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Increased aortic blood pressure augmentation in patients with congenital heart defects — A cross-sectional study in 1125 patients and 322 controls

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ABSTRACT

Objective: Multiple studies have demonstrated the predictive value of arterial stiffness parameters like augmentation index (AIx) for cardiovascular events, the onset of hypertension, and the progression of heart failure. There is evidence that arterial stiffness is increased in some diagnostic subgroups of patients with congenital heart defects (CHD). This study aims to investigate AIx in a large cross-sectional cohort of patients with CHD.
Patients and methods: We prospectively examined 1125 consecutive patients with various congenital heart defects (27.3 ± 12.1 years, 464 female) referred for routine cardiopulmonary exercise testing (CPET) in our institution, and 322 healthy volunteers (29.4 ± 18.4 years, 165 female). AIx was estimated in supine position using the oscillometric Vicorder device (SMT medical, Würzburg, Germany). Afterward patients performed a CPET.
Results: In multivariable regression, presence of a CHD emerged as independent risk factor for higher AIx ($p < .001$). AIx was also higher in older ($p < .001$), smaller ($p < .001$) and heavier ($p < .001$) patients and in females ($p = .008$).
Patients with aortic stenosis ($p < .001$), Tetralogy of Fallot ($p < .001$), transposition of the great arteries after atrial switch ($p < .001$) or Rastelli procedure ($p = .013$) and after Fontan procedure ($p = .002$) had higher AIx. Higher peak oxygen uptake ($p < .001$) and an ACE-inhibitor ($p = .088$) were associated with a lower AIx.
Conclusions: AIx is increased in patients with CHD. Several diagnostic subgroups are at risk. A better understanding of pathophysiologic mechanisms, genetic predisposition, the role of surgical aortic scars or implanted conduits/patches and medication is needed to define the value of AIx for further cardiovascular risk assessment in this cohort.

1. Introduction

Life expectancy in patients with congenital heart disease (CHD) is constantly increasing throughout the last decades. This growing cohort has to deal now with issues associated with aging like the prevention of acquired cardiovascular disease [1,2].

In general, quantifying the risk for cardiovascular events, traditional risk factors like age, gender, smoking, activity status and blood pressure were used. Recent recommendations [3,4] for risk stratification advocate measuring the arterial stiffness of the cardiovascular system that is characterized either by an increase in total peripheral resistance and/or by a decrease in arterial compliance. A consequence of arterial stiffening is an increased velocity of the aortic pulse wave and earlier reflection of the wave back toward the heart. The latter results in the augmentation of systolic blood pressure (Fig. 1). Augmentation index (AIx) is defined as the augmented pressure as percentage of the pulse pressure. Higher AIx is associated with higher cardiovascular risk and left ventricular dysfunction [3–7]. This holds true not only in primary prevention, where the increased arterial stiffness is considered as an early stage of atherosclerosis. It holds true also in patients with heart failure to predict disease progression and outcome.

In several patient groups with CHD, an enhanced arterial stiffness or impaired distensibility of the aorta has yet been reported [8–17]. Unfortunately, the results are hard to compare, since study groups were small and different method and devices for measurement were used.

Thus, this study aimed to compare AIx of patients with CHD with healthy subjects and to find independent risk factors for AIx in a large cohort of various CHD.

2. Patients and methods

2.1. Study subjects

From June 2011 to August 2013 we prospectively examined 1125 consecutive patients with various CHD (27.3 ± 12.1 years, 464 female)

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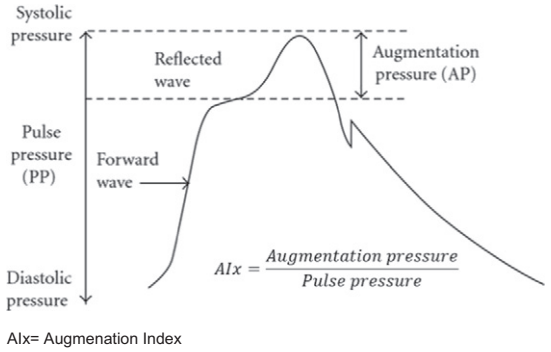

Fig. 1. Aortic pulse pressure waveform. AIx = augmentation index.

referred for routine cardiopulmonary exercise testing (CPET) in our institution, and 322 healthy volunteers (29.4 ± 18.4 years, 165 female) for their arterial stiffness. Afterward patients performed a CPET. Our reference population includes subjects from our outpatient department of the Institute of Preventive Pediatrics, students from the faculty of sports and health sciences (Technische Universität München), employees from two companies, accompanying persons, friends and family members of patients at the German Heart Center and the Institute of Preventive Pediatrics. Patients' characteristics are displayed in detail in Table 1.

The study was prospectively designed and approved by the local ethical board (reference number 5126/11). Patients gave written informed consent.

