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Left ventricular hypertrophy in adults with previous repair of coarctation of the aorta; association with systolic blood pressure in the high normal range

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ABSTRACT

Background: Arterial hypertension is common in adults with repaired coarctation of the aorta (CoA). The associations between the diagnosis of hypertension, actual blood pressure, other factors affecting left ventricular overload, and left ventricular hypertrophy (LVH) are not yet fully explored in this population.
Material and results: From the national register for congenital heart disease, 506 adult patients (≥18 years old) with previous repair of CoA were identified (37.0% female, mean age 35.7 ± 13.8 years, with an average of 26.8 ± 12.4 years *post* repair). Echocardiographic data were available for all patients, and showed LVH in 114 (22.5%) of these. Systolic blood pressure (SBP) (mm Hg) (OR 1.02, CI 1.01–1.04), aortic valve disease, (OR 2.17, CI 1.33–3.53), age (years) (OR 1.03, CI 1.01–1.05), diagnosis of arterial hypertension (OR 3.02, CI 1.81–5.02), and sex (female) (OR 0.41, CI 0.24–0.72) were independently associated with LVH. There was an association with LVH at SBP within the upper reference limits [130, 140] mm Hg (OR 2.23, CI 1.05–4.73) that further increased for SBP > 140 mm Hg (OR 8.02, CI 3.76–17.12).
Conclusions: LVH is common *post* repair of CoA and is associated with SBP even below the currently recommended target level. Lower target levels may therefore become justified in this population.
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1. Introduction

Coarctation of the aorta (CoA) represents 5–10% of all congenital heart lesions. Surgical treatment of CoA has been possible since the mid-forties [1] but late complications such as arterial hypertension and left ventricular hypertrophy (LVH) still pose a problem after intervention [2–9]. Before treatment was possible, morbidity and mortality were largely caused by left ventricular dysfunction and failure due to arterial hypertension.

Arterial hypertension is the most common complication in patients with repaired CoA, with a prevalence between 25 and 68%, the great variation largely dependent on the definition of hypertension, the studied population, and differences in the diagnostic methods [8]. Furthermore, arterial hypertension is associated with early mortality in patients with repaired CoA [6,7,10].

In up to 70% of the cases, CoA is associated with bicuspid aortic valve, and thus often leads to development of aortic valve disease [11]. Advanced stages of aortic valve disease are clearly related to LVH. Moderate aortic lesions, not yet requiring intervention, are also associated with LVH in patients with repaired CoA [12]; a situation that is particularly unfavourable, as the pressure overload may act over decades on the left ventricle, in these relatively young patients.

Regarding the prevalence of LVH in an unselected contemporary adult population *post* surgical repair of CoA, the available data are very limited [9,13]. Furthermore, it is unclear if other factors are linked to the development of LVH, and to what extent reaching blood pressure values below target in arterial hypertension actually protects against LVH. The same blood pressure target levels are currently applied in CoA as in essential hypertension. This is despite the fact that patients with CoA generally are younger, have other factors that may affect left ventricular afterload, and that all these factors may act over long periods

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of time. Therefore, we have analysed the effects of several variables on the development of LVH. This has been done for (a) the entire study population, as well as for (b) patients with diagnosed arterial hypertension, and (c) patients without diagnosed arterial hypertension. Analyses of (d) the association between systolic blood pressure at different levels, including "high" normal blood pressure, and LVH have also been performed.

2. Material and methods

2.1. SWEDCON

This register study is based on data in SWEDCON, the Swedish National Register on Congenital Heart Disease (www.ucr.uu.se/swedcon/). Since 1998, the register has covered all seven health care regions in Sweden, although registration started earlier in some centres. Data are collected by each centre and contains information on diagnoses, interventions, demographics, functional class, symptoms, quality of life (EQ-5D), social variables, ECG, exercise tests, self-reported level of physical exercise, echocardiography, medications and pacemakers/ICD:s. All data collected until 17 February 2013 were searched.

2.2. Patients

SWEDCON was used to identify all patients with surgically repaired CoA and echocardiographic data on LVH, who were at least 18 years of age at the time of their last registered clinic visit with a recorded systolic blood pressure, excluding those with complex pathologies.

Out of 9864 patients in the SWEDCON register, 1026 had been diagnosed with CoA. 853 of these patients were at least 18 years of age both at the time of their last registered clinic visit, and at the time of their last echocardiography. Patients with associated simple lesions, such as ventricular septal defect and aortic stenosis, were included, whereas those with major, complex pathologies or syndromes were excluded, reducing the population to 754 patients. Patients with uncorrected coarctation and patients with an intervention within six months before their last clinic visit with a recorded systolic blood pressure were also excluded, leaving 506 patients eligible for inclusion in the study.

