

Does bradykinin play a role in the regulation of vascular tone in humans?

Helmut Drexler, MD

Professor of Medicine - Chairman of Medicine - Chief of Cardiology - Medizinische Hochschule Hannover - GERMANY

Recent experimental studies suggest that bradykinin, which induces endothelial release of nitric oxide (NO), prostacyclin, and/or endothelium-derived hyperpolarizing factor, plays an important role in the regulation of vascular tone at rest and during flow-stimulated conditions. In humans, endothelium-dependent vasodilation induced by bradykinin can be blocked by specific B₂-receptor blockers, and, in part, by NO synthase. Endogenous bradykinin contributes in an important way to the regulation of coronary vascular tone under resting and flow-stimulated conditions, in human peripheral and coronary arteries. The beneficial effects exerted by the angiotensin-converting enzyme (ACE) inhibitors in heart failure and coronary artery disease could in part be explained by an increased availability of bradykinin, hence improved endothelial function, since ACE is identical to kininase II, which degrades bradykinin.

Keywords: endothelium; nitric oxide; flow-dependent vasodilation; endothelium-derived hyperpolarization factor; bradykinin; vascular tone; ACE inhibition

Address for correspondence: Prof Dr med Helmut Drexler, Chief of Cardiology, Medizinische Hochschule Hannover, Carl-Neubergstr 1, 30625 Hannover, Germany (e-mail: Drexler.Helmut@MH-Hannover.de)

The endothelium plays a fundamental and obligatory role in the regulation of vascular tone throughout the circulation as a result of the release of a variety of substances that modulate the contractile behavior of underlying vascular smooth muscle cells.¹ The phenomenon of endothelium-dependent relaxation has been demonstrated in human arteries² and has been attributed to the actions of the endogenous vasodilators such as endothelium-derived nitric oxide (NO) and prostacyclin.^{1,3} Recent evidence has also emerged of an endothelium-derived hyperpolarizing factor (EDHF),⁴ which also causes vasodilation and is distinct from NO and prostacyclin.^{4,5} NO is released constantly in the basal state,⁶ but the release of endothelium-derived vasodilators is also influenced by dynamic factors. The change in vascular tone in response to changes in flow,⁷ which has been documented in the human coronary and peripheral arteries,⁸ is also mediated by endothelium-dependent mechanism(s).⁹ While the importance of the endothelium in regulating the aggregate hemodynamic properties of vascular networks is therefore beyond doubt,¹⁰ the specific role of the different endogenous agents in mediating vasodilator responses in the human coronary circulation remain poorly understood.

Bradykinin is a vasoactive kinin that is liberated from its substrate kininogen by the action of kallikrein¹¹ and that is known to be involved in a wide range of biological processes. Bradykinin is a potent vasodilator which acts through endothelial bradykinin B₂ receptors to stimulate the release of endothelium-derived NO, prostacyclin,¹² and EDHF.⁴ It was shown previously that bradykinin is released from endothelial cells^{13,14} and that cultured human endothelial cells are able to generate vasoactive kinins in basal conditions.¹⁵ In addition, there is evidence of basal bradykinin release in the heart¹⁶ and of an endogenous kininogen/kinin system within the vascular wall.¹⁷ The local concentration of bradykinin is affected by several enzymes, such as kininase II (angiotensin-converting enzyme) or the enzymes that degrade bradykinin to inactive peptides. Thus, there is evidence of an endogenous kininogen/kinin system within the vascular wall, raising the possibility that bradykinin plays an important role in mediating vasomotor responses in vivo. Numerous experimental studies have addressed the vascular effects of bradykinin and have reported physiological vascular effects of bradykinin in animal models. However, the role of bradykinin in modulating vascular tone in humans remains controversial. There is evidence that physiological doses of bradykinin exert vasodilator



