

Late morbidity after repair of aortic coarctation

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THE THREE ORIGINAL PAPERS ARE

1. High Long-Term Morbidity in Repaired Aortic Coarctation - Weak Association to Residual Arch Obstruction. Pedersen TAL, Munk K, Andersen NH, Lundorf E, Pedersen EB, Hjortdal VE, Emmertsen K. *Congenit Heart Dis.* 2011 Nov-Dec;6(6):573-82
2. Left ventricular and renal function and vasoactive hormones late after repair of aortic coarctation - Relation to hypertension and mild residual aortic arch obstruction. Pedersen TAL, Munk K, Andersen NH, Lundorf E, Hjortdal VE, Emmertsen K, Pedersen EB. Submitted to *International Journal of Cardiology* in August 2011.
3. Functional Health Status Late After Surgical Correction of Aortic Coarctation. Pedersen TAL, Røpcke DM, Hjortdal VE. *Congenit Heart Dis.* 2011 Nov-Dec;6(6):566-72.

1. INTRODUCTION

Aortic coarctation (CoA) is an obstruction of the aortic arch. The classic presentation is a localized narrowing in the isthmus, but more proximal parts of the aortic arch are often hypoplastic and may even be atretic [1]. CoA occurs in approximately 10% of all cases of congenital heart disease [2] and may be an isolated lesion, but is frequently associated with a bicuspid (BAV) and often dysfunctional aortic valve. Associated ventricular and atrial septal defects are also common, and hypoplasia of left heart structures and other complex malformations are not infrequent [3].

Repair at an early age is indicated in order to improve survival [4, 5]. Surgical correction through a left thoracotomy with resection and end-to-end anastomosis was first described by Crafoord and

Nylin in 1945 [6]. Repair by subclavian flap aortoplasty and insertion of prosthetic material as a patch or interposition graft were subsequently described [7, 8]. More recently, extended resection with end-to-end anastomosis performed through a left thoracotomy and total arch repair through a sternotomy were introduced to deal with CoA and associated aortic arch hypoplasia [9]. For complex lesions and especially in surgical reinterventions, an ascending-to-descending aortic bypass graft may be used [10]. As an alternative to surgery, catheter ballooning and insertion of stents have been used for over 20 years with good anatomic results [11].

Surgical repair provided satisfactory anatomic results and was previously considered curative [12]. However, since the late 1970s, long-term follow-up studies have shown increased cardiovascular morbidity and mortality late after repair [13, 14]. Left ventricular dysfunction, aortic and mitral valve dysfunction, ischemic heart disease, aortic recoarctation (ReCoA), aortic aneurysms and rupture, and in particular systemic hypertension are among the most common complications [13-15].

Long-term studies on this issue have mainly been retrospective, based on small case series, and with many patients lost to follow-up. Furthermore, these studies showed considerable difference in the prevalence of late morbidity, as it depended on the diagnostic criteria used, the duration of follow-up, and the selection of the cohort [13, 16, 17].

Thus, we lack consistent knowledge about the true prevalence of long-term morbidity after CoA repair in unselected cohorts of patients.

ReCoA after prior CoA repair may be caused by remnant ductal tissue, unrelieved aortic arch hypoplasia, incomplete repair or failure of growth after surgical anastomosis or stenting [18]. ReCoA has been correlated with young age at repair, use of surgical techniques other than end-to-end anastomosis [19], and repair by angioplasty rather than surgery [20], but not all studies find this correlation [21]. In theory, resection with an extended end-to-end anastomosis addresses more properly the substrates for ReCoA and may result in a lower incidence of residual arch obstruction in the short- and mid-term [18]. Severe ReCoA imposes significant afterload on the left ventricle, resulting in increased wall stress, compensatory left ventricular hypertrophy and dysfunction, and may induce or aggravate systemic arterial hypertension [22]. In contrast, the role of a mild-to-moderate ReCoA is not yet well established. For this reason, studies assessing the role of milder degrees of ReCoA on late morbidity are needed.

The pathogenesis of persistent hypertension is obscure in the majority of patients. Different mechanisms have been proposed, including abnormal baroreceptor function [23], decreased aortic compliance [24], arterial wall abnormalities [25], ventricular stiffness [26], endothelial dysfunction [27], inflammatory response [28], and neuroendocrine activation [29]. There is, hence,

still a need for studies looking into the possible origins of late morbidity after CoA repair.

Despite the high level of comorbidity, self-reported functional health in adult patients with repaired CoA seems only slightly impaired compared with a similarly-aged general population [30]. This impairment is more evident in the presence of a reduced exercise capacity [31], but the surgical technique used for repair and the presence of ReCoA does not seem to have noteworthy impact [32]. However, the influence of daily medication intake on self-perceived functional health status has not been investigated in adult CoA patients despite the high number of patients taking antihypertensive treatment and despite studies on other patient groups having shown a negative impact of daily medication on health perception [33, 34].

