Captopril in Children With Cardiomyopathies

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In this issue of Circulation, Bengur et al report their studies of the acute effects of captopril on the hemodynamics of children with congestive and restrictive cardiomyopathies. Captopril and other orally effective angiotensin converting enzyme (ACE) inhibitors have been studied in several large trials in adults with congestive heart failure, but relatively little has been published about the effects of these agents in children, especially those with primary myocardial diseases. In pediatric populations, the overwhelming majority of patients with the symptom complex of congestive heart failure have a congenital cardiac defect rather than a cardiomyopathy as the underlying cause of their symptoms. It is not surprising, therefore, that earlier pediatric studies of afterload reducing agents, including ACE inhibitors, have largely been done in patients with heart defects, primarily left-to-right shunt lesions. These studies have shown encouraging improvements in hemodynamics and symptoms in some affected children, but the ultimate therapy in most children with a heart defect is surgical correction of the defect, not long-term medical management. In patients with cardiomyopathy, on the other hand, the goal of therapy is survival, or at least postponement of the only surgical option, cardiac transplantation. Therefore, the importance of new modes of medical management for this latter group of children takes on additional significance.

Because the loading conditions of one or both ventricles can be dramatically altered in patients with heart defects, and the effects of many drugs are different in children than in adults (quantitatively if not qualitatively), studies performed specifically in pediatric patients with cardiomyopathies and no significant heart defects are important. Bengur et al evaluated the acute hemodynamic effects of oral captopril in a small group of 12 children with congestive cardiomyopathy and a very small group of four children with restrictive cardiomyopathy. They found that within 1 hour, systemic vascular resistance in both groups dropped by 34–37%. This acute change is similar to that seen in adult patients and is considerably more than the decrease in systemic resistance noted in previous studies of children with congenital heart defects given similar doses of captopril. In contrast to adult patients, the children with cardiomyopathy showed no significant changes in ventricular filling pressures; as the authors point out, this finding remains unexplained. Although they suggest that fasting or diuretics may have decreased the pretreatment preload so far that treatment effects were obscured, inspection of the data tends not to support this possibility. In fact, patients with the highest pulmonary capillary wedge pressures did not show the expected decrease in filling pressure, and in those with the lowest initial pressures (suggesting mild dehydration) the wedge pressures actually increased slightly. In the children with congestive cardiomyopathy, the captopril-induced reduction in systemic vascular resistance resulted in an increase in both stroke volume and cardiac index of 22%. These changes are similar to those reported in adult patients with congestive heart failure, but the concomitant fall in blood pressure was less than that usually seen in adults. These apparent differences between adult and pediatric patients may simply be artifactual due to the small number of pediatric patients, but they may indicate a fundamental difference between the balance of compensatory mechanisms at work in children and those in adults.

Data from the small group of four children with restrictive cardiomyopathy are particularly interesting because very little has previously been reported concerning the effects of ACE inhibitors in this rare condition in children. The observed change in systemic vascular resistance in these patients was similar to that seen in patients with congestive cardiomyopathy, but there was no concomitant increase in stroke volume or cardiac index. The authors' speculation that this lack of benefit was due to the fact that systolic volume and function were already near normal, so that there was little reserve to further improve stroke volume, seems intuitively to be reasonable. As systemic resistance fell, aortic mean pressure therefore decreased by approximately 25% for the group. Although this decrease in blood pressure did not reach statistical significance in this small group of patients, the authors correctly point out that this uniform effect should alert the clinician to use...
captopril cautiously in restrictive cardiomyopathy patients until further data becomes available.

It is important to accumulate data on the short-term effects of ACE inhibitors in children because these data may help to clarify differences in the development of various compensatory mechanisms stimulated by heart failure at different ages. Abundant evidence, however, indicates that the acute effects of oral ACE inhibitors, probably mediated through abrupt changes in circulating ACE, do not necessarily predict the longer term effects probably related to inhibition of tissue ACE.4,8,9 The intricacies of local tissue effects of angiotensin and other mediators (such as bradykinin) affected by ACE inhibitors are only beginning to be explored and should provide fertile ground for further research into ways to more precisely manipulate the body's compensatory mechanisms at all ages.10,11

From a clinical standpoint, the true test of the value of ACE inhibitors in children will be whether they can provide a significant improvement in quality of life, growth, and most importantly, survival. In adult patients, long-term ACE inhibition is one of the few medical therapies for moderate to severe congestive heart failure that has been shown in well-controlled clinical trials to actually improve exercise tolerance and decrease mortality.2,3,12,13 Confirmation of this beneficial effect in the pediatric population may be more difficult because of the very small numbers of patients seen in most centers. Indeed, recent single-center studies of the natural history and prognosis of children with cardiomyopathies have yielded widely varying results and, therefore, differing recommendations for when transplantation may be needed.14–16 In the future, more children with severe cardiomyopathies should be evaluated in a small number of centers with special expertise in pediatric heart transplantation. This concentrated effort should provide a unique opportunity for such centers to provide meaningful data about this uncommon pediatric condition much more quickly than has heretofore been possible. We hope that some of these centers will have the foresight to accept the responsibility for developing prospective, preferably multicenter, trials to prove or disprove the real value of new modes of therapy (like ACE inhibition) in the shortest possible time.

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