Journal of Cardiology 75 (2020) 697–701

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Growth differentiation factor 15 as a useful biomarker of heart failure in young patients with unrepaired congenital heart disease of left to right shunt

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ARTICLE INFO

Article history:
Received 2 September 2019
Received in revised form 29 November 2019
Accepted 4 December 2019
Available online 26 December 2019

Keywords:
Growth differentiation factor 15
Congenital heart disease
Child
Heart failure
Shunt

ABSTRACT

Background: Growth differentiation factor 15 (GDF 15) is a member of the transforming growth factor-beta superfamily and is considered to be a useful biomarker for severity of heart failure (HF) in repaired congenital heart disease (CHD). The aim of this study was to determine the clinical implication of GDF 15 in children with unrepaired CHD.

Methods: Subjects included 69 patients (≤14 years old) who had unrepaired CHD with left to right shunt and underwent cardiac catheterization. Demographic and hemodynamic data, including oxygen demand–supply relationship, were collected from medical records. Severity of HF was evaluated using modified Ross score. Serum GDF 15 levels were determined using enzyme-linked immunosorbent assay and correlated with patients' demographics, hemodynamic data, and blood chemistry data.

Results: Subjects had median age of 71 (range 1–173) months and simple acyanotic CHDs with mean pulmonary to systemic flow ratio of 2.0 (1.0–5.6), median N-terminal pro type Brain natriuretic peptide (NT-pro-BNP) of 162.8 (17.1–8789) pg/mL, and median GDF 15 of 242.1 (13.6–1116.7) pg/mL. GDF 15 significantly positively correlated with the modified Ross score, mean pulmonary artery pressure, oxygen extraction rate (OER), and Ln NT-pro-BNP, but negatively correlated with age, oxygen delivery and its components, and estimated glomerular filtration rate (eGFR). Multiple linear regression analysis revealed significant correlation of GDF 15 levels with the modified Ross score, OER, and eGFR.

Conclusions: GDF 15 mainly reflects oxygen demand–supply relationship and can be used as a diagnostic marker of HF in unrepaired CHD with left to right shunt for a wide range of age and diagnoses.

Introduction

Growth differentiation factor 15 (GDF 15), also known as a macrophage inhibitory cytokine-1 (MIC-1), is a stress responsive member of the transforming growth factor beta cytokine superfamily [1]. GDF 15 shows low expression in nearly all tissues except for the placenta and prostate in healthy humans; however, its expression sharply increases in various invasive environments and it shows an anti-inflammatory effect [2]. Yatsuga et al. found that GDF 15 is a useful biomarker for diagnosis and potential severity of mitochondrial disease [3]. They further state that GDF 15 level was high in patients with heart failure (HF). GDF 15 has been reported to be a cardioprotective protein in some cardiovascular injuries such as pressure overload, oxidative stress, HF, ischemia/reperfusion, and atherosclerosis. Moreover, GDF 15 is highly expressed in cardiomyocytes, macrophages, endothelial cells, and vascular smooth muscle cells [4–6].

Recent studies suggested that high plasma GDF 15 levels are associated with an increased mortality in patients with acute coronary syndrome [7] and acute heart failure [8]. In congenital heart disease (CHD), high GDF 15 levels have been reported as an early diagnostic biomarker of HF in repaired CHD [9,10] and a biomarker for dysfunction of the Fontan circuit [11].

To the best of our knowledge, no study has evaluated GDF 15 as a putative biomarker of HF in unrepaired CHDs with left to right shunt and preserved ventricular function. Therefore, we hypothe-

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https://doi.org/10.1016/j.jjcc.2019.12.008
0914-5087/

sized that GDF 15 is a useful biomarker for HF with unrepaired CHD with left to right shunt in young patients.

Materials and methods

A total of 96 pediatric (age under 14 years) patients with simple CHD with left to right shunt and who underwent cardiac catheterization in the Kurume University Hospital from March 2016 to August 2017 were enrolled. Patients with significant obstructive lesion with pressure gradient ≥30 mmHg or bidirectional shunt were excluded. The cardiac diagnoses were determined using echocardiography or X-ray cardiac computed tomography. The study protocol was approved by ethical committee of the Kurume University School of Medicine and written informed consent was obtained from the guardians of all subjects.

