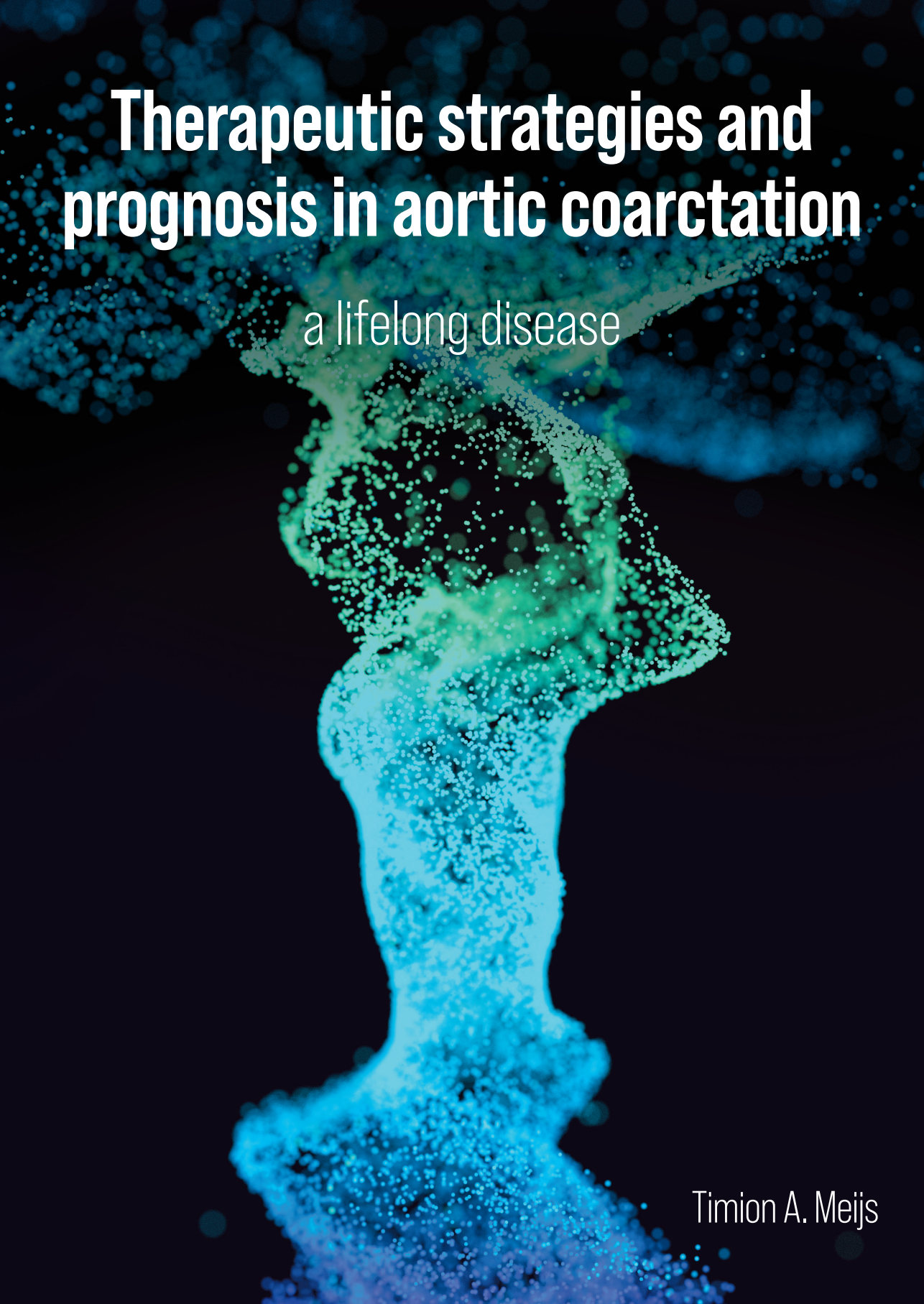
# Therapeutic strategies and prognosis in aortic coarctation

## a lifelong disease



Timion A. Meijs

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# Therapeutic strategies and prognosis in aortic coarctation: a lifelong disease

**Therapeutische strategieën en prognose bij coarctatio aortae: een levenslange aandoening**

(met een samenvatting in het Nederlands)

**Proefschrift**

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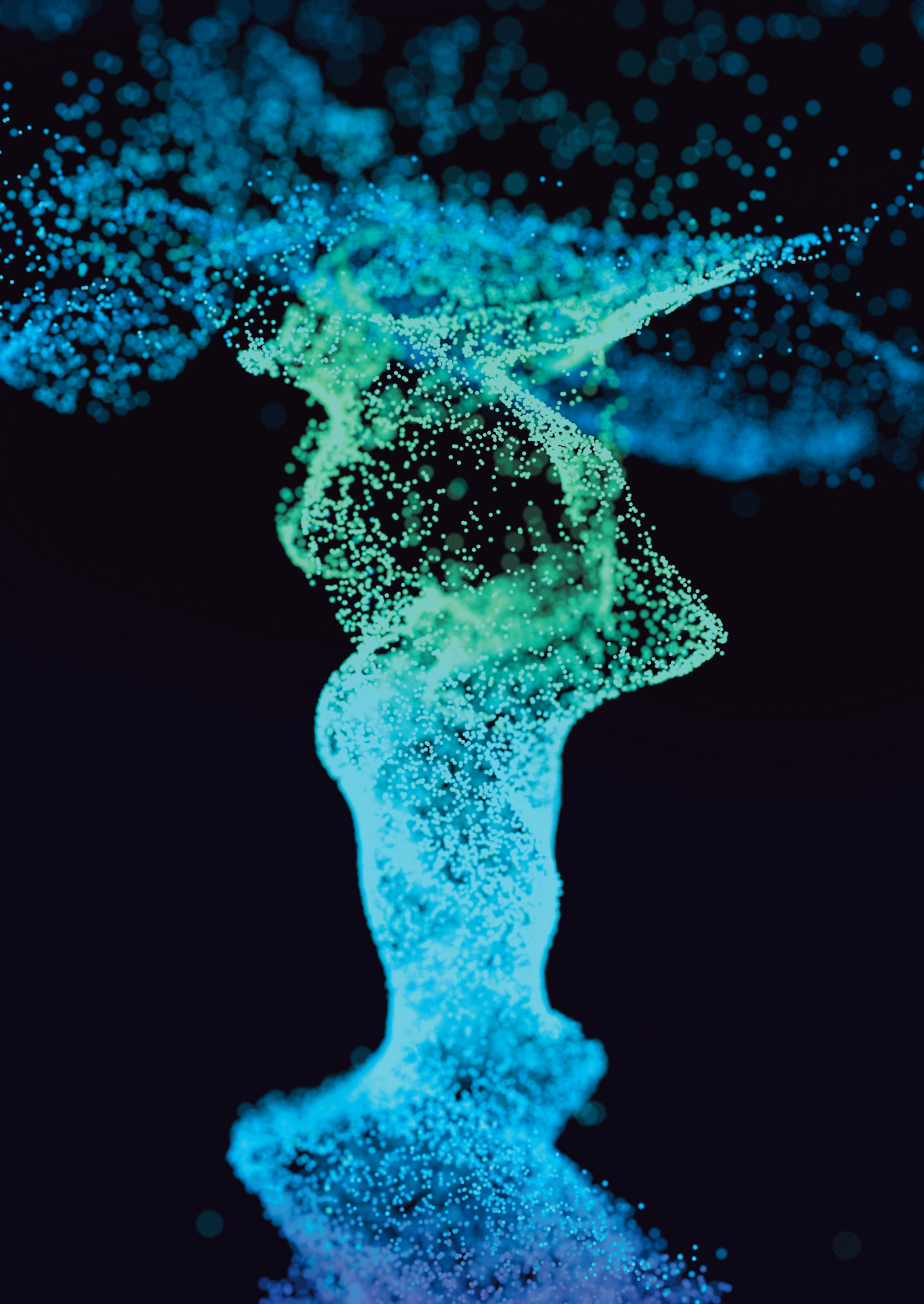

# CHAPTER 1

## General introduction and thesis outline

## GENERAL INTRODUCTION

Congenital heart disease is referred to as a structural abnormality of the heart or the heart's great vessels, which is present at birth. It is commonly classified as cyanotic or acyanotic. Coarctation of the aorta (CoA) is an acyanotic congenital heart defect, characterized by a focal narrowing of the proximal descending aorta, typically located at the insertion of the ductus arteriosus (Figure 1). It affects 3-4 per 10,000 newborns and thereby accounts for 5-6% of all congenital heart defects.[1,2] The prevalence of CoA is approximately twice as high in males compared to females. Although CoA may occur as an isolated condition, it is frequently present in association with other congenital heart defects, most commonly a bicuspid aortic valve (50-85%) and a ventricular septal defect (~20%).[3,4] In addition, CoA is present in approximately 10% of patients with Turner syndrome.[5] This suggests that genetic factors play a role in the etiology of CoA. In the pre-surgical era, the condition carried a poor prognosis with 50% mortality before the age of 32 years.[6] Nowadays, due to early detection methods and advances in surgical and percutaneous treatment, long-term survival has improved markedly. However, follow-up after repair is still characterized by a high prevalence of hypertension and consequent cardiovascular complications.[7] The management and long-term clinical outcome of CoA patients are discussed in more detail in the next paragraphs.

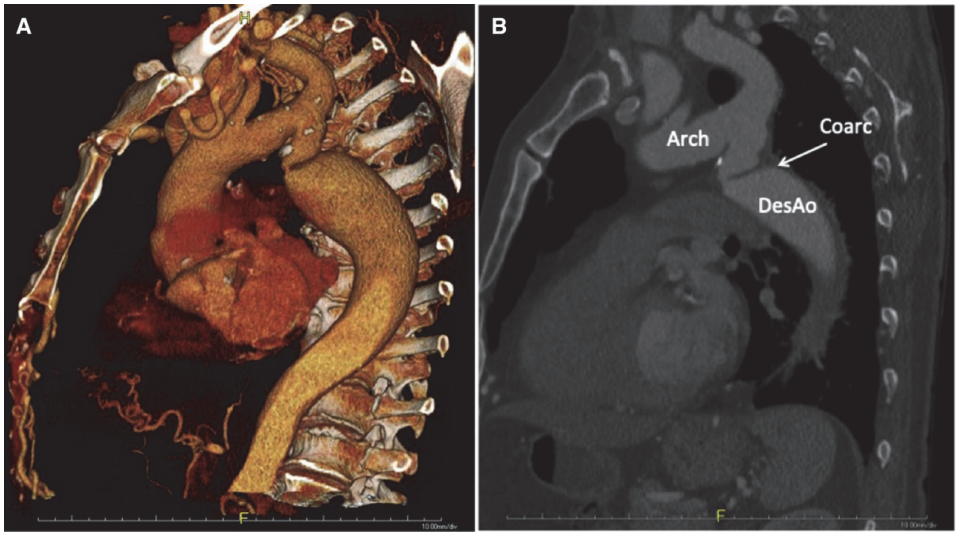


**Figure 1. Coarctation of the aorta.** (A) Three-dimensional computed tomography showing a native CoA in the proximal descending aorta (sagittal view). (B) Computed tomography angiography of the chest in the same patient. Arch, aortic arch; Coarc, coarctation; DesAo, descending aorta. Reproduced from Haeffele with permission from BMJ Publishing Group Ltd.[8]

**Management**

The first surgical repair of CoA was performed in 1944 by dr. Crafoord and his team in Sabbatsberg Hospital in Stockholm, Sweden.[9] Since then, surgical correction has remained the treatment of choice in neonates, infants, and young children. Several surgical techniques have been developed and implemented, each with specific indications based on age, anatomy, and associated lesions. Nowadays, the most widely used technique is resection with extended end-to-end anastomosis, if technically feasible. Meanwhile, percutaneous techniques have emerged as a less invasive treatment option. Balloon angioplasty was first implemented, resulting in an immediate relief of the pressure gradient across the CoA. However, the drawbacks of this technique became visible in the following years. Particularly, an increased risk of aneurysm formation and restenosis were observed in comparison to surgery.[10,11] The limitations associated with balloon angioplasty were largely overcome by the introduction of stent implantation (Figure 2). Compared to balloon angioplasty, stenting is associated with a reduced risk of aortic wall injury and restenosis, whereas a relevant decrease in pressure gradient (to <20 mmHg) is more frequently achieved.[12] Therefore, stent implantation is currently the preferred treatment for adults with native or recurrent CoA, if the anatomy is suitable.[13,14] However, data on the medium- and long-term effectivity of stenting, particularly its effect on systemic blood pressure, remain scarce. Although stenting can be safely performed in patients <30 kg, these patients often require re-dilatations of the stent to compensate for somatic growth, which is a limitation of stent implantation.[15] A subset of patients with CoA has a concomitant stenosis in the aortic arch, which is often caused by hypoplastic or gothic geometry. Although stenting of the aortic arch may be technically challenging, previous studies have shown promising results.[16,17]

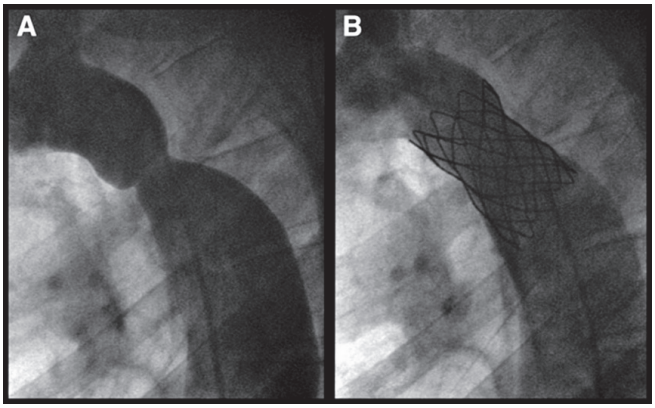


**Figure 2. Angiography of the descending aorta in a CoA patient before (A) and after (B) stent implantation.** Reproduced from Meadows et al. with permission from Wolters Kluwer Health, Inc.[18]

**Long-term clinical outcome**

In the years following the introduction of surgical repair of CoA, it was thought that the condition could be cured by surgery.[19] Despite initial relief of the obstruction, it became clear that a substantial proportion of patients developed recurrent CoA during follow-up, requiring one or more re-interventions.[20] Furthermore, although most patients have adequate blood pressure control in the first years after surgery, hypertension is present in nearly 70% of patients after 15 years of follow-up.[21] Importantly, most of these hypertensive patients have no evidence of recurrent CoA.[22] The origin of hypertension remains widely debated to this day. Multiple studies have found that the stiffness of the pre-stenotic aorta is markedly increased in patients with CoA, even after adequate repair.[23,24] Moreover, the brachial arteries show less responsiveness to flow-mediated and chemical stimuli and the retinal arteries have a characteristic "corkscrew" shape.[25,26] These findings suggest that CoA is not a localized condition of the descending aorta, but is rather characterized by a more widespread arteriopathy. It is likely that the resulting arterial dysfunction contributes to the development of hypertension. Other proposed causes of hypertension in CoA patients include an overactivation of the renin-angiotensin-aldosterone system, baroreceptor dysfunction, and an aberrant aortic arch morphology such as a hypoplastic or gothic arch.[27,28]

Patients with CoA are at increased risk to experience hypertension-related cardiovascular complications during follow-up, including arrhythmias, ascending aortic aneurysm formation, coronary artery disease, and stroke.[29] The hazard of hemorrhagic and ischemic stroke is approximately 15-fold and 4-fold increased, respectively, compared to the general population.[30,31] Furthermore, stroke occurs 15 to 30 years earlier in these patients.[32] Interestingly, intracranial aneurysms are present in 10% of adult CoA patients.[33-35] Although these aneurysms are generally small, their growth and risk of rupture are unclear due to the lack of longitudinal follow-up studies.[35] Hence, the benefit of routine screening for intracranial aneurysms remains questionable.[14] Despite the high risk of cerebrovascular accidents in patients with CoA, little is known about the characteristics of the cerebral circulation. It is of particular interest to determine whether the cerebral arteries show similar signs of vascular dysfunction as observed in the pre-stenotic aorta.

## THESIS OUTLINE

In **chapter 2**, we present a case of a young adult with a long history of hypertension despite antihypertensive medication. She was eventually diagnosed with CoA and treated by stent implantation. Based on this case, we discuss the clinical characteristics of CoA with particular emphasis on the typical findings during physical examination. Additionally, current treatment options are addressed. The remaining chapters of this thesis are subdivided into two parts.

**Part I: Evaluation and optimization of stent implantation for aortic coarctation**
In the first part, we evaluate the efficacy and safety of stent implantation for aortic coarctation and seek to optimize patient selection. Although stent implantation generally leads to a favorable anatomical result and effective reduction of the pressure gradient, it is unclear whether this results in a sustained blood pressure reduction during follow-up. In **chapter 3**, we present a systematic review and meta-analysis in which we examine changes in blood pressure from pre-implantation to medium-term follow-up after stenting. The decision to perform stent implantation is (partly) based on the invasive peak systolic gradient across the CoA, although this gradient may be underestimated during cardiac catheterization. In **chapter 4**, we evaluate whether the use of epinephrine stress testing during cardiac catheterization may be helpful in assessing the hemodynamic relevance of CoA. Patients with CoA may have concomitant hypoplasia of the aortic arch, which is a known risk factor for hypertension.[28] The outcomes of stent implantation for a hypoplastic aortic arch are described in **chapter 5**. In **chapter 6**, we present a case of aortic arch stenting complicated by a pseudoaneurysm. We illustrate that the challenging anatomy of these aneurysms may require a less conventional approach.

**Part II: Long-term clinical outcome in aortic coarctation**
In this part, we assess the clinical outcome of CoA patients during long-term follow-up. In **chapter 7**, we provide an overview of the cardiovascular events observed in a nationwide cohort of adult CoA patients. Furthermore, we identify risk factors for the occurrence of these cardiovascular events and compare all-cause mortality to an age- and sex-matched cohort from the general population. Apart from resting hypertension, a hypertensive response to exercise is also frequently present in patients with CoA, although its clinical implications remain unclear. In **chapter 8**, we report on the prevalence, risk factors and prognostic consequences of a hypertensive response to exercise. As stroke is a frequent long-term complication in CoA patients, in **chapter 9** we use 3 tesla and 7 tesla MRI to examine aortic and cerebral hemodynamics and the presence of vascular brain injury.

In **chapter 10**, we discuss the main findings of this thesis and elaborate on their implications for clinical practice and future research.

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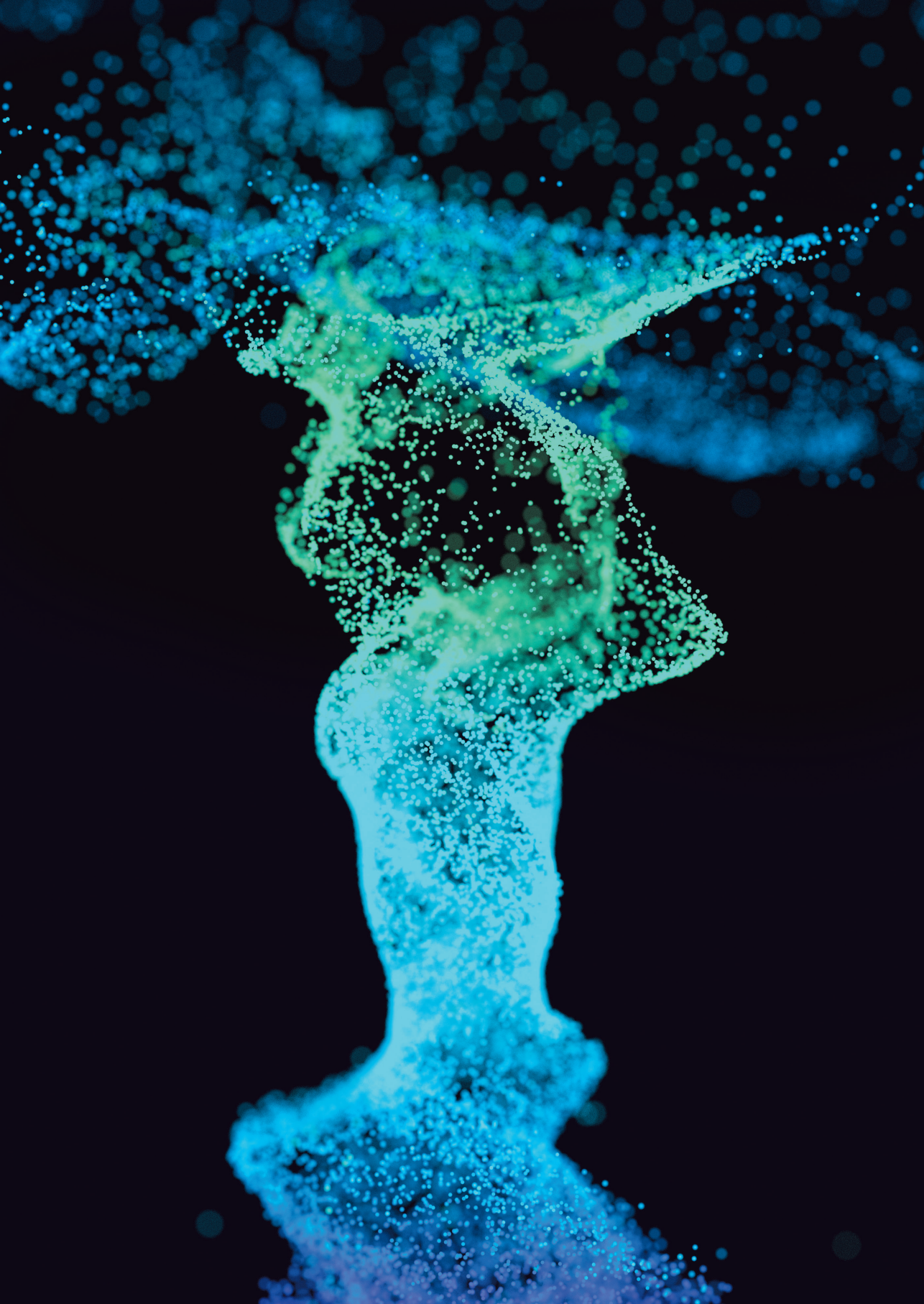

# CHAPTER 2

# Coarctatio aortae: een oorzaak van moeilijk behandelbare hypertensie

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Jesse Peek, A. (Sander) Limburg, Michiel Voskuil

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**SAMENVATTING**

**Achtergrond**
Coarctatio aortae is een aangeboren vernauwing van de proximale aorta descendens die zich bij kinderen en jongvolwassenen kan uiten in onbegrepen of moeilijk behandelbare hypertensie.

