Hypercholesterolaemia and its potential role in the presentation and exacerbation of hypertension

ANDREI C SPOSITO, JOSE AUGUSTO S BARRETO-FILHO

Abstract

Hypertension is a major cardiovascular risk factor and its pathogenesis remains elusive. For a long time, hypertension and dyslipidaemia have been viewed as independent but synergistic cardiovascular risk factors increasing the risk of premature atherosclerosis. Recently, a growing body of evidence has indicated that hypercholesterolaemia promotes impairment in several mechanisms implicated in blood pressure control such as nitric oxide bioavailability, renin-angiotensin activity, the sympathetic nervous system, sodium and fluid homeostasis and ion transport/signal transduction. Moreover, recent clinical studies have pointed out a beneficial effect of cholesterol-lowering treatment in reducing blood pressure to a small but significant degree. Our assumption is that depending on the complex inter-relationships between genetic background and life style, hypercholesterolaemia may be a trigger to blood pressure elevation. An integrated approach to the treatment of hypertension and dyslipidaemia can, therefore, maximise both blood pressure control and prevention of cardiovascular disease. In this review, we discuss recent important data from our and other groups, demonstrating the clinical evidence of the hypertensinogenic effects of hypercholesterolaemia, and the biological mechanisms which underlie them.

Key words: hypertension, hypercholesterolaemia, blood pressure.

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Introduction

Hypertension is a major cardiovascular risk factor and its pathogenesis remains elusive. Nevertheless, a growing body of evidence has suggested a complex interplay between genetic and environmental factors in the development of hypertension. From a pathophysiological point of view, hypertension is a final complex phenotype, influenced by environmental factors, and multiple redundant and regulatory systems that participate in the control of cardiac output and systemic vascular resistance. Multiple mechanisms may lead to the same final phenotype.[1]

For a long time, hypertension and dyslipidaemia have been viewed as two independent but synergistic cardiovascular risk factors increasing the risk of premature atherosclerosis. The introduction of the concept that elevation of blood pressure typically occurs in conjunction with metabolic abnormalities, raised the possibility of a pathophysiological link between these two disorders. Initially, hyperinsulinaemia was proposed as a central pathophysiological mechanism to explain the frequent co-existence of hypertension and dyslipidaemia.[2] More recently, a large number of studies have indicated that alterations in lipid metabolism, itself may modulate several mechanisms implicated in blood pressure regulation such as endothelium-dependent vasodilatation, secretion of vasoactive substances, cellular handling of calcium and sodium, and autonomic cardiovascular control.[3-6] Therefore, from a mechanistic point of view, dyslipidaemia may predispose to an increased sensitivity to hypertensinogenic stimuli or even elicit the clinical manifestation of hypertension in subjects with a pathophysiological background favourable to hypertension development. Moreover, recent data have also indicated that lipid-lowering treatment may ameliorate blood pressure control, adding to the evidence for the role of dyslipidaemia in the regulation of blood pressure.[7-9] This review will look at: i) potential mechanisms of dyslipidaemia affecting blood pressure regulation systems and ii) the potential role of lipid-lowering drugs in ameliorating hypertension control.

Potential mechanisms of dyslipidaemia altering blood pressure regulation systems

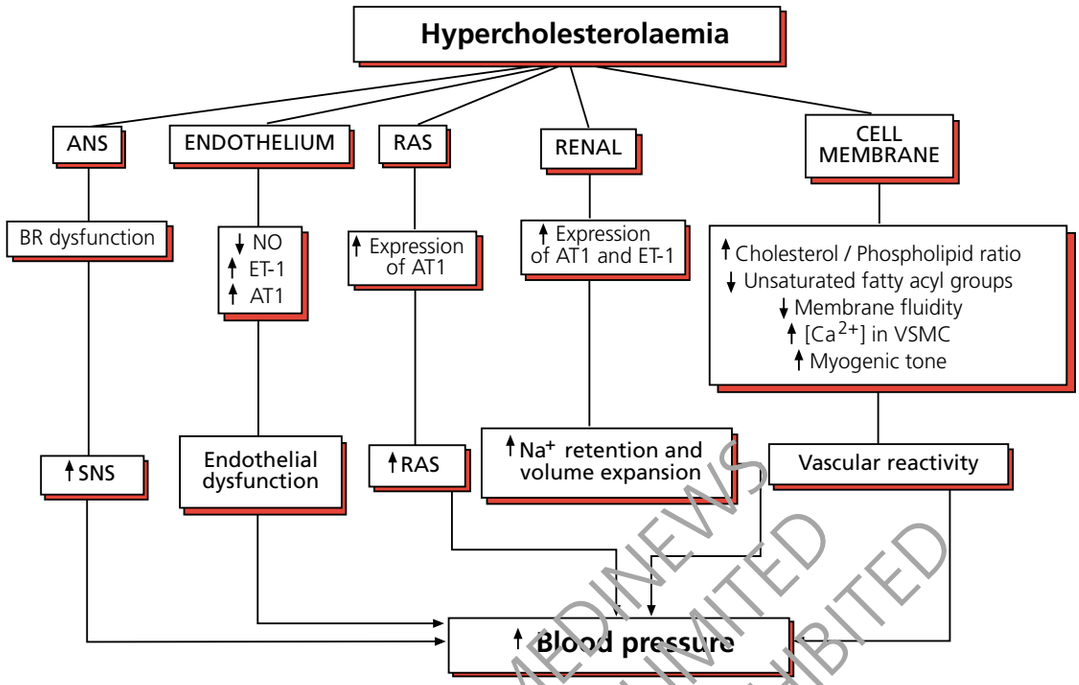
These are summarised in figure 1.