effects in the human circulation, both in the forearm vasculature and the coronary circulation. This effect can be blocked either by specific bradykinin B₂ receptor blockers¹⁸ or by the inhibition of NO synthesis.^{19,20} Kuga et al showed that intracoronary infusion of bradykinin dilated human epicardial coronary arteries in vivo, and that the vasodilator effect of bradykinin was impaired in stenotic coronary arteries.²¹ The degree of endothelium-dependent relaxations to bradykinin appears to be comparable between large vessels and microvessels. However, the contribution of NO and EDHF is markedly dependent on vessel size: in large arteries, both NO and EDHF were shown to contribute equally to the vasorelaxation, whereas in microvessels most of the vasorelaxation was attributed to EDHF.²² These in vitro observations have been confirmed, in part, by in vivo studies, which showed that the intracoronary infusion of bradykinin increased coronary diameter, but that the latter was significantly attenuated by N^G-monomethyl-L-arginine (L-NMMA), an inhibitor of NO synthesis.^{23,24} Systemic plasma levels of bradykinin are very low, but can now be measured by sensitive techniques.²⁵ Systemic administration of bradykinin lowers blood pressure in a dose-related manner through marked reduction in peripheral vascular resistance.²⁶ The release of NO by bradykinin has been confirmed in vivo by direct measurement of NO in the hand circulation of healthy volunteers.²⁷ These studies in humans in vivo or in human vessels in vitro have clearly confirmed a large body of experimental data that bradykinin is a vasodilating agent by release both prostaglandins, NO, and EDHF. However, these studies did not elucidate the role of endogenously produced bradykinin (or kinins) in the regulation of vascular tone in

humans. The determination of the relative contribution of bradykinin to the regulation of vascular tone in humans in vivo has only recently been possible since the development of selective bradykinin antagonists, specifically those directed at the B₂ receptor through which bradykinin mediates its endogenous physiological actions. In this regard, the development of D-Arg[Hyp³, Thi⁵, D-Tic⁷, Oic⁸]bradykinin (HOE 140) has represented a major advance since it has been shown to be highly specific, to be 500 times more potent than the early bradykinin B₂ receptor antagonists,^{28,29} and to abolish bradykinin-mediated cardiac effects in rats as well as inhibit the vasodilatory actions of exogenous bradykinin in man.¹⁸

A study carried out by us in 1995 represented the first time HOE 140 was used in the human coronary circulation, and was the first demonstration of the endogenous role of bradykinin in human coronary vasomotor control.³⁰ This study evidenced a consistent reduction in epicardial coronary area following bradykinin B₂ receptor blockade. Since flow is largely determined by changes in the caliber of resistance vessels (those less than 400 μ in diameter³¹), the reduction in coronary blood flow implies that endogenous bradykinin is also important in the regulation of normal basal vascular tone at the level of resistance vessels. These findings are consistent with the results of experimental studies that have also shown that bradykinin B₂ receptor blockade leads to a significant reduction in coronary blood flow in normotensive rats.³² Similarly, Koller et al³³ showed that HOE 140 decreased the basal diameter of muscular arterioles, suggesting that bradykinin actively participated in the development of basal vascular tone in skeletal muscle microcircu-

lation. In contrast, in isolated perfused human placenta, bradykinin was found to induce a thromboxane-mediated constriction,³⁴ suggesting that there were differences in the effects and mechanisms of action of bradykinin in different vascular regions. Our aforementioned study³⁰ also showed that, in addition to the influence on basal coronary tone, HOE 140 reduced the flow-dependent dilator response to papaverine. Flow-dependent dilation was thus shown to be an important mechanism in the regulation of the aggregate hemodynamic properties of vascular networks, and its presence in resistance as well as epicardial vessels was confirmed by Kuo et al.³⁵ The degree of flow-dependent dilation observed by us³⁰ (23.4±7.0%) was equivalent to that reported in our previous studies in patients with normal coronary arteries,⁸ and the magnitude of the effects of HOE 140 on basal epicardial coronary area correlated significantly with those on flow-dependent dilation at the same site in the proximal vessel. These findings imply that the vasoconstrictive effects of the bradykinin B₂ receptor antagonist may be due to suppression of the effects of endogenous bradykinin released in response to increases in flow both at the level of conduit and resistance vessels. Indeed, Mombouli and Vanhoutte³⁶ showed that a bradykinin antagonist decreased the basal production (or release) of EDRF in perfused canine carotid arteries, suggesting the existence of local kinin-generating system(s) that would contribute to basal flow-dependent release of EDRF.

