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Endothelial dysfunction: its role in hypertensive coronary disease

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Abstract

Purpose of review—Coronary artery disease is the major cause of death worldwide. Hypertension is a major risk factor for developing coronary disease. It is now recognized that endothelial dysfunction is an early marker of coronary artery disease before structural changes to the vessel wall are apparent on angiography or intravascular ultrasound and that it has a prognostic value in predicting cardiovascular events in hypertensive patients. This review addresses recent developments in hypertension-induced endothelial dysfunction.

Recent findings—Hyperaldosteronism causes endothelial dysfunction independent of high blood pressure. Exaggerated exercise blood pressure response has been related to endothelial dysfunction. Cyclosporin-A-induced endothelial dysfunction is related to reduced cholesterol content in caveolae. Chronic kidney disease induces changes in caveoli-1 and thus contributes to the reduced nitric oxide bioavailability, and causes oxidative stress independent of the high blood pressure. Asymmetric dimethylarginine plays a role in endothelial dysfunction in hypertensive patients independent of insulin resistance. 20-Hydroxyeicosatetraenoic acid is an independent predictor of hypertension in postmenopausal women. Endothelial dysfunction precedes and predicts the development of hypertension in postmenopausal women. Oral treatment with L-arginine improves endothelial dysfunction in hypertensives and lowers the blood pressure.

Summary—The pathophysiology of endothelial dysfunction in hypertension is multifactorial. Recent findings have contributed to our understanding of mechanisms of endothelial dysfunction and support a role for early intervention to prevent irreversible vascular and organ damage.

Keywords

coronary artery disease; endothelial dysfunction hypertension; nitric oxide

Introduction

The endothelium is the largest organ in the body. As a regulator of vascular homeostasis, the endothelium maintains a balance between vasodilation and vasoconstriction, inhibition and stimulation of smooth muscle cell proliferation and migration, inhibition of platelet activation, adhesion and aggregation, thrombogenesis and fibrinolysis [1]. Essential hypertension was first recognized to cause endothelial dysfunction (ED) early in the last decade [2]. Endothelial dysfunction is now known to play an important role in the pathogenesis of atherosclerosis and is an early marker of vascular damage before structural changes to the vessel wall become apparent on angiography or by intravascular ultrasound [3].

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Hypertension and endothelial dysfunction

It is now recognized that ED occurs in hypertension irrespective of whether the etiology is primary essential hypertension or whether the hypertension is secondary to endocrine or renal etiological factors [4].

Hypertension has a direct influence on vascular function independent of other cardiovascular risk factors. Ward *et al*. [5] assessed 24-hr ambulatory blood pressure (BP) and brachial artery endothelial and smooth muscle function in patients with hypertension and normotensive controls. Twenty-four-hour ambulatory systolic BP was significantly inversely related to flow-mediated responses. Both systolic and diastolic BP were significantly inversely related to the nitroglycerine response, and the relationships were largely unaltered after further adjustment for body mass index, antihypertensive treatment or the presence of other risk factors.

Endothelial dysfunction does not seem to occur in middle-aged white coat hypertensive patients without other cardiovascular risk factors [6]. The left ventricular hypertrophy associated with hypertension has an additional negative effect on endothelial function in hypertensive patients [7]. In a LIFE substudy [8], hypertensive patients with electrocardiographic left ventricular hypertrophy without coronary artery disease had impaired vasodilatory function in the coronary and noncoronary circulation.

Exaggerated exercise BP has been related to ED. Stewart *et al*. [9•] examined the relation of endothelial vasodilator function and exercise BP in men and women aged 55 to 75 years, with untreated high normal BP or mild hypertension, who were otherwise healthy. Exercise was performed on a treadmill and endothelial vasodilator function was assessed as brachial artery flow-mediated vasodilation (FMD). The FMD was the only independent correlate of the difference between resting and maximal pulse pressure among both men and women. This suggests that ED may be a mechanism contributing to exercise hypertension.

