Resistant Arterial Hypertension and Hyperlipidemia: Atorvastatin, not Vitamin C, for Blood Pressure Control

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Abstract

Background: Hypertension is considered resistant if blood pressure cannot be reduced to < 140/90 mmHg with an appropriate triple-drug regimen, including an oral diuretic, with all agents administered at maximal dosages. This definition has evolved with the development of new therapies and evidence-based data supporting treatment to lower BP goals.

Objective: To assess whether vitamin C and atorvastatin improve endothelial function and blood pressure control in subjects with resistant arterial hypertension and dyslipidemia.

Methods: Forty-eight hyperlipidemic subjects with RH (office systolic BP > 140 mmHg and/or office diastolic BP > 90 mmHg notwithstanding antihypertensive treatment with three medications in maximal doses) were randomized into three groups to receive additional medication for 8 weeks. Group VTC (n = 17) – mean 24 hour SBP 150.6 ± 5.2 mmHg, DBP 86.1 ± 3.3 mmHg, low density lipoprotein 158.1 ± 24.5 mg/dl – received vitamin C 500 mg per day; Group ATR (n = 15) – mean 24 hour SBP 153.1 ± 4.8 mmHg, DBP 87.1 ± 6.7 mmHg, LDL 162.6 ± 13.6 mg/dl – received atorvastatin 20 mg/day; and Group PLA (n = 16) – mean 24 hour SBP 151.1 ± 7.4 mmHg, DBP 84.8 ± 5.9 mmHg, LDL 156.7 ± 26.1 mg/dl – received a placebo. High resolution ultrasound was used to calculate brachial artery flow-mediated dilation, and 24 hour ambulatory BP monitoring was performed at study entry and after 8 weeks.

Results: In the ATR group there were significant reductions of SBP (ΔSBP1-2: 13.7 ± 5.6 mmHg, *P* 0.001), DBP (ΔDBP1-2: 7.8 ± 5.7 mmHg, *P* 0.01), LDL (ΔLDL1-2: 67.7 ± 28.3 mg/dl, *P* < 0.001) and improvement of brachial artery FMD (ΔFMD2-1: 4.2 ± 2.6%). No significant changes in BP, LDL and FMD were observed in the other two groups.

Conclusions: In subjects with RH and dyslipidemia, atorvastatin 20 mg/day compared to vitamin C 500 mg/day may help to achieve better BP control and improve endothelial function in a finite period. A larger trial is needed to assess the drug's efficacy in this population for longer periods.

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Refractory or resistant hypertension is conventionally defined as systolic or diastolic blood pressure that remains uncontrolled (above 140/90 mmHg) despite sustained therapy with at least three different classes of antihypertensive agents. Although RH is estimated to affect less than 5% of the general population with hypertension, its prevalence increases with increasing severity of blood pressure [1]. Other common contributing factors to RH include obesity, non-adherence to medication, suboptimal medical regimens, excessive dietary salt ingestion, secondary forms of hypertension, sleep apnea, and ingestion of substances that interfere with treatment. Combination therapy that includes appropriate doses of a diuretic is recommended [2]; however, a significant percentage of these subjects remain with uncontrolled hypertension despite non-pharmacologic and pharmacologic interventions [3,4]. Several short-term studies have shown that statins can improve endothelial function and the endothelium-dependent arterial vasodilation that is typically altered in persons with increased plasma cholesterol levels [5]. Dyslipidemia, endothelial dysfunction, and hypertension are frequently coexisting conditions, even in the absence of documented atherosclerotic lesions [6]. In several animal and human studies, statins decreased resting or stress-induced blood pressure [7].

A randomized double-blind placebo-controlled study has shown that treatment of hypertensive patients with ascorbic acid lowers blood pressure [8], raising interest in the mechanism of this effect. The mechanism has been attributed to an antioxidant function of the vitamin C that enhances the synthesis or prevents the breakdown of nitric oxide and reverses endothelial dysfunction through regulation of eNOS and NAD(P)H oxidase activities [9]. Epidemiologic studies [10] have demonstrated that the dietary intake and plasma concentrations of ascorbic acid correlate inversely with hypertension and its clinical sequelae – namely, stroke and cardiovascular disease, and a diet containing antioxidant-rich foods can substantially lower blood pressure [11]. In randomized trials, treatment with ascorbic acid 500 mg/day for 4 weeks lowered systolic and mean blood pressure in patients with "controlled" hypertension, apparently as a result of dilatation of resistance vessels [12].

