Assessment of Perindopril's Efficacy on Arterial Distensibility in Mild to Moderate Hypertension

COMPLIOR COLLABORATIVE STUDY GROUP*

Abstract

Objective : Angiotensin Converting Enzyme Inhibitors (ACEIs) have been clearly proven to be effective in blood pressure control and haemodynamic control in heart failure patients. Moreover, there is evidence that ACEIs, both in animal models and in humans, also possess the ability to reduce remodeling in cardiovascular structures. Therefore, the reduction of the occurrence of arterial stiffness, leading to an increase in distensibility, is also anticipated.

Method : Other than physically measuring arterial wall, the assessment of Pulse Wave Velocity (PWV) is also a widely used index of arterial distensibility, which deteriorates through the course of remodeling. To determine the efficacy of a particular ACEI, perindopril, in increasing arterial distensibility, thus reducing PWV, a 6-month multi-center study was conducted in 146 patients with mild to moderate hypertension. The study population consisted of 70 men and 76 women, aged 56.36 (SD 9.4, range 28-73) years. 73 patients were newly diagnosed, 65 were treated patients but the blood pressure was not controlled, and 8 were treated patients with their blood pressure controlled but with adverse effects in need of switching treatment regimens.

Results : Mean blood pressure at the beginning of the study was 164.25/97.49 mmHg and 11.71 m/s (SD 2.29 range 7.35-20.12 m/s) in mean PWV. Perindopril was prescribed tritrating from 4 mg/day to 8 mg/day and adding a diuretic. 106 patients completed the study with 76.4 per cent of patients having their blood pressure controlled (Mean Blood pressure 138.6/85.18 mmHg, SD 11.34 and 7.10 Range 110-170/70-110 mmHg) ($p<0.05$). Mean PWV reduced to 10.56 m/s (-9.89%) (SD 1.84 range 7.27-15.96 m/s) ($p< 0.05$).

Conclusion : Anti-hypertensive treatment with perindopril for 6 months was effective in controlling blood pressure and reducing Pulse Wave Velocity reflecting the increase of arterial distensibility.

Key word : ACE-I, Arterial Distensibility, Perindopril, Pulse Wave Velocity

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Arteries and arterioles

In controlling normal blood circulation, large elastic arteries, so called "conduit arteries", play a completely different role to the arterioles. Conduit arteries, with mechanical properties are determined by multiple elastic lamellae contained within its medial coat, has two roles-one is to act as low resistance conduits, supplying blood to peripheral arterioles,- the second is to act as cushions by damping out the pulsations that are generated by left ventricular ejection so that blood may flow through the resistance arterioles in a steady stream, with minimal energy loss. Arterioles play a role in maintaining an appropriate mean pressure for preservation of blood flow to vital low resistance organs (brain, heart, kidney) by maintenance of vascular tone, but they also have the ability to vary the tone according to local and general bodily needs. Therefore, every pulse emitted by a left ventricular contraction is conveyed through a low resistance conduit artery, and at the same time, damping out the pulsations, creating a steady stream of blood flow to vital organs *via* arterioles(1).

Wave reflections and arterial stiffness

Reflection of a wave occurs when a wave approaches a point of discontinuity of impedance, which is where stiffness increases. The reflected wave influences the overall blood pressure by the summation of it to the new coming forward wave, the more substantial the summation, the higher the pulse pressure. The major sites of wave reflection in a normal system are the arterial/arteriolar junctions. But its effect is minimized by the ratio of daughter to parent vessel diameter, and also the distance of the occurring site. The effects of wave reflection from sites of arterial stiffness are more pronounced(2).

