Decline of estimated glomerular filtration-rate are mainly related to low cardiac output and combination use of spironolactone in adult Fontan patients

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【 **Background** 】Criterion values of creatinine (Cre) are different according sex and ages, which makes difficult for us to evaluate renal function by raw Cre value. Japanese Society of Nephrology provides formula of estimated glomerular filtration-rate (eGFR), by which we can estimate renal function in Japanese adults. We predicted reduced eGFR was provoked by cardiac hypofunction or heart medicines.

【 **Objective** 】 We assessed reduction of kidney functions by means of eGFR in Fontan adults and sought backgrounds of reduced eGFR.

【 **Methods** 】**Subjects and examinaions.** The medical records of 63 Fontan adults were reviewed aged from 19 years to 46 years. They underwent cardiac catheterization and routine blood test between 2010 and 2016.

Table 1. Characteristics of pediatric patients with reduced eGFR

	reduced eGFR (n=17)	Non (n=46)	P value
Cath. age(yrs)	33.4±7.9	28.5±6.6	0.016
Fon age (yrs)	21.2±12.8	14.8±10.7	0.055
Right isomerism (%)	3/17 (17)	5/46 (10)	0.77
Major ventricle	R (9) L (3) B (5)	R (16) L (17) B (13)	0.45
Single LV	3/17 (17)	5/46 (10)	0.77
1st strategy	Shunt (9) PAB (3) NPS (5) Norwood (0)	Shunt (27) PAB (11) NPS (8) Norwood (0)	0.76
TAPVC repair	1/17 (5)	1/46 (2)	0.94
AVV repair	4/17 (23)	7/46 (15)	0.69
Fenerstrated Fontan	1/17 (5)	3/46 (6)	0.62
PTA	1/17 (5)	8/46 (17)	0.45
Coil embolization	8/17 (47)	17/46 (36)	0.46

Table 2. Hemodynamics of pediatric patients with reduced eGFR

	reduced eGFR (n=17)	Non (n=46)	P value
CVP (mmHg)	11.2±3.4	11.1±3.5	0.95
PCWP (mmHg)	8.1±4.2	7.5±4.2	0.63
SVEDP (mmHg)	8.6±4.0	9.3±4.2	0.53
SVESP (mmHg)	106±18	106±17	0.91
SVEDV (%)	77±27	100±39	0.040
SVESV (%)	37±18	54±27	0.029
SVEF(%)	50±11	47±12	0.28
Ao syst Press.(mmHg)	102±21	105±18	0.48
Ao dias Press.(mmHg)	62±13	64±11	0.56
Qs (L/min/m2)	2.1±0.7	2.4±0.7	0.11
Rs (U・m2)	35.9±14.5	31.2±14.4	0.31
Rp (U・m2)	1.8±1.0	1.6±0.7	0.51
PAI (mm/m2)	263±85	262±91	0.98
AVVR≥ II (%)	3/17 (17)	9/46 (19)	0.84
Ao SatO2 (%)	93±3	92± 4	0.40
NT-proBNP (pg/ml)	534.7±270.8	376.9±400.2	0.17

【Results】

Hemodynamics of adult Fontan patients (Table 2).

Adult Fontan patients with reduced eGFR possessed significantly smaller ventricular volumes than those with non-reduced eGFR, such as SVEDV and SVESV. Contrary to our expectance, pressure parameters, which appeared to influence kidney functions, were almost same between two groups: aortic pressure on end-systole and end-diastole, and central venous pressure. As indexes which would be connected with renal functions, the frequency of strong AVVR (AVVR ≥ II) and levels of NT-proBNP were not significantly different between two groups.

Relation between reduced eGFR and internal medicine (Table 3).

Almost all internal remedies which had renal activities were not connected with reduced eGFR in adult patients after Fontan, such as ACEI, ARB, and diuretics. In contrast, the rate of patients who took spironolactone, which was used as diuretics or drug for heart failure, was higher in reduced eGFR group. Combination of spironolactone and Enarapril, which would occasionally provoke kidney injury, was employed at the nearly same rate between two groups.

As for non-renal activity remedies, the patient-rate with β-blocker was not different between adult patients after Fontan with reduced eGFR and without reduced eGFR; that with pulmonary vasodilator was not different between two groups.

AUROC for predicting reduced eGFR (Table 4) .

We gained significant AUROC ($p < 0.1$) for predicting reduced eGFR by 3 cardiac paraneters, such as %SVEDV(AUROC: 0.310), %SVESV (0.310), and Qs (0.295). Similarly, we gained significant by 2 age-related indexes , such as study age (0.683) and Fontan age (0.647). No significant AUROCs were obtained by cardiac pressure performances, such as central venous pressure, ventricular pressure on end-systole, and ventricular pressure on end-diastole.

Monovariate and Multivariate analysis (Table 5).

Of 63 Fontan patients, 46 did not have defects in 6 indexes above. Using these 46 patients, we penetrated into backgrounds of reduced eGFR in adult Fontan patients. We divided continuous data, which had significant differences between patients with and without reduced eGFR, into two groups by checking their distributions (Table 4). Categorization data were directly employed, such as sorts of internal medicines (Spironolactone). In monovariate analysis decreased eGFR was related to age-related indexes, such as study age (Study age ≥ 40 yrs) and Fontan age (Study age ≥ 32 yrs). Reduced eGFR was also associated with cardiac output (Qs ≤ 1.8 L/min/m2), ventricular volume on end-diastole (SVEDV<70%) and on end-systole (SVESV ≤ 36%). As for internal medicine, only Spironoractone was related to reduced eGFR. Of 6 factors which got significant differences in monovariate analysis, 3 were independent factors for reduced eGFR with high odds ratio after multivariate analysis: low cardiac output(odds ratio 28.0), reduced ventricular volume on end-diastole (odds ratio 19.6), and usage of Spironolactone (odds ratio 14.0). Explanatory coefficient for reduced GFR by these 6 factors was much high (R-square=0.64).