Data collection

Blood samples were collected from the femoral vein before beginning cardiac catheterization. Each sample was centrifuged, and serum was collected, aliquoted, and frozen at −80 °C before analysis. GDF 15 levels were measured using the Human GDF 15 Quantikine ELISA Kit (R&D systems, Minneapolis, MN, USA) with a sensitivity of 4.39 pg/mL and an assay range of 23.4 – 1500 pg/mL.

Clinical and laboratory data such as vital signs, echocardiography, electrocardiography, serum N-terminal pro type Brain natriuretic peptide (NT-pro BNP), blood hemoglobin, and serum creatinine were collected within two days before cardiac catheterization. Estimated glomerular filtration rate (eGFR) values of all patients were calculated using polynomial formulae for reference serum creatinine and body length [12]. All patients underwent right heart catheterization using standard techniques with inspired oxygen fraction of 0.21, and mean right atrial pressure, mean left atrial pressure or mean pulmonary capillary wedge pressure, mean pulmonary artery pressure (mean PAp), mean arterial pressure, and left ventricular end-diastolic pressure (LVEDP) were recorded in all patients. Blood samples were also collected from the superior vena cava (upper and lower), main pulmonary artery and the bilateral pulmonary artery, left ventricle, or femoral artery in order to measure oxygen saturation. Systemic venous oxygen saturation (SvO_2) was represented by oxygen saturation of superior vena cava (except for patients with partial anomalous pulmonary venous connection, in which SvO_2 was determined as oxygen saturation in the superior vena cava distal to the anomalous pulmonary venous return). Pulmonary arterial oxygen saturation was determined as the average of all pulmonary arterial oxygen saturation, and systemic arterial oxygen saturation (SaO_2) and pulmonary venous oxygen saturation were substituted by left ventricular or femoral arterial oxygen saturation. Oxygen consumption (VO_2) was calculated using Lindahl's formula [In children with body weight (BW) <10 (kg), $VO_2 = 6.8 * BW + 8.0$, and in children with BW > 10 (kg), $VO_2 = 4.0 * BW + 35.8$]. Cardiac index (CI), the pulmonary to systemic blood flow ratio (Qp/Qs), and pulmonary vascular resistance index (PVRI) were calculated using the Fick principle. In addition to arterial oxygen content (CaO_2 = 1.36 × Hb x SaO_2 × 10), oxygen delivery (DO_2), and oxygen extraction ratio (OER) were calculated as the following equation: $DO_2 = CO \times CaO_2$, $OER = (SaO_2 - SvO_2) / SaO_2$.

In order to evaluate clinical symptoms of HF, modified Ross score was calculated for all patients [13]. In brief, the modified Ross score consisted of patient's symptoms (diaphoresis, tachypnea) and findings of physical examination (breathing style, respiratory rate, heart rate, and hepatomegaly), assigning 0 to +2 points for each parameter with a distribution of 0–12 points. In addition, the score was originally made to suit children younger than 14 years old that included all subjects of this study. Higher modified Ross score indicates more severe HF.

We evaluated the relationship between GDF 15 levels and clinical and hemodynamic parameters stated above. To identify the difference of underlying heart defect, patients were divided into two subgroups of supra-tricuspid shunt (volume overload to right ventricle) and infra-tricuspid shunt group (pressure load to right ventricle). Patients with ventricular septal defect (VSD), patent ductus arteriosus (PDA), and double outlet right ventricle (DORV) were included as in infra-tricuspid group and atrial septal defect (ASD), partial atrioventricular defect (pAVSD), and partial anomalous pulmonary venous return (PAPVR) were in supra-tricuspid group. For the reason of difficulty in definitive separation of pressure overload to volume overload, one patient with coronary artery fistula (CAF) which right coronary artery drained into right ventricle was excluded from subgroup analysis.

Statistical analyses

Statistical analyses were performed using JMP pro version 14.0.0 (SAS, Cary, NC, USA). Raw data are provided for several variables. Continuous variables or ordinal variables are expressed as mean ± standard deviation when data showed normal distribution, and others are expressed as median and range. As the distribution of NT-pro BNP was skewed, NT-pro BNP was log transformed. Correlations between GDF 15 levels and variables were evaluated using the Spearman rank correlation coefficient. The differences between groups were evaluated using the Wilcoxon rank sum test. Multiple linear regression analyses were performed using least-square method. Values of $p < 0.05$ were considered statistically significant.