Whether HMG-CoA reductase inhibitor or ascorbic acid supplementation to the antihypertensive treatment can transform the unique subgroup of hypertensive patients – i.e., with resistant arterial hypertension – to "controlled" hypertension has yet to be clarified. The aim of the present study was to assess the effect of

BP = blood pressure
RH = resistant arterial hypertension
SBP = systolic BP
DBP = diastolic BP
LDL = low density lipoprotein
FMD = flow-mediated dilation

atorvastatin 20 mg/day or ascorbic acid 500 mg/day in decreasing blood pressure and/or endothelial function in persons with primary dyslipidemia and resistant essential hypertension.

Patients and Methods

The study was a randomized, open, placebo-controlled trial, conducted at the WHO Collaborative Center for Prevention of Cardiovascular Disease, Barzilai Hospital, Israel. The local ethics committee approved the protocol and the participants gave written informed consent according to Helsinki Guidelines. Inclusion criteria to participate in the study were: a) essential hypertension treated with three blood-lowering medications (one of them a diuretic) in maximal doses for at least 6 months, systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg measured by 24 hour ambulatory blood pressure monitoring; and b) hypercholesterolemia not treated with any lipid-lowering drug before study entry, with a fasting total plasma low density lipoprotein level >130 mg/dl. Exclusion criteria were: a) diabetes mellitus treated with medications, although diabetic patients treated with diet only were allowed to participate in the study; b) fasting hyperglycemia >150 mg/dl; c) liver or kidney disease; d) cancer; e) acute myocardial infarction, or unstable angina within 6 months; f) heart failure; g) smoking >10 cigarettes per day; h) use of corticosteroids or other immunosuppressive therapy; i) abnormal levels of plasma aldosterone, supine and standing plasma renin activity, and 24 hour urinary catecholamines; and j) anomalies in the renal ultrasound scan or in renal arterial duplex, which was performed to exclude renal artery stenosis.

The patients were assigned to a daily diet containing 120 mmol of sodium and 2,200 kcal, 30% of which came from fatty acids (10% saturated fatty acids). They were instructed to maintain the same diet throughout the study. Routine blood examination tests and a physical examination were performed to exclude other co-morbid conditions.

Study protocol

At the end of the run-in phase of 4 weeks the participants who met the inclusion/exclusion criteria were randomized in a single blind manner to receive, in addition to the antihypertensive medications, 20 mg atorvastatin, 500 mg ascorbic acid, or placebo, given between 9 and 10 p.m. every day for 8 weeks. Follow-up clinic visits were scheduled every 4 weeks to monitor blood pressure and biochemical levels. Fasting blood samples were drawn between 8 and 10 a.m. Plasma total and high density lipoprotein-cholesterol and triglycerides, serum glucose, creatinine, sodium, potassium, uric acid and creatine phosphokinase were measured every 4 weeks.

- *Blood pressure measurements.* BP was measured at study entry and after 8 weeks in the dominant arm by the automatic 24 hour ambulatory BP measuring device Profilomat (Dinamap, USA). The 24 hour average BP value was evaluated from a total of 66 measured values.
- *Endothelium-dependent and independent vasodilations of brachial artery.* Endothelium-dependent (flow-mediated) and independent (nitroglycerin-induced) vasodilatations in the brachial artery were measured by the same examiner. The measurements were performed according to the guidelines [13]. The arterial diameter was measured using an ultrasonic phase-locked echo-tracking system that was equipped with a high resolution, real-time 7.5 MHz linear scanner in B-mode (SSD 610, Aloka, Tokyo), to obtain longitudinal images of the brachial artery at a marked point 5–10 cm proximal to the antecubital fossa on the dominant arm. Patients underwent imaging in a supine position after at least 15 minutes of equilibration in a climate-controlled environment. All the subjects were fasted for at least 8 hours before the study. They were also instructed to abstain from cigarette smoking before the study. Two-dimensional images were obtained at baseline with Doppler ultrasound scanning to assess arterial diameter and flow velocity. Angle correction software was used during Doppler imaging to approximate a 20 degree angle of incidence to blood flow. Color-flow Doppler imaging was also used to localize arterial flow before measuring Doppler velocities and to confirm the cessation and resumption of flow with cuff occlusion and reactive hyperemia, respectively. Images were acquired with electrocardiogram gating, with measurements made at end-diastole. Increased shear stress was achieved by producing reactive hyperemia. After inflating a blood pressure cuff to 200 or 50 mmHg above systolic pressure for 5 minutes, arterial diameter and flow velocity measurements were taken 60 seconds after cuff deflation. This conduit vessel flow-mediated dilation with this cuff position has been shown to be nitric oxide-dependent [14]. Arterial diameter was measured from the near to far wall at the intima-media interface or to the clearest echocardiography line. The mean values of three to five measurements were averaged for each datum point, and results were expressed as the change in arterial diameter divided by baseline diameter. After FMD was assessed, sublingual nitroglycerin (0.4 mg) was administered and imaging was repeated to document flow-independent vasodilatation. [13].
- After 8 weeks of treatment with 20 mg atorvastatin daily, 500 mg ascorbic acid daily, or placebo, patients returned for reassessment of endothelium-dependent and independent vasodilation. Healthy controls attended on one occasion and underwent the same vascular function protocol [Table 1].

