VENTRICULAR FUNCTIONS IN CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AFTER ACE-INHIBITORS

Kriengsak Anuroj, Chotima Pathmanand, Viroj Sueblinvong, Chule Thisyakorn and Piroj Chotivitayatarakorn

Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Abstract. Nine pediatric symptomatic patients infected with human immunodeficiency virus with elevated pulmonary arterial pressure (MPA pressure) and ejection fraction (EF); and with fractional shortening, (FS) mean velocity of circumferential fiber shortening (MVCfc) and left ventricular peak systolic wall stress (PS) were prospectively evaluated using 2-dimensional and M-mode serial echocardiography and Doppler cardiography after administration of an ACE inhibitor (Inhibace 0.025 mg/kg/D orally) for 12 weeks.

The MPA pressure was not decreased, however the MVCfc and PS improved significantly ($p < 0.05$). Further, long term evaluation is required to determine its effect in preventing dilated cardiomyopathy and elevated mean pulmonary pressure.

INTRODUCTION

Human immunodeficiency virus infection in children causes numerous abnormal cardiovascular functions including dilated cardiomyopathy (Cheitlin, 1994; Harson and Shearer, 1990; Kavanaugh-McHugh *et al,* 1991). Although various pathogenic mechanisms for the dilated cardiomyopathy had been postulated, abnormal cardiac functions such as mean pulmonary arterial pressure (MPA pressure), ejection fraction (EF), fractional shortening (FS), mean velocity of circumferential fiber shortening (MVCfc) and left ventricular peak systolic wall stress (PS) had not been considered to be causes of the dilated cardiomyopathy (Farror *et al,* 1993; Grogan *et al,* 1992; Juilliere *et al,* 1994; Olsen, 1992).

Although angiotensin converting enzyme inhibitors (ACEI) enhance improvement of coronary blood flow and systemic vascular dilatation, a potent ACE inhibitor, Cilazapril, as demonstrated by recent studies (Clozel and Hefti, 1988; Deget and Brogden, 1991; Doyle, 1992; Hoffman, 1992; Kiowski *et al,* 1991; Kloner and Przyklenk, 1993), can improve myocardial metabolism and prevent or reduce end-organ damage. The aforementioned effects may improve those abnormal ventricular functions.

The purpose of this study was to compare the mean pulmonary arterial pressure and other ventricular functions before and after treatment with ACEI (Cilazapril) in order to provide baseline data for further studies about the dilated cardiomyopathy in HIV infected children.

MATERIALS AND METHODS

Nine of twelve patients who had high levels of mean pulmonary arterial pressure in our previous studies (Pathmanand *et al,* 1997) with the age ranged from 9 to 26 months, received ACEI (Cilazapril, Inhibace® 0.025 mg/kg/day oral route) after informed consent had been granted. The study was performed during January to December 1993. An Aloka SSP 860 M-mode and two dimensional echocardiography with 3.5 mHz phase array with doppler tranducer was used for the doppler interrogation, in which the standard views were obtained (Feigenbaum, 1986). The patients were completely sedated with chloral hydrate 50-70 mg/kg/dose oral route. Serial follow up was obtained on the first, fourth, eighth and twelveth weeks respectively.

Data analysis

The methods of determining ejection fraction and fractional shortening were standard. The mean pulmonary arterial pressure was culculated by the method of Chotivittayatarakorn *et al* (1992).

MPA pressure = 120-2.4 (AT/ET × 100), where

MPA pressure is the mean pulmonary arterial pressure (mmHg). Onset of ejection time (ET) was defined as the first point following the QRS complex at velocity exceeded zero. End of ejection time was definded as the point at which the velocity had fallen to zero. Acceleration time (AT) was definded as the time between the onset of ejection time and the time at the point with the highest flow velocity (Fig 1).

The mean velocity of circumferential fiber shortening (MVCfc) and left ventricular peak systolic wall stress (PS) were obtained by the methods of Colan *et al* (1984), Franklin *et al* (1990).

MVCfc = LVED - LVES/LVED × (ET/√R-R), where MVCfc is the mean velocity of circumferential fiber shortening corrected by heart rate (cir/sec), LVED = left ventricular end-diastolic dimension (cm), LVES = left ventricular end-systolic dimension (cm), ET = ejection time (sec) and √R-R = the square root of R-R interval from the EKG monitoring.

PS = 1.35 × PSP × LVES /4x PWS (1 + PWS/LVES), where PS is the stress at peak systole (gm/cm^2), PSP = pressure at peak systole (mmHg), PWS = left ventricular posterior wall thickness at systole (cm) (Fig 2). The normal values are 1.1 ± 0.15 (cir/sec) and 63.3 ± 12 (gm/cm^2) respectively.

