CHAPTER 4

RESULTS

This clinical trial was conducted in Children's Hospital of Shanghai Medical University from September 1998 through February 1999. A total number of 84 children with congestive heart failure were stratified by the cause of CHF (congenital heart defect or impaired cardiac function) and then randomly assigned into Enalapril treatment group and placebo group. Age ranged from 3 to 36 months (average 20 months). In these 84 patients, the CHF caused by congenital heart defects in Enalapril group was 66.3%, and 64.3% in controlled. The demographic, hemodynamic and clinical characteristics noted at baseline are listed in table 4.1 to 4.3. The following data analysis was based upon 84 cases with 42 in each group. All statistic tests were two-tailed. p value less than 0.05 was considered being statistically significant. All data were entered into the Microsoft Execl program and transferred to SPSS for windows program for analyzing. There were no any significant differences between the groups with respect to any of those baseline characteristics or measurement.

During the trial, 2 patients died at day 10 and day 12. The cause of those deaths were due to virus infected pneumonia (1 in Enalapril group), and deteriorate myocardiol dysfunction (1 in controlled group). Three patients withdrawn from the trial, 2 in control group and 1 in Enalapril group. These events happened were due to family or economic reasons. During data analysis, we treated these patients as an intention to treat case, and added them as same worst outcome as those in the same group in the final outcome. No one dropped out because of severe side effect. 3(7%)

patients in Enalapril group and 1 (2%) patients in control group remained in lower dose of Enalapril or placebo during the trial because of lower blood pressure (decreased more than 15% from their original level but with no hypotension symptom).

Table 4.1 Baseline demographic data of two groups

Items	Enalapril group(n=42)	control group(n=42)
Age (month)	25±9.3 (17.7~23.3)	19.9±8.4 (17.3~22.5)
Gender		
Male	24 (57%)	23 (54.8%)
Female	18 (43%)	19 (45.2%)
Body weight (kg)	10.5±2.8	10.3±2.7
Dose of Digoxin (mg/d/kg)	0.04	0.04
Dose of diuretics		
Lasix	1.5±0.5	1.5±0.4
Type of cardiac disease		
Congenital heart defects	28(66.3%)	27 (64.3%)
L-to-R shunt w/AI	5	3
L-to-R shunt w/MI	4	2
L-to-R shunt w/CoArc	3	5
Multi L-to-R shunt	6	9
L-to-R shunt	10	8
Impaired cardiac function	14(33.3%)	15(35.7%)
Dilated myocardiopahy	5	8
Post cardiac operation	9	7
Conventional therapy before trial(days)	3.1±1.6	2.8±1.4

*Value indicated are mean± standard division. L-to-R = left to right; w/ = with; n = number of patient; AI = aortic insufficiency; MI-mitravalve insufficiency. CoArc=Aortic coarctation.

No statistic difference between two groups base on demographic data. For most cases total deditalizing dose is 0.004mg/kg, later on, the maintaining dose (0.01mg/kg/day) were remained during the whole trial period. Additional diuretic

regimens were added in 9 patients (21%) in Enalarpril group and 14 patients (33%) in control group. Enalapril dose administrated was followed the proposed protocol, started from 0.08mg/kg/day, escalated to 0.25mg/kg/day within 3 days by adjusting the vital signs.

Table 4.2 The laboratory safety measure at baseline

	Enalapril group	Control group
Serum potassium(mmol/L)	4.3±0.4 (4.1~4.4)	4.3±0.6(3.9~4.3)
Serum sodium(mmol/L	134±4(136~138)	136±4.2(135~138)
Serum creatinine(umol/L)	66.1±9.3 (63.2~69)	67.3±9.2(64.4~70.2)
Serum urea(mmol/L)	4.6±0.85(4.29~4.82)	4.5±0.99(4.2~4.8)

Value are mean±SD and (95% confidence interval), all data shows no significant difference between two groups

Table 4.3 hemodymanic variables at baseline

	Enalapril group	Control group
LVWS(g/cm^2)	61.3±13.5 (57.1~65.4)	60±13 (56.1~64.3)
VCFc(circ/s)	0.99±0.11 (0.96~1.03)	1.01±0.1 (0.98~1.04)
SF(%)	0.33±0.04 (0.33~0.34)	0.33±0.03 (0.32~0.34)

Values indicated are mean±standard division and (95% confidence interval). LVWS=left ventricular wall stress; VCFc=rate corrected velocity of fiber shortening; SF=shortening fraction

4.1 Hemodynamic effects

42 patients in Enalapril and 42 in placebo group provided pre- and post-treatment data on left ventricular systolic function: Relation of Left Ventricular Wall Stress and Rate Corrected Velocity Fiber Shortening, which is the load independent index of cardiac contractility(Table 4.4). By plotting the individual LVWS-VCFc data into a normal range of LVWS-VCFc relation figure, results show a shifting pattern of thiscontractility index in both group from lower level up to the high level. Enalapril

group show a stronger move after treatment (Fig 4.2). 23 (55%) patients in Enalapril group had their index move up to the normal range after 14 days treatment, compare only 14 (23%) in control group had their index shift to the normal range, the difference is 22%. Z test show z ratio is 2.2, which two-tailed value is 0.03. The difference is statistically significant.

