European Review for Medical and Pharmacological Sciences 2018; 22: 8096-8103

Diagnostic value of growth differentiation factor-15 and β2-microglobulin in children with congenital heart disease combined with chronic heart failure and its relationship with cardiac function

X.-J. ZHOU[1], X. ZHANG[2], J. ZHANG[3], L. ZHOU[4], T.-T. ZHOU[5], J.-W. ZHANG[3]

[1]Department of Clinical Laboratory, The Second Hospital of Shandong University, Jinan, Shandong, China
[2]Department of Clinical Laboratory, Qingdao Municipal Hospital, Qingdao, Shandong, China
[3]Department of Clinical Laboratory, Yongchuan Hospital, Chongqing Medical University, Chongqing, China
[4]Department of Medical Administration, Yongchuan Hospital, Chongqing Medical University, Chongqing, China
[5]Department of Clinical Laboratory, the Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Abstract. – OBJECTIVE: This study aimed to investigate the diagnostic value of growth differentiation factor-15 (GDF-15) and β2-microglobulin (β2-MG) in infants with congenital heart disease (CHD) combined with chronic heart failure and its relationship with cardiac function.

PATIENTS AND METHODS: A total of 100 cases of infants diagnosed with CHD combined with chronic heart failure in our hospital from July 2015 to July 2018 were selected as the experimental group, and 80 cases of healthy subjects underwent health examination in our hospital during the same period were selected as the control group. The levels of serum GDF-15 and β2-MG and LVEF index of the two groups were compared. The correlation analysis of GDF-15 and β2-MG levels and cardiac function classification was conducted. The diagnostic value of GDF-15 and β2-MG was analyzed by ROC curve.

RESULTS: The levels of GDF-15 and β2-MG were significantly higher in severe and moderate heart failure groups than those in mild heart failure group, and the levels were significantly higher in severe heart failure group than those in moderate heart failure group ($p<0.001$). Levels of GDF-15 and β2-MG in the experimental group were significantly higher than those in the control group ($p<0.001$) and the LVEF index in the experimental group was significantly lower than that in the control group ($p<0.001$). There was a positive correlation between levels of GDF-15 and β2-MG and the severity of heart failure. The sensitivity, specificity, and AUC of GDF-15 alone in diagnosis of CHD combined with chronic heart failure were respectively 91.25%, 74.00% and 0.821, those of β2-MG alone were 82.50%, 62.00% and 0.819, and those of GDF-15 combined with β2-MG were 82.50%, 82.00% and 0.888. In the prognosis, the sensitivity of GDF-15 and β2-MG was respectively 91.30%, 56.52%, specificity was 62.96%, 94.44%, and AUC was 0.806, 0.817.

CONCLUSIONS: Levels of GDF-15 and β2-MG are positively correlated with the severity of cardiac function, which can be used as an ideal indicator for early diagnosis of CHD combined with chronic heart failure, as well as a clinical indicator to judge the condition.

Key Words:
Growth differentiation factor-15, β2-microglobulin, Congenital heart disease in children combined with chronic heart failure, Cardiac function classification, Diagnostic value.

Introduction

Congenital heart disease (CHD) is the most common birth defect disease and the main cause of increased infant mortality[1]. The occurrence of CHD seriously affects the heart function and daily life of infants[2]. The signs of heart failure in infants are not clear, and specific diagnostic methods are

Corresponding Author: Jiwang Zhang, MD; e-mail: jiwangzhang2020@163.com

insufficient. Moreover, the clinical manifestations of CHD are similar to heart failure, so the diagnosis becomes more difficult when the two appear together[3,4]. The subjects of most clinical studies are adults, and the results of these studies cannot be used in infants. Therefore, finding biomarkers that can quickly diagnose and detect diseases has a significant impact on infants.

Growth differentiation factor-15 (GDF-15) is related to cardiovascular disease[5], and the expression levels of different severity of heart failure are different. Under physiological conditions, GDF-15 is low expressed in many cell tissues[6], and when pathological conditions such as hypoxia and apoptosis occur, the expression level increases[7]. There are also studies support[8] that GDF-15 can be regarded as a growth regulating hormone secreted by heart. In children with CHD, GDF-15 was synthesized and secreted by cardiac muscle, which acts on liver and inhibits growth hormone, thereby affecting organ function and body metabolism.

