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Review

Clinical Implications of Endothelial Dysfunction

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Summary: Endothelial dysfunction is increasingly recognized as an early event in the pathogenesis of cardiovascular disease. This observation is consistent with the growing appreciation of the role of endothelium in maintaining cardiovascular health. Endothelial dysfunction and coronary artery disease are both linked to hypertension, hypercholesterolemia, diabetes mellitus, and cigarette smoking. Modification of these conditions improves both endothelial function and coronary artery disease outcomes. Dietary and lifestyle modifications and antioxidant vitamin supplementation have a beneficial effect on endothelial function, as do angiotensin-converting enzyme inhibitors and lipid-lowering agents. Future studies will determine whether interventions that specifically target endothelial dysfunction can reduce rates of clinical disease.

Key words: angiotensin-converting enzyme inhibitors, atherosclerosis, coronary artery disease, endothelial dysfunction, hypercholesterolemia, hypertension, nitric oxide, statins

Introduction

An important area of research focuses on identification of mechanisms responsible for physiologic alterations that lead to disease. To this end, endothelial dysfunction is increasingly recognized as an early component of a variety of cardiovascular diseases, and many conditions associated with altered function of endothelium are also well-established risk factors for coronary artery disease (CAD). There is abundant evidence that some pharmacologic agents used to treat cardiovascular diseases, such as hypertension and atherosclerosis, can exert direct beneficial effects on endothelium, suggesting that at least part of their therapeutic action is associated with improvement in endothelial function. A number of new findings about endothelial dysfunction may have potential clinical relevance. The purpose of this review is to place these findings in perspective for the clinician.

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Risk Factors for Endothelial Dysfunction

Common disorders frequently associated with endothelial dysfunction include hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, and many others.

Hypertension

Persons with essential hypertension have been shown to have abnormal endothelium-dependent vascular function. This has been documented in studies exhibiting reduced vasodilator response to administration of acetylcholine.[1,2] This effect has been attributed to decreased active endothelium-dependent vasodilator nitric oxide (NO).[3] In addition to its potent vasodilator effects, NO inhibits vascular smooth muscle cell growth and platelet aggregation. Nitric oxide is synthesized from L-arginine, and its release from endothelium is induced by a number of substances, including acetylcholine and bradykinin, and in response to processes such as shear stress and oxidative stress.

Although studies of forearm resistance vessels in hypertensive subjects have failed to demonstrate improvement in flow-mediated vasodilation following normalization of blood pressure,[4,5] studies in large conduit arteries did show that control of hypertension restores the vasodilator response to acetylcholine.

Hypercholesterolemia

Studies in cholesterol-fed animals have shown dysfunction of endothelium-dependent vasodilation both prior to and after the development of atherosclerotic lesions[6] as well as impaired response to acetylcholine in rabbit aorta after brief incubation with low-density lipoprotein (LDL) cholesterol.[7] In

humans, endothelium-dependent vascular relaxation is impaired in hypercholesterolemic patients regardless of the presence of other coronary artery risk factors.[8,9] A high-fat meal was shown to impair vasoreactivity in normocholesterolemic men for up to 6 h.[10] Use of an NO synthase inhibitor acting on the L-arginine-NO pathway resulted in an increase in neointimal thickness and impairment of endothelial function in hypercholesterolemic rabbits; the findings suggest that the changes in the neointima resulted from factors responsible for the initiation and progression of atherosclerosis, including monocyte recruitment and adherence, oxidation of LDL, and formation of macrophage foam cells.[11] It thus appears that endothelial dysfunction resulting in reduced availability or activity of NO precedes the onset of atherosclerosis.[8,9] Studies by Harrison *et al.* have shown that endothelial dysfunction induced by increased levels of LDL is reversible with reduction of LDL.[12]

