Effects of perindopril on elastic and structural properties of large arteries in essential hypertension

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Y Lacourcière, R Béliveau, HS Conter, et al. Effects of perindopril on elastic and structural properties of large arteries in essential hypertension. Can J Cardiol 2004;20(8):795-799.

BACKGROUND: Perindopril, an angiotensin-converting enzyme (ACE) inhibitor, is a well-recognized antihypertensive drug. Its ability to protect against cardiovascular events in hypertension has also been demonstrated. It decreases the stiffness of the larger arteries; questions remain as to the mechanisms involved and whether it is blood pressure (BP) control-dependent.

OBJECTIVES: To correlate the BP response to ACE inhibition therapy with changes in arterial stiffness as evaluated by pulse wave velocity (PWV), and to correlate these changes in arterial stiffness with alterations in indicators of vascular collagen metabolism serum levels of metalloproteinase (MMP)-1 and tissue inhibitor of MMP-1 (TIMP-1).

METHODS: A total of 162 patients aged 18 to 70 years with stage 1 and 2 essential hypertension (diastolic BP 95 mmHg to 114 mmHg) were enrolled to receive six months (M6) of therapy with the ACE inhibitor, perindopril. Patients were either treatment-naïve or had not received any antihypertensive treatment for at least six months before the study.

RESULTS: Mean BP was significantly reduced after two months (M2) of therapy (P=0.00001) and remained stable thereafter. In addition to the significant mean changes in PWV observed at M2 (P=0.00001), further reductions in PWV were noted at M6 (P=0.007). The change in PWV between baseline (M0) and M2 was significantly correlated to all BP parameters at M0 (correlation coefficient at M2 was 0.189 or greater). However, no correlation was seen regarding BP parameters at M2 and further M2 to M6 changes in PWV, suggesting a decrease of arterial stiffness independent of BP reduction. The expression of TIMP-1 and MMP-1 was highly variable and demonstrated no correlation with BP or PWV.

CONCLUSIONS: Reductions in BP and PWV appear to be correlated during the first two months of perindopril therapy. After six months, PWV continues to decrease independently of any further reduction in BP, suggesting the occurrence of a pressure-independent pharmacological remodelling of the arterial wall. A long-term, double-blind, randomized trial could be required to confirm that the observed increase in vascular distensibility induced by perindopril is related to a mechanism of action other than a reduction in BP.

Key Words: *Angiotensin-converting enzyme inhibitors; Compliance; Hypertension; Metalloproteinase*

Effets du périndopril sur les propriétés élastiques et structurelles des grosses artères dans l'hypertension artérielle

HISTORIQUE : L'inhibiteur de l'enzyme de conversion de l'angiotensine périndopril, est un antihypertenseur bien connu et la protection qu'il confère contre les complications cardiovasculaires de l'hypertension n'est plus à démontrer. On sait qu'il réduit la rigidité des grosses artères, mais il reste à vérifier quels mécanismes sont en jeu et si cette propriété est dépendante ou non de son effet hypotenseur.

OBJECTIFS : Vérifier s'il y a corrélation entre la réponse de la TA à l'IECA et les variations de la rigidité des artères mesurées par la vitesse de l'onde pulsée (VOP); et vérifier s'il y a corrélation entre les variations de la rigidité des artères et les taux des indicateurs du métabolisme du collagène vasculaire, soit les taux sériques de métalloprotéinase (MMP-1) et de son inhibiteur tissulaire (TIMP-1).

MÉTHODES : En tout, 162 patients de 18 à 70 ans souffrant d'hypertension essentielle de stade 1 ou 2 (diastolique entre 95 et 114 mm Hg) ont été inscrits et ont reçu l'IECA périndopril pendant six mois. Les patients n'avaient jamais reçu de traitement antihypertenseur, ou alors, le plus récent remontait à au moins six mois avant leur participation à l'étude.

RÉSULTATS : La TA moyenne avait significativement diminué après deux mois de traitement (P = 0,0001) et est restée stable par la suite. En plus des changements moyens significatifs de la VOP observés au deuxième mois (P = 0,0001), des réductions plus marquées de la VOP ont été notées sixième mois (P = 0,007). Le changement de VOP enregistré entre le début (mois 0) et le deuxième mois a été en corrélation significative avec tous les paramètres de TA au M0 (coefficient de corrélation de 0,189 ou plus, au deuxième mois). Par contre, aucune corrélation n'a été observée sur le plan des paramètres de TA au deuxième mois et des changements plus marqués de la VOP entre le deuxième et le sixième mois, suggérant une diminution de la rigidité artérielle indépendante de la réduction de la TA. L'expression du TIMP-1 et de la MMP-1 s'est révélée très variable et a témoigné de l'absence de corrélation avec la TA ou la VOP.