Left ventricular wall stress, rate corrected velocity of fiber shortening and shortening fraction were measured at baseline and day 4 day 14 after trial started. There is a trend that after 14 days treatment wall stress is slightly decrease in both groups. Enalapril group tend to be decrease more than control group, no signs of significant differences compared mean change between two groups (p=0.07). Rated corrected velocity of fiber shortening in both groups increased significantly after 14 days treatment. Enalapril group had about absolute 0.1 mean of VCFc increased to compare with control group (p<0.001).

Table 4.4 Hemodymanic variables measured at baseline, during enalapril treatment and during placebo treatment

Hwmodymanic variables	Enalapril group			Control group		
	Pre-	Post-	Change(mean)	Pre-	Post-	Change(mean)
LVWS(g/cm2)	61.2±13.5 (57-65)	58.3±12.6 (54-62)	3±4.8 (1.47-4.5)	59.9±13 (55.8-63.9)	58.7±12†† (55-62.4)	1.1±4.3 (1.4-2.5)
VCFc(circ/s)	0.99±0.11 (0.96-1.03)	1.12±0.11†† (1.1-1.16)	0.13±0.11 (0.09~0.17)	1.0±0.1 (0.98-1.04)	1.1±0.1† (1.02-1.09)	0.04±0.09** (0.02~0.07)
SF(%)	0.33±0.04 (0.32-0.35)	0.34±0.04 (-0.4-3.7)	0.01±0.03 (-0.008-0.01)	0.33±0.04 (0.32-0.34)	0.32±0.03 (0.31-0.34)	0.01±0.03 (-0.001-0.02)

Variables indicated by mean±standard deviation and (95% confidence interval). **The difference between two groups is statistically significant (p<0.01). ††The difference within group after treatment is statistically significant (p<0.01), † (p<0.05). pre-=before trial, post=after study

Comparison of shortening fraction changes within and between groups show no significant differences, but enalapril group has a trend of increase shortening fraction after treatment.

Fig 4.2 Comparative shift of LVWS-VCFc index between two groups

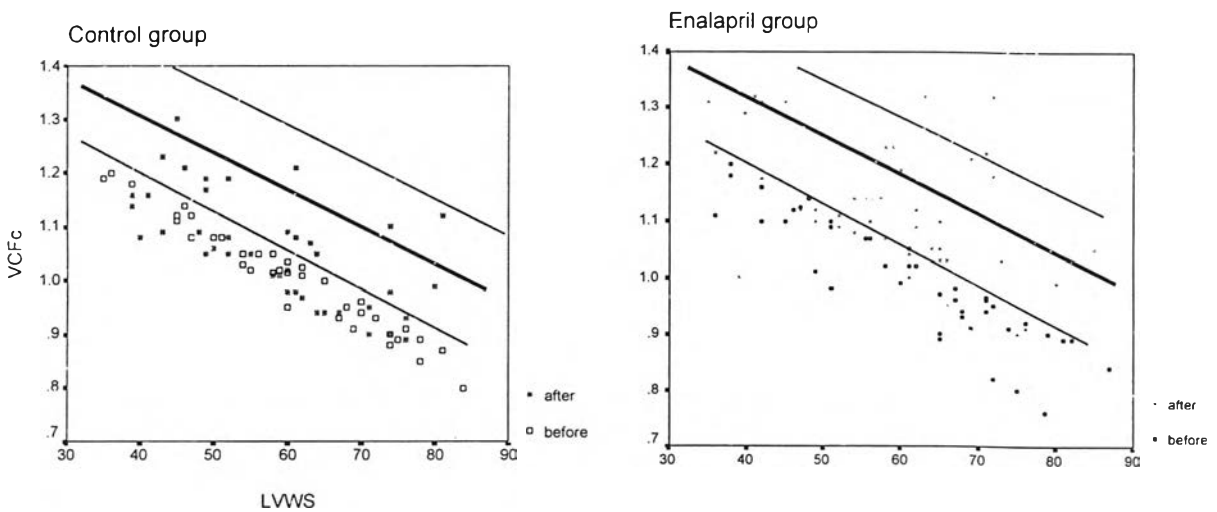
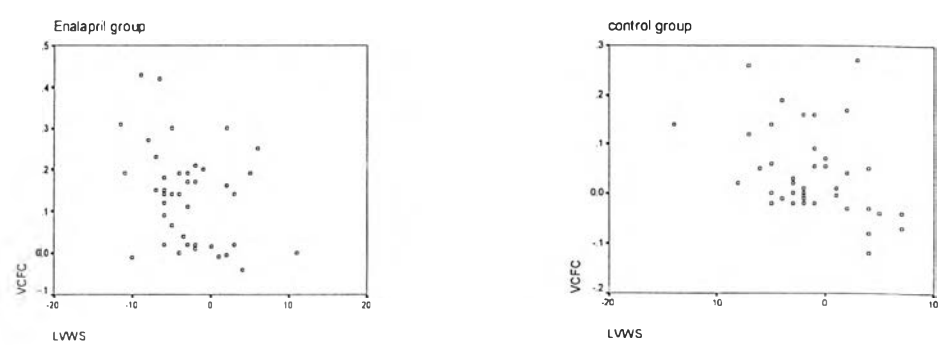