**Casus**
Een 25-jarige vrouw heeft al 9 jaar hypertensie. Vanwege persisterende hypertensie ondanks behandeling met telmisartan en amlodipine wordt zij verwezen naar de polikliniek Interne Geneeskunde. Bij lichamelijk onderzoek wordt een systolische souffle gehoord. Zij wordt naar de cardioloog verwezen. Bij beeldvormend onderzoek stelt de cardioloog een ernstige coarctatio aortae met uitgebreide collateraalvorming vast, naast een goed functionerende bicuspide aortaklep. Vanwege de coarctatio wordt patiënte behandeld met een stent. Na 7 maanden is patiënte normotensief zonder dat zij antihypertensiva gebruikt.

**Conclusie**
Hypertensie bij kinderen en jongvolwassenen is een ongewone bevinding en heeft vaak een secundaire oorzaak. Coarctatio aortae wordt gekenmerkt door een combinatie van hypertensie en een systolisch bloeddrukverval tussen de bovenste en onderste extremiteiten. Vroegtijdige diagnostiek en behandeling zijn essentieel om cardiovasculaire complicaties op de lange termijn te voorkomen.

Het belang van een goed lichamelijk onderzoek mag niet uit het oog worden verloren in het huidige tijdperk van moderne medische technologie. Aangeboren hartafwijkingen, zoals coarctatio aortae, kunnen relatief eenvoudig worden opgespoord bij lichamelijk onderzoek. Hoewel de prevalentie van coarctatio aortae laag is, moet men bedacht zijn op de aanwezigheid ervan bij kinderen en jongvolwassenen met onbegrepen of moeilijk behandelbare hypertensie. Aan de hand van een casus bespreken wij de diagnostiek en behandeling van deze aandoening.

## ZIEKTEGESCHIEDENIS

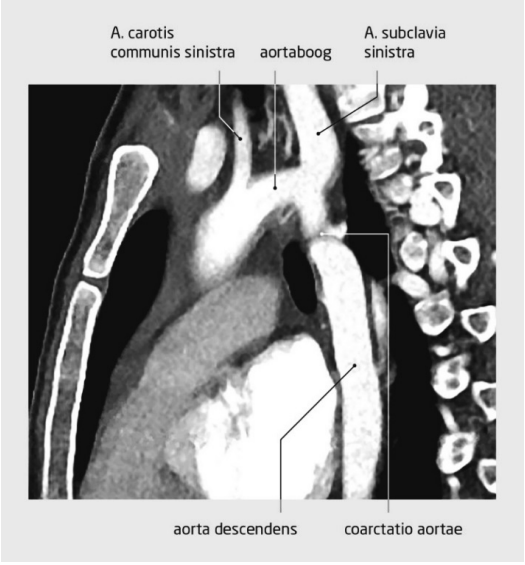
Patiënte, een 25-jarige vrouw, heeft sinds 9 jaar een hypertensie die moeilijk te behandelen is. Zij ervaart geen klachten, rookt niet en heeft geen overgewicht. Ook heeft zij geen familieleden die op jonge leeftijd een hart- of vaatziekte kregen. De huisarts verricht een 24-uursbloeddrukmeting; de gemiddelde bloeddruk is 151/82 mmHg, ondanks behandeling met telmisartan en amlodipine. Hierop verwijst de huisarts patiënte naar de internist.

Bij lichamelijk onderzoek meet de internist geen verschil tussen de bloeddruk aan de rechter en de linker arm; de bloeddruk wordt niet aan het been gemeten. Bij auscultatie van het hart hoort de internist precordiaal een systolische souffle graad 3/6, met het punctum maximum op de 2e intercostaalruimte aan de rechterzijde. De internist ausculteert niet op de rug van patiënte. Over het traject van de abdominale aorta wordt geen souffle gehoord. In de liezen zijn beiderzijds pulsaties voelbaar. Vanwege de precordiale souffle verwijst de internist patiënte naar de polikliniek Cardiologie.

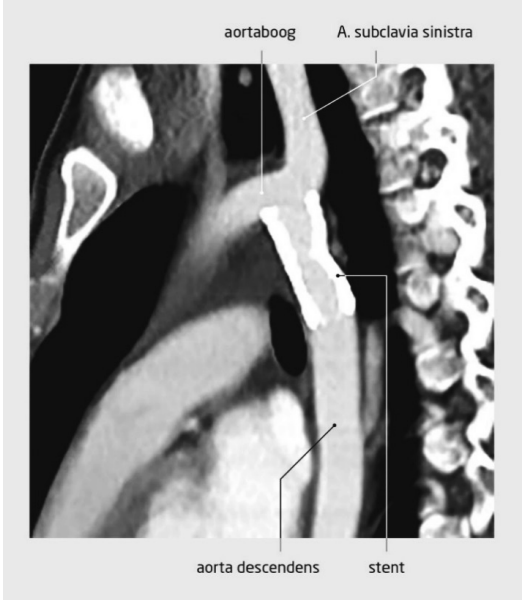
Bij transthoracale echocardiografie zien wij een goed functionerende bicuspide aortaklep met een behouden hartfunctie. Gezien de hypertensie en aanwezigheid van een bicuspide aortaklep verrichten wij aanvullend een CT-angiografie van de thorax. De CT-angiografie laat een significante coarctatio aortae zien met uitgebreide collateraalvorming (figuur 1). Wij verwijzen patiënte naar een specialistisch centrum, waar zij wordt behandeld met een stent (figuur 2). Nadien kan de bloeddrukmedicatie volledig worden afgebouwd. 7 maanden na de stentplaatsing heeft patiënte een gemiddelde bloeddruk van 127/60 mmHg bij 24-uursmeting.

## BESCHOUWING

Bij kinderen en jongvolwassenen is hypertensie een ongewone bevinding, met een geschatte prevalentie van 4%.[1] Bij > 50% van de kinderen met hypertensie is sprake van een secundaire oorzaak, wat naast een coarctatio aortae ook een renale of endocriene aandoening kan betreffen.[2] Deze casus illustreert de vertraging die kan optreden bij het vaststellen van een coarctatio aortae. Wat zijn de klinische kenmerken en hoe kan dit ziektebeeld vroegtijdig worden opgespoord?




**Figuur 1. Coarctatio aortae.** CT-angiografie van de thorax van een 25-jarige vrouw met sinds 9 jaar hypertensie ondanks behandeling met telmisartan en amlodipine. Er is een ernstige coarctatio aortae zichtbaar in de proximale aorta descendens, distaal van de origo van de A. subclavia sinistra.




**Figuur 2. Na stentplaatsing.** CT-angiografie van de thorax van dezelfde patiënte nadat zij is behandeld met een stent. Er is een 'BeGraft covered stent' (Bentley; Hechingen, Duitsland) geïmplanteerd in de aorta descendens op de plaats van de coarctatio aortae.

**Epidemiologie**

Coarctatio aortae is een aangeboren hartaandoening die voorkomt bij 3-4 op de 10.000 levendgeborenen, wat neerkomt op ongeveer 60 nieuwe patiënten per jaar in Nederland.[3] De aandoening wordt gekenmerkt door een lokale vernauwing van de proximale aorta descendens, die meestal net distaal van de origo van de linker A. subclavia is gelokaliseerd. Coarctatio aortae kan voorkomen als een opzichzelfstaande afwijking, maar gaat veelal gepaard met andere cardiovasculaire aandoeningen, waarvan een bicuspide aortaklep de meest voorkomende is (50-85%).[4]

**Diagnostiek**

Meestal wordt een coarctatio aortae prenataal of vroeg na de geboorte gediagnosticeerd, waarbij sprake kan zijn van acuut linkerventrikelfalen en hypoperfusie van de onderste extremiteiten na sluiting van de ductus arteriosus. Een minder ernstige coarctatio aortae wordt vaak pas op latere leeftijd ontdekt en uit zich dan klassiek in een onbegrepen of moeilijk behandelbare hypertensie.[5] Kenmerkend is dat naast hypertensie in de bovenste extremiteiten sprake is van een relatief lage bloeddruk in de onderste extremiteiten, wat gepaard kan gaan met claudicatieklachten van de benen. Een systolisch bloeddrukverval > 20 mmHg tussen de armen en de benen wijst op een hemodynamisch belangrijke coarctatio aortae, hoewel ook bij een lager bloeddrukverval – bijvoorbeeld als gevolg van uitgebreide collateraalvorming – sprake kan zijn van een significante coarctatio.[6] Het verdient de voorkeur om de bloeddruk aan beide armen te meten, aangezien deze patiënten vaak aortabooghypoplasie hebben, wat zich uit in een bloeddrukverval tussen de rechter en de linker arm.[6] Tevens kunnen bij patiënten met een coarctatio aortae de liespulsaties zwak of niet palpabel zijn. Daarom is palpatie van de liezen een standaard onderdeel van het onderzoek van een pasgeborene. Vaak zijn de liespulsaties vertraagd in vergelijking met de pulsaties van de A. radialis, wat 'radiofemoral delay' wordt genoemd.

Bij auscultatie kan een kenmerkende systolische souffle worden gehoord langs de mediale scapularand aan de linkerzijde. Bij aanwezigheid van collaterale arteriën kan sprake zijn van een continu geruis. Daarnaast kan precordiaal een souffle worden waargenomen als gevolg van bijkomende hartziekten, zoals een bicuspide aortaklep. De afwezigheid van een souffle sluit de diagnose 'coarctatio aortae' echter niet uit.

Wanneer het klinische vermoeden van een coarctatio aortae bestaat, moet de patiënt worden verwezen naar een (kinder-)cardioloog voor aanvullende diagnostiek. Bij een transthoracale echocardiografie kan de coarctatio aortae worden gevisualiseerd op een suprasternale opname van de aortaboog en de aorta descendens; ook kunnen bijkomende cardiale afwijkingen worden vastgesteld. Met een MRI- of CT-scan met angiografie wordt de exacte locatie en ernst van de coarctatio aortae bepaald en kunnen eventuele collateralen worden opgespoord.[3]

**Behandeling en follow-up**

Bij kinderen < 16 jaar wordt een coarctatio aortae meestal chirurgisch gecorrigeerd; soms wordt eerst een ballondilatatie verricht vanwege hemodynamische instabiliteit bij patiënten met een zeer ernstige coarctatio aortae.[7] Stentplaatsing is op jonge leeftijd onaantrekkelijk vanwege de somatische groei die nog te verwachten is. Bij oudere kinderen (≥ 16 jaar) en volwassenen daarentegen is stentplaatsing wel de aangewezen therapie indien het technisch mogelijk is. Behandeling met een stent heeft voornamelijk de voorkeur vanwege het minder invasieve karakter. Daarnaast heeft het een aangetoond gunstig effect op de bloeddruk op middellange termijn.[8] Ondanks een goed anatomisch resultaat van een chirurgische correctie of stentplaatsing kan de hypertensie persisteren of recidiveren. Hierdoor blijft op lange termijn sprake van een verhoogd risico op onder andere ischemisch hartlijden, hartritmestoornissen en cerebrovasculaire accidenten.[9] Daardoor is levenslange follow-up noodzakelijk.[4]

**Wat had er anders gekund?**

Bij deze jongvolwassene met een slecht gereguleerde hypertensie ondanks behandeling met meerdere antihypertensiva had de coarctatio aortae eerder herkend kunnen worden. Door bij lichamelijk onderzoek de bloeddruk te meten aan beide armen en benen en te ausculteren op de rug ter hoogte van de mediale scapularand aan de linkerzijde had de diagnose vroegtijdig opgespoord kunnen worden. Ook hoort bij een jongvolwassene met een moeilijk behandelbare hypertensie te worden gedacht aan andere secundaire oorzaken van hypertensie, zoals een nierarteriestenose of schildklierdisfunctie.

## CONCLUSIE

Bij een kind of jongvolwassene is hypertensie een ongewone bevinding, waarbij gericht (lichamelijk) onderzoek naar potentiële secundaire oorzaken van hypertensie moet plaatsvinden. Coarctatio aortae wordt gekenmerkt door hypertensie in combinatie met een systolisch bloeddrukverval tussen de bovenste en onderste extremiteiten. Tevens kan sprake zijn van een souffle, al sluit de afwezigheid hiervan de diagnose niet uit. Vroegtijdige diagnostiek en behandeling zijn noodzakelijk om het risico op persisterende hypertensie en hieraan gerelateerde cardiovasculaire complicaties te verlagen.

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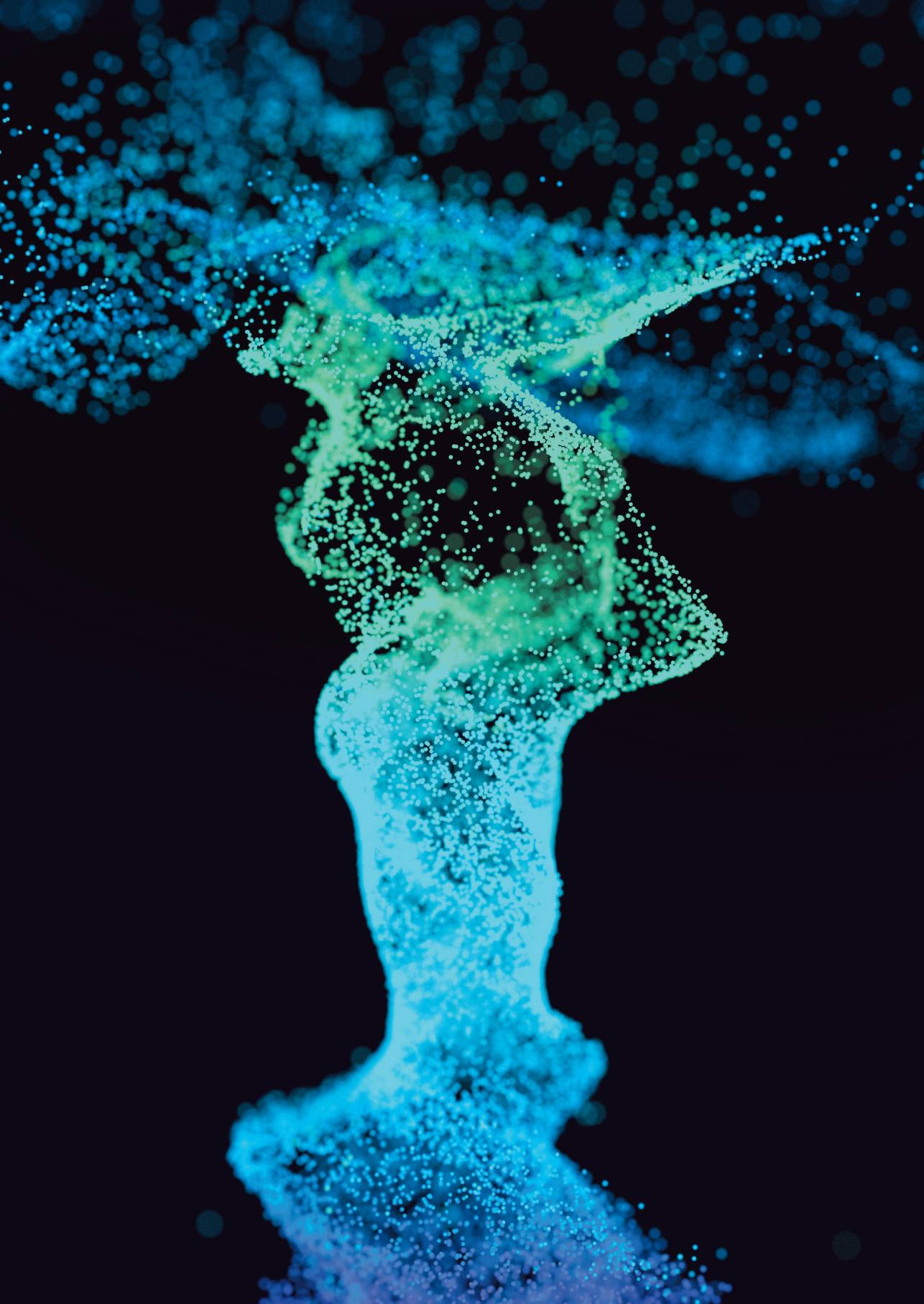
# PART I

# Evaluation and optimization of stent implantation for aortic coarctation



# CHAPTER 3

# Medium-term systemic blood pressure after stenting of aortic coarctation: a systematic review and meta-analysis

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**Heart. 2019;105(19):1464-1470.**

**ABSTRACT**

**Objective**

Long-term prognosis of patients with aortic coarctation (CoA) is impaired due to the high prevalence of hypertension and consequent cardiovascular complications. Although stent implantation results in acute anatomical and hemodynamic benefit, limited evidence exists regarding late clinical outcome. In this meta-analysis we aimed to evaluate the medium-term effect of stent placement for CoA on systemic blood pressure (BP).

**Methods**

PubMed, EMBASE, and Cochrane databases were searched for non-randomized cohort studies addressing systemic BP ≥ 12 months following CoA stenting. Meta-analysis was performed on the change in BP from baseline to last follow-up using a random-effects model. Subgroup analyses and meta-regression were conducted to identify sources of heterogeneity between studies.

**Results**

Twenty-six studies with a total of 1,157 patients and a median follow-up of 26 months were included for final analysis. Meta-analysis showed a 20.3 mmHg (95% confidence interval (CI) 16.4-24.1 mmHg; $P < 0.00001$) reduction in systolic BP and an 8.2 mmHg (12 studies; 95% CI 5.2-11.3 mmHg; $P < 0.00001$) reduction in diastolic BP. A concomitant decrease in the use of antihypertensive medication was observed. High systolic BP and peak systolic gradient at baseline and stenting of native CoA were associated with a greater reduction in systolic BP at follow-up**.**

**Conclusions**

Stent implantation for CoA is associated with a significant decline in systolic and diastolic BP during medium-term follow-up. The degree of BP reduction appears to be dependent on baseline systolic BP, baseline peak systolic gradient, and whether stenting is performed for native or recurrent CoA.

