CHAPTER 1

BACKGROUND AND RATIONALE

In recent years, there has been considerable interest in, and development of, new therapeutic agents and strategies for managing Congestive Heart Failure(CHF). Much of this interest stems from the increasing awareness of the importance of the public health impact of this condition. In adults, CHF has become a major cause of cardiovascular death[1]. An even greater burden on the health care system is the considerable morbidity associated with CHF. In pediatric populations, CHF is usually caused by the congenital cardiac malformations and variety of conditions of acquired cardiac diseases. This medical condition not only severely impaired the cardiac function, caused mortality, but also had severe impact on child growth and development. In New England Regional Infant Cardiac Program, where approximately 350 to 450 high-risk infants were admitted each year, upwards of 80% had heart failure as a major component of their clinical presentation[2]. Recent epidemiology study in China showed that the prevalence of congenital heart malformations is 7 ‰[3], it is estimated that there are about 150,000 new born babies with congenital cardiac malformations every year in China. With addition of cardiomyopathy and rheumatic heart disease, heart diseases associated for the fourth leading causes of mortality for the children under age 5 in 1993 according to the official annual report. Traditional medical therapy for congestive heart failure consists of the administration of digoxin and diuretics. From 1980s vasodilators have emerged as an important additional agents in the management of heart failure. Of the

vasodilators, the angiotensin converting enzyme (ACE) inhibitors appear to be the most promising[4]. ACE inhibitors block the enzymatic generation of the pressor substance angiotensin II. This inhibitor results in vasodilatation. The typical hemodynamic response in hypertensive patients includes a decrease in systemic vascular resistance and systemic arterial pressure. In patients with congestive heart failure, systemic vascular resistance and left ventricular filling pressure decrease, cardiac output increases. Heart rate is usually unaltered or even slightly decreases[5]. On the other hand, ACE inhibitor exerts its effects on pre-load by increasing the capacitance of the systemic vascular bed and lowering filling volumes. This will diminish pulmonary and systemic venous congestion[6]. Following 20 years of research, development and clinical application, ACE inhibitor has firmly been shown to provide beneficial hemodynamic effects, improve symptoms, increase exercise capacity, and prolong survival in patients when added to anti-failure treatment[7-11]. From later 1980s, ACE Inhibitor began to be applied in pediatric practice. By using Captopril(the first synthesized orally effective ACE-I) in infants and children with CHF, captopril can exert beneficial hemodynamic effects, and these effects are in addition to those achieved by preexisting standard therapy[12]. Recently, a new ACE inhibitor Enalapril have been introduced to pediatric patients. This new long-acting ethyl ester converting-enzyme inhibitor is deesterified to an active metabolite. It has more gradual onset of effect, and prolonged duration action to compare with captopril. Since enalapril lacks a sulfydryl group, it has fewer side effects than captopril. There have been a number of clinical reports which indicate the benefit on hemodynamic and clinical improvement in children with congestive heart failure by adding Enalapril into conventional therapy[13-17]. ACE inhibitors are now recommended as an

additional drug to anti-failure therapy in pediatric patients with low output status by some pediatric text books and literature. However, the information on enalapril in management of children with heart failure is still limited. There has been so far no controlled study to confirm the efficacy of this drug in pediatric population. Without the controlled study, the questions still remains: whether adding enalapril into anti-failure therapy really make difference in improving hemodynamic and clinical outcome, whether it should be applied in a large different categories of pathophysiological circumstances or only in some specific subgroups? It is therefore offering a rationale approach for carrying on a desirable randomized, placebo-controlled trial, to approve the role of the Enalapril in infant and child with CHF.