2. AIMS AND HYPOTHESES

2.1. Substudy I

Aims: To establish in a consecutive unselected cohort of patients the prevalence of previous cardiovascular reinterventions, current cardiac and valvular function, exercise capacity, blood pressure levels at rest and during exercise, presence of recurrent or residual aortic arch obstruction and/or aortic aneurysms late after CoA repair; and to assess the association of these parameters of late morbidity with the presence of ReCoA.

Hypotheses: Patients after repair of CoA are at high risk of developing cardiovascular complications in the long term despite a satisfactory repair; the complications are more common in the presence of ReCoA.

2.2. Substudy II

Aims: To assess left ventricular systolic and diastolic function, renal function, and vasoactive hormone levels in adult patients with repaired CoA; and to relate these findings to the presence of hypertension and ReCoA.

Hypotheses: Adult patients with repaired CoA have abnormal left ventricular function, abnormal levels of vasoactive hormones, decreased renal function, and abnormal renal handling of sodium and water; these changes are more pronounced with persisting hypertension and ReCoA.

2.3. Substudy III

Aims: To investigate self-reported functional health status among adults previously operated on for CoA compared with healthy subjects; and to assess the influence of medication and exercise capacity on the functional health of these patients.

Hypotheses: The functional health status of adults previously operated on for CoA is impaired compared with that of healthy subjects; the impairment in functional health is more evident in the presence of a reduced exercise capacity and daily use of medication.

MATERIAL AND METHODS

3.1. Study Population and design

This dissertation is based on observational substudies performed on long-term survivors who underwent surgical repair of a CoA during 1965–85 at our institution, as illustrated in Figure 1. Echocardiography (including tissue Doppler), bicycle exercise testing, measurements of renal function and vasoactive hormones, 24-h ambulatory blood pressure monitoring, MRI or CT scan of the thoracic aorta, and assessment of functional health status were performed. Detailed descriptions of the study design and patient inclusion are given in each manuscript.

3.1.1. Substudy I

The main study assessed the frequency of reinterventions and prevalence of current cardiovascular morbidity in the entire cohort of participants, and assessed the influence of ReCoA on study findings. Results of echocardiography, bicycle exercise testing, 24-h ambulatory blood pressure monitoring, plasma creatinine, and MRI/CT scan of the thoracic aorta are included.

3.1.2. Substudy II

This study assessed left ventricular and renal function as well as vasoactive hormones in the 68 unmedicated patients with no associated cardiovascular morbidity by means of echocardiography (including tissue Doppler), exercise testing, measurements of renal function and vasoactive hormones, 24-hour blood pressure monitoring, and MRI/CT of the thoracic aorta. Study findings were related to the presence of hypertension and ReCoA. Findings in the patients were, in addition, compared with those obtained in 20 normotensive healthy volunteers.

3.1.3. Substudy III

In this study, we performed a questionnaire-based investigation of functional health status using the SF-36 health survey. Of the 156 patients in the cohort, 119 patients filled out the questionnaire. Scores in patients were compared with those obtained in 36 healthy subjects comparable to the patients in terms of age and gender. In addition, the association between exercise capacity / use of daily medication and functional health status was assessed. Exercise capacity was measured by symptom-limited bicycle ergometer testing.

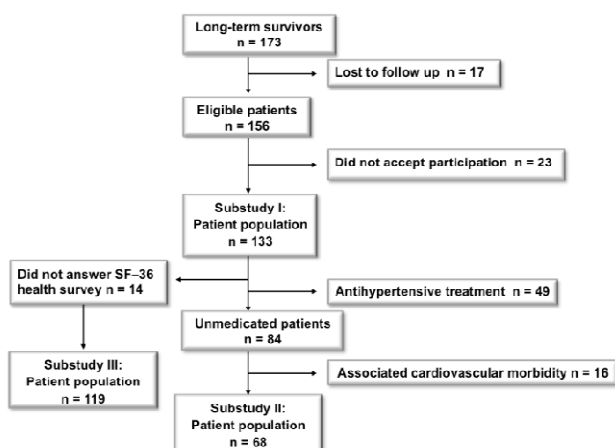


Figure 1
Inclusion of patients in the three substudies

3.2. Methodological considerations

3.2.1. Study participants

3.2.1.1. Patients

The present study is unique in terms of a follow-up of a consecutive cohort of patients who had surgical repair of CoA during two decades at one institution. Only a few were not identified, the participation among eligible patients was high, and patients were comprehensively examined.

However, the present patient group is selected, because the patients had survived until the diagnosis was made and repair was performed during the early years of congenital heart surgery. They were furthermore selected by their survival for more than 24 years after surgery. They were also older at repair and had less cardiovascular comorbidity compared with patients who undergo CoA repair today. Besides, the surgical repair technique used today has evolved and now includes extended end-to-end anastomosis, a technique which probably addresses vascular abnormalities surrounding the CoA site more adequately than does conventional end-to-end anastomosis. Thus, the results of this study may not apply to patients undergoing neonatal repair today.

In addition, the present patient cohort is very heterogeneous, both regarding associated morbidity and follow-up. Some were seen regularly in specialized centers for congenital heart disease, others at their local hospital (secondary center) with adult cardiovascular services, while the majority of the patients were seen by only their general practitioners or had no regular contact with the health care system at all. Thus, the study's results are based on a very mixed patient population.