Fig 4.2 the bold line is the mean of normal range, and 95% confidence interval present by dotted line.

In order to observe the variation of the mean change of contractility before and after treatment in each group, Fig 4.3 illustrate the different variation trend of two group

Fig 4.3 Comparison of different variation of VCFc(adjusted by LVWS) between Enalapril group and controlled group (mean change = after treatment-before treatment)



The variation in Enalapril group is obviously wide than Controlled group. Levene's Test for equality of variances show P=0.054. either pooled or nonpooled t-test show significant difference of VCFc mean change between two groups.

In comparison of improving rate of cardiac contractility in the patients with different cause of CHF, Table 4.4 show the proportional difference in Enalapril group and controlled group.

Table 4.5 comparison of improving rate of contractility in patients with different cause of CHF

	Enalapril group	Controlled group
Congenital heart defect	61% (43%-79%)	44% (24%-64%)
Impaired cardiac function	43% (18%-68%)	27% (7%-47%)

Variable indicated by percentage and (95% confidence interval)

Statistically There are no difference within and between two group.

4.2 Symptoms and signs of Congestive Heart Failure

During the course of double-blind therapy, all patients in the Enalapril- and placebo- treated groups provided data suitable for comparing the change in severity of specific symptoms and signs. The symptoms compared were the change of body weight, heart rate, respiratory rate, liver size, and cardiothorecic ratio (Table 4.6).

The results show Enalapril group and control group after treatment all had significant improvement in some clinical symptoms and signs. Both groups have significant improvement in reducing heart rate, respiratory rate, liver size and gaining

body weight by comparing results before treatment and after treatment within groups. Enalapril group show a significant reduce of cardiacthorecic ratio after treatment ($p< 0.01$). The results importantly demonstrate an additional significant superiority for Enalapril group over control group in reducing heart rate , respiratory rate, liver size. The mean changes of cardiacthorecic ratio and body weight between two groups can not achieve statistical significance.

Table 4.6 Comparative change in symptoms and signs of congestive heart failure in Enalapril and placebo treatment groups during 14 days double-blind therapy

Clinical variables	Enalapril group			Control group		
	Pre-	Post-	Change(mean)	Pre-	Post-	Change(mean)
Heart rate (bpm)	140±10 (136-142)	134±7†† (132-137)	5±5 (3-6)	141±8 (138-144)	138±7†† (137-141)	2.5±3* (2-4)
Respiratory rate	38±6 (36-40)	35±5†† (33-36)	4±4 (3-5)	39±5 (37-40)	37±6†† (35-39)	2±3* (1-3)
Liver size(cm)	2.8±0.4 (2.7-3)	2.5±0.5†† (2.4-2.7)	0.3±0.3 (0.21-0.4)	2.9±0.4 (2.7-3)	2.7±0.4†† (2.6-2.8)	0.2±0.2* (0.1-0.2)
CT Ratio	0.63±0.03 (0.62-0.63)	0.62±0.05 (0.62-0.64)	0.01±0.02 (0.01-0.02)	0.64±0.03 (0.62-0.64)	0.63±0.01†† (0.62-0.63)	0.01±0.01 (0.01-0.02)
BW(kg)	10.5±2.2 (9.6-11.3)	10.5±2.8† (9.7-11.4)	0.07±0.3 (0.01-0.5)	10.3±2.7 (9.5-11.2)	104±2.7† (9.6-11.2)	0.07±0.1 (0.03-0.1)

Variable indicated by mean ± standard deviation . **The difference of mean change between two groups is statistically significant ($p<0.01$), *($p<0.05$). ††The difference within group after treatment is statistically significant ($p<0.01$), † ($p<0.05$).
Pre=baseline; after=14days after treatment