Nitric oxide bioavailability

Endothelial production of nitric oxide (NO) plays a central role in the regulation of blood pressure and in the control of organ blood flow. In studies in healthy subjects, the inhibition of NO production by L-arginine analogues induces dose-dependent changes in several hypertensive components, including reduc-

Heart Institute (InCor), Zerbini Foundation, Brasília, D.F., Brazil.
Andrei C Sposito, Director, Department of Cardiology
Jose Augusto S Barreto-Filho, Senior Assistant Cardiologist
Correspondence to: Dr AC Sposito, Instituto do Coração (InCor), Estrada Parque do Contorno do Bosque s/n, Brasília, Cruzeiro Novo – DF 70658-900, Brazil.
(email: sposito@zerbini.org.br)

Figure 1. Potential mechanisms that underlie the hypertensive effect of hypercholesterolaemia



Key: ANS = autonomic nervous system; RAS = renin-angiotensin system; BR = baroreceptor; NO = nitric oxide; ET-1 = endothelin 1; AT1 = angiotensin II type 1 receptor; VSMC = vascular smooth muscle cell; SNS = sympathetic nervous system; Na^+ = sodium; Ca^{2+} = calcium

tion in urine flow, sodium excretion, renal blood flow, glomerular filtration rate, endothelial dysfunction and, at higher levels of inhibition, elevation in blood pressure.[10,11] The inactivation of NO by reactive oxygen species is a key feature of the endothelial dysfunction induced by both hypercholesterolaemia and hypertension.[12] Hypercholesterolaemia promotes an increased endothelial production of oxygen free radicals via activation of NAD(P)H-dependent oxidases, which rapidly degrade NO molecules.[13] In addition, hypercholesterolaemia reduces the synthesis of NO in endothelial cells via transcriptional inhibition of the endothelial NO synthase (NOS) gene, post-transcriptional mRNA destabilisation and competitive inhibition of NO generation by NOS.[14-16] Thus, hypercholesterolaemia strongly reduces NO-induced vasodilatation via a broad range of mechanisms involving both reduced production and increased degradation of NO.

In a large sample of more than 1,500 individuals from the general population, we compared the risk of hypertension according to Glu298Asp NOS polymorphism and plasma cholesterol levels (Pereira 2003, submitted for publication). We found that in the general population, the risk of hypertension was doubled in subjects with a total cholesterol above 5.40 mmol/L (209 mg/dL). The risk of hypertension was three times higher if the hypercholesterolaemic patients were also homozygous for the Asp298 allele, which represents a defective NOS variant more vulnerable for intracellular cleavage. Interestingly, for subjects with a total cholesterol below 5.40 mmol/L (209 mg/dL), the risk of hypertension was unchanged no matter whether or not they presented with the defective Asp298 allele. Thus, our findings confirmed that hypercholesterolaemic patients present a higher risk of manifest hypertension and also that the NO production rate is a major mechanism underlying the interaction between hypertension and hypercholesterolaemia.

Renin-angiotensin system activity

Abnormal activation of renin-angiotensin system (RAS) plays a critical role in several regulatory systems implicated in hypertension pathophysiology. By increasing extracellular volume expansion, total peripheral resistance and cardiac output, the RAS participates in several of the intermediate phenotypes that may ultimately lead to elevation of blood pressure.

