



Emerging insights into hypertension and dyslipidaemia synergies

A.C. Sposito*

Heart Institute (InCor), Zerbini Foundation, Brasilia, Brazil

KEYWORDS

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Hypertension frequently occurs in conjunction with metabolic disturbances, most notably hypercholesterolaemia. If there is an association between hypertension and hypercholesterolaemia, it is important to understand the mechanisms responsible and investigate whether elevated blood pressure (BP) increases the atherogenicity of cholesterol-rich lipoproteins. Evidence from studies suggests that hypercholesterolaemia contributes to the progression of hypertension via a number of possible mechanisms: low nitric oxide bioavailability, enhanced activity of the renin–angiotensin–aldosterone system, enhanced endothelin levels and receptor expression, and endothelial dysfunction. Other possible mechanisms include salt sensitivity (which is worsened by endothelial dysfunction), the secretion of vasoconstrictive molecules and an enrichment of cholesterol in cellular membranes, all of which reduce membrane fluidity and ion channel transporter activity. In response to cholesterol-enriched cellular membranes, the fractional clearance rate of sodium is reduced, which, in turn, favours sodium retention. Enriched cellular membrane cholesterol can also affect the transport of calcium in vascular smooth muscle cells, allowing an influx of calcium into these cells, which in turn increases conductivity and leads to microvessel constriction. Conversely, it is also evident that arterial distension and increased intra-luminal pressure induced by hypertension can increase the accumulation of atherogenic lipoproteins in the arterial wall. To optimize the management of cardiovascular disease, future treatment strategies should be directed at controlling both BP and cholesterol, particularly in high-risk patients.

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Introduction

Hypertension frequently occurs in conjunction with metabolic disturbances and in particular with hypercholesterolaemia, which affects up to 36% of hypertensive subjects.¹ This may explain why reducing blood pressure (BP) is not always effective in the prevention of coronary artery disease (CAD). It is also possible that hypertension

and hypercholesterolaemia may act synergistically to exacerbate the pathogenesis of cardiovascular disease. A combination of hypercholesterolaemia and a genetic susceptibility to hypertension may induce a broad range of abnormalities, including endothelial dysfunction and premature CAD, while hypercholesterolaemia alone may predispose an individual to increased sensitivity of hypertensive stimuli, and may even elicit the clinical manifestation or aggravation of hypertension. If such an association between hypertension and hypercholesterolaemia exists, it is important to understand the mechanism that is responsible and to investigate whether elevated BP can increase the atherogenicity of cholesterol-rich lipoproteins.

* Correspondence: Andrei C. Sposito, Department of Cardiology, Heart Institute (InCor-DF), Zerbini Foundation, Brasilia, Brazil. Tel.: +55 61 403 5404; fax: +51 61 403 5486.

E-mail address: sposito@zerbini.org.br (A.C. Sposito).

In the last few decades, several investigations have demonstrated functional genetic polymorphisms, which are implicated in the elevation of BP. However, only 30% of BP variation could be accounted for by these genotypes. Wide BP variability in monozygotic twins indicates that an additional element is required to trigger its elevation: among the potential triggers are salt intake, physical inactivity, smoking, the western diet and metabolic disorders. Only 20% of hypertensive patients are believed to have isolated hypertension – the remaining 80% are affected by metabolic disorders such as the metabolic syndrome, insulin resistance, thyroid dysfunction, adult-onset growth hormone deficiency and hypercholesterolaemia,² with the latter being the most frequent cause, accounting for 36% of metabolic disorders.¹

Is hypercholesterolaemia a potential trigger for the hypertensive state?

Even prior to the development of elevated BP, the offspring of hypertensive patients exhibit a low bioavailability of the potent vasodilator nitric oxide (NO), enhanced activity of the renin–angiotensin–aldosterone system (RAAS), enhanced endothelin levels and receptor expression, and endothelial dysfunction,^{3,4} all of which are associated with the development and potentiation of hypertension. (Interestingly, a similar observation is made in normotensive patients with primary hypercholesterolaemia.^{5,6}) Furthermore, plasma cholesterol levels are closely correlated to each one of these mechanisms involved in regulating endothelial function and BP. In support of this hypothesis, hypercholesterolaemic individuals manifest an exaggerated elevation of BP during exercise or mental stress,^{7,8} and cholesterol-

lowering treatment with statins prevents the BP hyper-reactivity induced by either mental stress or the infusion of angiotensin II and norepinephrine.^{9,10}

In our group, the effect of acute isocapnic hypoxic stress on the elevation of BP in 14 subjects who were heterozygous for familial hypercholesterolaemia (FH) was measured. Oxygen saturation was reduced from 98% to 80%, which coincided with an elevation of systolic blood pressure (SBP) in both control and FH groups. However, the rise in BP was significantly greater in the FH group compared with control.¹¹ Subsequent treatment of the FH patients with 40 mg simvastatin for 12 weeks caused significant attenuation in the hyper-reactivity of BP.¹¹ This demonstrates that hypercholesterolaemia increases the sensitivity of several hypertensive stimuli, and that cholesterol-lowering treatment appears to prevent the resulting hyper-reactivity.

