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Growth differentiation factor 15 and arterial remodeling in adult patients after successful repair of aortic coarctation (RCD code: IV-5.A.1)

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Abstract

Background: Coarctation of aorta (CoAo) is a congenital heart anomaly associated with high cardiovascular morbidity and mortality attributable to vascular remodeling in adult survivors following surgical management of aortic stenosis. This study sought to adjudicate the significance of novel stress-responsive biomarker, growth differentiation factor 15 (GDF-15), as an indicator of vascular remodeling and its correlation with numerous laboratory and vascular parameters in patients after successful CoAo repair.

Methods and results: This research is a case-control study comprising 33 consecutive patients (19 men, 57.58%; mean age 33.9 ±9.3 years; mean age at surgery: 9.1 ±7 years; mean follow-up duration 24.8 ±6.8 years) admitted to outpatient clinic for routine follow-up after repair of CoAo (mainly Dacron patch technique) and matched with 20 healthy controls (10 men, 50%; mean age 34.8 ±9.9 years). Laboratory (GDF-15, high-sensitivity C-reactive protein) and vascular parameters (intima-media thickness, flow- and nitrate-mediated dilation, pulse-wave velocity, central arterial pressure) were assessed. Significant aortic residual gradient was present in 24 (72.7%). The circulating GDF-15 level was lower in CoAo survivors than in control group (539.56 vs. 744.98 pg/ml respectively; $p < 0.001$). GDF-15 concentration <550 pg/ml successfully differentiated patients after CoA repair (odds ratio [OR] = 9.2; 95%CI: 2.45–34.56, $p = 0.0005$). There was no difference in GDF-15 level depending on the presence of significant residual gradient ($p = 0.19$). No significant correlation between GDF-15 and other variables was observed.

Conclusions: Low concentration of GDF-15 is characteristic of asymptomatic patients following CoAo repair, however, its clinical significance and relationship with vascular remodeling substantiates further investigation. JRCD 2013; 1 (2): 41–48

Key words: coarctation of aorta, GDF-15, growth differentiation factor 15, vascular remodeling

Background

Coarctation of aorta (CoAo) pertains to one of the most intriguing congenital heart defects, which frequently leads to severe neonatal heart failure [1]. Conversely, latent forms of CoAo may pose a true diagnostic conundrum when disclosed in an adult life [2-3]. Despite considerably low prevalence of 0.34 per 1000 live births [4], a growing number of adult patients after successful correction of CoAo triggers the need for meticulous follow-up programme [5]. Notwithstanding the relatively early introduction of effective CoAo surgical treatment in 1944 [6] and a further successful implementation of transcatheter approach in 1982 [7], long-term outcome is still compromised on account of the process of arterial remodeling in pre-stenotic vascular bed, associated with arterial stiffness [8-11] and baroreceptor dysfunction [12]. The resultant markedly increased prevalence of arterial hypertension of 30-50%, regarded as a hallmark of CoAo [13-14], leads to diffuse atherosclerosis [11,15-17] and notably reduced life expectancy [18-19]. Yet, even normotensive CoAo patients exhibit both functional and structural vascular abnormalities [15, 20-21]. Data concerning optimal timing of surgery is inconsistent, with the predominance of reports implying improved long-term outcome in patients operated within the first year after birth [22-24]. Nonetheless, even an early intervention does not utterly preclude arterial remodeling, as assessed by ultrasonographic vascular parameters [9-10,21,23]. This phenomenon seems to be unrelated

Conflict of interest: none declared.

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with the occurrence of aortic restenosis [24], hence CoAo may represent a widespread systemic vascular anomaly [13, 21].

Previous reports corroborated the role of transforming growth factor β1 signaling in vascular remodeling in response to shear stress [25-26]. Accordingly, a novel anti-apoptotic stress-induced member of the TGF-β1 cytokine superfamily, namely growth differentiation factor 15 (GDF-15) [27-28], has been recently recognised as a surrogate marker of increased mortality in heart failure [29], particularly with preserved ejection fraction (HF-PEF) [30], along with myocardial infarction [31], idiopathic pulmonary hypertension [32] and pulmonary embolism [33]. GDF-15 level also independently contributed to risk stratification in acute chest pain [34] and predicted symptomatic response to cardiac resynchronisation therapy [35]. More to the point, it was recently demonstrated that serum concentration of GDF-15 corresponds with the risk of heart failure in grown-up congenital heart disease (GUCHD) patients [36] and identifies early abnormal function of Fontan circuit [37]. Since no data exists regarding possible role of GDF-15 in CoAo, we intended to scrutinise its potential applicability as a determinant of arterial remodeling, with respect to several laboratory and vascular parameters in subjects after successful repair of CoAo, in the setting of GUCHD outpatient clinic.