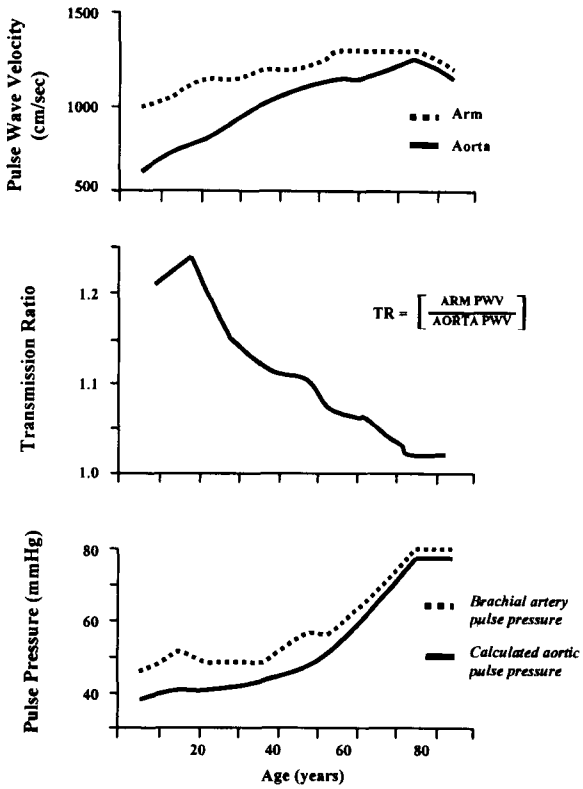

Fig. 1. Relations between age/aortic and arm PWV[12].

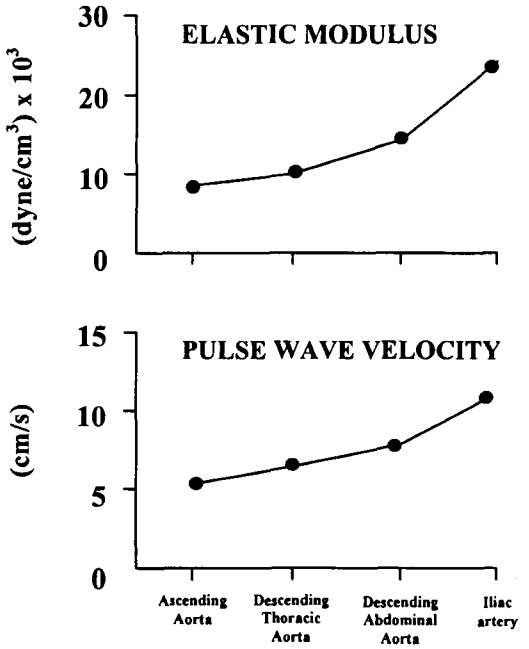

Fig. 2. Elastic modulus and PWV in different arterial sites. Both increases as the distance from the heart increase[13].

Arterial stiffness, aging and hypertension

Age-related changes occur in every part of the vessel. In the intima layer endothelial cells become more irregular in size and shape, the number of giant mulitnucleated cells increases, the subendothelial layer becomes thickened, and there is also an increase in connective tissue. The media loses its orderly arrangements of its elastic fibres which become thin and fragmented. Collagen, which is the stiffer component than elastin, increases from 15-21 per cent at the age of 20, to 25-40 per cent at the age of 70, while elastin decreases from 32-37 per cent to only 22-27 per cent. Accumulation of lipids is also a feature of age-related change that progressively occurs in the media of human arteries. The macroscopic result of these changes is the increase in size of the artery, with increases in both arterial radius and wall thickness[3].

The process of age-related changes has proven to accelerate in subjects with systemic hypertension, as well as the increase in pulse wave velocity, measuring arterial distensibility, with age it is less apparent in populations with low prevalence of hypertension.

With aging and high blood pressure, due to progressive arterial stiffness, the conduit artery loses its dampening function causing pulses to propagate with high velocity. Moreover, reflecting waves occurs closer to the heart producing a more pronounced backward wave[4].

Clinical importance of arterial stiffness and wave reflections

Alterations in the geometry and the elastic properties of the arterial system have a profound influence on ventricular function. The amount of energy and oxygen consumed by the ventricle to produce stroke volume is dependent upon both the myocardial contractile state and the physical properties of the arterial system. The load acting against the ventricle consists of both the static and dynamic components. The static components are dependent

on blood viscosity and arteriolar caliber, while the dynamic component is dependent on the elastic and geometric properties of arteries and also pulse wave reflections. Thus, increasing arterial stiffness causes increasing left ventricular oxygen consumption, and high pulse pressure with decreased stroke volume would likely result from the increase in the amplitude of wave reflects[5].

Pulse Wave Velocity and arterial distensibility

Arterial distensibility has long been a determination of overall cardiovascular health. Reduced arterial distensibility contributes to a disproportionate increase in systolic blood pressure and an increase in arterial pulsatility, which has been shown to be associated with an increase in cardiovascular morbidity and mortality. Reflecting the physical arterial structure, arterial distensibility can be estimated as the degree of remodeling the artery has been through. Since fluid is contained in a system of elastic conduits, energy propagation occurs predominantly along the arterial wall but not through the incompressible blood. The physical properties of the arterial wall, its thickness and the lumen diameter, thus become the major determinants of arterial distensibility.