Several factors may favour the activation of the RAS in hypercholesterolaemia. Firstly, the activity of the circulating and arterial wall RAS is up-regulated in hypercholesterolaemic patients.[17-19] Secondly, hypercholesterolaemia up-regulates angiotensin II type 1 receptor (AT1) expression, intensifying a broad range of responses to angiotensin II including vasoconstriction, salt retention and oedema.[20] In fact, in a study performed in healthy subjects, low-density lipoprotein (LDL) cholesterol emerged from a

multivariate analysis as an independent powerful determinant of vascular responsiveness to angiotensin II.[21]

Such a combination of increased angiotensin II synthesis (systemically or within the arterial wall) and AT1 responsiveness increases blood pressure through a variety of mechanisms in different tissues, including the increase of vascular resistance in small arteries, enhanced activity of the sympathetic nervous system and salt retention.[22] In this respect, NO down-regulates the synthesis of angiotensin II in endothelial cells and the expression of AT1 in vascular smooth muscle cells.[23-26] Thus, decreased NO bioavailability in hypercholesterolaemic patients may also play a significant role in up-regulation of the RAS.

More recently, a growing number of studies has indicated that hypercholesterolaemia is associated with increased circulating levels of endothelin 1 (ET-1) and enhanced activity of ET receptors, an autocrine-paracrine system directly implicated in the regulation of arterial vascular tone and sodium and water homeostasis.[27-29] Modulation of the activity of the ET-1 system interacts closely with the NO-ang II balance, as ET-1 synthesis is up-regulated by angiotensin II and down-regulated by NO.[28,29]

Sympathetic nervous system activity

It is widely established that the sympathetic nervous system plays a key role in the short- and long-term regulation of blood pressure through modulation of cardiac output, fluid retention, and vascular resistance.[30-34] Afferent inputs from baroreceptors along the artery wall interact with the central autonomic areas in buffering acute variations in blood pressure via regulation of the sympathetic nervous system tone to several organs.[35] Therefore, baroreflex dysfunction is a possible mechanism to explain pathophysiological cardiovascular hyperreactivity and sympathetic overactivity characteristic of pre-hypertension.[31,33-35] Indeed, recent studies have indicated that hypercholesterolaemia promotes baroreflex dysfunction, contributing to cardiovascular hyperreactivity and sympathetic overactivity associated with pre-hypertensive status.[31,33,34,36-38]

Pathophysiological pathways by which dyslipidaemia may lead to baroreflex impairment are barely understood. Nevertheless, studies are providing a conceptual framework for such speculation. At a cellular and molecular level, dyslipidaemia modifies the physiological transmembrane transport of ions such as sodium, calcium and potassium,[39] thus interfering with the electrochemical gradients needed for various cell functions including neural function.[40] In addition, decreases in endothelial NO bioavailability may alter the signal transduction in autonomic reflex and tonic control of cardiovascular function.[41] Moreover, hypercholesterolaemia favours the vasoconstrictor response to norepinephrine via a mechanism related to membrane calcium channels. Therefore, hypercholesterolaemic patients may present vascular sympathetic overactivity despite a normal output from the central autonomic system.[5]

In parallel to the functional effects of hypercholesterolaemia on baroreflex control, hypercholesterolaemia may also increase aortic and carotid arterial rigidity[42] underlying the mechanism of baroreflex dysfunction.[43] Thus, in addition to the functional effects of dyslipidaemia altering neural physiology at cellular and molecular levels, the chronic vascular structural alterations induced by dyslipidaemia (i.e. atherosclerosis and increase in arterial stiffness) may also contribute to deregulation of cardiovascular autonomic control (i.e. increase sympathetic nervous activity). This ultimately leads to chronic elevation of blood pressure.[44] Furthermore, a recent novel study in rabbits indicated that hypercholesterolaemia induces nerve sprouting and sympathetic hyperinnervation, which ultimately increases calcium inward currents in the heart.[45] Thus sympathetic stimulation, triggered by environmental factors such as smoking in hypercholesterolaemic patients, may elicit an exaggerated cardiovascular response compared with that observed in healthy individuals.

