Abnormal glucose metabolism in patients with Fontan circulation: Unique characteristics and associations with Fontan pathophysiology

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Background Fontan patients exhibit a high prevalence of abnormal glucose metabolism (AGM). We aimed to characterize AGM and clarify its association with Fontan pathophysiology.

Methods We prospectively evaluated AGM with plasma glucose dynamics [mg/dL; fasting glucose (FPG), and maximum glucose increase (PG-spike)] during oral glucose tolerance test and hemoglobin A1c (HbA1c) in 276 consecutive Fontan patients (aged 19 ± 7 years). Of these, 176 patients had serial AGM assessments with a mean interval of 6.5 years.

Results Initial analysis revealed a high prevalence of impaired glucose tolerance (38.4%) and diabetes mellitus (DM) (4.7%), and positive family history, high HbA1c, and high central venous pressure independently predicted presence of DM. HbA1c was independently determined by hypersplenism and presence of DM ($P < .05$). Serial assessments revealed an increased PG-spike and a decreased HbA1c ($P < .001$ for both). Prevalence of DM increased (6.3% to 10.3%), and positive family history, high liver enzymes, and AGM predicted new onset of DM ($P < .05$ for all). Twenty-one patients died during 7.1-year follow-up. FPG ($P < .01$) and PG-spike ($P < .05$) independently predicted all-cause mortality. Particularly, patients with FPG ≤ 74 and/or PG-spike ≥85 had a mortality rate 8.7 times higher than those without ($P = .0129$).

Conclusions AGM progressed even in young adult Fontan patients, and HbA1c showed limited predictive value for progression. Oral glucose tolerance test plays important roles in uncovering unique Fontan AGM as well as predicting all-cause mortality. (Am Heart J 2019;216:125-135.)

Most children who undergo Fontan operation reach adulthood; however, morbidity and mortality remain high.[1,2] Multiple organ dysfunction is involved in a variety of morbidities including heart failure, arrhythmia, pulmonary arteriovenous fistulae, protein-losing enteropathy, thromboembolism, and Fontan-associated liver disease (FALD).[3] Therefore, a multidisciplinary management strategy is crucial to maintain multiple organ function and improve long-term outcome. Abnormal glucose metabolism (AGM) is an important "silent" pathophysiology that leads to multiple organ dysfunction, especially in the cardiovascular system.[3] Long-term adverse effects of AGM on Fontan pathophysiology may be significant because of the high prevalence of AGM.[4,5] However, there is limited knowledge about this "silent" pathophysiology of AGM such as its impact on prognosis as well as the applicability of a traditional diagnostic approach to Fontan pathophysiology. Accordingly, the present study aimed to (1) assess current and serial changes in AGM using standard diagnostic approaches including measurement of hemoglobin A1c (HbA1c) and 75-g oral glucose tolerance test (OGTT), (2) compare AGM status with current Fontan pathophysiology, and (3) clarify determinants of AGM-related variables that predict future new onset of diabetes mellitus (DM) as well as all-cause mortality.

Methods

Participants

We prospectively studied 276 clinically stable patients after Fontan operation (aged 10-55 years) (Table I) and 28 healthy volunteers (aged 13-39 years) who served as controls and showed no significant lung or heart

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Table I. Clinical characteristics of the study subjects

	Fontan			
	Cross-sectional	Serial		
		Baseline	Follow-up	*P*
Cases	276	175		–
Age (y)	19 ± 7	20 ± 7	27 ± 7	<.0001
Male gender (%)	58	63		–
BMI (kg/m^2)	19 ± 3	19 ± 3	20 ± 3	<.0001
Follow-up (y)	12.6 ± 5.1	11.8 ± 5.1	15.6 ± 6.7	<.0001
Disease (%)	UVH (26), TA (24) DORV (15), MA (9) PA (7), others (19)	UVH (26), TA (22) DORV (15), MA (9) PA (10), others (15)		–
APC/TCPC	29/247	20/155	2/173	–
Heterotaxy	69 (25%)	45 (26%)		
PLE	13 (4.7%)	6 (3.4%)	11 (6.3%)	.2106
NYHA class	1.4 ± 0.6	1.4 ± 0.6	1.5 ± 0.7	.009
Peak Vo_2 (mL/kg/min)	25 ± 7	25 ± 7	23 ± 7	<.0001
Peak Vo_2 (% of normal)	59 ± 14	57 ± 15	54 ± 15	<.0001
Hemodynamics (n)				
CVP (mm Hg)	10.5 ± 2.3	10.5 ± 2.2	9.6 ± 2.7	<.0001
CI (L/min/m^2)	2.7 ± 0.7	2.6 ± 0.7	2.7 ± 0.6	.1821
EF (%)	55 ± 9	55 ± 10	53 ± 9	.0003
Rp (U•m^2)	1.5 ± 0.6	1.5 ± 0.6	1.2 ± 0.5	<.0001
Rs (U•m^2)	28 ± 8	29 ± 8	26 ± 8	<.0001
Hemoglobin (g/dL)	15.2 ± 1.8	15.3 ± 2.0	15.1 ± 2.1	.1179
Sao_2 (%)	94.5 ± 2.5	94.5 ± 2.4	93.7 ± 4.0	.0063
Neurohumoral factors				
Norepinephrine (pg/mL)	416 ± 226	398 ± 195	453 ± 278	.0094
BNP (pg/mL)	37 ± 60	38 ± 53	37 ± 57	.9356
Renin activity (ng/mL/h)	11.9 ± 15.7	11.2 ± 14.4	12.7 ± 16.0	.1888
Biochemical variables				
Albumin (g/dL)	4.5 ± 0.4	4.4 ± 0.4	4.5 ± 0.5	.0003
Total bilirubin (mg/mL)	1.1 ± 0.6	1.1 ± 0.7	1.3 ± 0.9	.0645
ALT (U/L)	25 ± 14	25 ± 15	24 ± 14	.2095
GGT (U/L)	79 ± 57	82 ± 63	94 ± 71	.0009
Uric acid (mg/mL)	6.0 ± 1.6	6.1 ± 1.7	6.2 ± 1.4	.9135
Creatinine (mg/dL)	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.2	<.0001
Medications (%)				
Diuretics	39	43	43	.9141
Anticoagulant	75	72	78	.2175
ACEI/ARB	36	33	47	.0063
β-Blocker	25	26	45	.0002
Antihyperuricemia	4	3	14	.0002