β2-microglobulin (β2-MG) is a kind of low molecular weight protein. It can easily pass through glomerular filtration membrane, but most of its uptake is achieved by renal proximal tubule in the form of pinocytosis. The synthesis and release of β2-MG in healthy people are very constant[9,10], when the kidney of the body is abnormal, however, the index value of β2-MG will also change accordingly.

GDF-15 and β2-MG were seldom studied in CHD in infants combined with chronic heart failure. Therefore, the purpose of this research is to investigate the diagnostic value and prognosis of GDF-15 and β2-MG in CHD combined with chronic heart failure and their relationship with cardiac function.

Patients and Methods

General Data

A total of 100 infants diagnosed with CHD combined with chronic heart failure in our hospital from July 2015 to July 2018 were selected as the experimental group, including 52 males and 48 females. The subjects were 1 month to 3 years old, with the median age of 1.5 years old. The diagnosis of heart failure is based on the modified Ross grading method[11] in the diagnosis and treatment recommendations for pediatric heart failure. Points ≥3 was regarded as heart failure. Among them, there were 29 cases of ventricular septal defect, 41 cases of atrial septal defect, 18 cases of patent ductus arteriosus and 12 cases of tetralogy of Fallot diagnosed clinically. The patients were graded into a mild heart failure group (3-6 points, 33 cases), a moderate heart failure group (7-9 points, 32 cases) and a severe heart failure group (10-12 points, 35 cases) in accordance with Ross grading method. A total of 80 cases of healthy infants who underwent health examination in our hospital during the same period were selected as the control group, including 42 males and 38 females. The controls were 1 month to 4 years, with the median age of 2 years. The inclusion and exclusion criteria were as follows: Inclusion criteria: patients who met the diagnostic criteria for pediatric heart failure and diagnosed by cardiac ultrasound with CHD. Exclusion criteria: patients with co-infection (including acute upper respiratory tract infection, pulmonary infection, etc.). Patients with liver and kidney dysfunction, diabetes, malignant tumors, thyroid diseases and autoimmune diseases. All patient guardians have agreed to participate in the experiment and signed the informed consent. This investigation has been approved by the hospital Ethics Committee.

Test Methods and Materials

In the experimental group, venous blood (3-5 mL) was taken from the subjects on an empty stomach in the morning, and then injected into the serum separator tubes, standing for 30 min, and then centrifuged at 3000 $r \cdot min^{-1}$ for 20 min for separation of serum. After rapid distribution, the blood serum was frozen at -80°C in the refrigerator. The serum GDF-15 level in each group was detected by enzyme-linked immunosorbent assay (ELISA). The specific operation was carried out according to the kit (SEC034Hu-1, Hengfei Biotech, Shanghai, China) instructions. β2-MG level was determined by Altair™240 automatic blood biochemical analyzer (Yuyan Instruments, Shanghai, China). Left ventricular ejection fraction (LVEF) was determined by ultrasonic cardiograph (JM2018110762, Jumu Medical Instruments, Shanghai, China). Blood samples of subjects in the control group were taken on the day of physical examination, and the determination method was the same as that of the experimental group.

Observational Indexes

1. Comparison of general data of the two groups
2. Comparison of GDF-15 and β2-MG levels in different types of CHD

3. Comparison of serum GDF-15 and β2-MG levels and LVEF index between the two groups
4. Comparison of GDF-15 and β2-MG levels in different cardiac staging
5. Correlation analysis between levels of GDF-15 and β2-MG and cardiac function classification
6. The diagnostic value of GDF-15 and β2-MG alone and in combination in detecting CHD combined with chronic heart failure

Statistical Analysis

SPSS 20.0 software (Bizinsight technology, Beijing, China) was used for statistical analysis of experimental data. All data were in line with normal distribution. Enumeration data were analyzed by chi-square test. Measurement data were represented by mean±standard deviation. Comparison between the two groups was analyzed by *t*-test, repeated measures analysis of variance was used for comparison among groups. Spearman coefficient was used to analyze the correlation between GDF-15, β2-MG levels and cardiac function grade. And the ROC curve was used to evaluate the diagnostic value of GDF-15 and β2-MG alone and in combination for CHD combined with chronic heart failure. $p<0.05$ was regarded to have statistical differences.

