Dose optimization study of arterial changes associated with angiotensin converting enzyme inhibition in hypertension

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Background: In treating hypertension the optimal dose of angiotensin converting enzyme (ACE) inhibitor is derived from dose–response curves that relate the quantity of drug taken to the resulting fall in blood pressure; the blood pressure fall reflects a decrease in vascular resistance and hence, a degree of arteriolar vasodilation. However, ACE inhibition dilates not only the small arteries but also the larger calibre arteries, which increases compliance. Given the differences in structure and function of large and small arteries, the optimal drug dose for a given vessel may differ according to the size and structure of the vessel.

Dose–response effects in clinical studies: Clinical studies indicate that in the brachial artery territory, larger doses are required to obtain arterial dilation than to produce a decrease in vascular resistance. In the aorta, an improvement in arterial compliance and distensibility is governed both by the fall in blood pressure and the drug dose. Finally, for the femoral artery, the degree of arterial dilation is influenced markedly only by the drug dose.

Application to treatment: An understanding of the drug dose required to produce a given change in the hypertensive arterial system may have important implications for the control of blood pressure. For a given mean arterial pressure, systolic blood pressure is lower and diastolic blood pressure higher when aortic compliance is increased, a haemodynamic change commonly seen following ACE inhibition. Recent double-blind studies have shown that ACE inhibitors produced a more pronounced decrease in systolic than diastolic blood pressure.

Conclusion: These findings indicate that the optimum doses required to improve the arterial wall in large arteries must be evaluated by long-term antihypertensive therapy.

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Keywords: Hypertension, angiotensin converting enzyme, large arteries, drug dose.

Introduction

The optimal drug dose required to obtain an effective reduction in blood pressure is determined from dose–response curves that relate the quantity of drug taken to the resulting decrease in blood pressure. With the angiotensin converting enzyme (ACE) inhibitors, additional information may be obtained from plasma hormonal changes and pharmacokinetic data [1], but dose–response curves contribute the most useful information. As the antihypertensive effect is the result of a decrease in vascular resistance [2], the relationship between the drug dose and vasodilation forms the basis of treatment.

Therapeutic trials in hypertension have shown that a blood pressure reduction induced by antihypertensive therapy can prevent congestive heart failure and cerebrovascular accidents, but has only minor effects on atherosclerotic complications, mainly those related to the coronary circulation [3]. These well established findings strongly suggest that antihypertensive drug

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treatment should produce not only arteriolar dilation but also have beneficial effects on major arteries.

ACE inhibitors dilate not only small arteries but also large musculoelastic vessels such as the brachial artery, which leads to increased arterial compliance and distensibility [4]. These arterial changes should not be ignored, as they may contribute to a decrease in cardiac work and may improve cardiac structure and function [5,6]. However, the optimal drug dose required to improve the hypertensive arterial wall is still difficult to determine for a number of reasons. First, the hypothesis that the optimal dose may be different in small and large arteries requires extensive investigation, since the number and affinity of receptors, particularly for angiotensin II, differ as vessels become smaller [7,8]. Second, ACE inhibitors may act specifically on large vessels through a tissue effect rather than a humoral effect [8]. Finally, the effects of ACE inhibition on hypertensive large arteries are difficult to determine, as the vasodilating properties may be offset by the mechanical effects of a blood pressure reduction [4].

In this present review, the problem of ACE inhibitor dose optimization in the production of beneficial arterial effects in hypertensive patients is discussed. The methodological basis is examined in detail and the dose–response curves for ACE inhibitors are investigated in relation to the heterogeneity of the arterial system. In addition, the effects of arterial changes on blood pressure regulation are discussed in relation to the management of hypertensive patients.

Basic concepts

In the investigation of the major arteries in hypertension, it is not sufficient to simply evaluate blood flow. The mechanical properties of the arteries must also be assessed. Physiologically, large vessels offer little resistance to flow but are distensible and therefore able to dampen the pulsatile ventricular systolic output. This characteristic buffering action is a result of the viscoelastic properties of the arterial wall.

