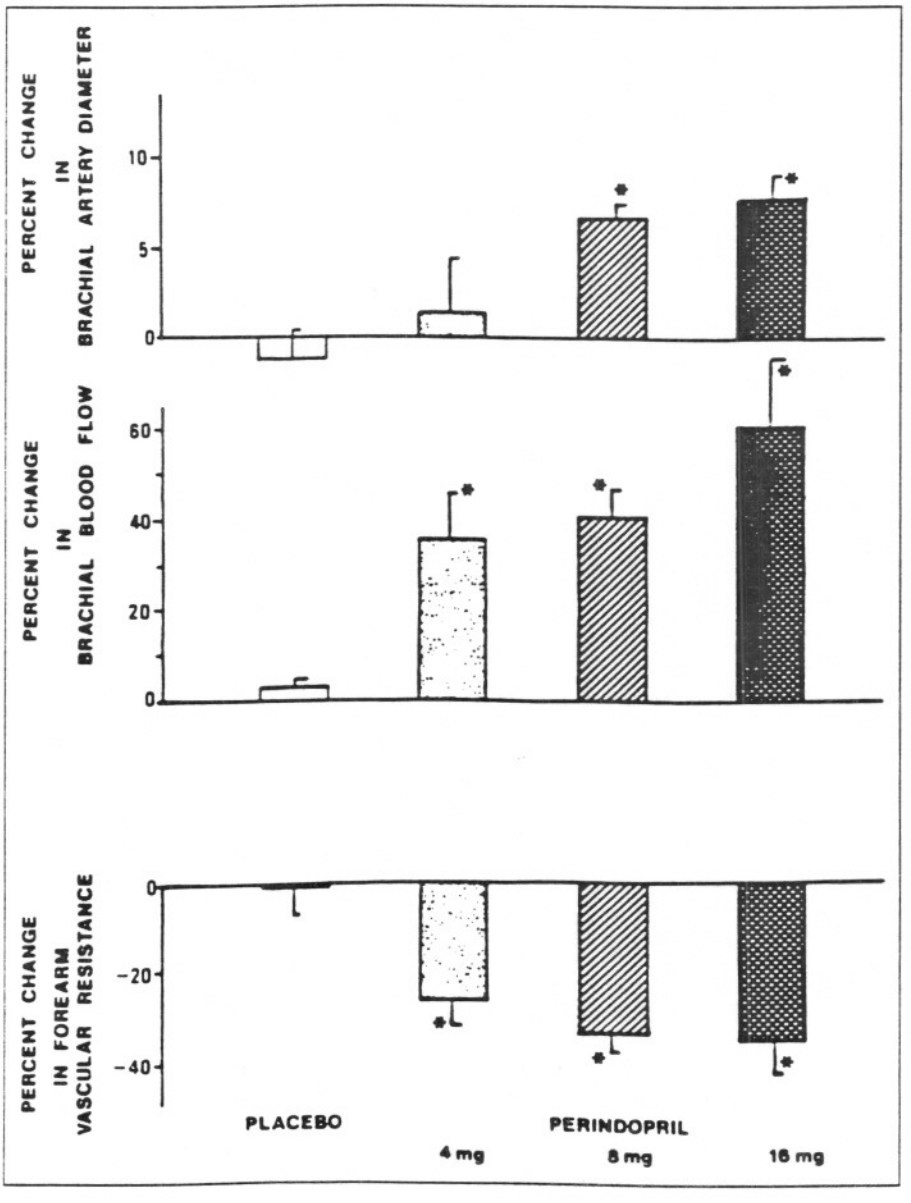

Figure 2. Peak percentage of changes in brachial artery diameter, brachial blood flow, and forearm vascular resistance induced by three doses of perindopril and placebo in normal volunteers. Significant change: * $p < 0.05$. Reproduced with permission from [19].

disappeared from the plasma even at the lower dosages, the diameter enlargement seemed to be predominantly related to tissue actions of ACE inhibition.

In patients with sustained essential hypertension, acute oral administration of captopril [12,21] caused a significant increase in arterial diameter of the brachial and (to a lesser extent) of the carotid arteries. With ramipril, the response was shown to be long-lasting, independent of blood pressure reduction (**Table I**). The increase was observed at the site of the brachial, but not the carotid, arteries [22]. With intravenous administration of the metabolite of perindopril, perindoprilat, the increase in brachial artery diameter was obtained at higher doses than those required for forearm arteriolar dilation, although a similar blood pressure reduction was achieved with the two dosages [23] (**Table II**). With enalapril or perindopril given orally, the brachial artery diameter enhancement was maintained in hypertensive subjects for 1–12 months [17,18,21]. Since such findings were obtained in the presence of a significant blood pressure reduction, it is clear that the mechanical effects of elevated blood pressure were offset by the dilating effect of ACE inhibition, at least at the site of the brachial artery. In the latter case, it has even been previously shown that the higher the blood pressure reduction, the less the increase in arterial diameter following captopril [21].