Results

Comparison of General Data of the Two Groups

There were no significant differences in age, BMI and other general data between the two groups ($p>0.05$). There were significant differences in blood oxygen saturation (SpO_2), creatinine, B-type natriuretic peptide (BNP), N-terminal brain natriuretic peptide (NT-proBNP), hemoglobin (Hb) ($p<0.05$; Table I).

Comparison of Serum GDF-15 and β2-MG Levels and LVEF Indexes Between the Two Groups

The GDF-15 and β2-MG levels in the experimental group were significantly higher than those in the control group, the echocardiography parameter LVEF in the experimental group was significantly lower than that in the control group, and the differences were statistically significant ($p<0.001$; Table II).

Comparison of GDF-15 and β2-MG Levels In Different Cardiac Staging

There were statistically significant differences in GDF-15 and β2-MG levels between patients with different severity of heart failure ($p<0.001$).

Table I. Comparison of general data of the two groups.

Factors	Experimental group n = 100	Control group n = 80	χ^2/t	*p*
Age (years old)	1.48 ± 0.32	1.56 ± 0.25	1.833	0.069
Gender (n/%)			0.004	0.947
Male	52 (52)	42 (52.5)		
Female	48 (48)	38 (47.5)		
BMI (kg/m^2)	14.90 ± 0.21	14.85 ± 0.24	1.489	0.138
Diastolic pressure (mmHg)	53.2 ± 3.65	52.3 ± 3.72	1.630	0.105
Systolic pressure (mmHg)	78.8 ± 2.48	79.4 ± 2.63	1.570	0.118
BUN (umol/L)	5.47 ± 1.23	5.68 ±1.14	1.176	0.241
Breathing (per minute)	25.21 ± 4.2	26.32 ± 3.6	1.876	0.062
Heart rate (beats)	121 ± 10.76	126± 8.78	1.656	0.101
Nutritional status (n/%)			0.167	0.897
Good	82 (82)	65 (81.25)		
Fair	18 (18)	15 (19.75)		
Disease type				
Ventricular septal defect	29 (29)	–		
Atrial septal defect	41 (41)	–		
Patent ductus arteriosus	18 (18)	–		
Tetralogy of Fallot	12 (12)	–		
SpO_2 (%)	89.41 ± 5.24	94.26±4.15	6.754	< 0.001
Creatinine (μmol/L)	108.28 ± 20.36	83.26 ± 15.13	9.152	< 0.001
BNP (ng/L)	284.13 ± 20.14	1.10 ± 0.15	125.622	< 0.001
NT-proBNP (ng/L)	1310.02 ± 325.12	102.96 ± 41.21	32.978	< 0.001
Hb (g/L)	84.10 ± 22.23	125.62 ± 12.81	14.845	< 0.001
Na (mmol/L)	135.26 ± 3.35	136.18 ± 3.06	1.902	0.059

Table II. Comparison of serum GDF-15 and β2-MG levels and LVEF indexes between the two groups.

Factors	Experimental group n = 100	Control group n = 80	*t*	*p*
GDF-15 (pg/ml)	1876 ± 167.3	1134 ± 138.6	31.87	$p < 0.001$
β2-MG (ug/ml)	4.5 ± 1.45	3.7 ± 1.62	3.491	0.0006
LVEF (%)	59 ± 3.27	66 ± 4.29	56.78	$p < 0.001$

GDF-15 and β2-MG levels in the severe and moderate heart failure groups were significantly higher than those in the mild heart failure group, with statistically significant differences ($p<0.001$). GDF-15 and β2-MG levels in the severe heart failure group were significantly higher than those in the moderate heart failure group, with statistically significant differences ($p<0.001$; Table III).

