Cardiac Effects of Angiotensin Converting Enzyme Inhibitors

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Summary. ACE inhibitors have provided a major advance in cardiovascular therapeutics. The rationale for their use in hypertension and heart failure, and their cardiac effects are well documented. Further information is required on the relevance of their direct myocardial and other tissue effects, and it is likely that their use in hypertension and heart failure will increase further over the next several years.

Key Words. ACE inhibitors, hypertension, heart failure

During the past 10 years, angiotensin converting enzyme (ACE) inhibitors have been the subject of intensive clinical cardiovascular research and have become firmly established as useful therapeutic agents for hypertension and heart failure. Their emergence as a first-line alternative treatment in hypertension relates to their efficacy, tolerability, and lack of adverse metabolic effects when used in an appropriate low dosage. Their role in the routine treatment of heart failure has not yet been fully accepted but will become so as further clinical experience is gathered in the near future. Such treatment in heart failure produces unequivocal hemodynamic and symptomatic improvement, correction of underlying neurohumoral disturbances, improved ventricular function, and increased survival.

In the future in hypertension treatment, ACE inhibitor usage is likely to increase further, particularly with low-dose combination treatment and treatment of the elderly hypertensive and certain patient groups such as diabetic hypertensives. In heart failure treatment, we are now moving from an era of symptomatic treatment to a more preventive approach, just as occurred with hypertension treatment some years ago.

Cardiac Effects of ACE Inhibitors in Hypertension

In the normal or hypertensive subject without heart failure, converting enzyme inhibitors reduce total peripheral resistance, with heart rate, cardiac output, and left ventricular filling pressure little changed [1, 2]. Reflex tachycardia does not occur with lowering of blood pressure, possibly because of altered baroreceptor reflexes [3] or modified parasympathetic activity [4]. Plasma volume and total blood volume are unchanged with long-term treatment [5, 6]. Regression of left ventricular hypertrophy in hypertensive patients can be achieved with converting enzyme inhibitors. ACE inhibitors and sympatholytic drugs appear to be more effective than other agents in causing regression of left ventricular hypertrophy, suggesting a role for the renin-angiotensin system in this sequel of hypertension [6-9].

Recent studies have established the existence of messenger RNA for renin, enzymatic renin activity, and angiotensin II in cardiac myocyte preparations, and evidence has accumulated suggesting that angiotensin II can function as a growth stimulant for specific cells, including cardiac muscle and vascular smooth muscle cells [10]. Thus it appears that tissue renin-angiotensin systems, as well as the adrenergic system, may contribute to cardiovascular growth regulation, and the effects of ACE inhibitors may be exerted both directly and indirectly on cardiac muscle and the peripheral vasculature.

Cardiac Effects of ACE Inhibitors in Heart Failure

Numerous studies have demonstrated beneficial hemodynamic and clinical effects of ACE inhibitors in the treatment of chronic congestive heart failure that are maintained with long-term use [11-19]. Systemic and pulmonary vascular resistances are considerably reduced, cardiac output is increased, and right and left ventricular filling pressures are reduced. Heart rate is also significantly reduced. These hemodynamic effects are associated with improved symptoms, functional class and exercise performance, and reduced cardiac dimensions. The most important potential adverse ef-
fect with the initial dosage is symptomatic hypotension, which may occur following previous diuretic treatment, particularly in the presence of hyponatremia [20]. ACE inhibitors should be avoided in patients with significant valvular stenosis, which may prevent increased cardiac output from maintaining blood pressure following peripheral vasodilatation. These agents are not of proven benefit in cases of predominant diastolic dysfunction.

The acute hemodynamic response to treatment with ACE inhibitors can vary considerably, however, and does not necessarily correlate with clinical efficacy or long-term hemodynamic status [21, 22]. In comparison with other vasodilators, captopril produces less marked increases in cardiac output than hydralazine, nitroprusside, or prazosin, but reduces left ventricular filling pressure to a similar degree as nitroprusside and prazosin, but more than hydralazine. Captopril and isosorbide dinitrate produce similar decreases in systemic vascular resistance and left ventricular filling pressure [23]. The heart rate is reduced with ACE inhibitors, unlike other vasodilators, as a result of reduced sympathetic activity [11, 13, 14].

The balance of myocardial oxygen supply and demand appears to be maintained in patients with congestive heart failure secondary to coronary artery disease who are treated with converting enzyme inhibitors [24, 25]. Double-blind clinical trials have shown a reduced frequency of ventricular arrhythmias in heart failure patients treated with converting enzyme inhibitors [26–29]. Several factors may contribute to this, including improved left ventricular size and function, correction of potassium and magnesium deficiency, and decreased sympathetic activity.

Preventive Treatment of Asymptomatic Ventricular Dysfunction

Although considerable benefit can be achieved with current treatment for congestive heart failure and the use of converting enzyme inhibitors, in particular, to achieve improved survival [30], such treatment is still often palliative, as severe ventricular dysfunction is often present at the time of clinical presentation. Earlier intervention and a preventive approach to treatment might delay progressive ventricular dilatation, irreversible structural damage, and the occurrence of clinical heart failure.

Progressive ventricular dilatation can occur following myocardial infarction [31, 32] and is prognostically important [33]. Congestive heart failure occurs increasingly during the years following myocardial infarction [34]. Experimental animal studies have shown that converting enzyme inhibition can reduce ventricular dilatation following myocardial infarction and can improve survival [35, 36].

In a recent clinical study we have shown that converting enzyme inhibition with captopril can improve asymptomatic ventricular dysfunction following myocardial infarction [37]. Patients with significant ventricular dysfunction 1 week following Q-wave myocardial infarction showed a reduction in left ventricular volumes and an improved ejection fraction during a year of captopril treatment, whereas further ventricular dilatation continued with furosemide or placebo treatment. The mechanism of improvement may relate to the peripheral vasodilating effect of captopril, but there may also be a beneficial effect exerted through a direct effect on the coronary circulation [38, 39] or a direct myocardial tissue effect [10, 40, 41].

With this preventive approach to treatment, a more substantial improvement in prognosis may be achieved. While a sound rationale for such intervention exists, additional ongoing studies will eventually provide a clear perspective on the value of this approach.

References