CONCLUSIONS : Les réductions de la TA et de la VOP ont semblé en corrélation au cours des deux premiers mois du traitement par périndopril. Après six mois, la VOP a continué de diminuer indépendamment de toute autre baisse de la TA, suggérant l'existence d'un remodelage pharmacologique de la paroi artérielle indépendant de la TA. Un essai randomisé à double insu à long terme serait nécessaire pour confirmer que l'augmentation de la distensibilité vasculaire induite par le périndopril observée est reliée à un autre mécanisme d'action que la réduction de la TA.

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Received for publication September 2, 2003. Accepted December 15, 2003

The aorta and large arteries are more than merely conduit vessels to transport blood from the heart; they have the capacity to buffer the intermittent output of the heart into a near continuous flow throughout the peripheral circulation. The ability of larger arteries to absorb energy and buffer the systolic component of pulsatile flow is directly related to arterial elasticity (ie, distensibility). The primary physiological benefit derived from adequate arterial compliance is a reduction in the amount of cardiac work required to produce a given cardiac output.

Abnormalities in the structural and functional properties of the arterial wall are seen in hypertensive patients, even at early stages of the disease (1-4) or before it develops (5). An important abnormality is the progressive increase in vascular stiffness that leads to further elevations in systolic blood pressure (SBP) and pulse pressure (PP), thus increasing the risk of morbid cardiovascular events (6).

Pulse wave velocity (PWV), defined as the rate of propagation of the pressure wave along the arterial system, is a well-established index of arterial distensibility (6,7). An increase in arterial stiffness (ie, decreased distensibility) can be determined by measuring the resultant increase in PWV. Additionally, elevated PWV has been demonstrated to be both an important indicator of vascular status and a predictor of cardiovascular risk (8-12).

Increased arterial stiffness and the resulting elevation of BP lead to cardiovascular remodelling characterized by an increase in extracellular matrix content, particularly fibrillar collagen (13). This excess of collagen appears to be the result of both increased collagen synthesis and unchanged or decreased collagen degradation (13,14). The rate-limiting step in the extracellular degradation of collagen is catalytic cleavage by interstitial matrix metalloproteinase (MMP)-1 (14,15). The net level of activity is dependent on the relative concentrations of active MMP-1 and naturally occurring tissue inhibitors of MMPs, specifically tissue-inhibitor of MMP-1 (TIMP-1) (15). Studies have shown that TIMP-1, which inhibits MMP activity, thus reducing collagen degradation, is elevated in essential hypertension patients (16,17). Moreover, chronic administration of an angiotensin-converting enzyme (ACE) inhibitor appears to reverse this effect (16-18).

Therefore, the authors decided to investigate the changes in BP and arterial stiffness (as measured by PWV) induced by chronic therapy with the ACE inhibitor perindopril and to determine whether an increase in serum MMP-1 and/or a decrease in serum TIMP-1 is associated with increased arterial distensibility. The objectives of the present study were to determine whether BP control induced by perindopril 4 mg/day or 8 mg/day is accompanied by an increase in arterial distensibility (ie, a decrease in PWV); and whether such changes in PWV are accompanied by alterations in vascular collagen metabolism (ie, MMP-1 and TIMP-1).

PATIENTS AND METHODS

This study was performed in accordance with the International Conference on Harmonization-Good Clinical Practices guidelines and respected the principles of the Declaration of Helsinki (October 1996). Each investigative site received local ethics review committee approval; all patients received information about the study and gave informed consent before study participation. This was a multicentre (six sites), open-label trial in which the subjects were treated with perindopril during a six-month period. Male and female patients aged 18 to 70 years with stage 1 and 2 essential hypertension (diastolic BP [DBP] 95 mmHg to 114 mmHg) were enrolled in the trial. Patients were either treatment-naïve or had not received any antihypertensive treatment for at least six months before study entry. Main exclusion criteria were the presence of secondary hypertension, severe hypertension (DBP greater than 114 mmHg), uncontrolled diabetes (glycemia greater than 10 mmol/L), insulin-dependent diabetes, renal insufficiency (plasma creatinine greater than 160 µmol/L) or hyperkalemia (potassium greater than 5.4 mmol/L). Moreover, patients with conditions that interfered with PWV assessments (ie, body mass index at least 35 kg/m^2, atrial fibrillation, significant aortic valvular disease or significant peripheral arterial disease) were excluded.

