Fixed Dose Combination of Perindopril and Indapamide Improves Peripheral Vascular Function in Essential Hypertensive Patients

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BACKGROUND
The effect on endothelium-dependent and independent vasodilation of 24-week treatment with a fixed-dose combination of perindopril/indapamide (2/0.625 mg, daily) and atenolol (50 mg, daily), was evaluated in 62 untreated essential hypertensive patients according a double-blind, parallel group, randomized study.

METHODS
Brachial artery flow-mediated dilation (FMD), response to sublingual glyceril trinitrate (GTN, 25 µg) and to cold pressor test (CPT) were measured at baseline and after treatments at 12 and 24 weeks, as change in diameter from ultrasound scans by a computerized system.

RESULTS
Blood pressure (BP) was ($P < 0.001$) reduced in both groups, but to a greater ($P < 0.01$) extent in the perindopril/indapamide group. After 24 weeks, FMD was significantly increased ($P < 0.01$) by perindopril/indapamide (from 5.0 ± 2.1 to $6.0 \pm 1.7\%$) but not by atenolol (from 5.1 ± 1.8 to $5.5 \pm 1.8\%$). Improvement in FMD was not statistically

related to BP reduction. Response to GTN was also significantly ($P < 0.05$) increased by perindopril/indapamide (from 6.2 ± 1.9 to $6.9 \pm 1.7\%$), but not by atenolol (from 6.1 ± 2.8 to $6.6 \pm 2.6\%$). Improvement in GTN response was significantly ($P < 0.05$) related to BP reduction. Response to CPT was significantly increased ($P < 0.001$) by perindopril/indapamide after 12 and 24 weeks, whereas atenolol significantly ($P < 0.05$) improved it only after 24 weeks.

CONCLUSIONS
Treatment with perindopril/indapamide improves endothelium-dependent vasodilation in comparison with atenolol. This improvement was observed without significant relations with BP changes, suggesting a pressure-independent effect. Improvement in endothelium-independent and sympathetic-associated vasodilation was also observed. These results suggests that long term therapy with a fixed-dose combination of perindopril/indapamide affords vascular protection in hypertensive patients.

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The endothelium plays a primary role in modulating vascular tone and structure by production of nitric oxide (NO).[1] Essential hypertension is characterized by impaired endothelium-dependent vasodilation[2,3] both in the coronary[4] and peripheral circulation,[5–7] due to impaired NO availability.[6,8] Increasing evidence suggests that endothelial dysfunction in coronary and peripheral circulation is an independent predictor of cardiovascular events in patients with cardiovascular disease or risk factors.[2,3,9] Indeed, impaired peripheral and coronary flow-mediated dilation (FMD) and response to the cold pressor test (CPT) in the coronary circulation have been associated with poor cardiovascular outcome,[10,11] even in uncomplicated hypertension.[11] In addition, improvement in brachial artery FMD with treatment was associated with a better cardiovascular prognosis in hypertensive post-menopausal women.[12]

For these reasons, it has been suggested that reversing endothelial dysfunction could represent a surrogate end-point for antihypertensive treatment. Although the beneficial effect of antihypertensive therapy on cardiovascular events in hypertensive patients is primarily based on blood pressure (BP) reduction[13,14] different antihypertensive drug classes have a different effect on target organ damage protection.[14] It has been widely demonstrated that mere BP reduction is not sufficient to improve or restore endothelial function.[15] In particular, ACE-inhibitors have been shown to be the most effective antihypertensive drug class in improving endothelium-dependent vasodilation in large arteries of patients with essential hypertension.[8,16,17] However, to date no data are available on their combination with diuretics after chronic administration.

Because fixed-dose combination of perindopril and indapamide has been already shown to be effective in reducing arterial stiffness in essential hypertensive patients,[18] the aim of the present randomized controlled study was to compare the effect of fixed-dose combination of perindopril/indapamide to the selective β-receptor blocker atenolol on endothelium-dependent and independent vasodilation in the brachial artery of untreated essential hypertensive patients.

METHODS

Patients. Sixty-two untreated essential hypertensive patients (51 males and 11 females) were recruited among outpatients of our Hypertension Unit. Patients had a history of no treatment or discontinuous antihypertensive treatment, with alcohol consumption <50 mg/day.