Results

Out of 96 patients, 27 patients were excluded (26 for missing or inadequate blood sample to measure GDF 15 levels and one for missing informed consent). The remaining 69 patients were considered as the subjects of this study. Patients' median age was 71 months old (range 1–173 months). Diagnosis was ASD in 40, PDA in 14, VSD in 11, CAF which right coronary artery drained into right ventricle in 1, DORV in 1, pAVSD in 1, and PAPVR in 1, respectively. The diagnoses of excluded patients were ASD in 17, PDA in 6, VSD in 2, AVSD in 1, and CAF in 1.

Median concentration of GDF 15 was 242.1 (13.6–1116.7) pg/mL, NT-pro BNP was 162.8 (17.1–8789) pg/mL. Patients' median modified Ross score ranged from 0 to 10. Clinical and biochemical characteristics of patients are presented in Table 1. In comparison, infra-tricuspid shunt group showed significantly higher levels of GDF 15 (median 400.9, range 101.9–1116.7 pg/mL vs median 170.8, range 13.6–530.6 pg/mL, $p < .0001$) than supra-tricuspid shunt group.

GDF 15 levels showed significantly positive correlation with the modified Ross score (r = 0.657), mean PAp (r = 0.497), OER (r = 0.437), and Ln NT-pro BNP (r = 0.429); however, it showed negative correlation with age (r = -0.637), body surface area (BSA) (r = -0.622), CaO_2 (r = -0.578), DO_2 (r = -0.568), GFR (r = -0.410), hemoglobin (r = -0.380), and SvO_2 (r = −0.330). GDF 15 levels did not show correlation with CI, Qp/Qs, PVRI, and LVEDP. In subgroup analysis, in both groups, GDF 15 showed good correlation to modified Ross score, mean PAp, CaO_2, DO_2, BSA, and age (Table 2).

Multiple linear regression analysis revealed significant correlation of GDF 15 levels with modified Ross score (β = 0.82), OER (β = 0.30), and eGFR (β = -0.16), however, not with age, mean PAp, Qp/Qs, Hb, Ln NT-pro BNP, or DO_2 (Table 3) (Fig. 1).

Table 1
Patients' demographics.

Parameters	Groups			
	All participants	Infra-tricuspid shunt	Supra-tricuspid shunt	*p*
Condition: numbers	ASD, PDA, VSD, DORV, CAF, pAVSD, PAPVR	PDA: 14, VSD: 11, DORV: 1	ASD: 40, pAVSD: 1, PAPVR: 1	
Number (Female)	69 (39)	26 (17)	42 (22)	
Age (months)	71 (1–173)	12.5 (1–114)	86 (5–173)	<0.0001
Body surface area (m^2)	0.75 (0.26–1.66)	0.42 (0.26–1.00)	0.83 (0.29–1.66)	<0.0001
CaO_2 (mL/L)	143.0 ± 19.5	127.2 ± 15.5	152.4 ± 15.2	<0.0001
Cardiac Index (L/min/m^2)	3.58 (2.52–6.22)	4.1 (2.77–6.22)	3.39 (2.52–4.93)	0.0002
eGFR (mL/min/1.73 m^2)	119.8 ± 22.5	111.6 ± 20.5	125.0 ± 22.6	0.03
GDF 15 (pg/mL)	242.1 (13.6–1116.7)	400.9 (101.9–1116.7)	170.8 (13.6–530.6)	<0.0001
Hemoglobin (g/dL)	12.8 ± 0.13	12.2 ± 0.10	13.2 ± 1.11	0.0014
LVEDP (mmHg)	11 (6–24)	13 (6–24)	10 (7–16)	0.0028
Mean PAp (mmHg)	19 (13–53)	27 (15–53)	18 (13–23)	0.0004
Modified Ross score	0 (0–10)	1 (0–10)	0 (0–5)	0.0004
NT-pro BNP (pg/mL)	162.8 (17.1–8789)	414.7 (18.2–8789)	131.3 (17.1–3598.5)	0.0037
DO_2 (mL/min)	391.8 (106.3–1075.5)	413.9 (90.1–605.3)	433.5 (119.9–1075.5)	<0.0001
Oxygen extraction rate	0.28 ± 0.049	0.28 ± 0.062	0.28 ± 0.042	n.s.
PVRI (Wood units × m^2)	1.36 (0.14–5.18)	1.54 (0.14–5.18)	1.36 (0.71–2.92)	n.s.
Qp/Qs	2.0 (1.0–5.6)	1.7 (1.0–5.6)	2.2 (1.2–4.5)	n.s.
Serum Creatinine (mg/dL)	0.3 (0.15–0.59)	0.2 (0.15–0.37)	0.35 (0.20–0.59)	<0.0001
SvO_2 (%)	68.7 ± 5.0	69.5 ± 6.7	69.4 ± 3.7	n.s.