Statistical analysis

Groups comparison between the first day to the twelveth week were analyzed by the Wilcoxon Signed Rank Test. A p value < 0.05 was considered significant.

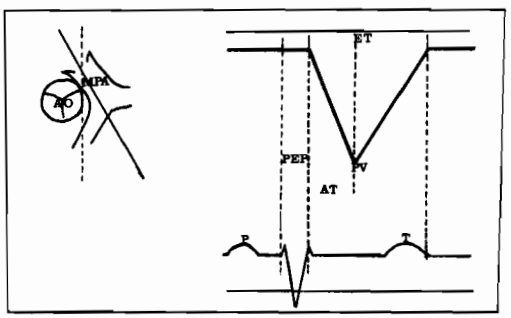

Fig 1– Parasternal Short-Axis view, with continuous wave Doppler superimposed in the main pulmonary artery and Doppler spectral wave form of the pulmonary flow velocity from this location. PEP = pre-ejection period, AT = acceleration time, ET = ejection time, PV = peak velocity.

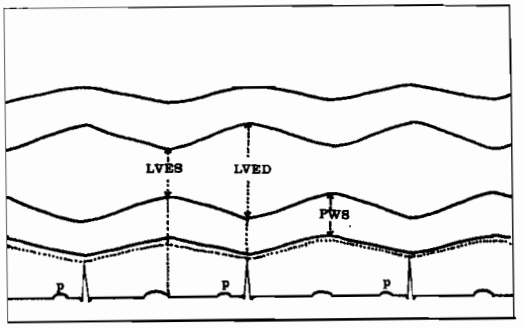

Fig 2– Parasternal Long-Axis view, with M-mode Doppler supperimposed in the left ventricle.
LVED = Left ventricular end diastolic diameter
LVES = Left ventricular end systolic diameter
PWS = Posterior wall thickness at peak systole
ET = Ejection time obtained from the standard view (Fig not shown)

RESULTS

The ejection fraction and fractional shortening were in high levels in most cases. After administered with Cilazapril, the levels were not lowered significantly. Together with the mean pulmonary arterial pressure which was abnormaly high, demonstrated no significant change (Tables 1, 2).

In contrast, the mean velocity of circumferential fiber shortening and the left ventricular peak systolic wall stress improved significantly, after Cilazapril on the twelveth week (Table 3).

DISCUSSION

There are many studies explaining the pathogenesis of the pulmonary hypertension in the patients with acquired immunodeficiency syndrome (AIDS), either directly from virus infection or mediated through the infected T-cells which cause pulmonary arteriolar endothelial cell proliferation and proliferating abnormal vessels (Coplan *et al*, 1990; Diaz and Clanton, 1993; Himeiman *et al*, 1989; Kane, 1992; Legoux *et al*, 1990; Mani and Smith, 1994; Polos *et al*, 1992; Speich *et al*, 1991).

In case of high pulmonary pressure secondary to the cardiovascular system, it may result from the obstruction of the pulmonary drainage, the high

Table 1

Age, sex and mean pulmonary arterial pressure (MPA).

Case	Age	Sex	Do	1st wk	4th wk	8th wk	12th wk
1	1Y 1M	F	60	50	52	48	45
2	1Y 4M	F	50	50	48	46	48
3	9M	F	43	40	42	37	40
4	1Y 11M	M	61	60	58	55	58
5	1Y 10M	M	47	46	44	48	44
6	1Y 10M	M	60	50	48	49	48
7	2Y 2M	F	60	50	54	46	51
8	1Y 9M	M	47	48	41	44	41
9	1Y 3M	F	43	40	42	44	40

M : F
$\overline{X}$ 1Y 4M 4 : 5
$p > 0.05$

Table 2

Ejection fraction and fractional shortening.

Case	Ejection fraction					% Fractional shortening				
No.	Do	1st wk	4th wk	8th wk	12th wk	Do	1st wk	4th wk	8th wk	12th wk
1	0.78	0.76	0.77	0.74	0.76	41	40	38	40	41
2	0.78	0.74	0.76	0.78	0.77	40	41	40	41	41
3	0.85	0.84	0.84	0.86	0.84	50	48	47	46	48
4	0.83	0.82	0.81	0.83	0.82	48	47	46	48	47
5	0.83	0.81	0.80	0.85	0.84	51	50	51	50	49
6	0.78	0.74	0.76	0.77	0.76	42	41	40	42	41
7	0.82	0.84	0.82	0.84	0.80	41	40	40	41	41
8	0.76	0.80	0.79	0.71	0.72	40	42	40	38	41
9	0.75	0.74	0.76	0.77	0.74	38	36	39	38	37

$p > 0.05$

Table 3

MVCfc and PS.