Data analysis

Results are presented as mean $\pm$ SD. Paired Students *t*-test was used to compare differences between means as appropriate. Two-way ANOVA with repeated measures was used to compare the effects of atorvastatin, ascorbic acid and placebo treatment on brachial artery FMD. A value of $P < 0.05$ was considered significant. The statistical analysis was performed using the software SPSS 9 for Windows (Chicago, USA).

Results

Patients

Fifty-two patients who met the inclusion criteria were enrolled in the study. Five of them were withdrawn during the study for several reasons: three patients refused nitroglycerin-mediated dilation testing, and two had fasting blood glucose level >150 mg/dl in

Table 1. Baseline characteristics of treatment groups at week 4 (at randomization)

Groups	Vitamin C (n=17)	Atorvastatin (n=15)	Placebo (n=16)	Control (n=14)
Male/Female	10/7	8/7	7/9	7/7
Age (yrs)	52.6 ± 12.3	54.1 ± 13.5	51.4 ± 12.8	54.4 ± 15.2
Body mass index (kg/m^2)	28.2 ± 2.2	27.9 ±1.8	27.7 ± 2.1	27.6 ± 2.3
History of smoking (n)	7	8	7	6
24 hour ABPM SBP (mmHg)	150.6 ± 5.4	153.1 ± 4.8	151.1 ± 7.4	129.3 ± 5.8
24 hour ABPM DBP (mmHg)	86.1 ± 3.3	87.1 ± 6.7	86.7 ± 5.9	76.8 ± 5.2
Heart rate (beats/min)	74 ± 11	75 ± 9	74 ± 12	77 ± 14
Glucose (mg/dl)	121.6 ± 18.4	127.3 ± 15.8	127.3 ± 15.8	121.1 ± 14.2
LDL (mg/dl)	157.1 ±24.5	162.6 ±13.3	158.4 ± 26.1	129.2 ± 41.7
Brachial artery FMD (%)	8.7 ± 6.4	8.5 ± 5.6	8.9 ± 6.1	11.8 ± 5.6
Resting arterial diameter (mm)	4.2 ± 0.9	4.1 ± 0.8	4.0 ± 0.7	4.1 ± 0.8
Reactive hyperemic blood flow (%Δ)	538 ± 287	494 ± 254	512 ± 262	748 ± 457
Brachial artery NTG-mediated dilatation (%)	14.4 ± 8.3	15.1 ± 8.7	14.9 ± 7.5	16.2 ± 7.9

Values are means ± SD.
ABPM = ambulatory blood pressure monitoring, NTG = nitroglycerin.

Table 2. Antihypertensive medications in treatment groups at randomization

Groups	Vitamin C	Atorvastatin	Placebo	Control
Beta-blockers	12 (17)	11 (15)	11 (16)	10 (14)
Atenolol	8	7	8	9
Bisoprolol	2	1	2	1
Propranolol	1	2	1	
Metoprolol	1	1	1	
Calcium channel blockers	7 (17)	8 (15)	7 (16)	5 (14)
Nifedipine SL	3	4	2	2
Amlodipine	1	2	1	
Lercanidipine	2	2	3	2
Penedil	1		1	1
Diuretics	17 (17)	15 (15)	16 (16)	14 (14)
Hydrochlorothiazide	17	15	16	14
ACE inhibitors	15 (17)	14 (15)	16 (16)	14 (14)
Captopril	3	2	4	3
Enalapril	4	5	4	2
Fosinopril				1
Cilazapril	4	5	5	4
Ramipril	4	2	3	4
AT-1 blockers	2 (17)	1 (15)	0	0
Candesartan	1			
Losartan	1			
Valsartan				
α-1 blockers	4 (17)	6 (15)	4 (16)	5 (14)
Doxazosin	4	6	4	5
Central α-agonists	2 (17)	2 (15)	1 (16)	1 (14)
Clonidine	2	2	1	1

Numbers in parentheses represent the number of patients treated with this medication (total number of patients in the group).

later blood testing. All five withdrawn patients did not return to follow-up and therefore were not included in the data analysis.