Impairment of sodium and fluid homeostasis

Approximately half of hypertensive patients manifest elevation of blood pressure during high dietary salt intake and are therefore considered salt-sensitive. Salt-sensitive hypertension has been linked to a decrease in renal production of NO, and increased ET-1 and angiotensin II levels.[46-54] In addition, in animal models and in healthy subjects, the infusion of angiotensin II or NOS inhibitors results in the development of salt-sensitive hypertension. By contrast, L-arginine treatment attenuates sodium retention and reduces blood pressure.[46-54]

Co-existence of salt sensitivity and hypercholesterolaemia are frequently found.[6,55] Moreover, recent evidence has suggested a potential causative role for hypercholesterolaemia in salt sensitivity. As discussed earlier, endothelium-dependent compensatory vasodilatation is impaired in hypercholesterolaemic patients. Thus, increased plasma volume and increased cardiac output following salt intake may not be adequately compensated by the endothelium-dependent reduction of systemic vascular resistance and cardiac afterload in hypercholesterolaemic patients.

Physiological adaptation to salt intake involves an increase in renal production of NO and in renal perfusion pressure, and a decrease in angiotensin II, ET-1 and aldosterone.[47,56] Hypercholesterolaemia induces the opposite response, increasing vasoconstrictive molecules, such as angiotensin II and ET-1, and reducing the vasodilator NO.[17-19, 27-29]

Thus, NO-ang II-ET1 imbalance and endothelial dysfunction may account for the frequent association between hypercholesterolaemia and salt sensitivity. In fact, the hypertensive effect of dietary salt-load is significantly higher in diet-induced hypercholesterolaemic rats than in controls.[57]

Cell membrane alterations

The activity of membrane transporters depends critically on the structure and composition of cellular membranes. Dynamic lipoprotein-cell and cell-cell interactions result in a rapid exchange of surface lipids, which lead to a remodelling of the structure and composition of cellular membranes. Thus, elevated plasma levels of cholesterol-rich lipoproteins favour cholesterol enrichment of cellular membranes. This reduces their fluidity and also affects signal transduction, receptor coupling, sodium trans-

port and cell calcium handling. All of these mechanisms are implicated in the regulation of blood pressure.[58-61] Membrane cholesterol enrichment reduces membrane fluidity, the activity of the sodium/potassium pump, sodium/lithium counter-transport, sodium/potassium/chlorine co-transport, sodium/hydrogen exchange and the passive leakage of sodium and potassium. This significantly reduces cellular sodium efflux.[62] Consistent with this finding, cholesterol-lowering treatment reduces cellular membrane cholesterol content and intracellular sodium concentration but increases the sodium/potassium pump activity.[63] Hypercholesterolaemia may, therefore, reduce cellular sodium transport and fluid balance, which are primarily mediated by sodium transporters along the nephron, and favour salt sensitivity and elevation of blood pressure.[64]

Cholesterol enrichment of the membrane of vascular smooth muscle cells (VSMC) may also favour a hypertensive response. Membrane cholesterol enrichment in VSMC stimulates calcium influx via L-type voltage-sensitive channels and, consequently, the myogenic tone of these cells.[65,66] Such an increase in the VSMC tone reduces the calibre of the microvascular arterial bed and increases peripheral vascular resistance and blood pressure. In fact, in hypertensive patients, the intracellular concentration of free calcium in platelets is positively correlated with membrane cholesterol content, plasma cholesterol levels and blood pressure.[67,68] Moreover, the exaggerated increase in blood pressure observed in normotensive hypercholesterolaemic individuals under mental or exercise stress is proportional to the increase in intracellular calcium concentration induced by LDL stimulation.[4]

Potential role of lipid-lowering drugs ameliorating blood pressure control

For over a decade, the suboptimal effectiveness of antihypertensive treatment on the prevention of coronary artery disease events compared to the preventive impact on the incidence of heart failure or stroke has been discussed.[69,70] One explanation is that certain elements of hypertension, such as hypercholesterolaemia or insulin-resistance, have not been adequately addressed. Thus, an enhanced risk of coronary artery disease in hypertensive patients may result from the pro-atherogenic effects of elevated blood pressure, but equally from other hypertensive components. Recently, this assumption was confirmed by the demonstration that even a low dose of statin (atorvastatin, 10 mg/day) when given to hypertensive patients with mild-to-moderate hypercholesterolaemia (LDL cholesterol < 6.5 mmol/L (250 mg/dL) greatly reduces the risk of cardiovascular events.[71] Thus, cholesterol-lowering treatment deserves special attention for the optimal treatment of hypertensive patients.