The study consisted of five study visits: baseline (M0) and at one month, two months, three months and six months (M1, M2, M3 and M6, respectively). Eligible patients initiated therapy with perindopril 4 mg/day. At M1, patients with a normalized BP (less than 140/90 mmHg) or who responded to treatment (10% decrease in SBP and/or a 10 mmHg decrease in DBP with a BP less than 170/100 mmHg) remained on perindopril 4 mg/day. Patients failing to demonstrate the aforementioned BP response were considered nonresponders and the dose of perindopril was increased to 8 mg/day. At M2, patients with a normalized or responding BP remained at their current dose of perindopril. Again, for nonresponders, the dose of perindopril was increased to 8 mg/day, unless they were already receiving 8 mg/day, in which case they were withdrawn from the study. At M3, normalized patients continued receiving their current dose of perindopril for the next three-month period. Responder patients previously receiving perindopril 4 mg/day had their dose increased to 8 mg/day, while responder patients previously receiving perindopril 8 mg/day remained at that dose for the rest of the study. Nonresponder patients were discontinued from the study.

TABLE 1
Baseline demography and clinical parameters

Parameter	Baseline, all patients, n=145; mean (SD)	Baseline, patients with valid PWV at M6 n=122; mean (SD)
Male/female	84/61	71/51
Age (years)	50.0 (9.5)	49.7 (9.5)
Weight (kg)	81.8 (17.3)	82.7 (18)
Height (cm)	168 (10)	169 (10)
Body mass index (kg/m^2)	28.8 (4.9)	29.1 (5.1)
Waist:hip ratio (%)	0.88 (0.08)	0.88 (0.08)
SBP (mmHg)	149 (14)	148 (13)
DBP (mmHg)	100 (4)	100 (4)
Pulse pressure (mmHg)	49 (13)	49 (12)
MAP (mmHg)	116 (6)	116 (6)
Heart rate (beats/min)	72 (10)	72 (10)
PWV (m/s)	12.2 (3.2)	12.0 (3)

DBP Diastolic blood pressure; M6 Six months; MAP Mean arterial pressure; PWV Pulse wave velocity; SBP Systolic blood pressure

TABLE 2
Effect of perindopril on blood pressure (BP) parameters and pulse wave velocity (PWV)

Parameter	M0	M2	M6	Δ(M6-M0)	P	Δ(M2-M0)	P	Δ(M6-M2)	P
n	145	145	127	127		145		127	
SBP (mmHg)	149±14	131±13	129±13	–20±13	0.00001	–18±13	0.00001	–1±10	NS
DBP (mmHg)	100±4	87±8	86±8	–14±8	0.00001	–13±8	0.00001	0±7	NS
MAP (mmHg)	116±6	102±9	101±9	–16±9	0.00001	–14±8	0.00001	–0.5±7.1	NS
PP (mmHg)	49±13	44±10	43±9	–6±11	0.00001	–5±10	0.00001	–1±8	NS
HR (beats/min)	72±9	72±9	72±8	–1.0±8.8	NS	–0.3±6.7	NS	–1.0±8	NS
PWV (m/s)	12.2±3.2	10.7±2.5	10.2±2.2*	–1.8±2.1*	0.00001	–1.4±2.2	0.00001	–0.4±1.7*	0.007

*Values are mean ± SD. *Valid PWV data available for 122 patients at six months (M6). DBP Diastolic BP; HR Heart rate; M0 Baseline; M2 Two months; MAP Mean arterial pressure; NS Not significant; PP Pulse pressure; SBP Systolic BP*

BP

BP measurements were performed at each study visit using a calibrated mercury sphygmomanometer with an appropriately sized cuff. Three consecutive BP measurements were recorded following a 10-min rest in the sitting position, the last two of which were averaged for analyses. SBP and DBP were measured at Korotkoff phases I and V, respectively.