Aldosterone may cause ED in patients with resistant hypertension independent of high BP. Nishizaka *et al*. [10•] demonstrated that brachial artery FMD was negatively and significantly correlated with plasma aldosterone, but was independent of BP, age, and body mass index in 80 consecutive subjects with resistant hypertension. In 30 subjects, 3 months of treatment with spironolactone significantly increased FMD independently of the BP change. These data demonstrate a strong association between aldosterone excess and impaired endothelial function in human subjects.

Pathophysiology of endothelial dysfunction

The endothelium is a major regulator of homeostasis and exerts a number of vasoprotective effects such as vasodilation, inhibition of inflammatory responses and suppression of smooth muscle cell growth. Dysfunction of the endothelium thus causes reduction or abolition of these vasoprotective effects. Factors that lead to reduction of vasodilation in ED include a reduction in nitric oxide (NO) production, increased oxidative stress, a decrease in NO bioavailability, and a reduction of hyperpolarizing factor. Inflammatory responses are initiated in ED by up-regulation of adhesion molecules, generation of chemokines and production of plasminogen activator inhibitor-1, and these also lead to a prothrombotic state. Levels of asymmetric dimethylarginine, vasoconstrictor peptides such as angiotensin and endothelin-1, and hypercholesterolemia and hyperglycemia all contribute to mechanisms of ED. Full discussion of the pathophysiologic mechanisms of ED is complex and outside the scope of this review. We hereby focus on some of these factors.

Nitric oxide

Vascular tone is maintained by release of numerous dilator and constrictor substances [3], nitric oxide (NO) being the major vasodilative substance. The hallmark of ED is impaired endothelium-dependent vasodilation. NO is formed by endothelial cells from L-arginine via the enzymatic action of endothelial NO synthase (eNOS), which is located in caveolae. The protein caveolin-1 binds to calmodulin to inhibit activity of eNOS. The binding of calcium to calmodulin displaces caveolin-1, activating eNOS and leading to production of NO, which diffuses to vascular smooth muscle and causes relaxation by activating guanylate cyclase, thereby increasing cyclic guanosine monophosphate.

Cyclosporin-A-induced ED and hypertension has recently been suggested to be caused by decreasing cholesterol content in caveolae by cyclosporin. Lungu *et al*. [11•] demonstrated that exposure of cultured bovine aortic endothelial cells to 1 μM cyclosporin for 1 hr significantly decreased cholesterol content in caveolae and displaced eNOS from caveolae. Treating bovine aortic endothelial cells for 24 hours with 30 μg/ml cholesterol blocked the cyclosporin effect and restored eNOS phosphorylation in response to flow.

Sindhu *et al*. [12] documented that chronic renal failure (CRF) induces changes in caveolin-1, soluble guanylate cyclase, and Akt expression, three proteins important in regulating eNOS functionality. CRF was induced in Sprague-Dawley rats via 5/6 nephrectomy. After 6 weeks there was elevation in BP and plasma creatinine with increase in caveolin-1 in aortic, liver, and renal tissues, a reduction in urinary cyclic guanosine monophosphate levels indicative of guanylate cyclase dysfunction, and a depression of Akt abundance in aorta, heart, and liver tissues. Thus, CRF contributes to hypertension and changes in NO bioactivity.

Oxidative stress

Healthy vascular endothelial cells metabolize oxygen and generate potentially deleterious reactive oxygen species. Normally, the rate and magnitude of oxidant formation is balanced by the rate of oxygen elimination [13•,14]. In ED, the imbalance between prooxidants and antioxidants results in oxidative stress, which is the pathogenic outcome of oxidant overproduction that exceeds the cellular antioxidant capacity. Increased reactive oxygen species production has been demonstrated in patients with essential, malignant and renovascular hypertension [15,16]. Reduced antioxidant activity also contributes to oxidative stress [17].