Values are mean ± SD. *UVH*, univentricular heart; *TA*, tricuspid valve atresia; *DORV*, double outlet right ventricle; *MA*, mitral atresia; *PA*, pulmonary atresia; *APC*, atriopulmonary connection; *TCPC*, total cavopulmonary connection; *PLE*, protein-losing enteropathy; *CI*, cardiac index; *EF*, systemic ventricular ejection fraction; *Rp*, pulmonary artery resistance; *Rs*, systemic artery resistance; Sao_2, arterial oxygen saturation.

problems at a routine physical checkup. Follow-up clinical evaluations, including cardiac catheterization with cardiovascular imaging, were performed for all but one Fontan patients as previously described.[4] The follow-up period from last operation to the time of study was at least 6 months for postsurgical patients, and all patients were free from intravenous medications and considered as clinically stable. Medications, including diuretics, anticoagulant agents, and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, and antiarrhythmic agents are shown in Table I. None of the patients were taking inotropic agents, except for digoxin. Information on body weight, gestational week at time of birth, and first-degree family history of DM was collected during routine practice.

Hemodynamics

Intracardiac pressure and blood oxygen saturation were measured as previously described.[4] Simpson's rule was used to estimate morphological right and left ventricular volumes in patients who underwent cineventriculography. End-diastolic ventricular volume was divided by body surface area to obtain end-diastolic

volume index, and ejection fraction of the systemic ventricle (SV) was calculated.[4]

Exercise protocol

Fontan patients (n = 274) underwent symptom-limited treadmill exercise within 1 week of cardiac catheterization,[6] and peak oxygen uptake (Vo_2; mL/kg/min) was measured.

Body composition

Fat mass and fat-free mass (kg) were estimated using bioelectrical impedance analysis performed using an InBody 720 (Biospace Co, Ltd, Seoul, Korea)[7] in 195 patients, and ratios (%) of fat and fat-free masses to total body weight (%Fat and %FFM, respectively) were calculated. Patients with pacemaker implantation were excluded from this analysis.

Spleen longitudinal length

After a 12-hour fast, the longitudinal length of the spleen was measured (n = 143) as an index of hypersplenism at the time of initial OGTT and was standardized using body height (cm/m) (SSA-700A, 790A; Toshiba Medical Systems, Tochigi, Japan; Doppler frequency: 3.5 MHz).

Plasma neurohormonal activities and biochemical variables

After resting in the supine position at least 15 minutes, plasma norepinephrine (NE) concentration (n = 275), brain natriuretic peptide (BNP; n = 276), and renin activity (n = 275) were determined in Fontan patients and healthy controls. We also measured plasma albumin, total bilirubin, uric acid, creatinine, and liver enzymes (alanine aminotransferase [ALT], γ-glutamyltransferase [GGT]).

Assessment of glucose metabolic abnormality

Glucose metabolic abnormalities were measured as previously described.[4] Briefly, glucose metabolic variables were measured, including fasting plasma glucose (FPG) (mg/dL), insulin (μU/mL), and HbA1c. A standard OGTT was performed with plasma glucose (PG) and plasma insulin levels measurements at 0, 30, 60, and 120 minutes postchallenge in all Fontan patients, except for 1 patient with known DM who was excluded from the OGTT-associated analysis. Glucose tolerance was defined as normal (NGT), impaired glucose tolerance (IGT), and DM according to the World Health Organization criteria.[8] We calculated areas under the PG response curve using fasting and 30-, 60-, and 120-minute PG concentrations with the trapezoid rule as indices of postprandial hyperglycemia. To determine the response, we used values of the area under the PG response curve − FPG × 120 min (AUC-PG) and the maximal increase in PG from FPG to the highest PG during OGTT (PG-spike). Homeostasis model assessment was used to assess hepatic insulin resistance. This study protocol was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center.

Serial assessment

Of the 276 patients, 175 underwent serial assessment of AGM, hemodynamics, exercise capacity, and neurohormonal activities with an interval of 6.5 ± 2.7 years (Table I).