In humans, the pharmacologic effect of ACE inhibition on the vessel wall is classically attributed to the blockade of AII production. Local injections of angiotensin I (AI) and AII and of various ACE inhibitors into the brachial artery have shown that this mechanism was operating at the site of the ar-

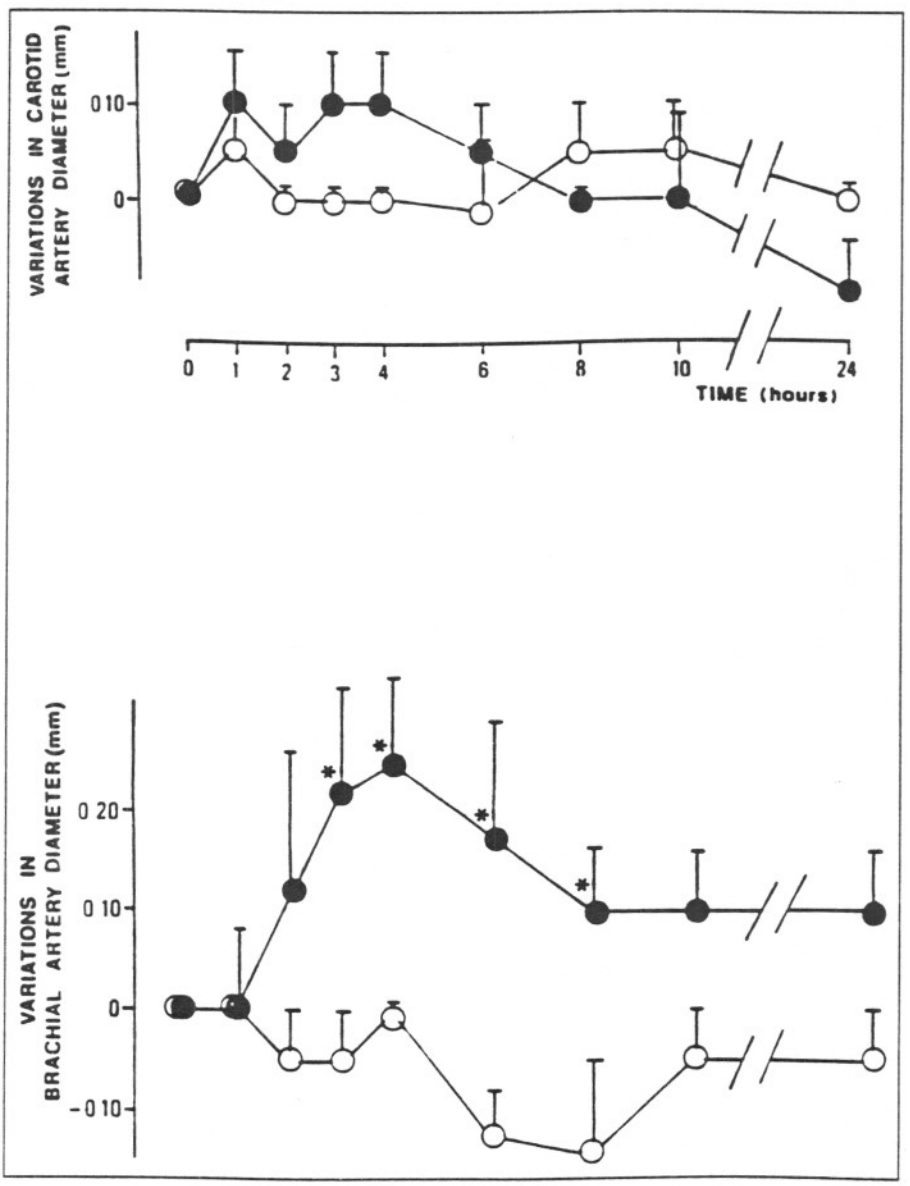

Figure 3. Kinetics of the variations in common carotid artery and brachial artery diameters induced by ramipril (10 mg) (●) and placebo (○) in the healthy volunteers. Significant variation compared with placebo: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Reproduced with permission from [20].