Further evidence linking hypercholesterolaemia and hypertension relates to the effect of statins on resting BP. To evaluate this cholesterol-lowering effect for the first time, our group enrolled 70 hypertensive patients (diastolic blood pressure [DBP] 95–120 mmHg) with primary hypercholesterolaemia, who had initially received either lisinopril ($n = 35$) or enalapril ($n = 35$) during the run-in phase to adjust their DBP. Half of the patients in each group subsequently received additional treatment with either pravastatin ($n = 17$) or lovastatin ($n = 18$), while the remaining half were maintained on diet only. A parallel and significant decrease in total cholesterol and mean SBP and DBP was observed in the groups receiving statins compared with diet after only 6 weeks.¹² After 12 weeks of treatment, a maximum difference in BP of 27%, which corresponded with a decrease of 7 mmHg, was demonstrated between the statin and diet-only groups (Fig. 1).

Further support of a synergistic relationship between hypercholesterolaemia and hypertension can be found in

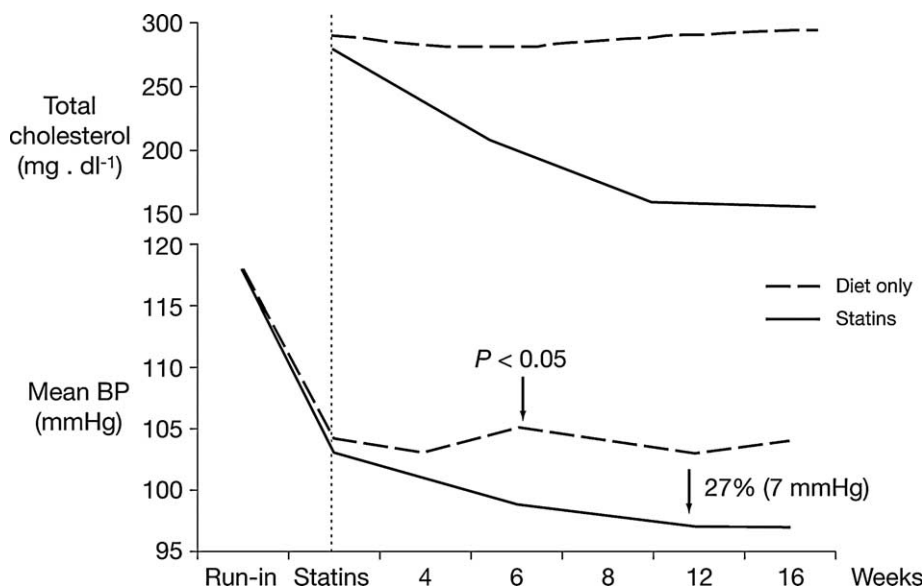


Fig. 1 Effect of statins versus diet only on total cholesterol and resting BP. Used with permission from Sposito AC, Ramires JA. Additional reduction in blood pressure after cholesterol-lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril). *Am J Cardiol* 1999;83:1497–9.

a study involving 22 hypercholesterolaemic patients with systolic hypertension who received atorvastatin (80 mg day⁻¹) and placebo for 3 months in a crossover design. Treatment with atorvastatin versus placebo produced small, but significant, decreases in both SBP and DBP.¹³

Which mechanisms link hypercholesterolaemia and hypertension?

Secretion of vasoactive molecules

The first proposed mechanism linking hypercholesterolaemia with hypertension is related to the secretion of several vasoactive molecules. Endothelial cells produce NO via the oxidation of L-arginine to L-citrulline, a process regulated by the action of endothelial NO synthase (eNOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Hypercholesterolaemia can reduce NO bioavailability by three mechanisms (Fig. 2):

- Increased production of oxygen-free radicals by NADPH oxidase, which inactivates the formation of NO.
- Increased formation of oxidized low-density lipoprotein (LDL) via free radicals, which down-regulates the transcription rate of eNOS and reduces the intracellular stability of its messenger RNA.
- Plasma cholesterol is strongly correlated with the concentration of asymmetric dimethylarginine, a natural analogue to L-arginine that competitively inhibits NO production.