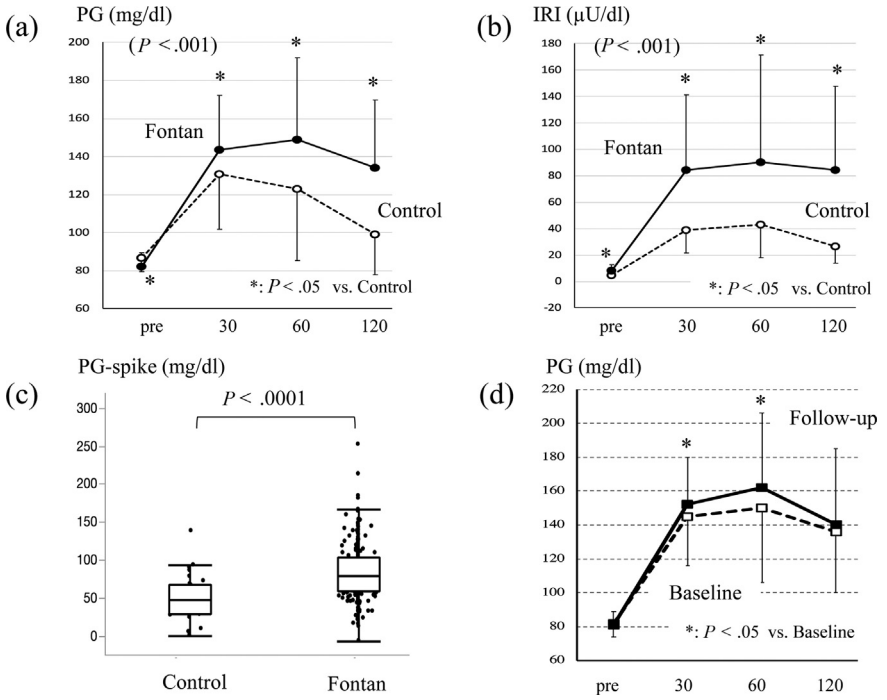
All-cause mortality

We prospectively followed the Fontan patients, and all-cause mortality was categorized as follows: heart failure, arrhythmia and/or sudden death, hemostatic problems, malignancy, and others as previously described.[1]

Statistical analysis

Data are expressed as mean ± SD. Differences in demographics, functional capacity, hemodynamics, glucose metabolism, and neurohormonal variables were evaluated using 1-way analysis of variance with Tukey post hoc test among at least 3 groups. Random-effects generalized least squares regression was used to compare time courses of PG and insulin during OGTT in Fontan patients and controls. Simple regression analysis was used to evaluate relationships between continuous variables, and multivariate linear regression analysis was used to detect the main correlates. Comparisons of prevalence of medications and glucose metabolic abnormalities were evaluated using χ^2 or Fisher exact test. Univariate Cox proportional hazards model was used to predict the associations of clinical factors such as age, gender, body mass index (BMI), functional capacity, SV systolic function, arterial oxygen saturation, neurohormonal levels, and glucose metabolic variables. To ease the interpretability of the results, hazard ratios were calculated for 100 pg/mL NE and 10 pg/mL BNP. For statistically significant variables, receiver operating characteristic curve analysis was applied to determine cutoff values to identify efficient prognostic prediction. Significant variables in the univariate analysis ($P < .10$) were included in the multivariate analysis of the Cox regression model to determine independent predictors. Survival rate was estimated using the Kaplan-Meier method, and differences between groups were assessed using log-rank tests. Analyses were performed using JMP 12 pro software (SAS Institute, Cary, NC) and STATA (Version IC 14.2, College Station, TX). All P values < .05 were considered statistically significant. No external funding was used to support this work, and the authors are solely responsible for the design and conduct of this study.

Figure 1



Plasma glucose (**A**) and immunoreactive insulin (**B**) levels during 75-g OGTT in Fontan (solid) and control (dotted) groups. **C**, Comparison of PG-spike between Fontan and control groups. **D**, Serial changes in PGs during 75-g OGTT at baseline (dotted) and follow-up (solid). Values represent mean ± SD.

Results

Prevalence of AGM and serial change

Cross-sectional assessment. Initial OGTT was performed in 275 patients. Time courses of PG and insulin and PG-spike in the Fontan and controls are shown in Figure 1, *A*, *B*, and *C*. The results showed that 60.9% (n = 168) had NGT, 34.4% (n = 95) had IGT, and 4.7% (n = 13) had DM.

Longitudinal assessment. Of the 275 patients, 172 underwent a second OGTT with an interval of 6.5 ± 2.7 years after the initial OGTT; however, 3 patients developed DM during the follow-up period and were excluded. Of the patients who had serial AGM (n = 175) measurements, 57.1% (n = 100) had NGT, 36.6% (n = 64) had IGT, and 6.3% (n = 11) had DM. The second OGTT revealed that 53.7% (n = 94) had NGT, 36.0% (n = 63) had IGT, and 10.3% (n = 18) had DM. Although the number of patients with DM patients increased from 11 (6.3%) to 18 (10.3%), this value did not reach statistical significance ($P = .17$).

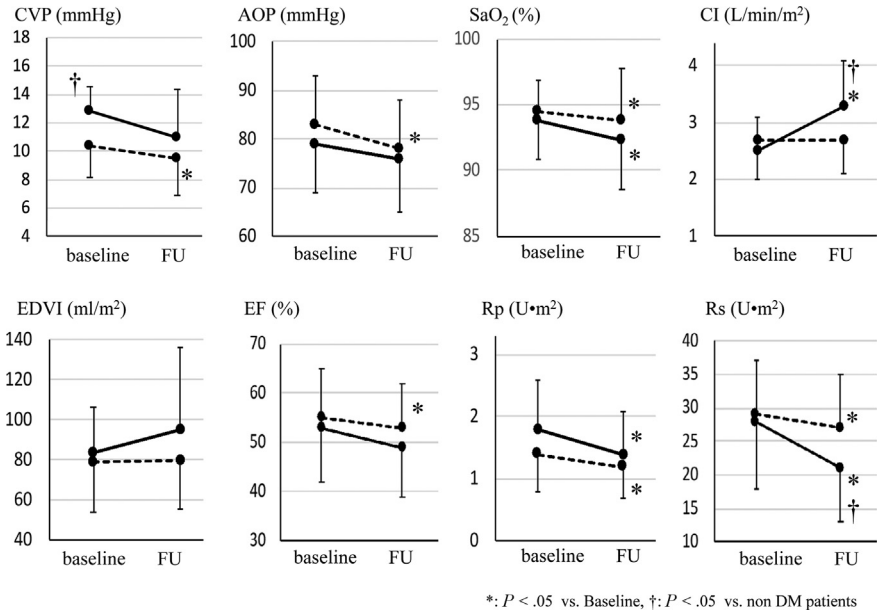
Of the 100 initial NGT patients, 28 (28%) and 3 (3%) developed IGT and DM, respectively. Of the 64 initial IGT patients, 30 (47%) remained with IGT and 11 (17%) developed DM, whereas 23 (36%) improved (ie, NGT). Of the 11 initial DM patients, 4 (36%) remained with DM, whereas the other 7 (64%) patients improved (2 [18%] had NGT and 5 [46%] had IGT).

