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Rates and determinants of progressive aortic valve dysfunction in aortic coarctation

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ABSTRACT

Purpose: Aortic valve dysfunction is common in coarctation patients(CoA). Bicuspid aortic valve (BAV) in CoA is associated with aortic valve stenosis (AS), aortic valve regurgitation (AR), and ascending aortic dilatation. The aim of this study was to evaluate the progression of and predictors for aortic valve dysfunction in CoA.
Methods: 96 CoA patients prospectively underwent echocardiography twice between 2001 and 2010. AS was defined as an aortic valve gradient ≥20 mm Hg, AR as none/minor, or moderate/severe. Aortic dilatation as an ascending aortic diameter ≥37 mm.
Results: All patients (median age 28.0 years, range 17–61 years; male 57%) were followed with a median follow-up of 7.0 years. Sixty patients (63%) had BAV. At baseline 10 patients had AS (10%, 9 BAV), 6 patients AR (6%, 3 BAV) and 11 patients aortic dilatation (11%, 11 BAV). At follow-up 15 patients had AS (15%, 13 BAV) and 12 patients AR. (13%, 8 BAV).
Median AS progression was 1.1 mm Hg/5 years (range − 13–28). Determinants for AS at follow-up were age (ß = 0.20, P = 0.01), aortic dilatation (ß = 4.6, P = 0.03), and baseline aortic valve gradient (ß = 0.93, P < 0.001). BAV was predictive for AR. (ß = 0.91, P = 0.049).
Conclusion: Progression of AS in adult CoA patients is mild in this young population. Older age, aortic dilatation and the baseline aortic valve gradient are determinants for AS at follow-up. BAV is predictive for AR. These findings point towards a common embryological pathway of both valvular and aortic disease in CoA.

1. Introduction

Coarctation of the aorta (CoA) is one of the most common congenital cardiovascular abnormalities and accounts for 5–8% of all congenital heart defects [1]. Without surgical correction, the mean life expectancy of CoA patients is 35 years and 90% of all patients die before the age of 50 years [2]. Patients who undergo successful coarctation repair at a young age have a much better life expectancy, but they do remain at increased risk of late mortality [1,3,4].

This increased mortality in CoA patients is partially explained by complications such as hypertension and aortic dilatation, but also because it is associated with bicuspid aortic valve (BAV) and its inherent complications [1,5,6]. In CoA patients, the prevalence of BAV is estimated to be between 60% and 80% [1]. According to echocardiographic and autopsy studies, BAV is present in up to 0.5–2% of the general population and is known to be associated with various complications, such as aortic valve stenosis (AS), aortic regurgitation (AR) and endocarditis [7–9]. BAV is also associated with abnormalities of the ascending aorta such as aortic dilatation and dissection. These vascular abnormalities have been attributed to accelerated smooth muscle cell apoptosis in the aortic media [10–12]. Tzemos et al. have demonstrated an association between moderate to severe AS and AR and aortic dilatation, which emphasizes the influence of aortic valve disease on aortic dilatation in isolated BAV patients [13].

In CoA patients it is known that aortic valve disease, i.e. AS and AR, is a frequent cause of morbidity and mortality, and hypertension is an important contributor to aortic valve disease in these patients. Moreover, the residual gradient across the coarctation region after repair might affect the aortic valve and aortic wall, which may be relevant for the progression to aortic valve disease [14]. However, little is known about the progression of aortic valve function over time in these patients. The

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purpose of this study was to assess the progression of aortic valve function, and to identify predictors of aortic valve dysfunction over time in patients after successful coarctation repair.

2. Methods

2.1. Patients

Between 2001 and 2010, consecutive adult post-coarctectomy patients were enrolled in this prospective follow-up study. Patients were recruited from the CONCOR database, the Dutch registry and DNA-bank for adult patients with congenital heart disease [15]. Routine clinical follow-up was performed at one of three tertiary referral centers. All patients considered for inclusion had participated in a previous observational study [16]. Patients were excluded if they had undergone aortic valve replacement since the observational study. Patients were included in the study if at least two follow-up echocardiographic studies had been performed between 2001 and 2010. A total of 144 patients were potentially eligible for inclusion; of these 96 patients were willing to participate. The following baseline characteristics were obtained from patients' medical records: age, sex, body surface area (BSA), age at CoA repair, other congenital cardiovascular anomalies and type of surgery. The protocol was approved by the Medical Ethics Committee of all participating centers. Signed informed consent was obtained from all patients prior to participating in the study. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Echocardiography

All examinations were performed at the same institution. The median follow-up between the serial echocardiographic examinations was 7.0 years, range 3.3–9.0 years. All patients underwent serial echocardiographic examinations performed with a Vivid 7 (GE, Vingmed Ultrasound, Horton, Norway) ultrasound imaging system. Images were obtained from standard parasternal, subcostal, suprasternal and apical windows. In the two dimensional parasternal long axis and short axis views the aortic valve morphology was examined. A BAV was identified when two cusps were clearly identified during systole and diastole in the short axis view. Diameters of the aortic root and ascending aorta were determined. Ascending aortic dilatation was defined as a diameter ≥37 mm [17]. The presence of AR or AS was determined by Doppler and color Doppler echocardiography. AS was defined as a maximal aortic valve gradient of ≥20 mm Hg [18]. AR was defined as none to minor, or moderate to severe [19]. The M-mode echocardiography tracings were used with the Devereux formula to calculate LV mass and were indexed for BSA [20,21]. Measurements were made according to the standards of the ACC/AHA guideline [22].