A total of 23 of the 156 eligible patients did not participate in the study. Registry-based information on the non-participants shows that these patients did not differ significantly from the participants with respect to gender, age at surgery, surgical techniques used, associated morbidity, and reintervention rate. Thus, we believe that the current results would not have been significantly different if the participation rate had been higher.

Patients with repaired CoA are at a higher risk of the development of coronary artery disease. We did not perform routine screening for ischemic heart disease in this cohort. Only patients

with chest pain or ECG changes at rest or during exercise were referred for further investigation for coronary artery disease. Not all patients underwent all examinations in the study protocol: nine patients did not complete the 24-h ABPM, five did not undergo bicycle exercise testing and assessment of vasoactive hormone levels and renal function parameters, 12 did not undergo a complete assessment of the thoracic aorta by MRI or CT scan, and 14 did not complete the SF-36 health survey. However, the overall participation rate was very high (86%), the examination program was comprehensive, and the patient cohort unselected. Therefore, we believe that the patient population is representative of adult patients who had CoA repair in childhood and youth. The examinations in the study protocol were not blinded. Nevertheless, data analyses were performed post-hoc off-line in an attempt to minimize bias.

3.2.1.2. Healthy subjects

For accurate gender and age matching, we should have included as many controls as patients. For logistical reasons, that was not possible.

The controls were recruited by written announcement in the form of posters with information about the study placed in the cities of Aarhus (the second largest city in Denmark) and Vejle (a large city in southern Jutland—the mainland part of Denmark). We only examined and included subjects without known cardiovascular disease. They had diverse educational backgrounds and occupations, and we consider them to be representative of the Danish population.

Among the 39 controls examined, seven did not complete the ABPM. Only the 20 normotensive controls were included in substudy II. We excluded the 12 subjects who according to the applied criteria were hypertensive, because they could not be considered healthy controls. Systemic hypertension in otherwise healthy subjects could, in principle, also be associated with left ventricular dysfunction, abnormal levels of vasoactive hormones, and renal dysfunction.

3.2.2. Echocardiography

Conventional transthoracic echocardiography is the most widely used method for assessing cardiac function. It provides rapid and valid information regarding left ventricular function and dimensions, valve anatomy and function, and associated abnormalities, but it has limitations, particularly regarding detection of the early subclinical stages of left ventricular dysfunction [35]. Tissue Doppler echocardiography provides improved quantitative assessment of regional myocardial function during the whole cardiac cycle and enhanced visual assessment of discrete regional wall motion abnormalities, identifying more subtle changes in cardiac performance than conventional echocardiography [36].

Substudy I does not include a detailed assessment of diastolic function or results of tissue Doppler echocardiography. Addition of these data would possibly have raised the quality of the substudy. However, the patients examined in this substudy were very heterogeneous. A noteworthy percentage of patients had valvular disease or associated cardiac malformations, and above one third of the patients were receiving medication that could cause subtle echocardiographic changes. Thus, the inclusion of measures of more sensitive parameters of diastolic function and tissue Doppler findings in this mixed cohort could have led to

unclear findings. We performed a more detailed echocardiographic assessment of left ventricular function in substudy II. High systolic flow velocities and diastolic runoff through the distal arch on echocardiography have often been used as indicators of ReCoA [37]. However, the visualization of the CoA site in adults is often suboptimal [38, 39], which results in a poor association between abnormal echocardiographic findings in the distal arch and anatomical ReCoA on MRI [38]. For this reason, we used MRI/CT to measure the thoracic aorta in the assessment of ReCoA.

Transthoracic echocardiography is able to show dilatations in the aortic root and the first part of the ascending aorta, but it does not properly visualize the upper parts of the ascending aorta and the descending aorta [40]. For that assessment, MRI and CT scans are more appropriate, and were used in this study. Transesophageal echocardiography can visualize the entire thoracic aorta, but the semi-invasive nature of this modality requiring sedation or general anesthesia restricts its application. Transesophageal echocardiography was not performed in this study.

3.2.3. Magnetic resonance imaging and computerized tomography

Recent advances in MRI hardware and software allow high-resolution imaging of complex anatomy and accurate quantitative assessment of cardiac anatomy and function [41]. Cardiac MRI is ideally suited for non-invasive evaluation of congenital, acquired, and post-operative anomalies of the aorta in adolescents and adults due to the high quality of the images produced and the non-invasive and safe characteristics of this technique [42]. Furthermore, MRI is suitable for serial measurements, because it does not require radiation or contrast [43].

Breath holds, size limitations, contraindications relative to metal, claustrophobia, and timeconsumption still limit the use of this modality as a universal choice.