Correlation Analysis Between Levels of GDF-15 and β2-MG and Cardiac Function Classification

GDF-15 and β2-MG levels were positively correlated with patients with different severity of heart failure ($p<0.001$; Figure 1).

The Diagnostic Value of GDF-15 and β2-MG Alone and In Combination In Detecting CHD Combined With Chronic Heart Failure and Its ROC Curve

The sensitivity, specificity and AUC of GDF-15 on CHD with chronic heart failure were 91.25%, 74.00% and 0.821 respectively. The sensitivity, specificity and AUC of β2-MG on CHD with chronic heart failure were 82.50%, 62.00% and 0.819, respectively. The sensitivity, specificity and AUC of GDF-15 and β2-MG in the combined diagnosis of CHD with chronic heart failure were 83.75%, 84.00% and 0.914, respectively. In addition, the sensitivity of LVEF to congenital heart disease with chronic heart failure was 74.00%, the specificity was 77.50%, and the AUC was 0.806 (Figure 2).

GDF-15 and β2-MG Predictive Value for Patients

Patients who deteriorated or died within six months were divided into the poor prognosis group (n = 54), patients whose conditions were improved were divided into the good prognosis group (n = 46). ROC curves for predicting poor prognosis for both groups were plotted. The sensitivity of GDF-15 to congenital heart disease with chronic heart failure was 91.30%, the specificity was 62.96%, and the AUC was 0.806. The sensitivity of β2-MG to congenital heart disease with chronic heart failure was 56.52%, the specificity was 94.44%, and the AUC was 0.817 (Figure 3).

Discussion

CHD is a cardiovascular malformation caused by abnormal cardiac vascular development in fetal period, which seriously impairs the health of infants[12]. The etiology of CHD is not completely clear yet, but most scholars believe that it is influenced by genetic and environmental factors[13]. Heart failure is one of the acute severe diseases in infants[14], and the most common cause of heart failure in infants is CHD[15]. At present, there is still a lack of simple laboratory test indicators for early diagnosis of CHD combined with chronic heart failure in infants, and there are still difficulties in early diagnosis. Therefore, finding detection factors is of great significance for the early diagnosis of diseases.

Table III. Comparison of GDF-15 and β2-MG levels in different cardiac staging.

Factors	Mild heart failure group n = 33	Moderate heart failure group n = 32	Severe heart failure group n = 35	*F*	*p*
GDF-15 (pg/ml)	1156.87 ± 146.64	1784.67 ± 152.53*	2279.32 ± 168.31#	438.6	$p < 0.001$
β2-MG (ug/ml)	3.34 ± 1.34	4.78 ± 1.67*	5.23 ± 1.23#	16.24	$p < 0.001$

Notes: Compared with moderate heart failure group and mild heart failure group, #means $p < 0.001$. Compared with mild heart failure group, *means $p<0.001$.