Arteries are tube-shaped, and their mechanical properties are usually described in terms of compliance, which is measured by increasing the distending pressure (P) inside the tube and measuring the resulting change in radius or 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 (Fig. 1). As the arterial wall is a mixture of smooth muscle cells and connective tissue containing collagen and elastin fibres, the pressure–volume relationship is curvilinear, and arterial compliance should be referred to a given pressure [4,5]. However, at any pressure, compliance is also influenced by the structure of the arterial wall and by the tone of arterial smooth muscle. This review examines the hypothesis that since ACE inhibition acts both on blood pressure and on arterial wall structure and function, the doses required to produce a blood pressure reduction alone (due to arteriolar dilation), a large artery dilation alone, or a combination of both, may be significantly different.

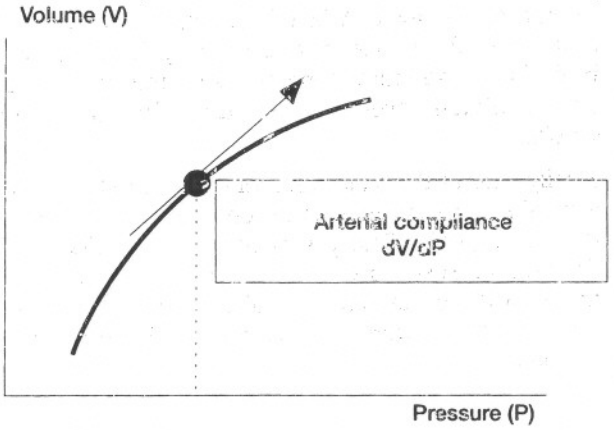

Fig. 1. Diagram of the pressure–volume relationship in a large artery.

In recent years, echocardiography and Doppler methods have been developed to permit non-invasive investigation of large arteries *in situ* and thus to measure the inner diameter and cross-sectional area of the thoracic aorta, brachial, femoral and common carotid arteries [9–12]. Since the overall pressure–volume relationship (Fig. 1) is still difficult to determine in humans, a number of models have been developed and validated for the evaluation of forearm and systemic arterial compliance and distensibility [4–6,9–13]. The most common index used is the velocity of a pulse wave along the arterial tree [5,13,14].

When an antihypertensive drug acts on large arteries, the decrease in distending pressure may affect the geometry of the vessel, resulting in a passive reduction in arterial diameter and volume, and a change in arterial compliance (dV/dP). Thus, if an antihypertensive agent acts specifically on the arterial wall independently of changes in transmural pressure, the arterial diameter may increase despite the blood pressure reduction or there may be a change in arterial stiffness that is unrelated to blood pressure levels.

Following drug treatment, changes in the calibre of larger arteries may be influenced not only by alterations in the distending pressure and the drug-induced changes in arterial smooth muscle, but also by several non-specific mechanisms, such as the myogenic response and flow-mediated dilation. The alterations in distending pressure have been explained by the Bayliss hypothesis which is 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 [5,13]. Among the non-specific mechanisms, high flow may cause arterial dilation by releasing endothelial vasoactive substances [15]. In the clinical setting, for example, the increase in brachial artery diameter in response to ACE inhibition is associated with increases in blood flow velocity, and it has been suggested that this increase in velocity, caused by forearm arteriolar dilation, further influences the increase in brachial artery diameter [16]. Therefore, following ACE inhibition, drug-induced arterial smooth muscle relaxation may be a result of both direct and indirect mechanisms; this makes it difficult to obtain dose–response curves for large arteries *in situ*.

Finally, one of the major difficulties in investigating the arterial system arises from heterogeneity of the vascular tree [5,8,13]. The pharmacodynamic effects of a drug on an elastic artery, such as the common carotid artery or the aorta, may be quite different from those on a muscular artery, such as the brachial or femoral arteries.