CT has been useful in evaluating vascular anatomy, and, with the advent of high-resolution CT and cardiac gating, it has emerged as a useful tool for assessing intracardiac anatomy and myocardial function [41]. Nevertheless, the exposure to ionizing radiation has limited the usefulness of cardiac CT until recently. Currently, advances in the technique permit a very rapid examination with extremely low radiation dose and excellent imaging, giving the cardiac CT a whole new place in the imaging of CoA [44, 45]. In the current study, we attempted to perform MRI scans using a Philips 1.5 Tesla Intera scanner (Philips Medical Systems, Best, the Netherlands) in all participants. The few patients with a known contra-indication for MRI were referred for a pre-booked CT scan of the thoracic aorta using the same examination protocol. For logistical reasons (capacity problems), patients who did not complete the MRI examination (due to claustrophobia or suboptimal images) were not referred for a subsequent CT scan, resulting in a total of 12 patients not having assessment of the thoracic aorta by either of these two modalities.

The definition of ReCoA is arbitrary and varies, even if MRI or CT is used for the assessment of the aortic diameters. In children and adolescents, the use of the z-scores is widespread, because they take the patient's size into account [46]. Nevertheless, there is an important conceptual problem in applying z-scores in adult patients, as cardiac and vascular dimensions do not increase with excess weight [47]. Thus, obese patients may be incorrectly classified as having a ReCoA. As an alternative to z-scores, a raw non-indexed measure of the aortic dimensions at the repair site could potentially provide a more correct assessment of ReCoA in adult

patients, and these measures have also been used to define ReCoA [48]. The definition of ReCoA by this classification has, nevertheless, not been validated, and its use should be standardized in a large cohort of patients before being applied in clinical practice. In this study, we chose to define ReCoA according to the ratio of the aortic diameter in the transverse or distal aortic arch divided by the aortic diameter at the diaphragm level, as recommended in recent guidelines [22].

Severe ReCoA, which by some is defined as a ratio aortic diameter in the transverse or distal aortic arch divided by the aortic diameter at the diaphragm level below 40% [49], was not seen in any patients in the present cohort.

Despite CoA being associated with a significantly increased risk of development of cranial aneurysms, neuroimaging was not routinely performed in this study for logistical reasons.

3.2.4. Blood pressure measurements

Given the lack of reliability of conventional office blood pressure measurements, recent guidelines recommend 24-hour or repeated daytime home blood pressure measurements for initial diagnosis and follow-up [50, 51]. Blood pressure measurement in CoA patients must be performed on the right upper arm using appropriate measuring techniques and equipment according to recommendations [50]. We performed 24-hour blood pressure measurements on the right upper arm every 15 minutes during day-time and every 30 minutes during diary-registered night-time using a validated oscillatory device (90217 ABP Monitor - Spacelabs Medical, Inc). Mean systolic and diastolic blood pressures were calculated for the 24-hour period.

Blood pressure levels were considered normal if they did not exceed 130 mm Hg systolic and 80 mm Hg diastolic during a 24-hour period according to recommendations [50]. These levels are similar to those used in other patient groups with increased cardiovascular risk, such as patients with diabetes and ischemic heart disease [52-54]. Nevertheless, this low threshold for the diagnosis of hypertension implies that a significant part of the otherwise healthy population would also be classified as hypertensive. Thus, 12 of the 39 otherwise healthy subjects were excluded from substudy II, because their blood pressure levels were above the rather low recommended limits.

A blood pressure difference between arm and leg of more than 20 mm Hg is often used as a definition of ReCoA [55, 56] because of its simplicity and availability in daily clinical practice. However, this measure may lack sensitivity and specificity in adults [57], being possibly influenced by lower limbs atherosclerosis, presence of collateral flow, arterial stiffness, and large intra-observer variation, and was therefore not used in this study.

3.2.5. Bicycle exercise testing

Patients with repaired CoA often have exercise-induced hypertension [58-61] and/or reduced exercise capacity [62].

Criteria such as a peak systolic blood pressure above the gender-specific 80th percentile [63], a maximal systolic blood pressure above 200 mm Hg [64] or 220 mm Hg [65], and an increase in systolic blood pressure of over 76 mm Hg [66] have been used to define exercise-induced hypertension.

Frequently used definitions for impaired exercise capacity after CoA repair include a maximal achieved workload below 80% or 85% of that expected for the age and gender [61, 67] or a maximal oxygen consumption below 32 ml/kg/min [68].

We performed a symptom-limited bicycle ergometer exercise testing (Schiller Ergosana ERG 910 S) at an initial workload of 25 Watts, increasing by 25 Watts every second minute. Electrocardiography and right upper arm blood pressures were recorded every second minute.

Exercise-induced hypertension was defined as a maximal systolic blood pressure above 220 mm Hg [65, 69] and reduced exercise capacity as a maximal workload below 85% of the expected for age and gender [67].

The measure of maximal oxygen uptake during exercise could have added valuable information on, for instance, cardiac output. Nevertheless, measurements of respiratory gas exchange are laborious and, for logistical reasons, were not included in the current study's examination protocol.

3.2.6. Blood and urinary analysis of vasoactive hormones, renal function, and electrolytes

Neuroendocrine activation is a key event in the pathogenesis and pathophysiology of heart failure [70] and may be involved in the pathogenesis of CoA-related hypertension [71, 72].

