

Importance of plasma endothelin-1 level in the evaluation of heart failure severity in infants with ventricular septal defect

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Abstract

Background: Haemodynamic disturbances due to ventricular septal defect (VSD) can lead to heart failure (HF) and cause neurohormonal activation. Endothelin-1 (ET-1) clearance takes place mainly in the pulmonary circulation. We hypothesized that increased pulmonary blood flow in children with VSD could influence ET-1 level and reflect haemodynamic disturbances in these patients.

Aim: To analyse usefulness of plasma ET-1 level in the evaluation of HF severity in infants with VSD without pulmonary hypertension.

Methods: The study group included 34 children (aged 38–338 days, mean 130 ± 81 days) with VSD. Evaluation included history, physical examination, ET-1 level measurement, standard 12-lead electrocardiogram, chest X-ray, and transthoracic echocardiography in all children. The control group consisted of 31 healthy children.

Results: Mean plasma ET-1 level was significantly ($p < 0.01$) higher in the study group compared to the control group. We found no significant difference ($p > 0.05$) in mean plasma ET-1 level between children with or without HF. No significant correlation was found between plasma ET-1 level and the severity of HF.

Conclusions: Infants with VSD show higher ET-1 level compared to healthy children. Plasma ET-1 level does not reflect the severity of HF in infants with VSD.

Key words: endothelin-1, heart failure, ventricular septal defect

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INTRODUCTION

Ventricular septal defect (VSD) is one the most common congenital heart defects in children. Its clinical course may vary from asymptomatic in case of a small defect to rapid development of heart failure (HF) during the first weeks of life in children with large defects. A detailed analysis of the pathophysiology of HF serves as a basis for search for prognostic markers that would correlate with the clinical status and haemodynamic parameters.

Endothelin-1 (ET-1) is the most potent known vasoconstricting factor [1]. It is synthesized in the vascular endothelium and degraded mainly in pulmonary vessels. An important but unresolved issue is whether increased pulmonary flow in patients with VSD might lead to changes in ET-1 level. In

the available literature on neurohormonal activation in HF in children with congenital heart disease, there are no such studies in infants with VSD uncomplicated by pulmonary hypertension, and few studies were reported for children in various age groups and with different cardiovascular anomalies, often complicated by pulmonary hypertension [2, 3]. Congenital heart defects are a very heterogeneous group with varying haemodynamic abnormalities. Their anatomy, complications, patient age, and coexisting chromosomal aberrations and concomitant diseases undoubtedly affect neurohormone levels, and thus also their potential clinical utility. In the present study, we attempted to analyse the role of ET-1 in the evaluation of HF in a homogeneous patient group.

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METHODS

We studied 34 consecutive patients with VSD (age range 38–338 days, mean age 130 ± 81 days). The exclusion criteria were: coexistence of other congenital heart defects (persistent foramen ovale was not an exclusion criterion), suspicion of a genetic syndrome, coexisting pulmonary hypertension, and diseases of other organs and systems. The control group consisted of 31 healthy children. The two groups did not differ significantly in regard to gender distribution, age, body weight, and body surface area (BSA).

Diagnostic procedures included detailed history and physical examination, laboratory examinations including measurement of plasma ET-1 level, 12-lead electrocardiogram to evaluate ventricular hypertrophy and atrial enlargement [4], chest X-ray to evaluate pulmonary flow and the size of cardiac silhouette (abnormal cardiothoracic index > 0.6), and transthoracic echo to measure the left atrial diameter to aortic diameter ratio (LA/Ao), left ventricular internal dimension at end diastole indexed for BSA (LVIDd/BSA), and Doppler pulmonary to systemic flow ratio (Qp/Qs). ET-1 level was measured using an immunoenzymatic assay (Biomedica Group, Vienna, Austria, catalogue number BI-20052).

The diagnosis of HF was based on the modified New York Heart Association (NYHA) classification [5]. Children without any symptoms were evaluated as class I; class II referred to children with mild tachypnoea and diaphoresis during feeding, with no abnormalities of physical development; class III referred to significantly tachypnoic children with diaphoresis during feeding with prolonged feeding time and physical growth retardation and class IV referred to children with symptoms (such as grunting, tachypnoea, dyspnoea, diaphoresis) at rest.

For qualitative data, frequencies and their standard errors were calculated based on binomial distribution. For quantitative data, we determined ranges and median values, and mean, standard error of the mean, and standard deviation were calculated based on normal distribution. Results were presented as histograms and cumulative distributions using intervals adjusted to the range of variability of the given variable. ET-1 level intervals were selected to provide 100% specificity for the diagnosis of HF compared to the control group. The nonparametric Whitney-Mann-Wilcoxon test was used to verify normal distribution of the data. We calculated correlation coefficients for correlations between ET-1 level and other variables. $P < 0.05$ was considered statistically significant.