Clinical and hemodynamic data from the cross-sectional aspect of the study are shown in Table 1. The ascorbic acid (VTC) (n = 17), atorvastatin (ATR) (n = 15) and placebo (PLA) (n = 16) groups were similar with respect to their baseline clinical characteristics [Table 1]. Systolic and diastolic blood pressure, heart rate and other clinical and biochemical characteristics were matched in the study groups [Table 1]. Brachial artery flow-mediated vasodilation was impaired in the patients with hypertension in all study groups, as compared to otherwise healthy, normotensive controls (VTC 8.7 ± 6.4; ATR 8.5 ± 5.6; PLA 8.9 ± 6.1 and 11.8 ± 5.6 respectively; $P < 0.05$), although nitroglycerin-mediated dilation was similar. The ischemia-induced reactive hyperemic stimulus for flow-mediated dilation tended to be less in the patients with hypertension [Table 1; $P < 0.05$).

Blood pressure

The baseline SBP and DBP were 150.6 ± 5.4, 153.1 ± 4.8 and 151.1 ± 7.4 mmHg, respectively [Table 1]. After 8 weeks, when compared with ascorbic acid and placebo, atorvasatatin significantly decreased SBP and DBP (Δ SBP 13.7 ± 5.6 mmHg, P 0.001; Δ DBP 7.8 ± 5.7 mmHg, P 0.01) [Table 2]. Low density lipoprotein-cholesterol levels were significantly decreased in the ATR group compared with the VTC and PLA groups (Δ LDL 67.7 ± 28.3 mg/dl, $P < 0.001$) and the BP reduction within the group showed a weak positive correlation with changes in LDL-cholesterol levels ($r = 0.42$, $P < 0.05$ for SBP; and $r = 0.46$, $P < 0.01$ for DBP). In the VTC and PLA groups there were no significant changes in BP and LDL [Table 2].

Brachial artery responses

As shown in Table 3, ascorbic acid and placebo treatment had no effect on brachial artery FMD ($P = 0.34$, by two-way repeated-measures ANOVA) or nitroglycerin-mediated dilation ($P = 0.48$). Similarly, ascorbic acid had no effect on baseline brachial artery diameter or hyperemic flow after cuff release (not shown). FMD in the ATR group was 8.5 ± 5.6% (SD) at baseline, and 11.3 ± 5.1% ($P < 0.001$) after 8 weeks.

Table 3. Effect of treatment on brachial artery, hemodynamic and biochemical parameters

	Vitamin C		Atorvastatin		Placebo	
	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks
24 hr ABPM						
SBP	150.6 ± 5.4	150.6 ± 5.4	153.1 ± 4.8	136.9 ± 6.1*	151.1 ± 7.4	150.9 ± 6.8
DBP	86.1 ± 3.3	87.4 ± 5.3	87.1 ± 6.7	78.3 ± 4.2*	84.7 ± 5.9	83.2 ± 5.7
LDL	151.1 ± 24.5	153.6 ± 26.8	162.6 ± 13.3	95.9 ± 17.5*	148.4 ± 26.1	155.2 ± 24.8
ΔFMD (%)	8.9 ± 6.4	8.5 ± 7.9	8.5 ± 5.6	11.3 ± 5.1*	8.3 ± 6.1	8.7 ± 6.6
ΔNTG (%)	14.4 ± 8.3	14.9 ± 8.1	15.1 ± 8.7	15.7 ± 8.4	14.9 ± 7.5	15.4 ± 8.2
Reactive hyperemic blood flow (% Δ)	538 ± 287	562 ± 328	494 ± 254	614 ± 318*	512 ± 262	581 ± 294

Results are presented as mean ± SD

* $P < 0.05$.

FMD = flow-mediated dilatation, NTG = nitroglycerin-induced dilatation

Discussion

Patients presenting with resistant hypertension usually deteriorate from mild or moderate to severe hypertension because of lack of or inadequate treatment. In our selected population with RH and dyslipidemia, the addition of the HMG-CoA reductase inhibitor atorvastatin 20 mg/day to the antihypertensive treatment significantly decreased both SBP and DBP and improved brachial artery FMD over the 8 week treatment period. In contrast, 500 mg/day ascorbic acid supplementation had no such effect in a similar population over the same period.