Both the renin-angiotensin-aldosterone system and arginine vasopressin are effective vasoconstrictors and stimulate sodium reabsorption in the renal collecting ducts, which is critical in the maintenance of electrolytes balance, extracellular fluid volume, and long-term blood pressure control [73]. The renin-angiotensin-aldosterone pathway is also influenced by atrial natriuretic peptide and brain natriuretic peptide. These natriuretic peptides act as an important counter-regulatory system, promoting natriuresis, diuresis, vasodilation, and suppression of the renin-angiotensin-aldosterone system [74].

Increasing levels of aldosterone stimulate an increase in renal potassium excretion and sodium and water reabsorption, resulting in increased blood pressure [75]. Aldosterone has also a vasoconstrictor effect, which can itself contribute to elevate blood pressures.

The level of the β -fraction of epithelial sodium channels in urine reflects the activity of sodium transport via the epithelial sodium channels, and urine aquaporin II reflects the functional status of the aquaporin II water channels [76-78].

Vasoactive hormones were in this study assessed by measurements of plasma concentrations of renin, angiotensin II, aldosterone, atrial natriuretic peptide, N-terminal pro brain natriuretic peptide, and vasopressin. Renal function was evaluated by plasma creatinine.

Shortly before the exercise, the participants were asked to empty their bladders, and 30 ml urine was sampled. Approximately 60 ml of blood was drawn from a cubital intravenous catheter for baseline measurements. The participants were then asked to drink water ad libitum and to continue doing so during exercise testing. After cessation of exercise, new blood and urine samples were collected. The urine sample collected after exercise was in some cases less than the 30 ml necessary for analysis. The infusion of intravenous isotonic sodium chloride solution after baseline blood and urine sample collection would probably have been beneficial in this matter. Not all blood- and urine-derived parameters could be measured in all participants.

Apart from the vasoactive substances measured in this study, there are diverse other substances not measured here that might play a role either locally or systemically in CoA-related morbidity. Endothelin 1, epinephrine, and norepinephrine are, for instance, associated with the pathogenesis of heart failure and are known to correlate well with left ventricular function and NYHA func-

tional class in other patient populations [79]. Plasma osmolarity has been shown to be somewhat higher in patients with congestive heart failure both at rest and during exercise compared with healthy peers [80]. Nevertheless, we chose to focus on the renin-angiotensin-aldosterone system, arginine vasopressin, and natriuretic peptides in the current study.

Plasma cholesterol and hepatic function parameters were not routinely measured in this study.

3.2.7. Functional health status

The SF-36 health survey is an extensively validated health survey which provides information on functional health relevant to all people [81]. It has good internal consistency and test-retest reliability and is strongly correlated with other well-established measures of functional health status [30][30]. Through this short form, general physical and mental functioning and well-being are assessed, yielding scores in the both physical and mental aspects of health. The transformation of the original scores into norm-based scores allows less biased estimates of missing responses and estimation of scores for more respondents with incomplete data. The use of a generic instrument instead of a disease-specific instrument allows comparison with the general population.

We applied the SF-36 health survey and subsequently transformed the original scores into norm-based scores as recommended [82]. Norm-based scores were compared with scores obtained in a Swedish population, because SF-36 norm-based scores of Danish inhabitants are not available. However, in view of the similarities between these two nations, we believe that the results are still valid.

In the analysis regarding the influence of medication intake on functional health, we only included cardiovascular medication, as data regarding other types of medication were often incomplete.

3. RESULTS AND DISCUSSION

4.1. Substudy I

The frequency of cardiovascular reinterventions before the start of the study was high (26%), and they were most often undertaken because of aortic valve dysfunction ($n = 20$), other cardiac malformations ($n = 18$), and ReCoA ($n = 8$), similar to what has been reported in other studies [83]. Current aortic valve dysfunction was also frequent ($n = 45$), whereas mitral valve dysfunction was less common ($n = 3$), in accordance with previous studies [5, 84, 85].

Hypertension was common, with 49 patients being on antihypertensive medication, and a further 30 being hypertensive without medical treatment. In this study the surgical repair technique and age at repair were not significantly associated with hypertension measured by ABPM, as otherwise described by some [19, 86] but not all authors [87].

Exercise capacity was reduced in 37 (29%) patients, and 47 (37%) had exercise-induced hypertension, to some extent comparable with other studies in this field [58-61]. Reduction in exercise performance has, in some studies, been associated with ReCoA [68] and hypertension [68], but this association was not confirmed in the present study.

A BAV was present in 47% of patients and was associated with ascending aortic ectasia and valve regurgitation, supporting previous findings [3, 19, 88-91].