Chronic kidney disease is associated with oxidative stress independent of hypertension. Agarwal *et al*. [18•] assessed the role of hypertension in causing increased oxidative stress in patients with CRF. They found that plasma level of malondialdehyde, a marker of oxidative stress, is higher in patients with CRF compared with those with essential hypertension without concomitant kidney disease despite similar BP, and thus nonhemodynamic factors such as inflammation and altered cellular redox state may play a greater role in the generation of oxidative stress in this patient population.

Antihypertensive treatment seems to improve the increased oxidative stress and the decreased antioxidant mechanisms, and the beneficial effect of treatment seems to increase over time. Saez *et al*. [19] nonrandomly allocated different antihypertensive treatments to hypertensive patients with a mean age of 46 years. After 3 months of nonpharmacologic, β-blocker, or angiotensin receptor blocker treatment, oxidized/reduced glutathione ratio and malondialdehyde were significantly reduced, and this was further reduced after 12 months in a subgroup of patients. Yasunari *et al*. [20] demonstrated that both carvedilol and propranolol reduced oxidative stress in patients with essential hypertension, although the effect was greater with carvedilol. Napoli *et al*. [21] demonstrated that treatment with the sulfhydryl angiotensin-converting enzyme inhibitor zofenopril induced sustained reduction of systemic oxidative stress and improved the NO pathway in patients with essential hypertension.

Asymmetric dimethylarginine

Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of NO synthase and has been shown to be increased in patients with hypertension [22]. A strong correlation between increased ADMA blood levels and impaired endothelial-dependent vasodilation, and cardiovascular morbidity and mortality has been documented in different populations [23].

In a study of essential hypertension patients without coronary artery disease or diabetes mellitus, Takiuchi *et al*. [24] demonstrated that increased plasma ADMA concentration appears to play a major role in ED, independent of insulin resistance or left ventricular hypertrophy. Seventy-five patients underwent measurements of coronary flow reserve and brachial artery endothelial-dependent vasodilation. A plasma ADMA assay and a 75-g oral glucose tolerance test were also performed. A significant correlation was found between coronary flow reserve and the brachial artery vasodilation, and both were significantly correlated with age and plasma ADMA concentration, but were not correlated with insulin resistance, plasma insulin, or left ventricular mass. Multiple regression analysis revealed that ADMA was the only statistically independent parameter associated with coronary flow reserve and the brachial artery vasodilation.

Kielstein *et al*. [25••] evaluated systemic cardiovascular effects of ADMA infusion in healthy subjects. ADMA infusion resulted in a decrease in cardiac output and in effective renal plasma flow, and an increase in renovascular resistance, sodium retention, and BP increase in a dose-related manner.

Angiotensin II

The vasoconstrictor peptide angiotensin II is a recognized factor in the development of hypertension. ED induces angiotensin II expression [26]. Animal studies have shown that infusion of angiotensin II causes vascular inflammation [27] and ED [28]. Angiotensin II levels are increased in atherosclerosis and increased angiotensin II amplifies atherosclerosis by modulating individual risk factors as well as by directly affecting lipid metabolism, the vascular response to lipid accumulation, and plaque stability [29].

Zhou *et al*. [30] investigated the effect of a calcium channel blocker (amlodipine) on vascular oxidative stress and endothelial function in angiotensin II-infused rats. Systolic BP, oxidative stress, and ED were significantly reduced with amlodipine treatment. Recently, da Chuna *et al*. [31] demonstrated that the angiotensin-converting enzyme inhibitor enalapril attenuated atherosclerosis and vascular inflammation induced by angiotensin II infusion in apolipoprotein E-deficient mice.

