Pulmonary-circulation disturbance arises in Glenn patients with high values of n-terminal pro-brain natriuretic peptide

Japan Research Promotion Society For Cardiovascular Disease Sakakibara Heart Institute
Nukaga S., Hamamichi Y., Komiya E., Sonoda K., Kobayashi T.,Ishii T., Kishiki. K., Inage A., Ueda T., Yazaki S., Yoshikawa T.

【 Background 】

We generally consider that values of n-terminal pro-brain natriuretic peptide (NT-proBNP) would be decreased in Glenn circulation. However, high values of NT-proBNP (high NT-proBNP) subsist in Glenn patients. We predict Glenn patients with high NT-proBNP would possess not only cardiac depression but also pulmonary circulation disturbance.

【 Objective 】

We investigated factors related to high NT-proBNP and the feature of pulmonary circulation in Glenn patients with high NT-proBNP.

【 Methods 】

Subjects and examinaions.

The medical records of 124 Glenn patients were reviewed aged from 10 months to 23 years. . They underwent cardiac catheterizations and blood tests between 2010 and 2015.

Table 1. Clinical characteristics in Glenn patients with high NT-proBNP (NT-proBNP ≥ 800pg/ml)

	high NT-proBNP (n=27)	Non (n=97)	p value
Study age (yrs)	3.4±5.0	3.3±4.3	0.99
Glenn age (yrs)	1.1±1.0	1.9±4.4	0.37
Right isomerism (%)	8/27 (29)	13/97 (13)	0.089
Ventriclular type (n)	R (15) L (2) B (10)	R (31) L (29) B (37)	0.049
RV type (%)	15/27 (55)	31/97 (31)	0.024
1st strategy (n)	Shunt (6) PAB/NPS (5/2) Norwood (14)	Shunt (37) PAB/NPS (31/11) Norwood (18)	0.0062
Norwood (%)	14/27 (51)	18/97 (18)	0.0011
RV-PA (%)	13/27 (48)	21/97 (21)	0.0063
Additional flow (%)	18/27 (66)	52/97 (53)	0.32
AVV repair (%)	2/27 (7)	11/97 (11)	0.81
AVVR ≥ II	10/27 (37)	15/97 (15)	0.013
NT-proBNP (pg/ml)	1380 (854 – 10610)	271 (44 – 788)	-
Creatinine (mg/dl)	0.34±0.12	0.32±0.11	0.44
Internal medicine			
Flosemid (%)	19/27(70)	42/97(43)	0.023
Spironolactone (%)	18/27(66)	39/97(40)	0.014
ACEI/ARB (%)	27/27(100)	78/97(80)	0.028
Enalapril (mg/kg)	0.22±0.08	0.22±0.07	0.70
Beta blocker (%)	22/27(81)	32/97(32)	<0.0001
Carvedilol (mg/kg)	0.24±0.10	0.39±0.20	0.0051
Pulm. Vasodilator (%)	12/27(44)	38/97(38)	0.62

Table 2. Cardiac performances in Glenn patients with high NT-proBNP (NT-proBNP ≥ 800 pg/ml)

	high NT-proBNP (n=27)	Non (n=97)	P value
SVEDV (%)	208±90	155±57	0.00056
SVESV (%)	117±81	68±33	<0.0001
SVEF (%)	49±12	56±10	0.0030
SVEDP (mmHg)	11.1±2.8	9.4±3.0	0.0094
SVESP (mmHg)	82±14	84±13	0.69
aAo Press. (mmHg)	80±13	79±10	0.58
Qs (L/min/m2)	4.3±1.5	4.7±1.3	0.21

【Results】

Cardiac performances. (Table 2).

As for ventricular performances, end-diastolic volume was larger in high NT-proBNP group than non-high NT-proBNP group (p=0.00056): end-systolic volume was larger (p<0.0001): ejection fraction was lower (p=0.0033). Cardiac output was not significantly different between two groups. As for pressure study, ventricular pressure on end-diastole was elevated in NT-proBNP (p=0.013).

Monovariate analysis of factors related to high NT-proBNP (Table 3).

Of 124 Glenn patients, 117 did not have defects in 8 indexes above. Using these 117 patients, we penetrated into backgrounds of high NT-proBNP in Glenn patients. We divided continuous data, which had significant differences between patients with and without high NT-proBNP, into two groups by means of checking their distributions. In monovariae analysis high NT-proBNP in Glenn patients was associated with major right ventricle, Norwood procedure, conduit from right ventricle, strong valve regurgitation, elevated SVEDP, expanded SVEDV, expanded SVESV, and decreased SVEF.

Independent factors related to high NT-proBNP (Table 4).

After multivariate analysis high NT-proBNP was independently associated with odds ratio of 10.4 for decreased ejection fraction of ventricle, 6.0 for Norwood procedure, 5.3 for elevated ventricular pressure on end-diastole, and 4.3 for expanded ventricular volume on end-systole. Explanatory coefficient was 0.39 for high NT-proBNP by these 8 factors.

Pulmonary parameters (Table 5).

As for pulmonary circulation, pressure of superior vena cava was much elevated in high NT-proBNP group; pressure of pulmonary capillary wedge (or left atrium) was elevated; pulmonary resistance was increased.

Conclusion.

Glenn patients with high NT-proBNP held elevated pressures of superior vena cava. Depressed cardiac functions would build up afterload on pulmonary arteries. Heart failure therapy might be useful for lowering pressure of pulmonary artery in Glenn patients.

Comparative methods.