PWV

PWV was measured at M0, M2 and M6 using the Complior device (Artech-Medical, France), a semiautomated device that calculates PWV based on simultaneous recordings from two specific pressure transducers. All investigators received comprehensive training regarding the proper use of the device. Appropriate software permitted online pulse wave recording and automatic calculation of PWV (19). Carotid-femoral PWV was calculated from the time delay between the recorded proximal foot of the wave (carotid), the distal foot of the wave (femoral) and the superficially measured distance separating the respective transducers. A total of about 10 pulses were recorded and averaged. All recordings were electronically forwarded to a coordinating centre (The CardioVascular Institute, France) for blind validation and analysis.

MMP-1 and TIMP-1

Serum levels of MMP-1 and TIMP-1 were measured in duplicate at M0, M2 and M6. Commercial ELISA kits were used in accordance with manufacturer recommendations (Amersham Pharmacia Biotech, Oncogene, USA). Serum samples were diluted 1:5 for MMP-1 and 1:40 for TIMP-1 to maintain assay linearity.

Blood biochemistry and hematology were performed at M0, M2 and M6.

Statistics

Demographic and clinical laboratory data were assessed using descriptive statistics. Paired Student's *t* tests were used to compare the changes in BP and PWV between visits. Results of parametric or nonparametric tests were considered according to the normality of the distributions. An analysis of variance for repeated measurements was performed for absolute and relative changes; adjustments for BP values were performed. Significance was considered to be at the level of $P<0.05$. Because a linear decrease over the six-month treatment period was not observed with either BP or PWV, analyses were divided into intervals of M6 to M0, M2 to M0 and M6 to M2. To test whether the relationship between PWV and clinical parameters remained constant over time, correlation between parameter levels and change in PWV were estimated using the Fisher (20) method to test the hypothesis that the correlation coefficients at M0 and M6 was two estimates of the same variable. Statistical analyses were performed using the NCSS software (Number Cruncher Statistical Systems, USA).

RESULTS

Although 162 patients were enrolled in the study, 17 (10%) patients had missing or invalid PWV recordings at M0 or thereafter, and 23 (14%) patients had missing or invalid PWV data between M6 and M2. Therefore, 145 (58% male) patients were included in the M2 to M0 analysis, and 122 (58% male) patients were included in the M6 to M0 and M6 to M2 analyses. As noted in Table 1, the baseline demographics and clinical characteristics of the 145 patients included in the M2 to M0 analyses and the reduced cohort of 122 patients included in the M6 to M0 analyses were comparable.

BP

At M2, 82 (57%) patients had normalized BP, 27 (19%) patients were responders without BP normalization, 22 (15%) patients did not respond to treatment, and 13 (9%) patients were discontinued from the study and were prescribed another antihypertensive therapy. BP and PWV mean values and mean changes at M0, M2 and M6 are provided in Table 2. All BP parameters (SBP, DBP, mean arterial pressure and PP) were significantly reduced at M2 and then remained stable to M6 ($P=0.00001$). The overall mean decreases in SBP and DBP were –20±13 mmHg and –14±8 mmHg, respectively, after six months of perindopril therapy. However, statistically significant differences were not noted for any BP parameter between M2 and M6.

PWV

Statistically significant mean changes in PWV from baseline of –1.4±2.2 m/s and –1.8±2.1 m/s were noted at M2 and M6, respectively ($P=0.00001$). Moreover, a statistically significant mean change in PWV of –0.4±1.7 m/s was noted at M6 to M2 ($P=0.007$), indicating a continued reduction in PWV. BP and PWV response to therapy were similar in patients regardless of sex. Table 3 illustrates the relationship between BP parameters and changes in PWV. The change in PWV between M2 and M0 was significantly correlated to all BP parameters at M0

TABLE 3
Correlation coefficients with change in pulse wave velocity (PWV) at two months (M2) and six months (M6)

Parameter	Change in PWV* (M2-M0)	Change in PWV† (M6-M2)
SBP	0.246‡	0.065
DBP	0.243§	0.038
PP	0.189‡	0.060
MAP	0.286¶	0.055
HR	0.100	–0.067

**Correlation determined between change in PWV with blood pressure (BP) and heart rate (HR) parameters at baseline (M0); †Correlation between change in PWV between M6 and M2 and BP and HR values measured at M2 in the 122 patients with validated PWV records at M2 and M6; ‡P<0.001; §P<0.05; ¶P<0.0001. DBP Diastolic BP; MAP Mean arterial pressure; PP Pulse pressure; SBP Systolic BP*

TABLE 4
Mean serum levels of metalloproteinase-1 (MMP-1) and tissue inhibitor of MMP-1 (TIMP-1) at baseline (M0), two months (M2) and six months (M6)

	M0 (mean ± SD)	M2 (mean ± SD)	M6 (mean ± SD)
MMP-1 (ng/mL)	3.92±2.98	3.95±3.18	4.16±3.21
TIMP-1 (ng/mL)	1065±337	1075±335	1035±334

(r^1 0.189 or greater). However, no correlation was seen regarding BP parameters at M2 and further M6 to M2 changes in PWV, suggesting that this further increase in arterial distensibility was independent of the change in BP induced between M0 and M2 by perindopril therapy.