20-Hydroxyeicosatetraenoic acid

20-Hydroxyeicosatetraenoic acid (20-HETE) is a cytochrome P450 metabolite of arachidonic acid with vasoconstrictor activity that may be involved in the pathogenesis of hypertension. In humans, there are few data relating 20-HETE to vascular pathophysiology. In a study of 66 subjects, including 29 with essential hypertension, Ward *et al*. [32••] demonstrated that 20-HETE is an independent predictor of endothelium-dependent vasodilation after adjustment for age, body mass index, and BP. In an analysis by gender, they revealed that in women, hypertensive subjects had significantly higher 20-HETE excretion than normotensive subjects, but this was not seen in men. This is the first demonstration of an association between 20-HETE excretion and in-vivo vascular function in humans.

Prognosis of endothelial dysfunction

Because ED is an early marker before structural changes to the vessel wall become apparent on angiography or by intravascular ultrasound [3], it is not surprising that ED has prognostic value in predicting cardiovascular events in hypertensive patients [33,34]. ED in the coronary resistance and conductance vessels clearly predicts both hard and soft outcomes, as does ED in the brachial artery [33].

During a 31.5-month mean follow-up period involving 225 untreated hypertensive patients (aged 35 to 54 years) with forearm ED assessed by acetylcholine testing, Perticone *et al*. [34] demonstrated that ED is a marker of future cardiovascular events in this patient population. Patients were divided into terciles on the basis of their increase in acetylcholine-stimulated forearm blood flow. During follow-up, there were 29 major adverse events at the cardiac (n = 19), cerebrovascular (n = 9), or peripheral vascular (n = 1) level. The excess risk associated with a forearm blood flow increase in the first tercile (lowest increase) was significant after controlling for individual risk markers, including 24-hr ambulatory BP. The same group has recently investigated the relation between forearm ED and renal function in 500 patients with uncomplicated, never-treated, essential hypertension and serum creatinine within the normal range, and they demonstrated that an impaired vasodilatory response was associated with renal function loss in patients with essential hypertension [35•].

Multiple studies demonstrated the prognostic significance of coronary ED in predicting cardiovascular outcomes [36,37]. Bugiardini *et al*. [38••] have recently demonstrated that chest pain in women with angiographically normal coronary arteries is not totally benign. In a study of 42 women (mean age 52 years), they demonstrated that women with de-novo angina, evidence of reversible myocardial perfusion defect on single photon emission computed tomography, and normal coronary angiogram and ED at baseline had increased cardiovascular outcomes and increased incidence of coronary artery disease over a mean follow-up period of 10.3 years.

ED has also been linked as a prognostic factor for the risk of developing hypertension. In a study of 952 normotensive healthy postmenopausal women (mean age 53 years), Rossi *et al*. [39••] showed that women with ED (reactive hyperemia FMD) had significantly higher incidence of developing hypertension during a mean follow-up period of 3.6 years. Each one-unit decrease of FMD was associated with a significant 16% increase in the multiple-adjusted relative risk of incident hypertension.

Therapy of hypertension-induced endothelial dysfunction

Therapy should be targeted towards treatment of the hypertension and the components that trigger ED.

Antihypertensive therapy seems to improve ED. However, not all antihypertensives have this property. Beta- and α-adrenergic blockers seem to have no direct effect on ED [40], although treatment with the third-generation β-blocker carvedilol has been shown to inhibit oxidative stress [20]. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers have been shown to improve ED in hypertensive patients [40,41]. Schiffrin *et al*. [42] demonstrated that crossing over essential hypertension patients from the β-blocker atenolol to the angiotensin 1 receptor antagonist irbesartan resulted in correction of endothelial function. They also demonstrated that treatment with the calcium channel blocker amlodipine improved endothelial function in hypertensive patients, whereas similar good control of BP with the β-blocker atenolol did not [43]. Treatment with the angiotensin-converting enzyme inhibitor lisinopril was previously shown to improve ED [44].

Another approach is the treatment of the components that trigger ED. Oral treatment with L-arginine, the precursor of NO, has been shown to reduce BP and improve ED [45]. Statins have been shown to improve ED in hypertensive animal models [46•], and may improve ED in hypertensive patients with normal cholesterol levels [47]. Long-term treatment with the antioxidant vitamins E and C have not been shown to improve ED *in vivo* [48•].