In our aforementioned study,³⁰ assessment of flow-dependent dilation before and after HOE 140 showed that there was a tendency for the papaverine-induced increase in blood flow to be smaller in the

presence than in the absence of the bradykinin B₂ receptor agonist. We had previously shown that repeated measurements of papaverine-induced flow-dependent dilation were highly reproducible in the same patient,⁸ and experimental studies evidenced a linear relationship between the extent of increase in flow and the subsequent dilator response.⁷ We observed³⁰ that the maximal blood flow increase in response to papaverine was similar before and after HOE 140 in half the patients studied and that in these, the degree of reduction in flow-dependent dilator response was comparable to that in the group as a whole. Therefore, the apparent reduction in flow-dependent dilation after HOE 140 was unlikely to merely reflect the change in papaverine-induced coronary flow reserve after bradykinin B₂ receptor blockade. Although the underlying mechanisms by which HOE 140 influences coronary vasomotor tone cannot be determined with certainty, the absence of any significant changes in blood pressure or heart rate during HOE 140 administration seems to indicate that the vasomotor response to HOE 140 is indeed attributable to the suppression of the local vasodilator actions of bradykinin rather than to compensatory hemodynamic mechanisms. Similarly, the presence of a normal dilator response to the endothelium-independent vasodilator nitroglycerin after HOE 140 suggests that its effects do not result from a change in vascular smooth muscle cell sensitivity. The vasodilator actions of bradykinin are largely mediated by the stimulated release of endothelium-derived NO, prostacyclin, and EDHF,⁴ and it is therefore likely that HOE 140 acts by reducing the endogenous bradykinin-stimulated release of one or more of these endothelium-derived vasodilators. Human vessels

obtained from the operating room have extended these findings by showing that the vasodilator effect of bradykinin is related, in part, to EDHF: previous observations have shown that the endothelium-dependent hyperpolarization response to bradykinin occurs in human coronary arteries from patients with different cardiac diseases including dilated and ischemic cardiomyopathy.⁴ These data suggest that endogenous bradykinin has a role in modulating coronary tone in healthy human vessels as well as diseased arteries. Interestingly, while bradykinin appears to modulate both the basal and flow-mediated vasomotor tone in the coronary circulation, its role in the forearm vasculature was restricted to flow-mediated vascular response.³⁷

Angiotensin-converting enzyme (ACE) inhibitors have undoubtedly become a cornerstone in the treatment of heart failure and are known to exert beneficial effects in patients with coronary artery disease.^{38,39} So far, the beneficial effects of ACE inhibitors have been attributed to a reduction in angiotensin II and norepinephrine levels.⁴⁰ However, since ACE is identical to kininase II which inactivates bradykinin, ACE inhibition not only reduces angiotensin II, but is also associated with increased levels of bradykinin.²⁵ The contribution of kinins to the hypotensive effect of ACE inhibitors has been postulated,⁴¹ but never established in humans for want of a bradykinin receptor antagonist suitable for use in humans. In this regard, the development of the bradykinin B₂-receptor antagonist HOE 140, now known as icatibant, has provided a valuable tool since it has been shown to be highly specific.²⁸ Furthermore, in humans, icatibant has been shown to inhibit bradykinin-induced vasodilation in the forearm resistance vessels.¹⁸