Measuring carotid-femoral Pulse Wave Velocity (PWV) is a non-invasive means to evaluate arterial distensibility. PWV is calculated from measurements of pulse transit time and the distance traveled by the pulse between two recording sites, in this case, the carotid artery and the femoral bifurcation. PWV = Distance (meters) / Transit Time (seconds). This method enables one to comprehensively evaluate indirectly the arterial distensibility and stiffness[6].

PATIENTS AND METHOD

In a 6-month open multi-center trial, 6 centers recruited 146 patients with mild to moderate hypertension, whereas, 72 patients were newly diagnosed hypertensives, 66 patients had been previously treated but had not achieved normal blood pressure, and 8 were treated with normal blood pressure but had intolerable adverse effects and needed a change in regimen. The inclusion criteria were patients with: hypertension with diastolic blood pressure ranging from 95-114 mmHg or systolic blood pressure ranging from 160-200 mmHg, others were treated patients who had not reached normal blood pressure or had side effects needing a change in regimen. The non-inclusion criteria were patients with: secondary hypertension, severe hypertension or hypertension with other concomitant diseases. Concomitant anti-hypertensive therapy were permitted and remained unchanged throughout the trial.

Table 1. Patient characteristics at inclusion.

	N	Percentage
Sex		
Male	70	47.9
Female	76	52.1
Hypertension type		
New cases	73	50.0
Uncontrolled cases	65	44.5
Controlled with S/E	8	5.5
Smoking		
Smoker	16	11.0
Non-smoker	130	89.0
Diabetes		
NIDDM	15	10.3
Hx of hyperglycemia	2	3.1
No known history	129	86.6
Hyperlipidemia		
Yes	30	20.5
No	116	79.5
Obesity		
Yes	24	16.4
No	122	83.6
Heart failure		
Yes	0	0
No	146	100
Hx of stroke/TIA		
Yes	3	2.0
No	143	98.0

Patients were first given perindopril 4 mg once daily, and if at next visit their blood pressure still remained diastolic over 90 mmHg or sytolic over 140 mmHg perindopril was increased to 8 mg once daily. Indapamide was added to the regimen if the condition persisted (other drugs were considered in patients previously treated with a diuretic).

Patients' examination consisted of PWV, supine blood pressure and laboratory examinations: plasma creatinine, potassium, sodium, plasma glucose, cholesterol levels, triglycerides and hematocrit. Blood pressure and electrolytes were examined at every visit: M0, M1, M2, M3 and M6, whereas, PWV was evaluated at every other visit and cholesterol profile on inclusion and M6.

Statistical analysis was performed for changes between inclusion and end of study. Student *t*-tests were performed on quantitative variables and Chi square tests on nominal variables.

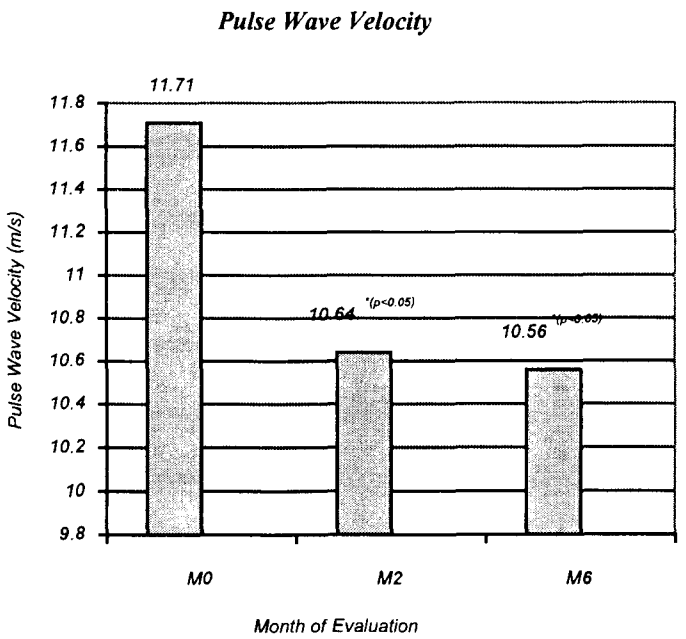

Fig. 3. **Mean Pulse Wave Velocity decrease over 6-month period in 146 patients. A significant reduction in Pulse Wave Velocity can be observed from M2 (p<0.05).**