Patients with diabetes mellitus, renal impairment, smoking history of >10 cigarette/daily and total cholesterol >240 mg/dl were excluded. Premenopausal women and postmenopausal women taking hormone replacement therapy were also excluded.

The University of Pisa's Ethical Committee approved the protocol and all patients gave written consent to the study.

Experimental design. CL3-05590-019-ITA was a prospective, double-blind, randomized, parallel group study (**Figure 1**). After 2 weeks placebo run-in, patients were randomized to treatment with perindopril/indapamide 2/0.625 mg/daily or atenolol 50 mg/daily. Medical examinations were scheduled every 6 weeks. Doubling of dosage was allowed starting from week 12 (W12), if BP values were still >140/90 mm Hg. Vascular studies were performed at baseline, W12 and 24 weeks (W24) of treatment.

Experimental procedure. Vascular ultrasound scans were performed in the morning, in a quiet air-conditioned room (22–24 °C). A B-mode scan of the right brachial artery was obtained in longitudinal section between 10 cm and 15 cm above the elbow using a 7.0 MHz linear array transducer (AU5 Armonic system, ESAOTE Biomedica, Florence, Italy), held at the same point throughout the scan by a stereo-tactic clamp. End-diastolic frames (ECG-triggered) were acquired every second on a personal computer using a commercial software program (miroVIDEO DC30/plus, Pinnacle Systems, Braunschweig, Germany).[19] Arterial flow velocity was obtained by pulsed Doppler (signal at 70° with the range gate, 1.5 mm in the center of the artery).

BP values were determined by an automatic digital device (Omron HEM-705CP) as the mean of three measurements obtained at 3-min intervals.

FMD was induced by reactive hyperemia (RH) obtained by inflating a cuff around the right forearm for 5 min at 250 mm Hg.[20] Sympathetic activation by cold pressor testing was performed by immersing the patient's left hand in iced water for 2 min.[21]

Endothelium-independent dilation was then obtained by administration of sublingual glyceril trinitrate (GTN, 25 μg).[7] This sequence was chosen since sympathetic activation negatively influences FMD but not the GTN response[22,23] and because of the long period required to recover baseline brachial artery diameter after GTN administration.

Data analysis. FMD, response to CPT and GTN were calculated as the maximal percent increase over baseline diameter (mean of measures obtained during 1 min before the stimuli) on acquired frames by a computerized edge detection system.[19]
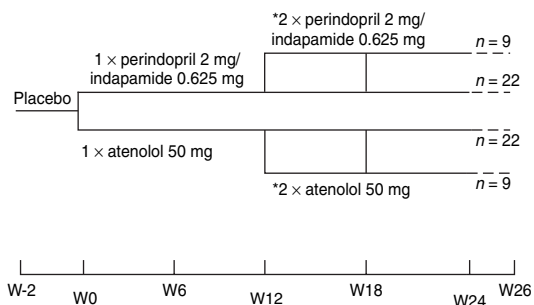

Figure 1 | Study design. Vascular study was performed at baseline (W0), after 12 (W12) and 24 weeks (W24) of treatment. Dose adjustments were allowed starting from W12 if systolic and/or diastolic blood pressure were above 140 and 90 mm Hg, respectively.

Blood flow volume was calculated at baseline and within 15 s after cuff release by multiplying heart rate, vessel cross-sectional area ($\pi \cdot r^2$) and Doppler flow velocity (corrected for the angle). RH was the percent increase in flow after cuff release.

Descriptive data are expressed as mean ± standard deviation. Sample size was calculated to have 80% power to detect a significant ($P < 0.05$) difference of 1.5% in FMD after treatment as compared to baseline. Within-group treatment effects were evaluated by parametric and nonparametric tests as appropriate (SAS version 8.2. statistical package). Moreover, comparison of the regression slope changes in FMD between the two treatment groups was tested by analysis of covariance for repeated measures, with adjustment for FMD and RH baseline values.

RESULTS

At baseline, clinical characteristics were similar in the two groups (**Table 1**). Brachial artery diameter and RH did not differ between the perindopril/indapamide and atenolol groups (**Table 2**). Baseline FMD, response and GTN and CPT were also similar (**Figures 2** and **3**, **Table 3**).