The study was approved by the Regional Ethical Review Board in Umeå, Sweden (Dnr 08–218 M and 2012–445-32 M).

2.3. Definition of LVH

Data regarding LVH were extracted from echocardiographic examinations reported in the SWEDCON register. In the register, data on LVH are semi-quantitative and reported as none, mild, moderate, or severe. The classification is performed at the discretion of the investigator, in line with local routines. In this, study, LVH was defined as the presence of any degree of LVH ranging from mild to severe.

2.4. Definition of diagnosed hypertension and systolic arm–leg blood pressure gradient

Cases of diagnosed hypertension in the selected population were identified by register diagnosis of arterial hypertension and/or by prescription medication—ACE-inhibitors (n = 63), angiotensin II antagonists (n = 26), beta blockers (n = 103), calcium blockers (n = 46), diuretics (n = 37), or miscellaneous other medications prescribed for systemic hypertension (n = 4)—at the latest registered clinic visit where systolic blood pressure data were available. It is thus important to note that the term hypertension, in this paper, is not used to describe the single blood pressure registration acquired at the clinic visit, but rather cases of diagnosed arterial hypertension, as defined above.

It is generally recommended that blood pressure is measured in both arms in patients with CoA, registering the highest value.

The systolic arm–leg blood pressure gradient was calculated using the last registered office blood pressures in arm and leg. Negative values, *i.e.* higher blood pressure in the lower extremity, were assumed to signify pulse-wave reflections and interpreted as no fall in pressure over the coarctation.

2.5. Statistics

All calculations were performed using SPSS 20–23 (IBM, Armonk, NY, USA). Differences in means and ratios between groups were tested with Student's *t*-test or chi^2-test as appropriate.

When examining variables associated with LVH for (a) the entire study population, (b) patients with diagnosed arterial hypertension, and (c) patients without diagnosed arterial hypertension, variables for multivariate analyses were selected by univariate logistic regression, excluding related variables. Body mass index (BMI) was allowed to take precedence over height and weight in the multivariate logistic regressions, to avoid interaction between these three variables. Height and weight were included in the multivariate regressions only if they were univariately significant when BMI was not. Similarly, age was allowed to take precedence over time from first intervention to follow-up. The number of anti-hypertensive medication classes simultaneously prescribed was excluded from the multivariate analyses, to avoid interaction with the blood pressure variables. Systolic blood pressure, diastolic blood pressure, and systolic arm–leg blood pressure gradient were tested as continuous variables. Multivariate logistic regression was performed in a manual backward manner.

For the model describing factors associated with LVH in the entire study population (a), the first step of the logistic regression included sex, age, age at first intervention, type of intervention, BMI, diagnosed arterial hypertension, systolic blood pressure, diastolic blood pressure, and aortic valve disease (Table 3).

For the model describing factors associated with LVH among the patients with diagnosed arterial hypertension (b), the first step of the logistic regression included age, weight, systolic blood pressure, and diastolic blood pressure (Table 4).

For the model describing factors associated with LVH among the patients without diagnosed arterial hypertension (c), the first step of the logistic regression included sex, age, height, weight, systolic blood pressure, and aortic valve disease (Table 5).

A *post hoc* analysis (d) examining the association between systolic blood pressure at different levels, and LVH, was performed for the entire study population with systolic blood pressure divided into mathematical quartiles. This yielded the ranges <120 mm Hg, [120, 130) mmHg, [130, 140] mmHg, and >140 mm Hg for systolic blood pressure. The lowest range (<120 mm Hg) was used as reference in a univariate logistic regression. Based on the outcome of this analysis, a final univariate logistic regression was subsequently performed, only including patients with diagnosed arterial hypertension, and using systolic blood pressure <130 mm Hg (no/yes) as independent variable.

In all analyses, the null hypothesis was rejected for *p*-values <0.05.

3. Results

3.1. General findings

Within the population of 506 patients, 187 (37.0%) were female, and the mean age was 35.7 ± 13.8 years with an average of 26.8 ± 12.4 years *post* coarctation repair. 114 patients (22.5%) had LVH (mild 18.4%, moderate 4.2%, no severe cases) (Table 1). Patients with LVH were, on average, older, included more men and the interventions on their coarctations had been performed later in life (Table 1). Among the patients with diagnosed arterial hypertension, beta-blockers were the most commonly prescribed medication type, followed by ACE-inhibitors (Table 2).

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