Perindopril, Pulse Wave Velocity, and Metalloproteinase-1 and its Inhibitor in Patients with Mild-to-Moderate Essential Hypertension

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Canadian Multicentre Study

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BACKGROUND

- Arterial compliance is related to the distensibility of the arterial wall
- Among factors influencing arterial compliance, the type of antihypertensive therapy is an important one
- ACE Inhibitors improve arterial compliance independently of blood pressure level
- Pulse wave velocity (PWV) is an arterial distensibility index of large and medium arteries
- Arterial hypertension is associated with cardiovascular remodeling, characterized by increased extracellular matrix content, especially fibrillar collagen
- Extracellular degradation of collagen occurs mainly through catalytic cleavage by matrix metalloproteinase-1 (MMP-1)
- Tissue inhibitor of MMP-1 plays an important role through its inhibitory effect on MMP-1 activity

OBJECTIVES

- To determine if the reduction in BP following the administration of perindopril 4 to 8 mg once daily is accompanied by a decrease in PWV after 2 and 6 months of treatment
- To determine if the serum levels of MMP-1 increase and its tissue-inhibitor (TIMP-1) decrease in parallel with the decrease in PWV when BP is returned to normal values

STUDY DESIGN

- Open-label, multicentre (6 sites) study
- Perindopril initial dose of 4 mg/day was increased to 8 mg/day if BP not controlled (DBP > 90 and/or SBP > 140 mmHg)
- Clinic BP measurements (sitting) at each visit after a 10-minute rest according to recommendations from the Canadian Society of Hypertension
- Carotid-femoral PWV (m/s) measured automatically with the Complior® device at M0, M2 and M6
- Duplicate analysis of serum MMP-1 and TIMP-1 measured at M0, M2 and M6 using an ELISA assay

SELECTION CRITERIA

- Adult patients (≥ 18 years) with mild-to moderate essential hypertension, defined by DBP ≥ 95 and ≤ 114 mmHg
- Treatment-naive patients or patients who discontinued antihypertensive therapy for ≥ 6 months prior to study entry

PATIENT CHARACTERISTICS AT INCLUSION

Male/Female*	84/61	PP (mmHg)*‡	49 ± 13
Mean Age (yrs)*‡	50 ± 9.5	MAP (mmHg)*‡	116 ± 6
Weight (kg)*‡	82 ±17	PWV (m/s)*‡	12.2 ± 3.2
BMI (kg/m2)*‡	29 ± 5	HR (bpm)*‡	72 ± 10
SBP (mmHg)*‡	149 ± 14	MMP-1 (ng/mL)†‡	3.92 ± 2.98
DBP (mmHg)*‡	100 ± 4	TIMP-1 (ng/mL)†‡	1065 ± 337

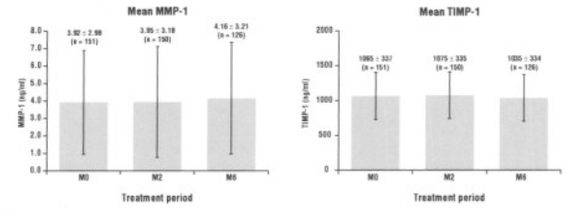
* n = 145 patients with valid PWV record at M2
† n = 151 patients
‡ Values are mean ± S.D.

EFFECT OF PERINDOPRIL ON CLINICAL PARAMETERS

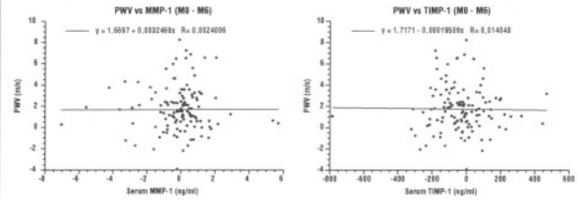
Clinical Parameter	M0	M2	M6	p (M0 - M6)	p (M0 - M2)	p (M2 - M6)
SBP (mmHg)	149 ± 14	131 ± 13	129 ± 13	0.00001	0.00001	NS
DBP (mmHg)	100 ± 4	87 ± 8	86 ± 8	0.00001	0.00001	NS
PP (mmHg)	49 ± 13	44 ± 10	43 ± 9	0.00001	0.00001	NS
MAP (mmHg)	116 ± 6	102 ± 9	101 ± 9	0.00001	0.00001	NS
Heart rate (bpm)	72 ± 9	72 ± 9	72 ± 8	NS	NS	NS
PWV* (m/s)	12.2 ± 3.2	10.7 ± 2.5	10.2 ± 2.2	0.00001	0.00001	0.007

Paired t-test between M6 or M2 and M0
Values are mean ± standard deviation
* Data are available for 122 patients at M6

EFFECT OF PERINDOPRIL ON MMP-1 AND TIMP-1



CORRELATION BETWEEN PWV AND MMP-1, AND TIMP-1



SUMMARY

- SBP, DBP, PP, MAP and PWV decreased significantly under perindopril treatment
- The reduction in BP was maximal between M0 and M2 without further significant reduction between M2 and M6
- The decrease in aortic PWV achieved statistical significance between M0 and M2 and between M2 and M6 although the greatest variation occurred between M0 and M2
- Serum levels of MMP-1 and TIMP-1 remained unchanged throughout the treatment period

CONCLUSIONS

- Perindopril markedly decreases PWV, an effect still present even after perindopril has reached its maximum effect on BP parameters.
  This confirms the role of PWV as an independent risk marker in hypertension and that the effects of perindopril are not limited to BP parameter changes.
- Whether collagen degradation is involved is not reflected in the serum.
  Changes may occur through a direct effect at the level of the vascular wall of large arteries. Other components of the vessel wall may also be involved with different expressions in the serum.