The serial changes in PG during OGTT in the 172 patients are shown in Figure 1, *D*. There was an increase in PG at 30 and 60 minutes after glucose load as well as in indices of postprandial hyperglycemia, such as PG-spike and AUC-PG (6.6 ± 3.1 to 7.5 ± 3.3; $P < .0001$). DM therapy was initiated in only 2 patients. After excluding these 2 patients, despite a worsening of postprandial hyperglycemia, HbA1c significantly decreased (5.8 ± 0.5 to 5.6 ± 0.4; $P = .0002$).

AGM, body composition, and hemodynamics

Cross-sectional assessment. A comparison of hemodynamics in the 13 DM patients with those without DM (n = 263) showed greater New York Heart Association (NYHA) class (2.1 ± 0.6 vs 1.3 ± 0.6; $P < .0001$), lower peak Vo_2 (48% ± 12% vs 59% ± 14%; $P = .007$), and higher central venous pressure (CVP; 12.4 ± 2.2 vs 10.4 ± 2.3; $P = .002$) in DM patients. There was no correlation between body composition variables such as BMI, %Fat, or %FFM and FPG, PG-spike, or AUC-PG, except for a significant correlation between BMI and FPG ($r = 0.20$, $P < .001$).

Figure 2



Serial hemodynamic changes at baseline and follow-up in Fontan patients with diabetes mellitus at baseline (solid) and those without (dotted).

Longitudinal assessment. At initial OGTT, DM patients (n = 11) were older than non-DM patients (24 ± 6 vs 20 ± 7; $P < .0001$). During follow-up, BMI remained unchanged in DM patients (21 ± 5 to 21 ± 5; $P = .96$) but was increased in non-DM patients (19 ± 3 to 20 ± 3; $P < .0001$). Peak Vo_2 decreased in both groups (58 ± 15 to 55 ± 14 for non-DM, $P < .0001$, and 45 ± 9 to 41 ± 12 for DM, $P = .058$).

There was no association between serial change in %Fat or %FFM and FPG, PG-spike, or AUC-PG (n = 105), except for an association between change in BMI and FPG ($r = 0.27$, $P < .001$). Serial changes in the main hemodynamics in DM and non-DM patients are shown in Figure 2. In the DM patients, CVP remained high, and systemic blood pressure and arterial oxygen saturation tended to be low. Pulmonary and systemic artery resistance and arterial oxygen saturation decreased in both groups. On the other hand, cardiac index increased ($P < .01$) and showed a greater decrease in systemic artery resistance in DM patients ($P < .05$).

AGM and all-cause mortality. During the follow-up of 7.1 ± 3.9 years after initial OGTT, 21 patients died (heart failure in 7, malignancy and surgery-related in 4 each, stroke in 3, sudden death in 2, and gastrointestinal bleeding in 1), and the associations between the clinical characteristics are summarized in Table II. Peak Vo_2 instead of NYHA class was used for multivariate analysis. Regarding glucose metabolic variables, low FPG (odds ratio [OR]: 0.94, 95% CI: 0.87-1.00, $P = .041$) and high PG-spike (OR: 1.02, 95% CI: 1.01-1.03, $P = .002$) were significantly associated with high mortality, and because the corresponding cutoff values were 74 and 86 (mg/dL), respectively, we used 3 models for the prediction of all-cause mortality. When the 2 variables were used as a continuous value (model 1), older age, higher BMI, high NE, and low FPG were independent predictors of all-cause mortality. When FPG and PG-spike were dichotomized using the above cutoff value (model 2), high PG-spike ≥86 (mg/dL) was an additional independent predictor. Low FPG and/or high PG-spike (ie, abnormal PG dynamics) (model 3) and older age and high NE were strong independent predictors of all-cause mortality. Associations between low FPG, high PG-spike, and DM and all-cause mortality are shown in Figures 3.

Predictors of current AGM and future DM

Current AGM. Associations between clinical characteristics and abnormal PG dynamics during OGTT that predicted all-cause mortality are summarized in Tables III-1 and III-2. Hypoxia, high total bilirubin, and use of ACEI/ARB were independently associated with low FPG ≤ 74 (mg/dL). Use of anticoagulants was independently associated with high PG-spike (≥86 mg/dL); however, HbA1c was not an independent determinant of high PG-spike ($P = .08$). Positive family history, high CVP (cutoff, 13 mm Hg), and high HbA1c (cutoff, 6.2%) were independently associated with presence of DM.

