

Fifteen years of ACE-inhibition in congestive heart failure

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The activation of the renin-angiotensin system is one of the major consequences of reduced cardiac output in chronic congestive heart failure (CHF). Together with other mechanisms, this activation promotes myocardial dysfunction which further stimulates the renin-angiotensin system as well as the sympathetic nervous system.

During the last 15 years suppression of angiotensin II formation by the inhibition of the angiotensin-converting enzyme (ACE) has produced exciting clinical results^{1,2}. Several large scale clinical trials have documented that ACE-inhibitors reduce mortality and morbidity in patients with CHF. It is now clear that these results are obtained not only by the hemodynamic and myocardial action of ACE-inhibitors but also by their vascular effects. The inhibition of the renin-angiotensin system can beneficially alter some of the structural and functional changes seen in the arteries of patients with hypertension or CHF. This effect is largely independent of the ability of these agents to lower blood pressure. Furthermore, endothelial plasminogen activator inhibitor-1 production and secretion appear to be regulated by angiotensin II, while tissue-type plasminogen activator production and secretion are regulated by bradykinin¹. Endothelial ACE is therefore strategically poised to regulate vascular fibrinolytic balance by virtue of its dual function in degrading bradykinin and converting angiotensin I to angiotensin II. These properties can explain the recently published results obtained in the HOPE trial³. It is now clear that ACE-inhibition can reduce death rate, myocardial infarction, and stroke in a broad range of high risk patients independently of the presence of low ejection fraction or heart failure.

From a clinical point of view it is important to underscore not only the advantages but also the adverse effects of ACE-inhibition and the limitations of their optimal use in the clinical area.

ACE-inhibitors may induce coughing as the result of bradykinin accumulation. Angioedema is a potentially life-threatening complication with an incidence of 0.1 to 0.2%. Renal dysfunction is a well-recognized complication which also may be partially mediated by bradykinin⁴⁻⁶.

Indeed, despite the clear evidence that ACE-inhibitors improve survival, only about 30 to 50% of CHF patients in the community medical care setting actually receive these drugs.

High doses of ACE-inhibitors have been shown to be superior to low doses with respect to CHF symptoms, exercise performance and suppression of neurohumoral stimulation³⁻⁶. Despite this line of evidence, suboptimal dosage is a frequent problem in clinical practice. The most important reasons for nonprescription or underutilization of ACE-inhibitors appear to be lack of familiarity with the drug and concern about safety and adverse reactions, especially hypotension, renal failure and coughing.

AT₁ receptor antagonists can now be considered as a good alternative to ACE-inhibitors for patients unable to tolerate ACE-inhibitors.

References

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