Methods

This research constitutes a case-control study comprising 33 asymptomatic patients with the history of surgical repair of CoAo, who were admitted to adult congenital heart disease outpatient clinic for routine follow-up visit. The control group consisted of 20 healthy individuals matched in terms of age and gender. Dacron patch repair accounted for the predominance of surgeries and was conducted by the same cardiac surgeon.

Subjects in both groups were examined and queried in terms of possible confounding factors that might interfere with assessed parameters. Following exclusion criteria were applied: acute and chronic inflammatory diseases in the preceding 3 months, underlying neoplasms, cigarette smoking within 12 h before the examination, history of diabetes mellitus, chronic kidney disease, concurrent valvular heart disease, left ventricle ejection fraction < 45%, congestive heart failure, evidence of coronary artery disease, cardiomyopathy, concomitant peripheral artery disease and liver dysfunction of any degree.

After enrolment in the study, blood samples were collected from radial vein to assess standard blood parameters, together with the following serum markers: growth differentiation factor 15 (GDF-15), high sensitivity C-reactive protein (hs-CRP). Above-mentioned analyses were performed by means of enzyme-linked immunosorbent assay (ELISA). All measurements were consistent with ISO 9001:2008.

Subsequently, following ultrasonographic indices of vascular function were acquired: brachial artery diameter (BAd), flow-mediated dilation (FMD), nitrate-mediated dilation (NMD), intima-media thickness (IMT) and pulse wave velocity (PWV).

Blood pressure was measured with the use of cuff sphygmomanometer in all participants after 15 minutes of rest. Arterial hypertension was diagnosed either if blood pressure exceeded the threshold of 140/90 mm Hg or in case of current antihypertensive therapy or prior diagnosis of arterial hypertension.

An echocardiographic examination was performed using a Vivid 7 (GE Healthcare) with a 2.5-MHz probe in 2D, M, and Doppler modes. A single investigator evaluated the cardiac anatomy and left ventricular systolic function using biplane Simpson method. The extent of the residual stenosis of the descending aorta was assessed from the suprasternal notch view. Patients after the surgical correction of aortic coarctation were stratified depending on the presence of haemodynamically significant residual stenosis (recoarctation, restenosis), defined as a descending aorta pressure gradient equal to or greater than 20 mm Hg or an arm-leg systolic blood pressure gradient exceeding 20 mm Hg at rest [23].

Flow-mediated dilatation

The acquisition of data was conducted in a specified time frame between 8.00 and 10.00 a.m. in a temperature-controlled room (20–22° C) with subjects resting in a supine position. Conduit-vessel endothelial function was assessed using the ultrasound measurement of brachial artery diameter during changes in brachial artery flow (7–12 MHz linear array transducer, Logic 7, GE). The study protocol required visualisation of at least 5-cm of the brachial artery in a longitudinal section above the antecubital fossa, with the optimal probe site on the skin marked. Baseline images of brachial artery diameter and Doppler velocities from the centre of the vessel were recorded and stored electronically. Afterwards, a cuff occluding forearm was placed just below the antecubital fossa and inflated to 50 mm Hg above systolic pressure for 3 min. A brachial artery scan was then acquired for 120 s after cuff deflation, including a repeat flow velocity recording for the first 15 s after cuff release. After 10 min of rest, sublingual nitroglycerin (NTG) in a dose of 500 μg was administrated to determine attainable peak exogenous vasodilation. Brachial artery diameter (BAd) and blood flow were measured following NTG administration. The response of the vessel diameter to reactive hyperaemia, namely flow-mediated dilatation (FMD), was calculated and expressed as the percentage change relative to the diameter immediately before cuff inflation. The shift in diameter triggered by NTG, further referred to as nitrate-mediated dilation (NMD), was expressed as the percentage change relative to the recovery scan [14].