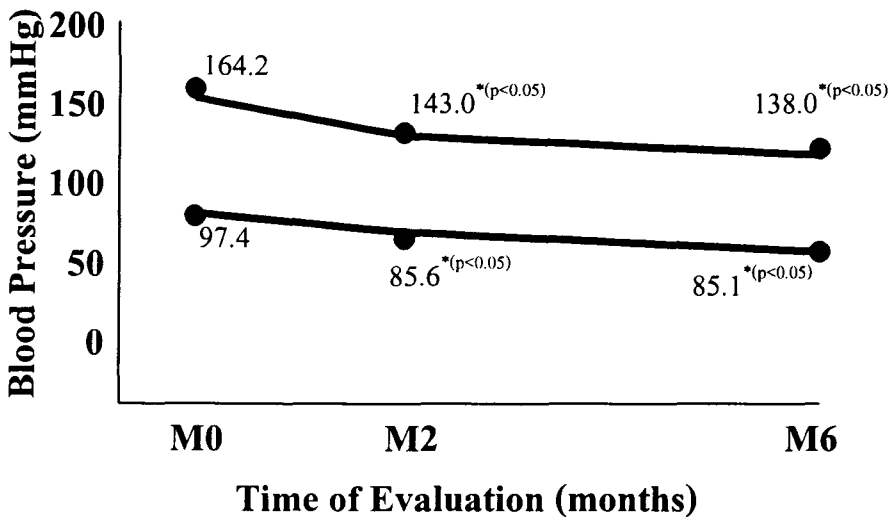

Fig. 4. **Mean blood pressure showed significant decrease from M2 (p<0.05).**

RESULTS

From 146 patients recruited, 130 patients remained at M2 and a total of 106 patients completed the study at M6.

At the end of the study 53 patients (49.5%) were taking perindopril monotherapy, 22 (20.5%) had a combination of perindopril and indapamide, and 32 (29.9%) had perindopril combined with their previous anti-hypertensive medications. The mean PWV at the beginning of the study was 11.71 m/s (range 7.35 – 20.12 m/s, standard deviation = 2.29), reducing to 10.64 m/s (± 2.27) at M2 (p<0.05), and

Table 2. Overall outcome of laboratory examinations.

	Pre-study values	Post-study values
Hematocrit (%)	42.88 ± 25	40.65 ± 4.9
Fasting blood glucose (mmol/L)	5.76 ± 1.4	5.94 ± 2.0
Plasma cholesterol (mmol/L)	6.31 ± 2.9	5.69 ± 1.1
LDL cholesterol (mmol/L)	4.26 ± 2.0	3.73 ± 1.4
HDL cholesterol (mmol/L)	1.50 ± 0.7	1.35 ± 0.5
Triglycerides (mmol/L)	4.56 ± 3.44	3.44 ± 2.9
Plasma creatinine (μmol/L)	95.00 ± 21.7	97.05 ± 20.8
Potassium (mmol/L)	4.13 ± 0.4	4.26 ± 0.5
Sodium (mmol/L)	141.22 ± 3.7	141.49 ± 3.5

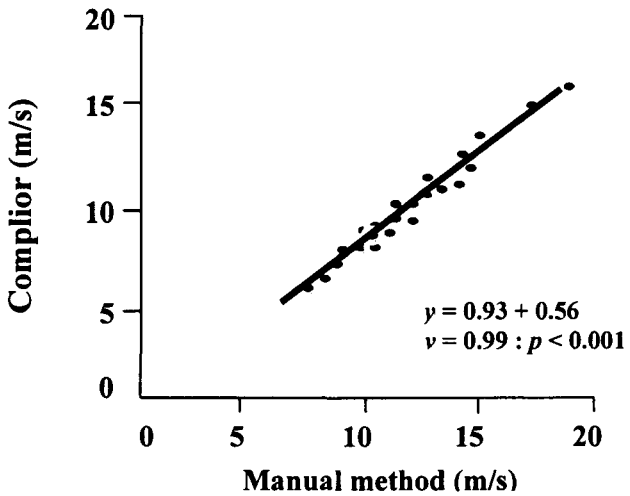

Fig. 5. Comparison of PWV values performed using the manual method and the Complior® device[14].