Cigarette Smoking

Studies in healthy young adults have shown that flow-mediated brachial artery dilation is impaired in response to cigarette smoking in a dose-dependent manner, with those smoking ≥ 20 pack-years having reduced or absent dilation.[13] Other investigations have shown impairment of endothelium-dependent dilation of forearm resistance vessels after long-term smoking and with hypercholesterolemia; a synergistic effect of the two conditions occurs in association with increases in oxidized LDL.[14] The latter finding supports the hypothesis that the effects of smoking and increased oxidized LDL are associated with alteration of the redox state of the vascular wall, particularly in the endothelium. An increase in reactive oxygen species is known to inhibit NO-mediated vasodilation.[15] We have recently shown that coronary endothelial dysfunction progresses rapidly in smokers compared with nonsmokers.[16]

Diabetes

Investigations in experimental models of diabetes have shown that impairment of endothelium-dependent dilation is associated with abnormalities of the NO pathway and increased endothelial release of constrictor prostanoids that inhibit the effects of NO.[17] Patients with noninsulin-dependent diabetes have impairment of both endothelium-dependent and endothelium-independent dilation, indicating an abnormality in the NO pathway.[18,19] Similarly, patients with insulin-dependent diabetes mellitus exhibit impaired endothelium-dependent dilation in forearm resistance vessels that is attributable to decreased release or activity of NO.[18,19]

Effects of Nonpharmacologic Interventions on Endothelial Dysfunction

The findings by Harrison *et al.*[12] strongly suggest that endothelial dysfunction may be reversible. Given the increasing evidence of early derangement of endothelial function in a variety of conditions associated with atherosclerosis and CAD, it is reasonable to consider endothelium as a likely target for therapeutic intervention.

A number of dietary and lifestyle changes have been shown to result in beneficial changes in endothelial function. Administration of L-arginine improved endothelium-dependent vasorelaxation and decreased atherosclerosis in hypercholesterolemic rabbits.[20] In other animal studies, L-arginine also improved neoendothelium-dependent vasodilation and reduced neointimal thickening after balloon injury,[21,22] and preserved endothelium-dependent vasodilation in resistance vessels.[23] In humans, L-arginine administration has been found to improve endothelial function in the coronary circulation,[24] and oral L-arginine supplementation improved endothelium-mediated flow-dependent dilation in the forearm of young subjects with hypercholesterolemia.[25]

Although preliminary findings[10] suggest an association of high-fat meals with derangement of endothelial function, there have been no published studies in humans of the effects of low-fat diets in improving damaged endothelium.

Patients who stop smoking after a myocardial infarction (MI) have a lower risk of a recurrent infarction than do those who continue smoking. We have shown that among patients with CAD with endothelial dysfunction in their coronary arteries, current smokers have more severe changes than do nonsmokers and remote past smokers, and these changes progress more rapidly.[16] Other studies have shown that flow-mediated dilation in the brachial artery is greater in former smokers than in current smokers, suggesting that the smoking-related impairment in endothelial function is at least partly reversible.[13]

Physical training has been associated with a beneficial effect on endothelial function in patients with chronic heart failure, possibly due to increased endothelial release of NO.[26]

Use of antioxidants has been associated with improved endothelial function. A possible mechanism is that antioxidant substances counteract oxidative stress; it is known that increased production of reactive oxygen species results in inactivation of NO and impairment of endothelium-dependent dilation.[27] Ascorbic acid, which also prevents oxidation of LDL, has been found to reverse endothelial-mediated dilator dysfunction in the brachial artery of patients with CAD.[27] In smokers, ascorbic acid reduced oxidant stress[28] and monocyte adhesion.[29] The recent Cambridge Heart Antioxidant Study[30] showed that high doses of vitamin E were associated with a decreased 1-year incidence of nonfatal MI but not with reduction in cardiovascular deaths among a group of patients with heart failure largely due to CAD.