A study to assess the relationship between eNOS and hypercholesterolaemia in vivo enrolled 1500 individuals

from the general population without a treatment routine (Pereira A, Sposito A, unpublished data). The individuals' risk of developing hypertension was evaluated according to plasma cholesterol levels or the presence of the eNOS Glu298Asp polymorphism (a common mutation of the eNOS gene, which results in unstable eNOS). Patients with a plasma cholesterol level above 209 mg dl⁻¹ were associated with twice the risk of developing hypertension than those with levels below that measurement. However, when this analysis was stratified according to those individuals with the eNOS polymorphism, it was evident that higher cholesterol levels were associated with a risk nearly three times greater than the group below 209 mg dl⁻¹. Another important observation was that at the lower plasma cholesterol levels (<209 mg dl⁻¹), the incidence of hypertension was similar in patients irrespective of whether the polymorphism was present. Therefore, hypercholesterolaemia and a genetic susceptibility resulted in a synergistic magnification of risk for developing hypertension.

Besides increasing the effect of high plasma cholesterol on the production and bioavailability of NO, hypercholesterolaemia also increases the secretion of vasoconstrictive molecules. It is well known that hypercholesterolaemia stimulates the activity of plasma and tissue renin and the subsequent production of angiotensin II.^{14,15} At the same time, there is also an increase in the activity of the angiotensin II type 1 receptor, which potentiates the effect of hypercholesterolaemia on renin activity.^{16,17} Recent data also indicate that hypercholesterolaemia increases endothelin-1 levels and endothelin receptor activity.^{5,18}

If all of these effects on endothelial function and the regulation of BP are considered, it is evident that hypercholesterolaemia leads to a reduction in the synthesis

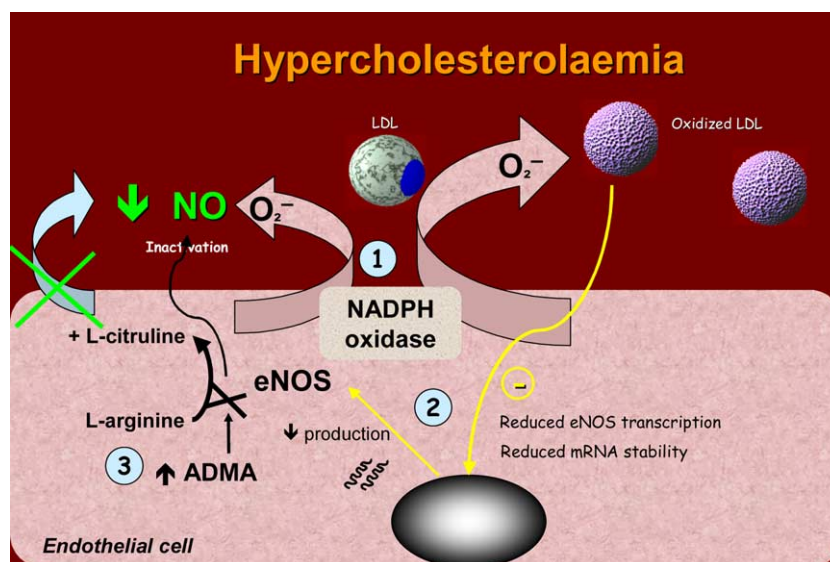


Fig. 2 Mechanisms by which hypercholesterolaemia interacts with and disrupts NO bioavailability in the endothelium. NO, nitric oxide; LDL, low-density lipoprotein; eNOS, endothelial NO synthase; NADPH, nicotinamide adenine dinucleotide phosphate; ADMA, asymmetric dimethylarginine; mRNA, messenger RNA.

and release of NO, and increases activity in the RAAS and endothelin – both involved in vasoconstriction – which results in a net increase in BP.