A significant ($P < 0.01$) reduction in systolic and diastolic BP in both groups (**Table 2**) was observed. By the end of the study, reductions in systolic ($P < 0.001$) and diastolic BP ($P < 0.01$) as well as in pulse pressure ($P < 0.001$) were greater in the perindopril/indapamide as compared to the atenolol group (**Table 2**). The percentage of patients whose BP was normalized (values <140/90 mm Hg) was similar in the perindopril/indapamide and atenolol groups at W12 (68 vs. 74%, $P = 0.58$), while at the end of the study it was greater in the perindopril/indapamide as compared to the atenolol group (84 vs. 58%, $P < 0.05$). The percentage of patients requiring dose adjustment during the study was the same in both groups (all 29%). Heart rate was significantly reduced ($P < 0.001$) only in the atenolol group (**Table 2**). Both treatments were well tolerated without unexpected adverse events. Treatment-related adverse events were cough in two patients of the perindopril/indapamide group and hypokalemia (<3.5 mEq/l) in six patients of the perindopril/indapamide group and in three patients of the atenolol group. Plasma potassium decreased by 0.42 ± 0.36 mEq/l in the perindopril/indapamide group and

Table 1 | Baseline clinical characteristics of essential hypertensive patients randomized to perindopril 2 mg/indapamide 0.625 mg (PER/IND) and atenolol 50 mg (ATE)

	PER/IND ($n = 31$)	ATE ($n = 31$)	*P* value
Gender (male %)	81	84	0.74
Smokers (%)	58	55	0.80
Age (years)	48.1 ± 10.7	49.1 ± 9.0	0.69
Body mass index (kg/m^2)	26.5 ± 2.1	26.4 ± 2.4	0.87
Systolic BP (mm Hg)	160 ± 5	160 ± 6	0.95
Diastolic BP (mm Hg)	100 ± 3	101 ± 4	0.09
Total cholesterol (mg/dl)	214 ± 37	210 ± 30	0.61
HDL cholesterol (mg/dl)	57 ± 12	54 ± 13	0.34
LDL cholesterol (mg/dl)	128 ± 32	127 ± 28	0.91
Triglycerides (mg/dl)	140 ± 77	138 ± 71	0.92
Plasma glucose (mg/dl)	93 ± 13	90 ± 10	0.29
Plasma potassium (mEq/l)	4.1 ± 0.4	3.9 ± 0.3	0.19
eGFR (ml/min)	110 ± 19	116 ± 22	0.26

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate (Cockroft–Gault formula).
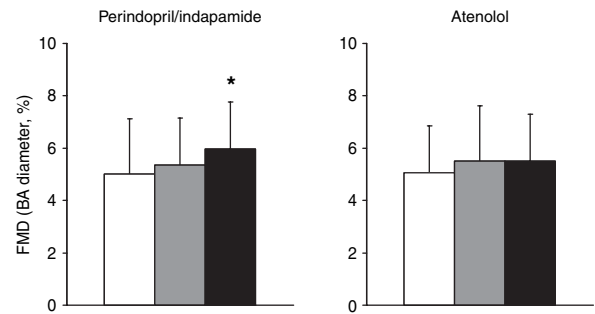

Figure 2 | Bars shows flow-mediated dilation (FMD) at baseline (white bars), after 12 (gray bars), and 24 weeks (black bars) of treatment with perindopril/indapamide or atenolol. Results are shown as brachial artery (BA) percentage increase in diameter compared to baseline. *$P < 0.01$ vs. baseline.