IMT B-mode carotid ultrasound

Carotid scans were performed using a Logic 7, GE ultrasound machine with a 7 to 12-MHz transducer. Following the acquisition of the scan, the diastolic images with the best demonstrated intimal-medial thickening (IMT) were analysed. Both the proximal and distal walls of the common carotid artery were visualized on the same scan to ensure the transducer was transecting the artery at 90°. Scans were read by a single observer blind to the other results. Images were analysed using a quantitative analysis package (Siemens) characterised by an axial resolution of 0.001 mm. Measurements of IMT were made at 1-mm intervals over a 10-mm segment of the vessel. The maximal and mean IMT measurements were determined for the proximal and distal walls of the left and right common carotid arteries.

Pulse wave velocity

Pulse wave velocity (PWV) (the velocity of propagation of the arterial pulse from the brachial to radial probe) was measured as the index of arterial stiffness by using a well-validated photo-plethysmographic technique. Signals from two photo-probes placed over the right brachial and radial arteries were converted from the delay measured as the time between the foot of the pulse wave and the R wave in concurrently recorded ECG. Pulse transit time was determined as the average of consecutive beats during the last 10 s. Thus, PWV was calculated as the ratio of the distance between the two probes and transit time (PWV = d/t [m/s]) [39].

Central aortic function assessment

Central parameters of the aortic pulse wave and arterial wall stiffness of the large conduit arteries were measured using pulse wave analysis performed with applanation tonometer (SphygmoCor PVx, Version 8.0, AtCor, Sydney, Australia). Brachial blood pressure (BP) required for the algorithm of the procedure was measured non-invasively after 15 min of rest in the supine position with Omron 705IT device (Omron Healthcare, Kyoto, Japan). For the assessment of the parameters of the central aortic pulse wave, the pulse waveform of the radial artery was recorded for 10 s and a radial to aortic transfer function was used to derive the central aortic pulse pressure (APP) waveform from which the aortic systolic pressure (ASP), aortic diastolic pressure (ADP), augmentation pressure (AP) and augmentation index (AI) were determined. The central aortic pulse wave peaks twice. The first peak is caused by ejection of blood from the left ventricle and the second is a result of the wave reflected from the periphery, overlapping the primary one. The AP is the difference between the second and the first peak, and the AI is the ratio of AP to APP expressed as a percentage [40].

Statistics

Statistical analysis was performed using Statistica 10.0 (StatSoft Poland) software. Quantitative variables were presented as the mean value ± standard deviation (SD) and qualitative parameters were expressed as number and percentage. The type of distribution was verified using Shapiro-Wilk test. For variables following normal distribution, statistical analysis was performed with Student's t test for unpaired samples and analysis of variance (ANOVA), while Mann– Whitney U test and Kruskal-Wallis test were implemented in non-normally distributed parameters. Qualitative variables were compared using the Chi-square test with Yates correction. Odds ratios (OR) with 95% confidence interval (CI) were then calculated. To determine the relationship between variables, the Pearson's coefficient of correlation was calculated. A 'p' value of less than 0.05 was regarded as statistically significant.

Each participant of the study gave their written informed consent for enrolment in the study. The research protocol was initially approved by applicable institutional Ethics Committee and complied with the Declaration of Helsinki as established in 1975.

Results

After meeting the inclusion criteria, 33 patients were incorporated into the analysis (19 males, 57.6%; mean age 33.9 ±9.3 years) and matched in terms of age and gender with a corresponding control group of 20 healthy individuals (10 males, 50%; mean age 34.8 ±9.9 years). Detailed demographic and laboratory characteristics of the study population are highlighted in Table 1. It was documented that body mass index (BMI) in patients after surgical repair of CoAo was considerably elevated, as opposed to the control group. Despite being generally normotensive, patients after CoAo repair presented with significantly higher systolic (SBP) and diastolic blood pressure (DBP), which corresponded with increased central systolic and pulse pressure.