The hypertensive patients participating in this study had relatively preserved brachial artery FMD (8.9%), compared to patients with other risk factors in another study [13]. Several groups of investigators previously reported blood pressure-lowering effects of statins in hypertensive and hyperlipidemic subjects in whom blood pressure was "controlled" [15].

There are several mechanisms to explain the blood pressure-lowering effects of HMG-CoA reductase inhibitors in hypertensive hypercholestolemic patients. Statins cause vasodilation and a decrease in BP by restoring the endothelial dysfunction that frequently coexists with hypertension and hypercholesterolemia [5]. Their beneficial effects on BP can be mediated in addition to a decrease in LDL-cholesterol but also by the up-regulation of nitric oxide synthase [16], reduction in pro-inflammatory cytokine production and the inhibition of nuclear factor-κB activity [17]. Cross-sectional independent associations between high blood pressure and plasma levels of C-reactive protein, interleukin-6, and tissue necrosis factor alpha have also been reported [18,19].

In this study we show the ability of HMG-CoA reductase inhibitor to cause short-term improvement of BP control in subjects with RH and dyslipidemia. The generalizability of the present findings is limited by the short duration of the trial. Additional studies are needed to assess whether HMG-CoA reductase inhibitors may sufficiently decrease BP in resistant hypertension over a longer period to affect morbidity and mortality, and to assess whether they could be effective in such a population with normal cholesterol levels.

Essential hypertension is associated with higher than normal lipoperoxidation and an imbalance in antioxidant status, suggesting that oxidative stress is important in the pathogenesis of essential hypertension or in arterial damage related to essential hypertension [12,20]. Vitamin C is a dietary antioxidant that inactivates oxygen free radicals, and its supplementation might prove to be an effective adjunct therapy in essential hypertension [12,20]. In these patients impaired endothelial vasodilation can be improved by the antioxidant vitamin C, an effect that can be reversed by the nitric oxide synthase inhibitor N(G)-monomethyl-L-arginine, which supports the hypothesis that nitric oxide inactivation by oxygen free radicals contributes to endothelial dysfunction in essential hypertension [21,22]. However, randomized, double-blind control trials did not show additional benefit for a dose higher than 500 mg daily; moreover, its daily supplementation lowered BP only in mildly hypertensive patients and the effect of vitamin C was not long lasting [21–24].

The present study involved physiologic concentrations of ascorbic acid and demonstrated absolutely no improvement, not even a trend for improvement, in brachial artery FMD. We excluded patients with treated diabetes mellitus or with fasting plasma glucose levels >140 mg/dl, because in a previous study treatment with vitamin C (1.5 g daily) for 3 weeks did not significantly improve oxidative stress, BP or endothelial function in patients with type 2 diabetes [24].

In conclusion, the present trial shows that in subjects with RH and dyslipidemia the BP reduction achieved by short-term treatment with atorvastatin 20 mg/day was significant, while vitamin C 500 mg/day was ineffective for this purpose. We can speculate that an advantage of statins over ascorbic acid in helping to achieve BP control in RH is associated with their ability to suppress a vascular low grade inflammation. Further studies are needed to assess the efficacy of statins as anti-inflammatory drugs in resistant arterial hypertension.

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I've been rich and I've been poor. Believe me, rich is better

Gloria Grahame (1824-81), American actress

★

I don't know anything about music. In my line you don't have to

Elvis Presley

Capsule

Understanding Timothy syndrome

Timothy syndrome is a rare human disorder characterized by diverse physiologic and developmental defects, including heart arrythmias, webbing of fingers and toes, and autism. Splawski et al. have identified a single mutation in a gene that encodes the calcium channel Cav1.2 as being responsible for the syndrome. The mutation occurs in a highly conserved region that is important for voltage-gated channel inactivation resulting in prolonged influx of calcium into cells. Other calcium channel-based disorders affect distinct organ systems. However, the mutated splice variant of Cav1.2 is widely expressed in tissues and organs, consistent with the scope of disease abnormalities. Mutant channels are sensitive to calcium channel blockers, suggesting the potential use of such drugs in treating this genetic disorder, which is often fatal by 2.5 years of age. The study also suggests that aberrant calcium signaling in the brain may contribute to autism, a condition whose molecular mechanism is not well understood.

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