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Mini Review

Angiotensin Converting Enzyme Inhibition in those with Functionally Univentricular Hearts: is there a Problem with Overuse?

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Abstract

Angiotensin converting enzyme inhibitors are being increasingly used in those with functionally univentricular hearts with minimal evidence of their efficacy in this population. Additional medications, such as angiotensin converting enzyme inhibitors can be a practical inconvenience to patients, increase the cost of care, and may even be detrimental to these patients in some respects. This short communication reviews the current evidence for angiotensin converting enzyme inhibition in patients with functionally univentricular hearts.

Introduction

The use of Angiotensin Converting Enzyme (ACE) inhibitors now occurs at all stages of functionally univentricular palliation. Recent data has shown that for many Fontan patients, the reported indication for ACE inhibition is either nonexistent or not one of the few generally accepted indications for ACE inhibition [1]. Anecdotally, this occurs in the interstage period and after superior cavopulmonary anastomosis as well. An increasing body of literature now exists, documenting that ACE inhibitions has minimally benefits and may actually have some associated risk. This short communication briefly summarizes the data regarding ACE inhibition in those with functionally univentricular hearts at various stages of palliation, demonstrating that there is likely an overuse of ACE inhibition in the functionally univentricular population.

Interstage Period

Few studies have formally evaluated ACE inhibitors during the interstage period. Perhaps the most well recognized study is that of Hsu and colleagues on the behalf of the Pediatric Heart Network. A total of 185 infants completed the study, with patients being randomized to either a treatment group consisting of receiving enalapril or a control group which did not receive enalapril. The primary outcome of interest in this study were growth parameters (weight, height, and head circumference) analyzed as for-age z-scores. No difference was found in weight-, or height-, for-age z-scores. A statistically significant difference was found in mean head circumference for-age z-score which was lower in those in the enalapril group. These results were noted with both an intention to treat analysis as well as with a non-intension to treat analysis. No difference was noted with subgroup analyses by palliation type or cardiac morphology [2].

The study by Hsu and colleagues also looked at a number of secondary endpoints as well. No significant difference was noted in ventricular function, atrioventricular valve regurgitations, and ventricular mass or overall neurodevelopmental outcomes between the two groups at the end of latest follow-up [2].

Moffett and colleagues retrospectively studied a cohort of 161 interstage patients. A majority of these patients had either hypoplastic left heart syndrome or an unbalanced atrioventricular canal defect. The study set forth the characterized the medications these patients received during the interstage period and to determine what medications impacted feeding and growth. The study found that patients were on a median of 4 outpatient medications, the most common being aspirin (79% of patients), furosemide (79% of patients), and ACE inhibitor (73% of patients). The effects of medications were then compared in those with decreased weight for age z-scores during the interstage period and in those with increased weight for age z-scores during the interstage period. Decreased weights for age z-scores during the interstage period were found to be independently associated with enalapril and digoxin. Thus, this study noted a potential negative impact of ACE inhibition on interstage weight gain [3].

Ghelani and colleagues retrospectively reviewed 395 interstage patients from the National Pediatric Cardiology Quality Improvement Collaborative registry. This study found that interstage patients were on a median of 5 medications with 38% of patients being on an ACE inhibitor. The primary endpoint of interest in this study was change in weight-for-age z-score. While ACE inhibitors were not found to be associated negatively with weight gain, they also did not improve weight gain in this study by univariate or regression analysis [4].

After Superior Cavopulmonary Anastomosis

A prospective study to identify the effects of enalaprilat on hemodynamic measures was conducted by Lee and colleagues. Patients with a superior cavopulmonary anastomosis undergoing pre-Fontan catheterization were identified. First, baseline hemodynamics was obtained in all patients. Next, the patients received a dose of enalaprilat after which hemodynamics were obtained once again. Any patients receiving ACE inhibitors had such therapies discontinued 48 priors to catheterization. The study demonstrated that enalaprilat significantly decreased aortic pressure while not having any impact on superior caval vein pressure or right atrial pressure. No difference was found in cardiac output with enalaprilat although distribution of cardiac output did differ. Pulmonary flow significantly decreased with enalaprilat while aortic flow significantly increased. As a consequence of this redistribution of flow, the aortic saturation decreased by 4% ($p=0.02$) and the superior caval vein saturation decreased by 3% ($p=0.02$). In light of these results, Lee and colleagues concluded that in the absence of an increase in cardiac output, ACE inhibitors should be used with caution in those with borderline aortic saturations [5].

A separate study by Mitali and colleagues describes additional findings from the same randomized cohort in the study by Hsu and colleagues. A total of 150 patients included in the randomized trial were genotyped for polymorphisms in 5 Renin-Angiontensin-Aldosterone-System (RAAS) genes. Randomization to the enalapril or control group occurred prior to superior cavopulmonary anastomosis and comparisons were made in characteristics after superior cavopulmonary anastomosis between those with RAAS up regulation phenotypes and those without. This study demonstrated that those with RAAS up regulation genotypes were less likely to experience remodeling (decrease in mass and/or volume) of the systemic ventricle [6].

When those who had received enalapril were compared to those who had not received enalapril, regardless of RAAS genotype, no difference was noted in ventricular size, ventricular volume, ventricular function, growth, or heart failure class. When only high-risk RAAS genotype patients in the enalapril were compared high-risk RAAS genotype patients in the control group, those in the enalapril group had significantly worse somatic growth. Thus, this study highlights the lack of clinical utility of enalapril started prior to superior cavopulmonary anastomosis on outcomes after superior cavopulmonary anastomosis [6].