Table 1. Demographic and clinical characteristics of the study population

Variable	CoAo (+) n = 33	p	CoAo (-) n = 20
Males n [%]	19 (57.58%)	0.8 [a]	10 (50%)
Age [years]	32 (27; 37)	0.79 [b]	31.5 (27; 41.5)
Weight [kg]	75.18 ± 12.04	0.09 [c]	69.15 ± 19.92
Height [m]	170.61 ± 9.21	0.25 [c]	173.8 ± 15.35
BMI [kg/m^2]	25.79 ± 3.39	0.002	22.72 ± 2.96
Glucose [mmol/l]	5.13 ± 0.67	0.83 [b]	5.29 ± 0.98
Creatinine [µmol/l]	72.87 ± 11.91	0.54 [c]	74.74 ± 8.41
TC [mmol/l]	5.2 ± 0.9	0.5 [b]	5.41 ± 1.02
LDL [mmol/l]	2.96 ± 0.72	0.8 [c]	3.01 ± 0.68
HDL [mmol/l]	1.42 ± 0.31	0.55 [c]	1.37 ± 0.24
TG [mmol/l]	1.38 ± 0.51	0.57 [b]	1.29 ± 0.53
HR [1/min]	71.85 ± 10.99	0.12 [c]	67.7 ± 5.32
PP [mmHg]	52.12 ± 8.66	0.45 [c]	50.0 ± 11.65
SBP [mmHg]	128.94 ± 9.58	0.02 [b]	123.45 ± 16.27
DBP [mmHg]	76.82 ± 6.47	0.002 [b]	69.9 ± 7.61
ASP [mmHg]	108.97 ± 10.32	0.04 [c]	103.15 ± 8.44
ADP [mmHg]	70.24 ± 8.04	0.64 [b]	70.5 ± 7.64
APP [mmHg]	38.21 ± 8.46	0.02 [c]	32.95 ± 6.78
AP [mmHg]	6.79 ± 4.54	0.08 [b]	4.5 ± 3.32
AI [mmHg]	17.62 ± 11.14	0.19 [b]	13.5 ± 9.58

[a] Yates Chi-square test, [b] U Mann-Whitney test, [c] Student t test, p – statistical significance, BMI – body mass index, TC – total cholesterol, LDL – low density lipoproteins, HDL – high density lipoproteins, TG – triglycerides, HR – heart rate, PP – peripheral pulse pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure , ASP – central systolic pressure, ADP – central diastolic pressure, APP – central pulse pressure, AP – augmentation pressure, AI – augmentation index, CoAo – coarctation of aorta

The study group consisted of patients in a relatively stable clinical condition (mainly in New Yeark Heart Association class I), with preserved ejection fraction (mean of 64.1 ±5.2%) and adequate diastolic function expressed by E/E' ratio (mean of 8.9 ±1.8). The subjects underwent surgery at the mean age of 9.1 ±7 years and were subsequently systematically followed-up for 24.8 ±6.8 years. Despite acceptable surgical results, mean residual pressure gradient in the descending aorta was 24.6 ±11.2 mm Hg and in 24 subjects (72.7%) the gradient met the criteria for aortic restenosis. Procedural aspects of the follow-up are denoted in Table 2.

Our study revealed that concentration of GDF-15 was notably reduced in the group of patients after CoAo repair in comparison to the control group (539.56 vs. 744.98 pg/ml respectively; $p < 0.001$) (Table 3). When expressed as a dichotomous variable, serum level of GDF-15 below the threshold of 550 pg/ml successfully differentiated patients after CoAo repair (OR = 9.2; 95% CI: 2.45–34.56, $p = 0.0005$). What is more, the analysis demonstrated no difference in GDF-15 concentration between patients with residual stenosis of descending aorta (aortic pressure gradient ≥20 mm Hg) and subjects devoid of this long-term complication (542.7 vs. 531.3 pg/ml, $p = 0.19$) (Table 4). Further sub-analysis proved statistical significance of lower level of GDF-15 among patients with recoarctation, as compared to healthy controls (542.7 vs. 744.98; $p < 0.001$).

In addition, the authors managed to document significantly declined values of flow-mediated (4.75 vs. 8.6%, $p = 0.001$) and nitrate-mediated dilation (11.86 vs. 20.95, $p < 0.001$) in post-coarctation individuals. The observed discrepancy was even more prominent between CoAo patients with aortic restenosis and the control group (Table 4).

The analysis of correlation failed to indicate any relationship between concentration of GDF-15 and laboratory markers of vascular remodeling and cardiovascular risk, i.e. hs-CRP ($r = 0.21$, $p = 0.25$). Moreover, GDF-15 did not correlate with other parameters of vascular function in the form of IMT, FMD and NMD in both groups, barring a slight trend for association with PWV in the study group ($r = 0.34$, $p = 0.053$) (Figure 1). Still, in subjects after CoAo correction GDF-15 concentration corresponded with brachial artery diameter ($r = 0.38$, $p = 0.27$), along with central systolic ($r = 0.43$, $p = 0.01$) (Figure 2) and diastolic pressure ($r = 0.45$, $p = 0.01$). Interestingly, the authors also documented a negative correlation between level of GDF-15 and body weight ($r = -0.56$, $p = 0.01$), which reached statistical significance in the control group.