The study was approved by the ethics committee at the Medical University of Warsaw.

RESULTS

A perimembraneous VSD was diagnosed in 32 (94%) patients, and a muscular VSD in the remaining 2 (6%) patients. No clinical, electrocardiographic, radiological, or echocardiographic evidence of pulmonary hypertension were found in

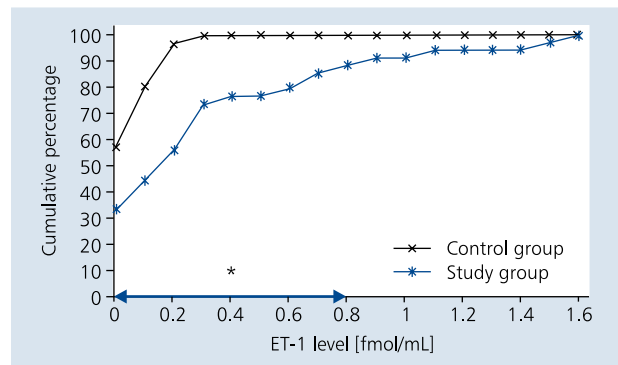


Figure 1. Cumulative percentages of patients within different endothelin-1 (ET-1) level intervals in the study and control groups. ET-1 level range with significant differences is indicated with an arrow; $p < 0.01$ for the range of 0.1–0.6 fmol/mL; $*p < 0.05$

any patients. Among 34 infants with VSD, HF was diagnosed in 18 (53%), including modified NYHA class II HF in 8 children, class II/III HF in 7 children, and class III HF in 3 children (mean modified NYHA class in the study group 1.72 ± 0.74).

In the study group, ET-1 level ranged from 0 to 1.6 (mean 0.36 ± 0.43 fmol/mL and was significantly higher ($p < 0.01$) compared to the control group (0–0.35 fmol/mL, mean 0.09 ± 0.11 fmol/mL).

Figure 1 shows cumulative percentages of patients within different ET-1 level intervals in the study and control groups.

We found no significant correlation between ET-1 level and the severity of HF ($r = 0.04$, $p > 0.05$).

Mean ET-1 level did not differ significantly between children with and without HF ($p > 0.05$, Fig. 2).

Based on these results (Fig. 1), a cut-off value of ET-1 level was set at 0.4 fmol/mL. In all children in the control group, ET-1 level was < 0.4 fmol/mL, and the study group was divided into two subgroups: subgroup I included 25 (73%) patients with ET-1 level < 0.4 fmol/mL, and subgroup II included 9 (27%) patients with ET-1 levels ≥ 0.4 fmol/mL. We compared these two subgroups in regard to clinical parameters considered evidence of HF in infants (Tables 1, 2).

No significant differences ($p > 0.05$) were found between patients with ET-1 level < 0.4 and ≥ 0.4 fmol/mL in regard to the rates of the following clinical parameters: feeding through a gastric tube, meal duration > 40 min, increased sweating, abnormal breathing pattern, heart rate > 130 bpm, hepatomegaly, and abnormal peripheral perfusion (Table 1).

When we analysed further clinical parameters (Table 2), we found that the mean body weight percentile among children with ET-1 level ≥ 0.4 fmol/mL was significantly lower ($p < 0.05$) compared to children with lower ET-1 level (6.56 ± 3.66 vs. 30.08 ± 6.52). No significant differences ($p > 0.05$) were found in regard to monthly weight gain, respiratory rate, and heart rate.

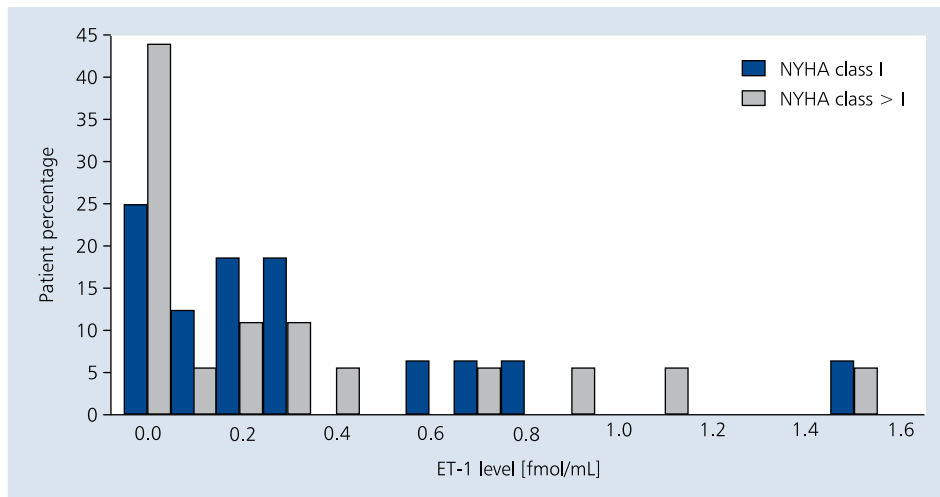


Figure 2. Proportion of patients with or without heart failure within different endothelin-1 (ET-1) level intervals; NYHA — modified New York Heart Association