Conclusions

Hypertension has an important direct effect on the development of ED and thus coronary artery disease. The role of caveolin-1, asymmetric dimethylarginine, and 20 HETE in the pathogenesis of ED in hypertension needs to be explored further, and more insights are likely to emerge from ongoing studies on endothelial cell signaling pathways. Clinical studies have shown so far that antioxidants do not improve ED and clinical outcomes; the reason for that is not fully understood and deserves further evaluation.

Abbreviations

ADMA	asymmetric dimethylarginine
BP	blood pressure
CRF	chronic renal failure
ED	endothelial dysfunction
eNOS	endothelial nitric oxide synthase
FMD	flow-mediated vasodilation
NO	nitric oxide
20-HETE	20-hydroxyeicosatetraenoic acid

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Luscher TF, Barton M. Biology of the endothelium. Clin Cardiol. 1997; 20:II-3–II-10.
2. Panza JA, Quyyumi AA, Brush JE Jr, et al. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med. 1990; 323:22–27. [PubMed: 2355955]
3. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004; 109:III27–III32. [PubMed: 15198963]
4. Rizzoni D, Porteri E, Castellano M, et al. Endothelial dysfunction in hypertension is independent from the etiology and from vascular structure. Hypertension. 1998; 31:335–341. [PubMed: 9453325]
5. Ward NC, Croft KD, Hodgson J, et al. Brachial artery vasomotor function is inversely associated with 24-h ambulatory blood pressure. J Hypertens. 2004; 22:967–972. [PubMed: 15097237]
6. Pierdomenico SD, Cipollone F, Lapenna D, et al. Endothelial function in sustained and white coat hypertension. Am J Hypertens. 2002; 15:946–952. [PubMed: 12441213]