Left ventricular hypertrophy was common, but ejection fraction was overall preserved, as previously reported [92]. When ReCoA was defined as a ratio between the minimal aortic diameter by MRI or CT in the transverse or distal aortic arch below 80% of the aortic diameter at the diaphragm, 48% of patients had some degree of ReCoA, which is more frequent than reported in some of the previous studies [15, 49, 55], despite the fact that no patients in the present cohort had severe ReCoA. Two other anatomical definitions of ReCoA based on aortic diameters in the MR or CT scans were also used in the present substudy. Defining the ReCoA as a z-score <-2 standard deviations below the mean value for the given body surface area [46] or as a minimal luminal diameter in the transverse or distal aortic arch below 12 mm [48], a somewhat different patient population with ReCoA emerged (Figure 2). This fact illustrates how arbitrary and inconsistent the definition of ReCoA can be. To our knowledge, no previous study performed a similar comparison in a similar patient cohort. In this study, mild to moderate ReCoA was associated with elevated blood pressures and use of antihypertensive medication, but not with hypertension in unmedicated patients or with echocardiographic or exercise parameters. A similar analysis has not previously been described. A high-velocity systolic flow and/or antegrade diastolic flow through the distal arch was not associated with anatomical ReCoA as assessed by MRI or CT, which is in contrast with previous findings [37, 55]. Of the 133 patients examined, only five (4%) had completely normal study findings. The applied examination protocol identified 16 patients with cardiovascular morbidity that required re-intervention at present. We concluded that CoA is associated with heart diseases, aortopathy, and hypertension in the long term. Mild to moderate ReCoA was only weakly associated with parameters for late morbidity.

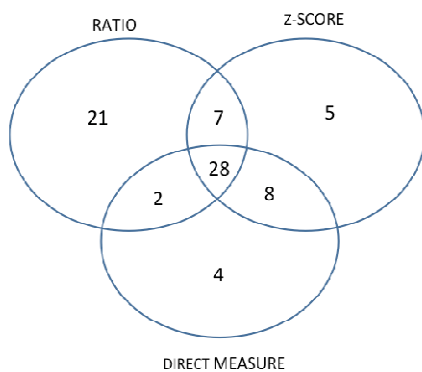


Figure 2
Distribution of the patients classified with ReCoA according to the three definitions based on aortic diameters on MRI or CT scan

4.2. Substudy II

In this substudy, we compared patients after surgical correction of CoA with healthy subjects of similar age and gender. Among the 133 patients examined in the first substudy, 49 were excluded due to use of antihypertensive medication, and a further 16 were excluded due to associated cardiovascular disease. The remaining

68 patients were included, and the 64 who completed a 24-h ABPM were subdivided into groups according to blood pressure levels. Of the 39 healthy subjects examined, seven did not complete the ABPM, and a further 12 were hypertensive. Only the 20 normotensive healthy subjects were included as controls. Left ventricular mass was significantly larger in patients, and diastolic function as assessed by tissue Doppler echocardiography was reduced (higher E/E' ratio), regardless of the presence of hypertension. The systolic mitral annular velocity (S') was lower in patients (especially those with hypertension) compared with controls. Similar findings of reduced long-axis systolic function, increased left ventricular mass, and diastolic dysfunction were reported in CoA patients late after repair and in patients with essential hypertension [92-94].

No clinically significant differences between patients and controls were found in plasma concentrations of vasoactive hormones, renal function parameters, plasma and urinary electrolytes, maximal heart rate, and maximal achieved workload among groups, either at rest or during exercise. A comparable analysis using the same parameters has not previously been reported in the literature on adult patients after CoA repair.

The exercise-induced increase in systolic blood pressure was similar in all groups. An exaggerated blood pressure response to exercise has been previously suggested as an indication of ReCoA [95], but the increase in systolic blood pressure in this study was similar in controls and patients with and without ReCoA.

Renal function parameters were similar in all patient subgroups and in healthy subjects.

Mild ReCoA had no major impact on study findings at rest or during exercise. This finding supports the results from substudy I, showing that milder degrees of ReCoA do not have a noteworthy effect on the examined parameters for late morbidity.

In conclusion, patients with repaired CoA had increased left ventricular mass and decreased systolic and diastolic function, even those with normal blood pressures and absence of ReCoA. Persistent left ventricular dysfunction and hypertension decades after repair could not be explained by changes in the renin-angiotensin-aldosterone system and in renal function, and may therefore represent irreversible changes associated with CoA, especially when repaired later in life.

4.3. Substudy III

The 119 patients who completed the SF-36 health survey were included in this study and compared with 36 healthy subjects. Overall, we found that functional health status in patients late after CoA repair was only slightly impaired compared to that of the normal population. More specifically, norm-based physical functioning scores were significantly lower among patients compared with controls (51.8 ± 7.1 versus 54.3 ± 4.7 , $p < 0.05$), as shown in Figure 3. Nevertheless, when patients with associated cardiovascular morbidity were excluded from the analysis, all scores were similar in patients and controls. The discrete impairment of self-perceived functional health status in adult patients after CoA repair is similar to previous findings [30].