## INTRODUCTION

Coarctation of the aorta (CoA) is a congenital narrowing of the thoracic aortic lumen and accounts for approximately 5% to 7% of all patients with congenital heart disease.[1] Although the majority of patients undergo successful surgical repair in early childhood, systemic hypertension remains an important concern with a prevalence reported up to 60% during long-term follow-up.[2] Consequently, the prognosis of CoA patients is reduced due to hypertension-related complications, including accelerated coronary artery disease, heart failure, aneurysm formation, and stroke.[3] Although the presence of residual obstruction is an important substrate for hypertension, many hypertensive CoA patients show no evidence of recurrent stenosis. Hence, the underlying cause of hypertension in this population remains subject of debate. It has been reported that abnormal aortic arch geometry, particularly a hypoplastic or gothic arch, is associated with hypertension.[4] Additionally, the presence of a generalized vasculopathy, reduced aortic wall distensibility, altered blood flow patterns, and impaired baroreceptor sensitivity have been suggested as predisposing factors for persistent hypertension.[5,6]

Over the last decades, stent implantation by transcatheter approach has replaced surgical repair as the treatment of choice for adolescents and adults with native CoA, since it is associated with fewer acute complications compared to surgery, while short-term hemodynamic outcomes are comparable.[7] Furthermore, stenting is preferred in adults with discrete, recurrent CoA.[8] Although stent implantation has shown to effectively reduce aortic gradient with favourable anatomical results, there is uncertainty concerning the late effects on blood pressure (BP) and adverse cardiovascular events.[9] To date, only a limited number of studies with significant heterogeneity in population characteristics and follow-up duration have addressed this issue.[10-12] Recent evidence indicates that in particular the systolic blood pressure (SBP) is predictive of cardiovascular risk in young and middle-aged adults.[13] Consequently, the primary aim of this meta-analysis was to elucidate the effect of stent placement on medium-term SBP in patients with CoA. Second, we sought to identify parameters influencing this effect of stenting in CoA.

## METHODS

### Search strategy and study selection

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] PubMed, EMBASE, and Cochrane Library were searched for non-randomized cohort studies reporting on mean SBP at baseline and at least 12 months after stent implantation, using keywords related to aortic coarctation, stent implantation, and blood pressure. The exact search terms used are provided in Supplemental Methods. Additionally, ClinicalTrials.gov, WHO ICTRP, Google Scholar, and

OpenGrey were searched for unpublished trials and grey literature. No restrictions regarding language and year of publication were applied. We excluded case reports, reviews, (editorial) comments, animal studies, and studies evaluating the outcomes of stenting as a bridging strategy to subsequent surgical intervention. Two authors (TM, EW) independently screened all titles and abstracts of articles identified by the initial search and then reviewed the full-text of potentially relevant articles. Any discrepancies were resolved by discussion with a third study member (MV). Reference lists of selected studies were manually searched to identify other eligible studies.

**Assessment of certainty of evidence**

The outcomes change in SBP and change in diastolic blood pressure (DBP) were assessed on certainty of evidence by two independent reviewers (TM, EW) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[15] GRADE criteria included risk of bias, inconsistency, indirectness, and imprecision. Risk of bias assessment of individual studies was based on the criteria for observational studies as described in the GRADE guidelines (Supplemental Table 1).[16] Control of potential confounding factors was evaluated, including the change in use of antihypertensive medication (AHM), restenosis and/or reintervention for CoA during follow-up, change in BMI and other secondary causes of hypertension (primary hyperaldosteronism, renal artery stenosis, chronic renal disease, obstructive sleep apnea).

**Data extraction**

Data from the eligible studies were extracted by one researcher (TM) using pre-specified forms and subsequently confirmed by a second study member (EW). Variables included first author, title, year of publication, study design, number of subjects, gender, age at stent implantation, type of CoA (native or recurrent), peak systolic gradient (PSG) pre- and directly post-intervention, average follow-up duration, mean SBP and DBP, prevalence of hypertension, and the use of AHM. PSG measurements were only extracted when measured invasively during cardiac catheterization. BP data were recorded prior to stent implantation, during follow-up, and at last follow-up. The prevalence of hypertension was recorded according to the definition of hypertension used in a particular study. When necessary, authors of the studies were contacted for additional data.

**Statistical analysis**

For the description of individual study characteristics, dichotomous variables are expressed as percentages and continuous variables as mean or median, depending on the description used in the study. Distributions across studies are shown as median and range. For pooled analysis, the absolute change in SBP and DBP from baseline to last follow-up and 95% confidence intervals

(CI) were used. This effect size metric was considered clinically relevant, as absolute reductions in SBP and DBP have shown to be highly associated with a reduction in adverse cardiovascular events.[17] In contrast, change in prevalence of hypertension was not considered an appropriate outcome measure, since definitions of hypertension may vary across studies, reference values for children and adults differ, and dichotomizing BP values may result in bias and loss of information.[18] When the standard deviation of BP change was missing, this was calculated using the corresponding P-value. A conservative approach was applied regarding non-exact P-values, e.g. < 0.05, by using the upper limit for analysis. When no P-value was provided, an imputed correlation coefficient was used according to the Cochrane Handbook for Systematic Reviews of Interventions section 16.1.3.2.[19] As the outcome may have been affected by the used material, technique of the operator and the age of participants, we expected the effect size to vary between studies. Therefore, a random-effects model was used. The inverse of the variance was used to weigh individual studies. Heterogeneity was assessed using the $I^2$ statistic and judged as substantial when $I^2 > 50\%$.[20] However, $I^2$ should be interpreted in relation to the sample size of included studies, as $I^2$ may increase with larger studies. To examine possible sources of between-study heterogeneity and to identify potential effect modifiers, subgroup analyses on SBP change were performed. The pre-specified selection of subgroup variables was based on clinical and methodological characteristics identified by previous studies and considered relevant by the authors. These included gender, age, native vs. recurrent CoA, baseline SBP, baseline and post-stenting PSG, change in AHM use, follow-up duration, study design, publication year, method of BP measurement, and incomplete follow-up. The impact of potential effect modifiers was further explored by bivariate random-effects meta-regression. Sensitivity analyses were conducted to assess the robustness of the overall effect on SBP by using a fixed-effects model and by subsequently leaving one study out of the meta-analysis. To identify potential publication bias, a funnel plot was created, which was visually inspected and quantified on asymmetry by the Egger's test. The 'trim and fill' method was used to adjust for potential publication bias.[21] P-values < 0.05 were considered statistically significant. For meta-regression and assessment of publication bias Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA) software was used and all other statistical analyses were conducted using Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

## RESULTS

### Literature retrieval and study characteristics

A total of 2,314 articles were identified by the initial search. After duplicate removal and screening of titles and abstracts, 128 articles were assessed on eligibility by full-text review. Subsequently, 26 studies met the criteria for inclusion in the meta-analysis.[7,10-12,22-43] An overview of the study selection and reasons for exclusion are presented in Figure 1. Table 1 provides the characteristics of the included studies. Age at intervention ranged from 11 to 41 years (median 29 years) and the majority of patients was treated for native CoA as opposed to recurrent CoA (67% versus 33%, respectively). Median length of follow-up was 26 months (range 12-120).

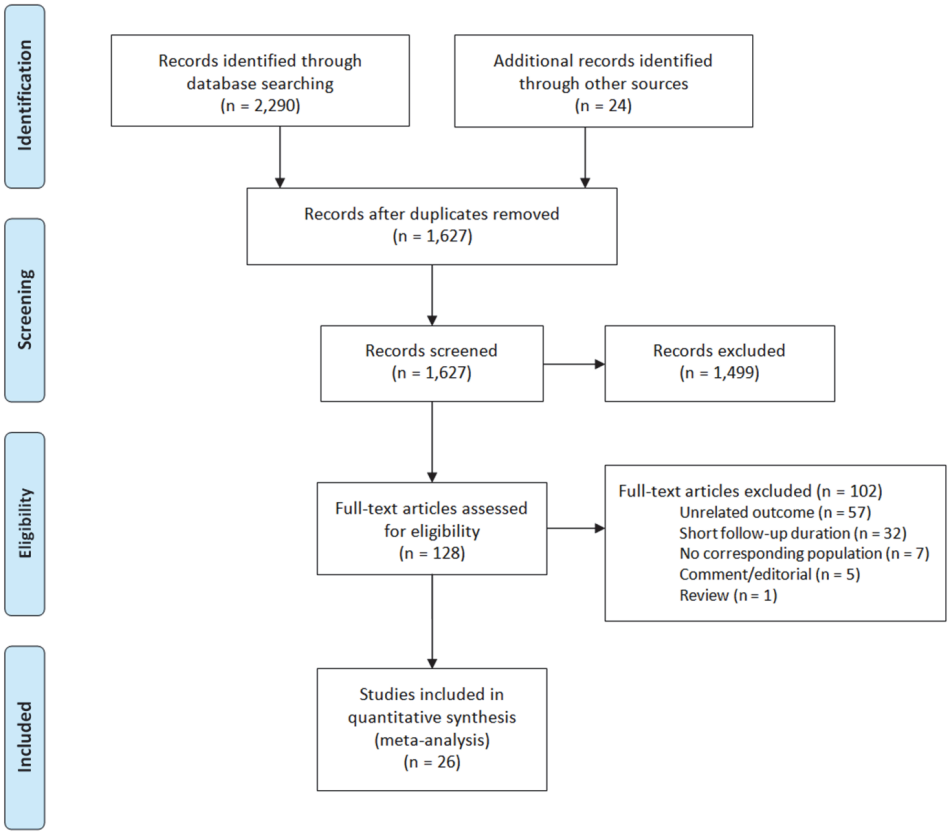


**Figure 1. PRISMA flow diagram showing the study selection process.**[14] PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 1. Characteristics of the individual studies assessing BP after CoA stenting.**

| First author, year | Sample size | Female (%) | Age (years) | Native CoA (%) | Recur-rent CoA (%) | PSG baseline (mmHg) | PSG post (mmHg) | Duration of FU (months) |
|---|---|---|---|---|---|---|---|---|
| Agnoletti, 2005[11] | 15 | NA | 17 | 0 | 100 | 27 | 4 | 22 |
| Bentham, 2013[10] | 40 | 28 | 25 | 50 | 50 | 25 | 3 | 52 |
| Bondanza, 2016[22] | 34 | 29 | 11 | 68 | 32 | 41 | 2 | 120 |
| Forbes, 2011[7] | 217 | 31 | 17 | 100 | 0 | 37 | 5 | 33 |
| Grondahl, 2017[23] | 9 | 22 | 34 | 0 | 100 | 14 | 2 | 21 |
| Haji Zeinali, 2017[24] | 62 | 36 | 31 | 95 | 5 | 62 | 3 | 46 |
| Hamdan, 2001[25] | 34 | 26 | 16 | 38 | 62 | 32 | 4 | 29 |
| Harrison, 2001[26] | 27 | 44 | 30 | 74 | 26 | 46 | 3 | 22 |
| Honing-H., 2003[27] | 33 | 33 | 21 | 33 | 67 | 37 | 7 | 21 |
| Kische, 2015[28] | 52 | 44 | 37 | 100 | 0 | 55 | 3 | 48 |
| Krasemann, 2011[29] | 68 | 38 | 26 | 60 | 40 | 25 | 5 | 41 |
| Lam, 2007[30] | 21 | 48 | 34 | 62 | 38 | 43 | 12 | 14 |
| Macdonald, 2003[31] | 15 | NA | 32 | 67 | 33 | 43 | 3 | 36 |
| Mahadevan, 2006[32] | 37 | 41 | 31 | 65 | 35 | 28 | 4 | 12 |
| Meadows, 2015[33] | 104 | NA | NA | NA | NA | 29 | 2 | 24 |
| Moltzer, 2010[34] | 24 | 50 | 35 | 25 | 75 | 19 | 0 | 27 |
| Musto, 2008[12] | 21 | 38 | 34 | 71 | 29 | 59 | 11 | 51 |
| Pedra, 2005[35] | 21 | 33 | 24 | 100 | 0 | 47 | 0 | 22 |
| Sadiq, 2013[36] | 56 | 31 | 22 | 100 | 0 | 51 | 5 | 46 |
| Sohrabi, 2014[37] | 120 | 33 | 24 | 100 | 0 | 55 | 3 | 31 |
| Tanous, 2010[38] | 22 | 50 | 39 | 64 | 36 | 29 | 3 | 12 |
| Tyagi, 2003[39] | 21 | 24 | 29 | 100 | 0 | 68 | 8 | 41 |
| Tzifa, 2006[40] | 30 | NA | 28 | 47 | 53 | 36 | 4 | 12 |
| van der Burg, 2018[41] | 43 | 40 | 41 | 60 | 40 | 28 | 3 | 20 |
| Yeaw, 2016[42] | 9 | 22 | 40 | 100 | 0 | 42 | NA | 14 |
| Zabal, 2003[43] | 22 | 36 | 26 | 100 | 0 | 64 | 3 | 22 |
| **Median (range)** | **32 (9-217)** | **35 (22-50)** | **29 (11-41)** | **67 (0-100)** | **33 (0-100)** | **39 (14-68)** | **3 (0-12)** | **26 (12-120)** |

Individual study data are presented as percentages for dichotomous variables and mean or median (according to the description provided by the study) for continuous variables. Across-study distributions are expressed as median and range. PSG, peak systolic gradient across coarctation site; FU, follow-up; NA, not available.

**Meta-analysis of studies evaluating systemic BP after CoA stenting**

Twenty-six studies enrolling a total of 1,157 subjects were used for random-effects meta-analysis on the absolute change in SBP from baseline to last follow-up (Figure 2A). In 25 studies only cuff SBP measurements were used and in 1 study a combination of cuff and invasive SBP measurements. Substantial heterogeneity was observed across the included studies ($I^2 = 75\%$). Stent implantation was associated with a pooled reduction in SBP of 20.27 mmHg (95% CI 16.41-24.13 mmHg; $P < 0.00001$). Additionally, 12 studies including 413 patients evaluated the change in DBP. Meta-analysis showed a significant decrease in DBP after stent implantation (8.23 mmHg [95% CI 5.17-11.30 mmHg]; $P < 0.00001$; Figure 2B). The certainty of evidence for both outcomes was rated as low (Supplemental Table 2).

Table 2 shows the stratification of studies by various subgroups. The overall decline in SBP was more pronounced in patients aged 18 years and older and patients treated for native compared to recurrent CoA. Furthermore, increased SBP and PSG at baseline and a decrease in AHM use were associated with a greater reduction in SBP at last follow-up. No significant association was found between study design and SBP change.

The course of SBP in the included studies is depicted in Supplemental Table 3. Median SBP decreased from 152 mmHg (132-178) at baseline to 128 mmHg (119-154) at last follow-up. Although various definitions of hypertension were used across studies, the proportion of patients with hypertension decreased from 78% (53-100%) to 27% (5-82%) after stenting (Supplemental Table 4). This was accompanied by a 40% reduction in patients using any AHM. Of patients remaining on AHM, the dosage was reduced in 70% of cases. The overall number of antihypertensive agents was decreased from 1.6 (0.8-2.3) at baseline to 1.1 (0.7-1.4) after stent implantation.

**Meta-regression**

Similar to subgroup analyses, the covariates native CoA, SBP at baseline, PSG at baseline, and change in AHM use were associated with SBP change in meta-regression (Supplemental Table 5). Outcome measurement by 24-hour ambulatory BP monitoring (ABPM) was associated with less SBP reduction compared to office BP measurement. Meta-regression showed no association between age and SBP change.

**Sensitivity analyses and publication bias**

The significant decrease in SBP after stent implantation observed in the random-effects model persisted in the fixed-effects model (mean difference -18.22 [95% CI -19.90, -16.53]; $P < 0.00001$). Further sensitivity analyses by excluding one study at a time from meta-analysis revealed that no single study significantly changed the pooled effect estimate.

Visual inspection of the created funnel plot showed relative asymmetry, thereby raising concerns of publication bias (Supplemental Figure 1). Although quantification of asymmetry by the Egger's test did not reach statistical significance ($P = 0.12$), we aimed to correct for potential publication bias using the 'trim and fill' method (Supplemental Figure 2). Application of this method did not change the overall effect.

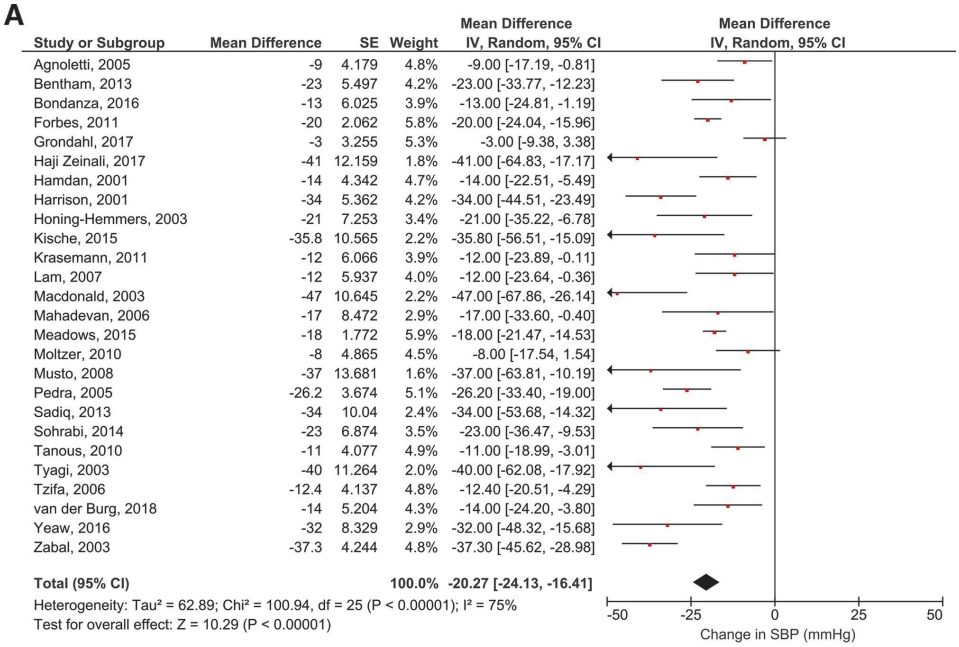


**Figure 2. Forest plots showing the pooled mean change in SBP (A) and DBP (B) from baseline to last follow-up using a random-effects model.** Data are presented as mean difference (mmHg) and 95% confidence interval. SE, standard error; IV, inverse variance; CI, confidence interval.

**Table 2. Mean change in SBP from baseline to last follow-up among various subgroups.**

| Subgroup | Studies | Mean difference in SBP (mmHg) | | |
|---|---|---|---|---|
| | | $I^2$ (%) | ES (95% CI) | P-value[a] |
| Gender | | | | 0.80 |
| ≥ 35% female | 11 | 78 | -21.82 (-29.76, -13.88) | |
| < 35% female | 11 | 75 | -20.51 (-26.41, -14.61) | |
| Mean age (years) | | | | **0.03** |
| > 25 | 16 | 82 | -22.38 (-29.43, -15.32) | |
| 18 - 25 | 5 | 0 | -24.96 (-29.90, -20.02) | |
| < 18 | 4 | 55 | -14.93 (-20.61, -9.25) | |
| Native versus recurrent CoA | | | | **< 0.00001** |
| Only native | 8 | 63 | -28.99 (-35.36, -22.63) | |
| ≥ 50% native | 11 | 65 | -20.95 (-27.60, -14.29) | |
| > 50% recurrent | 4 | 0 | -12.76 (-17.48, -8.05) | |
| Only recurrent | 2 | 22 | -5.43 (-11.20, 0.34) | |
| SBP baseline (mmHg) | | | | **0.009** |
| > 160 | 6 | 79 | -32.77 (-47.07, -18.47) | |
| 140 - 160 | 17 | 65 | -19.64 (-23.42, -15.87) | |
| < 140 | 3 | 60 | -9.22 (-17.09, -1.36) | |
| PSG baseline (mmHg) | | | | **< 0.00001** |
| > 40 | 13 | 56 | -29.63 (-35.54, -23.72) | |
| 20 - 40 | 11 | 20 | -16.21 (-18.75, -13.67) | |
| < 20 | 2 | 0 | -4.55 (-9.85, 0.76) | |
| PSG post-stenting (mmHg) | | | | 0.22 |
| > 8 | 3 | 69 | -27.39 (-47.90, -6.87) | |
| 4 - 8 | 7 | 47 | -15.85 (-20.53, -11.17) | |
| < 4 | 15 | 82 | -21.56 (-27.39, -15.74) | |
| Change in AHM use[b] | | | | **0.004** |
| Reduction > 25% | 6 | 0 | -27.97 (-32.79, -23.14) | |
| Reduction ≤ 25% | 7 | 83 | -17.93 (-25.12, -10.74) | |
| Increase or no change | 2 | 58 | -7.82 (-20.85, 5.22) | |
| Follow-up duration (years) | | | | 0.85 |
| > 4 | 3 | 37 | -20.66 (-31.08, -10.23) | |
| 2 - 4 | 11 | 63 | -21.18 (-26.22, -16.15) | |
| < 2 | 12 | 84 | -18.70 (-25.59, -11.81) | |
| Study design | | | | 0.80 |
| Prospective cohort study | 12 | 64 | -20.92 (-25.36, -16.49) | |
| Retrospective cohort study | 14 | 80 | -19.90 (-26.55, -13.26) | |
| Year of publication | | | | 0.13 |
| 2010 - 2018 | 14 | 70 | -17.35 (-21.81, -12.90) | |
| Prior to 2010 | 12 | 78 | -23.74 (-30.72, -16.76) | |
| Method of BP measurement | | | | 0.05 |
| 24-hour ABPM | 2 | 58 | -7.82 (-20.85, 5.22) | |
| Office BP | 24 | 70 | -21.12 (-24.85, -17.40) | |
| Incomplete follow-up[c] | | | | 0.79 |
| < 5% | 14 | 84 | -21.74 (-28.84, -14.63) | |
| 5 - 20% | 7 | 48 | -18.68 (-23.83, -13.53) | |
| > 20% | 5 | 56 | -19.44 (-26.79, -12.09) | |

Data are presented as mean difference (mmHg) and 95% confidence interval using a random-effects model. [a] Between subgroups. [b] Change in percentage of patients using any antihypertensive medication from baseline to last follow-up. [c] Percentage of patients with no available BP data ≥ 12 months after CoA stenting. ES, effect size; CI, confidence interval; PSG, peak systolic gradient across coarctation site; AHM, antihypertensive medication; ABPM, ambulatory blood pressure monitoring.