As far as other parameters are concerned, concentration of hs-CRP negatively correlated with NMD ($r = -0.48$, $p = 0.005$) (Figure 3) and positively corresponded with creatinine concentration

Table 2. Surgery-related features of patients after coarctation of aorta repair

Procedural variable	Mean	Min.	Max.
Age at surgery [years]	9.12 ±7.03	1	29
Time after surgery [years]	24.79 ±6.78	10	41
Residual gradient [mm Hg]	24.64 ±11.15	3	48

Table 3. Vascular and laboratory parameters related with vascular remodeling in patients after CoAo repair and healthy controls

Variable	CoAo (+) n = 33 Mean ±SD	p	CoAo (-) n = 20 Mean ±SD
PWV [m/s]	6.9 ±1.14	0.77[c]	6.99 ±0.77
IMT [mm]	0.58 ±0.16	0.17[b]	0.53 ±0.11
BAd [mm]	4.83 ±0.74	0.22[c]	4.57 ±0.78
BAD1 [mm]	5.44 ±0.86	<0.001[c]	4.53 ±0.75
NMD [%]	11.86 ±4.77	<0.001[b]	20.95 ±7.43
FMD [%]	4.75 ±2.83	0.001[b]	8.6 ±4.08
hs-CRP [mg/l]	8.16 ±5.16	0.16[b]	5.79 ±3.23
OPG [pmol/ml]	3.38 ±1.68	0.19[b]	4.0 ±1.88
TGF-β1 [ng/ml]	10.25 ±7.78	0.24[b]	15.62 ±13.22
GDF-15 [pg/ml]	539.56 ±113.23	< 0.001[b]	744.98 ±202.4

[a] - Yates Chi-square test, [b] - U Mann-Whitney test, [c] - Student t test, 'p' – statistical significance, PWV – pulse wave velocity, IMT – intima-media thickness, BAd – brachial artery diameter, NMD – nitrates-mediate dilation, FMD – flow-mediated dilation, hs-CRP – high sensitivity C-reactive protein, OPG – osteoprotegerin, TGF-β – transforming growth factor beta 1, GDF-15 – growth differentiation factor 15, CoAo – coarctation of aorta

Table 4. Results of the sub-analysis of different vascular and laboratory parameters of arterial remodeling depending on the presence of residual coarctation

Variable	CoAo (+) n = 33		CoAo (-) n = 20	p
	Residual CoAo [a] (+) n = 24	Residual CoAo [a] (-) n = 9		
PWV [m/s]	6.95 ±1.05	6.76 ± 1.4	6.99 ±0.77	0.9[b]
BAd [mm]	4.99 ±0.65	4.43 ±0.92	4.57 ±0.78	0.06[b]
FMD [%]	4.25 ±2.12	6.07 ±4.05	8.6 ±4.08	<0.001[c]
NMD [%]	11.63 ±4.79	12.47 ±4.95	20.94 ±7.43	<0.001[c]
IMT [mm]	0.54 ±0.09	0.69 ± 0.2	0.53 ±0.11	0.45[c]
hs-CRP [mg/l]	8.27 ±5.57	7.85 ±4.14	5.79 ±3.23	0.2[c]
OPG [pmol/ml]	3.04 ±0.99	4.27 ±2.7	4.0 ±1.88	0.11[c]
TGF-β1 [ng/ml]	9.6 ±7.38	11.97 ±8.0	15.62 ±13.22	0.21[c]
GDF-15 [pg/ml]	542.66 ±87.63	531.3 ±170.59	744.98 ±202.4	<0.001[c]

[a] – residual coarctation defined as a persistent residual gradient of ≥ 20 mmHg, [b] – analysis of variance (ANOVA) test, [c] – Kruskal-Wallis test, 'p' – statistical significance, PWV – pulse wave velocity, IMT – intima-media thickness, BAd – brachial artery diameter, NMD – nitrate-mediated dilation, FMD – flow-mediated dilation, hs-CRP – high sensitivity C-reactive protein, OPG – osteoprotegerin, TGF-β1 – transforming growth factor beta 1, GDF-15 – growth differentiation factor 15, CoA – coarctation of aorta