Experimental studies have shown that ACE inhibitors stimulate the endothelial release of NO and prostacyclin by a bradykinin-mediated mechanism,⁴² thereby enhancing endothelium-dependent vasodilation. These experimental studies raised the question of whether or not ACE inhibition may improve endothelial function in humans and whether the potential beneficial effect of ACE inhibition is bradykinin-mediated. To answer these questions, we performed experiments in healthy volunteers and examined the effects of the ACE inhibitor quinaprilat, the selective bradykinin B₂-receptor antagonist icatibant, and their combination, on resting tone and flow-dependent, endothelium-mediated vasodilation of the radial artery in healthy volunteers. The major result was that ACE inhibition enhances flow-dependent, endothelium-mediated dilation in humans by a bradykinin-dependent mechanism (*Figure 1*).³⁷ Icatibant attenuated flow-dependent, endothelium-mediated dilation of the radial artery consistent with our previous observations in coronary arteries.³⁰ Similarly, experimental studies have shown that a bradykinin antagonist decreases the production or release of endothelium-derived relaxing factors in isolated perfused arteries.³⁶ Conversely, quinaprilat, but not placebo, improved flow-dependent, endothelium-mediated dilation, an effect that was completely abolished during infusion of icatibant. Thus, our data support the concept that ACE inhibitors exert endothelium-dependent vascular effects related to increased local concentrations of endogenous kinins. In this respect, it is noteworthy that administration of ACE inhibitors causes an increase in plasma levels of bradykinin in humans.²⁵

