International Journal of Cardiology 159 (2012) 211–216

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Neurohormonal activity and vascular properties late after aortic coarctation repair ☆

Antonia C. Moutafi [a], Themis Alissafi [a], Aikaterini Chamakou [a], Stavros Chryssanthopoulos [a], Vassilios Thanopoulos [b], Christos Dellos [c], Georgina Xanthou [a], Dimitrios Tousoulis [d], Christodoulos Stefanadis [d], Michael A. Gatzoulis [e], Constantinos H. Davos [a,*]

[a] Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, Athens, Greece
[b] Department of Paediatric Cardiology, Agia Sophia General Children's Hospital, Athens, Greece
[c] Department of Congenital Heart Disease, Tzanio Hospital, Piraeus, Greece
[d] 1st Cardiology Department, University of Athens, Hippokratio Hospital, Athens, Greece
[e] Royal Brompton Adult Congenital Heart Programme, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College School of Medicine, London, UK

ARTICLE INFO

Article history:
Received 5 August 2010
Received in revised form 21 February 2011
Accepted 25 February 2011
Available online 22 March 2011

Keywords:
Coarctation of aorta
Neurohormones
Inflammation
Vascular

ABSTRACT

Background: Coarctation of aorta (CoA) patients present cardiovascular complications late after repair the causes of which are not fully understood. Our study investigates the neurohormonal and immune activation and the elastic properties of the aorta and peripheral vessels in adult patients with coarctation of aorta (CoA), late after repair.

Methods: Nineteen adult patients with repaired CoA and 29 matched healthy controls underwent aortic distensibility, stiffness index, a study of the elastic properties of peripheral vessels proximal to the coarctation site and measurement of plasma cytokine and neurohormone levels.

Results: Distensibility index was reduced ($p=0.02$) and stiffness index was increased ($p=0.005$) in CoA patients compared to control. Augmentation index ($p=0.0007$) and augmented pressure ($p=0.001$) were higher in CoA patients and Forearm Blood Flow (FBF) index was reduced ($p=0.009$). Plasma levels of sICAM-1 ($p=0.01$), sVCAM-1 ($p=0.05$), E-selectin ($p=0.01$), sFas-ligand ($p=0.02$) and IL-10 ($p=0.01$) were also elevated in CoA patients vs control. TNF-a, IL-6, Endothelin-1 and NT-pro-BNP levels were not.

Conclusions: Adults with repaired CoA seem to develop a late inflammatory reaction, which reflects a functional problem in all vessels, regardless of the initial lesion. This may explain the late complications of the disease despite early repair and improved surgical procedures.

1. Introduction

Adults with congenital heart disease (CHD) show a broad spectrum of diagnoses and their number is increasing due to early management and improved surgical procedures. However, their follow-up and medical treatment is residual and late complications are of great importance [1]. Most studies imply that apart from simple anomalies, adult CHD patients long-term after repair show residual hemodynamic abnormalities, causing volume or pressure overload that may be significant determinants of future morbidity and mortality [2,3]. Moreover, patients with CHD show a pattern of neurohormonal and immune activation and an autonomic nervous system imbalance which is apparent in chronic heart failure (CHF) patients [4–7]. It is well known that the degree of neurohormonal and immune activation in CHF relates to heart functional capacity and is a predictor of morbidity and mortality [8]. The diversity of diagnoses and the different heart anatomy of the CHD population included in these studies raise the question whether this pattern applies to every discrete cardiac anatomy and pathophysiology. Patients with coarctation of aorta (CoA) are poorly represented in these studies because CoA is relatively uncommon (5–8% of all CHD) [9]. It is well documented that life expectancy is not normal even after repair. These patients present cardiovascular complications late after repair with most important being hypertension, aneurism formation and coronary artery disease [10,11] which may be partly related to vascular dysfunction [12]. The aim of our study was to evaluate adult patients with CoA, late after repair, by investigating neurohormonal and immune activation and evaluating the elastic properties of the aorta and the peripheral vessels proximal to the coarctation site in a single series of patients.

☆ This work was supported by a grant award from the Hellenic Ministry of Development, General Secretariat of Research and Technology '[grant number V.P.; 03ED258]'.