MMP-1 and TIMP-1

A total of 125 patients were successfully assayed for MMP-1 and TIMP-1 at M0, M2 and M6. The mean serum levels of MMP-1 and TIMP-1, which are presented in Table 4, did not change from baseline values over the six-month perindopril treatment period. Surprisingly, the expression of TIMP-1 and MMP-1 varied among patients by factors of five and 10, indicating a high degree of heterogeneity within the patient population. No correlations were found among BP, PWV and the expression of these proteins, or among changes in BP, PWV and the changes in these matrix macromolecular measures including collagen metabolism.

DISCUSSION

Six months of treatment with the ACE inhibitor perindopril significantly decreased BP and PWV in patients with essential hypertension. The majority of the reductions in SBP, DBP, PP and mean arterial pressure were observed between M0 and M2; these parameters did not show any further statistically significant changes after M2. Indicative of an increase in vascular distensibility, significant reductions in PWV were also noted. However, while the greatest reduction in PWV was observed between M0 and M2, further statistically significant reductions in PWV were observed after M2. It is unlikely that the reduced BP level at M2, or any further BP reduction between M2 and M6, can account for the increase in arterial distensibility observed after M2. The correlation seen between the BP parameters at M0 and the change in PWV was absent when the BP parameters at M2 or M6 were used and when the further reductions in PWV were used, indicating that this decrease in PWV may have occurred independent of further modifications of BP.

Previous pharmacological controlled studies performed in limited numbers of patients demonstrated that ACE inhibition produces arterial changes independent of BP reduction (21-28). ACE inhibition has been associated with an increase in isobaric compliance and distensibility which, either in acute or chronic conditions, does not appear to be due to the exclusive effect of BP reduction (21,22). Interestingly, PWV was also decreased after six-month perindopril treatment in a recent nonrandomized study and this decrease could not be fully explained by the decrease in BP (29).

A pressure-independent increase in arterial elasticity may imply a perindopril effect of its own on the arterial wall (30). The current study measured MMP expression in an effort to correlate such remodelling with collagen metabolism. While the levels of serum expression of MMP-1 in this study, as measured by ELISA, were generally lower than the 50 ng/mL typically observed in hypertensive patients, the observed levels of TIMP-1 appeared in concordance with the 890 ng/mL previously reported (16). The values obtained were within the linear area of the standard curve; therefore, the assays appeared to function properly.

Despite the significant changes in BP and PWV observed with perindopril treatment, no changes in serum MMP-1 or TIMP-1 were seen. It is, however, impossible to conclude whether enzymatic changes undetectable in the serum occurred at the vascular wall level. Modifications of other systems and/or processes independent of MMPs might also be responsible for the increased vascular elasticity observed in these subjects.

The present study design allows for the possibility that the observed decrease in BP and PWV could be exclusively related to a regression toward the mean or to a placebo effect. However, because the patient selection criteria were based on BP values and not on PWV levels, regression to the mean is more likely to be observed for BP than for PWV. Additionally, the observed changes from baseline in the present study are markedly higher than the estimated placebo effect and regression to the mean effect. From previous double-blind studies, the proportion of the placebo effect and the regression to the mean effect was estimated to be –6±11 mmHg, –5±8 mmHg and –0.18±1.20 m/s for SBP, DBP and PWV, respectively (31-33), whereas the reductions seen in this study were –20±13 mmHg, –14±8 mmHg and –1.8±2.1 m/s, respectively.

CONCLUSIONS

Following two months of perindopril therapy, statistically significant reductions in BP and PWV occurred. After six months, the BP reduction was stable whereas PWV continued to decrease, suggesting a reduction of arterial stiffness independent of BP reduction. A long-term, double-blind, randomized trial would be required to confirm that the observed increase in vascular compliance induced by perindopril is related to a mechanism of action other than a reduction in BP.

ACKNOWLEDGEMENTS: This work was supported by a grant from Servier Canada.

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