## DISCUSSION

This meta-analysis provides insight in the medium-term BP course of patients who underwent stenting of aortic coarctation. Combining the outcomes of 26 studies with a total of 1,157 patients, we show that stent implantation is associated with a significant reduction in SBP and DBP, which is sustained up to 10 years of follow-up. The most pronounced effects were observed in patients aged 18 years and older, patients with high SBP and PSG at baseline, and those treated for native CoA. The decline in SBP was in conjunction with a decrease in the use of AHM.

Short-term outcomes of CoA stenting have been extensively studied and are generally considered satisfying with significant decrease of aortic gradient.[9,25] Furthermore, the CCISC reported that stenting compares favourably to surgical repair and balloon angioplasty in terms of acute complications.[7] Although treatment success is often measured by short-term results, little is known about the medium-term efficacy of stent implantation. Our results suggest a clinically relevant reduction in SBP and DBP during medium-term follow-up, as it has been shown that an SBP reduction of 10 mmHg and DBP reduction of 5 mmHg significantly attenuate the risk of major cardiovascular events.[17] Importantly, as stated above, this effect could not be attributed to an increased use of AHM post-stenting. In contrast, we report a concomitant 40% decline in patients using any AHM, which is likely a consequence of the SBP reduction. However, at late follow-up over a third of patients were still in need of AHM for adequate BP control.

Although most patients in the included studies were normotensive at late follow-up, a substantial minority remained hypertensive. The mechanisms responsible for persistent or recurrent hypertension in CoA are poorly understood. Over the last years, there is increasing evidence suggesting that the compliance of the aortic wall plays a role in the origin of persistent hypertension.[5,44] Since CoA is considered not merely a discrete lesion but instead part of a generalized vasculopathy, increased resistance of the peripheral vasculature may comprise an additional substrate for hypertension.[6] Furthermore, reduced baroreceptor sensitivity and abnormal arch geometry, particularly a hypoplastic or gothic arch, have been linked to the development of hypertension in CoA patients.[4,45] A small retrospective study found that stent implantation for aortic arch hypoplasia may significantly attenuate BP, despite potential technical difficulties.[46] Inadequate recognition of hemodynamically relevant CoA may provide another explanation for hypertension in this patient cohort. For instance, the influence of anesthesia during cardiac catheterization may lead to an underestimation of PSG in an active state. The application of pharmacological agents mimicking physical activity (e.g. catecholamines) could be of additional value to determine the true extent of obstruction. Furthermore, more sensitive non-invasive techniques, such as 4-dimensional flow magnetic

resonance imaging and computational flow dynamics, may be useful to distinguish between hemodynamically relevant and non-relevant stenosis.[47]

In this study, several parameters were found to influence the extent of BP reduction after stenting. Notably, a high baseline PSG was associated with a more pronounced decrease in SBP, while no significant SBP decline was observed with a baseline PSG value < 20 mmHg. These results are in accordance with current guidelines, stating that a PSG > 20 mmHg is suggestive of hemodynamically relevant CoA requiring intervention.[8] In contrast, mild residual PSG directly after stent implantation was not associated with persistent hypertension during follow-up. Interestingly, our results indicate that patients treated for recurrent CoA are at greater risk to develop residual hypertension compared to native CoA patients. It is known that prior surgical repair is associated with increased aortic stiffness, which may be partly due to the use of non-compliant prosthetic material and scar tissue.[5,44] Discrepancies in baseline BP offer another potential explanation for this difference. Since patients with a previous intervention are closely followed up, re-intervention may already be considered in the case of borderline hypertension, whereas native CoA patients generally present with more severe hypertension. It is well known that high baseline BP is predictive of a greater response to antihypertensive treatment, which is consistent with the Wilder's principle.[48] This association may have biased our observation that patients < 18 years of age, who typically have a lower baseline BP compared to adults, show less decline in SBP after stenting. In fact, stent implantation in children has shown to adequately protect from developing late hypertension, possibly by counteracting the maladaptive vascular changes that are frequently seen in older patients.[49] The prognostic implications, rather than the expected absolute BP decline, may guide clinical decision making in children. Although it is known that late surgical repair is associated with the development of chronic hypertension in CoA, the effect of age at stent implantation is less clear.[2] Our results do not show a disadvantage for older patients in terms of blood pressure reduction. However, no definite conclusions can be drawn considering the median follow-up of 26 months, which underlines the importance of studies with longer follow-up after stenting.

**Limitations**

This meta-analysis has several limitations. First, the included studies were observational, which may have resulted in an under- or overestimation of the true effect size. Furthermore, significant heterogeneity was observed across studies, which could not be sufficiently explained by subgroup analyses and meta-regression. This heterogeneity may be partly due to differences in selection criteria between studies, including SBP and PSG at baseline and treatment of native or recurrent CoA. Therefore, one should be cautious to directly extrapolate these findings to individual patients. Another limitation is the dubious reliability of BP assessment, which consisted of regular office measurements in most studies. Previous studies have reported that ABPM is superior to office measurements in the prediction of cardiovascular events and may

therefore be a more useful tool in clinical practice.[50] Due to the lack of ABPM, patients may have been falsely classified as either normotensive or hypertensive. Studies using ABPM showed less decline of SBP in meta-regression, thereby suggesting that the true effect on SBP may be smaller than the overall observed effect. However, only two studies used ABPM and therefore no definite conclusions can be drawn. We believe it is of major importance to include ABPM in future studies with CoA patients. Moreover, a significant number of studies failed to specify whether the right or left arm was used for BP assessment. Since hypoplasia of the aortic arch is frequently seen in CoA patients, this may have affected BP measurements. Additionally, our results suggested the presence of publication bias. Although adjustment did not significantly alter the pooled outcome, intrinsic limitations when correcting for publication bias have to be taken into account.[19] Using GRADE, the certainty of evidence for both outcomes was rated as low, which was due to inconsistency and high risk of bias caused by unreliable BP measurements, failure to control for confounding, and incomplete follow-up.



## CONCLUSIONS

Significant medium-term hemodynamic improvement is observed after stent implantation for CoA, which may effectively reduce the hazard of late cardiovascular complications. Stenting of native CoA and high baseline SBP and PSG were associated with the most pronounced BP reduction after stenting. Controversy exists regarding the underlying mechanisms causing persistent or recurrent hypertension in individual patients. To identify patients at high risk of persistent hypertension, studies focusing on aortic flow dynamics and optimization of invasive gradient assessment may help in future clinical decision making in this patient cohort.

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**SUPPLEMENTAL MATERIAL**

**Supplemental Methods. Search strategy.**

On May 28, 2018 a systematic search was conducted in PubMed, EMBASE, and Cochrane Library. To identify additional grey literature and unpublished trials, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), Google Scholar, and OpenGrey were searched. The following search strategy was used (format represents PubMed search):

coarctation* OR co arctation OR coarctated OR coarctate OR recoarctation* OR re-coarctation* OR aortic coarctation [MeSH]
AND
stent OR stents OR stenting OR stented OR percutaneous OR catheter* OR transcatheter OR trans catheter OR catheter-based OR transluminal OR trans luminal OR endovascular OR endo vascular OR intravascular OR intra vascular OR transvascular OR angioplast* OR stent [MeSH]
AND
blood pressure* OR arterial pressure* OR systolic OR diastolic OR hypertension OR hypertensive OR normotension OR normotensive OR antihypertensive* OR anti hypertensive* OR blood pressure [MeSH] OR hypertension [MeSH]

No limits were used regarding language and year of publication. A total of 2,314 articles were found using this search strategy (PubMed = 779; EMBASE = 1,493; Cochrane Library = 18; additional sources listed above = 24). Of these, 687 were identified as duplicates, leaving 1,627 articles for title and abstract screening.

**Supplemental Table 1. Assessment of risk of bias in the included studies based on the criteria for observational studies in GRADE guidelines*.**

| First author, year | Method of outcome measurement | Confounding factors reported[a] | Confounding factors adjusted for | Incomplete follow-up[b] |
|---|---|---|---|---|
| Agnoletti, 2005 | Office BP | Change in patients using any AHM | None | 0/15 (0%) |
| Bentham, 2013 | Office BP (+ 24-hour ABPM)[c] | Change in number of AHM | None | 4/40 (10%) |
| Bondanza, 2016 | Office BP | Restenoses and reinterventions during FU | None | 10/34 (29%) |
| Forbes, 2011 | Office BP | Reinterventions during FU | None | 140/217 (65%) |
| Grondahl, 2017 | 24-hour ABPM | Change in patients using any AHM | None | 0/9 (0%) |
| Haji Zeinali, 2017 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 0/62 (0%) |
| Hamdan, 2001 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 3/34 (9%) |
| Harrison, 2001 | Office BP | Change in patients using any AHM; restenoses during FU | None | 1/27 (4%) |
| Honing-H., 2003 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 6/33 (18%) |
| Kische, 2015 | Office BP | Change in patients using any AHM; restenoses during FU | None | 0/52 (0%) |
| Krasemann, 2011 | Office BP | Restenoses and reinterventions during FU | None | 2/68 (3%) |
| Lam, 2007 | Office BP | Change in number of AHM | None | 0/21 (0%) |
| Macdonald, 2003 | Office BP | Change in number of AHM; restenoses during FU | None | 5/15 (33%) |
| Mahadevan, 2006 | 24-hour ABPM | Change in patients using any AHM; change in number of AHM | None | 20/37 (54%) |
| Meadows, 2015 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 13/104 (13%) |
| Moltzer, 2010 | Office BP (+ 24-hour ABPM)[c] | Change in patients using any AHM; restenoses and reinterventions during FU | None | 2/24 (8%) |

| | | | | |
|---|---|---|---|---|
| Musto, 2008 | Office BP (+ 24-hour ABPM)[c] | Change in number of AHM; reinterventions during FU | None | 0/21 (0%) |
| Pedra, 2005 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 0/21 (0%) |
| Sadiq, 2013 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 6/56 (11%) |
| Sohrabi, 2014 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 0/120 (0%) |
| Tanous, 2010 | Office BP | Change in number of AHM; restenoses and reinterventions during FU | None | 0/22 (0%) |
| Tyagi, 2003 | Office BP | Change in number of AHM; restenoses and reinterventions during FU | None | 0/21 (0%) |
| Tzifa, 2006 | Office BP | Change in patients using any AHM; restenoses and reinterventions during FU | None | 0/30 (0%) |
| van der Burg, 2018 | Office BP | Change in number of AHM; restenoses and reinterventions during FU | None | 17/43 (40%) |
| Yeaw, 2016 | Office BP | - | None | 1/9 (11%) |
| Zabal, 2003 | Office BP | Change in patients using any AHM; restenoses during FU | None | 0/22 (0%) |

[a] Including the change in patients using any AHM, change in number of AHM, restenosis and/or reintervention for CoA during FU, change in BMI and other secondary causes of hypertension (primary hyperaldosteronism, renal artery stenosis, chronic renal disease, obstructive sleep apnea). [b] Patients with no available BP data ≥ 12 months after CoA stenting. [c] 24-hour ABPM was performed in addition to office measurements, but was missing either at baseline or at last follow-up. ABPM, ambulatory blood pressure monitoring; AHM, antihypertensive medication; FU, follow-up.

[*] Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407-15.

**Supplemental Table 2. GRADE approach to evaluate the certainty of evidence.**

| Quality assessment | | | | | | | | Summary of findings | |
|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design (studies)** | **Risk of bias** | **Inconsis-tency** | **Indirect-ness** | **Imprecision** | **Other considera-tions** | **Certainty of evidence** | **№ of patients** | **Absolute effect (95% CI)** |
| **Change in systolic blood pressure (follow-up: range 12 to 120 months)** | | | | | | | | | |
| 26 | PCS (12) RCS (14) | Serious risk of bias[a] | Serious inconsis-tency[b] | No serious indirectness | No serious imprecision | Publication bias may be present[c] | ⊕⊕◯◯ LOW[d] | 1,157 | Mean **20.3 mmHg lower** (24.1 lower to 16.4 lower) |
| **Change in diastolic blood pressure (follow-up: range 12 to 48 months)** | | | | | | | | | |
| 12 | PCS (7) RCS (5) | Serious risk of bias[a] | Serious inconsis-tency[b] | No serious indirectness | No serious imprecision | - | ⊕⊕◯◯ LOW[d] | 413 | Mean **8.2 mmHg lower** (11.3 lower to 5.2 lower) |

[a] Due to the lack of reliable outcome measurement by ambulatory blood pressure monitoring, failure to adjust for confounding, and incomplete follow-up in a significant number of studies (Supplemental Table S1).
[b] Due to substantial heterogeneity across studies.
[c] Funnel plot shows visual asymmetry. However, this was considered insufficient to downgrade the quality of evidence, since the Egger's test was not significant (P = 0.12) and the search for grey literature and unpublished studies did not suggest the presence of publication bias.
[d] Since GRADE was not designed for this type of studies (i.e. pre-post studies with an intervention arm only), we considered the proposed baseline rating for observational studies in GRADE not applicable. In the absence of a control group, we expected the patient cohorts to be well comparable before and after the intervention. Consequently, we considered a baseline rating of high certainty of evidence as appropriate. This baseline rating was downgraded by one level due to serious risk of bias and by one level due to serious inconsistency, resulting in low certainty of evidence.
CI, confidence interval; PCS, prospective cohort study; RCS, retrospective cohort study.

**Supplemental Table 3. Course of SBP from baseline to last follow-up.**

| First author, year | SBP baseline (mmHg) | SBP post (mmHg) | SBP ≤ 18 mo FU (mmHg) | SBP last FU (mmHg) | Duration of FU (mo) |
|---|---|---|---|---|---|
| Agnoletti, 2005 | 140 | NA | NA | 131 | 22 |
| Bentham, 2013 | 155 | NA | 133 | 132 | 52 |
| Bondanza, 2016 | 132 | NA | 123 | 119 | 120 |
| Forbes, 2011 | 143 | 125 | 121 | 123 | 33 |
| Grondahl, 2017 | 134 | NA | NA | 131 | 21 |
| Haji Zeinali, 2017 | 167 | 131 | NA | 126 | 46 |
| Hamdan, 2001 | 136 | NA | NA | 122 | 29 |
| Harrison, 2001 | 164 | 132 | NA | 130 | 22 |
| Honing-Hemmers, 2003 | 149 | 124 | NA | 128 | 21 |
| Kische, 2015 | 162 | 139 | 128 | 126 | 48 |
| Krasemann, 2011 | 153 | 129 | NA | 141 | 41 |
| Lam, 2007 | 147 | NA | NA | 135 | 14 |
| Macdonald, 2003 | 178 | NA | 126 | 131 | 36 |
| Mahadevan, 2006 | 142 | NA | 131 | 125 | 12 |
| Meadows, 2015 | 140 | NA | 123 | 122 | 24 |
| Moltzer, 2010 | 162 | NA | NA | 154 | 27 |
| Musto, 2008 | 157 | NA | 123 | 120 | 51 |
| Pedra, 2005 | 152 | 141 | NA | 126 | 22 |
| Sadiq, 2013 | 155 | 125 | NA | 121 | 46 |
| Sohrabi, 2014 | 146 | 126 | NA | 123 | 31 |
| Tanous, 2010 | 140 | NA | NA | 129 | 12 |
| Tyagi, 2003 | 178 | NA | NA | 138 | 41 |
| Tzifa, 2006 | 147 | NA | NA | 134 | 12 |
| van der Burg, 2018 | 151 | NA | 135 | 137 | 20 |
| Yeaw, 2016 | 159 | NA | NA | 127 | 14 |
| Zabal, 2003 | 158 | NA | NA | 121 | 22 |
| **Median** | **152** | **129** | **126** | **128** | **26** |
| **(range)** | **(132-178)** | **(124-141)** | **(121-135)** | **(119-154)** | **(12-120)** |

Individual study data are expressed as mean and across-study distributions as median and range. mo, months; FU, follow-up; NA, not available.

**Supplemental Table 4. Prevalence of hypertension and use of antihypertensive medication at baseline and last follow-up.**

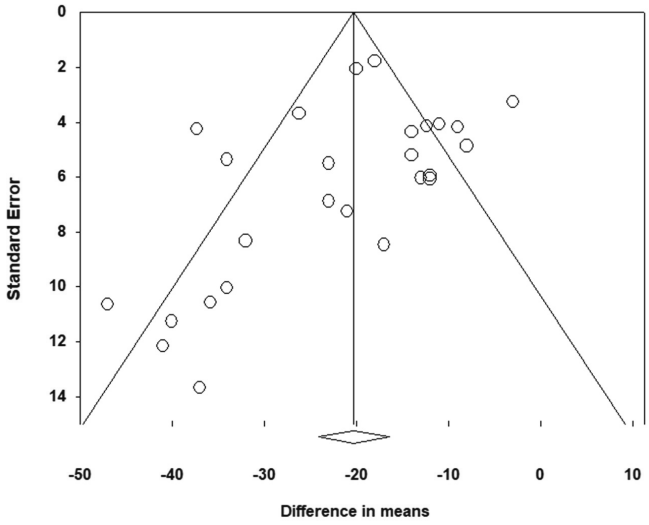
| First author, year | Definition of hypertension | % hypertension baseline | % hypertension last FU | % using AHM baseline | % using AHM last FU |
|---|---|---|---|---|---|
| Agnoletti, 2005 | SBP > 95th percentile for age and gender | 53 | 27 | 33 | 27 |
| Bentham, 2013 | SBP > 140 mmHg | NA | 33 | NA | NA |
| Bondanza, 2016 | NA | NA | NA | 0 | NA |
| Forbes, 2011 | SBP ≥ 97.5th percentile for age and gender | NA | 18 | NA | 31 |
| Grondahl, 2017 | NA | NA | NA | 33 | 33 |
| Haji Zeinali, 2017 | NA | 77 | NA | 77 | 32 |
| Hamdan, 2001 | NA | 65 | 26 | 42 | 26 |
| Harrison, 2001 | NA | 96 | NA | 59 | 27 |
| Honing-H., 2003 | NA | 58 | NA | 100 | 36 |
| Kische, 2015 | BP > 140/90 mmHg | 100 | 12 | 100 | 43 |
| Krasemann, 2011 | NA | 59 | 45 | NA | 47 |
| Lam, 2007 | BP > 140/90 mmHg | 71 | NA | 71 | NA |
| Macdonald, 2003 | NA | NA | NA | NA | NA |
| Mahadevan, 2006 | BP > 140/90 mmHg | 78 | NA | 68 | 70 |
| Meadows, 2015 | BP > 95th percentile for age and gender (< 18 y), BP > 140/90 mmHg (≥ 18 y) | 61 | NA | 38 | 26 |
| Moltzer, 2010 | BP > 140/90 mmHg | 79 | 82 | 75 | 67 |
| Musto, 2008 | BP > 140/90 mmHg | 100 | 33 | 76 | NA |
| Pedra, 2005 | NA | NA | NA | 76 | 10 |
| Sadiq, 2013 | NA | 100 | 6 | 100 | 94 |
| Sohrabi, 2014 | NA | 84 | 24 | 84 | 24 |
| Tanous, 2010 | NA | NA | NA | NA | NA |
| Tyagi, 2003 | NA | 100 | NA | 100 | NA |
| Tzifa, 2006 | NA | NA | NA | 70 | 60 |
| van der Burg, 2018 | SBP > 140 mmHg | 74 | 27 | NA | NA |
| Yeaw, 2016 | NA | NA | NA | NA | 88 |
| Zabal, 2003 | NA | NA | 5 | 82 | 68 |
| **Median (range)** | | **78 (53-100)** | **27 (5-82)** | **75 (0-100)** | **35 (10-94)** |

Individual study data are presented as percentages and across-study distributions as median and range. FU, follow-up; AHM, antihypertensive medication; y, years; NA, not available.

