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 hypoten-
sion, which may occur following previous diuretic
treatment, particularly in the presence of hypo-
nonatremia [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 pre-
dominant 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 compari-
son 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 re-
duced sympathetic activity [11, 13, 14].

The balance of myocardial oxygen supply and de-
mand appears to be maintained in patients with con-
gestive heart failure secondary to coronary artery dis-
ase 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 en-
zyme inhibitors [26–29]. Several factors may contrib-
ute 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. Ear-
lier intervention and a preventive approach to treat-
ment might delay progressive ventricular dilatation,
irreversible structural damage, and the occurrence of
clinical heart failure.

Progressive ventricular dilatation can occur follow-
ing myocardial infarction [31, 32] and is prognostically
important [33]. Congestive heart failure occurs in-
creasingly during the years following myocardial in-
farction [34]. Experimental animal studies have shown
that converting enzyme inhibition can reduce ventric-
ular 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 im-
prove asymptomatic ventricular dysfunction following
myocardial infarction [37]. Patients with significant
ventricular dysfunction 1 week following Q-wave
myocardial infarction showed a reduction in left ven-
tricular 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 cap-
topril, 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 interven-
tion exists, additional ongoing studies will eventually
provide a clear perspective on the value of this ap-
proach.

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