Table II. Univariate and independent multivariate predictors of all-cause mortality in Fontan patients

	Mortality											
	Univariate			Multivariate (model 1)			Multivariate (model 2)			Multivariate (model 3)		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Patient characteristics												
Age (y)	1.09	1.04-1.12	.0002	1.12	1.04-1.19	.0012	1.10	1.03-1.17	.0085	1.08	1.01-1.14	.0102
BMI	1.17	1.05-1.30	.0061	1.23	1.02-1.49	.0342						
NYHA class	4.34	2.45-7.84	<.0001		–	–	–	–	–	–	–	–
Peak Vo_2 (per %)	0.92	0.88-0.95	<.0001									
Hepatitis B or C	4.39	1.43-11.2	.0125									
Hemodynamics												
CVP (mm Hg)	1.33	1.10-1.59	.0028									
EDVI (mL/m^2)	1.02	1.01-1.03	.0015									
Sao_2 (per 1%)	0.82	0.73-0.92	.0017									
Medications												
Diuretics	6.11	2.26-21.2	.0002									
Neurohumoral factors												
Norepinephrine (per 100 pg/mL)	1.34	1.15-1.53	.0003	1.32	1.05-1.65	.0174	1.24	1.01-1.56	.0430	1.25	1.03-1.55	
BNP (per 10 pg/mL)	1.05	1.01-1.08	.0102									
Glucose metabolism												
FPG (mg/dL)	0.95	0.89-1.01	.0869	0.91	0.85-0.97	.0078	–	–	–	–	–	
Low FPG (≤74 mg/dL)	4.45	1.74-10.8	.0027	–	–	–	5.72	1.40-25.6	.0154			–
PG (OGTT 120′)	1.01	1.00-1.02	.0367				–	–	–	–	–	–
PG-spike	1.02	1.01-1.03	.0036				–	–	–	–	–	–
High PG-spike (≥85 mg/dL)	5.17	1.91-18.0	.0007	–	–	–	5.07	1.36-24.9	.0142	–	–	–
Low FPG or high PG-spike	18.90	3.95-340	<.0001	–	–	–				9.01	1.56-172	1.56-172
DM	4.57	1.49-11.7	.0106	–	–	–						

Hepatitis B or C indicates a history of carrier of hepatitis B or C virus. EDVI, systemic ventricular end-diastolic volume index; FPG, fasting plasma glucose; PG, plasma glucose; OGTT, oral glucose tolerance test; DM, diabetes mellitus.

Future onset of DM. In the second assessment of AGM in 175 patients, 18 (10.3%) patients were categorized as DM. The associations between clinical characteristics at initial OGTT and presence of DM at second OGTT are summarized in Table IV. Plasma ALT and GGT levels were correlated ($r = 0.53$, $P < .0001$). When ALT, instead of GGT, was used in multivariate analysis, positive family history, high ALT (cutoff, 21), and presence of AGM (IGT or DM) were associated with future onset of DM (model 1). When GGT, instead of ALT, was used in multivariate analysis, positive family history and presence of AGM were associated with future onset of DM (model 1). When FPG and PG-spike were included in the multivariate analysis (model 2), high PG-spike was an additional independent predictor of future onset of DM.

Determinants of HbA1c. To our surprise, HbA1c decreased despite progression of postprandial hyperglycemia during follow-up. Therefore, we tried to find a unique association between HbA1c and Fontan pathophysiology. Positive family history, right isomerism heart, protein-losing enteropathy, and presence of DM were associated with high HbA1, whereas higher cardiac output, larger spleen size, lower counts of white blood cell and platelet, lower hemoglobin, and lower levels of GGT and uric acid were associated with low HbA1c ($P < .05$-$.0001$). Of these, presence of DM independently raised HbA1c, whereas enlarged spleen size and low platelet count (ie, hypersplenism) independently decreased HbA1c (Figure 4).