Case	MVCfc					PS				
No.	Do	1st wk	4th wk	8th wk	12th wk	Do	1st wk	4th wk	8th wk	12th wk
1	1.41	1.41	1.39	1.22	1.02	84.64	84.44	82.44	80.16	78.66
2	1.36	1.36	1.34	1.04	0.96	129.23	128.24	116.83	106.14	88.16
3	1.61	1.54	1.42	1.34	0.94	141.33	141.12	132.54	124.11	74.36
4	1.60	1.56	1.40	1.24	0.93	132.34	131.13	122.31	114.33	84.86
5	1.40	1.41	1.26	1.16	0.88	134.72	131.24	121.16	111.33	81.84
6	1.44	1.42	1.31	1.13	0.83	104.12	102.31	96.34	93.91	93.34
7	1.42	1.36	1.22	1.02	0.84	122.14	121.42	112.31	82.84	75.91
8	1.40	1.40	1.31	1.09	0.91	92.32	93.96	91.32	89.31	85.84
9	1.36	1.32	1.21	0.95	0.88	96.44	92.94	90.10	89.84	71.08

$p > 0.05$ $p > 0.05$

MVCfc = Mean Velocity of Circumferential fiber shortening
PS = Left Ventricular peak systolic wall stress

flow into the pulmonary bed and the low cardiac output state which is severe enough to cause reduced mixed venous PO_2 (Mercy and Reynolds, 1981; Nunn, 1993). Nine of our twelve cases revealed an increased pulmonic component of the second heart sound and increased mean pulmonary arterial pressure by echocardiogram.

Relief of the chronic hypoxia is considered effective (Kane, 1992). Other specific drugs, either acetylcholine or nitric oxide which require continuous administration will also lower the pulmonary pressure (Nunn, 1993).

Although vasodilators such as calcium channel blockers or ACEI have the effect of lowering the pulmonary arterial pressure (Benedict, 1994; Nunn, 1993), they contain no specific action on the pulmonary circulation. However, Cilazapril (ACE inhibitor), as reported in many studies, provided a cardioprotective mechanism and improved the vascular compliance. Its action is either through a biochemical change of neurohormonal systems or its local action in reducing fibroblast proliferation and collagen synthesis which might decrease the pulmonary pressure level (Benedict, 1994; Mani and Smith, 1994; Nunn, 1993; Polos *et al,* 1992).

From our study, although the high level of pulmonary arterial pressure was not significantly lower after Cilazapril administration, nevertheless the mean velocity of circumferential fiber shortening and left ventricular peak systolic wall stress, a load independent parameter, were reduced significantly, either through its local effects upon the tissue angiotensin converting enzyme in the myocardium or at the medial wall of the vessels.

Although many researchers have concentrated on defining the pathogenesis of the dilated cardiomyopathy (*eg* direct viral cytotoxicity, immunological responses such as antimyosin antibody in myocytes, spasm of the coronary microvasculature or abnormal cardiac function and heart failure (Joshi, 1988; Martino *et al,* 1994; Olsen, 1992), such studies were not performed in an HIV infected group. Moreover the study Of MVCfc, PS had not been documented in patients with dilated cardiomyopathy or patients with HIV infection.

Our study has shown that Cilazapril decreases the MVCfc and PS level, the mechanism of which needs to be explained. The MVCfc and PS should be studied in a larger group of either HIV infected or dilated cardiomyopathic patients in order to test the hypothesis that Cilazapril may prevent dilated cardiomyopathy in HIV infected children.

ACKNOWLEDGEMENTS

Dr K Anuroj was supported in part by grant from the Cardiac Children's Foundation of Thailand under the Royal Patronage of HRH Princess Galyani Vadhana and from Roche Co Thailand Ltd.

REFERENCES

Benedict CR. Neurohormonal aspects of heart failure. *Cardiol Clinics* 1994; 12 : 9-19.

Cheitlin MD. Cardiac involvement in the patient with AIDS. In : Broder S, Merigan TC, Bolognesi D, eds. Textbook of AIDS. Baltimore : Williams and Wilkins, 1994 : 609-16.

Chotivittayatarakorn P, Pathmanand C, Sueblinvong V, *et al.* Doppler echocardiographic predictions of pulmonary artery pressure. *J Med Assoc Thai* 1992; 75 : 80-4.

Clozel JP, Hefti. Cilazapril prevents the development of cardiac hypertrophy and the disease of coronary vascular reserve in spontaneously hypertensive rats. *J Cardiovasc Pharmacol* 1988, 11 : 562-72.

Colan SD, Brow KM, Neumann A. Left ventricular end systolic wall stress-velocity of fiber shortening relation; a load independent index of myocardial contractility. *JACC* 1984; 4 : 715-24.

