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Original article

Arterial stiffness and arterial function in adult cyanotic patients with congenital heart disease

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ABSTRACT

Background: Mortality in cyanotic patients with congenital heart diseases (CHD) is high, mainly due to cardiovascular complications. It is known that endothelial dysfunction, increased arterial stiffness, and impaired vascular function have negative influence on cardiovascular prognosis. The aim of the study was to assess parameters of arterial stiffness and vascular dysfunction in cyanotic patients with CHD as well as their potential relation to impaired blood oxygen saturation and polycythemia parameters typical for cyanosis.

Methods: A total of 36 CHD cyanotic patients (17 males) (42.3 ± 16.3 years) and 35 healthy individuals (16 males) (39.6 ± 10.4 years) were enrolled. Assessed parameters were intima media thickness and flow-mediated dilatation (FMD). Assessed parameters using applanation tonometry methods were aortic systolic pressure, aortic pulse pressure (AoPP), augmentation pressure (AP), augmentation index (AI), pulse pressure amplification (PPampl), and pulse wave velocity (PWV).

Results: AoPP (37.3 ± 11.1 mmHg vs. 29 ± 6.5 mmHg; $p = 0.002$), AP (10.1 ± 7.3 mmHg vs. 1.1 ± 3.9 mmHg; $p = 0.00001$), AI (24.7 ± 13.5% vs. 3.0 ± 13.6%; $p = 0.00001$), and PWV (7.4 ± 2.1 m/s vs. 6.3 ± 0.7 m/s; $p = 0.003$) were higher, and PPampl was lower (135.3 ± 16.1% vs. 160.4 ± 12.8%; $p = 0.00001$) in the studied group compared to controls and proved the presence of the increased stiffness of arteries. Impairment of FMD was observed (9.0 ± 5.6 vs. 10.9 ± 4.7; $p = 0.04$). No significant correlations were found between analyzed arterial parameters and biochemical ones characterizing cyanotic patients depicting rheological properties of blood.

Conclusions: Cyanotic patients with CHD are characterized by increased arterial stiffness estimated with pulse wave analysis parameters and by deteriorated arterial function expressed with worse vasodilatative response in comparison with healthy population. It may confirm relevance of those mechanisms in development of increased rate of cardiovascular events in this population. Association between oxygen saturation or polycythemia and arterial stiffening or vascular dysfunction was not found in these patients.

Introduction

Observation of patients with congenital heart diseases (CHD) has shown that cyanotic subpopulation is overburdened with the highest mortality, mainly due to increased number of cardiovascular complications [1,2]; 14% suffer from stroke [1,3,4], and around one-third with Eisenmenger syndrome die because of massive arterial pulmonary thrombosis [5,6], some due to rupture of one of the pulmonary arteries [1,7,8]. Although not well understood, the background of these dramatic complications seems to be vascular changes accompanying cyanosis. Secondary erythrocytosis as a result of chronic hypoxemia leads to increased blood viscosity and as a consequence changes in function of vascular endothelium which is a complex regulatory structure that

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mediates vascular tone, hemostasis, and angiogenesis [9,10]. The majority of [10–14], although not all [15], studies in the literature to date, show that endothelium function in cyanotic CHD patients assessed by flow-mediated distensibility is impaired. It is postulated to be related to disturbed production of endothelial-derived nitric oxide, an important regulator of smooth muscle cell relaxation, and has a pathognomonic relation with increased arterial wall stiffness.

Direct biochemical assessment of NO production is methodologically difficult in clinical conditions due to its short life span and thus overburdened with significant bias. One of the indirect, biophysical methods of endothelium dysfunction with proven significance and correlation in other conditions than CHD is pulse wave analysis with applanation tonometry. In this noninvasive method several parameters of arterial wall stiffness are derived from peripheral radial, femoral, and carotid pulse wave. Key parameters from this method related to arterial stiffness – a further result of endothelial dysfunction – are: augmentation pressure (AP), augmentation index (AI), pulse pressure amplification (PPampl), as well as pulse wave velocity (PWV) [16].

Population studies have shown that increased values of aforementioned parameters of pulse wave analysis as well as PWV have proven to correlate positively with the cardiovascular risk [17–19]. Such correlation was also fund for intima media thickness (IMT) – another indicator of detrimental changes in structure of arterial wall [20]. Based on that ground lately also for patients with CHD, studies on vascular changes started to appear in the literature. Unfortunately available papers concerning cyanotic CHD present data from small groups of patients [5,11–14,21–26], often from children [27–30].

To the best of our knowledge, there are no available studies analyzing phenomenon of vascular stiffness with applanation tonometry method parameters in adult patients with cyanotic congenital heart diseases.

The aim of our study was to assess parameters of central and peripheral arterial stiffness and vascular dysfunction in cyanotic patients with CHD as well as their potential relation to impaired blood oxygen saturation and red blood cell polycythemia parameters typical for cyanosis.

Table 1
Baseline characteristics of the study population and the control group.