Patients using antihypertensive medication scored significantly lower in all physical categories (physical component summary = 48.9 ± 10.4 versus 54.9 ± 4.9 , $p < 0.05$) as well as in vitality (46.4 ± 10.5 versus 51.4 ± 10.4 , $p < 0.05$) compared with patients not taking medication. These differences did not, in general, change when patients with associated cardiovascular morbidities other than hypertension were excluded. The influence of daily medication intake on CoA patients' functional health found in this study

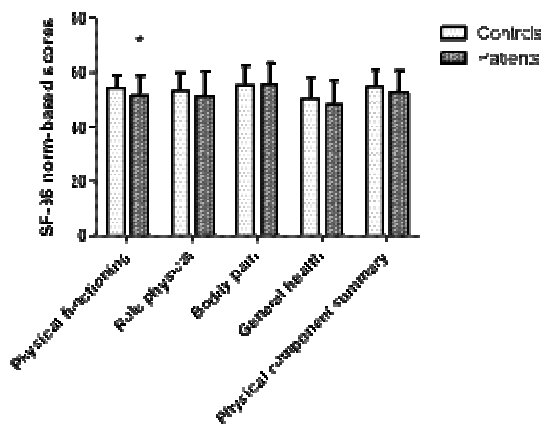
has not been previously reported, but is in accordance with findings in patients with other diseases [33, 34].

The 31 patients with impaired exercise capacity scored significantly lower in several mental and physical categories compared with patients with normal exercise capacity (physical component summary = 49.7 ± 10.7 versus 54.0 ± 6.2 , $p < 0.05$; mental component summary = 44.9 ± 14.6 versus 50.1 ± 10.0 , $p < 0.05$). The negative effect of reduced exercise capacity on self-reported functional health status in this study supports previous findings in similar patient cohorts [31].

In linear regression models, both use of medication and maximal achieved workload were significantly negatively related to lower scores in physical (but not mental) component summary with adjustment for age, gender, BMI, and comorbidity.

In conclusion, self-perceived functional health status in patients after surgical correction of CoA was, in general, similar to that seen in healthy controls. Nevertheless, use of medications even in patients without significant comorbidity apart from hypertension was associated with lower physical scores. Similarly, reduced exercise capacity was associated with lower scores both in physical and in mental aspects of functional health.

Physical component scores for controls and patients



Mental component scores for controls and patients

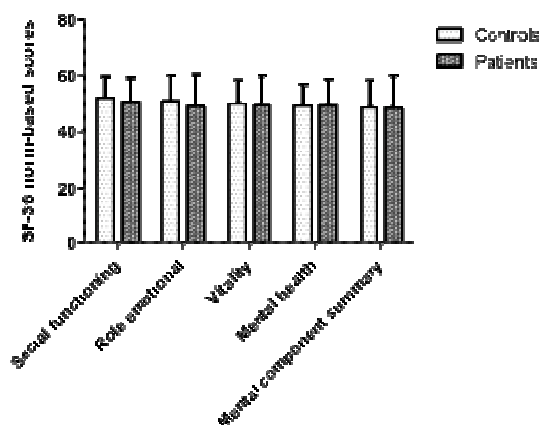


Figure 3
Physical and mental component norm-based scores in patients and controls

4. GENERAL LIMITATIONS

The main limitation, which applies for all three substudies, is that the study was performed in a patient population which may not be representative of patients currently undergoing CoA repair.

The present cohort underwent repair at an older age and with a slightly different surgical technique than is often used today. Severe ReCoA was not seen in any patients in the present cohort, because the patients who had developed severe ReCoA prior to the current study had already undergone reintervention. Thus, conclusions for all three substudies may not necessarily apply to patients with more significant degrees of residual arch obstruction.

In addition, the present study included a large spectrum of patients, from those with significant associated morbidity who had regular follow-up in specialized centers to those who were asymptomatic and had not had regular contact with the health care system for decades.

Another limitation is that 23 patients from the cohort did not participate in the study. However, data available in the Danish registries on the non-participants show that these 23 patients did not differ significantly from the study population. Thus, we believe that the current results would not have been significantly different if we had the opportunity to examine all the patients.

Due to the extension of the examination protocol and the fairly large number of patients, it was not possible to include as many controls as patients.

The examinations in the study protocol were not blinded. Nevertheless, we attempted to minimize the bias of this fact by analyzing data post-hoc off-line.

5. GENERAL CONCLUSIONS

CoA is rarely cured by surgery. Surgical correction of this malformation only repairs the anatomical narrowing, but not the associated vasculo- and valvulopathy. Increased left ventricular mass, systolic and diastolic dysfunction, aortic valve dysfunction, aortopathy, and hypertension are common. Morbidity is only weakly associated with mild and moderate degrees of ReCoA, and not associated with changes in vasoactive hormone levels and renal function. Thus, preoperative changes may be partly irreversible, in particular when CoA repair is performed later in life.

Despite the high occurrence of late morbidity, functional health status is overall only slightly impaired in patients after surgical correction of CoA compared with healthy subjects. Nevertheless, the subgroup with reduced exercise capacity and need for cardiovascular medications have a considerable impairment of both physical and mental aspects of functional health.

6. PERSPECTIVES

The recognition of the high prevalence of late cardiovascular morbidity after repaired CoA even in the absence of hypertension and ReCoA leads to further questions, for instance:

7.1. Could aortic arch geometry influence late hypertension and left ventricular dysfunction more markedly than does the arch diameter itself? Previous studies have given contradictory results

[96-98]. Because most of these studies have been performed in children and young patients repaired in early childhood, it would be interesting to study the aortic arch geometry in adults late after repair and correlate findings with blood pressure levels (rest and exercise), left ventricular and renal function parameters, and vasoactive hormone levels.