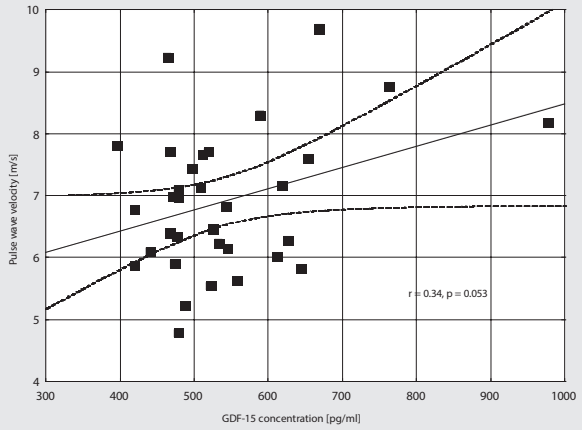

Figure 1. Correlation between pulse wave velocity (PWV) and serum concentration of GDF-15 in patients after aortic coarctation repair; r – Pearson's coefficient of correlation, p – level of statistical significance, GDF-15 – growth differentiation factor 15

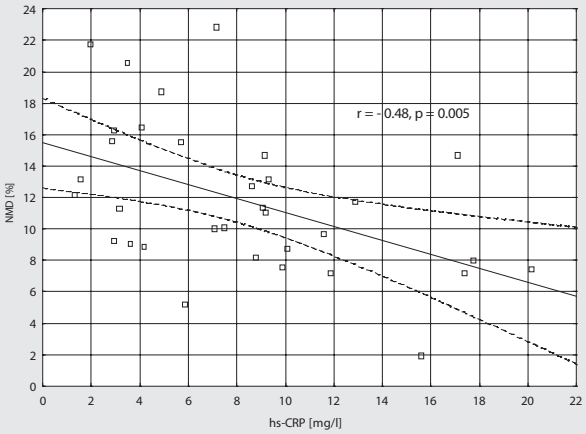

Figure 3. Correlation between nitrate-mediated dilation (NMD) and serum concentration of high sensitivity C-reactive protein (hs-CRP)in patients after aortic coarctation repair; r – Pearson's coefficient of correlation, p – level of statistical significance, NMD – nitrate-mediate dilation, hs-CRP – high sensitivity C-reactive protein

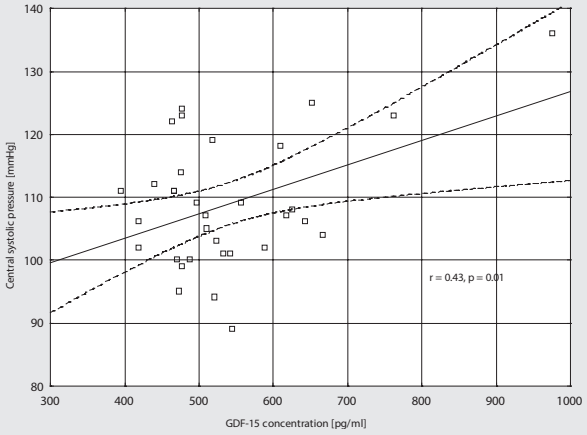

Figure 2. Correlation between central systolic pressure (ASP) and serum concentration of GDF-15 in patients after aortic coarctation repair; r – Pearson's coefficient of correlation, p – level of statistical significance, GDF-15 – growth differentiation factor 15

(r = 0.35, p = 0.045). A well-known relationship between thickness of intima-media complex and age was observed in patients after CoAo repair (r = 0.5, p = 0.003).

Discussion

This manuscript constitutes, by far, the first report in literature focused on the analysis of GDF-15 concentration in patients after CoAo repair. The crucial finding of this study consists in the markedly low concentration of GDF-15 estimated in subjects after CoAo repair. Accordingly, the level of GDF-15 did not correspond with peripheral vascular remodeling reflected by decreased FMD and NMD in upper limb conduit vessels observed in the study group. These results need to be confronted with previous reports on serum level of GDF in GUCHD patients, which were the incentive to performing this analysis.