TABLE I

Arterial Effects of Acute and Chronic ACE Inhibition with Ramipril*

	Placebo	Ramipril (3 hr)	Ramipril (24 hr)
Systolic blood pressure (mm Hg)	166.1 ± 3.3	148.7 ± 3.9†	156.6 ± 3.7‡
Diastolic blood pressure (mm Hg)	104.3 ± 2.2	92.7 ± 2.9†	99.6 ± 1.9‡
Heart rate (beats/min)	69.3 ± 2.5	70.5 ± 2.4	71.9 ± 2.5
Brachial artery diameter (mm)	4.7 ± 0.2	4.8 ± 0.3	5.1 ± 0.2§
Brachioradial pulse wave velocity (m/sec)	11.6 ± 0.3	12.5 ± 1.3	11.3 ± 1.1
Carotid–femoral pulse wave velocity (m/sec)	13.0 ± 1.1	11.3 ± 0.7‖	11.3 ± 0.7‡

*Acute effects were measured 3 hours after a single 5 mg dose of ramipril; 24-hour effects were measured 24 hours after the last drug administration following 1 month of treatment.
†$p < 0.001$, placebo vs ramipril (3 h); ‡$p < 0.05$, placebo vs ramipril (24 hr); §$p < 0.01$; ‖$p < 0.05$.
Arterial compliance is proportional to $D^2/4$ and inversely related to the square of pulse wave velocity. Reproduced with permission from [22].

terioles of the forearm [24]. In humans, it is probable that this mechanism acts on the brachial artery wall and contributes to the arterial dilation. However, following intravenous administration of subpressor doses of AII in normotensive and hypertensive subjects, no significant change in brachial artery diameter was observed [25] (**Table III**). As for the apparent discrepancy between the effects of AII and ACE inhibitors, additional pathways, such as those related to bradykinin, prostaglandin, and blockade of the autonomic nervous system [24–26], may be proposed to explain the differential responses.

Finally, both in normotensive and hypertensive subjects, arterial dilation is obtained for higher doses of ACE inhibition than those producing arteriolar dilation. This finding is more obvious for muscular (brachial) than for elastic (common carotid) arteries and appears to be independent of the disappearance of ACE from the plasma.

TABLE II

Brachial Artery Hemodynamics and Carotid–Femoral Pulse Wave Velocity Changes Before and After Perindoprilat Infusion with Two Different Dosages in Hypertensive Subjects

	1 μg/kg/min	2.5 μg/kg/min
Diameter (cm)		
Before	0.480 ± 0.026	0.437 ± 0.014
After	0.492 ± 0.028	0.479* ± 0.019
Mean blood velocity (cm/sec)		
Before	3.83 ± 0.29	4.62 ± 0.66
After	3.79 ± 0.36	4.32 ± 0.68
Blood flow (mL/min)		
Before	42.5 ± 4.7	41.9 ± 7.7
After	45.6 ± 8.0	46.3 ± 8.0
Pulse wave velocity (m/sec)		
Before	11.6 ± 1.1	12.0 ± 0.5
After	10.8 ± 0.7	10.6 ± 0.3

Mean ± standard error of the mean.
*$p < 0.02$ (variance analysis). Reproduced with permission from [23].

CHANGES IN BRACHIAL ARTERY COMPLIANCE FOLLOWING ACE INHIBITION

A significant increase in systemic and brachial compliance has been observed following both short-term and long-term administration of captopril, enalapril, perindopril, or ramipril to patients with essential hypertension (Tables I and II) [17,21,22,27,28]. The mechanism for the compliance enhancement could result from several possibilities [7,10,27,28]. The blood pressure reduction itself could favor the compliance increase through a decreased stretch of the arterial wall. However, with ACE inhibition, the diameter enlargement contributes to maintain an unchanged stretch despite the blood pressure reduction. Indeed, stretch is related to tangential tension, which is the product of blood pressure times arterial radius. On the other hand, the drug-induced arterial smooth muscle relaxation favors also an increase in compliance, as previously observed in animal hypertension [29,30]. For the understanding of the increase in compliance, a mechanism has been suggested [31] whereby, at normal distending pressure, smooth muscle in the arterial wall is in series with some of the stiffer collagenous components, but in parallel with the elastic laminae. Contraction of smooth muscle tenses the collagenous components, whereas dilation transfers stresses to the elastic laminae. Such an explanation appears to account for the results observed with ACE inhibitors and is consistent

TABLE III

Changes in Mean Arterial Pressure, Brachial Artery Diameter and Forearm Vascular Resistances in Response to Placebo (Glucose) or Angiotensin II in Normotensive Subjects or Hypertensive Patients