These observations may explain some of the beneficial effects of

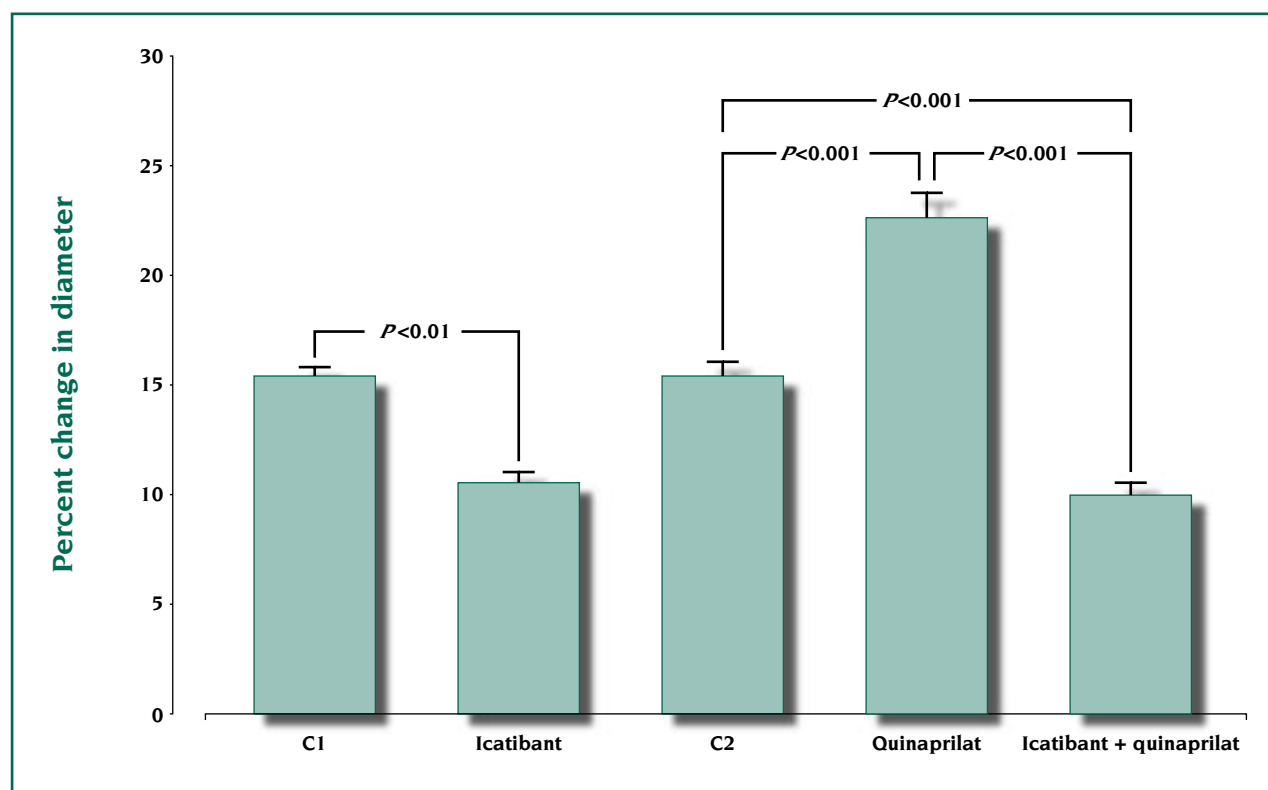


Figure 1. Effect of bradykinin antagonism and ACE inhibition on flow-dependent dilation. Percentage change in radial artery diameter during reactive hyperemia (flow-dependent dilation) at control measurements 1 and 2 (C1 and C2) and during infusion of icatibant (HOE 140), quinaprilat, and both icatibant (HOE 140) and quinaprilat. Reproduced from ref 37: Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. *Circulation*. 1997;95:1115-1118. Copyright © 1997, American Heart Association. With permission.

ACE inhibition, including those related to coronary artery disease. Two megatrials have shown that ACE inhibition reduces mortality and recurrence of angina after myocardial infarction.^{38,39} Risk reduction in these trials was significant after 1 to 1.5 years of treatment, raising the question of whether or not ACE inhibition improves vascular function rather than the degree of coronary artery stenosis. In this respect, it is interesting to note that experimental⁴³ and clinical data⁴⁴ have shown that ACE inhibition restores coronary flow reserve, probably by a bradykinin-dependent mechanism, as suggested by the experimental study. It is conceivable that an improved endothelial function, related to accumulation of bradykinin, might provide vascular

protection during long-term treatment with ACE inhibitors. The results of the Trial on Reversing Endothelial Dysfunction (TREND)⁴⁵ support this concept. In this study, the effect of ACE inhibition on coronary artery endothelial function was determined in patients with established coronary atherosclerosis. In the quinapril-treated group, the initial vasoconstrictor response to intracoronary infusion of acetylcholine was dramatically reduced and, in part, normalized to a vasodilator response, whereas no change was observed in the placebo-treated group. These results suggest that quinapril, an ACE inhibitor with high tissue-binding affinity, attenuates impaired endothelial function in patients with coronary artery

disease. This beneficial effect of long-term ACE inhibition could be due to reduction of angiotensin-II and/or an increase in bradykinin. Inhibition of angiotensin II generation may attenuate smooth muscle contraction and generation of superoxide anions through stimulation of NADH/NADPH oxidase systems of smooth muscle cells.⁴⁶ The latter would inactivate endothelium-derived NO and thereby cause endothelial dysfunction. In addition, bradykinin-induced augmentation of NO release by endothelial cells is promoted by ACE inhibition.

Supported in part by the Deutsche Forschungsgemeinschaft (De148/7-2)