7. Ercan E, Tengiz I, Ercan HE, et al. Left ventricular hypertrophy and endothelial functions in patients with essential hypertension. Coron Artery Dis. 2003; 14:541–544. [PubMed: 14646675]
8. Olsen MH, Wachtell K, Meyer C, et al. Association between vascular dysfunction and reduced myocardial flow reserve in patients with hypertension: a LIFE substudy. J Hum Hypertens. 2004; 18:445–452. [PubMed: 15014539]
9. Stewart KJ, Sung J, Silber HA, et al. Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. Am J Hypertens. 2004; 17:314–320. [PubMed: 15062884] This is the first study to demonstrate the extent to which systolic arterial and pulse pressure increases during exercise are associated with endothelial dysfunction.
10. Nishizaka MK, Zaman MA, Green SA, et al. Impaired endothelium-dependent flow-mediated vasodilation in hypertensive subjects with hyperaldosteronism. Circulation. 2004; 109:2857–2861. [PubMed: 15173035] This study demonstrates a direct relationship between endogenous aldosterone excess and impaired endothelial function in humans.
11. Lungu AO, Jin ZG, Yamawaki H, et al. Cyclosporin A inhibits flow-mediated activation of endothelial nitric-oxide synthase by altering cholesterol content in caveolae. J Biol Chem. 2004; 279:48794–48800. [PubMed: 15383526] This suggests that the major mechanism of Cyclosporin A–mediated hypertension might be through reduction in caveolae cholesterol content.
12. Sindhu RK, Ehdaie A, Vaziri ND, et al. Effects of chronic renal failure on caveolin-1, guanylate cyclase and AKT protein expression. Biochim Biophys Acta. 2004; 1690:231–237. [PubMed: 15511630]
13. Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? Hypertension. 2004; 44:248–252. [PubMed: 15262903] A good review on the role of oxidative stress in hypertension-associated vascular damage.
14. Ogita H, Liao J. Endothelial function and oxidative stress. Endothelium. 2004; 11:123–132. [PubMed: 15370071]
15. Lip GY, Edmunds E, Nuttall SL, et al. Oxidative stress in malignant and non-malignant phase hypertension. J Hum Hypertens. 2002; 16:333–336. [PubMed: 12082494]
16. Higashi Y, Sasaki S, Nakagawa K, et al. Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med. 2002; 346:1954–1962. [PubMed: 12075056]
17. Redon J, Oliva MR, Tormos C, et al. Antioxidant activities and oxidative stress byproducts in human hypertension. Hypertension. 2003; 41:1096–1101. [PubMed: 12707286]
18. Agarwal R. Chronic kidney disease is associated with oxidative stress independent of hypertension. Clin Nephrol. 2004; 61:377–383. [PubMed: 15224800] This research shows that nonhemodynamic factors may play a greater role in the generation of oxidative stress in chronic kidney disease.
19. Saez GT, Tormos C, Giner V, et al. Factors related to the impact of antihypertensive treatment in antioxidant activities and oxidative stress by-products in human hypertension. Am J Hypertens. 2004; 17:809–816. [PubMed: 15363824]
20. Yasunari K, Maeda K, Nakamura M, et al. Effects of carvedilol on oxidative stress in polymorphonuclear and mononuclear cells in patients with essential hypertension. Am J Med. 2004; 116:460–465. [PubMed: 15047035]
21. Napoli C, Sica V, de Nigris F, et al. Sulfhydryl angiotensin-converting enzyme inhibition induces sustained reduction of systemic oxidative stress and improves the nitric oxide pathway in patients with essential hypertension. Am Heart J. 2004; 148:e5. [PubMed: 15215814]
22. Kielstein JT, Bode-Boger SM, Frolich JC, et al. Asymmetric dimethylarginine, blood pressure, and renal perfusion in elderly subjects. Circulation. 2003; 107:1891–1895. [PubMed: 12681993]
23. Fliser D, Kielstein JT, Haller H, et al. Asymmetric dimethylarginine: a cardiovascular risk factor in renal disease? Kidney Int. 2003 Suppl:S37–S40.
24. Takiuchi S, Fujii H, Kamide K, et al. Plasma asymmetric dimethylarginine and coronary and peripheral endothelial dysfunction in hypertensive patients. Am J Hypertens. 2004; 17:802–808. [PubMed: 15363823]
25. Kielstein JT, Impraim B, Simmel S, et al. Cardiovascular effects of systemic nitric oxide synthase inhibition with asymmetrical dimethylarginine in humans. Circulation. 2004; 109:172–177.

[PubMed: 14662708] This is the first report that systemic administration of ADMA has definite effects on the cardiovascular and renal function in healthy individuals.