As previously discussed, much evidence supports the concept that hypercholesterolaemia could contribute to the complex interactions which trigger blood pressure elevation, or which may exacerbate this condition in patients with overt hypertension. Salt sensitivity, endothelial dysfunction, elevated blood pressure and atherosclerosis must be considered less as isolated clinical features but rather a result of a cluster of cardiovascular risk factors, such as hypercholesterolaemia and insulin resistance, which exhibit an intimate and synergistic association. In this context, cholesterol-lowering treatment with statins has proved to attenuate a spectrum of cardiovascular diseases.[7,72-74]

Some years ago we reported for the first time that cholesterol-lowering treatment with statins promotes a significant reduction in systolic and diastolic blood pressure,[7] an observation subsequently confirmed by others.[8,9,75] This finding is consistent with clinical studies which demonstrated that statin treatment attenuates the rise of blood pressure induced by mental stress as well as that induced by infusion of angiotensin II or norepinephrine.[76,77] Recently, our group investigated the cardiovascular responses during systemic hypoxia stress in normotensive patients heterozygous for familial hypercholesterolaemia (FH), a severe monogenic form of dyslipidaemia. We observed that FH patients presented a marked blunted forearm vasorelaxation associated with an enhanced pressor response as compared with normocholesterolaemic controls.[3] Interestingly, when we treated these patients with statins, they presented a cardiovascular response equivalent to that observed in the controls (Barreto-Filho, 2003, unpublished results).

Several mechanisms might underlie the blood pressure-lowering effect of statins. Cholesterol lowering-dependent and -independent actions of statins improve endothelial dysfunction and vasomotor properties, leading to a decreased systemic peripheral resistance and, consequently, reduced blood pressure hyper-reactivity.[74] NO bioavailability is increased and activity of both the ET-1 and angiotensin II systems is reduced after statin treatment, which contributes to normalisation of vasomotor

Key messages

- In addition to its atherogenic effects, hypercholesterolaemia equally influences a wide spectrum of biological mechanisms intimately associated with the initiation and progression of hypertension
- Hypertensinogenic mechanisms, such as low nitric oxide bioavailability, increased activity of the renin-angiotensin-aldosterone and endothelin-1 systems, sympathetic overactivity, and impairment of the cellular handling of ions such as sodium and calcium, are frequently found in hypercholesterolaemic subjects
- In hypertensive patients, cholesterol lowering reduces blood pressure to a small but significant degree and, equally, significantly attenuates the incidence of coronary artery disease events
- An integrated approach to blood pressure- and lipid-lowering treatments represents an optimal therapeutic strategy to attenuate atherogenesis and prevent cardiovascular disease in patients who display hypertensive dyslipidaemia

properties.[24] Moreover, in hypercholesterolaemic, normotensive patients, statin treatment improves the elasticity of small arteries leading to reduced systolic and diastolic blood pressure.[75]

Conclusion and perspectives

In summary, the frequent co-existence and extensive interaction between hypercholesterolaemia and hypertension is consistent with the observation that these clinical abnormalities constitute key elements of the syndrome of hypertension. The mechanisms which underlie the complex interaction between these two major cardiovascular risk factors remain only partially understood. In hypertensive patients, cholesterol lowering reduces blood pressure to a small but significant degree and attenuates the incidence of coronary artery disease events. An integrated approach to blood pressure- and lipid-lowering treatments, therefore, represents an optimal therapeutic strategy to prevent cardiovascular disease in patients who display hypertension associated with dyslipidaemia. Despite a large amount of data indicating that hypercholesterolaemia constitutes one element, in the complex condition of hypertension, additional clinical and mechanistic studies are required to provide a more comprehensive understanding of the pathophysiology and therapeutic strategies needed to attenuate hypertensive dyslipidaemia.

Conflict of interest

Andrei C Sposito has received support from Pfizer, Merck Sharp & Dohme, AstraZeneca and Roche for lectures on cholesterol metabolism.