10.55 m/s (±1.84) at the end of the study. Blood pressure also reduced from 164.25±14.7 mmHg systolic and 97.49±8.5 mmHg diastolic to 138.60± 11.3 mmHg systolic and 85.18±7.1 mmHg diastolic ($p<0.05$).

Events leading to termination of study

Of the 48 patients withdrawn; 19 (13%) were from loss of follow-up; 20 (13.7%) from an occurring adverse event, cough; 4 (2.7%) from failure of treatment; and 1 (0.7%) from poor compliance. No deaths, allergic reactions or renal function disturbances had occurred throughout the study.

DISCUSSION

Arterial stiffness is an on going process through the length of age resulting in the loss of the artery to dampen the pulsatile flow in to a steady stream ready to deliver to target organs. The change in impedance of the artery not only results in the degree of pulsatile flow, but also has the effect of the reflection wave which summarizes to the amplitude of the forward wave causing a profound change dependent on the distance of the site of reflection. For clinical relevance, this change in arterial stiffness may lead to an increased resistance to the left ventricle causing an increase in heart oxygen consumption[5], and also high pulse pressure and low cardiac output from the reflection wave[3]. Clinical importance urges the need to measure arterial stiffness, which may aid in the prognosis of various patients. Pulse Wave Velocity (PWV), a means of measuring the time a pulse travels in an artery and back from its reflection destination, has long been

the means to determine arterial distensibility. With the ability to calculate the approximate site of wave reflection, PWV suite as an indicator to the degree of arterial stiffness or loss of distensibility[3].

As with other technological means, the measurement of PWV has evolved, from being formerly dependent on the pulse and its backward reflection wave to determine site of reflection, computerized equipment dependent only on the velocity of the forward pulse has been brought to practice.

This study utilized the COMPLIOR machine, which consists of a COMPLIOR software version 3.0 installed IBM computer complete with two acoustic sensors and a trigger pedal, in the determination of PWV. After having been tested for repeatability, the COMPLIOR machine serves as an ideal, convenient and accountable device in the measurement of arterial distensibility[6].

Knowing that hypertension accelerates the process of arterial stiffness, the treatment of hypertension aims to retard the process which primarily is thought to be achieved by means of mere blood pressure control. This concept was changed when improvement of arterial distensibility and structure was more substantial in hypertensive patients treated by a particular group of antihypertensive agents despite having a similar degree of blood pressure control[7]. Angiotensin Converting Enzyme Inhibitors are considered as a group of drugs which benefits arterial distensibility over some other antihypertensive agents. ACE inhibition acts on arterial diseases through 2 mechanisms, first reducing intraluminal pressure by the general blood pressure lowering effect, second, by an additional effect independent of any blood pressure change, possibly related to the effects of angiotensin II in stimulating vascular growth[10]. Specifically, there were reductions in smooth muscle hypertrophy and in collagen density[2]. Perindopril, a widely prescribed ACE Inhibitor, has also been proven beneficial by inhibiting the process of remodeling in human arteries. The COMPLIOR study is to determine the effects of perindopril on arterial distensibility by contributing countries worldwide, including Thailand. A total of 146 patients, after being recruited, received perindopril 4 mg once daily which was adjusted according to blood pressure response for 6 months. The monitoring of PWV took place at the first inclusion visit (M0), the end of the second month (M2) and the end of the 6th month (M6). The study showed a significant increase in arterial distensibility from the decrease in mean PWV from M0 to M2, and the improvement continued through to M6. Blood pressure was also significantly reduced, from a mean blood pressure of 164/98 mmHg to 143/86 mmHg from M0 to M2, and continued decreasing to 139/85 mmHg in M6 with the majority of patients being treated with perindopril monotherapy.

Arterial structural improvements leading to functional improvements are considered a long-term process, by gradually normalizing endothelial functions and inhibiting the process of remodeling. Perindopril has proven to improve the elastin/collagen ratio[8] and reduce arterial wall thickness in long-term treatments (1 year) with the mechanism of inhibiting. Angiotensin II production and the increasing amount of bradykinin are to be accounted for[9]. Contradictory to the results of this study was significant improvement of PWV, which reflexes arterial distensibility, occuring more profoundly during the first 2 months of perindopril administration. This effect can also be observed in studies that experience a significant reduction in blood pressure, leading to the conclusion that the vasodilating mechanism of perindopril, causing a relaxation in smooth muscle, also has a direct effect on arterial distensibility[7], making the further long-term decrease in PWV relatively less substantial.