Figure 3 | Bars shows response to glyceril trinitrate (GTN) at baseline (white bars), after 12 (gray bars) and 24 weeks (black bars) of treatment with perindopril/indapamide or atenolol. Results are shown as brachial artery (BA) percentage increase in diameter compared to baseline. *$P < 0.05$ vs. baseline.
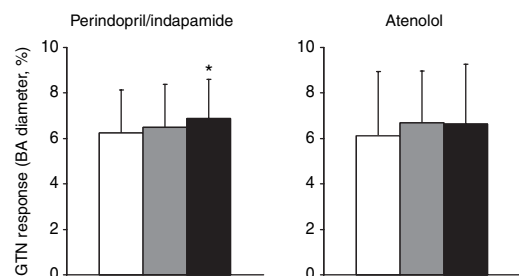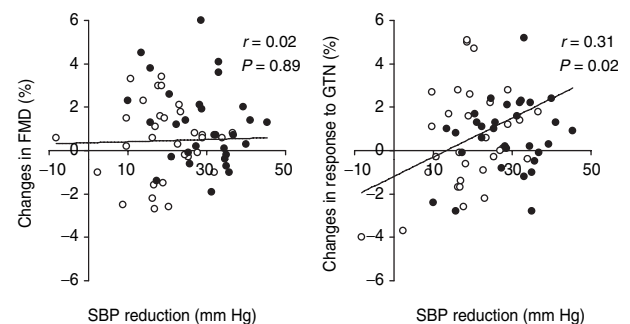

Figure 4 | Graph shows the relationship between absolute changes in flow-mediated dilation (FMD, left) or response to glyceril trinitrate (GTN, right) and reduction in systolic blood pressure (SBP) from baseline after 12 and 24 weeks of treatment with perindopril/indapamide (dots) and atenolol (empty circles).

by 0.06 ± 0.33 mEq/l in the atenolol group. Plasma glucose and lipid profile were not significantly changed by either treatment (data not shown).

FMD significantly ($P < 0.01$) increased at W24 in the perindopril/indapamide, but not in the atenolol group (**Figure 2**). The mean relative increase in FMD was greater in the perindopril/indapamide as compared to the atenolol group (33.4 vs. 16.7%, $P = 0.37$). Comparison of the slope changes in FMD with adjustment for baseline FMD and RH shows a difference between the two groups approaching statistical significance ($P = 0.057$).

Among patients with BP normalized at W24, FMD was significantly increased within patients treated with perindopril/indapamide (from 5.1 ± 2.1 to $6.0 \pm 1.7\%$, $+0.9\%$, $P < 0.05$) but not in the atenolol group ($n = 18$, from 5.2 ± 1.8 to $5.6 \pm 1.9\%$, $+0.4\%$, $P = 0.25$). In patients with BP not normalized, the differences were similar, but not statistically significant, in both perindopril–indapamide ($n = 5$, from 4.9 ± 1.8 to $6.0 \pm 2.0\%$, $+1.1\%$, $P = 0.44$) and atenolol group (from 4.9 ± 2.0 to $5.4 \pm 1.8\%$, $+0.6\%$, $P = 0.39$).

No significant correlation was observed between FMD changes (from baseline to the end of the study) and changes in systolic BP, both in the perindopril/indapamide group ($r = 0.03$; $P = 0.88$) and in the atenolol group ($r = -0.02$; $P = 0.54$) (**Figure 4**).

During the study, BA diameter remained unchanged in both groups. RH was significantly reduced at W24 in the

perindopril/indapamide group, while it was unchanged after atenolol (**Table 2**).

No significant difference was observed in response to GTN at W12 as compared to baseline. Response to GTN was significantly ($P < 0.05$) increased at W24 as compared to baseline in the perindopril/indapamide but not the atenolol group (**Figure 3**). FMD/response to GTN ratio after perindopril/indapamide was not statistically significant at W24 ($P = 0.51$). Changes in response to GTN from baseline to the end of the study were significantly and inversely related to change in systolic BP ($r = -0.31$; $P < 0.05$) (**Figure 4**).

Table 2 | Blood pressure, brachial artery (BA) diameter, basal and maximal blood flow and reactive hyperemia of essential hypertensive patients at baseline, after 12 (W12) and 24 (W24) weeks of randomized treatment with perindopril 2 mg/indapamide 0.625 mg and atenolol 50 mg