REFERENCES

- 1. Moncada S, Palmer RMJ, Higgs EA.** Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacol Rev.* 1991;43:109-142.
- 2. Förstermann U, Mügge A, Frölich JC.** Endothelium-dependent relaxation of human epicardial coronary arteries: frequent lack of effect of acetylcholine. *Eur J Pharmacol.* 1986;128:277-281.
- 3. Moncada S, Vane JR.** Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A₂ and prostacyclin. *Pharmacol Rev.* 1978;30:293-331.
- 4. Nakashima M, Mombouli JV, Taylor AA, Vanhoutte PM.** Endothelium-dependent hyperpolarization caused by bradykinin in human coronary arteries. *J Clin Invest.* 1993;92:2867-2871.
- 5. Chen G, Suzuki H, Weston AH.** Acetylcholine releases endothelium-derived hyperpolarizing factor and EDRF from rat blood vessels. *Br J Pharmacol.* 1988;95:1165-1174.
- 6. Vallance P, Collier J, Moncada S.** Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. *Lancet.* 1989;2:997-1000.
- 7. Holtz J, Förstermann U, Pohl U, Giesler M, Bassenge E.** Flow-dependent endothelium-mediated dilation of epicardial coronary arteries in conscious dogs. Effects of cyclooxygenase inhibition. *J Cardiovasc Pharmacol.* 1984;6:1161-1169.
- 8. Drexler H, Zeiher AM, Wollschläger H, Meinertz T, Just H, Bonzel T.** Flow-dependent coronary artery dilation in humans. *Circulation.* 1989;80:466-474.
- 9. Cooke JP, Stamler S, Andon N, Davies PF, McKinley G, Loscalzo J.** Flow stimulates endothelial cells to release a nitrovasodilator that is potentiated by reduced thiol. *Am J Physiol.* 1990;259:H804-H812.
- 10. Griffith TM, Edwards DH, Davies RL, Harrison TJ, Evans KT.** EDRF coordinates the behaviour of vascular resistance vessels. *Nature.* 1987;329:442-445.
- 11. Regoli D, Barabe J.** Pharmacology of bradykinin and related kinins. *Pharmacol Rev.* 1990;32:1-46.
- 12. Cherry P, Furchgott RF, Zawadzki JV, Iothianandan D.** Role of endothelial cells in relaxation of isolated arteries by bradykinin. *Proc Natl Acad Sci USA.* 1982;79:2106-2110.
- 13. Busse R, Lamontagne D.** Endothelium-derived bradykinin is responsible for the increase in calcium produced by angiotensin-converting enzymes in human endothelial cells. *Naunyn-Schmiedeberg's Arch Pharmacol.* 1991;244:126-129.
- 14. Wiemer G, Schölkens BA, Becker RHA, Busse R.** Ramiprilat enhances endothelial autacoid formation by inhibiting breakdown of endothelium-derived bradykinin. *Hypertension.* 1991;18:558-563.
- 15. Van Iwaarden F, deGroot PG, Sixma JJ, Berretini M, Bouma BN.** High molecular weight kininogen is present in cultured human cells: localization, isolation and characterization. *Blood.* 1988;71:1268-1276.
- 16. Baumgarten CR, Linz W, Kunkel G, Schölkens BA, Wiemer G.** Ramiprilat increases bradykinin outflow from isolated hearts of rats. *Br J Pharmacol.* 1993;108:293-295.
- 17. Oza NB, Schwartz JH, Goud HD, Levinsky NG.** Rat aortic smooth muscle cells in culture express kallikrein-kininogen and bradykininase activity. *J Clin Invest.* 1990; 85:597-600.
- 18. Cockcroft JR, Chowienczyk PJ, Brett SE, Bender N, Ritter JM.** Inhibition of bradykinin-induced vasodilation in the human forearm vasculature by icatibant, a B₂-receptor antagonist. *Br J Clin Pharmacol.* 1994;38:317-321.
- 19. O'Kane KPJ, Webb DJ, Collier JG, Vallance PJT.** Local L-NG^G-monomethyl-arginine attenuates the vasodilator action of bradykinin in the human forearm. *Br J Clin Pharmacol.* 1994;38:311-315.
- 20. Cockcroft JR, Chowienczyk PJ, Brett SE, Ritter JM.** Effect of N^G-monomethyl-L-arginine on kinin-induced vasodilation in the human forearm. *Br J Clin Pharmacol.* 1994;38:307-310.
- 21. Kuga T, Egashira K, Mohri M, et al.** Bradykinin-induced vasodilation is impaired at the atherosclerotic site but is preserved at the spastic site of human coronary arteries in vivo. *Circulation.* 1995;92:183-189.
- 22. Harasawa L, Shimokawa H, Nakashima M, Egashira K, Takeshita A.** Importance of endothelium-derived hyperpolarizing factor in human arteries. *J Clin invest.* 1997;100:2793-2799.
- 23. Kuga T, Mohri M, Egashira K, et al.** Bradykinin-induced vasodilation of human coronary arteries in vivo: role of nitric oxide and angiotensin-converting enzyme. *J Am Coll Cardiol.* 1997;30:108-112.
- 24. Kato M, Shiode N, Yamagata T, Matsuura H, Kajiyama G.** Bradykinin-induced dilatation of human epicardial and resistance coronary arteries in vivo: effect of inhibition of nitric oxide synthesis. *Heart.* 1997;78:493-498.



25. Pellacani A, Brunner HR, Nussberger J.

Plasma kinins increase after angiotensin-converting enzyme inhibition in human subjects.
Clin Sci. 1994;87:567-574.

26. Bönner G, Preis S, Schunk U, Toussaint C, Kaufmann W.

Hemodynamic effects of bradykinin on systemic and pulmonary circulation in healthy and hypertensive humans.