References

1. Staessen JA, Wang J, Bianchi G, Birkenhager WH. Essential hypertension. *Lancet* 2003;**361**:1629-41.
2. Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. *J Clin Endocrinol Metab* 2003; **88**:2399-403.
3. Barreto-Filho JAS, Consolim-Colombo FM, Guerra Riccio GM *et al*. Hypercholesterolaemia blunts forearm vasorelaxation and enhances the pressor response during acute systemic hypoxia. *Arterioscler Thromb Vasc Biol* 2003;**23**:1660-6.
4. Minami M, Atarashi K, Ishiyama A, Hirata Y, Goto A, Omata M. Pressor hyperreactivity to mental and hand-grip stresses in patients with hypercholesterolaemia. *J Hypertens* 1999;**17**:185-92.
5. McCalden TA, Nath RG. Mechanisms of vascular supersensitivity in hypercholesterolaemia. *Stroke* 1989;**20**:238-41.
6. Miyoshi A, Suzuki H, Fujiwara M, Masai M, Iwasaki T. Impairment of endothelial function in salt-sensitive hypertension in humans. *Am J Hypertens* 1997;**10**:1083-90.
7. Sposito AC, Mansur AP, Coelho OR, Nicolau JC, 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, A8.
8. Glorioso N, Troffa C, Filigheddu F *et al*. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolaemia. *Hypertension* 1999;**34**:1281-6.
9. Ferrier KE, Muhlmann MH, Baguet JP *et al*. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002;**39**:1020-5.
10. Lahera V, Salom MG, Miranda-Guardiola F, Moncada S, Romero JC. Effects of NG-nitro-L-arginine methyl ester on renal function and blood pressure. *Am J Physiol* 1991;**261**:F1033-7.
11. Spieker LE, Sudano I, Hurlimann D *et al*. High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation* 2002;**105**: 1399-402.
12. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000;**87**:840-4.
13. Guzik TJ, West NE, Black E *et al*. Vascular superoxide production by NAD(P)H oxidase: association with endothelial dysfunction and clinical risk factors. *Circ Res* 2000;**86**:E85-E90.
14. Liao JK, Shin WS, Lee WY, Clark SL. Oxidized low-density lipoprotein decreases the expression of endothelial nitric oxide synthase. *J Biol Chem* 1995;**270**:319-24.
15. Boger RH, Bode-Boger SM, Szuba A *et al*. Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterolaemia. *Circulation* 1998;**98**:1842-7.
16. Valkonen VP, Paiva H, Salonen JT *et al*. Risk of acute coronary events and serum concentration of asymmetrical dimethylarginine. *Lancet* 2001; **358**:2127-8.
17. Uehara Y, Urata H, Sasaguri M *et al*. Increased chymase activity in internal thoracic artery of patients with hypercholesterolaemia. *Hypertension* 2000;**35**:55-60.
18. Kotchen TA, Talwalkar RT. Increased enzymatic activity of renin and hyperlipidemia. *Am J Physiol* 1981;**240**:E60-4.
19. Alderman MH, Ooi WL, Cohen H, Madhavan S, Sealey JE, Laragh JH. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens* 1997;**10**(1):1-8.
20. Ferrario CM. Importance of the renin-angiotensin-aldosterone system (RAS) in the physiology and pathology of hypertension. An overview. *Drugs* 1990;**39**(suppl 2):1-8.
21. John S, Delles C, Klingbeil AU, Jacobi J, Schlaich MP, Schmieder RE. Low-density lipoprotein-cholesterol determines vascular responsiveness to angiotensin II in normocholesterolaemic humans. *J Hypertens* 1999;**17**: 1933-9.
22. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens* 1999;**12**:205S-213S.
23. Ichiki T, Usui M, Kato M *et al*. Downregulation of angiotensin II type 1 receptor gene transcription by nitric oxide. *Hypertension* 1998;**31**:342-8.
24. Ichiki T, Takeda K, Tokunou T *et al*. Downregulation of angiotensin II type 1 receptor by hydrophobic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2001;**21**:1896-901.
25. Takemoto M, Egashira K, Usui M *et al*. Important role of tissue angiotensin-converting enzyme activity in the pathogenesis of coronary vascular and myocardial structural changes induced by long-term blockade of nitric oxide synthesis in rats. *J Clin Invest* 1997;**99**:278-87.
26. Usui M, Ichiki T, Katoh M, Egashira K, Takeshita A. Regulation of angiotensin II receptor expression by nitric oxide in rat adrenal gland. *Hypertension* 1998;**32**:527-33.
27. Yanagisawa M, Kurihara H, Kimura S *et al*. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;**332**: 411-15.
28. Schiffrin EL. State-of-the-art lecture. Role of endothelin-1 in hypertension. *Hypertension* 1999;**34**:876-81.
29. Cardillo C, Kilcoyne CM, Waclawiw M, Cannon RO, 3rd, Panza JA. Role of endothelin in the increased vascular tone of patients with essential hypertension. *Hypertension* 1999;**33**:753-8.
30. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. *Am J Hypertens* 2000;**13**:112S-122S.
31. Julius S, Majahalme S. The changing face of sympathetic overactivity in hypertension. *Ann Med* 2000;**32**:365-70.
32. van Zwieten PA, Julius S. The importance of the sympathetic nervous system in hypertension. Introduction. *J Hypertens* 1999;**17**(suppl 3):S1.
33. Julius S. Borderline hypertension. *Clin Exp Hypertens* 1999;**21**:741-7.
34. Julius S, Valentini M. Consequences of the increased autonomic nervous drive in hypertension, heart failure and diabetes. *Blood Press* 1998;(suppl 3):5-13.
35. Mussalo H, Vanninen E, Ikaheimo R *et al*. Baroreflex sensitivity in essential and secondary hypertension. *Clin Auton Res* 2002;**12**:465-71.
36. Morita H, Nishida Y, Motochigawa H, Watanabe Y, Hosomi H. Depressed baroreflex control of renal nerve activity in conscious WHHL rabbits.