Perindopril/indapamide	Baseline	W12	P value vs. baseline	P value vs. atenolol	W24	P value vs. baseline	P value vs. atenolol
Systolic blood pressure (mm Hg)	160 ± 6	139 ± 13	<0.001	0.72	131 ± 9	<0.001	<0.001
Diastolic blood pressure (mm Hg)	100 ± 4	87 ± 9	<0.001	0.45	84 ± 5	< 0.001	< 0.01
Pulse pressure (mm Hg)	59 ± 6	52 ± 10	< 0.001	0.74	47 ± 6	< 0.001	< 0.01
Heart rate (beats/min)	74 ± 11	69 ± 7	0.013	<0.001	73 ± 12	0.39	<0.01
BA diameter (mm)	4.91 ± 0.59	4.87 ± 0.61	0.47	0.98	4.90 ± 0.61	0.86	0.96
Basal flow (ml/100 ml/min)	1.9 ± 1.2	1.8 ± 1.0	0.87	0.85	2.0 ± 0.8	0.28	0.28
Maximal flow (ml/100 ml/min)	7.8 ± 2.4	7.5 ± 2.3	0.25	0.31	7.5 ± 2.0	0.44	0.92
Reactive hyperemia (%)	410 ± 204	418 ± 272	0.92	0.57	315 ± 134	<0.05	0.062
Atenolol	**Baseline**	**W12**	P value vs. baseline		**W24**	P value vs. baseline	
Systolic blood pressure (mm Hg)	159 ± 6	139 ± 10	<0.001		140 ± 10	<0.001	
Diastolic blood pressure (mm Hg)	101 ± 4.0	88 ± 7	<0.001		88 ± 6	<0.001	
Pulse pressure (mm Hg)	59 ± 6	51 ± 5	<0.001		51 ± 8	<0.001	
Heart rate (beats/min)	73 ± 6	63 ± 8	<0.001		64 ± 9	<0.001	
BA diameter (mm)	5.26 ± 0.91	5.23 ± 0.88	0.43		5.25 ± 0.84	0.59	
Basal flow (ml/100 ml/min)	2.0 ± 1.2	1.9 ± 1.1	0.52		1.9 ± 1.2	0.62	
Maximal flow (ml/100 ml/min)	8.8 ± 3.3	7.9 ± 3.1	0.059		8.6 ± 3.2	0.61	
Reactive hyperemia (%)	408 ± 196	388 ± 213	0.50		427 ± 198	0.47	

Response to CPT was significantly ($P < 0.01$) increased by perindopril/indapamide both at W12 and W24 as compared to baseline (**Table 3**), while atenolol significantly ($P < 0.05$) improved response to CPT only at W24. Blood flow was similarly reduced by CPT in both treatments during the study (**Table 3**). At W24, as compared to baseline, CPT induced a significantly greater increase of BP after perindopril/indapamide and atenolol group treatment (**Table 3**).

DISCUSSION

This prospective, randomized, double-blind study demonstrated that 24 week-treatment with the fixed dose of perindopril/indapamide improved vascular function in the peripheral macrocirculation of essential hypertensive patients, an effect which was not exerted by atenolol.

Baseline endothelium dependent FMD, response to CPT and endothelium independent response to GTN were similar in patients randomized to treatment with perindopril/indapamide or atenolol.

FMD was not significantly changed after 12 weeks in either group. Conversely, FMD was significantly increased in the perindopril/indapamide group, but not in the group receiving atenolol after 24 weeks of treatment. Moreover, the mean relative increase in FMD was greater in the perindopril/indapamide than in the atenolol group and a difference, albeit not statistical significant, in favor of perindopril/indapamide was observed when comparing the slopes changes in FMD during treatment in the perindopril/indapamide group, as compared to the atenolol group.

Overall, these results suggest that perindopril/indapamide, but not atenolol, treatment improved endothelium-dependent FMD in the brachial artery of essential hypertensive patients.

It is known that the β-blocker atenolol is not effective in modulating endothelial response in the peripheral circulation.[15,17,24]

Table 3 | Changes in blood pressure, diameter and blood flow induced by cold pressor test in essential hypertensive patients at baseline and after 12 (W12) and 24 (W24) weeks of randomized treatment with perindopril 2 mg/indapamide 0.625 mg and atenolol 50 mg

