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Clinical implications for therapy: possible cardioprotective effects of ACE inhibition

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1 The circulating and tissue renin-angiotensin systems (RAS) contribute importantly to cardiovascular homeostasis. Systemic and/or local activation of the RAS is seen in many pathological conditions of the cardiovascular system (e.g. hypertension and congestive heart failure). Increased angiotensin production participates in the pathophysiology of these and other disease states. Accordingly, inhibitors of the renin angiotensin system have a broad spectrum of therapeutic efficacy.

2 Angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensive agents that do not adversely affect serum lipid levels. In addition, they reduce left ventricular hypertrophy.

3 ACE inhibitors cause coronary vasodilation and reduce ventricular work and wall stress. They have been shown to reduce experimental infarct size and to increase anginal threshold in humans.

4 After experimental or human myocardial infarction that results in significant left ventricular dysfunction, ACE inhibitors prevent ventricular dilatation and development of congestive heart failure, and may improve survival.

5 ACE inhibitors can prevent ventricular fibrillation and contractile impairment (stunned myocardium) associated with reperfusion injury after experimental myocardial ischaemia.

6 ACE inhibitors reduce preload and afterload, improve exercise capacity, reduce ventricular arrhythmias, and improve patient survival in clinical cardiac failure.

7 Taken together, inhibition of the RAS may potentially result in primary as well as secondary protective effects on the cardiovascular system.

Keywords ACE inhibition cardioprotection cardiovascular pharmacology renin angiotensin system

Introduction

One of the major discoveries in cardiovascular pharmacology of the modern era is the nonapeptide angiotensin converting enzyme inhibitor in the snake venom of *Bothrops jaracaca* (Ferreira, 1965). This discovery quickly translated into the development of synthetic orally active drugs that inhibit the renin angiotensin system in man (Ondetti *et al.*, 1977). In the early 1980s, angiotensin converting enzyme inhibitors were introduced into the clinical arena. Since then, this class of drug has emerged as one of the most important cardiovascular therapeutic agents in modern medicine. At about the same time, cellular and molecular biologic techniques were introduced to cardiovascular research. Molecular research has enabled physiologists

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Table 1 ACE inhibitors and potential cardioprotection

Effective antihypertensive agent
Regression of LVH
Reduces infarct size
Increases anginal threshold (unloading effect) (coronary vasodilation)
Attentuate reperfusion-induced myocardial dysfunction
Reduces reperfusion-induced ventricular arrhythmias
Improves survival in CHF
Prevention of ventricular enlargement (LV dysfunction, MI)

and biochemists to re-examine, in greater depth, many of the basic concepts of cardiovascular regulation. One of the outcomes of molecular research is an improved understanding of the biology of the renin angiotensin system (Dzau *et al.*, 1988; Dzau & Pratt, 1986). It is now appreciated that angiotensin is not only synthesized in the circulation but also locally in many tissues. The concept of an autocrine-paracrine mechanism of renin angiotensin action has evolved from the traditional endocrine concept (Dzau 1986, 1987). Inhibitors of renin angiotensin system, such as the angiotensin converting enzyme (ACE) inhibitor may exert much of their pharmacological effects via the blockade of local angiotensin production (Dzau, 1987). This mechanism may explain the general efficacy of this class of drug in the treatment of several major cardiovascular disorders, irrespective of the plasma renin level of the patients. Clinical and experimental data to date suggest that ACE inhibition might reduce coronary heart disease risk in hypertensive subjects, improve survival in patients with heart failure, and may influence coronary ischaemia and reperfusion injury. This paper will review briefly these potential protective effects of ACE inhibitors (Table 1) and speculate on their clinical implications.