Results of studies on dose–response curves for arterial changes following ACE inhibition

Brachial artery

Increasing doses of the ACE inhibitor perindopril were given orally in the acute phase of a double-blind, placebo-controlled study of healthy volunteers on a free sodium diet (Fig. 2) [17]. Although there was no change in systemic blood pressure, the drug had a preferential vasodilator effect on the arterioles in the brachial territory at lower doses. In contrast, doses two to three times higher were required to produce changes in the brachial artery diameter. As ACE disappeared from the plasma even at lower doses in these experiments, the increase in diameter appeared to be predominantly related to tissue actions of the ACE inhibitor [8].

In patients with sustained essential hypertension, two different doses of intravenous perindopril produced a similar reduction in blood pressure [18] (Table 1). Brachial blood flow did not change, confirming that the same degree of forearm arteriolar dilation was obtained. An increase in the brachial artery diameter was seen only at the higher dose (Table 1). Since there was a significant fall in blood pressure, it is clear that this mechanical effect was offset by the dilating effect of ACE inhibition in the brachial artery territory. Another study, using acute doses of captopril, showed that as the blood pressure reduction increased, the increase in brachial artery diameter became smaller [4].

Aortic circulation

Significant increases in aortic compliance and distensibility have been observed following oral administration of captopril [4] and ramipril [19] in patients with essential hypertension. The aorta is predominantly elastic, and different mechanisms may account for the increase in compliance. The blood pressure reduction itself could lead to increased compliance by reducing arterial wall tension. Drug-induced arterial smooth muscle relaxation could also increase compliance, as shown in animal models of hypertension [20]. To explain the increase in compliance associated with ACE inhibition, it has been suggested that at a normal distending pressure, the dilating effect of the drug leads to an increase in arterial compliance [5]. Structurally, smooth muscle in the arterial wall lies in series with some of the stiffer collagenous components, but in parallel with the elastic lamellae. Contraction of smooth muscle therefore increases tension in the col-

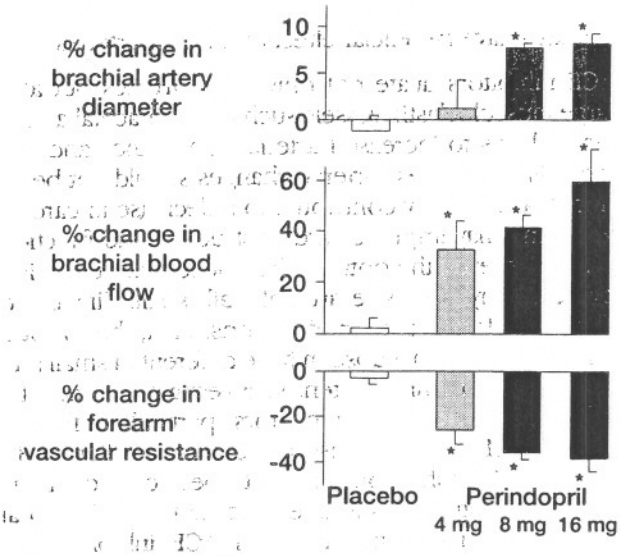

Fig. 2. Peak changes in brachial artery diameter, brachial blood flow and forearm vascular resistance induced by three doses of perindopril and placebo in normal volunteers. *$P < 0.05$. From [17] with permission.

Table 1. Brachial artery haemodynamics before and after perindopril infusion at two different doses in hypertensive subjects.

	Perindopril dose	
	1 μg/kg per min	2.5 μg/kg per min
Brachial artery parameters		
Diameter (cm)		
Before	0.480 ± 0.026	0.437 ± 0.014
After	0.492 ± 0.028	0.479 ± 0.019*
Mean blood velocity (cm/s)		
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
Diastolic blood pressure (mmHg)		
Before	101 ± 4	102 ± 4
After (change)	−10 ± 2	−13 ± 1

Means ± s.e.m. *$P < 0.02$ (analysis of variance). Adapted from [18].

lagenous components whereas dilation transfers stress to the elastic lamellae. In particular, the collagenous lattice within the wall closes (and elongates) when the muscle relaxes, and opens (and shortens) with muscular contraction. Aortic arterial changes should be considered in relation to these structural findings.