The study by Norozi et al. states that GDF-15 positively correlated with New York Heart Association (NYHA) symptomatic class, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and reduced maximal uptake of oxygen ($VO_{2max\%}$) in population of patients following successful correction of miscellaneous congenital heart anomalies. It suggested that the highest mean GDF-15 was found in groups characterised by NT-proBNP > 300 pg/mL and $V_{O2max\%}$ < 65% [36]. However, the sub-analysis of patients following surgery of coarctation revealed notably low concentration of GDF-15 (508 ±174 pg/ml) [36], which is comparable with our findings (539.56 ±113.23 pg/ml). The same document implied that patients after surgery for coarctation of aorta had the lowest risk of developing heart failure among all GUCHD patients. Other paper by Raedle-Hurst et al. concerned patients after correction of single-ventricular heart and gave evidence that patients with reduced ejection fraction (EF < 50%) distinguished themselves with higher mean GDF-15 level (987.2 ±440.5 pg/mL) in contrast to patients with normal systolic function (520.2 ±143.1 pg/mL) [37].

In the light of aforementioned reports, low concentration of GDF-15 found in our study corresponds with the relatively good clinical condition of the study population. As the majority of the participants exhibited virtually no symptoms and signs of heart failure (NYHA I), we hypothesized that GDF-15 should stay in line with the clinically asymptomatic process of vascular remodeling accountable for the majority of adverse cardiovascular events. On the contrary, our study revealed that an isolated pathology of vascular bed, which occurs in case of early correction of aortic stenosis, is not associated with increased GDF-15 concentration. We may speculate that timely intervention prevents the myocardium from detrimental hypertrophy, since myocardial expression of stress-

Table 5. Matrix of correlation concerning different vascular and laboratory parameters in the study group

		BAd	FMD	NMD	IMT	hs-CRP	OPG	TGF-β1	GDF-15
Age	r	0.11	0.18	0.01	0.5	-0.06	0.29	-0.12	0.2
	p	0.55	0.33	0.97	0.003	0.74	0.1	0.5	0.26
BMI	r	0.4	0.19	0.16	-0.17	0.15	-0.01	0.07	-0.07
	p	0.02	0.29	0.37	0.33	0.41	0.97	0.69	0.69
ASP	r	0.32	0.01	-0.14	0.57	-0.05	0.06	-0.16	0.43
	p	0.07	0.96	0.45	0.001	0.78	0.76	0.37	0.01
ADP	r	0.09	0.14	0.07	0.28	-0.02	0.19	-0.03	0.45
	p	0.62	0.44	0.69	0.11	0.93	0.3	0.87	0.01
PWV	r	0.11	0.11	-0.17	0.29	0.1	-0.002	0.07	0.34
	p	0.53	0.55	0.34	0.11	0.59	0.99	0.69	0.053
BAd	r		-0.16	-0.05	0.19	0.018	-0.05	0.05	0.38
	p		0.39	0.8	0.28	0.92	0.79	0.77	0.03
FMD	r	-0.16		0.43	-0.04	-0.01	-0.12	-0.01	-0.15
	p	0.39		0.01	0.83	0.96	0.5	0.96	0.41
NMD	r	-0.05	0.43		-0.09	-0.48	-0.01	0.2	-0.08
	p	0.8	0.01		0.63	0.005	0.94	0.28	0.65
IMT	r	0.19	-0.04	-0.09		0.09	0.19	0.03	0.24
	p	0.28	0.83	0.63		0.64	0.29	0.89	0.18
hs-CRP	r	0.02	-0.01	-0.48	0.09		-0.13	-0.41	0.21
	p	0.92	0.96	0.005	0.64		0.46	0.02	0.25
OPG	r	-0.05	-0.12	-0.01	0.19	-0.13		0.07	0.2
	p	0.79	0.5	0.94	0.29	0.46		0.71	0.26
TGF-β1	r	0.05	-0.01	0.2	0.03	-0.41	0.07		-0.21
	p	0.77	0.96	0.28	0.89	0.02	0.71		0.25
GDF-15	r	0.38	-0.15	-0.08	0.24	0.21	0.2	-0.21	
	p	0.03	0.41	0.65	0.18	0.25	0.26	0.25	