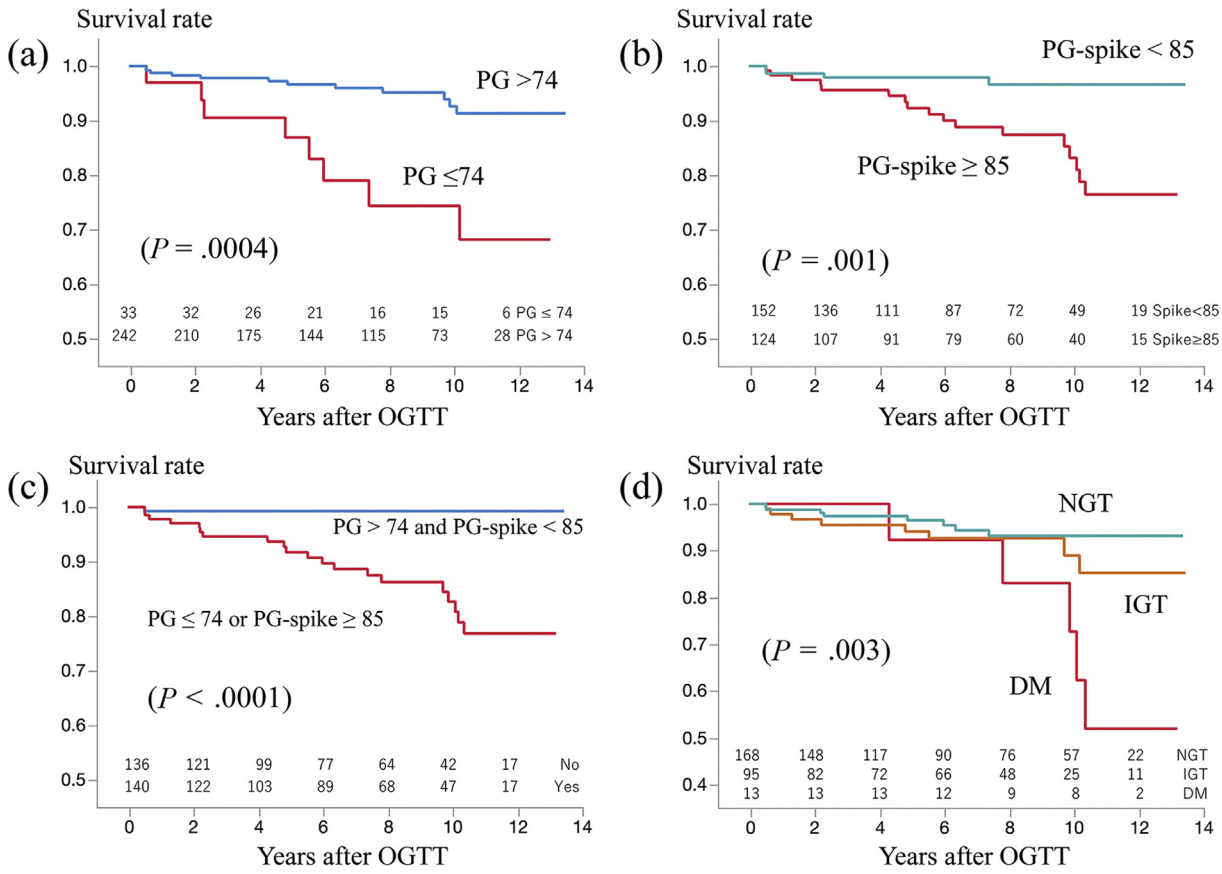
Discussion

The main results of the present study are as follows: First, we confirmed that Fontan patients exhibited a high prevalence of AGM, including DM. However, few DM therapies were initiated during the follow-up. Second, although AGM (ie, postprandial hyperglycemia) progressed over time, this abnormality might be reversible at the early stage. Thus, there may be significant scope for interventions. Third, PG dynamics during OGTT (low FPG and high PG-spike) as well as a diagnosis of DM had strong independent prognostic value for all-cause mortality. Fourth, current AGM and elevated plasma levels of ALT and GGT predicted future onset of DM. Finally, we should be aware that HbA1c has a limited predictive value of AGM in patients with hypersplenism, as shown in patients with Fontan circulation.

Importance of assessment of AGM

The present study highlights the importance of AGM assessment in Fontan patients because this

Figure 3



Kaplan-Meier all-cause mortality curves were stratified into 2 groups according to FPG level (**A**), 2 groups according to PG-spike, (**B**) 2 groups according to those with or without hypoglycemia and greater PG-spike (**C**), and groups according to glucose tolerance abnormality status (normal glucose tolerance, impaired glucose tolerance, and diabetes mellitus) (**D**).

pathophysiology is asymptomatic and progressive as well as the potential reversibility for preventive and/or therapeutic opportunity. OGTT may be recommended in Fontan patients with a family history of DM, elevated HbA1c, and high CVP. Some traditional risk factors of future development of DM are applicable to our Fontan patients, such as high levels of ALT and GGT, and PG dynamics during OGTT, especially PG-spike and presence of AGM.[9] Furthermore, considering its powerful prognostic value, OGTT could provide useful information on the management strategy as well as insight into Fontan pathophysiology.

AGM and prognosis

Adults without congenital heart disease. Hyperglycemia after acute myocardial infarction and AGM in heart failure as well as PG dynamics during OGTT predict poor prognosis.[9] In addition to an association between hypoglycemia and high mortality rate,[10] OGTT is recommended in adults with cardiovascular disease, especially after acute myocardial infarction.[11] Because the prognostic value of IGT is thought to be similar to that of DM in these patients,[12] application of OGTT to identify IGT patients is also emphasized.

Adults with congenital heart disease

We previously demonstrated that young adults with complex congenital heart disease had a high prevalence of AGM and possible association of AGM with high morbidity, especially in Fontan patients.[4] However, postprandial hyperglycemia, including DM, was not associated with mortality in a previous study.[13] The present study used a large number of patients and a longer follow-up, and found that hypoglycemia and DM were predictors of all-cause mortality in Fontan patients. Association of AGM due to insulin resistance with enhanced sympathetic nervous activity and renin-angiotensin-aldosterone system[14,15] may be responsible for the poor prognosis. In addition, PG-spike had a stronger prognostic value, indicating that oxidative

Table III-1. Univariate predictors of current hypoglycemia, high postprandial hyperglycemia, and DM in Fontan patients

	FPG ≤ 74			PG-spike ≥ 85			Current DM		
Cases (n)	33			124			13		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Male gender (%)			NS	1.92	1.18-3.15	.009	4.04	1.09-27.1	.0364
BMI			NS			NS	1.15	0.97-1.34	.0867
Family history ≤1 degree			NS			NS	5.14	1.29-17.7	.0121
Age at Fontan (y)			NS			NS	1.09	1.02-1.15	.0044
Follow-up (y)			NS			NS	0.90	0.80-1.00	.0614
NYHA class (I/II/III)	2.85	1.65-4.93	.0002	2.13	1.40-3.33	.001	4.80	2.24-10.9	<.0001
Peak Vo_2 (% of normal)	0.96	0.94-0.99	.0111	0.99	0.97-1.00	.091	0.94	0.89-0.98	.0084
Hepatitis B or C	7.46	2.26-24.1	.0015			NS			NS
Hemodynamics (n)									
CVP (mm Hg)	1.16	1.00-1.36	.0555			NS	1.43	1.13-1.85	.0032
Hemoglobin (g/dL)			NS	1.13	0.99-1.30	.067			NS
Sao_2 (%)	0.79	0.69-0.89	.0002			NS			NS
Neurohumoral factors									
Renin activity (ng/mL/h)			NS	1.02	1.00-1.04	.025			NS
Biochemical variables									
Albumin (g/dL)	0.46	0.22-0.99	.0408			NS			NS
Total bilirubin (mg/mL)	3.33	1.77-6.51	.0003			NS	1.61	0.86-2.94	.0819
GGT (U/L)			NS			NS	1.01	1.00-1.01	.0873
Uric acid (mg/mL)			NS	1.29	1.11-1.51	.001	1.52	1.10-2.11	.0104
Creatine (per 0.1 mg/dL)			NS	1.19	1.01-1.41	.045	1.39	0.98-1.93	.0552
Medications (%)									
Diuretics	2.74	1.31-5.91	.0081	2.03	1.25-3.33	.005	3.73	1.18-14.0	.0322
Anticoagulant			NS	2.55	1.44-4.66	.002			NS
ACEI/ARB	2.80	1.34-5.97	.0064	1.61	0.98-2.66	.059			NS
β-Blocker			NS	1.72	1.00-3.00	.052	3.78	1.21-12.2	.0225
HbA1c (%)			NS	1.06	1.00-1.13	.048	1.16	1.05-1.33	.0172