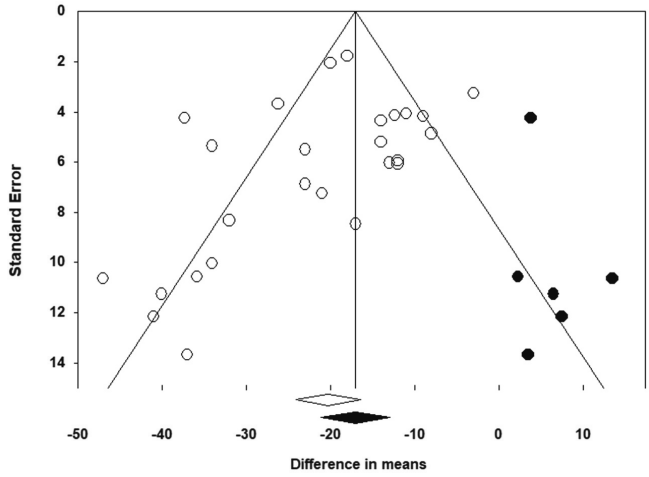
**Supplemental Table 5. Meta-regression of the mean change in SBP from baseline to last follow-up.**

| Subgroup | Studies | Coefficient[a] (95% CI) | $R^2$ (%) | P-value |
|---|---|---|---|---|
| Female gender (%) | 22 | 0.14 (-0.42, 0.70) | 0 | 0.62 |
| Mean age (years) | 25 | -0.08 (-0.64, 0.48) | 0 | 0.77 |
| Native CoA (%) | 25 | -0.24 (-0.34, -0.15) | 64 | **< 0.00001** |
| SBP baseline (mmHg) | 26 | -0.72 (-1.00, -0.44) | 56 | **< 0.00001** |
| PSG baseline (mmHg) | 26 | -0.65 (-0.82, -0.48) | 92 | **< 0.00001** |
| PSG post-stenting (mmHg) | 25 | -0.36 (-1.92, 1.20) | 0 | 0.65 |
| Change in AHM use (%)[b] | 15 | 0.23 (0.02, 0.45) | 27 | **0.03** |
| Follow-up duration (months) | 26 | -0.06 (-0.24, 0.13) | 0 | 0.55 |
| Study design[c] | 26 | -2.43 (-10.31, 5.46) | 0 | 0.55 |
| Year of publication | 26 | 0.52 (-0.18, 1.21) | 7 | 0.15 |
| Method of BP measurement[d] | 26 | 13.48 (0.48, 26.48) | 21 | **0.04** |
| Incomplete follow-up (%)[e] | 26 | 0.02 (-0.21, 0.24) | 0 | 0.89 |

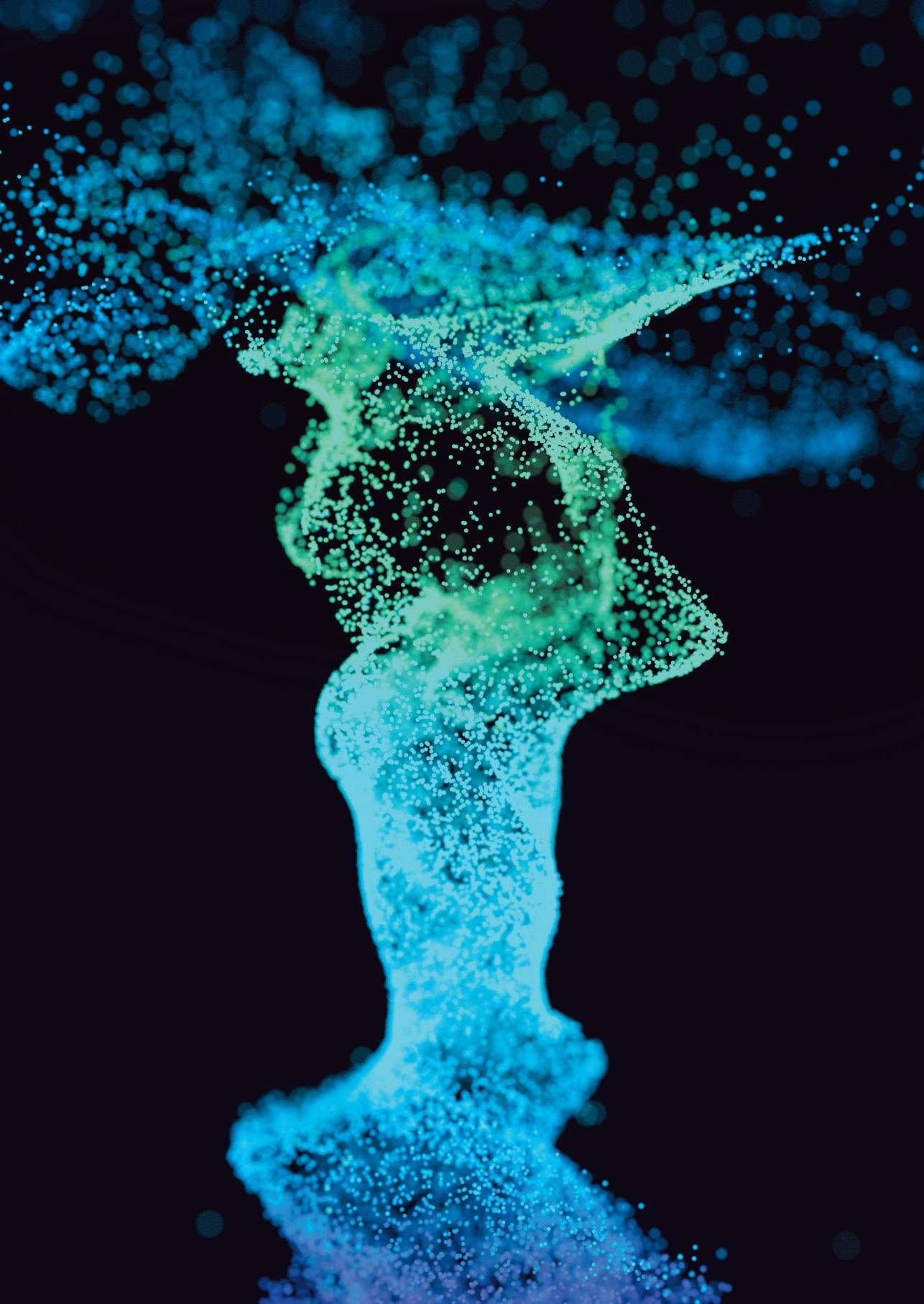
Data are presented as regression coefficient and 95% confidence interval using random-effects meta-regression. [a] Represents the change in SBP (mmHg) per unit increase of the covariate. [b] Change in percentage of patients using any antihypertensive medication from baseline to last follow-up. [c] As a dichotomous variable, including prospective (1) and retrospective (0) cohort studies. [d] As a dichotomous variable, including 24-hour ambulatory BP monitoring (1) and office BP (0). [e] Percentage of patients with no available BP data ≥ 12 months after CoA stenting. CI, confidence interval; PSG, peak systolic gradient across coarctation site; AHM, antihypertensive medication.




**Supplemental Figure 1. Funnel plot.** Data are plotted as the difference in mean SBP (mmHg) from baseline to last follow-up (x-axis) against the standard error of the difference in means (y-axis). The funnel plot shows visual asymmetry, although this was not confirmed by the Egger's test (P = 0.12).




**Supplemental Figure 2. Adjustment for potential publication bias using the 'trim and fill' method.** Data are plotted as the difference in mean SBP (mmHg) from baseline to last follow-up (x-axis) against the standard error of the difference in means (y-axis). The overall effect on SBP was sustained after implementation of the 'trim and fill' method.



# CHAPTER 4

# Epinephrine stress testing during cardiac catheterization in patients with aortic coarctation

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**ABSTRACT**

**Background**

The severity of aortic coarctation (CoA) may be underestimated during cardiac catheterization. We aimed to investigate whether epinephrine stress testing improves clinical decision making and outcome in CoA.

**Methods**

We retrospectively evaluated CoA patients >50 kg with a peak systolic gradient (PSG) ≤20 mmHg during cardiac catheterization, who underwent epinephrine stress testing. Subsequent interventional management (stenting or balloon dilatation), complications, and medium-term clinical outcome were assessed.

**Results**

Fifty CoA patients underwent cardiac catheterization with epinephrine stress testing. Patients with a high epinephrine PSG (>20 mmHg; n=24) were younger and more likely to have a hypertensive response to exercise compared to patients with a low epinephrine PSG (≤20 mmHg; n=26). In total, 21 patients (88%) with a high epinephrine PSG underwent intervention and 20 patients (77%) with a low epinephrine PSG were treated conservatively. After a mean follow-up of 25 ± 18 months, there was a lower prevalence of hypertension in patients with a high epinephrine PSG who underwent intervention compared to patients with a low epinephrine PSG treated conservatively (19% vs. 76%; $p$=0.001). In a multivariate model, intervention was independently associated with a 14.3 mmHg reduction in systolic blood pressure ($p$=0.001) and a decrease in the use of antihypertensive agents.

**Conclusions**

In CoA patients with a low baseline PSG but high epinephrine PSG, percutaneous intervention is associated with a substantial reduction in systemic blood pressure and the use of antihypertensive medication. Accordingly, epinephrine stress testing may be a useful addition in the evaluation of CoA.

## INTRODUCTION

Although most patients with aortic coarctation (CoA) are successfully managed by surgical or percutaneous repair in early childhood, they remain at considerable risk to develop systemic hypertension during long-term follow-up.[1,2] As a consequence, these patients are prone to suffer from various cardiovascular sequelae, including aneurysm formation, thromboembolic events, and heart failure.[3] The presence of hypertension may be caused by a residual or recurrent stenosis at the original CoA site or the aortic arch.[4] According to current guidelines, interventional treatment is indicated when hypertension is accompanied by a gradient >20 mmHg between upper and lower extremities and anatomical evidence of obstruction.[5] However, clinical findings may be inconsistent, resulting in a questionable indication for intervention. Therefore, in many centers the peak systolic gradient (PSG) across the stenotic segment is measured invasively during cardiac catheterization.[5,6] Although the invasive PSG plays an important role in the decision whether or not to perform an intervention, it is often measured in a state of relative hypotension and may therefore be underestimated. This hypotensive state is largely due to the vasodilatory effects of anesthesia during cardiac catheterization.[7,8] Hence, clinically relevant CoA may be masked and thus undertreated.



Pharmacological stress testing is routinely used in the evaluation of ischemic and valvular heart disease. However, it is not implemented in the diagnostic work-up of CoA, with only a few small studies describing the use of the chronotropic agent isoproterenol as a stress test in this patient cohort.[9-11] At our institution, we use the α- and β-adrenergic receptor agonist epinephrine to counteract the anesthetic effects during cardiac catheterization. In this study, we retrospectively evaluated the effect of epinephrine stress testing on PSG, interventional management, complications, and medium-term clinical outcome in patients with CoA.

## METHODS

### Study design

For this retrospective analysis, we included CoA patients weighing >50 kilograms with a low PSG (≤20 mmHg) during cardiac catheterization between 2012 and 2018. The indication for cardiac catheterization was determined by a multidisciplinary team. Patients were considered for cardiac catheterization when they had a right arm-leg gradient >20 mmHg and/or arterial hypertension, in the presence of anatomical evidence of a stenosis at the CoA site or aortic arch by magnetic resonance imaging (MRI) or computed tomography. All procedures were performed at the University Medical Center Utrecht and the affiliated Wilhelmina Children's Hospital. During cardiac catheterization, all patients with an angiographically mild (re)stenosis with a low invasive PSG underwent epinephrine stress testing, which was referred to as the invasive measurement of PSG after the intravenous administration of epinephrine. CoA patients

with a functionally univentricular circulation or with transposition of the great arteries not treated by an arterial switch procedure, were excluded. Data were extracted from the Dutch congenital heart disease registry, for which patients provided informed consent. The study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

**Procedural description**

The use of antihypertensive medication was continued prior to cardiac catheterization. Cardiac catheterizations were performed under conscious sedation or general anesthesia. Vascular access was obtained by puncture of the femoral artery according to current clinical practice. Invasive systolic arterial pressures were measured in the ascending aorta and descending aorta distal to the stenotic segment using a pullback of an end-hole catheter during cardiac catheterization. Subsequently, epinephrine was administered intravenously by intermittent boluses to reach a target systolic blood pressure (BP) of 175 mmHg. The starting dose was 10-15 μg in patients weighing 50-65 kg and 20-30 μg in patients weighing >65 kg. If necessary, repeat boluses were administered every 1-2 minutes until the target systolic BP was reached. Invasive pressure measurements were then repeated under epinephrine. The indication for intervention was based on current ESC guidelines.[6] Interventions included stenting of CoA and/or aortic arch, redilatation of previously placed CoA stents, and primary balloon angioplasty of CoA. The choice of stent was based on the geometry of the proximal aorta and branches and the operator's preference. These included covered and non-covered Cheatham-Platinum stents (NuMED, Hopkinton, NY, USA), IntraStent Max and Mega LD (Medtronic, Minneapolis, MN, USA), AndraStent XXL (Andramed, Reutlingen, Germany), and Atrium Advanta V12 (Getinge, Gothenburg, Sweden). The balloon-in-balloon (NuMED) and Cristal balloon (Balt, Montmorency, France) were used for placement of the stents. Postdilatation (when deemed necessary) and redilatation of the stents were performed using a Cristal balloon (Balt) or Atlas PTA balloon (Bard Peripheral Vascular, Tempe, AZ, USA). The femoral access site was closed by manual compression or by the Perclose ProGlide (Abbott, Santa Clara, CA, USA) or Angio-Seal (Terumo, Tokyo, Japan) vascular closure devices.

**Data collection**

Demographics, medical history, BP data, and procedural data were extracted from medical records. Transverse arch hypoplasia was defined as a proximal arch diameter <60% or distal arch diameter <50% compared to the ascending aortic diameter by echocardiography or cardiac MRI, or prior surgical or percutaneous intervention for transverse arch hypoplasia.[12] Office BP was measured at the right arm. Office hypertension was defined as a BP ≥140/90 mmHg.[13] For

children ≤16 years, office hypertension was defined as BP ≥95th percentile for age, sex, and height.[14] The right arm-leg BP cuff gradient was used for non-invasive gradient assessment. Echocardiography and cardiac MRI were not used for gradient assessment, as this is not routine practice in our hospital. Hypertension on 24-hour ambulatory BP monitoring (ABPM) was classified according to ESC criteria in adults and ESH criteria in children ≤16 years.[13,14] A hypertensive response to exercise (HRE) was defined as a maximum systolic BP ≥210 mmHg for males and ≥190 mmHg for females during peak exercise.[15] For children <18 years, HRE was referred to as a maximum systolic BP ≥95th percentile for age and sex during peak exercise.[16] Antihypertensive medication included β-blockers, α-blockers, ACE-inhibitors, angiotensin II receptor blockers, calcium channel blockers, and diuretics. Left ventricular (LV) mass was assessed on echocardiography and indexed for height (g/m$^{2.7}$). LV hypertrophy was defined as an LV mass index >50 g/m$^{2.7}$ for males, >47 g/m$^{2.7}$ for females, >45 g/m$^{2.7}$ for boys <18 years, and >40 g/m$^{2.7}$ for girls <18 years.[13,17]



**Outcome measures**

Periprocedural (≤30 days) and late (>30 days) complications were assessed. Periprocedural complications included (pseudo)aneurysm formation, aortic dissection and rupture, stent migration, myocardial infarction, stroke, bleeding, and death. Bleeding was classified based on the Bleeding Academic Research Consortium (BARC) criteria and reported when BARC ≥2.[18] Late complications consisted of (pseudo)aneurysm formation, stent fracture, and unanticipated re-intervention. Re-interventions were regarded as unanticipated when they were not due to somatic growth and not planned as a part of a staged procedure. The last outpatient clinic visit was used to gather medium-term clinical follow-up data, including office BP, 24-hour BP, and use of antihypertensive medication.

**Statistical analyses**

Baseline characteristics and procedural data were compared between patients with an epinephrine PSG >20 mmHg (high epinephrine PSG) and ≤20 mmHg (low epinephrine PSG). A cut-off point of 20 mmHg was chosen, as this cut-off value is used in current guidelines for resting gradient assessment, except in patients with decreased LV function, aortic regurgitation, or extensive collateral flow.[5,6] Complications and medium-term clinical outcome were compared between patients with a high epinephrine PSG who underwent intervention and patients with a low epinephrine PSG who were treated conservatively. The independent-samples t-test was used for continuous variables and the Fisher's exact test for categorical variables. Since the number of antihypertensive agents is a count variable, we could not assume a normal distribution. Hence, differences in the number of antihypertensive agents were analyzed using the Mann-Whitney U test. Additionally, a within-group pre-post analysis was performed using the paired-samples t-test for continuous variables and McNemar's test for

categorical variables. The effect of intervention on medium-term systolic BP was further explored by multiple linear regression. Adjustments were made for potential confounding factors, including age, baseline systolic BP, and the use of antihypertensive medication. All independent variables were entered into the regression model by forced entry. Additionally, a Poisson regression was used to examine the effect of intervention on the number of antihypertensive agents at follow-up, adjusting for age, baseline number of antihypertensive agents, and systolic BP. The significance of the variables in the model was tested using the Wald chi-square statistic. P-values <0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics 25 (Armonk, NY, USA).

## RESULTS

### Patient characteristics

Fifty patients with low-gradient CoA (invasive baseline PSG ≤20 mmHg) underwent epinephrine stress testing during cardiac catheterization. Of these, 24 patients had a high epinephrine PSG (>20 mmHg) and 26 patients a low epinephrine PSG (≤20 mmHg). Baseline characteristics are presented in Table 1. Nine patients (18%) had native CoA and 17 patients (34%) were known with concomitant transverse arch hypoplasia. The mean age at first CoA intervention was 6.0 ± 1.7 years. Compared to patients with a low epinephrine PSG, patients with a high epinephrine PSG were younger, more likely to have HRE, and tended to be less frequently treated surgically as first CoA repair (although not statistically significant). Younger age and HRE remained significantly associated with a high epinephrine PSG when using lower cut-off points for epinephrine PSG (10 and 15 mmHg), but the association between HRE and epinephrine PSG was not observed when using a higher cut-off point of 25 mmHg (Supplemental Table 1). Figure 1 displays the course of the systolic BP and PSG from non-invasive cuff measurements prior to cardiac catheterization to invasive measurements during cardiac catheterization (baseline and with epinephrine). There were no differences in epinephrine dosage between the groups (Table 2). In four patients, of which two in either group, a reflex bradycardia was observed after epinephrine administration and therefore right atrial pacing to 100-140 bpm was performed. Figure 2 shows that the epinephrine PSG was significantly higher in patients who were under general anesthesia compared to those under conscious sedation, despite a similar PSG at baseline.