After Completion Fontan

The utility of ACE inhibition has been studied to greatest extent during the Fontan period for those with functionally univentricular hearts. Wilson and colleagues characterized the use of ACE inhibitors in Fontan patients using the Australia and New Zealand Fontan registry. A total of 1,268 patients were included in their study. Of these, 462 (36%) were on an ACE inhibitor. The most common indications for initiating treatment with an ACE inhibitor were ventricular dysfunction (29%), atrioventricular valve regurgitation (19%), preservation of normal ventricular function (7%), prolonged effusions at time of Fontan (6%), hypertension (6%), other (6%). The indication was unknown or there was no indication in 27%. The authors determined that only 36% of the patients treated with an ACE inhibitor had an indication that would be used for ACE inhibitions in those with a biventricular circulation [1].

The median age at which an ACE inhibitor was started in the Fontan patients was 4.8 years of age with a median duration of 7.7 years. Treatment had been started prior to Fontan in 36%, during Fontan hospitalization in 23%, and after Fontan hospitalization in 39%. Mean cost of ACE inhibitor therapy converted to approximately 108 US dollars per patient per year. The study estimated that the estimated cost of ACE inhibitors for those without a reasonable indication was approximately 32,137US dollars a year [1].

Data for 546 patients cared for across seven different centers from the Pediatric Heart Network Fontan Cross-Sectional Study was utilized to similarly characterize the use of ACE inhibitors in Fontan patients. In this study, 57% of Fontan patients were on an ACE inhibitor. Those with a systemic ventricle felt to be of right ventricular morphology, atrioventricular valve regurgitation, and shorter duration from Fontan were more likely to be on an ACE inhibitor. There was no association with systolic or diastolic ventricular function on ACE inhibitor therapy noted in this study. Cost data or physician reported indication for ACE inhibition was not captured in this study. Nonetheless, this study highlights the number of Fontan patients who are receiving such therapy.

Francois and colleagues retrospectively reviewed the somatic growth of 64 patients who had undergone Fontan completion. Data was available through all palliative stages. This study found that z-scores for weight and height at most recent follow-up were both significantly lower in patients who were on ACE inhibitor therapy, confirming the growth concerns noted in earlier stages [7].

A few studies have also set forth to determine whether or not ACE inhibitors can help in the management of pleural effusions in the postoperative period after Fontan. A total of six such manuscripts have been published. One of these studies demonstrated a decrease in volume and duration of pleural effusions, two of these studies found no difference in volume or duration of pleural effusions, and the remaining three studies found an increased volume and duration of pleural effusions [8-13].

Two studies have also studied the impact of ACE inhibition on exercise capacity. Ohuchi and colleagues included 63 Fontan patients and found that there was no significant difference in exercise testing parameters between those who were and were not on ACE inhibitors [14]. Another study by Kouatli and colleagues included 18 Fontan patients who were randomized to either receiving enalapril or not receiving it. Interestingly, this study noted a statistically significant difference in the change in cardiac index from rest to peak exercise between those in the two study arms with those receiving enalapril having a lower change in cardiac index. Exercise time, total work, or power did not differ between the two groups [15].

Additional Considerations

Anecdotally, many pediatric cardiologists and adult congenital cardiologists believe that ACE inhibitors may provide a ventricular remodeling benefit. None of the studies of ACE inhibitors in those with functionally univentricular hearts have demonstrated any decrease in ventricular mass or function, thus demonstrating that this effect is likely not occurring. It must be kept in mind that functionally univentricular hearts are initially subjected to volume overload. In a rat model of eccentric left ventricular hypertrophy secondary to volume overload, ACE inhibitors did not lead to any reverse modeling [16]. This lack of remodeling, and a lack of decrease in myocardial oxygen consumption, has also been demonstrated to be the case in human patients with other congenital malformations of the heart resulting in volume overload ventricles [17,18].

Another consideration must be that of acute kidney injury. Those with congenital malformations of the heart are at increased risk for acute kidney injury. Several studies have demonstrated risk for acute kidney injury in the postoperative period after cardiac surgery may be as high as 50%. ACE inhibitors have been demonstrated to increase the risk of postoperative acute kidney injury. Thus, this must be taken into consideration when ACE inhibitions are being considered in those with functionally univentricular hearts. ACE inhibitors started in the interstage period or prior to the Fontan may increase the risk of acute kidney injury after the superior cavopulmonary anastomosis or Fontan [19].

Yet others cite endothelial dysfunction in adult Fontan patients as a reason to start ACE inhibition. Two studies have been published to date regarding this and both demonstrated no significant improvement in endothelial dysfunction after initial of ACE inhibitors [20,21].

Conclusion

While the management of patients with complex congenital malformations of the heart, particular those with functionally univentricular hearts, requires a balance of art and science, we must strive for a true balance of these [22]. Cardiologists must be mindful of extrapolating data from other patient populations and applying them to a very different set of patients. Additionally, current data must be completely understood and reevaluated continuously.

The data that is currently available regarding the use of ACE inhibition in those with functionally univentricular hearts demonstrates no benefit with ACE inhibition at any stage but demonstrates potential risks at each stage. While patients with moderate or greater atrioventricular valve regurgitation, systolic or diastolic ventricular dysfunction, or those with hypertension may benefit from such therapy, it is clear that all patients with functionally univentricular hearts do not benefit from ACE inhibition.

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