26. Kitamoto S, Egashira K. Endothelial dysfunction and coronary atherosclerosis. Curr Drug Targets Cardiovasc Haematol Disord. 2004; 4:13–22. [PubMed: 15032649]
27. Lim HS, Felmeden D, Lip GY. Angiotensin II-mediated vascular inflammation: the balance between vascular endothelial growth factor and angiopoietins. Hypertension. 2005; 45:e3. [PubMed: 15583069]
28. Wolkart G, Stessel H, Brunner F. In vivo administration of D-arginine: effects on blood pressure and vascular function in angiotensin II-induced hypertensive rats. Atherosclerosis. 2004; 176:219–225. [PubMed: 15380443]
29. Kon V, Jabs K. Angiotensin in atherosclerosis. Curr Opin Nephrol Hypertens. 2004; 13:291–297. [PubMed: 15073487]
30. Zhou MS, Jaimes EA, Raij L. Inhibition of oxidative stress and improvement of endothelial function by amlodipine in angiotensin II-infused rats. Am J Hypertens. 2004; 17:167–171. [PubMed: 14751660]
31. da Cunha V, Tham DM, Martin-McNulty B, et al. Enalapril attenuates angiotensin II-induced atherosclerosis and vascular inflammation. Atherosclerosis. 2005; 178:9–17. [PubMed: 15585195]
32. Ward NC, Rivera J, Hodgson J, et al. Urinary 20-hydroxyeicosatetraenoic acid is associated with endothelial dysfunction in humans. Circulation. 2004; 110:438–443. [PubMed: 15262846] First demonstration of significant association between 20-HETE excretion and endothelial function in humans.
33. Quyyumi AA. Prognostic value of endothelial function. Am J Cardiol. 2003; 91:19H–24H.
34. Perticone F, Ceravolo R, Pujia A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation. 2001; 104:191–196. [PubMed: 11447085]
35. Perticone F, Maio R, Tripepi G, et al. Endothelial dysfunction and mild renal insufficiency in essential hypertension. Circulation. 2004; 110:821–825. [PubMed: 15289371] Mild to moderate renal impairment in patients with uncomplicated essential hypertension is affected in part by endothelial dysfunction unrelated to arterial pressure.
36. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation. 2002; 106:653–658. [PubMed: 12163423]
37. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000; 101:1899–1906. [PubMed: 10779454]
38. Bugiardini R, Manfrini O, Pizzi C, et al. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. Circulation. 2004; 109:2518–2523. [PubMed: 15136498] This research further emphasizes the fact that endothelial dysfunction in a setting of normal coronary arteries predicts future development of coronary disease.
39. Rossi R, Chiurlia E, Nuzzo A, et al. Flow-mediated vasodilation and the risk of developing hypertension in healthy postmenopausal women. J Am Coll Cardiol. 2004; 44:1636–1640. [PubMed: 15489096] This research suggests that ED might be an important etiological factor in hypertension.
40. Nadar S, Blann AD, Lip GY. Antihypertensive therapy and endothelial function. Curr Pharm Des. 2004; 10:3607–3614. [PubMed: 15579057]
41. Schiffrin EL. Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. Am J Hypertens. 2004; 17:1192–1200. [PubMed: 15607629]
42. Schiffrin EL, Park JB, Pu Q. Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure and on endothelial function. J Hypertens. 2002; 20:71–78. [PubMed: 11791028]
43. Schiffrin EL, Pu Q, Park JB. Effect of amlodipine compared to atenolol on small arteries of previously untreated essential hypertensive patients. Am J Hypertens. 2002; 15:105–110. [PubMed: 11863244]

44. Rizzoni D, Muiesan ML, Porteri E, et al. Effects of long-term antihypertensive treatment with lisinopril on resistance arteries in hypertensive patients with left ventricular hypertrophy. J Hypertens. 1997; 15:197–204. [PubMed: 9469796]

45. Palloshi A, Fragasso G, Piatti P, et al. Effect of oral L-arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. Am J Cardiol. 2004; 93:933–935. [PubMed: 15050504]

46. Zhou MS, Jaimes EA, Raij L. Atorvastatin prevents end-organ injury in salt-sensitive hypertension: role of eNOS and oxidant stress. Hypertension. 2004; 44:186–190. [PubMed: 15238570] Statins improve endothelial dysfunction and prevents end organ injury in salt-sensitive hypertension by maintaining vascular eNOS and inhibiting oxidative stress.

47. Danaoglu Z, Kultursay H, Kayikcioglu M, et al. Effect of statin therapy added to ACE-inhibitors on blood pressure control and endothelial functions in normolipidemic hypertensive patients. Anadolu Kardiyol Derg. 2003; 3:331–337. [PubMed: 14675884]

48. Kinlay S, Behrendt D, Fang JC, et al. Long-term effect of combined vitamins E and C on coronary and peripheral endothelial function. J Am Coll Cardiol. 2004; 43:629–634. [PubMed: 14975474] This study does not support the role of the antioxidant vitamins E and C for the treatment of coronary and peripheral endothelial dysfunction in patients with coronary artery disease.