Table III-2. Independent predictors of current hypoglycemia, high postprandial hyperglycemia, and DM in Fontan patients

	FPG ≤ 74			PG-spike ≥ 85			Current DM		
Cases (n)	33			124			13		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Family history ≤1 degree							19.80	2.09-279	.0096
Hepatitis B or C	6.88	1.56-30.1	.0120						
Hemodynamics (n)									
CVP (mm Hg)							1.68	1.14-2.73	.0072
Sao_2 (%)	0.80	0.68-0.93	.0034						
Biochemical variables									
Total bilirubin (mg/mL)	3.09	1.52-6.44	.0012						
Medications (%)									
Anticoagulant				2.09	1.11-4.05	.023			
ACEI/ARB	3.40	1.42-8.52	.0059						
HbA1c (%)							3.25	1.07-19.4	.0359

stress due to the magnitude of excessive postprandial hyperglycemia leads to low-grade inflammation, thereby reducing nitric oxide release and causing endothelial dysfunction and reduced fibrinolysis.[16] In addition to possible hypokalemia due to postprandial hyperinsulinemia combined with hyperglycemia,[17] acute hypoglycemia induces a catecholamine surge due to sympathetic nervous activation that leads to Ca^{2+} overload of the cardiomyocyte, both of which cause QT prolongation, one of the major precursors of lethal arrhythmias, such as ventricular tachycardia/fibrillation.[18] In fact, arrhythmia is one of the main causes of all-cause mortality in adult Fontan patients,[1]

Table IV. Predictors of future onset of DM in Fontan patients

Cases	Future DM (n = 18/175)								
	Univariate			Multivariate					
				Model 1			Model 2		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age (y)	1.10	1.03-1.17	.004						
Male gender (%)	3.26	1.02-14.5	.045						
Family history ≤1 degree	6.95	2.23-21.0	.001	*5.80* (6.39	*1.21-28.2* 1.34-30.9	*.028* .021)*	*4.83* (5.82	*0.93-25.7* 1.11-31.5	*.061* .037)*
Age at Fontan (y)	1.10	1.04-1.16	.001						
PLE	10.30	1.77-59.9	.012						
NYHA class (I/II/III)	3.99	1.94-8.63	<.001	–	–	–	–	–	–
Peak Vo_2 (% of normal)	0.94	0.89-0.97	.003						
Hemodynamics									
Sao_2 (%)	0.83	0.70-1.00	.042						
Biochemical variables									
Albumin (g/dL)	0.36	0.12-1.07	.060						
ALT (U/L)	1.03	1.01-1.06	.006	*1.04*	*1.00-1.07*	*.031*	*1.04*	*1.01-1.08*	*.021*
GGT (U/L)	1.01	1.00-1.02	.003	(1.01	1.00-1.02	.076)*	(1.01	1.00-1.02	.051)*
Uric acid (mg/mL)	1.41	1.06-1.91	.021						
Medications (%)									
β-Blocker	2.59	0.92-7.06	.062						
HbA1c (%)	2.72	1.20-8.68	.043						
HOMA-IR	1.60	1.08-2.36	.016						
75-g OGTT									
Glucose (mg/dL)									
0	1.09	1.03-1.17	.007	–	–	–			
30	1.03	1.01-1.04	.002	–	–	–	–	–	–
60	1.02	1.01-1.03	.003	–	–	–	–	–	–
120	1.02	1.01-1.03	.005	–	–	–			
PG-spike	1.03	1.01-1.05	<.001	–	–	–	*1.03* (1.03	*1.00-1.06* 1.00-1.06	*.039* .027)*
IGT/DM	5.81	1.98-21.3	.003	*5.26* (6.23	*1.29-27.2* 1.56-33.3	*.020* .009)*	–	–	–

Table entries in italics indicate results of multivariate analysis using values of ALT instead of GGT. *HOMA-IR,* homeostasis model assessment for insulin resistance.
* Indicates those using values of GGT instead of ALT.

and 2 patients died suddenly in our cohort. Furthermore, a detrimental effect of hypoglycemia on myocardial metabolism with insulin resistance may lead to impaired SV contraction.[19] To our surprise, PG dynamics showed strong prognostic power of all-cause mortality independent of the hemodynamics and exercise capacity in Fontan patients.