Effects of Pharmacologic Interventions on Endothelial Dysfunction

Lipid-lowering drugs have been shown to improve endothelial function. Hypercholesterolemic patients had restored response to acetylcholine in epicardial coronary arteries after

6 months of a cholesterol-reducing diet and cholestyramine treatment.[31] The degree of residual vasomotor impairment was related to post-treatment cholesterol levels.

Lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is associated with a reduced risk of all cardiovascular events in hypercholesterolemic patients. This clinical benefit may result, at least in part, from improvements in endothelial function. The use of statins alone or in combination with cholestyramine or antioxidant treatment improved vasomotor activity in large coronary artery and resistance vessels,[32–35] with the benefits observed as soon as 4 weeks after initiation of therapy in one study.[32] The amount of improvement of endothelium-dependent flow in resistance vessels correlated with the degree of lipid lowering. Statins have also been shown to reduce exercise-induced ischemia, as well as ischemia during daily life, after only 6 months of treatment.[36] It is unlikely that the modest changes noted in CAD progression even after many years of statin therapy would account for such early anti-ischemic effects. Rather, these observations suggest a more direct early effect, such as improved endothelial function. Indeed, this has recently been shown to occur in 1 month.[37]

Angiotensin-converting enzyme (ACE) inhibitors have been associated with reduced rates of ischemic events in patients with left ventricular dysfunction or acute MI and are being intensely investigated in patients with CAD without left ventricular dysfunction. Angiotensin-converting enzyme converts angiotensin I to the potent vasoconstrictor, angiotensin II; inhibition of this process may account for the anti-ischemic effects of ACE inhibitors observed in large clinical trials.[38–43] Angiotensin-converting enzyme also degrades bradykinin, a substance that stimulates the L-arginine-NO pathway to increase production of NO. Thus, ACE inhibition might be expected to improve NO-mediated endothelial function.

The ACE inhibitor enalaprilat was shown to improve acetylcholine-mediated and bradykinin-mediated epicardial and microvascular dilation in subjects with CAD or its risk factors, but did not affect the activity of the endothelium-independent vasodilator nitroprusside.[44] Subjects with the greatest impairment of acetylcholine-mediated dilation exhibited the greatest improvements with enalaprilat administration. In another study, enalaprilat also improved endothelium-dependent vasodilation with no effect on nitroprusside-mediated dilation in femoral arteries of patients with CAD or risk factors; again, the degree of potentiation of acetylcholine-mediated dilation was inversely proportional to baseline response.[45] Administration of the NO-synthase inhibitor L-NG monomethyl arginine (L-NMMA) inhibited the dilatative effects of bradykinin and acetylcholine but not those of nitroprusside. In the presence of L-NMMA, enalaprilat did not improve bradykinin- or acetylcholine-mediated response, indicating that the effect of the ACE inhibitor in improving endothelial function resulted from increased NO activity.[45]

The Trial on Reversing ENdothelial Dysfunction (TREND)[46] showed a significant effect after only 6 months of quinapril (40 mg/day) in improving endothelial function (compared with placebo) in patients with CAD but with preserved left ventricular function. Overall, the net change in coronary segment response was significantly greater ($p = 0.002$) among patients who received the ACE inhibitor. Logistic regression analysis showed that the only independent predictor of improved coronary endothelial function was assignment to quinapril ($p = 0.022$).[46] The level of improvement in response and the short time period (6 months) over which benefit was demonstrated were similar to those observed with statins. Several subsequent subgroup analyses of the response seen in the TREND population have been conducted. One report[47] categorized patients according to whether they had LDL levels above or below 130 mg/dl. Patients with higher LDL levels who were treated with the ACE inhibitor exhibited the greatest improvement in endothelial function, whereas patients with LDL levels >130 mg/dl assigned to placebo exhibited a worsening of endothelial function over the same time period. Another analysis examining the effect of smoking status found that endothelial dysfunction progressed in smokers assigned to placebo treatment but not in those assigned to quinapril.[48]

The ability of quinapril to improve endothelial function in this patient population suggests that ACE inhibition has the potential of exerting beneficial effects to prevent or reduce myocardial ischemia, a syndrome also associated with endothelial dysfunction. Anti-ischemic effects of ACE inhibitors in both daily life and exercise-induced ischemic syndromes have been reported in small pilot studies.[49,50] The ongoing placebo-controlled, randomized, double-blind Quinapril Anti-Ischemia and Symptoms of Angina Reduction (QUASAR) trial will assess the effects of quinapril on ischemia.