Coplan NL, Shimony RY, Ioachim HL, *et al.* Primary pulmonary hypertension associated with human immunodeficiency viral infection. *Am J Med* 1990, 89 : 96-9.

Deget F Brogden RN. Cilazapril, a review of its pharmacodynamic and pharmacokinetic properties. *Drugs* 1991; 41 : 799-820.

Diaz PT, Clanton TL. Marked pulmonary function abnormalities in a case of HIV-associated pulmonary hypertension. *Chest* 1993, 104 : 313-5.

Doyle AE. Role of Angiotensin converting enzyme inhibitors in preventing or reducing end organ damage in hypertension. *J Cardiovasc Pharmacol* 1992; 19 (suppl 5) : 21-7.

Farror DJ, Woodard JC, Chow E. Pacing-induced dilated cardiomyopathy increases left to right ventricular systolic interaction. *Circulation* 1993; 88 : 720-4.

Feigenbaum H. Echocardiography. Philadelphia: Lea and Rabiger 1986; 188-230.

Franklin RG, Wyse RH, Graham TP, *et al.* Normal values for noninvasive estimation of left ventricular contractile state and afterload in children. *Am J Cardiol* 1990; 65 : 505-10.

Grogan M, Smith HC, Gersh BJ, *et al.* Left ventricular dysfunction due to atrial fibrillation in patients initially beleived to have idiopathic dilated cardiomygsathy. *Am J Cardiol* 1992; 69 : 1570-3.

Harson CG, Shearer WT. Pediatric Acquire Immune Deficiency Syndrome. In : Garson A Jr, Bricker JT, Mcnamara DG, eds. The science and practice of pediatric cardiology. Philadelphia : Lea and Febiger, 1990 : 1605-16.

Himeiman RB, Dohrmann M, Goodman P, *et al.* Severe pulmonary hypertension and cor pulmonale in the acquired immunodeficiency syndrome. *Am J Cardiol* 1989 : 1396-9.

Hoffman F. Hypertension and target organ damage. Basel, Switzerland Roche Ltd. 1992 : 43-57.

Joshi VV. Dilated cardiomyopathy in children with acquired immunodeficiency syndrome. *Hum Pathol* 1988; 19 : 69-73.

Juilliere Y, Buffet P, Marie P, *et al.* Right ventricle in dilated cardiomyopathy. *Am J Cardiol* 1994; 73 : 588-90.

Kane GC. Primary pulmonary hypertension in HIV infection. *Chest* 1992; 102 : 1918-9.

Kavanaugh-McHugh A, Ruff AJ, Rowe SA, *et al.* Cardiovascular manifestations. In : Pizzo PA, Wilfert CM, eds. Pediatric AIDS. Baltimore : Williams and Wilkins, 1991 : 355-72.

Kiowski W, Zuber M, Elsasser S, *et al.* Coronary and myocardial effects of Cilazapril. *Am Heart J* 1991; 110 : 1382-8.

Kloner RA, Przyklenk K. Cardioprotection with angiotensin converting enzyme inhibitor. *Adis Inter* 1993; 2 : 46.

Legoux B, Piette AM, Bouchet PF, *et al.* Pulmonary hypertension and HIV infection. *Am J Med* 1990; 89 : 122.

Mani S, Smith W. HIV and pulmonary hypertension. *Southern Med J* 1994; 87 : 357-62.

Mercy TW, Reynolds HY. Pulmonary consequences of congenital and acquired pulmonary immunodeficiency states. *Clinics Chest Med* 1981; 10 : 503-21.

Martino TA, Liu P, Sole MJ. Viral infection and the pathogenesis of dilated cardiomyopathy. *Circ Res* 1994; 74 : 182-8.

Nunn JF. Pulmonary vascular pressures. In : The Nunn's applied, respiratory physiology. London : Butterworth-Heinemann, 1993 : 139-50.

Olsen EG. The pathogenesis of dilated cardiomyopathy. *Postgrad Med J* 1992, 68 (Suppl 1) : S 7-10.

Pathmanand C, Anuroj K, Thisyakorn C, Sueblinvong V. Cardiovascular manifestations and left ventricular functions in human immunodeficiency virus infection in infants and children in Thailand. *Southeast Asian J Trop Med Public Health* 1997; 28 : (this volume).

Polos PG, Wolfe D, Harley RA, *et al.* Pulmonary hypertension and human immunodeficiency virus infection. *Chest* 1992; 101 : 474-8.

Speich R, Jenni R, Opravil M, *et al.* Primary pulmonary hypertension in HIV infection. *Chest* 1991; 100 : 1268-71.