Prediction formulae for eGFR in adults (19 years or over).

We calculated eGFR by a formula which was composed of power function for serum Cr values (SCr) and ages.

GFR (male) = 194*SCr-1.094*age-0.287

GFR (female) = GFR (male) *0.739

This formula indicates two facts: eGFR values are lower in older patients; eGFR values are slightly higher in males than in females.

In this study patients with eGFR 80 mL/min/m2 under (n=17) were defined as reduced eGFR.

Comparative methods.

We used the area under a receiving operating characteristics curve (AUROC) to investigate relations between continuous variables and reduced eGFR. Next, continuous data which had significant differences ($p<0.1$) by AUROC between patients with and without reduced eGFR were divided into two groups by referring to their distributions (chi-square test). Similarly, we used chi-square tests as monovariate analysis to compare the frequency of each internal medicine between patients with and without reduced eGFR.

For indexes which had significant differences in monovariate analysis ($p<0.1$) we performed multiple logistic regession model to identify independent predictors for reduced eGFR.

Table 3. Relation between reduced eGFR and internal medicine

	reduced eGFR (n=17)	Non (n=46)	P value
renal activity			
ACEI (%)	6/17 (35)	17/46 (36)	0.86
ARB (%)	5/17 (29)	13/46 (28)	0.82
ARB + ACEI (%)	0/17 (0)	4/46 (8)	0.50
Flosemid (%)	8/17 (47)	14/46 (30)	0.35
Spironolactone (%)	12/17 (70)	14/46 (30)	0.0097
Spironolactone + ACEI (%)	3/17 (17)	2/46 (4)	0.22
Non-renal activity			
B-blocker (%)	13/17 (76)	28/46 (60)	0.39
Pulmonary vasodilator (%)	1/17 (5)	6/46 (13)	0.72

Table 4. AUROC for predicting reduced eGFR in 63 adult Fontan patients

	AUROC	95%CI	p value
Study age (yrs)	0.683	0.527 - 0.838	0.027
Fon age (yrs)	0.647	0.488 - 0.806	0.075
SVEDV (%)	0.332	0.173- 0.491	0.059
SVESV (%)	0.310	0.143- 0.476	0.041
SVEF (%)	0.539	0.367- 0.712	0.657
SVEDP (mmHg)	0.461	0.291 - 0.630	0.636
SVESP (mmHg)	0.458	0.284 - 0.632	0.614
Qs (L/min/m2)	0.295	0.132- 0.457	0.017
PCWP (mmHg)	0.553	0.393- 0.713	0.528
SVCP (mmHg)	0.507	0.341 - 0.673	0.932
Ao syst Pres. (mmHg)	0.413	0.244 – 0.583	0.292
Ao diast Pres. (mmHg)	0.436	0.274 – 0.598	0.439
Ao SatO2 (%)	0.576	0.414 - 0.739	0.362

Table 5. Multivariate analysis for predicting reduced eGFR

	Mono.	Multi.		
Factors	p value	p value	O. R.	95%CI
Study age ≥ 40 yrs	0.010	-	-	-
Fon. age ≥ 32 yrs	0.043	-	-	-
Qs ≤1.8 L/min/m2	0.002	0.012	28.0	2.1 – 373.4
SVEDV < 70%	0.009	0.010	19.6	2.1 – 373.4
SVESV ≤ 36%	0.011	-	-	-
Spironolactone	0.060	0.019	14.0	1.5 – 127.7

R-square = 0.64

【 Discussion】

Two major findings.

First, low cardiac output provoked reduced eGFR in adult patients after Fontan. In contrast, low systemic pressure and high central-venous pressure were not associated with reduced eGFR at all. Second, reduced eGFR appeared in adult patients after Fontan who took Spironolactone.

Low cardiac output and low systemic pressure.

Low cardiac output and low systemic pressure were risk factors for renal insufficiency in adult patients with bi-ventricle. Both of these provokes low renal flow, which induces kidney impairment. Our study showed low cardiac output was highly associated with decreased eGFR in adult Fontan patients. Small ventricular volumes, which would be connected with low cardiac output, were also related to decreased eGFR in adult Fontan patients. In contrast, low systemic pressure was not significantly related to decreased eGFR by ROC analysis. However, Ao systolic pressure≦ 96 mmHg was connected with decreased eGFR by square test (9/17 vs. 12/46: p=0.044). After multianalysis using Ao systolic pressure≦ 96 mmHg along with 6 factors we gained higher explanatory coefficient (0.67). Because of distribution bias in systemic pressure we would not gain a significant difference by ROC analysis.

Diuretics and nonsteroidial anti-inflammatory agents.

Volume depletion by diuretic use is risk factor for decreased eGFR in heart-failure patients with bi-ventricle. Contrary to our expectance, Fontan patients with Lasix did not have decreased eGFR. This would be because Lasix-dose was not so much that it would induce low volume in this population. Nonsteroidal anti-inflammatory agents have been reported to cause reduced eGFR by its vasoconstrictive acting. All Fontan patients, including this population, got aspirin every day. So we could not investigate decreased eGFR by aspirin.

Conclusion.

In adult Fontan patients reduced eGFR was intensely related to low cardiac output and small ventricle. Shortage of renal blood-flow may be the main cause of deteriorating renal function in adult Fontan patients. Besides, reduced eGFR was associated with Spironolactone. We should to estimate eGFR in adult Fontan patients with these risk factors.