Cardiovasc Res 1988;**22**:679-85.
37. Piccirillo G, Di Giuseppe V, Nocco M *et al*. Influence of aging and other cardiovascular risk factors on baroreflex sensitivity. *J Am Geriatr Soc* 2001;**49**:1059-65.
38. Gadegbeku CA, Dhandayuthapani A, Sadler ZE, Egan BM. Raising lipids acutely reduces baroreflex sensitivity. *Am J Hypertens* 2002;**15**:479-85.
39. Wu CC, Su MJ, Chi JF, Chen WJ, Hsu HC, Lee YT. The effect of hypercholesterolaemia on the sodium inward currents in cardiac myocyte. *J Mol Cell Cardiol* 1995;**27**:1263-9.
40. Mauch DH, Nagler K, Schumacher S *et al*. CNS synaptogenesis promoted by glia-derived cholesterol. *Science* 2001;**294**:1354-7.
41. Xia LY WN, Shen J, Liu BY. Effects of NO and endothelium on carotid baroreceptor activity. *Sheng Li Xue Bao* 1998;**50**:611-17.
42. Wilkinson IB, Prasad K, Hall IR *et al*. Increased central pulse pressure and augmentation index in subjects with hypercholesterolaemia. *J Am Coll Cardiol* 2002;**39**:1005-11.
43. Lage SG, Kopel L, Monachini MC *et al*. Carotid arterial compliance in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994;**74**:691-5.
44. Sa Cunha R, Pannier B, Benetos A *et al*. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertens* 1997;**15**:1423-30.
45. Liu YB, Wu CC, Lu LS *et al*. Sympathetic nerve sprouting, electrical remodeling, and increased vulnerability to ventricular fibrillation in hypercholesterolemic rabbits. *Circ Res* 2003;**92**:1145-52.
46. Campese VM. Salt sensitivity in hypertension. Renal and cardiovascular implications. *Hypertension* 1994;**23**:531-50.
47. Elijovich F, Laffer CL. Participation of renal and circulating endothelin in salt-sensitive essential hypertension. *J Hum Hypertens* 2002;**16**:459-67.
48. Poch E, Gonzalez D, Giner V, Bragulat E, Coca A, de La Sierra A. Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. *Hypertension* 2001;**38**:1204-09.
49. Franco M, Tapia E, Santamaria J *et al*. Renal cortical vasoconstriction contributes to development of salt-sensitive hypertension after angiotensin II exposure. *J Am Soc Nephrol* 2001;**12**:2263-71.
50. Lombardi D, Gordon KL, Polinsky P, Suga S, Schwartz SM, Johnson RJ. Salt-sensitive hypertension develops after short-term exposure to Angiotensin II. *Hypertension* 1999;**33**:1013-19.
51. Nakanishi K, Hara N, Nagai Y. Salt-sensitive hypertension in conscious rats induced by chronic nitric oxide blockade. *Am J Hypertens* 2002;**15**: 150-6.
52. Zhou MS, Kosaka H, Tian RX *et al*. L-arginine improves endothelial function in renal artery of hypertensive Dahl rats. *J Hypertens* 2001;**19**:421-9.
53. Berger ED, Bader BD, Rub N *et al*. Changes in renal and systemic hemodynamics after NO-synthase inhibition in males with family history of hypertension. *Kidney Blood Press Res* 2002;**25**(1):42-9.
54. Castejon AM, Hoffmann IS, Jimenez E, Cubeddu RJ, Baldonedo RM, Cubeddu LX. Differential blood pressure effects of oral glucose and intravenous L- arginine in healthy lean normotensive and obese hypertensive subjects. *J Hum Hypertens* 2002;**16**(suppl 1):S133-136.
55. Bragulat E, de la Sierra A, Antonio MT, Coca A. Endothelial dysfunction in salt-sensitive essential hypertension. *Hypertension* 2001;**37**:444-8.
56. Boegehold MA. Microvascular structure and function in salt-sensitive hypertension. *Microcirculation* 2002;**9**:225-41.
57. Hayakawa H, Raij L. Relationship between hypercholesterolaemia, endothelial dysfunction and hypertension. *J Hypertens* 1999;**17**:611-19.