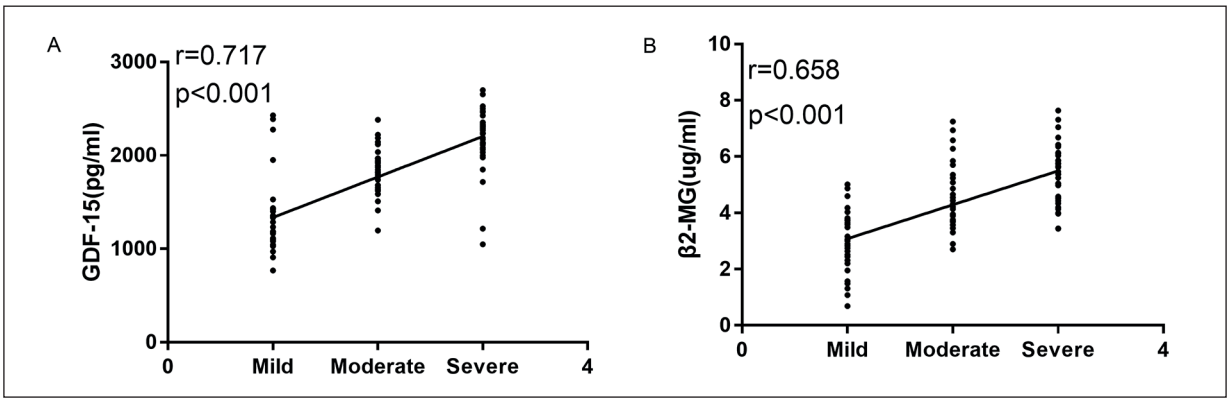

Figure 1. Correlation analysis between levels of GDF-15 and β2-MG and cardiac function classification. **A,** GDF-15 level was positively correlated with different cardiac function classification (r=0.717, p<0.001). **B,** β2-MG was positively correlated with different cardiac function classification (r=0.658, p<0.001).

First, it was revealed in this study that GDF-15 and β2-MG levels of patients in the experimental group were significantly higher than those in the control group, and the echocardiography parameter LVEF in the experimental group were significantly lower than those in the control group. LVEF was positively proportional to cardiac function, which meant that the smaller LVEF was, the worse cardiac function was. The results of this study indicate that patients with chronic heart failure have abnormal cardiac function, which is consistent with the results of research on adult chronic heart failure[16]. GDF-15 is associated with heart failure, myocardial hypertrophy, coronary heart disease and other cardiovascular diseases[17]. A large number of reactive oxygen species and oxygen free radicals can be produced in various cardiovascular diseases under pathological conditions[18], causing oxidative stress damage to cardiomyocytes and tissues, thereby inducing apoptosis of cardiomyocytes. GDF-15 is an important protective factor for cardiovascular diseases. When myocardial tissue cells are damaged, the expression level of GDF-15 increases significantly[19]. β2-MG is a sensitivity indicator reflecting the function of proximal renal tubules[20]. The results suggest that congenital heart disease is not only a cardiovascular disease, renal arterioles may also be involved in it, leading to an increase of concentrations in serum β2-MG, which changes as the disease progresses. This also suggests that GDF-15 and β2-MG can be used as biological markers for the determination of heart failure.

Then, we compared the GDF-15 and β2-MG levels in patients at different heart function stages, the results showed that GDF-15 and β2-MG levels in the mild, moderate and severe heart

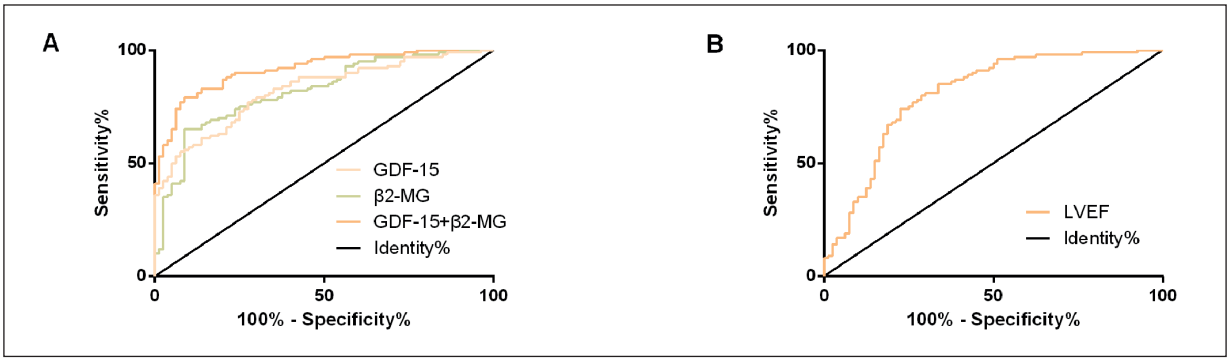

Figure 2. ROC curve of diagnostic value of GDF-15 and β2-MG alone and in combination in detecting CHD combined with chronic heart failure. **A,** The sensitivity, specificity and AUC of GDF-15 on CHD with chronic heart failure were 91.25%, 74.00% and 0.821, respectively. The sensitivity, specificity and AUC of β2-MG on CHD with chronic heart failure were 82.50%, 62.00% and 0.819, respectively. The sensitivity, specificity and AUC of the diagnosis of GDF-15 combined with β2-MG on CHD with chronic heart failure were 82.50%, 82.00% and 0.914, respectively. **B,** The sensitivity of LVEF to congenital heart disease with chronic heart failure was 74.00%, the specificity was 77.50%, and the AUC was 0.806.