All data are shown as median (range) or mean ± standard deviation.
ASD, atrial septal defect; CAF, coronary artery fistula; CaO_2, arterial oxygen content; DO_2, oxygen delivery; DORV, double outlet right ventricle; eGFR, estimated glomerular filtration rate; LVEDP, left ventricular end-diastolic pressure; PAp, pulmonary artery pressure; NT-pro BNP, N-terminal pro type brain natriuretic peptide; PAPVR, partial anomalous pulmonary venous return; pAVSD, partial atrioventricular defect; PDA patent ductus arteriosus; PVRI, pulmonary vascular resistance index; Qp/Qs, the ratio of flows to the pulmonary and systemic circuits; SvO_2, systemic venous oxygen saturation.

Table 2
Correlation between growth differentiation factor 15 and clinical/hemodynamic parameters.

Variables	Groups					
	All participants n = 69		Infra-tricuspid shunt n = 26		Supra-tricuspid shunt n = 42	
	R (s)	*p*	R (s)	*p*	R (s)	*p*
Modified Ross score	0.657	<0.0001	0.84	<0.0001	0.59	<0.0001
mean PAp	0.497	<0.0001	0.59	0.002	0.33	0.029
OER	0.437	0.0002	0.56	0.003		n.s.
Ln NT-pro BNP	0.429	<0.0001	0.71	<0.0001		n.s.
SvO_2	−0.330	0.0057	−0.62	0.0007		n.s.
Hemoglobin	−0.380	0.0013		n.s.		n.s.
eGFR	−0.410	0.0005	−0.69	0.0001		n.s.
Oxygen delivery	−0.568	<0.0001	−0.76	<0.0001	−0.33	0.033
CaO_2	−0.578	<0.0001	−0.46	0.019	−0.45	0.0025
Body surface area	−0.622	<0.0001	−0.76	<0.0001	−0.36	0.017
Age	−0.637	<0.0001	−0.76	<0.0001	−0.39	0.009
Cardiac Index		n.s.		n.s.		n.s.
PVRI		n.s.		n.s.		n.s.
LVEDP		n.s.		n.s.		n.s.
Qp/Qs		n.s.		n.s.		n.s.

CaO_2, arterial oxygen content; eGFR, estimated glomerular filtration rate; GDF, growth differentiation factor; Ln NT-pro BNP, log transformed N-terminal pro type brain natriuretic peptide; LVEDP, left ventricular end diastolic pressure; OER, oxygen extraction rate; PAp, pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; Qp/Qs, the ratio of flows to the pulmonary and systemic circuits; SvO_2, systemic venous oxygen saturation.

Table 3
Multiple linear regression analysis of correlation with growth differentiation factor 15.

Parameters	Estimate	95 % CI	Standard β	VIF	*p*-value
Modified Ross score	76.4	55.8 – 97.1	0.82	4.86	< 0.0001
Oxygen extraction rate	1338.8	114.0 – 2563.6	0.30	7.37	0.033
eGFR	−1.58	−2.7 – -0.5	−0.16	1.24	0.006

Regression formula: y = 396.72664428 + 76.522633749 × modified Ross score + -1.704565969 × estimated glomerular filtration rate + 18.516920778 × oxygen extraction rate.
CI, confidence interval; VIF, variance inflation factor; eGFR, estimated glomerular filtration rate.

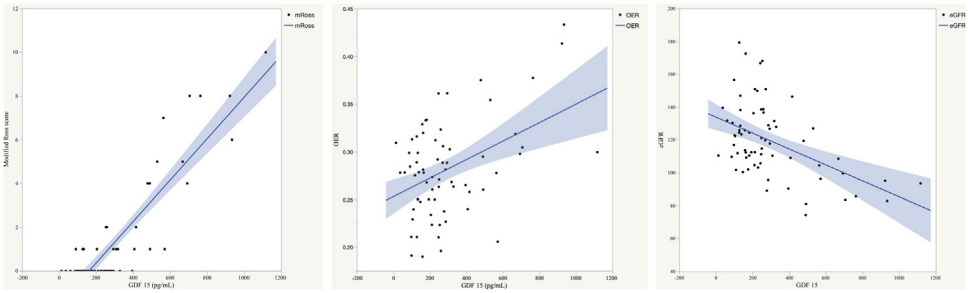

Fig. 1. Scatter plot of correlations between growth differentiation factor 15 and modified Ross score, OER, and eGFR in Table 3.
eGFR, estimated glomerular filtration rate; GDF, growth differentiation factor; OER, oxygen extraction rate.

