Editorial

Fibrinolytic actions of ACE inhibitors: a significant plus beyond antihypertensive therapeutic effects

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See article by Labinjoh et al. [14] (pages 707–714) in this issue.

Hypertension is one of the most common diseases, shown by the fact that about 35% of adult males in the Western World suffer from it. The incidence is getting higher with age, since over 65 years of age more than half of the population has high blood pressure. The situation is similar or even less favorable in Middle and Eastern European Countries. Untreated hypertension poses an acute life threatening condition. For more than 100 years, several attempts have been made to classify forms of hypertension by etiology and severity, and introduce antihypertensive therapy [1]. Thanks to very intense basic and clinical research on this field, several types of antihypertensive drugs have been developed with different mechanisms of action. Currently diuretics (e.g. thiazides), beta-receptor antagonists, calcium channel blockers, alpha-receptor antagonists, and angiotensin-converting enzyme (ACE) inhibitors are commonly used for the management of hypertension. Some other drugs (vasodilators, drugs that act on central and peripheral sympathetic nervous system) are less frequently used [2].

Hypertension is dangerous not only per se, but also because it is one of the most severe cardiovascular risk factors in man. Hypertension may elicit changes in the arterial wall, causing a reduction in internal diameter and elasticity of vessels subsequent to intimal and medial thickening, smooth muscle cell hypertrophy, and deposition of collagen. Hypertension can contribute to the acceleration of atherosclerosis if concomitant hyperlipoproteinemia is present, and it can also lead to functional changes in endothelial permeability, but not to complete denudation. Under hypertensive conditions a significant accumulation of different cells takes place in the subendothelial space, and there is an adherence of blood-borne cells to the endothelial surface. A very serious consequence of these changes in cerebral vessels is an increased incidence of both hemorrhagic and ischemic strokes [3]. In addition, hypertension affects the heart causing left ventricular hypertrophy and structural changes in the myocardium. Elevated vascular resistance represents an increased afterload. These changes may lead to decreased contractility, and an overall decrease in left ventricular performance [4].

In multi-center clinical trials conducted in the 1980s monitoring the effects of antihypertensive therapy favorable effects such as reduction of major cardiac and stroke complications were observed, however, difficulties also emerged. For example, it was a great disappointment that in the Australian Mild Hypertension Study and The Multiple Risk Factor Intervention Trial aggressive thiazide diuretic, or beta adrenergic blocker therapy resulted in adverse effects such as greater mortality, hyperglycemia, or increased triglyceride and VLDL levels [3].

ACE inhibitors acting on the renin–angiotensin system represent a powerful tool to reduce blood pressure. Major advantages of ACE inhibitor therapy are few side effects, no metabolic effects, and no water retention in the course of treatment. It has been established that ACE inhibitors not merely control hypertension, but they can prevent further cardiovascular events. A number of large scale trials including Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), Veteran’s Administration Cooperative Vasodilator Heart Failure Trial (V-HeFT), Studies of Left Ventricular Dysfunction (SOLVD), and Survival and Ventricular Enlargement (SAVE) trial have shown that ACE inhibitors can reduce mortality of heart failure. They also reduced left ventricular preload and afterload. Enalapril was found to have beneficial effects in patients with left ventricular dysfunction, as well as to
reduce long-term mortality in severe congestive heart failure (for reviews see [5,6]). Similar beneficial effects were found in the Assessment of Treatment with Lisinopril and Survival Study (ATLAS) [7]. In addition, prolonged ACE inhibitor therapy reversed left ventricular hypertrophy. ACE inhibitors had also beneficial effects on the vessels, improving endothelial function [6]. Long-term perindopril treatment increased arterial diameter and compliance [8].

Whether ACE inhibitors can favorably alter the course of diseases, such as atherosclerotic vascular disease, diabetic microalbuminuria and nephropathy, is a matter of debate. Will cardiovascular benefit be greater than that attributable to the decrease in blood pressure? Could ACE inhibitors be used for primary and secondary prevention in such diseases? This is currently one of the hottest issues in type scripts, as well as in electronic publications, of the research field [5,6,9]. Before we attempt to answer these questions, let us take a closer look at the action of ACE inhibitors on the renin–angiotensin and the kallikrein–kinin systems.