7.2. Could arterial stiffness play an important role in this cohort of patients repaired late in life [93, 99, 100]? Do these patients have “inappropriately high” left ventricular mass contributing to the adverse outcomes [101, 102]? What is the relationship between arterial stiffness/inappropriately high left ventricular mass and vasoactive hormone levels? A study involving these parameters could contribute to the current knowledge in this field.

7.3. There is a very high prevalence of arterial hypertension in patients after repaired CoA and many patients take antihypertensive agents [86]. Do these patients benefit from antihypertensive medication beyond a reduction in blood pressures? It would be relevant to assess whether patients taking antihypertensive agents have better myocardial function, exercise capacity, and functional health status compared with untreated hypertensive patients.

7.4. There are guidelines for intervention in patients with primary CoA [22]. However, indications for reintervention in patients with ReCoA, especially those with less severe obstructions, are not well established. It would be valuable to assess parameters for systolic and diastolic function, arterial stiffness, left ventricular mass, vasoactive hormone levels, as well as blood pressures before and after reintervention in a prospective study in patients with milder degrees of aortic arch obstruction.

7.5. Cardiovascular physiology undergoes profound changes during pregnancy. Hypertension places additional hemodynamic stress on a vascular system already exposed to increased heart rate, stroke volume, and total plasma volume. Exacerbation of pre-existing hypertension or pregnancy-induced hypertension puts women with repaired CoA at a higher risk of pregnancy complications compared with healthy pregnant women [103-105]. Previous reports are based on single-center experiences and lack comparisons with unaffected pregnant women. Besides, they lack linkage between mother and child on nation-based registries. Use of the Danish Registry System gives a unique opportunity to investigate the effect of the hypertensive complications of pregnancy on neonatal outcomes as well as on the prevalence of congenital cardiac disease in the offspring of all women with a repaired CoA, and to compare these data with those of the general age-matched female population.

7. SUMMARY

Background: Repaired aortic coarctation (CoA) is associated with high long-term cardiovascular mortality and morbidity. Persisting hypertension and left ventricular dysfunction are possibly associated with residual or recurrent aortic arch obstruction (ReCoA) and abnormal activation of vasoactive hormones. Furthermore, knowledge regarding these patients' functional health status late after repair is missing.

Study subjects: A total of 133 adults who underwent surgical repair of CoA in childhood and youth (84 men) were examined in this observational cohort study. Median age (range) at surgery was 10 (0.1–40) years and 44 (26–74) years at examination. Thirty-six age and gender-matched healthy subjects served as controls.

Outcome measures: Prevalence of previous cardiovascular reintervention, current cardiac and valvular function, exercise capacity, blood pressure levels, as well as the presence of residual or recurrent aortic arch obstruction (ReCoA) and aortic aneurysms.

Methods: Echocardiography (including tissue Doppler), bicycle exercise testing, 24-h ambulatory blood pressure monitoring, MRI/CT scan of the thoracic aorta were performed. Analysis of renal function and vasoactive hormones was performed by blood and urine tests at rest and after maximal physical effort. Functional health status was assessed by means of the SF-36 health survey.

Results: The prevalence of hypertension was high (44% of the cohort had blood pressure levels above the recommended levels, half of those despite medication). Reinterventions were common (26%) and most often performed due to aortic valve dysfunction and ReCoA. Above half of the cohort had a bicuspid aortic valve, which was strongly associated with ascending aorta aneurysms and aortic valve regurgitation. A total of 48% of the patients had a mild to moderate ReCoA, which was only weakly associated with the presence of hypertension as well as to exercise capacity and echocardiographic measurements of cardiac function. Both normotensive and hypertensive patients had increased left ventricular mass, normal ejection fraction, reduced long-axis systolic function, and impaired diastolic function compared with controls, with differences being more pronounced in hypertensive patients. Natriuretic hormone levels were slightly increased among normotensives, whereas renin-angiotensin-aldosterone and renal function parameters were normal at rest and during exercise. Mild to moderate ReCoA had no significant influence on the measured parameters. SF-36 scores among patients were only slightly lower compared with those from controls. However, patients with reduced exercise performance and those taking daily cardiovascular medication scored significantly lower in several mental and physical categories compared with patients with unmedicated patient and with those with preserved exercise capacity.

Conclusions: Surgical correction of CoA only repairs the anatomical narrowing, but not the associated vasculo- and valvulopathy. Increased left ventricular mass, systolic and diastolic dysfunction, aortic valve dysfunction, aortopathy, and hypertension are common. Morbidity is only weakly associated with mild and moderate degrees of ReCoA, and not associated with changes in vasoactive hormone levels and renal function.

Despite late morbidity, functional health status is overall only slightly impaired in patients after surgical correction of CoA compared with healthy subjects. Nevertheless, the subgroup with reduced exercise capacity and need for cardiovascular medications have a considerable impairment of both physical and mental aspects of functional health.

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