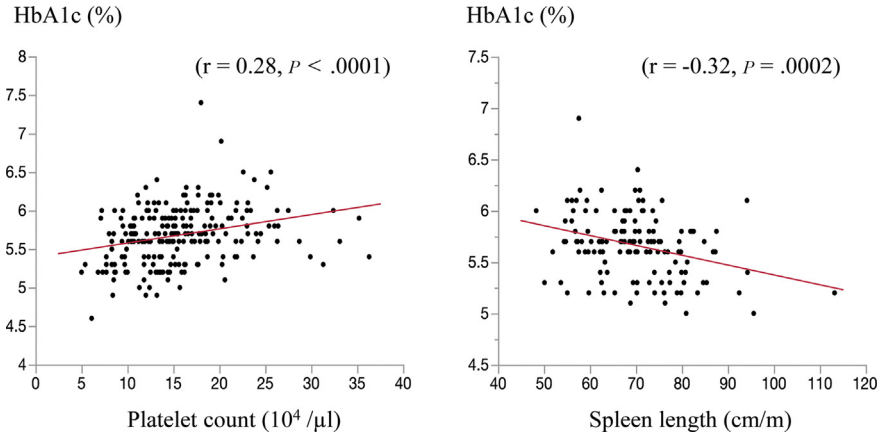
Unique associations of AGM with Fontan pathophysiology

Hemodynamics. High CVP, low cardiac output, and mild hypoxia characterize Fontan circulation.[1,20] Although cardiac output was not related to PG dynamics, high CVP was predictive of current DM, whereas hypoxia was predictive of hypoglycemia. The association between high CVP and DM remains unclear, and liver congestion may have been related to the pathogenesis of DM because GGT was elevated in DM patients.[21] Regarding hypoxia-associated hypoglycemia, hypoxia could have decreased hepatic gluconeogenesis due to decreased levels of hepatic pyruvate.[22] However, although short-term hypoxia has an adverse influence on glucose tolerance,[23] the long-term effects may be opposite.[24] In fact, hypoxia was not predictive of DM or PG-spike. Further studies are required to clarify the causality of hypoxia on AGM.

FALD and hypersplenism. The liver is the major gluconeogenetic organ, and FALD may influence PG dynamics. Hypoxia-related polycythemia as well as upregulation of hemeoxygenase could be responsible for the significant association between high total bilirubin and hypoglycemia.[25] In addition, although the mechanisms remain unknown, elevated plasma ALT and GGT levels are predictive of future onset of DM in the general population.[26]

To our surprise, HbA1c decreased over time despite worsening of postprandial hyperglycemia. A possible

Figure 4



Association of blood platelet count (**A**) and standardized spleen size (**B**) with HbA1c.

explanation is the shortened life span of erythrocytes due to hypersplenism in Fontan patients because HbA1c independently determined spleen size and platelet count.[27] Therefore, care should be taken when interpreting HbA1c values in Fontan patients, especially in those with liver cirrhosis. The predictive value of HbA1c for future onset of DM was limited. Furthermore, HbA1c was significantly higher in patients with right isomerism heart (asplenia) compared with those without (5.9% ± 0.7% vs 5.7% ± 0.4%, $P = .0002$). These findings indicate that Fontan patients with AGM, especially those with DM, may have a similar pathophysiology to "hepatogenous DM" in patients with liver cirrhosis.[28] In fact, high model for end-stage liver disease excluding INR (MELD-XI) score was associated with hypoglycemia (FPG <74 mg/dL, OR: 2.7, 95% CI: 1.6-4.7, $P < .0001$) and greater PG-spike (>85 mg/dL) (OR: 1.5, 95% CI: 1.0-2.3, $P < .05$), indicating an association of liver fibrotic progression and AGM.[29] Therefore, OGTT is required to assess AGM.[28]

Other factors. Muscle is one of the main organs that consume PG, and skeletal muscle abnormalities are reported in Fontan patients. Therefore, sarcopenia may contribute to AGM in these patients; however, body composition, especially %FFM, was not related to AGM. In addition, failure to thrive due to multiple surgical interventions during the early phase of life and a later high prevalence of overweight[30] raise concerns about the Barker hypothesis.[31] However, this hypothesis may not be applicable in Fontan patients in terms of birth weight probability due to a stronger contribution of Fontan pathophysiology on glucose metabolism, although growth trajectory was not assessed in the present study.

Study limitations. First, the number of healthy controls was small, and the follow-up duration was relatively short. However, regarding the small number, because mass screening of 499 young Japanese adults (aged 20-39 years) uncovered 22 with AGM (4.4%) (19 [3.8%] with IGT and 3 [0.6%] with DM) (http://www.mhlw.go.jp/ shingi/2004/03/s0318-15.html), which is similar to our volunteer group, we believe that our control subjects could be representative of the Japanese general population. Second, there are concerns about the reproducibility of OGTT; however, 1 study indicated the sufficient reproducibility of OGTT.[32] Recent continuous monitoring systems may provide more detailed information on AGM in future studies; the cutoff values of hypoglycemia and PG-spike may change with age. Although *hypoglycemia* is usually defined as <70 mg/dL and the prevalence of our Fontan patients and controls was 4.4% (n = 12) and 0%, respectively, the definition is still controversial.[33,34] Whether our cutoff values of AGM, 74 for hypoglycemia and 85 for PG-spike, are applicable to other type of congenital heart disease needs more studies. Finally, ethnic differences should be taken into account, and our results may not be generalized.[35]

Conclusions

AGM is highly prevalent and progressive in adolescent and young adult Fontan patients. However, there may be scope for interventions due to the reversibility of AGM status. PG dynamics (hypoglycemia and postprandial hyperglycemia) and DM have a powerful prognostic value of all-cause mortality. Considering the limited predictive value of HbA1c and the unique characteristics of "hepatogenous DM" in Fontan patients, OGTT may be an important diagnostic modality to provide useful information and a deeper insight into Fontan pathophysiology as well as a better long-term management strategy.

Conflicts of interest

None.

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