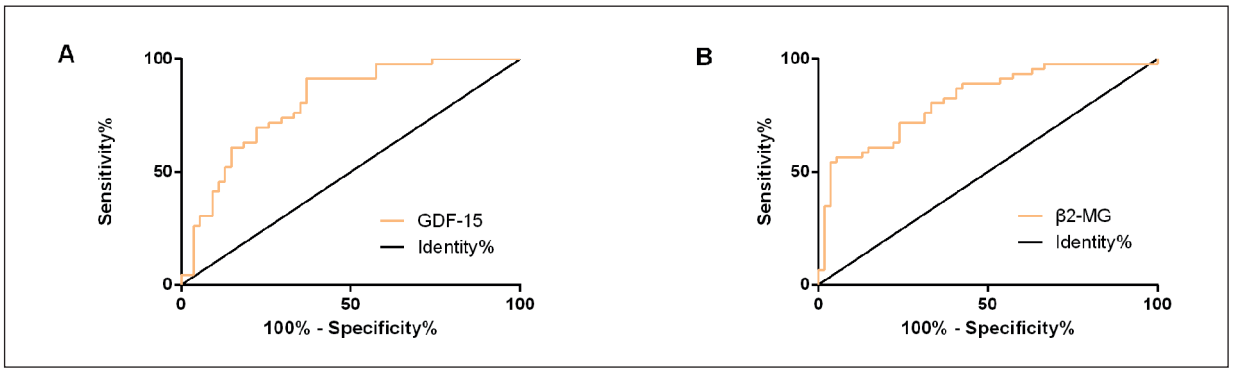

Figure 3. ROC curves of GDF-15 and β2-MG predicting the prognosis of congenital heart disease with chronic heart failure. **A,** The sensitivity of GDF-15 to congenital heart disease with chronic heart failure was 91.30%, the specificity was 62.96%, and the AUC was 0.806. **B,** The sensitivity of β2-MG to congenital heart disease with chronic heart failure was 56.52%, the specificity was 94.44%, and the AUC was 0.817.

failure groups increased in sequence, indicating that GDF-15 and β2-MG levels would gradually increase with the aggravation of disease degree. It is speculated that with the aggravation of the disease, the severity of the kidney increases. In adult heart failure, serum GDF-15 level is related to the severity of cardiac function classification, and the level increases with the increase of cardiac function classification in patients with heart failure[21,22]. Heart failure not only affects patients' cardiac function, but also cause damage to other target organs, such as kidneys and liver[23]. By analyzing the significance of GDF-15 and β2-MG levels and cardiac function classification, this paper hopes to further reveal the association between GDF-15 and β2-MG levels and cardiac function classification. Therefore, we analyzed the correlation between GDF-15 and β2-MG levels and different cardiac function classification of mild, moderate and severe diseases, and the results showed that GDF-15 and β2-MG levels were positively correlated with patients with different severity of heart failure, indicating that with the aggravation of cardiac function classification, the degree of renal injury increases, and the GDF-15 and β2-MG levels also increase. There is a significant correlation between serum GDF-15 level and the severity of heart failure in patients with heart failure[24]. GDF-15 level can be used to assess risk stratification of various cardiovascular diseases[25,26]. It is of clinical significance for the evaluation and further treatment of cardiac function in patients with CHD.

To clarify the diagnostic value of GDF-15 and β2-MG in CHD with chronic heart failure, we performed predictive analysis. The results showed that GDF-15 and β2-MG alone or combined detection has a high diagnostic value for CHD combined with chronic heart failure, better than ultrasound indicator LVEF. In addition, we also analyzed the prognostic value of GDF-15 and β2-MG for congenital heart disease with chronic heart failure. The results showed that the areas under the curve for the prognosis of GDF-15 and β2-MG were not less than 0.800, suggesting GDF-15 and β2-MG have high predictive value for the prognosis of patients. Therefore, GDF-15 and β2-MG can play a positive role in the diagnosis and prognosis prediction of CHD combined with chronic heart failure.