**Table 1. Baseline characteristics.**

| | Overall | Epinephrine PSG >20 mmHg | Epinephrine PSG ≤20 mmHg | |
|---|---|---|---|---|
| | n=50 | n=24 | n=26 | *p*-value* |
| Age at catheterization (years) | 27.3 ± 13.2 | 22.4 ± 11.5 | 31.7 ± 13.4 | **0.011** |
| Female sex | 18 (36) | 7 (29) | 11 (42) | 0.39 |
| BMI (kg/m$^2$) | 23.1 ± 3.8 | 22.7 ± 4.2 | 23.4 ± 3.6 | 0.49 |
| Number of prior CoA interventions | | | | 0.93 |
| 0 | 9 (18) | 4 (17) | 5 (19) | |
| 1 | 25 (50) | 13 (54) | 12 (46) | |
| ≥2 | 16 (32) | 7 (29) | 9 (35) | |
| First CoA intervention | | | | 0.06 |
| Surgery | 25 (61) | 9 (45) | 16 (76) | |
| Stenting | 9 (22) | 5 (25) | 4 (19) | |
| Balloon angioplasty | 7 (17) | 6 (30) | 1 (5) | |
| Type of surgical repair | | | | 0.86 |
| End-to-end anastomosis | 11 (44) | 4 (44) | 7 (44) | |
| Patch angioplasty | 10 (40) | 3 (33) | 7 (44) | |
| Unknown | 4 (16) | 2 (22) | 2 (13) | |
| Age at first CoA intervention | 6.0 ± 1.7 | 4.0 ± 1.3 | 7.9 ± 3.1 | 0.25 |
| Concomitant congenital heart defects | | | | |
| Bicuspid aortic valve | 22 (44) | 8 (33) | 14 (54) | 0.17 |
| Persistent ductus arteriosus, surgically closed | 7 (14) | 3 (13) | 4 (15) | 1.0 |
| Ventricular septal defect | 16 (32) | 8 (33) | 8 (31) | 1.0 |
| Atrial septal defect | 4 (8) | 2 (8) | 2 (8) | 1.0 |
| Patent foramen ovale | 1 (2) | 1 (4) | 0 | 0.48 |
| Transverse arch hypoplasia | 17 (34) | 10 (42) | 7 (27) | 0.37 |
| Non-invasive systolic right arm-leg gradient (mmHg) | 8 ± 14 | 12 ± 12 | 4 ± 15 | 0.12 |
| Office hypertension | 34 (68) | 16 (67) | 18 (69) | 1.0 |
| Hypertension on 24-hour ABPM† | 29 (78) | 15 (75) | 14 (82) | 0.70 |
| Hypertensive response to exercise‡ | 18 (67) | 11 (92) | 7 (47) | **0.019** |
| Use of any antihypertensive agent | 18 (36) | 9 (38) | 9 (35) | 1.0 |
| Number of antihypertensive agents | 0.7 ± 1.0 | 0.9 ± 1.1 | 0.5 ± 0.8 | 0.26 |
| LV mass index (g/m$^{2.7}$)§ | 38 ± 14 | 36 ± 17 | 39 ± 11 | 0.58 |
| LV hypertrophy§ | 8 (21) | 3 (15) | 5 (26) | 0.45 |

Data are presented as number (percentage) or mean ± standard deviation. *Indicates the difference between high and low epinephrine PSG groups, as determined by the independent-samples t-test (Mann-Whitney U test for number of antihypertensive agents) or Fisher's exact test, where appropriate. †Available for 20 patients (83%) in the high epinephrine PSG group and 17 patients (65%) in the low epinephrine PSG group. ‡Available for 12 patients (50%) in the high epinephrine PSG group and 15 patients (58%) in the low epinephrine PSG group. §Available for 20 patients (83%) in the high epinephrine PSG group and 19 patients (73%) in the low epinephrine PSG group. ABPM, ambulatory blood pressure monitoring; BMI, body mass index; LV, left ventricular; PSG, peak systolic gradient.

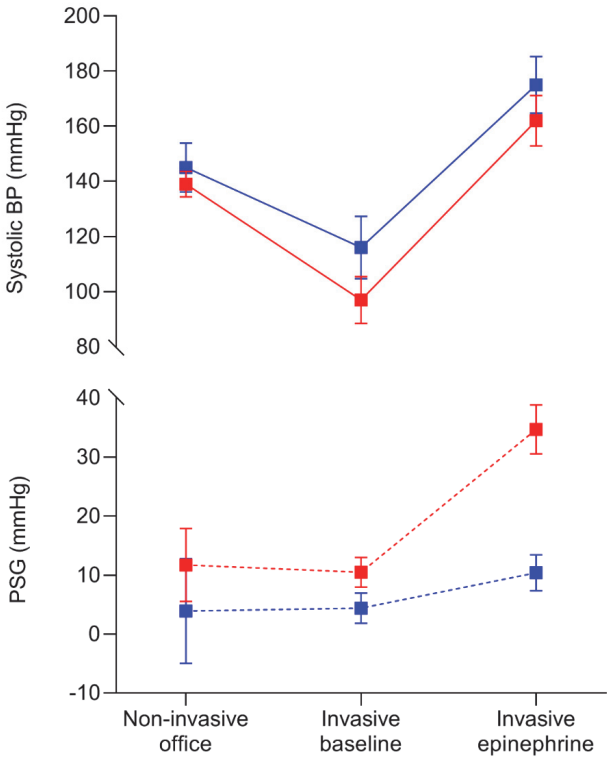


**Figure 1. Graphic display of the systolic BP and PSG measured non-invasively prior to cardiac catheterization (office) and invasively during cardiac catheterization (baseline and with epinephrine).** Systolic BP and PSG in patients with a high epinephrine PSG are indicated by the red solid line and red dotted line, respectively. Systolic BP and PSG in patients with a low epinephrine PSG are displayed by the blue solid line and blue dotted line, respectively. Values are presented as mean and 95% confidence interval. BP, blood pressure; PSG, peak systolic gradient.

As depicted in Figure 3, 21 patients (88%) with a high epinephrine PSG underwent intervention at the index catheterization and 20 patients (77%) with a low epinephrine PSG were treated conservatively. The majority of interventions consisted of CoA stenting or redilatation of a previously placed CoA stent. In one patient, balloon angioplasty without stent placement was performed. The complex location of the stenosis, between the left carotid and left subclavian artery, would have required angular positioning of the stent. Hence, the risk of stent dislocation was considered too large to pursue stent placement in this patient. Overall, the invasive PSG decreased to 2 ± 4 mmHg after intervention.

**Table 2. Procedural data before and during epinephrine stress testing.**

| | Overall | Epinephrine PSG >20 mmHg | Epinephrine PSG ≤20 mmHg | |
|---|---|---|---|---|
| | n=50 | n=24 | n=26 | *p*-value* |
| **Type of anesthesia** | | | | 0.27 |
| General anesthesia | 29 (58) | 16 (67) | 13 (50) | |
| Conscious sedation | 21 (42) | 8 (33) | 13 (50) | |
| **Baseline** | | | | |
| Systolic BP (mmHg) | 106 ± 21 | 97 ± 17 | 116 ± 22 | **0.007** |
| PSG (mmHg) | 8 ± 6 | 10 ± 6 | 4 ± 6 | **0.001** |
| **Epinephrine stress testing** | | | | |
| Epinephrine dosage (µg) | 52 ± 28 | 48 ± 27 | 55 ± 29 | 0.40 |
| Systolic BP (mmHg) | 170 ± 23 | 162 ± 19 | 175 ± 25 | 0.06 |
| Increase vs. baseline (mmHg) | 62 ± 25 | 64 ± 22 | 61 ± 28 | 0.77 |
| PSG (mmHg) | 22 ± 15 | 35 ± 10 | 10 ± 8 | **<0.001** |
| Increase vs. baseline (mmHg) | 16 ± 13 | 24 ± 10 | 5 ± 6 | **<0.001** |

Data are presented as number (percentage) or mean ± standard deviation. *Indicates the difference between high and low epinephrine PSG groups, as determined by the independent-samples t-test or Fisher's exact test, where appropriate. BP, blood pressure; PSG, peak systolic gradient.

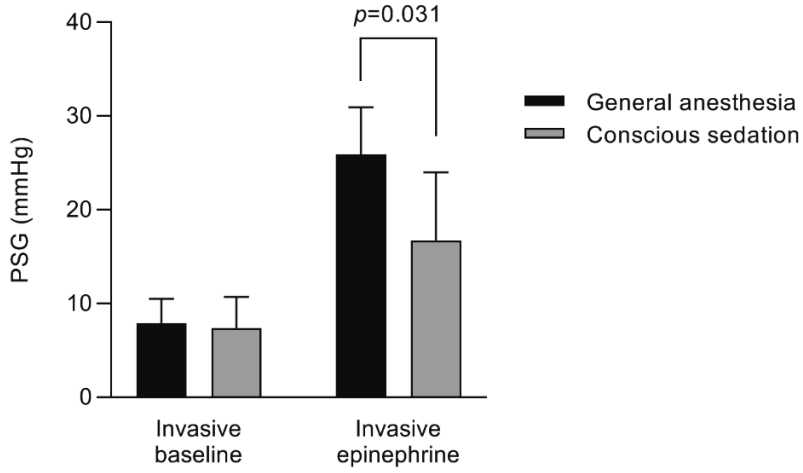


**Figure 2. Invasive baseline PSG and epinephrine PSG by type of anesthesia.** Values are presented as mean and 95% confidence interval. PSG, peak systolic gradient.

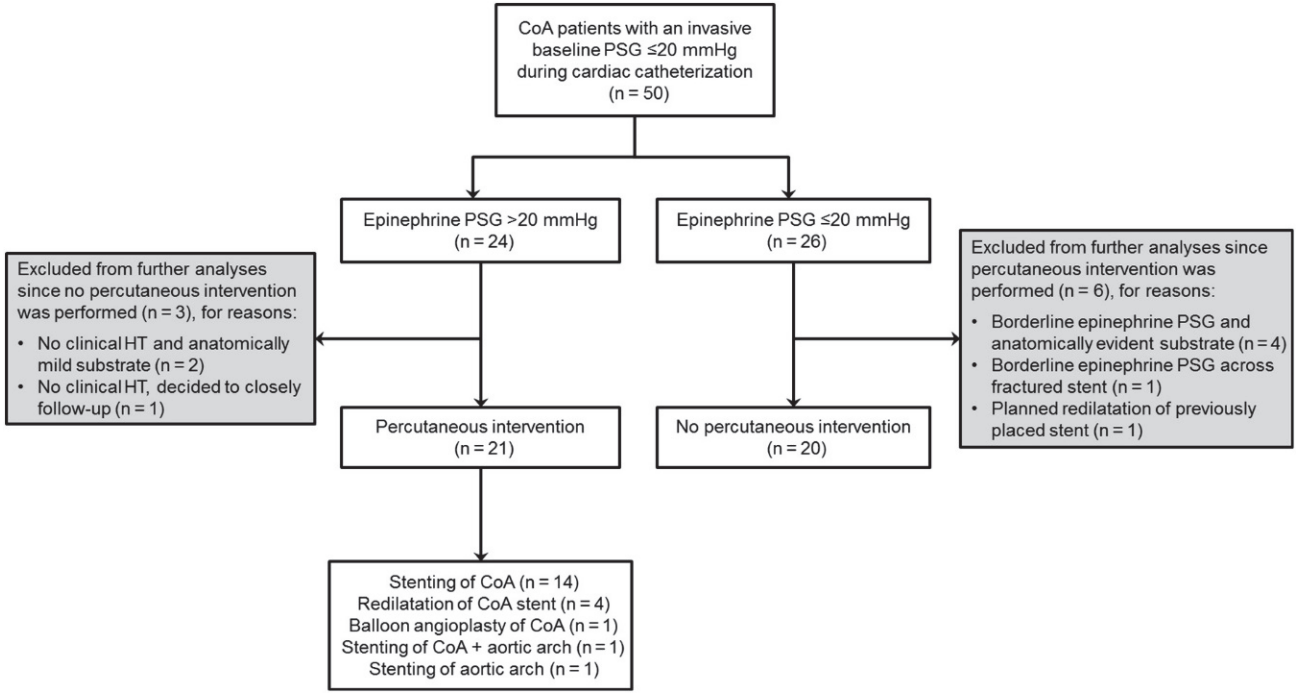


**Figure 3. Flow diagram showing the stratification of included patients based on invasive epinephrine PSG and subsequent interventional management during the index catheterization.** HT, hypertension; PSG, peak systolic gradient.

**Periprocedural and late complications**

Periprocedural complications (≤30 days) occurred in two patients. One patient developed an ischemic stroke due to occlusion of the right posterior cerebral artery within the first hours after stent implantation. This stroke was considered to be an embolic complication from the procedure. Another patient experienced an access site bleeding, which was successfully managed by manual compression in the absence of a significant hemoglobin drop. Late complications (>30 days) were observed in two patients. One of these underwent an unanticipated re-intervention, which consisted of stenting of hemodynamically relevant re-CoA. In another patient re-catheterization revealed a fracture of the implanted stent, whereupon an additional stent was placed. There were no significant differences in periprocedural or late complications between both groups.



**Medium-term clinical outcome**

Clinical outcome was assessed after a mean follow-up of 25 ± 18 months, with no difference in follow-up duration between the groups. The prevalence of office hypertension (19% vs. 76%; $p$=0.001) and hypertension on 24-hour ABPM (33% vs. 86%; $p$=0.030) was lower in the intervention group compared to the conservative group, although 24-hour ABPM was only performed in 25 patients (Table 3). Compared to baseline, patients in the intervention group showed a significant decline in the prevalence of hypertension and systolic blood pressure (Supplemental Table 2). In contrast, in the conservative group hemodynamic data were unchanged compared to baseline, except for an increase in the use of antihypertensive medication at follow-up (Supplemental Table 3). In multiple linear regression, intervention was associated with a 14.3 mmHg decrease in office systolic BP ($p$=0.001), independent of age, baseline systolic BP, and number of antihypertensive agents (Table 4). Furthermore, intervention was independently associated with a decrease in the number of antihypertensive agents ($p$=0.015). Similar results were found when including all patients who underwent epinephrine stress testing, irrespective of treatment strategy (Supplemental Table 4).

## DISCUSSION

This is the first study to evaluate the addition of epinephrine stress testing in CoA patients with a low PSG (≤20 mmHg) during cardiac catheterization. Epinephrine significantly increased PSG with nearly half of the patients exceeding the threshold of 20 mmHg. Subsequent percutaneous intervention in these patients was associated with a marked decrease in systolic BP during medium-term follow-up, irrespective of age, baseline systolic BP, and the use of antihypertensive medication. Furthermore, intervention was independently associated with a reduction in the number of antihypertensive agents.

**Table 3. Medium-term clinical outcome.**

| | **Intervention (epinephrine PSG >20 mmHg)** n=21 | **No intervention (epinephrine PSG ≤20 mmHg)** n=20 | *p*-value* |
|---|---|---|---|
| Office hypertension† | 4 (19) | 13 (76) | **0.001** |
| Office systolic BP (mmHg) | 130 ± 10 | 145 ± 17 | **0.002** |
| Office diastolic BP (mmHg) | 69 ± 8 | 80 ± 9 | **<0.001** |
| Hypertension on 24-hour ABPM‡ | 6 (33) | 6 (86) | **0.030** |
| 24-hour systolic BP (mmHg) | 122 ± 11 | 134 ± 7 | **0.020** |
| 24-hour diastolic BP (mmHg) | 66 ± 7 | 78 ± 10 | **0.005** |
| Use of any antihypertensive agent§ | 8 (38) | 11 (61) | 0.21 |
| Number of antihypertensive agents§ | 0.6 ± 0.9 | 1.2 ± 1.2 | 0.14 |
| Follow-up duration (months) | 30 ± 21 | 20 ± 13 | 0.09 |

Data are presented as number (percentage) or mean ± standard deviation. *Determined by the independent-samples t-test (Mann-Whitney U test for number of antihypertensive agents) or Fisher's exact test, where appropriate. †Available for 21 patients (100%) in the intervention group and 17 patients (85%) in the conservative group. ‡Available for 18 patients (86%) in the intervention group and 7 patients (35%) in the conservative group. §Available for 21 patients (100%) in the intervention group and 18 patients (90%) in the conservative group. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; PSG, peak systolic gradient.

It is known that up to 60% of CoA patients develop hypertension late after initial repair, which substantially increases the risk of accelerated coronary artery disease, stroke, aneurysm formation, and early mortality.[1,3] The exact etiology of hypertension in this patient cohort remains unclear. Various mechanisms have been proposed, including impaired aortic wall compliance, reduced baroreceptor sensitivity, elevated sympathetic nerve activity, and increased activation of the renin-angiotensin system.[19,20] Interestingly, many hypertensive CoA patients show no evidence of clinically relevant re-stenosis.[21] However, it remains difficult to determine the true clinical relevance of CoA. This is at least partly due to the artificial hypotension caused by general anesthesia and conscious sedation during cardiac catheterization.[7,8] Accordingly, in our cohort the systolic BP during catheterization was 35 mmHg lower compared to office measurements. The main goal of epinephrine stress testing was to counteract this effect by increasing cardiac output. Secondly, we aimed to mimic exercise to obtain a gradient that reflects the hemodynamic relevance of the stenosis in active daily life. Therefore, we tentatively chose a target systolic BP of 175 mmHg. However, due to the novelty of this technique, an optimal epinephrine protocol has yet to be established.

**Table 4. Multiple linear regression to examine the effect of percutaneous intervention on systolic BP and the use of antihypertensive medication at medium-term follow-up, after correction for potential confounding factors.**

| | **Office systolic BP (mmHg)** | | |
|---|---|---|---|
| | Unstandardized coefficient* | 95% CI | *p*-value |
| Intervention performed | -14.27 | -22.15, -6.39 | **0.001** |
| Age at catheterization (years) | -0.12 | -0.40, 0.15 | 0.37 |
| Office systolic BP at baseline (mmHg) | 0.50 | 0.28, 0.73 | **<0.001** |
| Number of antihypertensive agents | 3.15 | -0.30, 6.59 | 0.07 |
| | **24-hour systolic BP (mmHg)†** | | |
| | Unstandardized coefficient* | 95% CI | *p*-value |
| Intervention performed | -13.45 | -30.20, 3.31 | 0.11 |
| Age at catheterization (years) | -0.04 | -0.64, 0.72 | 0.90 |
| 24-hour systolic BP at baseline (mmHg) | 0.01 | -0.54, 0.56 | 0.97 |
| Number of antihypertensive agents | 0.21 | -6.03, 6.46 | 0.94 |
| | **Number of antihypertensive agents** | | |
| | Unstandardized coefficient* | 95% CI | *p*-value |
| Intervention performed | -1.84 | -3.32, -0.36 | **0.015** |
| Age at catheterization (years) | 0.002 | -0.04, 0.04 | 0.91 |
| Number of antihypertensive agents at baseline | 0.82 | 0.34, 1.29 | **0.001** |
| 24-hour systolic BP (mmHg) | -0.01 | -0.07, 0.06 | 0.82 |

*Indicates the change of the dependent variable per unit increase of the covariate. †Available for 25 patients (61%). BP, blood pressure.

Although in this study epinephrine was used to attempt to determine the clinical relevance of CoA, it is unknown which pharmacological agent is most appropriate for this purpose. It was previously shown that 50% of CoA patients have elevated plasma epinephrine levels, thereby suggesting that epinephrine plays a role in the pathophysiology of persistent hypertension in CoA.[22] Additionally, CoA patients frequently show HRE, even in the absence of resting hypertension.[23] It has been reported that HRE is independently associated with the occurrence of adverse cardiovascular events in CoA patients.[23] Interestingly, we found that patients with HRE were more likely to have an increase of PSG beyond 20 mmHg with epinephrine. This association remained present when using lower cut-off points of 10 and 15 mmHg for epinephrine PSG, but not with a higher cut-off point of 25 mmHg. Nevertheless, this finding suggests that epinephrine may be an adequate surrogate for exercise. Furthermore, it was previously shown that CoA patients with HRE have a 10-fold larger increase in plasma epinephrine during exercise compared to CoA patients with a normal BP response to exercise.[24] However, a potential disadvantage of the use of epinephrine is the occurrence of a paradoxical reflex bradycardia shortly after the hypertensive maximum in some patients. This reflex is due

to the stimulatory effect of epinephrine on α-adrenergic receptors, resulting in peripheral vasoconstriction. The consequent sudden raise in BP may trigger the baroreceptors in the carotid sinus and aortic arch, leading to a bradycardic reflex.[25] Alternatively, three previous studies performed stress testing during cardiac catheterization using isoproterenol, a β-adrenergic receptor agonist with low affinity for α-receptors.[9-11] Isoproterenol infusion led to a significant increase in PSG in these studies, similar to our findings with epinephrine. However, although isoproterenol substantially increases heart rate, it tends to lower blood pressure due to a β2-mediated decrease in systemic vascular resistance.[26] Hence, it is questionable whether exercise is appropriately mimicked by isoproterenol. Pharmacological stress testing in CoA has also been performed using dobutamine stress echocardiography, which showed a good correlation with BP and PSG during exercise.[27] However, the use of dobutamine in the cardiac catheterization laboratory has not yet been described. Potentially the most appropriate method to determine the clinical relevance of CoA is to perform exercise testing during cardiac catheterization. Lower extremity cycle ergometry is increasingly used during diagnostic right heart catheterization.[28] However, this is only possible in CoA when a radial access site would be used for the diagnostic part of the procedure. Alternatively, dynamic arm exercise could be performed. Exercise may also be incorporated in the non-invasive hemodynamic assessment by cardiac MRI, even though there is limited evidence on its feasibility in CoA patients thus far.