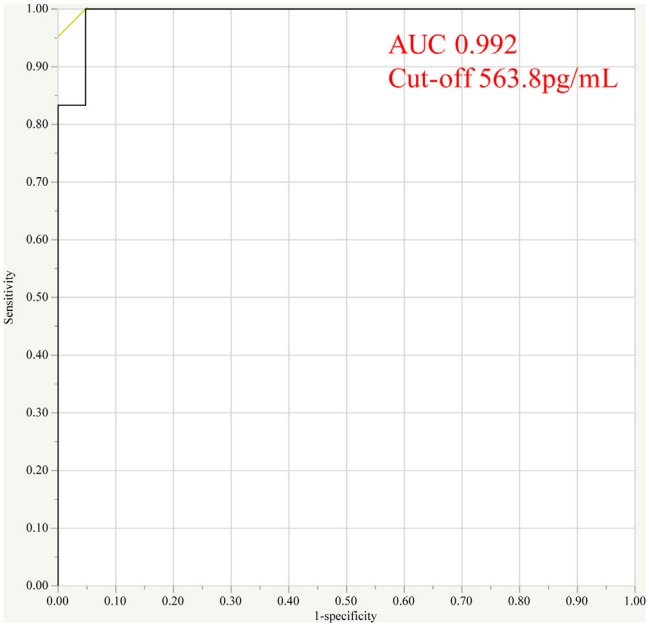

Fig. 2. Receiver–operator characteristics curves about the higher modified Ross score of $>=6$ points. AUC value was 0.992 with cut-off value of 563.8 pg/mL.
AUC, area under the curve.

Modified Ross score weakly correlated with OER ($r=0.303$, $p=0.011$) as well as eGFR ($r=-0.242$, $p=0.045$) however, no correlation was observed between eGFR and OER.

The higher modified Ross score (≥ 6) was predicted based on GDF 15 levels with an area under the curve of 0.992, in cut-off value of 563.8 pg/mL (Fig. 2). The AUC of GDF 15 in prediction of modified Ross score was slightly higher than that of NT-pro BNP (AUC 0.963, cut-off value of 679.4 pg/mL) (data not shown).

Discussion

Our results indicate that GDF 15 could be a useful biomarker for HF in young patients with unrepaired CHD. In our cohort, GDF 15 levels showed significant correlation with established clinical and biochemical markers of HF such as modified Ross score and NT-pro BNP and hemodynamic parameters of reduced oxygen delivery. GDF 15 levels did not correlate with the magnitude of left to right shunt; however, it might simply reflect oxygen demand–supply relationship regardless of CHD.

To the best of our knowledge, this is the first study to show the correlation between GDF 15 levels and HF in patients with unrepaired CHDs with left to right shunt. By simplifying hemodynamic pathologies and selecting young patients to eliminate various confounding factors such as postoperative ventricular dysfunction, single ventricular physiology, or systemic arterial desaturations we could clarify the factors associated with elevation of GDF 15 levels in common left to right shunt pathologies.

Kempf et al. first introduced GDF 15 as an independent biomarker of mortality in adult patients with HF in 2007 [14]. In their report, GDF 15 levels closely related to those specified in the New York Heart Association (NYHA) functional class and patients with high GDF 15 levels showed significantly higher mortality than those with low GDF levels 15 in various NYHA classes. Recently, GDF 15 has become a well-known biomarker of severity in adult ischemic HF [7,8]. GDF 15 is also described as a useful severity biomarker of HF in patients with repaired CHD [9–11], who usually have no significant shunt lesion and potentially have ventricular dysfunctions and/or arrhythmias. However, there are pathological differences in HF between unrepaired CHD and acquired heart disease or repaired CHD, because HF in most adults is caused by ventricular dysfunction due to ischemic or postoperative myocardial damage. In unrepaired left to right shunt CHD patients, HF is not a result of ventricular dysfunction and of decreased systemic circulation. In our study, GDF 15 levels showed a strong correlation with modified Ross score; however, not with LVEDP or Qp/Qs. Identically, even in subgroup analysis, GDF 15 showed correlation with clinical HF score and signs of low oxygen supply but no correlation with magnitude of shunt. This may indicate that elevation of GDF 15 may reflect oxygen demand/supply unbalance and may not simply reflect volume overload to the ventricles.