The curve relating blood pressure to carotid femoral and femorotibial pulse-wave velocity was investigated in a double-blind study using the ACE inhibitor lisinopril [21]. This study was carried out in 24 patients with essential hypertension (mean ± s.d. age 49 ± 10 years) who were randomly allocated to placebo, or 5, 10 or 20 mg of the drug, given orally and acutely. The maximum antihypertensive effect lasted for 6 h [22], during which time lisinopril decreased blood pressure and carotid femoral and femorotibial pulse-wave velocities, particularly at the 20-mg dose (Table 2). The decrease in carotid femoral pulse-wave velocity was correlated significantly with both the decrease in blood pressure ($r = 0.45$; $P < 0.04$) and the increase in the drug dose ($r = -0.44$; $P < 0.04$). A multiple regression analysis showed that the decrease in carotid femoral pulse-wave velocity was explained to a larger extent by the decrease in blood pressure than by the increase in drug dose. This result is not surprising as the elastic aortic wall is known to be very sensitive to pressure changes. In this particular study, however, the 20-mg dose of lisinopril only affected the early phase of the dose–response plateau. Therefore, with higher doses affecting the later stages of this plateau, changes in carotid femoral pulse-wave velocity might have been seen, in response to a better recruitment of aortic smooth muscle fibres.

Table 2. Dose–response curves for lisinopril (based on analysis of variance and Kruskal–Wallis test)

	Placebo	Lisinopril dose (mg/day) 5	10	20
Mean arterial pressure (mmHg)				
Before	125 ± 7	125 ± 8	119 ± 8	123 ± 5
After	125 ± 9	122 ± 16	111 ± 20	115 ± 9**
Carotid femoral pulse-wave velocity (m/s)				
Before	10.5 ± 1.4	10.3 ± 1.4	9.3 ± 1.9	10.1 ± 1.7
After	11.2 ± 1.7	10.2 ± 2.4	8.2 ± 1.2	9.1 ± 0.8†
Femorotibial pulse-wave velocity (m/s)				
Before	12.8 ± 2.2	14.2 ± 1.7	11.8 ± 2.4	12.4 ± 1.6
After	12.5 ± 2.7	13.8 ± 1.6	10.9 ± 2.1	10.6 ± 1.0†

Means ± s.d. **$P < 0.03$ versus before 20-mg dose; †$P < 0.04$ versus placebo.

In order to address this problem, we performed a second study in patients with essential hypertension using the ACE inhibitor trandolapril [23] at four different doses, placebo, 2, 4 and 8 mg, given for an 8-day period. The maximum antihypertensive effect was obtained with the 1-mg dose [23] and no significant correlation was noticed between the drug dose and the size of the blood pressure reduction in this study (as previously observed with lisinopril; Table 2). In contrast, the drug dose alone was significantly related to changes in pulse-wave velocity (Fig. 3); the higher the dose, the greater the reduction in pulse-wave velocity, and consequently, the greater the aortic distensibility. No significant correlation was found between changes in blood pressure and changes in pulse-wave velocity. This study suggested that aortic improvement was obtained with higher doses than those producing arteriolar dilation (and therefore the maximal blood pressure reduction) in hypertensive patients.