As a future direction, it would be beneficial for clinicians to predict which patients may respond to epinephrine stress testing and which patients may not. In our study, younger patients, patients with HRE, and possibly patients with an initial non-surgical CoA repair were more likely to have an epinephrine PSG >20 mmHg. However, larger studies are needed to identify independent predictors of gradient response, which could aid clinicians in the selection of patients that may benefit from epinephrine stress testing. During cardiac catheterization, the type of anesthesia was associated with the hemodynamic response to epinephrine. Even though the baseline PSG was similar in patients under general anesthesia and patients under conscious sedation, the epinephrine PSG was higher in the general anesthesia group. This suggests that the effect of epinephrine is greater during general anesthesia, presumably by counteracting the decrease in systemic vascular resistance induced by general anesthesia.

In the current study, we found that the majority of patients with both a low baseline PSG and a low epinephrine PSG remained hypertensive during follow-up and even an increase in the use of antihypertensive medication was observed. This may raise the concern that relevant restenosis cannot be adequately ruled out using epinephrine stress testing. However, there are no available data indicating that intervention in these patients could result in a BP decrease, and if so, that it could outweigh the risks of invasive management. A restenosis may not be the cause of hypertension in these patients, but rather a combination of other factors associated with hypertension in CoA, such as elevated RAS-activation, increased arterial wall stiffness, and reduced baroreceptor sensitivity. Further research is needed to determine whether persistent

hypertension in these patients is caused by hemodynamically relevant obstruction, which in that case epinephrine stress testing failed to identify, or is caused by other, less modifiable factors.

In contrast, patients with a low baseline PSG but a high epinephrine PSG that underwent intervention showed a substantial BP reduction during follow-up. These results raise the question whether a more aggressive treatment strategy in a subset of patients with low-gradient CoA is justified. Naturally, the benefit of intervention in terms of decreasing cardiovascular risk should outweigh the risks. The current threshold of 20 mmHg for PSG has been defined rather arbitrarily. As noted by Rosenthal, this threshold was determined by the perceived risk-benefit ratio of surgery and balloon angioplasty.[29] However, with the introduction of stent implantation, the risks associated with intervention have steadily decreased while a clear BP reduction is achieved.[30,31] Furthermore, it has been shown that the presence of mild residual CoA is associated with hypertension and pre-stenotic vascular injury.[32] In light of these considerations, we propose to implement epinephrine stress testing in the catheterization laboratory for the evaluation of CoA in case of a low baseline PSG. We believe this will aid in the clinical decision making in this patient cohort. However, prospective studies are needed to further evaluate the risks and benefits associated with this novel approach. Additionally, it would be interesting to observe how the outcomes compare to patients with an invasive baseline PSG >20 mmHg in whom no epinephrine stress testing is performed.



**Limitations**

Several limitations of our study should be taken into account. First, this was a retrospective study with a relatively small sample size. Therefore, the results should be interpreted with caution. Due to the retrospective nature of this study, 24-hour ABPM was not available for a substantial number of patients. Hence, no definite conclusions can be drawn regarding this endpoint, due to the diminished power and potential overfitting of the multiple regression model. The superior reliability of 24-hour ABPM in comparison to office measurements underlines the importance of reporting this outcome, if available. Furthermore, the choice to perform an intervention was not solely based on the epinephrine PSG but also on factors evaluated prior to cardiac catheterization, such as the presence of hypertension and the anatomical substrate. To reduce the impact of these factors, we limited the analyses regarding treatment outcome to patients with a high epinephrine PSG who underwent intervention and patients with a low epinephrine PSG who were treated conservatively. Lastly, the dosage of epinephrine needed to reach the target blood pressure varied between patients. This may decrease the generalizability of the results, although the epinephrine dosage did not differ between both groups.

## CONCLUSIONS

The implementation of epinephrine stress testing during cardiac catheterization may aid in the clinical decision making in patients with CoA. In the subset of patients with a high epinephrine PSG, percutaneous intervention is associated with a reduction in systemic BP and the use of antihypertensive medication during medium-term follow-up. Prospective studies are warranted to further assess the potential risks and benefits of this novel approach in the evaluation of CoA.

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## SUPPLEMENTAL MATERIAL

**Supplemental Table 1. Association between clinical parameters and epinephrine PSG when using different cut-off points (25, 15, and 10 mmHg, respectively) for epinephrine PSG.**

| | **Epinephrine PSG >25 mmHg** | **Epinephrine PSG ≤25 mmHg** | |
|---|---|---|---|
| | n=18 | n=32 | *p*-value* |
| Age at catheterization (years) | 21.9 ± 12.2 | 30.3 ± 13.0 | **0.031** |
| Non-invasive systolic right arm-leg gradient (mmHg) | 13 ± 14 | 5 ± 14 | 0.09 |
| Office hypertension | 11 (61) | 23 (72) | 0.53 |
| Hypertension on 24-hour ABPM† | 11 (73) | 18 (82) | 0.69 |
| Hypertensive response to exercise‡ | 8 (89) | 10 (56) | 0.19 |
| | **Epinephrine PSG >15 mmHg** | **Epinephrine PSG ≤15 mmHg** | |
| | n=31 | n=19 | *p*-value* |
| Age at catheterization (years) | 23.5 ± 11.8 | 33.5 ± 13.4 | **0.008** |
| Non-invasive systolic right arm-leg gradient (mmHg) | 10 ± 14 | 4 ± 14 | 0.27 |
| Office hypertension | 22 (71) | 12 (63) | 0.76 |
| Hypertension on 24-hour ABPM† | 19 (76) | 10 (83) | 1.0 |
| Hypertensive response to exercise‡ | 14 (93) | 4 (33) | **0.003** |
| | **Epinephrine PSG >10 mmHg** | **Epinephrine PSG ≤10 mmHg** | |
| | n=37 | n=13 | *p*-value* |
| Age at catheterization (years) | 23.9 ± 11.0 | 36.7 ± 14.8 | **0.002** |
| Non-invasive systolic right arm-leg gradient (mmHg) | 9 ± 15 | 7 ± 9 | 0.81 |
| Office hypertension | 25 (68) | 9 (69) | 1.0 |
| Hypertension on 24-hour ABPM† | 23 (77) | 6 (86) | 1.0 |
| Hypertensive response to exercise‡ | 16 (84) | 2 (25) | **0.006** |

Data are presented as number (percentage) or mean ± standard deviation. *Determined by the independent-samples t-test or Fisher's exact test, where appropriate. †Available for 37 patients (74%). ‡Available for 27 patients (54%). ABPM, ambulatory blood pressure monitoring; PSG, peak systolic gradient.

**Supplemental Table 2. Clinical outcome in patients with a high epinephrine PSG who underwent intervention, compared to baseline**.

| | **Baseline** | **Follow-up (mean 30 ± 21 months)** | |
|---|---|---|---|
| | n=21 | n=21 | *p*-value* |
| Office hypertension | 14 (67) | 4 (19) | **0.006** |
| Office systolic BP (mmHg) | 140 ± 10 | 130 ± 10 | **0.001** |
| Office diastolic BP (mmHg) | 73 ± 10 | 69 ± 8 | 0.06 |
| Hypertension on 24-hour ABPM† | 14 (78) | 6 (33) | 0.07 |
| 24-hour systolic BP (mmHg) | 136 ± 12 | 122 ± 11 | **0.017** |
| 24-hour diastolic BP (mmHg) | 71 ± 8 | 66 ± 7 | 0.16 |
| Use of any antihypertensive agent | 9 (43) | 8 (38) | 1.0 |
| Number of antihypertensive agents | 0.9 ± 1.1 | 0.6 ± 0.9 | 0.21 |

Data are presented as number (percentage) or mean ± standard deviation. *Determined by the paired-samples t-test or McNemar's test, where appropriate. †Available for 18 patients (86%) at baseline and follow-up. ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

**Supplemental Table 3. Clinical outcome in patients with a low epinephrine PSG treated conservatively, compared to baseline.**

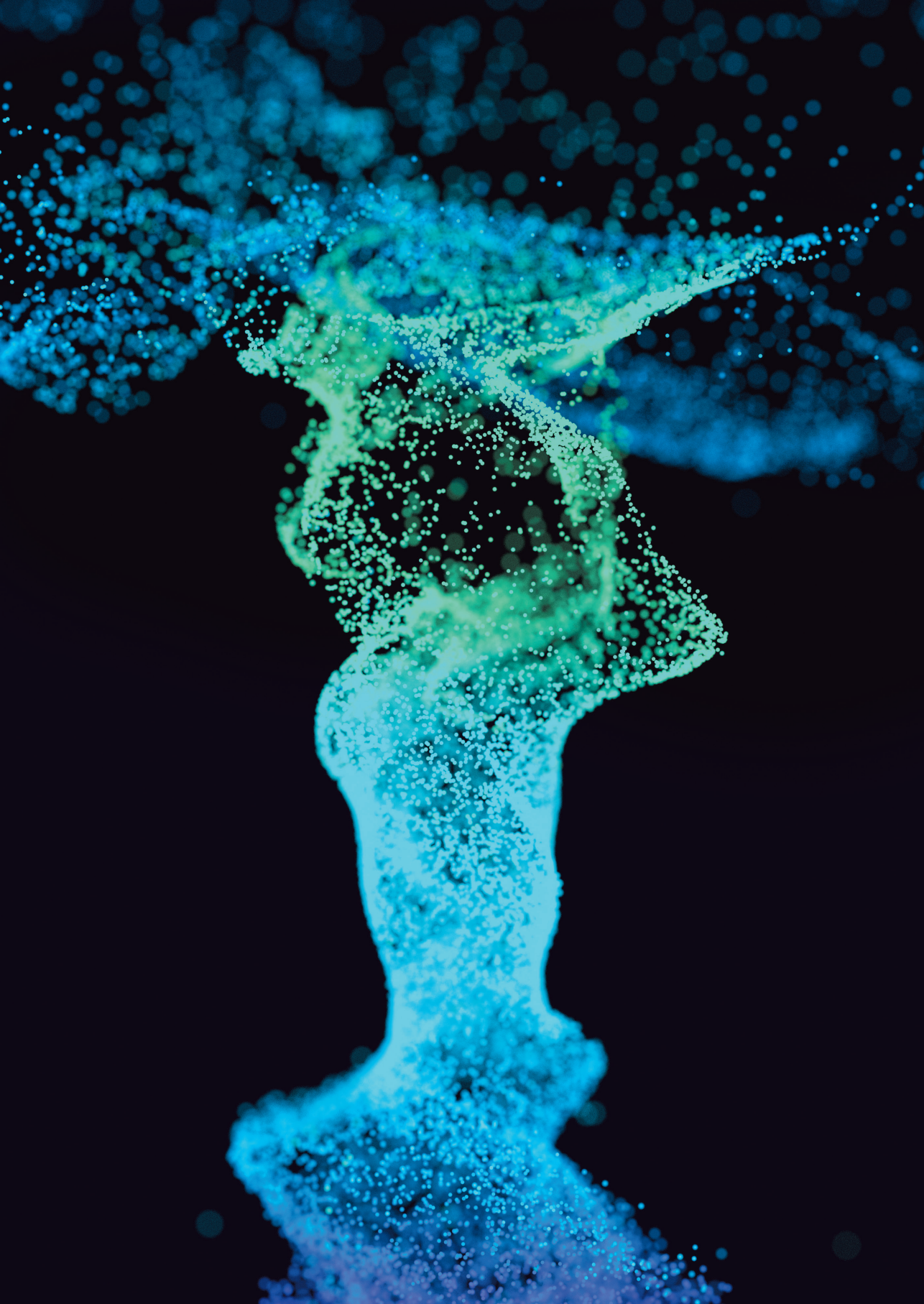
| | **Baseline** | **Follow-up (mean 20 ± 13 months)** | |
|---|---|---|---|
| | n=20 | n=20 | *p*-value* |
| Office hypertension† | 12 (60) | 13 (76) | 0.38 |
| Office systolic BP (mmHg) | 144 ± 24 | 145 ± 17 | 0.15 |
| Office diastolic BP (mmHg) | 81 ± 17 | 80 ± 9 | 0.78 |
| Hypertension on 24-hour ABPM‡ | 11 (92) | 6 (86) | 1.0 |
| 24-hour systolic BP (mmHg) | 135 ± 13 | 134 ± 7 | 0.51 |
| 24-hour diastolic BP (mmHg) | 75 ± 14 | 78 ± 10 | 0.57 |
| Use of any antihypertensive agent§ | 6 (30) | 11 (61) | **0.031** |
| Number of antihypertensive agents§ | 0.5 ± 0.8 | 1.2 ± 1.2 | **0.001** |

Data are presented as number (percentage) or mean ± standard deviation. *Determined by the paired-samples t-test or McNemar's test, where appropriate. †Available for 20 patients (100%) at baseline and 17 patients (85%) at follow-up. ‡Available for 12 patients (60%) at baseline and 7 patients (35%) at follow-up. §Available for 20 patients (100%) at baseline and 18 patients (90%) at follow-up. ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

**Supplemental Table 4. Multiple linear regression to examine the effect of percutaneous intervention on systolic BP and the use of antihypertensive medication at medium-term follow-up in all patients who underwent epinephrine stress testing, irrespective of treatment strategy (n=50).**

| | **Office systolic BP (mmHg)** | | |
|---|---|---|---|
| | Unstandardized coefficient* | 95% CI | *p*-value |
| Intervention performed | -12.64 | -20.01, -5.26 | **0.001** |
| Age at catheterization (years) | -0.18 | -0.46, 0.09 | 0.18 |
| Office systolic BP at baseline (mmHg) | 0.45 | 0.23, 0.66 | **<0.001** |
| Number of antihypertensive agents | 3.89 | 0.70, 7.08 | **0.018** |
| | **24-hour systolic BP (mmHg)†** | | |
| | Unstandardized coefficient* | 95% CI | *p*-value |
| Intervention performed | -12.73 | -23.87, -1.59 | **0.027** |
| Age at catheterization (years) | -0.04 | -0.43, 0.51 | 0.85 |
| 24-hour systolic BP at baseline (mmHg) | 0.20 | -0.18, 0.58 | 0.29 |
| Number of antihypertensive agents | -0.24 | -4.76, 4.29 | 0.91 |
| | **Number of antihypertensive agents** | | |
| | Unstandardized coefficient* | 95% CI | *p*-value |
| Intervention performed | -1.62 | -2.97, -0.26 | **0.019** |
| Age at catheterization (years) | 0.02 | -0.03, 0.06 | 0.46 |
| Number of antihypertensive agents at baseline | 0.90 | 0.50, 1.29 | **<0.001** |
| 24-hour systolic BP (mmHg) | 0.01 | -0.04, 0.07 | 0.65 |

*Indicates the change of the dependent variable per unit increase of the covariate.
†Available for 34 patients (68%). BP, blood pressure.



# CHAPTER 5

# Safety and efficacy of stenting for aortic arch hypoplasia in patients with coarctation of the aorta

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**ABSTRACT**

**Background**

Despite a successful repair procedure for coarctation of the aorta (CoA), up to two-thirds of patients remain hypertensive. CoA is often seen in combination with abnormal aortic arch anatomy and morphology. This might be a substrate for persistent hypertension. Therefore, we performed endovascular aortic arch stent placement in patients with CoA and concomitant aortic arch hypoplasia or gothic arch morphology. The goal of this retrospective analysis was to investigate the safety and efficacy of aortic arch stenting.

**Methods**

A retrospective analysis was performed for patients who underwent stenting of the aortic arch at the University Medical Center Utrecht. Measurements collected included office blood pressure, use of antihypertensive medication, invasive peak-to-peak systolic pressure over the arch, and aortic diameters on three-dimensional angiography. Data on follow-up were obtained at the date of most recent outpatient visit.

**Results**

Twelve patients underwent stenting of the aortic arch. Mean follow-up duration was $14 \pm 11$ months. Mean peak-to-peak gradient across the arch decreased from $39 \pm 13$ mm Hg to $7 \pm 8$ mm Hg directly after stenting ($p < 0.001$). There were no major procedural complications. Mean systolic blood pressure decreased from $145 \pm 16$ mm Hg at baseline to $128 \pm 9$ mm Hg at latest follow-up ($p = 0.014$).

**Conclusion**

This retrospective study shows that stenting of the aortic arch is successful when carried out in a state-of-the-art manner. A direct optimal angiographic and haemodynamic result was shown. No major complications occurred during or after the procedure. At short- to medium-term follow-up a decrease in mean systolic blood pressure was observed.

## INTRODUCTION

Coarctation of the aorta (CoA) accounts for approximately 5–8% of all forms of congenital heart disease.[1] It is characterised by a narrowing of the upper descending aorta, most commonly distal to the origin of the left subclavian artery near the insertion of the arterial ligament. CoA can occur as an isolated lesion, but frequently occurs in combination with other lesions such as a bicuspid aortic valve (50% of patients), ventricular septal defect (15% of patients), or a hypoplastic aortic arch (13% of patients).[1-4] Clinical characteristics depend on the severity of the CoA and may vary from acute congestive heart failure in the neonate to systemic hypertension in late childhood or adulthood. Currently, percutaneous stent placement is the standard of care for adults and older children.[5]

Even after successful CoA repair, residual or late-onset systemic hypertension is not uncommon. It is seen in up to two-thirds of the adult patients after an initial successful repair.[6,7] Systemic hypertension contributes to a higher morbidity and mortality in these patients, due to an increased incidence of cerebrovascular diseases, heart failure, and acceleration of the progression of coronary artery disease.[8] Although successful stenting of native or recurrent CoA does not always eliminate the need for treatment with antihypertensive drugs, it can facilitate optimal medical treatment.[9]

A substantial number of patients with CoA have an abnormal aortic arch anatomy or geometry. It is thought that neonatal aortic arch hypoplasia in CoA patients is caused by a decreased flow to the aorta in utero and that catch-up growth of the transverse aortic arch after repair is limited.[10,11] Several studies have found that aortic arch hypoplasia is associated with late systemic hypertension[12,13], even in the absence of an arm-leg blood pressure gradient.[8]

The influence of abnormal aortic arch geometry on systemic hypertension is still a subject of debate. An abnormal aortic flow and increased aortic stiffness have been observed in aortic arches with gothic morphology.[14] Deviating morphology may lead to hypertension.[15,16] Both systemic hypertension and abnormal blood pressure response to exercise have been reported in this population.[17,18] A hypoplastic or gothic aortic arch might be a substrate for persistent hypertension and stenting of the aortic arch could be beneficial for this patient cohort. The main objectives of this study were to investigate the safety of this treatment strategy and to investigate the effect on blood pressure regulation of aortic stenting in adolescent and adult patients.

## METHODS

### Study population

A retrospective review of the cardiac interventional database at the University Medical Center Utrecht (Utrecht, the Netherlands) was performed to identify patients for this study. Patients were selected when they met the following inclusion criteria: (1) diagnosed with CoA; (2) undergone stent implantation that included the aortic arch; (3) a body weight > 50 kg. Arch stenting was defined as stenting between the brachiocephalic trunk and the left subclavian artery. Due to the retrospective nature of this study, an ethics waiver was granted by the local Medical Ethical Committee.

### Data acquisition

Data on demography, biometry, blood pressure, medication use, cardiac imaging, and catheterisation procedures were collected from the electronic patient records. Data were collected at two different time points: before stent implantation and at the most recent outpatient visit.

### Measurements

The office blood pressure was measured in a seated position in the right upper limb with an automated cuff in accordance with the European Society of Cardiology (ESC) guideline.[19] The ascending and descending aortic pressure were measured during cardiac catheterisation for evaluation of the peak-to-peak systolic pressure over the arch. During catheterisation both two-dimensional angiograms and three-dimensional rotational angiograms were obtained, before and after stent implantation. In three-dimensional rotational angiography the measurements were performed using multi-planar reconstructions. The ascending aorta was measured just before the brachiocephalic trunk, the descending aorta was measured at the level of the diaphragm and the transverse aortic arch was measured at the narrowest diameter. In case the aorta had an ‘oval’ shape, surface area was calculated using the formula: surface area = radius a $*$ radius b $*$ $\pi$.

### Stent implantation technique

All procedures were performed under general anaesthesia. In all patients, vascular access was achieved using the right femoral artery. The DynaCT Artis Zee system (Siemens Healthcare, Erlangen, Germany) was used for performing three-dimensional rotational angiography. The three-dimensional reconstructions gathered with this system were used as an overlay over our fluoroscopy images for optimal procedure guidance, as previously published.[20] The decision to proceed to stent placement was made taking into account several parameters: the peak-to-peak gradient across the aortic arch, the presence of an anatomical substrate, the presence of

collaterals, and the presence of hypertension in daily life (preferably confirmed with 24-hours ambulatory blood pressure measurements). Target stent diameter and length were determined based on three-dimensional rotational angiography measurements, conventional two-dimensional angiography measurements of dimensions of the ascending aorta just before the brachiocephalic trunk and the descending aorta at the level of the diaphragm, and balloon interrogation. In complex arch morphology a steerable long sheath (Oscor, 12–13.8 French) as well as rapid pacing were used. Mainly, ev3 Max LD (Medtronic, Plymouth, MN, USA), Andra XXL (Andramed GmbH, Reutlingen, Germany) and Cheatham-Platinum (CP) stent (NuMED Inc., Hopkinton, NY, USA) were used. Strut dilatation to side branches was performed when deemed necessary to enhance left carotid or left subclavian flow. In selected patients with complex aortic morphology two procedures were planned. Stents were placed in the first procedure and consequently dilated further in the second procedure. Major complications were defined as stroke, myocardial infarction, bleeding classified as Bleeding Academic Research Consortium scale (BARC) > 2, or death.