Conclusions

To sum up, high levels of GDF-15 and β2-MG can be detected in patients with CHD and chronic heart failure, and their levels are positively correlated with different cardiac function levels. With the aggravation of disease degree, the measured level increased, indicating that these two biomarkers have important significance in the treatment of disease and prognosis. There are differences between children and adults in the etiology and clinical manifestations with congenital heart disease combined with chronic heart failure; however, the management principles including diagnosis and prognosis are similar. Therefore, research on infants is needed[27], and our study could fill in this blank. There are also some deficiencies in this study. Some studies have indicated that[28] patients with heart failure have abnormal cardiac electrical activity, which

is manifested as prolonged Q-T time limit and widened R wave, etc. In this study, however, we did not explore whether there is association between electrocardiogram performance and levels of GFD-15 and β2-MG, so we will further improve this in subsequent experiments.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This work was supported by Shandong Province Natural Science Foundation of China (ZR2019BH053).

References

1) Chakravarti B, Yang J, Ahlers-Dannen KE, Luo Z, Flaherty HA, Meyerholz DK, Anderson ME, Fisher RA. Essentiality of regulator of G protein signaling 6 and oxidized Ca2+/calmodulin-dependent protein kinase II in Notch signaling and cardiovascular development. J Am Heart Assoc 2017; 6: e007038.
2) Gładki MM, SkładzieÐ T, Skalski JH. The impact of environmental factors on the occurrence of congenital heart disease in the form of hypoplastic left heart syndrome. Kardiochir Torakochirurgia Pol 2015; 3: 204-207.
3) Romer AJ, Rajagopal SK, Kameny RJ. Initial presentation and management of pediatric heart failure. Curr Opin Pediatr 2018; 30: 319-325.
4) Picchio FM, Formigari R, Balducci A. Pediatric heart failure. Minerva Cardioangiol 2008; 56: 311-319.
5) Wollert KC, Kempf T, Wallentin L. Growth differentiation factor 15 as a biomarker in cardiovascular disease. Clin Chem 2017; 63: 140-151.
6) Sharma A, Stevens SR, Lucas J, Fiuzat M, Adams KF, Whellan DJ, Donahue MP, Kitzman DW, Piña IL, Zannad F, Kraus WE, O'Connor CM, Felker GM. Utility of growth differentiation Factor-15, a marker of oxidative stress and inflammation, in chronic heart failure: insights from the HF-ACTION study. JACC Heart Fail 2017; 5: 724-734.
7) Xiang Y, Zhang T, Guo J, Peng YF, Wei YS. The association of growth differentiation Factor-15 gene polymorphisms with growth differentiation Factor-15 serum levels and risk of ischemic stroke. J Stroke Cerebrovasc Dis 2017; 26: 2111-2119.
8) Wang T, Liu J, Mcdonald C, Lupino K, Zhai X, Wilkins BJ, Hakonarson H, Pei L. GDF15 is a heart-derived hormone that regulates body growth. EMBO Mol Med 2017; 9: 1150-1164.
9) Barcelo R, Pollak VE. A preliminary immunologic study of urinary proteins: the questionable value of protein clearances in kidney disease. Can Med Assoc J 1966; 94: 269-275.
10) Zhang RF, Ma JG, Liu XX. The test of KIM-1, Cys C and β2-MG to assess the early renal damage in OSAHS patients and its clinical significance. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2017; 31: 174-179.
11) Ross RD. Grading the graders of congestive heart failure in children. J Pediatr 2001; 138: 618-620.
12) Khatami M, Heidari MM, Kazeminasab F, Zare Bidaki R. Identification of a novel non-sense mutation in TBX5 gene in pediatric patients with congenital heart defects. J Cardiovasc Thorac Res 2018; 10: 41-45.
13) Courtney JA, Cnota JF, Jones HN. The role of abnormal placentation in congenital heart disease; cause, correlate, or consequence? Front Physiol 2018; 9: 1045.
14) Lam CS, Solomon SD. Fussing over the middle child: heart failure with mid-range ejection fraction. Circulation 2017; 135: 1279-1280.
15) Hinton RB, Ware SM. Heart failure in pediatric patients with congenital heart disease. Circ Res 2017; 120: 978-994.
16) Suzuki H, Matsumoto Y, Ota H, Sugimura K, Takahashi J, Ito K, Miyata S, Fukumoto Y, Taki Y, Shimokawa H. Structural brain abnormalities and cardiac dysfunction in patients with chronic heart failure. Eur J Heart Fail 2018; 20: 936-938.
17) Xu XY, Nie Y, Wang FF, Bai Y, Lv ZZ, Zhang YY, Li ZJ, Gao W. Growth differentiation factor (GDF)-15 blocks norepinephrine-induced myocardial hypertrophy via a novel pathway involving inhibition of epidermal growth factor receptor transactivation. J Biol Chem 2014; 289: 10084-10094.
18) Wang X, Chen LL, Zhang Q. Increased serum level of Growth Differentiation Factor 15 (GDF-15) is associated with coronary artery disease. Cardiovasc Ther 2016; 34: 138-143.
19) Arslan F, Lai RC, Smeets MB, Akeroyd L, Choo A, Aguor EN, Timmers L, van Rijen HV, Doevendans PA, Pasterkamp G, Lim SK, de Kleijn DP. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress, activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury. Stem Cell Res 2013; 10: 301-312.
20) Shin JR, Kim SM, Yoo JS, Park JY, Kim SK, Cho JH, Jeong KH, Lee TW, Ihm CG. Urinary excretion of β2-microglobulin as a prognostic marker in immunoglobulin A nephropathy. Korean J Intern Med 2014; 29: 334-340.
21) Eindhoven JA, van den Bosch AE, Oemrawsingh RM, Baggen VJ, Kardys I, Cuypers JA, Witsenburg M, van Schaik RH, Roos-Hesselink JW, Boersma E. Release of growth-differentiation factor 15 and associations with cardiac function in adult patients with congenital heart disease. Int J Cardiol 2016; 202: 246-251.
22) Du W, Piek A, Schouten EM, van de Kolk CWA, Mueller C, Mebazaa A, Voors AA, de Boer RA, Silljé HHW. Plasma levels of heart failure bio-