ACE inhibition and hypertension

ACE inhibitors are effective antihypertensive agents (VA Cooperative Study, 1984; Williams, 1989). They have multiple targets of action including the blood vessels, the heart, the kidney, and the adrenal. Blockade of angiotensin production results in the dilation of the resistance vessels as well as an increase in the compliance of the large arteries (Simon *et al.*, 1984). Unlike conventional antihypertensive drugs (e.g. diuretics), ACE inhibitors have no metabolic effects and produce few symptomatic side effects. They maintain the quality of life of the hypertensive patient (Croog *et al.*, 1986). Thus, ACE inhibitors appear to be a promising class of antihypertensive agent.

ACE inhibition and cardiac hypertrophy

ACE inhibitors can prevent or even regress cardiac and vascular hypertrophy in experimental and human hypertension (Tarazi & Fouad, 1984; Ventura *et al.*, 1985). Recent data demonstrate that angiotensin has a direct growth promoting effect on vascular myocytes (Campbell-Boswell & Robertson, 1981; Geisterfer & Owens, 1988; Naftilan *et al.*, 1989) and may have a similar effect on cardiac myocytes (Khairallah *et al.*, 1972). In addition, angiotensin can facilitate noradrenaline release from noradrenergic nerve endings (Zimmerman, 1981). This angiotensin-induced sympathetic activation may also be involved with the growth promoting effect of angiotensin *in vivo*. Since left ventricular hypertrophy (LVH) is a major risk factor (Kannel *et al.*, 1970), regression of LVH by ACE inhibition may reduce cardiovascular complications. However, whether ACE inhibitors have any important clinical advantages over other antihypertensive agents remains to be established.

ACE inhibition in ischaemic heart disease

Angiotensin is a potent systemic and coronary vasoconstrictor. An inhibition of angiotensin production has been shown to cause direct coronary vasodilation (Kiowski & Burkart, 1988; Linz *et al.*, 1986; van Gilst *et al.*, 1986, 1987). ACE inhibitors also reduce the loading condition of the heart and decrease ventricular wall stress. Do ACE inhibitors exert clinically significant effects on coronary ischaemia? Daly and co-workers (1985) demonstrated that captopril increased the anginal threshold in patients with coronary artery disease. In addition to inhibiting angiotensin production, the vasodilatory effects of an ACE inhibitor may be due to non-angiotensin dependent effects (Zusman, 1984). For example, it has been shown that captopril stimulates prostaglandin biosynthesis. The data of van Gilst and co-workers (1987) demonstrated that the SH-containing ACE inhibitor, captopril, potentiates the vasodilatory effect of isosorbide dinitrate. This effect is postulated to be due to the SH group of captopril which may serve as

tissue SH donors to increase guanylate cyclase activity, the enzyme responsible for cyclic GMP production. This effect was not seen with a non-SH-containing ACE inhibitor. The clinical relevance of these SH effects of captopril remains to be proven.

Recently, the existence of a cardiac renin angiotensin system has been demonstrated (Dzau & Re, 1987; Lindpainter *et al.*, 1988). The production of angiotensin within the heart may exert direct influence on myocardial metabolism and function. Using an isolated perfused heart preparation, Linz and co-workers (1986) demonstrated that the inhibition of cardiac angiotensin converting enzyme by ramiprilat during coronary ischaemia reduced ventricular arrhythmia and improved myocardial metabolism which included enhanced ATP formation, increased glycogen stores, and reduced lactate production. These observations have been confirmed by van Gilst *et al.* (1986). Furthermore, in the canine reperfusion injury model, Mullane & Westlin (1988) showed that captopril attenuated the contractile impairment ('stunned myocardium') seen under this condition. These data suggest that angiotensin may influence cardiac membrane electrical stability, myocardial metabolism and function and that ACE inhibitors may prevent ventricular arrhythmia during coronary ischaemia. These studies also raise the question whether ACE inhibitors should be administered to patients during coronary ischaemia and be used as an adjunct to coronary angioplasty and thrombolysis. Currently, these actions must be considered to be of theoretical clinical relevance only and require confirmation in patient populations.