A recent preliminary report indicates that the ACE inhibitor lisinopril also improves endothelial function with 6 months' administration.[51] In this study, hyperlipidemic patients received lisinopril 20 mg/day or placebo, and forearm arterial response to endothelial-dependent (acetylcholine) and endothelial-independent (nitroprusside) dilators was assessed via plethysmography at baseline and at 6 months. Comparison of the response in the arms that receive infusions with those that did not showed that lisinopril treatment was associated with a significant increase in vasodilator response to acetylcholine, whereas placebo-treated subjects showed deteriorated response to acetylcholine over this brief time period.

Conclusion

Endothelial dysfunction and CAD share common risk factors, and endothelial dysfunction is present in a variety of cardiovascular pathologic conditions. Growing recognition of the importance of endothelium in cardiovascular health and disease has made it an increasingly attractive target for therapeutic intervention. Both nonpharmacologic and pharmacologic interventions show promise in improving endothelial dysfunction, most notably, in the latter category, statins and ACE inhibitors. Further study is required to determine whether intervention targeted at endothelial dysfunction can prevent clinical expression of disease.

References

1. Zeiher AM, Drexler H, Saurier B, Just H: Endothelium-mediated coronary blood flow modulations in humans: Effects of age, atherosclerosis, hypercholesterolemia, and hypertension. *J Clin Invest* 1993;92:652–662
2. Linder L, Kiowski W, Bühler FR, Lüscher TF: Indirect evidence for release of endothelium-derived relaxing factor in human forearm circulation in vivo: Blunted response in essential hypertension. *Circulation* 1990;81:1762–1767
3. Panza JA, Casion PR, Kilcoyne CM, Quyyumi AA: Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. *Circulation* 1993;87:1468–1474
4. Panza JA, Quyyumi AA, Callahan TS, Epstein SE: Effect of antihypertensive treatment on endothelium-dependent vascular relaxation in patients with essential hypertension. *J Am Coll Cardiol* 1993;31:1145–1151
5. Creager MA, Roddy M-A: Effect of captopril and enalapril on endothelial function in hypertensive patients. *Hypertension* 1994; 24:499–505
6. McLenachan JM, Williams JK, Fish RD, Ganz P, Selwyn AP: Loss of flow-mediated endothelium-dependent dilation occurs early in the development of atherosclerosis. *Circulation* 1991;84:1273–1278
7. Andrews HE, Bruckdorfer KR, Dunn RC, Jacobs M: Low-density lipoproteins inhibit endothelium-dependent relaxation in rabbit aorta. *Nature* 1987;327:237–239
8. Drexler H, Zeiher AM: Endothelial function in human coronary arteries in vivo: Focus on hypercholesterolemia. *Hypertension* 1991;18(suppl II):II-90–II-99
9. Seiler C, Hess OM, Buechi M, Suter TM, Krayenbuehl HP: Influence of serum cholesterol and other coronary risk factors on vasomotion of angiographically normal coronary arteries. *Circulation* 1991;88(pt. 1):2139–2148
10. Plotnick GD, Corretti MC, Vogel RA: Transient impairment of endothelium-mediated brachial artery reactivity following a fatty meal (abstr). *J Am Coll Cardiol* 1996;27:287A
11. Cayatte AJ, Palacino JJ, Horten K, Cohen RA: Chronic inhibition of nitric oxide production accelerates neointima formation and impairs endothelial function in hypercholesterolemic rabbits. *Arterioscler Thromb* 1994;14:753–759
12. Harrison DG, Armstrong ML, Freiman PC, Heistad DD: Restoration of endothelium-dependent relaxation by dietary treatment of atherosclerosis. *J Clin Invest* 1987;80:1808–1811
13. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE: Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88: 2149–2155
14. Heitzer T, Yla-Herttuala S, Luoma J, Kurz S, Munzel T, Just H, Olschewski M, Drexler H: Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia: Role of oxidized LDL. *Circulation* 1996;93: 1346–1353