	Cyanotic patients ($n=36$)	Controls ($n=35$)	Cyanotic patients vs. controls (p-value)
Male: female	17:19	16:19	–
Age (years)	42.33 ± 16.27 (41; 20–72)	39.6 ± 10.4 (38; 19–64)	0.074
BMI (kg/m^2)	21.82 ± 4.55 (21.2; 14.36–34)	22.71 ± 3.15 (22.5; 15–32)	0.069
Height (cm)	167.83 ± 8.71 (169; 150–184)	172.09 ± 10.63 (171; 151–185)	0.069
Weight (kg)	61.78 ± 14.85 (60.7; 39.2–98)	67.71 ± 13.33 (62.1; 42.1–99.1)	0.081
Oxygen blood saturation (%)	82.93 ± 8.92 (86.25; 62–92)	98.2 ± 1.1 (98; 97–100)	0.00001
Hematocrit (%)	54.7 ± 10 (51; 39–80)	42.3 ± 2.1 (43; 42–46)	0.00001
Hemoglobin (mmol/l)	11.16 ± 1.62 (10.6; 8.8–15.4)	8.35 ± 1.2 (8.1; 7.6–9.2)	0.00001
RBC (10^{12}/l)	5.97 ± 1.09 (5.56; 4.47–8.37)	4.81 ± 0.01 (4.7; 4.6–4.9)	0.01
HR (beats/min)	73.06 ± 12.5 (71.5; 53–105)	66.6 ± 10.87 (64; 53–78)	0.023
SBP (mmHg)	121.17 ± 17.33 (118; 85–166)	118.5 ±17.3 (114; 83–149)	0.654
DBP (mmHg)	71.92 ± 11.07 (71; 50–104)	69.4 ± 5.3 (68; 50–97)	0.272
Total cholesterol (mmol/l)	4.49 ± 1.21 (4.3; 2.6–7.64)	5.4 ± 0.9 (5.0; 4.1–5.85)	0.00001
LDL cholesterol (mmol/l)	2.75 ± 1.06 (2.55; 1.4–6)	3.0 ± 0.4 (2.67; 1.5–3.8)	0.195
HDL cholesterol (mmol/l)	1.28 ± 0.3 (1.2; 0.75–1.98)	1.3 ± 0.2 (1.2; 0.78–1.87)	0.99
Glucose (mmol/l)	5.38 ± 0.4 (4.94; 3.1–6.2)	5.2 ± 0.2 (4.6; 2.9–5.6)	0.16
Creatinine (umol/l)	82.77 ± 21.94 (80.3; 49–134.3)	72.9 ± 11.2 (82.4; 47.6–129.4)	0.41
Usage of drugs			
Beta-adrenolytics	13	0	–
ACE-I	4	0	–
Diuretics	6	0	–
Warfarin	9	0	–

BMI, body mass index; HR, heart rate; RBC, red blood cell count; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE-I, angiotensin-enzyme converting enzyme inhibitors.

Materials and methods

Studied group and control group

A total of 36 cyanotic patients (17 males) aged 20–72 (42.3 ± 16.3 years) with arterial blood oxygen saturation less than 92% were examined in the study, cared for by our adult CHD outpatient clinic. The control group consisted of 35 healthy individuals (16 males), aged 23–52 (39.6 ± 10.4 years), as volunteers for the study. All examinations for both – patients and healthy volunteers were done during one visit for each patient. Examinations took place in clinical hospital setting from June 2014 until June 2015. Baseline characteristics of the studied population and control group are presented in Table 1. Types of CHD recognized as a reason for central cyanosis are presented in Table 2. Patients with Down syndrome were excluded from the study. No patients had undergone phlebotomy for at least 3 months before the study. In order to avoid other factors which might influence the values of vascular parameters the following exclusion criteria were taken into consideration: acute and chronic inflammatory diseases (in the preceding 3 months), concomitant malignancies, diabetes mellitus, smoking cigarettes. All examinations were done in the morning hours of the day, before morning dose of pharmacotherapy.

Informed consent was obtained from each patient, and our study protocol, as approved a priori by our institution's human research ethic committee (decision 325/14), conformed to the ethical guidelines set forth by the 1975 Declaration of Helsinki.

Central aortic function assessment

Central parameters of the aortic pulse wave and arterial wall stiffness of the large conduit arteries were measured using pulse

Table 2
Clinical characteristics of cyanotic patients with congenital heart diseases.

Eisenmenger syndrome, n(%)	10 (27.8)
VSD	7
ASD	2
PDA	1
Univentricular heart, n(%)	13 (36.1)
Unoperated	5
Pulmonary banding	3
Fontan operation	5
Pulmonary atresia, VSD, MAPCA'S, n(%)	3 (8.3)
Tetralogy of Fallot, n(%)	5 (13.9)
Ebstein anomaly with ASD, n(%)	4 (11.1)
CCTGA, VSD, n(%)	1 (2.8)

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, persistent ductus arteriosus; MAPCA's, major aortopulmonary collaterals; CCTGA, corrected transposition of the great arteries.

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