[a] r – Pearson's coefficient of correlation, p – statistical significance, BMI – body mass index, ASP – central systolic pressure, ADP – central diastolic pressure, PWV – pulse wave velocity, BAd – brachial artery diameter, FMD – flow-mediated dilation, NMD – nitrate-mediated dilation, IMT – intima-media thickness, CRP – C-reactive protein, OPG – osteoprotegerin, TGF-β1- transforming growth factor beta 1, GDF-15 – growth differentiation factor 15

responsive cytokines is not induced. Conversely, the majority of molecular studies on the significance of GDF-15 in myocardial injury underscored its role as an anti-apoptotic and pro-hypertrophic cytokine involved in pathogenesis of heart failure. The expression of *GDF-15* was also up-regulated in vascular smooth muscle cells and endothelium in response to oxidative stress and inflammation [41]. Consequently, increased expression of anti-apoptotic TGF-β-1 and reduced expression of pro-apoptotic *Bcl-xS* and *Fas* ligand were demonstrated in response to acute sustained elevation of blood pressure in a coarctation model of hypertension [25,42]. The overexpression of members of TGF-β1 superfamily seems to disappear after the correction of coarctation and does not account for the stiffness of peripheral vessels expressed by diminished NMD and FMD response [11].

Presented study managed to denote some correlation between GDF-15 and central systolic and diastolic pressure, as well as a trend for association with PWV. Vascular remodeling was documented to be a spatiotemporal process [43] and therefore the association between GDF-15 and pathology of different vascular beds may vary. However, the significance of this finding remains unknown.

Moreover, the authors restrain from considering relatively low concentration of GDF-15 in the study group as diagnostic marker of vascular remodeling. This notion stems from moderately elevated concentration of GDF-15 in the control group, as opposed to former studies on GDF-15 reference values in different age groups. According to the report based upon Framingham Heart Study population, serum concentration of GDF-15 varied with age but not by gender and the median GDF-15 level was 651 pg/ml for men aged 30-39 years [44]. The study also underpinned its positive correlation with smoking, antihypertensive treatment, diabetes, declined glomerular filtration rate, and current intake of non-steroidal anti-inflammatory drugs. A negative association with total and HDL cholesterol was found. Although an upper reference limit of 1200 pg/ml was established for the elderlies [45], paucity of reports concerning young population, especially below the age of 30, generates statistical difficulty due to lack of liable benchmark.

The concentration of GDF-15 did not correspond with an acute-phase reactant, hs-CRP, which, in turn, was found reversibly proportional to NMD. In this way, GDF-15 did not adequately reflect overall cardiovascular burden of CoAo survivors. These findings should be interpreted with respect to one of our institution's previous reports, which demonstrated a markedly elevated concentration of asymmetric dimethylarginine (ADMA) in this group of patients, highly suggestive of underlying diffuse atherosclerosis [46].

Last but not least, all the assessed vascular and laboratory parameters were irrespective of the presence of aortic restenosis, suggesting that residual trans-aortic gradient does not determine impaired vasodilatation in adult survivors of CoAo, which remains in accordance with our different publication [47].

Study limitations

The results of our analysis may be disputed due to relatively low amount of participants, which could affect statistical significance. In turn, the observed difference between the study and control group in terms of GDF-15 concentration was not confirmed in an analysis performed on 77 patients, in which statistical significance was not reached (data not shown). The reason for this result probably derives from extremely high values of GDF-15 among few participants. Regrettably we could not publish the above-mentioned statistics due to considerable data incompleteness regarding the more extensive study group, which could interfere with study's consistency.

Although the authors vouch for the veracity of presented analysis, the paper constitutes an observational case-control study and is subject to limitations of its design. Therefore, its results should be interpreted with caution.

Since the study merely encapsulated patients treated in an outpatient clinic and in good general condition, the significance of GDF-15 in the setting of cardiology ward or intensive care unit merits further research.

Furthermore, all the patients were treated with Dacron patch repair surgery. The homogenous procedural characteristics of study population, with no use of widespread balloon angioplasty and stenting [48], and relatively old age at surgery (at average 9 years) may dispute the representativeness of the study population and prevent extensive application of its results.

Conclusions

Serum level of GDF-15 is decreased among patients after CoAo repair and does not correlate with the impaired peripheral vasodilation. Yet, on account of several caveats, these results ought to be carefully interpreted. High-volume prospective studies may provide an insight into the clinical significance of GDF-15 and its relationship with vascular remodeling inherent in CoAo. Early identification of GUCHD patients, predisposed to major adverse cardiovascular and cerebral events, could facilitate better outcome by means of prevention and diligent follow-up.

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