* Corresponding author at: Biomedical Research Foundation, Academy of Athens, 4 Soranou Ephessiou Street, 11527 Athens, Greece. Tel.: +30 2106597392; fax: +30 2106597405.
E-mail address: cdavos@bioacademy.gr (C.H. Davos).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.02.071

2. Materials and methods

2.1. Patients

Nineteen stable patients (9 male) with previous CoA, aged 14 or older, at least 5 years after repair, were included in the study. Exclusion criteria included diabetes mellitus, atrial fibrillation, clinical instability within the preceding 3 months and echocardiographic findings of recoarctation or aortic valve regurgitation. The patients' symptomatic status was defined according to the NYHA functional classification. Twenty-nine age- and sex-matched healthy controls were also studied. All investigations were performed at the Cardiovascular Research Laboratory of the Academy of Athens Biomedical Research Foundation. The Ethics Committee of the Foundation approved the study and informed consent was obtained from each patient (or their parents). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Measurements

All subjects were studied under standardized conditions, in a quiet room, at a comfortable temperature. All were fasted for at least 2 h before testing and were not allowed to smoke or drink alcohol- or caffeine-containing beverages for 24 h before the study. They rested supine for 15 min and then underwent clinical examination, blood pressure measurement, ECG recording, transthoracic echocardiography, strain gage plethysmography and arterial applanation tonometry. All data were digitally stored for subsequent analyses. Finally, peripheral venous blood samples were collected until further analyses.

2.3. Transthoracic echocardiography – aortic distensibility – stiffness index

All echocardiographic examinations were performed by the same investigator using a 5 MHz probe (VIVID 7, GE Medical Systems) and images were analyzed using the Echopac PC SW 3.1.3/software (GE). Left Ventricular (LV) measurements were taken from two-dimentional guided M-mode tracings of the long axis view and LV function was evaluated by measuring LV end-diastolic (LVEDD) and end-systolic (LVESD) dimensions, and percentage fractional shortening (FS%) calculated as (LVEDD–LVESD)/LVEDD. Three beats were averaged for each measurement. Ascending aorta diameters were measured 2–2.5 cm above the aortic valve by two-dimentional-guided M-mode transthoracic echocardiography of the aortic root at the left parasternal long-axis view. Aortic systolic diameter (ASd) was measured at the time of full opening of the aortic valve, and aortic diastolic diameter (Add) was measured at the peak of the QRS complex using a simultaneous ECG recording. Aortic Distensibility and aortic stiffness were calculated using the following equations [13]:

$$\text{Aortic Distensibility}\left(\text{dyn}^{-1}\text{cm}^{2}10^{-6}\right) = 2 \text{ x } (\text{Asd–Add}) / \text{Add x } (\text{SBP}-\text{DBP})$$

$$\text{Stiffness index} = \log[\text{SBP x } (\text{Asd–Add}) / (\text{DBP x Add})]$$

2.4. Arterial applanation tonometry

The Sphygmocor Pulse Wave Analysis System model SCOR-Px was used to evaluate arterial stiffness. Left radial and right carotid pulse waves were recorded with an arterial tonometer sensor array. The tonometer sensor array adjusted itself automatically to obtain the optimal waveform. At that point, 30-second-long analog tracings of the radial and carotid artery waveform were digitized at 200 samples per second and stored. A beat-marking algorithm determined the beginning of systole, peak systole, onset of diastole, and end diastole for all beats in the 30-second measurement period. The augmentation index (AI%) and the augmented pressure (AP) of the central aortic pressure, which are indices of the reflected pulse wave to the aorta, were calculated using a specific software (SphygmoCor 2000, AtCor Medical, Australia). AP was calculated as the difference between the second and first systolic peaks of the waveform and Aix was defined as AP expressed as a percentage of pulse pressure [14,15].