GDF 15 has been described as an anti-inflammatory or stress-responsive cytokine secreted from peripheral tissues or macrophages [1,4–6]; however, the underlying mechanism and the source of GDF 15 secretion in HF remains unknown. In non-ischemic dilated cardiomyopathies, Lok et al. described that high circulating GDF 15 levels rapidly decreased after left ventricular assist device implantation. They further described that GDF 15 mRNA and protein expression was considerably low in myocardial tissues of dilated heart [15]. Fuernau et al. stated that, in patients with myocardial infarction, patients with cardiogenic shock showed markedly high GDF 15 levels than those without shock and GDF 15 levels correlated with serum lactate levels [16]. These studies suggest that GDF 15 expression is not simply caused by myocardial injury, but by peripheral tissue hypoxia or imbalance of oxygen demand–supply relationship, and it might explain why GDF 15 levels showed a significant correlation with OER in our study. The pathology of HF is owing to an imbalance of tissue oxygen demand–supply relationship, not to a myocardial damage or an overload to the heart; in this context, GDF 15 may be a useful severity biomarker of HF.

GDF 15 has also been reported to be an independent diagnostic biomarker in renal dysfunction with HF [17]. Renal excretion of GDF 15 was described in fetal investigation [18], as renal dysfunction should be taken into consideration when interpreting the correlation of GDF 15 levels with HF. Although GDF 15 levels

showed a good correlation with eGFR levels in our study, our cohort did not have patients with chronic kidney disease (eGFR <60 mL/min/1.73 m^2). As univariate analysis showed negative correlation between modified Ross score and eGFR level, decreased eGFR levels might be an indirect result of HF but not an inherent renal failure; it may indicate that renal function did not have a strong influence on GDF 15 levels in our study.

Under pressure overload to the heart, GDF 15 is expressed in myocardium and functions to prevent cardiac hypertrophy as revealed by animal experiments [2]. Li et al. reported plasma GDF 15 as a biomarker for pediatric pulmonary hypertension (PH) with CHDs. They showed significant difference in GDF 15 levels between patients with CHDs with or without PH and no difference between patients with CHDs without PH and healthy controls [19]. Consistent with their findings, GDF 15 levels positively correlated with pulmonary artery pressure in our study, although multiple regression analysis showed no correlation between GDF 15 levels and mean PAp or PVRI.

Limitation of this study

In this study, subjects were enrolled upon clinical indication when the physician decided the requirement of catheterization, and therefore there was selection bias regarding the timing of evaluation and diagnosis and severity of disease.

There was a substantial number of missing samples in our study; however, this should not affect our results because missing subjects showed similar demographic profile to our cohort and there were no significant differences between groups in modified Ross score, mean PAp, OER, Qp/Qs, NT-pro BNP, and so on. As this was a cross-sectional study and this study did not include follow-up data, the prognostic utility of GDF 15 in HF of unrepaired CHDs was not determined. Further studies to investigate the utility of GDF 15 as a prognostic biomarker of HF in patients with CHD are necessary.

Conclusion

GDF 15 mainly reflects the oxygen demand–supply relationship and can be used as a diagnostic marker and a potential severity biomarker of HF in patients with unrepaired CHD with left to right shunt in a wide age range and different diagnoses.

Funding

This research was supported by Grants #25461571 (Yasutoshi Koga) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), by grants No. JP17ek0109088h00 (Yasutoshi Koga) from the Japan Agency for Medical Research and Development (AMED), and by Grants-in-Aid of the Research on Intractable Diseases (Mitochondrial Disorder) from the Ministry of Health, Labour and Welfare of Japan (Yasutoshi Koga).

Disclosures

The authors declare that there is no conflict of interest.

Acknowledgments

We wish to thank China Ohinata (MT) for all analyses of GDF 15.

This study was presented at the American College of Cardiology scientific session 2018.

We would like to thank Editage (www.editage.com) for English language editing.

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