Perindopril/indapamide	Baseline	W12	P value vs. baseline	P value vs. atenolol	W24	P value vs. baseline	P value vs. atenolol
Systolic blood pressure (mm Hg)	15.4 ± 12.4	17.9 ± 12.3	0.30	0.94	21.8 ± 15.2	0.056	0.81
Diastolic blood pressure (mm Hg)	11.4 ± 11.0	11.4 ± 15.6	1.0	0.67	16.2 ± 13.2	0.071	0.11
Mean blood pressure (mm Hg)	12.7 ± 8.9	13.5 ± 12.6	0.67	0.77	18.1 ± 11.6	<0.05	0.38
Pulse Pressure (mm Hg)	4.0 ± 15.4	6.5 ± 15.7	0.27	0.51	5.6 ± 16.1	0.62	0.09
Diameter changes (%)	1.4 ± 0.9	2.0 ± 0.9	<0.001	0.15	1.9 ± 0.8	<0.001	0.75
Flow changes (%)	−27.7 ± 31.3	−25.1 ± 30.3	0.93	0.38	−32.2 ± 24.8	0.23	0.97
Atenolol	Baseline	W12	P value vs. baseline		W24	P value vs. baseline	
Systolic blood pressure (mm Hg)	17.4 ± 12.5	18.5 ± 14.0	0.69		23.9 ± 15.8	<0.01	
Diastolic blood pressure (mm Hg)	9.3 ± 10.7	11.9 ± 12.4	0.40		11.1 ± 9.3	0.47	
Mean blood pressure (mm Hg)	12.0 ± 9.7	14.1 ± 10.7	0.42		15.4 ± 10.7	0.13	
Pulse Pressure (mm Hg)	8.1 ± 12.6	6.5 ± 14.3	0.60		12.8 ± 11.1	<0.05	
Diameter changes (%)	1.5 ± 1.2	1.7 ± 1.3	0.10		1.8 ± 0.8	<0.05	
Flow changes (%)	−23.6 ± 29.7	−23.0 ± 25.8	0.98		−30.2 ± 23.0	0.30	

Conversely, ACE-inhibitors have been demonstrated to be effective in improving endothelial function in the coronary[16] and peripheral macrocirculation[8,15,17] of essential hypertensive patients. However, the present study is the first demonstration that long term treatment with a fixed-dose combination of an ACE-inhibitor and a diuretic can improve endothelial function. This observation is of interest, since a greater fall in plasma potassium was observed in the perindopril/indapamide group as compared to the atenolol group, a finding which may have limited the beneficial effect of perindopril/indapamide on endothelial function.[25] Moreover, it is relevant to observe that the improvement in FMD was obtained even though RH, the stimulus for FMD, was significantly reduced. This finding could be related to the increase as compared to baseline, albeit non-significant, in brachial artery resting flow after treatment with perindopril/indapamide as compared to atenolol, while maximal flow after ischemia changed similarly. This effect of perindopril/indapamide on basal flow could be related to a specific effect on microcirculation, as observed in animal models.[26]

However, it is conceivable that these results could be explained by the greater effectiveness of perindopril/indapamide in reducing BP values as compared to atenolol. Thus, after 24 weeks both treatments had significantly reduced systolic and diastolic BP, but by the end of the study the reductions in systolic and diastolic BP, as well as in pulse pressure, were greater in the perindopril/indapamide group than in the group treated by atenolol. Moreover, the percentage of patients reaching BP control (<140/90 mm Hg) was greater in the perindopril/indapamide than the atenolol group. This hypothesis is in contrast with the evidence that endothelial function is not related to BP values[27] and that BP reduction *per se* is not sufficient to modify endothelial response in hypertensive patients.[15] Recently, Joannides *et al.* assessed the effect of acute administration of a fixed combination of perindopril-indapamide at two doses (2 mg/0.625 mg and 4 mg/1.25 mg) in placebo-controlled double-blind, randomized, crossover study in 13 hypertensive patients.[28] Compared with placebo, FMD was improved by both dosages of perindopril/indapamide doses, although only the higher dosage significantly decreased mean arterial pressure.[28] In the present study no significant relationship between fall in mean BP and FMD improvement after perindopril/indapamide, suggesting a possible effect independent of BP reduction. Moreover, FMD was increased by perindopril/indapamide in the subgroup of patients with BP normalized or not normalized. Thus, the effect of perindopril/indapamide could be mediated by an improvement in endothelium dependent vasodilation and possibly NO availability, as shown for treatment with ACE-inhibitors alone.[8,17]