Functioning of the renin–angiotensin system, and the participation of angiotensin converting enzyme in that process is well known. Briefly, renin forms angiotensin I acting on angiotensinogen, a globulin of liver origin. Angiotensin I is converted to the octapeptide angiotensin II by ACE. ACE is a carboxypeptidase localized on the endothelial cell surface in the lung and other vascular beds. Renin is released into the circulation from juxtaglomerular cells in the wall of afferent arterioles to kidney glomeruli. Various factors including reduced renal perfusion pressure, salt depletion, and beta-receptor activation stimulate renin release, which in turn promotes the formation of angiotensin I and angiotensin II at the endothelium. Physiological effects of angiotensin II are mediated via the G-protein coupled AT₁ receptors. The renin–angiotensin system participates in both short-term and long-term blood pressure regulations. Immediate hypertensive effect of angiotensin II is due to an increase in peripheral vascular resistance subsequent to direct vasoconstriction and peripheral sympatho-adrenal stimulation. Long-term pressure elevation is the consequence of sodium retention, aldosterone secretion, and direct effects on kidney hemodynamics. Finally, increased angiotensin II concentration promotes cardiac hypertrophy and vascular remodelling [10].

The significance of the kallikrein–kinin system in cardiovascular regulation is not always recognized. Kinins are produced both within the vascular system and in different tissues. In the plasma, high molecular weight kininogens are cleaved by plasma kallikrein yielding the nonapeptide bradykinin, while in tissues kallidin (lysyl-bradykinin) is formed from low molecular weight kininogens [10]. Plasma kinins are quickly metabolized by kininase II (same as ACE) and kininase I enzymes. The effects of bradykinin are mediated via the G-protein coupled constitutive B₂ receptor. Bradykinin is a potent vasodilator. Its effect is mediated by multiple mechanisms: endothelium-derived nitric oxide, release of prostacyclin, and the so-called endothelium-derived hyperpolarizing factor (EDHF) [11]. Bradykinin plays no significant role in the blood pressure regulation in normotension, but in hypertension increased bradykinin levels seem to mediate compensatory vasodilation. Kinins also increase the permeability of post-capillary venules, which results in an elevated plasma filtration to tissues. On the other hand, kallikrein may also elevate blood pressure by directly converting prorenin to renin [12].

The hemostatic and the kallikrein–kinin systems are interconnected at least via two important mechanisms. One of them relates to the formation of endothelial mediators of the fibrinolysis. Vasoactive agents, of which bradykinin is 1000-fold more potent than the others, induce the release of tissue plasminogen activator (t-PA) into the circulation [13]. Endothelial cells are major sites of t-PA synthesis, which is substantially enhanced by blood flow-induced shear stress. In plasma most of the t-PA forms complex with its physiological inhibitor PAI-1, which is also an endothelial cell product. Endothelial cell surface has a t-PA binding site, bound t-PA functions as one of the plasminogen activators, and plasmin serves as the effector of fibrinolysis. Note, that kallikrein stimulates the formation of another plasminogen activator, urokinase [12].

The other mechanism involves the contact activation of Factor XII (Hageman) during which this factor gets into contact with a negatively charged surface (e.g. collagen), and in turn XIIa further activates the intrinsic pathway of blood coagulation. In addition to the initiation of thrombus formation, XIIa cleaves plasma prekallikrein, resulting in plasma kallikrein, and then the latter will produce bradykinin [12]. The consequent t-PA release inhibits microthrombus formation, whose dissolution is also much more effective if t-PA is incorporated during its formation [14].

From the above mechanisms it arises that the angiotensin-converting enzyme elevates blood pressure producing angiotensin II, as well as inactivating bradykinin, while ACE inhibitors can effectively reduce blood pressure. In addition, there is a possibility for ACE inhibitors to enhance fibrinolysis by preserving bradykinin from its breakdown. However, the exact relationship of the renin–angiotensin and the kinin systems with the fibrinolytic mediators in man has not been established yet. In this issue of Cardiovascular Research Labinjoh et al. [14] addressed this question. They determined the local effect of intra-arterial angiotensin II and bradykinin on the local forearm release of t-PA and PAI-1. They have shown, that angiotensin II, contrary to earlier results, does not directly affect local release of t-PA or PAI-1 from endothelial cells. However, systemic effects of angiotensin II may explain PAI-1 reducing effect of ACE inhibitor therapy, a previous finding. On the other hand, they found that intra-arterial bradykinin infusion substantially, and dose-dependently
increased local t-PA release in humans. These data suggest, that bradykinin contributes to local regulation of fibrinolysis in man.

Taken together, among antihypertensive agents ACE inhibitors proved to be particularly beneficial. They not only control high blood pressure, but also reduce mortality, the incidence of stroke, and re-infarction after heart failure. This is best seen in the recent Heart Outcome Prevention Evaluation (HOPE) trial with ramipril [9]. The mechanism of the benefit from this, and the aforementioned studies is unsettled, but according to Pepine ‘it is unlikely to be entirely due to reduced blood pressure’ [5]. Mechanisms and new data reviewed here suggest that enhanced endogenous fibrinolytic potential may significantly contribute to these beneficial effects of ACE inhibitor therapy. Therefore, I agree with the opinion that ACE inhibitors provide hope in cardiovascular complications related to hypertension [9], and they might serve as tools for primary or secondary prevention in such diseases [6].

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References

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