Table 1. Rates of clinical parameters in children in subgroups I and II

Clinical parameter	ET-1 < 0.4 fmol/mL		ET-1 ≥ 0.4 fmol/mL		P
	N	Per cent ± SE	N	Per cent ± SE	
Feeding through a gastric tube	25	4.0 ± 3.9	9	0.0 ± 0.0	> 0.05
Meal duration > 40 min	25	16.0 ± 7.3	9	11.1 ± 10.5	> 0.05
Diaphoresis	25	20.0 ± 8.0	9	44.4 ± 16.5	> 0.05
Abnormal breathing pattern	25	68.0 ± 9.3	9	5.5 ± 16.5	> 0.05
Heart rate > 130 bpm	25	4.0 ± 3.9	9	0.0 ± 0.0	> 0.05
Liver enlargement > 2 cm	25	28.0 ± 8.9	9	44.4 ± 16.5	> 0.05
Abnormal peripheral perfusion	25	12.0 ± 6.5	9	0.0 ± 0.0	> 0.05

ET-1 — endothelin-1; N — number of patients; SE — standard error

Table 2. Clinical parameters in children with endothelin-1 (ET-1) level < 0.4 or ≥ 0.4 fmol/mL

Clinical parameter	ET-1 < 0.4 fmol/mL		ET-1 ≥ 0.4 fmol/mL		P
	N	Mean ± SE	N	Mean ± SE	
Body weight [percentile]	25	30.08 ± 6.52	9	6.56 ± 3.66	0.043
Body weight gain [g/month]	25	629.00 ± 44.00	9	611.00 ± 52.00	> 0.05
Respiratory rate [/min]	25	50.00 ± 3.40	9	49.00 ± 6.00	> 0.05
Heart rate [bpm]	25	127.00 ± 3.00	9	129.00 ± 5.00	> 0.05

N — number of patients; SE — standard error

We found no significant differences ($p > 0.05$) in the severity of HF between the two subgroups (mean modified NYHA class 1.68 ± 0.14 vs. 1.83 ± 0.28).

The electrocardiographic criteria of chamber enlargement/hypertrophy were met in 20 (59%) children, including left ventricular hypertrophy in 17 (50%) children and left atrial enlargement in 8 (23%) children (the criteria for both left ventricular hypertrophy and left atrial enlargement were met in 5 infants).

Increased pulmonary vessel markings indicating increased pulmonary flow were seen on chest X-ray in 20 (59%) infants, and the cardiothoracic index was increased in 4 children.

The two subgroups also did not differ significantly ($p > 0.05$) in mean Qp/Qs (2.43 ± 0.2 vs. 2.58 ± 0.44), LA/Ao (1.52 ± 0.06 vs. 1.71 ± 0.11), and LVIDd/BSA (85.5 ± 4.5 vs. 89.9 ± 5.7 mm/m²). No significant correlations ($p > 0.05$) were found between ET-1 level and Qp/Qs, LA/Ao, LVIDd/BSA (correlation coefficients r were 0.01, 0.27, 0.05, respectively).

DISCUSSION

Neurohormonal activation is seen in adults and children with HF resulting from congenital heart disease [6, 7]. A search continues for parameters that would be related to the severity of HF and thus prove useful when making diagnostic and therapeutic decisions [8, 9]. In studies on ET-1 in children with congenital heart disease, its role was mostly evaluated in the context of coexisting pulmonary hypertension [10, 11]. In the present study, we excluded children with pulmonary vascular disease and analysed ET-1 level in a homogeneous group of infants with VSD uncomplicated by pulmonary hypertension.

In infants with VSD, the mean ET-1 level was significantly higher compared to the control group. The mean ET-1 level in our study was comparable to results reported by other authors [12, 13] but it did not differ significantly between children with or without HF. We also did not find ET-1 level to reflect the severity of HF, as it did not correlate with the latter. No significant differences were also found in the severity of HF when we compared subgroups with different ET-1 levels. This may be related to the fact that HF symptoms were relatively mild in most children in the study group (modified NYHA class ranged from I to III, mean 1.72 ± 0.74). Also in adult patients, ET-1 level did not differentiate between patients with mild HF (NYHA class I–II) and healthy subjects [14, 15].