Interestingly, a parallel significant improvement in endothelium-independent response to GTN was observed at the end of the study as compared to baseline in the perindopril/indapamide group, but not in the group treated with atenolol. These findings suggest that perindopril/indapamide can effectively improve large artery vascular responsiveness, possibly by increasing the sensitivity of vascular smooth muscle cells to exogenous NO, an effect that could contribute, in addition to the regression of endothelial dysfunction, to reduce arterial stiffness and peripheral wave reflection, however not measured in our patients, as reported the REASON study.[18]

It has to be pointed out that the improvement in response in GTN could explain the increase in FMD observed after perindopril/indapamide. Indeed, at 24 weeks improvement in FMD after perindopril/indapamide, adjusted for response to GTN, was not significantly different from baseline. However, different mechanisms seems to be involved, since no significant relationship between fall in BP and FMD improvement was observed, while changes in response to GTN were significantly related to reduction in systolic and diastolic BP. Furthermore, it can be also speculated that improvement in endothelial function may have influenced the GTN response by affecting vascular smooth muscle cells responsiveness or wall structure.[29] In addition, this beneficial effect of the treatment on GTN dilatation could be due to the lower inactivation of exogenous NO by reactive oxygen species after endothelial function improvement inasmuch the doses of GTN used are low and may not saturate vascular smooth muscle cells as standard doses. Differences in FMD and GTN response after treatment are not influenced by dosage adjustment since this was similar, and one third of patients required dosage adjustment in both groups. Furthermore, plasma glucose and lipid profile were not significantly changed by either treatment.

Systemic sympathetic activation to CPT stimulates endothelial response both by increasing cardiac output, and directly by stimulating β2-receptors on the endothelium. This response has been shown to be altered in the coronary circulation of patients with coronary artery disease[30,31] and hypertensive patients.[4,11] In the peripheral circulation, Corretti et al.[21] showed a very small mean increase in brachial artery diameter at 1 min after CPT in control subjects, and a significant decrease in patients with coronary artery disease. In borderline hypertensive patients, CPT was associated 4% increase in diameter with a parallel decrease in brachial artery distensibility.[32] Accordingly, we observed a modest increase in diameter after CPT at baseline. Discrepancy with previous results,[21] might be related with the population studied and with the more sensitive methods to measure diameter changes.[19,32] Response to CPT was significantly improved as compared to baseline by perindopril/indapamide both at 12 weeks and 24 weeks of treatment. On the other hand, atenolol significantly improved response to CPT only at the end of the study. In both treatment arms, brachial artery blow flow decreased similarly, while higher increase in BP during CPT from lower values at baseline was observed at the end of the study, according to previous results.[33] Thus, changes in CPT response could be secondary to pressure induced passive distension. The positive effect of atenolol could be also related to the selective β1-blockade which results in specific stimulation of β2-receptors on the endothelium. However, the increase in response to CPT after perindopril/indapamide might be specifically related to the improvement in endothelial response to the mixed stimulus, since it was also observed after W12, when BP increase was not present.

Some limitations have to be outlined. Overall, as already stated, we cannot exclude that the improvement in vascular responsiveness to NO, can explain at least in part, the observed improvement in endothelium-dependent vasodilation.

Moreover, it should be noticed that the relevance of the results of this study is limited to patients with essential hypertension without cardiovascular disease. Finally, the study was powered to investigate significant differences after treatment as compared to baseline within each treatment arm. Therefore, it is underpowered to detect differences between the two treatment groups and subgroup analysis (e.g., patients with or without BP normalization or receiving double dosages) have limited relevance.

In conclusion, treatment with fixed-dose combination of perindopril/indapamide was associated with an improvement in endothelium-dependent vasodilation in the brachial artery of essential hypertensive patients in a randomized, double blind, prospective study. This beneficial effect was not exerted by atenolol and appeared to be independent of BP reduction. An improvement in endothelium-independent response was also observed, an effect which, however, was related to the degree of BP reduction. Both perindopril/indapamide and atenolol improved sympathetic-mediated vasodilation, after different treatment times and possibly by different mechanisms. Therefore, it is tempting to speculate that improved vascular function by perindopril/indapamide might represent one of the likely mechanisms responsible for the reduction in macrovascular and microvascular events recently observed in high-risk patients.[34]

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