In this study, it was concluded that the ACE Inhibitor perindopril has the ability to improve arterial distensibility, as shown by PWV parameters. The effect of ACE Inhibition on arterial distensibility without the influence of vasodilatation requires further indepth studies.

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การประเมินความสามารถของยาเพริลโดพริลในการเพิ่มความสามารถในการขยายตัวของหลอดเลือดในผู้ป่วยความดันโลหิตสูง

กลุ่มผู้ร่วมทำการวิจัย COMPLIOR

วัตถุประสงค์ : ยากลุ่ม Angiotensin Converting Enzyme Inhibitors (ACEIs) ได้รับการยอมรับว่าเป็นยาที่มีประสิทธิภาพในการลดความดันโลหิต รวมถึงการควบคุมสภาวะไหลเวียนของของเหลวในร่างกายในผู้ป่วยที่มีภาวะหัวใจวาย นอกจากนั้น ยาในกลุ่มนี้ยังมีหลักฐานการศึกษาที่แสดงให้เห็นถึงความสามารถในการลดการเกิด remodeling ในระบบหัวใจและหลอดเลือด การศึกษานี้จึงมีวัตถุประสงค์ที่จะวัดความสามารถของยา perindopril ที่จะเพิ่มความสามารถในการยืดตัวของหลอดเลือด (distensibility) ทำให้ลดความตีบของหลอดเลือด

วิธีการศึกษา : การวัดค่า Pulse Wave Velocity (PWV) เป็นวิธีหนึ่งในการประเมินความสามารถในการยืดขยายของหลอดเลือด (distensibility) ซึ่งความสามารถนี้จะสูญเสียไปเรื่อย ๆ เมื่อเกิดกระบวนการ remodeling การทดลองนี้จะทำในผู้ป่วยความดันโลหิตสูง โดยใช้ยา perindopril ซึ่งเป็น ACEI ที่มีประสิทธิภาพในการควบคุมความดันโลหิต และติดตามผลด้วยการวัดค่า PWV

ผลการศึกษา : ผู้ป่วยความดันโลหิตสูงที่เข้าร่วมการศึกษามีจำนวน 146 คนเป็นชาย 70 คนและหญิง 76 คน อายุเฉลี่ย 56.36 ปี ในจำนวนนี้เป็นผู้ป่วยใหม่ 73 คน และเป็นผู้ป่วยเดิมที่ไม่สามารถควบคุมความดันโลหิตได้จากการรักษาเดิม 65 คน อีก 8 คนเป็นผู้ป่วยเดิมที่ควบคุมความดันโลหิตได้ดีแต่ไม่สามารถทนยาเดิมได้ และมีความจำเป็นต้องเปลี่ยนยาที่รักษา ค่าความดันเฉลี่ยขณะเริ่มต้นเท่ากับ 164.25/97.49 ม.ม.ปรอท ค่า PWV ขณะเริ่มต้นเท่ากับ 11.71 เมตร/วินาที ผู้ป่วยจะได้รับยา perindopril เริ่มต้นที่ขนาด 4 ม.ก.ต่อวันจนถึง 8 ม.ก.ต่อวัน ผู้ป่วยที่ร่วมการศึกษาจนจบโครงการมีจำนวน 106 คน ในจำนวนนี้ผู้ป่วยที่สามารถควบคุมค่าความดันโลหิตได้ดีมีถึง 76.4% (ค่าความดันมีตั้งแต่ 110–170/70–110 ม.ม.ปรอท ค่าเฉลี่ยเท่ากับ 138.6/85.18 ม.ม.ปรอท) ค่า PWV เฉลี่ยลดลงมาอยู่ที่ 10.56 เมตร/วินาที

สรุป : การใช้ยา perindopril ในการรักษาความดันโลหิตสูงในผู้ป่วยเป็นระยะเวลา 6 เดือนจะมีประสิทธิภาพในการควบคุมค่าความดันโลหิตได้ดี รวมถึงยังสามารถลดค่า PWV นั่นคือทำให้ความสามารถในการยืดขยายของหลอดเลือดในผู้ป่วยความดันโลหิตสูงดีขึ้น

คำสำคัญ : ความสามารถในการยืดขยายของหลอดเลือด, ยาต้านแองจิโอเทนซิน

กลุ่มผู้ร่วมทำการวิจัย COMPLIOR
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 1006–1014

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