Salt sensitivity

Another mechanism that may underlie the association between hypercholesterolaemia and hypertension is salt sensitivity. Increasing plasma cholesterol induces vasoconstrictive factors, decreases NO bioavailability and leads to endothelial dysfunction, which are the most important mechanisms for inducing salt sensitivity.^{19,20,21} In addition, during hypercholesterolaemia there is a rapid transfer of surface cholesterol between lipoproteins and cellular membranes; this reduces membrane fluidity and changes the ion channel transporter's activity. With regard to sodium, cholesterol enrichment in renal cellular membranes decreases sodium efflux along the nephron, consequently reducing the fractional clearance rate of sodium and favouring its retention.^{22,23} Consistent with these data, cholesterol-lowering treatment with statins reduces the cholesterol content of cellular membranes and the cellular concentration of sodium, thus increasing the activity of sodium transporters.²⁴

The first study to address the relationship between salt sensitivity and hypertension and hypercholesterolaemia was published in 1999 by Hayakawa et al.²⁵ A salt-rich diet was given to two groups of rats; one of the groups had hypercholesterolaemia and a deficiency of antioxidants (vitamin E and selenium) and the other group had normal cholesterol levels. A significant increase in SBP was observed in both groups. However, the increase was most evident in the group with hypercholesterolaemia.²⁵

Calcium influx in vascular smooth muscle cells

The enrichment of cell membranes with cholesterol can also affect the transport of calcium. In vascular smooth muscle cells, cholesterol enrichment increases the activity of L-type channels and the influx of calcium into these cells; conductivity is thus increased, which leads to microvessel constriction. There is a strong, positive correlation between intra-cellular-free calcium and plasma cholesterol levels, cellular membrane cholesterol and also BP.^{26,27}

Does hypertension increase atherogenicity of cholesterol-rich lipoproteins?

It is known that hypertension increases oxidative stress and can subsequently increase atherogenicity and the formation of oxidized LDL. Further to these findings, a recent study investigated the effect of intra-luminal pressure on the accumulation of LDL. Rabbit aortas were removed, infused with labelled LDL, and exposed to three BP levels: 160, 120 and 70 mmHg. After the infu-

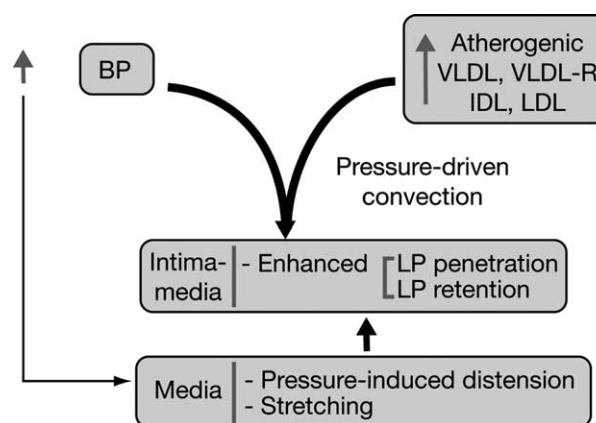


Fig. 3 Schematic showing how hypertension can: (a) increase the pressure-driven convection of atherogenic lipoproteins into the intima-media and (b) induce a pressure-related distension of the artery wall, facilitating the penetration and potential retention of atherogenic lipoproteins. BP, blood pressure; VLDL, very low-density lipoprotein; VLDL-R, very low-density lipoprotein receptors; IDL, intermediate-density lipoprotein; LP, lipoprotein.

sion, very small cuts were made in the artery wall and the retention of labelled LDL was analyzed. A positive association was observed between BP and the concentration of labelled LDL in the intima and the inner media layers of the arterial wall. This procedure was then repeated but this time rigid polyester sleeves of varying diameters were wrapped externally around half of the arterial segments to prevent arterial distension. The transmural distribution of relative concentrations of LDL was assessed in each of the 'wrapped' arterial segments. A progressive reduction in the retention of LDL occurred every time the diameter of the sleeve was reduced.²⁸ This indicated that increasing BP went on to increase the pressure-driven convection of atherogenic lipoproteins, and also induced a pressure-related distension of the artery wall – this distension then facilitated the penetration and potential retention of atherogenic lipoproteins therein (Fig. 3).

Conclusion

To summarize, hypercholesterolaemia may be associated with hypertension via a number of mechanisms. These include decreased NO bioavailability, an increased activity of several vasoconstrictive factors (most importantly angiotensin II and endothelin-1), lowered salt sensitivity, increased calcium influx in vascular smooth muscle cells, and increased oxidative stress and pressure-induced distension of the artery wall. Cholesterol-lowering treatment with statins appears to benefit hypertension associated with hypercholesterolaemia, and BP reduction may attenuate the atherogenicity of hypercholesterolaemia too. Future treatment strategies should be encouraged to address both the cholesterol-lowering and BP-lowering components to optimize global cardiovascular risk reduction.

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