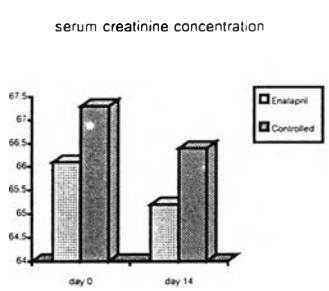
In some cases, CHF caused by congenital heart defects which need to be surgically corrected, the remaining variable is to compare the number of patients would be suitable for cardiac surgery after 14 days treatment between two groups. All these cases with congestive heart defects were all reviewed by an evaluation committee at

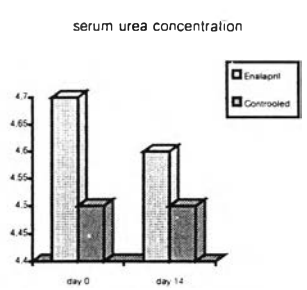
the end point, this evaluation include some specific criteria, heart function is the one of most important element. 3 (7%) in control group and 5 (12%) in Ealapril group were approved to proceed heart surgery process. Statistically there is no difference between two proportions.

4.3 Laboratory safety test

Comprehensive laboratory safety tests and side effects monitoring were performed in all patients before and during the therapy. The effects on change of serum sodium show sodium concentration in control group slightly increased after treatment($p=0.1$). In Enalapril group the sodium concentration changed from 134.6(±4)mmol/L to 138(±4)mmol/L ($p<0.01$). Comparing the mean change of serum sodium between two groups after treatment, 0.67±1.3(enalapril) vs 0.57±2.4(controlled), $p=0.8$. no significant difference has been found.

In measuring serum potassium, results demonstrate no significant change within group or between groups during the treatment. 5(12%) patients in control group and 4 (10%) patients in Enalapril group received potassium supplements during the study period because of serum potassium was lower than 3.5mmol/L. In both group serum creatinine and urea show a trend of decreasing after treatment in both group, though





statistically has no difference.

Table 4.7 Comparative change in laboratory tests before and after study

Hwmodymanic variables	Enalapril group			Control group		
	Pre-	Post-	Change(mean)	Pre-	Post-	Change(mean)
Serum sodium	135±3.9	138±4.4††	0.67±1.3	136±4	137±4.4	0.57±2.4
(mmol/L)	(136-138)	(136-138)	(-1—0.24)	(135-138)	(136-137)	(-1.32-0.18)
Serum potassium (mmol/L)	4.3±0.4 (4.1-4.4)	4.5±0.4 (4.3-4.6)	0.14±0.3 (-0.2—0.04)	4.3±0.6 (3.9-4.3)	4.5±0.39 (4.3-4.6)	0.23±0.6 (-0.4-0.04)
Serum creatinine (umol/L)	66.1±9.3 (63.2-69)	65.2±9.1 (62-68)	0.88±3.3 (-0.15-1.9)	67.3±9.2 (64.4-70.2)	66.4±8.6 (63.7-69.1)	0.9±3.3 (-0.09-1.9)
Serum urea (mmol/L)	4.7±0.9 (4.4-4.9)	4.6±0.85 (4.29-4.82)	0.1±0.3 (-0.001-0.2)	4.5±0.99 (4.2-4.8)	4.5±0.9 (4.1-4.8)	0.05±0.17 (0.002-0.11)

Variables indicated by mean±standard deviation and (95% confidence interval). ††The difference within group after treatment is statistically significant ($p<0.01$).

4.4 Side-effects monitoring

During the 14 days trial period, none of the patient in both group had discontinued enalapril or placebo because of the severe side effects. Mean of systolic blood pressure slightly decreased in both group ($p>0.05$). Within group, systolic blood pressure decreased not significantly as well ($p>0.05$). See (Table 4.8).

Table 4.8 Comparative change of systolic blood pressure between to groups

Systolic blood pressure (mmHg)	Enalapril group	Control group
Baseline	105±11(102-109)	105±9(101-108)
Day 4	105±14(100-108)	104±12(98-107)
Day 14	104±10(101-107)	104±11(100-107)
Mean Change (baseline-day 14)	1.19±6.6 (-0.7-3)	1.1±6.1(-0.97-3.16)

Value indicated by Mean ± Standard deviation and (95% confidence interval)

There had no syncope accrued. However, during the trial period, there had been 16 patients (30%) in control group and 20 patients (48%) appearing several episodes of cough, this clinical symptoms was some time related for their upper respiratory infection, as a variable of side effect measurement in this study is not accountable.

(Table 4.8) summarized general performance of Enalapril group and control group during the 14 days trial.

Table 4.9 General performance of Enalapril and control group during the treatment period

	Enalapril group	Control group
Cardiac contractility back to normal	23(55%)	14(23%)
Drop out	3(7%)	2(5%)
Death	1(2%)	1(2%)
Receiving addition diuretics	9(21%)	14(33)
Receiving potassium supplement	5(12%)	12(29%)
Maintaining low dose of enalapril Or placebo	3(7%)	1(2%)