markers are primarily a reflection of extracardiac production. Theranostics 2018; 8: 4155-4169.

23) Brisco MA, Cheng SJ, Laur O, Kula AJ, Testani JM. Evidence of mild liver dysfunction identifies stable heart failure outpatients with reversible renal dysfunction. Cardiorenal Med 2015; 5: 229-236.

24) Richter B, Koller L, Hohensinner PJ, Zorn G, Brekalo M, Berger R, Mörtl D, Maurer G, Pacher R, Huber K, Wojta J, Hülsmann M, Niessner A. A multi-biomarker risk score improves prediction of long-term mortality in patients with advanced heart failure. Int J Cardiol 2013; 168: 1251-1257.

25) Zhang S, Dai D, Wang X, Zhu H, Jin H, Zhao R, Jiang L, Lu Q, Yi F, Wan X, Cui H. Growth differentiation factor–15 predicts the prognoses of patients with acute coronary syndrome: a meta-analysis. BMC Cardiovasc Disord 2016; 16: 1-7.

26) Shin JR, Kim SM, Yoo JS, Park JY, Kim SK, Cho JH, Jeong KH, Lee TW, Ihm CG. Urinary excretion of β2-microglobulin as a prognostic marker in immunoglobulin A nephropathy. Korean J Intern Med 2014; 29: 334-340.

27) Jayaprasad N. Heart failure in children. Heart Views 2016; 17: 92-99.

28) Sauer A, Wilcox JE, Andrei AC, Passman R, Goldberger JJ, Shah SJ. Diastolic electromechanical coupling: association of the ECG T-peak to T-end interval with echocardiographic markers of diastolic dysfunction. Circ Arrhythm Electrophysiol 2012; 5: 537-543.