We defined high NT-proBNP as NT-proBNP 800pg/ml or over (by Japan heart failure society, n=27). First, cardiac performances and clinical characteristics were determined which would act on secretion of NT-proBNP. Continuous variables which would become predictive factors were transformed to a binary categorical variables, such as SVEDP ≥ 13 mmHg positive and SVEDP < 13 mmHg negative. We examined the association of each factor with hNT-proBNP by using chi-square test. Predictors that had associations in univariate analysis (p<0.1) were then taken forward to multiple logistic-regression models. R-square values were used as explanatory coefficients for hNT-proBNP by predictive factors which were significant in monovariate analysis.

Second, we compared clinical features between patients with and without high NT-proBNP.

Table. 3 Monovariate analysis of factors related to high NT-proBNP (NT-proBNP ≥ 800pg/ml) in 117 Glenn patients

	high NT-proBNP (n=24)	Non (n=93)	p value
RV type	13/24 (54)	29/93 (31)	0.036
Norwood	13/24 (54)	19/93 (20)	0.00094
RV-PA shunt	12/24 (50)	21/93 (22)	0.0077
AVVR ≥ II	10/24 (41)	15/93 (16)	0.0065
SVEDP ≥ 12 mmHg	13/24 (54)	20/93 (21)	0.0015
%SVESV≥ 80%	16/24 (66)	26/93 (27)	0.0010
%SVEDV≥ 178%	13/24 (54)	24/93 (22)	0.0077
SVEF ≤ 35%	4/24 (16)	2/93 (2)	0.018

Table4. Independent factors related to high NT-proBNP (NT-proBNP ≥ 800pg/ml) in 117 pre-Fontan patients

Factors	O. R.	95%CI	p value
RV type	-	-	-
Norwood	6.0	1.8 – 19.5	0.0030
RV-PA shunt	-	-	-
AVVR ≥ II	-	-	-
SVEDP ≥ 12 mmHg	5.3	1.6 – 17.2	0.0050
%SVESV≥ 80%	4.3	1.4 – 13.2	0.0090
%SVEDV≥ 178%	-	-	-
SVEF ≤ 35%	10.4	1.1 – 96.0	0.038

R-square = 0.39

Table 5. Pulmonary parameters in Glenn patients with high NT-proBNP (NT-proBNP ≥ 800 pg/ml)

	high NT-proBNP (n=27)	Non (n=97)	P value
Qp (L/min/m2)	3.3±1.4	3.3±1.0	0.88
Rp (U*m2)	1.9±0.8	1.5±0.7	0.047
PAI (mm2/m2)	218±120	261±112	0.091
LPA (mm/m2)	16.2±6.0	16.4±5.3	0.51
RPA (mm/m2)	18.0±5.0	18.9±5.1	0.40
LAP/PCWP (mmHg)	9.6±4.4	8.0±3.1	0.031
SVCP (mmHg)	15.0±4.3	12.1±3.4	0.00044
AoSatO2 (%)	83±6	85±4	0.14

【 Discussion】

Major findings.

First, high NT-proBNP values in Glenn patients were connected with myocardial stretch, which has been said in Fontan patients. Our study also showed history of Norwood was independently related to high NT-proBNP in Glenn patients. Second, pressures of pulmonary capillary wedge and superior vena cava were increased in Glenn patients with high NT-proBNP.

Systolic dysfunction and Diastolic dysfunction.

Systolic dysfunction and diastolic dysfunction are reported to affect levels of NT-proBNP in adult heart-failure patients with bi-ventricle . We also suggested in this study high NT-proBNP in Glenn patients were independently associated with systolic dysfunction (SVEF ≤ 35%) or diastolic dysfunction (SVEDP ≥ 12 mmHg). In addition, large ventricular volume on end-systole (%SVESV≥ 80%), which indicated decreased contractile force, was independently related to high NT-proBNP. Large ventricular volume (%SVEDV≥ 178%), which was connected with high NT-proBNP in monovariate analysis, was absorbed into larger systolic ventricular-volume. Similarly, strong AVVR (≥ II) would assimilated into larger ventricular volumes or decreased ejection fraction.

Not only systolic dysfunction but also diastolic dysfunction for was disadvantageous as Fontan candidate, which, moreover, persist after Fontan procedure possibly. However, we are practically hard to detect these dysfunction in mon-ventricular wall motion. We should perform further examination employing high NT-proBNP as indicator.

Norwood procedure.

This study showed Glenn patients with Hx of Norwood procedure accounted for 51 percent of all patients with high NT-proBNP, althogh non-Hx of Norwood patients did only 18 percent of high NT-proBNP patients. Moreover, “Norwood procedure” was independent risk factor for high NT-proBNP in Glenn patients. The factor “RV-PA conduit” would be internalized into “Norwood procedure” after multivariate analysis. The causes of high NT-proBNP have not been reported in Glenn patients with Hx of Norwood. We suspected implant of RV- conduit would induce direct myocardial injury. It can also be possible that poor supply of coronary blood flow would damage myocardium in patients with hypoplastic aorta.

Pulmonary circulation in Glenn patients with high NT-proBNP.

Our study showed Glenn patients with high NT-proBNP possessed higher pressures of left atrium or pulmonary capillary wedge than those without high NT-proBNP. This would be provoked by major ventricular overloads in high NT-proBNP patients, such as higher SVEDP , larger SVEDV, and larger SVESV. Our study also showed pressures of superior vena cava more rose in high NT-proBNP group. this would be induced by higher LAP/PCWP in this group. These results indicated that medical management by means of heart failure remedies hold the potential for lowering pressures of superior vena cava.