Our results are in agreement with the results reported by Shah et al. [16] who found no correlation between ET-1 level and HF severity in children with single ventricle. Bieganowska et al. [17] also did not find a significant difference in the mean ET-1 level in children with congenital heart disease with a left-to-right shunt, when then compared children with or without HF. In that study, a significant difference in ET-1 level was found between children without HF and those with HF and coexisting pulmonary hypertension. This was also confirmed in other studies in patients with pulmonary hypertension, suggesting a predominant role of increased pulmonary artery pressure in stimulation of ET-1 overproduction. In patients with pulmonary hypertension, increased ET-1 level is related to its increased synthesis and decreased pulmonary clearance [18, 19].

In our study, increasing severity of clinical symptoms was not associated with an increase in ET-1 level, as we found no correlation between ET-1 level and clinical parameters. We also did not find significant differences in most clinical parameters between subgroups I and II. In subgroup II, only body weight percentile did differ significantly ($p < 0.05$) compared to subgroup I. A negative effect of malnutrition on endothelial function has been shown in both experimental and clinical studies [20, 21]. It cannot be thus excluded that ET-1 metabolism in underweight children is affected by factors secondary to disturbances in physical growth.

In our study, no correlation was found between ET-1 level and Qp/Qs, and no significant differences in Qp/Qs

were seen between subgroups of children with ET-1 level < 0.4 or ≥ 0.4 fmol/mL. Divergent data on the relation between ET-1 level and this echocardiographic parameter were published in the literature. In most studies, similarly to our study, no relation between ET-1 level and Qp/Qs was found [12, 22]. There are also reports in the literature indicating such a relation [17, 23] but these studies included children with a left-to-right shunt complicated by pulmonary hypertension, and patients with Down syndrome. Regarding the study published by Kageyama et al. [24], inclusion of children with chromosomal aberration might have had a significant effect on the results of such studies, as these authors showed that among children with congenital heart disease scheduled for cardiac surgery, mean ET-1 level in children with trisomy 21 was significantly higher compared to children without such a genetic defect.

In some recent studies on the endothelin system, C-terminal pro-endothelin-1 was measured [25]. It seems that physicochemical properties of this propeptide, including longer half-time, may increase its diagnostic utility, but no studies on this issue have been reported in children.

Limitations of the study

Due to small study sample and a significant proportion of patients without HF or with only mild HF, this issue deserves further studies.

CONCLUSIONS

1. Plasma ET-1 level in infants with VSD is increased compared to healthy infants.
2. Plasma ET-1 level does not reflect the severity of HF in infants with VSD uncomplicated by pulmonary hypertension.

Conflict of interest: none declared

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Przydatność endoteliny-1 do oceny zaawansowania niewydolności serca u niemowląt z ubytkiem przegrody międzykomorowej: doniesienie wstępne

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Streszczenie

Wstęp: Zaburzenia hemodynamiczne u pacjentów z ubytkiem przegrody międzykomorowej (VSD) skutkują rozwojem niewydolności serca (HF), która prowadzi do aktywacji układów neurohormonalnych. Endotelina-1 (ET-1) jest metabolizowana w krążeniu płucnym, dlatego wpływ zwiększonego na skutek VSD przepływu krwi przez łożysko płucne stanowi interesujące zagadnienie.

Cel: Celem pracy było zbadanie przydatności ET-1 w ocenie zaawansowania HF u niemowląt z VSD niepowikłanym nadciśnieniem płucnym.

Metody: Grupę badaną stanowiło 34 niemowląt w wieku 38–338 dni, śr. 130 ± 81 dni) z VSD. U wszystkich wykonano badania podmiotowe i przedmiotowe, EKG, przeglądowe zdjęcie klatki piersiowej, przezklatkowe badanie echokardiograficzne i oznaczono stężenia ET-1. Grupę kontrolną stanowiło 31 zdrowych dzieci.

Wyniki: Średnie wartości ET-1 w grupie badanej były statystycznie istotnie wyższe ($p < 0,01$) w porównaniu z wartościami uzyskanymi u dzieci z grupy kontrolnej. Średnie wartości stężeń ET-1 u dzieci z HF nie różniły się statystycznie istotnie ($p > 0,05$) w porównaniu z wartościami uzyskanymi u dzieci bez HF. Nie stwierdzono znamienych statystycznie korelacji między stężeniami ET-1 a stopniem zaawansowania HF.

Wnioski: Niemowlęta z VSD charakteryzują się wyższymi stężeniami ET-1 w porównaniu z dziećmi zdrowymi. Ocena stężenia ET-1 nie odzwierciedla stadium zaawansowania HF u niemowląt z VSD.

Słowa kluczowe: endotelina-1, niewydolność serca, ubytek przegrody międzykomorowej

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