2.2. Measurement of augmentation index (AIx)

Measurements were performed in supine position after a 5 minute rest using the Vicorder (SMT medical, Würzburg, Germany) device according to the actual guidelines and as previously described [18]. According to the upper arm circumference, a blood pressure cuff was placed around the right upper arm and a normal blood pressure measurement was performed. Afterwards the cuff was inflated to diastolic blood pressure and waveforms were recorded over at least 10 consecutive heartbeats, free from arrhythmia, to pick up the pulse wave. AIx was estimated with the inbuilt and evaluated algorithm [19].

2.3. Cardiopulmonary exercise test (CPET)

All patients underwent a symptom limited cardiopulmonary exercise test on a bicycle ergometer in an upright position according to international guidelines and as previously described [20,21].

The exercise test featured a breath-by-breath gas exchange analysis using a metabolic chart (Encore, SensorMedics, CareFusion, San Diego, California). Peak oxygen uptake ($\dot{V}O_2$) was defined as the highest mean uptake of any 30-second time interval during exercise. Reference values for age, body mass, body height, and gender, expressed in "% predicted" were calculated like previously described [22].

2.4. Data analyses

Gauss' normal distribution of the primary outcome variable "augmentation index" was approved by a Shapiro–Wilk-test. All descriptive data were expressed as mean ± standard deviation.

Univariate associations of AIx in patients with CHD with demographic parameter, peak oxygen uptake and blood pressure were assessed using Pearson correlation or Student's t-test if appropriate.

Primary objective was to evaluate whether patients with CHD had elevated AIx in comparison to healthy peers. Therefore, a multivariable stepwise regression model was calculated using all anthropometric variables, blood pressure, heart rate during measurement and medication (ACE-inhibitor and beta-blocker), together with the grouping variable (CHD or healthy control).

Secondary objective was to determine solely in the cohort of patients with CHD, which diagnostic subgroups were at risk, and the impact of CPET variables and medication on AIx. Therefore, 70 patients were excluded from exercise related analyses. They terminated exercise before reaching their cardiovascular limit, defined as respiratory exchange ratio at peak exercise <1.05 or heart rate at peak exercise <85% of predicted [23]. In those final 1055 patients with CHD, multivariable stepwise regression was performed to find predictors of AIx using all anthropometric variables, blood pressure, heart rate during measurement, medication (ACE inhibitor and beta-adrenergic blockade), peak oxygen uptake, saturation at rest, open heart surgery (yes/no) and all diagnostic subgroups.

p-Values < 0.050 in a two-sided analysis were considered significant. For the multivariable stepwise regression model the p-values in the F-test for inclusion was set to $p < .050$ and exclusion $p > .100$. All analyses were performed using SPSS 20.0 software (IBM Inc., Armonk, New York, USA).

3. Results

An overview regarding blood pressure and AIx is provided in Table 2.

In stepwise multivariate regression, higher age ($p < .001$), smaller height ($p < .001$), lower heart rate ($p < .001$), overweight ($p < .001$), female ($p = .008$) and a presence of a congenital heart disease ($p < .001$) emerged as independent risk factors for higher AIx (Table 3).

Table 1
Demographic variables and medication of the 1125 patient with various CHD and 322 controls.

Diagnosis	n	sex ♀/♂	Age mean ± SD	Body mass index	Beta-blocker	ACE-inhibitor
Native/palliated cyanotic CHD	54	27/27	35.3 ± 14.8	21.4 ± 4.1	37	9
Fontan circulation	87	37/50	23.9 ± 10.5	21.9 ± 5.0	34	10
TGA (Rastelli & ccTGA)	59	18/41	27.3 ± 12.2	22.7 ± 4.0	18	11
TGA (Senning & Mustard)	89	34/55	31.5 ± 6.2	25.4 ± 4.0	22	7
TGA (arterial switch)	65	17/48	16.8 ± 4.7	21.5 ± 3.2	3	2
Tetralogy of Fallot	217	110/107	27.3 ± 11.0	22.6 ± 4.2	25	6
Ebstein anomaly	66	39/27	35.4 ± 15.3	23.5 ± 4.1	19	4
PS/PR	51	23/28	29.6 ± 10.9	22.9 ± 4.2	2	0
Coarctation of the aorta	127	42/85	25.5 ± 10.4	22.6 ± 4.1	23	29
Aortic stenosis	189	48/141	25.9 ± 11.5	23.6 ± 4.3	22	15
Isolated shunt (ASD, VSD, AVSD)	121	69/52	27.4 ± 14.6	22.6 ± 4.4	9	5
All patients with CHD	1125	464/661	27.3 ± 12.1	22.9 ± 4.3	194	98
Healthy controls	322	165/157	29.4 ± 18.4	23.0 ± 4.4	8	20
p-Values (CHD vs. controls)	–	***.001***	***.003***	n.s.	***<.001***	n.s.

TGA: transposition of the great arteries, ccTGA: congenital corrected transposition of the great arteries, PS: pulmonary stenosis, PR: pulmonary regurge, ASD: atrial septal defect, VSD: ventricular septal defect, AVSD: atrioventricular septal defect, ACE: angiotensin-converting-enzyme, and n.s.: not significant.