J Cardiovasc Pharmacol. 1990;15(suppl 6):46-56.

27. Vallance P, Patton S, Bhagat K, MacAllister R, Radomski M, Moncada S.

Direct measurement of nitric oxide in human beings.

Lancet. 1995;345:153-154.

28. Wirth K, Hock FJ, Albus U, et al.

HOE 140, a new potent and long-acting bradykinin antagonist: in vivo study.

Br J Pharmacol. 1991;102:774-777.

29. Hock FJ, Wirth K, Albus U, et al.

HOE 140, a new potent and long-acting bradykinin antagonist: in vitro studies.

Br J Pharmacol. 1991;102:769-773.

30. Groves P, Kurz S, Just H, Drexler H.

Role of endogenous bradykinin in human coronary vasomotor control.

Circulation. 1995;92:3424-3430.

31. Marcus ML, Chillian WM, Kanatsuka H, Dellsperger KC, Eastham CL, Lamping KG.

Understanding the coronary circulation through studies at the microvascular level.

Circulation. 1990;82:1-7.

32. Wang YX, Gavras I, Lammek B, Bresnahan M, Gavras H.

Effects of bradykinin and prostaglandin inhibition on systemic and regional hemodynamics in conscious normotensive rats.

J Hypertens. 1991;9:805-812.

33. Koller A, Rodenburg JM, Kaley G.

Effects of Hoe-140 and ramiprilat on arteriolar tone and dilation to bradykinin in skeletal muscle of rats.

Am J Physiol. 1995;168:H1628-H1633.

34. Wilkes BM, Mento PF.

Bradykinin-induced vasoconstriction and thromboxane release in perfused human placenta.

Am J Physiol. 1988;254:E681-E686.

35. Kuo J, Davis MJ, Chilian WM.

Endothelium-dependent flow-induced dilation of isolated coronary arterioles.

Am J Physiol. 1990;259:H1063-H1070.

36. Mombouli JV, Vanhoutte PM.

Kinins and endothelium-dependent relaxations to converting enzyme inhibitors in perfused canine arteries.

J Cardiovasc Pharmacol. 1991;18:926-927.

37. Hornig B, Kohler C, Drexler H.

Role of bradykinin in mediating vascular effects of ACE-inhibitors in humans.

Circulation. 1997;95:1115-1118.

38. Pfeffer MA, Braunwald E, Moye LA, et al.

Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction.

N Engl J Med. 1992;327:669-677.

39. Yusuf S, Pepine CJ, Garces C, et al.

Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fraction.

Lancet. 1992;340:1173-1178.

40. Drexler H, Banhardt U, Meinertz T, Wollschläger H, Lehmann M, Just H.

Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with chronic heart failure.

Circulation. 1986;74:245-251.

41. Vanhoutte PM, Auch-Schwelk W, Biondi ML, Lorenz RR, Schini VB, Vidal MJ.

Why are converting-enzyme inhibitors vasodilators?

Br J Clin Pharmacol. 1989;28:95S-104S.

42. Mombouli JV, Illiano S, Nagao T, Scott-Burden T, Vanhoutte PM.

Potential of endothelium-dependent relaxations to bradykinin by angiotensin I converting enzyme inhibitors in canine coronary arteries involves both endothelium-derived relaxing and hyperpolarizing factors.

Circ Res. 1992;71:137-144.

43. Schieffer B, Wollert K, Burzan R, Drexler H:

ACE-inhibitors restore coronary flow reserve in postinfarction reactive hypertrophy by a bradykinin-dependent mechanism.

Eur Heart J. 1996;17(suppl):191. Abstract.

44. Motz W, Strauer BE:

Improvement of coronary flow-reserve after long-term therapy with enalapril.

Hypertension. 1996;27:1031-1038.

45. Mancini GBJ, Henry GC, Macaya C, et al.

Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND study.

Circulation. 1996;94:258-265.

46. Rajogapalan S, Kurz S, Münzel T, et al.

Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: contribution to alterations of vascular tone.

J Clin Invest. 1996;97:1916-1923.