	Group I Normotensive, Angiotensin II (n = 9)	Group II Hypertensive, Glucose (n = 9)	Group III Hypertensive, Angiotensin II (n = 9)
Baseline values			
Age (years)	36 ± 1	46 ± 3	44 ± 3
BSA (m^2)	1.79 ± 0.03	1.67 ± 0.03	1.70 ± 0.06
PRA (ng/mL/hr)	1.23 ± 0.55	1.27 ± 0.20	0.92 ± 0.09
PA (ng/100 mL)	8.0 ± 1.5	11.0 ± 2.3	9.7 ± 1.5
MAP (mm Hg)	89 ± 3	116 ± 3	115 ± 3†
D (10^{-3} cm)	449 ± 13	481 ± 10	512 ± 18*
R_f (mm Hg sec/mL)	147 ± 35	167 ± 21	134 ± 23
Changes in response to angiotensin II (2 ng/kg/min)			
MAP (mm Hg)	6 ± 1	2 ± 1	7 ± 7‡
D (10^{-3} cm)	−13 ± 6	−3 ± 4	−21 ± 10
R_f (mm Hg sec/mL)	49 ± 24	12 ± 6	20 ± 6

BSA = body surface area; PRA = plasma renin activity; PA = plasma aldosterone; MAP = mean arterial pressure; D = diameter; R_f = forearm vascular resistance.
*P <0.05, †P <0.01, versus group I; ‡P <0.05 versus group II. Reproduced with permission from [25].

with the arrangement of elastin, smooth muscle, and collagen within the arterial wall. Indeed, it has been pointed out that the collagenous lattice within the wall would permit the wall to behave in this way by closing (and elongating) when the muscle relaxes and opening (and shortening) when the muscle contracts [31].

For the investigation of the changes in arterial compliance following ACE inhibition, we studied the dose–response curve of blood pressure and carotid femoral pulse wave velocity in a double-blind investigation [32] carried out in 24 patients with essential hypertension, who were randomized between placebo and 2, 4, and 8 mg of the ACE inhibitor trandolapril [33] given for an 8-day period. The complete antihypertensive effect was shown to be already achieved with 1 mg [32,33], and there was no significant correlation between the dosage and the degree of blood pressure reduction. In contrast, the dosage was significantly related to the changes in pulse wave velocity: the higher the dosage, the more the pulse wave velocity was reduced, and consequently the more the aortic rigidity was improved. No significant correlation was found between the change of blood pressure and the change in pulse wave velocity. The study indeed suggested that the arterial improvement was obtained even for higher doses than those causing the maximal blood pressure reduction in patients treated for hypertension with trandolapril.

PROSPECTIVE VIEWS

The present review has suggested that : (a) Following antihypertensive therapy, the drug effect on the arterial wall has different characteristics than the drug effect on the arteriolar wall (which is responsible for the blood pressure reduction); (b) with ACE inhibition, the dose required to cause arterial dilation seems to be higher than the dose achieving a significant blood pressure reduction; (c) the arterial changes predominate on muscular (brachial) rather than on elastic (carotid) arteries; and (d) relaxation of arterial smooth muscle following ACE inhibition has two principal consequences: modifications in arterial geometry and compliance enhancement. Whether these consequences are important to consider for an adequate antihypertensive therapy requires several observations.

The increase in compliance following antihypertensive treatment may be due either to the mechanical effect of blood pressure reduction, to smooth muscle relaxation, or to a combination of both mechanisms. The former predominates on elastic arteries, whereas the latter predominates on muscular arteries [8,31]. Whatever the mechanisms involved, at any given value of mean arterial pressure, compliance enhancement contributes to decrease systolic pressure selectively and to maintain (or even increase) diastolic pressure, thus favoring reduction of cardiac hypertrophy and the magnitude of coronary perfusion [8,9]. The opposite hemodynamic effect, i.e., the decrease in arterial compliance with a resulting increase in pulse pressure (due to an increase in systolic pressure and a decrease in diastolic pressure), has been shown to act on cardiovascular risk, independently of mean arterial pressure, and to contribute significantly to an increased incidence of cardiac deaths [9]. However, the point that compliance enhancement might contribute to decrease cardiovascular risk has not yet been demonstrated with adequate therapeutic trials.

The increase in arterial diameter following ACE inhibition has specific consequences on arterial wall tension (T) [8–10]. Indeed, in hypertensive patients, any increase in diameter (D) in the presence of blood pressure (P) reduction contributes to maintain the $[(P \cdot D)/2]$ product. This mechanical effect could contribute to maintain arterial thickness (h) in order to keep constant arterial wall tension:

$$T = (P \cdot D)/2h$$

[7,8]. Nevertheless, experimental studies in rats have readily shown that long-term ACE inhibition effectively reduces arterial thickness (h) at the site of the carotid artery and the aorta [29,30]. However, in such investigations, arterial diameter was not measured. Thus, the point at which arterial wall tension, one of the principal mechanical factors acting on the large vessels in hypertension, might be modified following antihypertensive drug treatment has not been fully verified and requires further investigations in the field of clinical hypertension.

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