2.5. Endothelial function of resistance arteries

This was assessed by measuring the forearm blood flow (FBF) using a mercury-filled silastic strain-gage plethysmography (EC6 plethysmograph, DE Hokanson, USA). The strain gage was attached to the upper part of the left arm, as previously described [12]. A wrist cuff was inflated to a pressure of 50 mmHg above the SBP to exclude the hand circulation 1 min before and throughout each FBF measurement. Venous return from the forearm was briefly interrupted by inflating a cuff, placed around the upper arm, to well above venous pressure but below DBP. An inflation pressure of 40 mmHg was used for intervals of 10 s, followed by 5 s of deflation, which did not alter the arterial inflow and allowed venous emptying. The FBF output signals were transmitted to a recorder, digitally analyzed (NIVP3 software, Hockanson, USA) and expressed as ml/min/100 ml of forearm tissue volume [16,17].

2.6. ECG

QRS, QT and QTc intervals were measured digitally from 12 lead ECG by using the special device software (Philips Page Writer 200/300pi).

2.7. Neurohormonal and cytokine assessment

Peripheral venous blood samples were collected into tubes containing EDTA and then centrifuged at 2000 rpm for 20 min at 4 °C. Plasma aliquots were stored at −75 °C until further analysis. Sandwich ELISA method special kits (R&D Systems, Minneapolis, USA) were used to determine the levels of the following parameters.

NT-pro-brain natriuretic peptide (NT-pro BNP) and endothelin-1 (ET-1) as indices of neurohormonal activation, proinflammatory cytokines interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNFα) as indices of immune activation and inflammatory response, soluble protein FAS (sFas) and of soluble ligand of protein FAS (sFas-L) as indices of cell mediated apoptosis and, E-selectin, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) as indices of vascular dysfunction.

2.8. Statistical analysis

Data were expressed as frequency for the nominal variables and as mean ± standard deviation (SD) for continuous variables. Data were analyzed by using Statview 5.0 (Abacus Concepts, SAS Institute, Cary, U.S.A.). Differences between the two subgroups were assessed by an unpaired Student's *t* test, or by the Mann–Whitney rank-sum for data that failed tests of normality. Simple linear regression analysis was performed to relate clinical variables (i.e. patients' age, age at first operation, years after last operation, systolic and diastolic BP, ECG and echocardiographic indices), to vascular and endothelial function parameters and serum levels of neurohormones and cytokines. Vascular and endothelial function parameters were also related to neurohormone and cytokine levels. For regression analyses purposes all not normally distributed variables were logarithmically (ln) transformed. All tests were two sided. A p value <0.05 was considered significant.

3. Results

Clinical, surgical, and haemodynamic data are shown in Table 1.

3.1. Aortic distensibility, vascular function and echocardiographic data

Patients after CoA repair show an impaired aortic function with lower aortic distensibility ($p=0.02$) and increased stiffness index ($p=0.005$). Pulse wave analysis indices i.e. AP and Aix differ significantly between patients and controls ($p=0.001$ and $p=0.0007$ respectively). Plethysmography indices also revealed an impaired capacity of the forearm vessels of patients during hyperemia (FBF, $p=0.009$) (Table 2, Fig. 1). Echocardiographic data on LV function revealed no statistically significance differences between patients and controls apart from left ventricular posterior wall thickness (LVPWT)

Table 1
Clinical, surgical, and haemodynamic characteristics of the study population.

	CoA patients (n = 19)	n	Controls (n = 29)	n	P value
Age, years	25.28 ± 9.33	19	26.13 ± 9.07	29	0.7
Female	22.63 ± 8.71	10	24.24 ± 6.24	15	0.6
Male	28.22 ± 9.59	9	28.16 ± 11.26	14	1
Years after last repair	18.27 ± 8.11				
Age at first repair, years	7.40 ± 7.54				
Only surgical repair	9				
Only stent implantation	6				
Surgical repair followed by stent implantation	4				
Bicuspid aortic valve	7				
NYHA class					
I	14				
II	5				
Systolic blood pressure (mmHg)	130.57 ± 19.40		118.06 ± 10.02		0.02
Diastolic blood pressure (mmHg)	70.36 ± 12.87		70.72 ± 7.22		0.9
QTc	392.2 ± 15.2		386.3 ± 21.8		0.3
QRS	31.5 ± 50.6		51.2 ± 24.4		0.08

Values in mean ± SD, (%).