58. Zicha J, Kunes J, Devynck MA. Abnormalities of membrane function and lipid metabolism in hypertension: a review. *Am J Hypertens* 1999;**12**: 315-31.
59. Ollerenshaw JD, Heagerty AM, Bing RF, Swales JD. Abnormalities of erythrocyte membrane fatty acid composition in human essential hypertension. *J Hum Hypertens* 1987;**1**(1):9-12.
60. Villar J, Montilla C, Muniz-Grijalvo O *et al*. Erythrocyte $Na^{(+)}$-Li^{+} countertransport in essential hypertension: correlation with membrane lipids levels. *J Hypertens* 1996;**14**:969-73.
61. Naftilan AJ, Dzau VJ, Loscalzo J. Preliminary observations on abnormalities of membrane structure and function in essential hypertension. *Hypertension* 1986;**8**:II174-9.
62. Lijnen P, Petrov V. Cholesterol modulation of transmembrane cation transport systems in human erythrocytes. *Biochem Mol Med* 1995;**56**(1): 52-62.
63. Lijnen P, Echevaria-Vazquez D, Petrov V. Influence of cholesterol-lowering on plasma membrane lipids and function. *Methods Find Exp Clin Pharmacol* 1996;**18**:123-36.
64. Rosskopf D, Dusing R, Siffert W. Membrane sodium-proton exchange and primary hypertension. *Hypertension* 1993;**21**:607-17.
65. Gleason MM, Medow MS, Tulenko TN. Excess membrane cholesterol alters calcium movements, cytosolic calcium levels, and membrane fluidity in arterial smooth muscle cells. *Circ Res* 1991;**69**:216-27.
66. Sen L, Bialecki RA, Smith E, Smith TW, Colucci WS. Cholesterol increases the L-type voltage-sensitive calcium channel current in arterial smooth muscle cells. *Circ Res* 1992;**71**:1008-14.
67. Miller MA, Sagnella GA, Markandu ND, MacGregor GA. Determinants of platelet intracellular free calcium in essential hypertension and effect of stimulation by arginine vasopressin. *Am J Hypertens* 1993;**6**:209-16.
68. Zhou Q, Imi S, Smith TL, Kummerow FA. The effect of cholesterol on the accumulation of intracellular calcium. *Biochim Biophys Acta* 1991; **1085**(1):1-6.
69. Collins R, Peto R, MacMahon S *et al*. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;**335**:827-38.
70. MacMahon S, Peto R, Cutler J *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;**335**:765-74.
71. Sever P, Dahlof B, Poulter N *et al*. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149-58.
72. Ramires JA, Sposito AC, Mansur AP, Coelho OR, Maranhao M, Cesar LA. Cholesterol lowering with statins reduces exercise-induced myocardial ischemia in hypercholesterolemic patients with coronary artery disease. *Am J Cardiol* 2001;**88**:1134-8.
73. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997;**95**:1126-31.
74. Sposito AC, Chapman MJ. Statin therapy in acute coronary syndromes: mechanistic insight into clinical benefit. *Arterioscler Thromb Vasc Biol* 2002;**22**:1524-34.
75. Leibovitz E, Hazanov N, Zimlichman R, Shargorodsky M, Gavish D. Treatment with atorvastatin improves small artery compliance in patients with severe hypercholesterolaemia. *Am J Hypertens* 2001;**14**:1096-8.
76. Sung BH, Izzo JL, Jr., Wilson MF. Effects of cholesterol reduction on BP response to mental stress in patients with high cholesterol. *Am J Hypertens* 1997;**10**:592-9.
77. Straznicky NE, Howes LG, Lam W, Louis WJ. Effects of pravastatin on cardiovascular reactivity to norepinephrine and angiotensin II in patients with hypercholesterolaemia and systemic hypertension. *Am J Cardiol* 1995;**75**:582-6.