15. Khan BV, Harrison DG, Olbrych MT, Alexander RW, Medford RM: Nitric oxide regulates vascular cell adhesion molecule 1 gene expression and redox-sensitive transcriptional events in human vascular endothelial cells. *Proc Natl Acad Sci USA* 1996;93: 9114–9119
16. Pepine CJ, Schlaifer JD, Mancini GBJ, Pitt B, O'Neill BJ, Haber HE, on behalf of the TREND Investigators: Influence of smoking status on progression of endothelial dysfunction. *Clin Cardiol* 1998;21:331–334
17. Lash JM, Bohlen HG: Structural and functional origins of suppressed acetylcholine vasodilation in diabetic rat intestinal arterioles. *Circ Res* 1991;69:1259–1268
18. Lieberman EH, Uehata A, Polak J, Ganz P, Selwyn AP, Creager MA, Yeung AC: Flow-mediated vasodilation is impaired in the brachial artery of patients with coronary artery disease or with diabetes mellitus (abstr). *Clin Res* 1993;41:217A
19. McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGrath LT, Henry WR, Andrews JW, Hayes JR: Impaired endothelium-dependent and -independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1992;35:771–776
20. Cooke JP, Singer AH, Tsao D, Zera P, Rowan RA, Billingham ME: Antiatherogenic effects of L-arginine in the hypercholesterolemic rabbit. *J Clin Invest* 1992;90:1168–1172
21. Weidinger FS, McLenachan JM, Cybulsky MI, Fallon JT, Cooke JP, Ganz D: Hypercholesterolemia enhances macrophage recruitment and endothelial vasodilator dysfunction after balloon injury. *Circulation* 1991;84:755–767
22. Hamon M, Vallet B, Bauters C, Wernert N, McFadden EP, Lablanche JM, Dupuis B, Bertrand ME: Long-term oral administration of L-arginine reduces intimal thickening and enhances neoendothelium-dependent acetylcholine-induced relaxation after arterial injury. *Circulation* 1994;90:1357–1362
23. Rossitch E, Alexander E III, Black PM, Cooke JP: L-arginine normalizes endothelial function in cerebral vessels from hypercholesterolemic rabbits. *J Clin Invest* 1991;87:1295–1297
24. Drexler H, Zeiher AM, Meinzer K, Just H: Correcting endothelial dysfunction in coronary microcirculation of hypercholesterolemic patients by L-arginine. *Lancet* 1991;338:1546–1550
25. Clarkson P, Adams MR, Powe AJ, Donald AE, McCredie R, Robinson J, McCarthy SN, Keech A, Celermajer DS, Deanfield JE: Oral L-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults. *J Clin Invest* 1996;97:1989–1994
26. Hornig B, Maier V, Drexler H: Physical training improves endothelial function in patients with chronic heart failure. *Circulation* 1996;93:210–214
27. Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF Jr, Vita JA: Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1996;93: 1107–1113
28. Reilly M, Delanty N, Lawson JA, FitzGerald GA: Modulation of oxidant stress in vivo in chronic cigarette smokers. *Circulation* 1996;94:19–25
29. Weber C, Erl W, Weber K, Weber PC: Increased adhesiveness of isolated monocytes to endothelium is prevented by vitamin C intake in smokers. *Circulation* 1996;93:1488–1492
30. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ: Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996;347:781–786
31. Leung W-H, Lau C-P, Wong C-K: Beneficial effect of cholesterol lowering therapy on coronary endothelium-dependent relaxation in hypercholesterolaemic patients. *Lancet* 1993;341:1496–1500
32. O'Driscoll G, Green D, Taylor RR: Simvastatin, an HMG-CoA reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997;95:1126–1131
33. Egashira K, Hirooka Y, Kai H, Sugimachi M, Suzuki S, Inou T, Takeshita A: Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. *Circulation* 1994;89:2519–2524
34. Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Bocuzzi SJ, Cedarholm JC, Alexander RW: Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995;332:481–487
35. Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P: The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med* 1995; 332:488–493
36. Andrews TC, Raby K, Barry J, Naimi CL, Allred E, Ganz P, Selwyn AP: Effect of cholesterol reduction on myocardial ischemia in patients with coronary disease. *Circulation* 1997;95:324–328