2.3. 24 hour ambulatory blood pressure monitoring (ABPM)

All patients underwent 24 hour ambulatory blood pressure monitoring at baseline. Patients were defined as hypertensive if the mean daytime systolic blood pressure was ≥135 mm Hg, if the mean daytime diastolic blood pressure was ≥85 mm Hg or if patients were using anti-hypertensive treatment, which was at the discretion of the treating physician [23].

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation, or in case of a skewed distribution as median (range). Categorical variables are presented as number of patients (percentage). Between-group comparisons of continuous variables with normal distribution were performed with an independent t-test. Between-group comparisons of continuous variables with a skewed distribution (i.e. AS progression rate) were performed by a Mann–Whitney-*U* test. The progression rate of the aortic valve gradient was calculated by comparing gradients between the first and second echocardiographic examination. Linear regression analysis was used to identify determinants of the maximal aortic valve gradient at follow-up, in which the baseline aortic valve gradient was used as an independent covariate. In order to identify independent determinants of the presence of AS, multivariate backward stepwise logistic regression was performed using $P<0.05$ as the criterion of significance for entry of the variables, and $P>0.1$ for removal. Binary logistic regression analysis was performed to identify determinants of the presence of aortic valve regurgitation at follow-up. Data analysis was performed using the SPSS statistical package (16.0 for windows; SPSS Inc., Chicago, Illinois, USA). All statistical tests were two-sided and differences were considered statistically significant at $P<0.05$.

3. Results

3.1. Subjects

Ninety-six adult post-coarctectomy patients were included, with a median age of 28.0 years (range 17–61 years); median age at repair 7.7 years (range 0–37 years). Of all patients, sixty patients (63%) had BAV. Of all BAV patients 52 (87%) patients had a left to right coronary cusp fusion, 7 (11%) patients had a right to non coronary cusp fusion and 1 (2%) patient had a left to non coronary cusp fusion. Baseline characteristics are shown in Table 1.

3.2. Aortic valve dysfunction at baseline and follow-up

At baseline, AS was present in 10 patients (10%, 9 with BAV), moderate to severe AR was found in 6 patients (6%, of which 3 with BAV and AS) and ascending aortic dilatation was present in 11 patients (11%, 11 with BAV). At the end of follow-up AS was present in 15 patients (15%, 13 with BAV), AR was present in 12 patients (13%, of which 8 with BAV, and 6 with BAV and AS) and ascending aortic dilatation was present in 15 patients (16%, 14 BAV patients). The overall mean maximal aortic valve gradient was 11.8 ± 9.9 mm Hg at baseline and 14.5 ± 11.4 mm Hg at follow-up. Mean maximal aortic valve gradient in the AS group was 32.0 ± 15.1 mm Hg at baseline and 42.5 ± 14.2 mm Hg at the end of follow-up.

In all patients combined, median AS progression was 1.1 mm Hg per 5 years (range − 13.3–28.3 mm Hg/5 years). Among patients with AS (gradient >20 mm Hg) at baseline, median progression of the maximal aortic valve gradient was 0.2 mm Hg/5 years (range − 13.3–28.3 mm Hg/5 years). Median progression of the maximal aortic valve gradient per 5 years in patients with tricuspid aortic valve (TAV) and BAV was 0.75 mm Hg/5 years (range − 5.5–28.3 mm Hg/5 years) and 1.3 mm Hg/5 years (range − 13.3–21.8) respectively ($P=0.72$) (Table 2). Median AS progression was significantly higher 111in patients >40 years of age compared to those <40 years (0.83 mm Hg (range − 5.5–16.7 mm Hg) versus 3.0 mm Hg (range − 13.3–28.33 mm Hg) $P=0.03$.

3.3. Predictors for an increased aortic valve gradient (AS) at follow-up

Univariate regression analysis demonstrated that male sex ($\beta=5.6$, $P=0.02$), older age ($\beta=0.22$; $P=0.049$), hypertension ($\beta=-4.6$, $P=0.05$), BAV ($\beta=7.3$, $P=0.002$), presence of a VSD ($\beta=7.1$; $P=0.003$), ascending aortic dilatation ($\beta=9.1$, $P=0.02$), aortic regurgitation ($\beta=6.1$; $P=0.009$), and baseline aortic valve gradient

Table 1
Baseline characteristics of 96 adult post-coarctectomy patients.

Characteristics		Baseline (N = 96)
Age (years)		28.0 (17–61)
Male		55 (57%)
BSA (kg/m^2)		
Hypertension		56 (58%)
Age at surgery (years)		7.7 (0.1–37)
Type of repair	End-to-end anastomosis	63 (66%)
	Patch angioplasty	14 (15%)
	Subclavian flap	15 (16%)
	Prothesis	4 (4%)
Associated cardiac anomalies	BAV	60 (63%)
	Left to right coronary cusp	52 (87%)
	Right to non coronary cusp	7 (11%)
	Left to non coronary cusp	1 (2%)
	VSD	14 (15%)
	Open ductus botalli	9 (9%)
	Hypoplastic aortic arch	6 (6%)
Aortic root (mm ± SD)		22.1 ± 4.6
Aorta ascendens (mm ± SD)		29.2 ± 8.5
Aortic dilatation (ø ≥ 35 mm Hg)		11 (11%)
Aortic valve stenosis (≥20 mm Hg)		10 (10%)
Aortic valve regurgitation		
None/trace/minor		90 (94%)
Moderate/severe		6 (6%)
LV mass index (≥130 g/m^2)		34 (35%)

Data are presented as mean ± standard deviation, median (range) or number (percentage). BAV = bicuspid aortic valve; BSA = body surface area; VSD = ventricular septal defect; lv mass index = left ventricular mass index.