ACE inhibitors in congestive heart failure

Several trials have documented the efficacy of this class of agents in the treatment of chronic heart failure. Improvement in subjective and objective parameters, such as symptomatology, cardiothoracic ratio, ejection fraction and exercise capacity have all been reported (Captopril Multicenter Research Group, 1983, 1985; Cleland *et al.*, 1985). The CONSENSUS study of enalapril therapy in heart failure demonstrated that an ACE inhibitor can prolong survival in patients with advanced heart failure (CONSENSUS Trial Study Group, 1987). The impact of this study is indeed far reaching. A recent study of ACE inhibition in mild to moderate heart failure demonstrated that these agents are also efficacious in earlier forms of heart failure (Captopril-Digoxin Multicenter Research Group, 1988). Captopril plus diuretic therapy compared favourably with digoxin and diuretic. Will the use of ACE inhibitors in early heart failure alter prognosis? In a preliminary report, captopril appears to improve event-free survival of patients with mild to moderate heart failure (Kleber, 1987). In experimental studies, ACE inhibitors improve the survival of rats with moderate sized myocardial infarction accompanied by significant left ventricular impairment (Pfeffer *et al.*, 1985). These studies also show that chronic inhibition of the renin angiotensin system prevents ventricular remodelling and dilation which proceed the development of frank congestive heart failure. Two recent clinical studies have demonstrated that captopril prevented ventricular dilatation when administered to patients 2 weeks after an anterior myocardial infarction with significant ventricular dysfunction (Pfeffer *et al.*, 1988; Sharpe *et al.*, 1988). Currently, several ongoing multicenter trials are studying the effects of ACE inhibition on cardiac mortality and the development of heart failure after myocardial infarction.

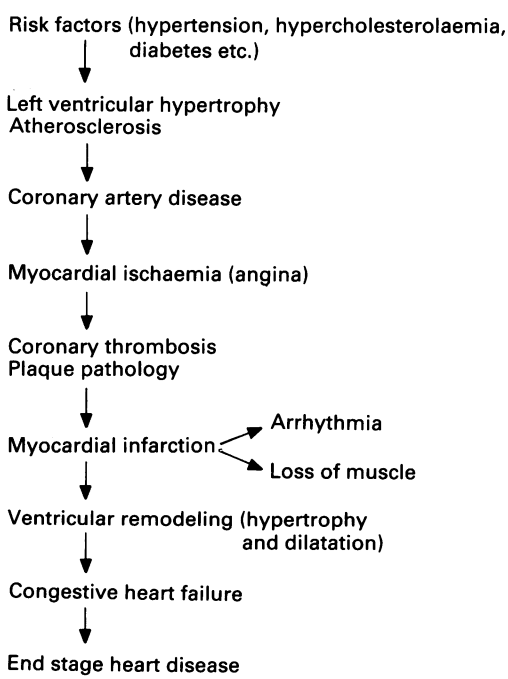

Figure 1 Events leading to the development of end-stage heart disease.

Clinical implications for therapy: concept of cardioprotection

To consider the clinical implications of ACE inhibition, one must examine its effect on cardiovascular pathophysiological processes. It has been demonstrated that a complex chain of events leads to irreversible cardiac damage and the development of end-stage heart disease (Figure 1). The initiating events are the risk factors which include hypertension, dyslipidaemia, smoking, diabetes, etc. The sequelae of risk factors include end-organ damage such as LVH, arteriosclerotic vascular disease, coronary heart disease, stroke, etc. Active ischaemic heart disease, including unstable angina, myocardial infarction can result in myocardial damage and arrhythmic death. A consequence of myocardial damage is the impairment of systolic and diastolic function, the remodelling of the ventricle (i.e. hypertrophy and dilatation) leading eventually to overt heart failure. Angiotensin plays a prominent role in many of these events which lead to end-stage heart disease. The interruption of these progressive deleterious events may protect the heart from irreversible damage. In this context, ACE inhibition is emerging as a potential modality of cardioprotection.

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