37. O'Driscoll G, Green D, Taylor RR: Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997;95:1126–1131
38. Yusuf S, Pepine CJ, Garces C, Pouleur H, Salem D, Kostis J, Benedict C, Rousseau M, Bourassa M, Pitt B: Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;340:1173–1178
39. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM, on behalf of the SAVE Investigators: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; 327:669–677
40. Rutherford JD, Pfeffer MA, Moyé LA, Davis BR, Falker GC, Kowey PR, Lamas GA, Miller HS, Packer M, Rouleau JL, on behalf of the SAVE Investigators: Effects of captopril on ischemic events after myocardial infarction: Results of the Survival and Ventricular Enlargement Trial. *Circulation* 1994;90:1731–1738
41. Acute Infarction Ramipril Efficacy (AIRE) Study Investigators: Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821–828
42. ISIS-4 (Fourth International Study of Infarct Survival) Collaboratory Group: ISIS-4: Randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 38,050 patients with suspected acute myocardial infarction. *Lancet* 1994;345:669–685
43. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico: GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343: 1115–1122
44. Prasad A, Husain S, Mincemoyer R, Panza JA, Cannon RO III, Quyyumi AA: Coronary endothelial dysfunction improves with angiotensin-converting enzyme inhibition (abstr 348). *Circulation* 1996;94(suppl):I-61
45. Prasad A, Husain S, Mincemoyer R, Hathaway L, Quyyumi AA: Converting enzyme inhibition improves endothelial dysfunction in humans by increasing nitric oxide activity (abstr 743-2). *J Am Coll Cardiol* 1997;27:192A
46. Mancini GBH, Henry GC, Macaya C, O'Neill BJ, Pucillo AL, Carere RG, Wargovich TJ, Mudra H, Lüscher TF, Klibaner MI: Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: The TREND (Trial on Reversing ENdothelial Dysfunction) Study. *Circulation* 1996;94:258–265
47. Pitt B, Pepine C, O'Neill B, Haber H, Pressler M, Mancini GBJ: Modulation of ACE inhibitor efficacy on coronary endothelial dysfunction by low-density lipoprotein cholesterol (abstr 714-5). *J Am Coll Cardiol* 1997;27:70A
48. Schlaifer JD, Mancini GBJ, O'Neill BJ, Pitt B, Haber HE, Pepine CJ: Influence of smoking status on angiotensin-converting enzyme inhibition-related improvement in coronary endothelial function (abstr 223). *Eur Heart J* 1997;18(suppl):15
49. Lai C, Onnis E, Orani E, Pirisi R, Soro A, Cherchi A: Effects of enalapril in normotensive patients with stable effort angina: A double blind, placebo controlled study. *Drugs Exp Clin Res* 1990; 16:299–305
50. Schneeweiss A, Marmor AT, Rettig-Sturmer G: Anti-ischemic effects of cilazapril in patients with both hypertension and angina. *Cardiology* 1991;79:46–48
51. Lee AFC, Dick JBC, Struthers AD: Can lisinopril improve endothelial function in hyperlipidemics? (abstr 921-93). *J Am Coll Cardiol* 1997;27:46A