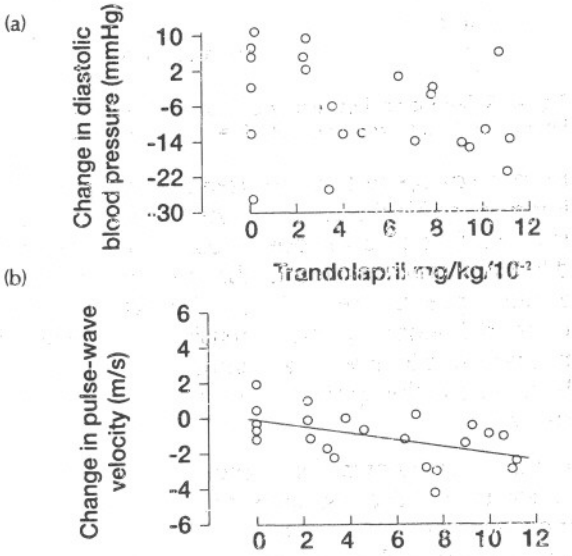

Fig. 3. Relationship between dose of trandolapril and (a) the changes in blood pressure ($r = -0.56$; $P < 0.01$) and (b) carotid femoral pulse-wave velocity ($r = -0.34$). From [22,23] with permission.

Common carotid and femoral arteries

Like the aorta, the common carotid artery has a predominantly elastic structure. Although a slight increase in arterial diameter was observed with captopril [24], no change or even a decrease was found with perindopril and ramipril [17,19]. The elastic carotid artery is highly sensitive to pressure changes and the dilating effect of the drug may be offset by the consequent fall in systemic blood pressure.

In contrast to the carotid artery, the common femoral artery is much less sensitive to pressure changes. In the double-blind study performed with lisinopril [21], pulse-wave velocity was significantly decreased in the femorotibial circulation, the decrease being closely related to the drug dose ($r = 0.59$; $P < 0.004$, Fig. 4) and not to blood pressure changes.

Discussion and implications for future studies

This review has demonstrated that with ACE inhibition, the drug effect on the arterial wall can be dissociated

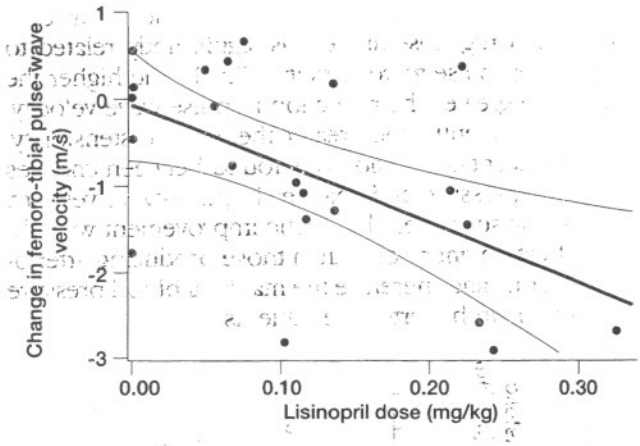

Fig. 4. Relationship between dose of lisinopril and change in femorotibial pulse-wave velocity ($r = 0.52$, $P < 0.004$).

from the drug effect on the arteriolar wall, the latter being responsible for the reduction in mean blood pressure. Furthermore, the dose required to obtain arterial dilation is somewhat higher than the dose required for a blood pressure reduction, as indicated by changes in arterial geometry and distensibility. Whether these haemodynamic aspects are important factors in antihypertensive therapy is a question that requires further study.

It has been known for some time [5] that an increase in vascular resistance produces a proportional increase in systolic, diastolic and mean arterial pressure. When a decrease in aortic compliance is associated with an increase in vascular resistance, this arterial change does not alter mean arterial pressure. There is only a change in the shape of the blood pressure curve, giving an increase in systolic pressure and a decrease in diastolic pressure. Both these effects may harm the myocardium [25,26]; the increase in systolic pressure causes an increase in end-systolic stress and may promote cardiac hypertrophy, while the decrease in diastolic pressure (which is the driving pressure of the coronary circulation) adversely affects coronary perfusion.

Following ACE inhibition, an increase in systemic compliance may be a mechanical effect of the blood pressure reduction or a result of smooth muscle relaxation, or both mechanisms may be involved. The former predominates in elastic arteries while the latter is the primary mechanism in muscular arteries. Whatever the mechanism, increased compliance, for any given value of mean arterial pressure, may contribute to a selective decrease in systolic pressure and may prevent a large fall in diastolic pressure. These two phenomena favour a reduction in cardiac hypertrophy and help to maintain coronary perfusion. Epidemiological studies have shown that an opposing haemodynamic mechanism, i.e. a decrease in arterial compliance with an increase in systolic pressure and a decrease in diastolic pressure for any given value of mean arterial pressure, contributes to the cardiovascular risk independently of mean arterial pressure, and is associated with a significant increase in the incidence of cardiac deaths [26]. There is strong evidence, therefore, that a selective decrease in systolic pressure through increased compliance may make a substantial contribution towards decreasing cardiovascular risk with antihypertensive drug treatment.

The ACE inhibitor lisinopril was compared to the β-blocking agent atenolol in a multicentre, parallel, double-blind study of treatment for mild to moderate essential hypertension [27]. Four hundred and ninety patients were randomly allocated to 20 mg lisinopril or 50 mg atenolol given once a day for 4 weeks. The doses of lisinopril or atenolol were increased at 4-week intervals up to 80 mg or 200 mg, respectively, if seated diastolic blood pressure was inadequately controlled. Lisinopril and atenolol produced similar reductions in diastolic blood pressure. All reductions in seated diastolic and systolic blood pressures were significant compared to baseline values, but lisinopril was associated with a significantly greater reduction in seated systolic blood pressure than atenolol (Table 3). This reduction in systolic blood pressure could not be explained on the basis of age, race or severity of hypertension. It was therefore suggested that the major part of the fall in systolic pressure associated with the ACE inhibitor could be explained by the increase in arterial compliance.

Table 3. Mean reduction in sitting blood pressure (mmHg) following 1–12 weeks of treatment with lisinopril or atenolol.

	Treatment	n	Before treat.	After treat.	Change mmHg	Change %
Diastolic blood pressure						
Week 4	Lisinopril	284	103.1	93.1	−10.0	−9.7
	Atenolol	203	102.0	93.0	−9.0	−8.8
Week 8	Lisinopril	285	103.1	90.5	−12.6	−12.2
	Atenolol	203	102.0	90.8	−11.2	−11.0
Week 12	Lisinopril	285	103.1	90.2	−12.9	−12.5
	Atenolol	203	102.0	90.5	−11.5	−11.3
Systolic blood pressure						
Week 4	Lisinopril	284	160.2	145.1**	−15.1	−9.4
	Atenolol	203	155.0	146.4	−8.6	−5.5
Week 8	Lisinopril	285	160.2	141.4**	−18.8	−11.7
	Atenolol	203	155.0	143.2	−11.8	−7.6
Week 12	Lisinopril	284	160.2	140.0**	−20.2	−12.6
	Atenolol	203	155.0	143.2	−11.8	−7.6

Treat., treatment. All changes represent significant reductions compared to baseline, $P \leq 0.01$, $^{**}P \leq 0.01$, versus atenolol. Adapted from [27].

Several arguments support this interpretation. The ACE inhibitor perindopril significantly decreased blood pressure according to both conventional blood pressure measurements and 24-h ambulatory blood pressure measurements [28]. The most important finding, however, was that systolic and diastolic blood pressure were strongly and positively related, according to the 24-h measurements. The slope of the curve relat-

ing systolic to diastolic blood pressure was shallower, however, after treatment with perindopril compared with baseline values. Other ACE inhibitors such as enalapril [29–31] also induce a greater reduction in systolic compared with diastolic pressure. This predominant effect on systolic blood pressure was greater with lisinopril than captopril [32] and metoprolol [33] and, to a lesser extent, nifedipine [34,35] and hydrochlorothiazide [36]. The results for hydrochlorothiazide were difficult to assess because lisinopril decreased diastolic blood pressure to a greater extent than hydrochlorothiazide did. Taken together, however, these findings strongly suggest that the dampening of pulse pressure is a potentially useful property of the ACE inhibitors, which is probably related to its specific arterial effects. The question of whether these pharmacological actions influence long-term cardiovascular morbidity and mortality in hypertension requires further investigation.

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