**Data analysis**

All analyses were performed using SPSS statistical software version 25 (IBM SPSS Data Collection, Chicago, IL, USA). Descriptive statistics were used for demographic data. Quantitative data are presented as mean ± standard deviation or absolute number (percentage). Group means before and after stent placement were compared using the paired samples t-test. Results were considered statistically significant if the probability value (p-value) was < 0.05.

## RESULTS

**Demographic data**

Between April 2014 and January 2018 a total of 12 patients with a mean age of 24 ± 8 years underwent stenting for aortic arch hypoplasia or gothic arch morphology. Eleven patients previously had some form of CoA repair, one patient had a native CoA. Eleven patients had a hypoplastic aortic arch, one patient had a gothic arch morphology. Ten patients had concomitant congenital cardiac defects. Follow-up data were available for all patients; mean follow-up duration was 14 ± 11 months. Patient characteristics are presented in Table 1.

**Table 1. Baseline characteristics.**

| Parameter | Patients (n=12) |
|---|---|
| Age (years) | 24 ± 8 |
| Male | 9 (75%) |
| Weight (kg) | 70 ± 7 |
| BMI (kg/m$^2$) | 23 ± 2 |
| Native CoA | 1 (8%) |
| *Concomitant cardiac defects* | |
| Bicuspid aortic valve | 6 (50%) |
| Ventricular septal defect | 4 (33%) |
| Persistent ductus arteriosus | 2 (17%) |
| Transposition of the great arteries | 1 (8%) |
| *Previous CoA repair* | |
| End-to-end anastomosis | 7 (58%) |
| Patch angioplasty | 4 (33%) |
| Balloon dilatation | 3 (25%) |
| Stent implantation | 5 (42%) |
| *Medication use* | |
| ACE inhibitor | 4 (33%) |
| Angiotensin II receptor blocker | 4 (33%) |
| Beta-blocker | 1 (8%) |
| Calcium-channel blocker | 4 (33%) |
| Diuretics | 3 (25%) |

Data are presented as number (percentage) or mean ± standard deviation. BMI: body mass index, CoA: coarctation of the aorta, ACE: angiotensin-converting enzyme inhibitor.

**Procedural data**

Femoral artery sheath sizes ranged from 8–14 French. During the stenting procedure 21 stents were used in a total of 12 patients: the CP stent was used in 6 (50%) patients, the ev3 Max LD stent was used in 5 (42%) patients, the ev3 Mega LD stent was used in 3 (25%) patients, and the Andra XXL stent was used in 1 (8%) patient. The length of the used stents varied from 26–57 mm. After stent implantation, post-dilatation of the stent was performed in 10 patients using the Atlas PTA Balloon (Bard Peripheral Vascular, Tempe, AZ, USA) in six (50%) patients and the Cristal balloon (ab medica, Dusseldorf, Germany) in four (33%) patients, with balloon inflation pressures ranging between 10–24 atm. Aortic arch vessels were crossed in all patients; in six patients the left subclavian artery was crossed, in two patients the left common carotid artery was crossed, and in four patients both the left subclavian artery and the left common carotid artery were crossed.

**Acute angiographic result**

The mean peak-to-peak gradient across the aortic arch decreased from 39 ± 13 mmHg to 7 ± 8 mmHg after stent placement ($p < 0.001$). The mean orthogonal diameters at the narrowest point of the transverse aortic arch increased from 12 ± 3 mm × 13 ± 3 mm to 18 ± 3 mm × 19 ± 4 mm after stent placement ($p < 0.001$ and $p < 0.001$, respectively). Resulting in an increase in mean surface area of 126 ± 56 $mm^2$ to 276 ± 107 $mm^2$ ($p < 0.001$). Data are presented in Table 2 and Figure 1.

**Table 2. Acute angiographic results.**

| | Pre | Post | p-value |
|---|---|---|---|
| PG (mmHg) | 39 ± 13 | 7 ± 8 | < 0.001 |
| Aortic arch narrowest point | | | |
| Sagittal diameter (mm) | 12 ± 3 | 18 ± 3 | < 0.001 |
| Corresponding orthogonal diameter (mm) | 13 ± 3 | 19 ± 4 | < 0.001 |
| Surface area ($mm^2$) | 126 ± 56 | 276 ± 107 | < 0.001 |
| Descending aorta caudal | | | |
| Sagittal diameter (mm) | 18 ± 5 | NA | NA |
| Corresponding orthogonal diameter (mm) | 18 ± 5 | NA | NA |
| Surface area ($mm^2$) | 716 ± 472 | NA | NA |

Orthogonal diameters were measured using three-dimensional rotational angiography. Data are presented as mean ± standard deviation. NA: not applicable, PG: peak gradient measured over the aortic arch during catheterization.

**Procedural complications**

No major complications occurred during the procedure or follow-up, we observed three minor complications. A temporary third-degree atrioventricular block occurred in one patient. During the post-implantation re-dilatation of one of the stents a stent fracture occurred in one patient, which was resolved by placement of a covered stent. One patient experienced minor rebleeding of the access site, which was managed with a simple bandage. No endovascular leaks occurred after stent implantation.

**Follow-up**

Four patients underwent a planned staged procedure, with successful further dilatation of the stent in the first year after the implantation. Data presented are at baseline (before stent implantation) and at latest follow-up (after further dilatation). No major complications occurred during mean follow-up of 14 ± 11 months.

**Blood pressure regulation**

There was a decrease in mean systolic blood pressure, measured at the right arm, from 145 ± 16 mm Hg at baseline to 128 ± 9 at latest outpatient visit (p = 0.014) (Figure 1). There was no significant decrease in mean diastolic blood pressure (p = 0.477). A decrease in the mean number of antihypertensive drug classes used was observed from 1.27 ± 1.10 before stent placement to 0.64 ± 1.03 at the most recent outpatient visit (p = 0.016). Data on blood pressure and antihypertensive medication for each individual patient are presented in Table 3.

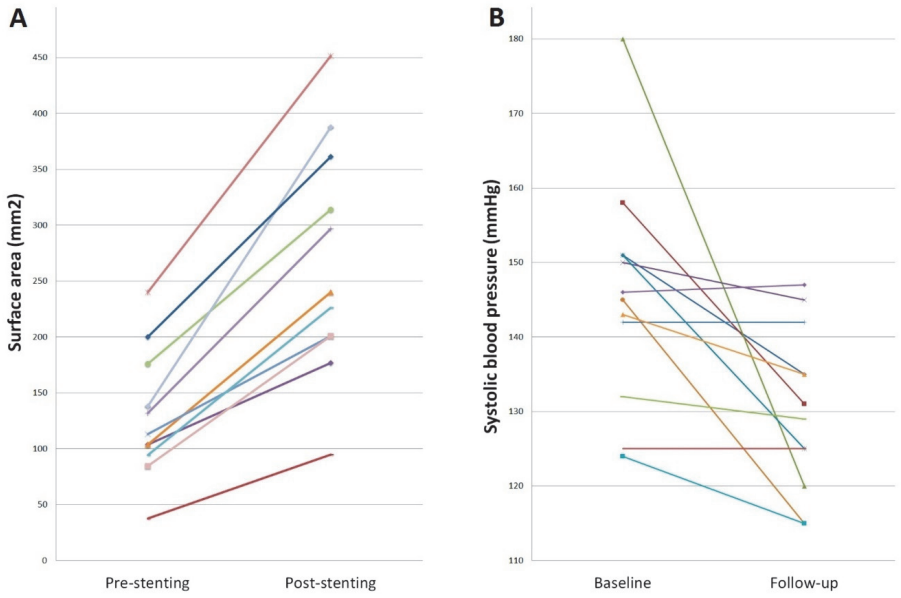


**Figure 1. Result of stenting on surface area and systolic blood pressure.** (A) Surface area ($mm^2$) as measured on three-dimensional rotational angiography multiplanar reconstructions pre- and post-stenting. (B) Systolic blood pressure (mmHg) measured at the right arm at baseline and follow-up.

**Table 3. Data on blood pressure and antihypertensive medication for each patient before stent placement and at latest follow-up after stent implantation.**

| Patient | BP baseline (mmHg) | AHD baseline | BP post stent (mmHg) | AHD post stent |
|---|---|---|---|---|
| 1 | 151/98 | None | 135/63 | None |
| 2 | 158/60 | Losartan 50 mg<br>Metoprolol 25 mg | 131/63 | None |
| 3 | 180/95 | Verapamil 240 mg | 120/91 | None |
| 4 | 150/74 | None | 145/85 | None |
| 5 | 151/71 | Telmisartan 80 mg | 125/75 | None |
| 6 | 145/90 | None | 115/70 | None |
| 7 | 142/80 | Lisinopril 20 mg | 142/77 | None |
| 8 | 125/80 | Telmisartan 40 mg<br>Amlodipine 5 mg | 125/70 | Telmisartan 40 mg<br>Amlodipine 5 mg |
| 9 | 124/57 | None | 129/69 | None |
| 10 | 124/56 | Lercanidipine 5mg<br>Lisinopril 20 mg<br>Hydrochlorothiazide 25 mg | 115/57 | Lisinopril 20 mg |
| 11 | 146/55 | Ramipril 10 mg | 147/68 | Ramipril 10 mg |
| 12 | 143/67 | Olmesartan 40mg<br>Amlodipine 10 mg<br>Hydrochlorothiazide 25 mg | 135/70 | Olmesartan 40mg<br>Amlodipine 10 mg<br>Hydrochlorothiazide 25 mg |

AHD: antihypertensive drugs, BP: blood pressure.



## DISCUSSION

In this retrospective study we analyzed a subset of patients with CoA and a concomitant hypoplastic or gothic aortic arch who underwent stenting of the aortic arch. Stenting of the aortic arch was successful in all selected patients and no complications occurred. The acute angiographic result was excellent, demonstrated by an increase in aortic arch surface area and a decrease in mean peak-to-peak gradient across the aortic arch. Most importantly, a significant decrease in mean systolic blood pressure was observed, with a concomitant decrease in the need for antihypertensive medication.

The target of interventional treatment in CoA is the relief of the obstruction and reduction of the pressure gradient. A large number of patients still suffer from residual or late-onset systemic hypertension despite successful initial percutaneous or surgical therapy. A substantial number of patients who have a CoA also have an abnormal aortic arch anatomy or morphology, which might be a substrate for hypertension. Percutaneous stent placement has become the standard of care for the treatment of CoA after childhood in the last decade. However, stent placement as treatment for aortic arch hypoplasia has only been described in

small series and case reports.[21-25] All reports on aortic arch stenting showed anatomical and physiological relief of obstruction. Boshoff et al. reported no peri-procedural complications[24], Holzer et al. reported a relatively high number of adverse events (in 31% of patients), although this was mostly in patients with a weight below 10 kg or with univentricular physiology.[25] In a study including 21 patients, Pushparajah et al. reported three major complications in two patients.[21] Stent migration occurred in two patients, of which one subsequently suffered from an embolic stroke. In these two cases stents were implanted without the use of rapid pacing, which was thought to have increased the risk of stent migration. In our cohort no major complications were observed peri-procedurally or during follow-up.

We believe several steps are important for a safe and successful procedure. Understanding the aortic arch anatomy and morphology is vital, cardiac magnetic resonance imaging (CMR) and computed tomography (CT) are therefore essential in the pre-procedural phase. During the procedure we use reconstructions derived from three-dimensional rotational angiography as an overlay on our fluoroscopy images for optimal guidance (see Figure 2 and 3). Balloon interrogation can provide information regarding correct size, tissue compliance and balloon stability. Rapid pacing and deployment of the stent through a steerable long sheath can enhance positioning effectively and reduce the risk of stent migration. A stent with moderate radial strength and good compliance—such as the ev3 Max LD and ev3 Mega LD—serves best to achieve an ideal aortic arch shape. True open cell design is mandatory to enable strut dilatation when necessary to enhance carotid or subclavian flow. Typically, we aim to position an arch stent between the brachiocephalic trunk and the left subclavian artery with the proximal and distal part reaching out into the ostia. We believe that this technique results in an optimal distribution of shear stress to reduce intimal trauma of the aortic arch.

Pushparajah et al. investigated the effect of stent implantation on blood pressure and antihypertensive medication at short- and medium-term follow-up. An improvement in blood pressure outcome was seen, with a decrease in median systolic blood pressure from 145 to 128 mmHg.[21] Antihypertensive medication could be reduced in 13 out of 17 patients.[21] These results are in line with our results on blood pressure regulation. Even though the goal of stent placement in the aortic arch is not to stop medical therapy, a decrease in antihypertensive medication is beneficial for this patient population. For these relatively young patients lifelong use of multiple medications is very demanding. Therefore, optimal treatment of the underlying substrate seems a sensible approach.

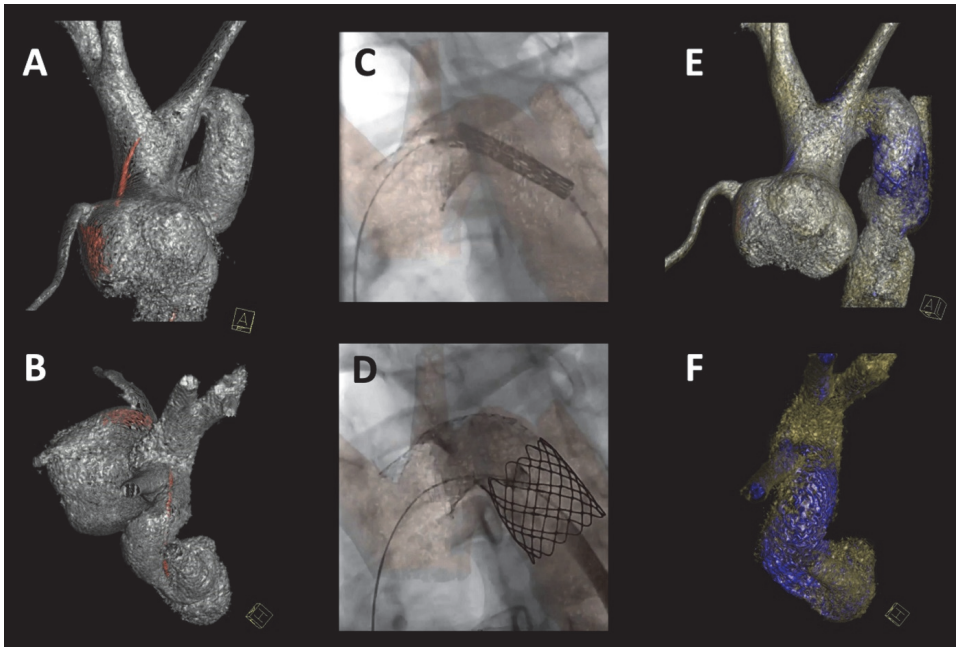


**Figure 2. Stent implantation in gothic aortic arch after arterial switch operation.** A 36-year-old male with a history of dextro-transposition of the great arteries and coarctation of the aorta. He presented with persisting hypertension late after arterial switch operation. Three ev3 Mega LD stents and one non-covered CP stent were implanted. A, B, E, F: Three-dimensional reconstructions made from three-dimensional angiography data. A: Anterior view before stent implantation. B: Cranial view before stent implantation. C and D: Conventional two-dimensional fluoroscopy images showing stent implantation. E: Anterior view after stent implantation. F: Cranial view after stent implantation.

Several mechanisms are thought to increase the risk of systemic hypertension after successful CoA repair. It is hypothesised that these patients have an abnormal baroreceptor function and a decreased aortic compliance. Furthermore, age at initial CoA repair is known to be of great influence on the risk of long-term hypertension.[26] A hypoplastic or gothic aortic arch morphology might also be a substrate for persistent hypertension.[11,12,16,17] The use of three-dimensional rotational angiography changed our understanding of the aortic arch anatomy and helped to accurately diagnose aortic arch hypoplasia and gothic morphology. Biplane angiographic projections as well as lateral and frontal views are not always sufficient; cranial and posterior views are typically essential to detect aortic arch hypoplasia. Such views can only be obtained from pre-procedural CT angiogram or CMR or peri-procedural three-dimensional rotational angiography.

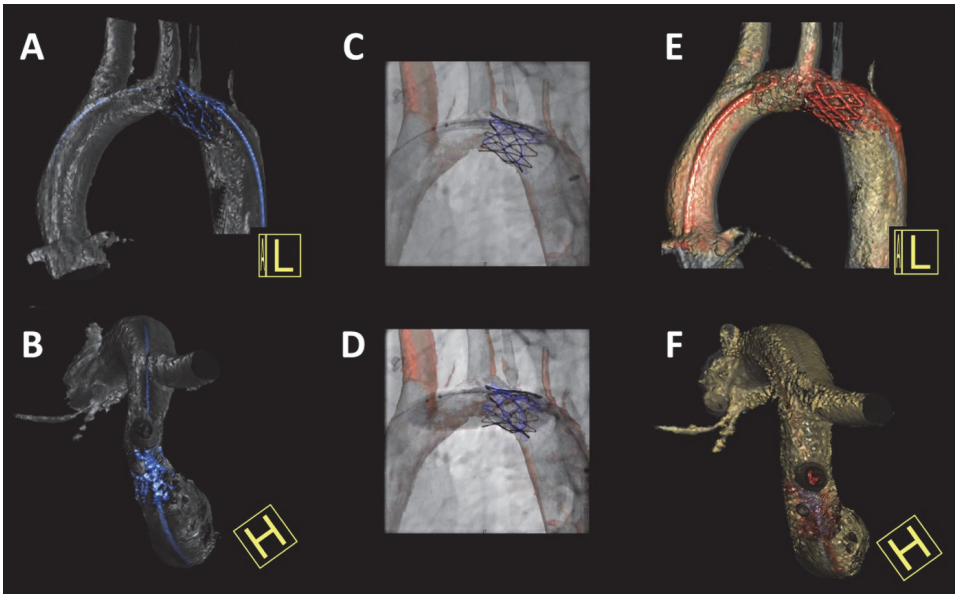


**Figure 3. Stent implantation in hypoplastic aortic arch.** An 18-year-old female with a history of coarctation of the aorta, for which she underwent surgical coarctation repair (end-to-end anastomosis) as an infant. At the age of seven a CP stent was implanted for re-coarctation. Since she remained hypertensive in the presence of a narrow aortic arch, an ev3 Mega LD stent was implanted in the aortic arch. A, B, E, F: Three-dimensional reconstructions made from three-dimensional angiography data. A: Lateral view before stent implantation. B: Cranial view before stent implantation. C and D: Conventional two-dimensional fluoroscopy images showing stent implantation. E: Lateral view after stent implantation. F: Cranial view after stent implantation.

Hypertension after CoA repair is not a benign condition and should be treated, regardless of its aetiology. Strict follow-up using advanced three-dimensional imaging and timely invasive haemodynamic evaluation and, if deemed necessary, intervention/reintervention is important in this patient group. When aortic arch hypoplasia is thought to play an important role in the presence of persistent hypertension, stent implantation should be considered to improve clinical outcome in the long term.

**Limitations**

First, due to the retrospective nature of the study there was no clear protocol for the measurements before and after stent implantation, which resulted in missing data. Second, the population size of this study was quite small. Third, very incomplete data on 24-hour ambulatory blood pressure measurements were available. It is well known that this is a more reliable technique than office blood pressure measurement and gives a more comprehensive assessment of the patient's blood pressure.[27,28] Finally, although blood pressure response to exercise would have been an interesting parameter to examine, only a limited number of

patients underwent exercise testing. Data on blood pressure response to exercise were therefore omitted.

## CONCLUSION

The present analysis shows that stenting of the aortic arch is successful when carried out in a state-of-the-art manner. It may lead to improved clinical outcome for this specific patient subset with abnormal aortic arch anatomy or morphology. Stent placement in our cohort achieved a direct optimal angiographic and haemodynamic result. No major complications occurred during or after the procedure. At short- to medium-term follow-up a significant decrease in systolic blood pressure was observed, combined with a parallel decrease in the use of antihypertensive medication.

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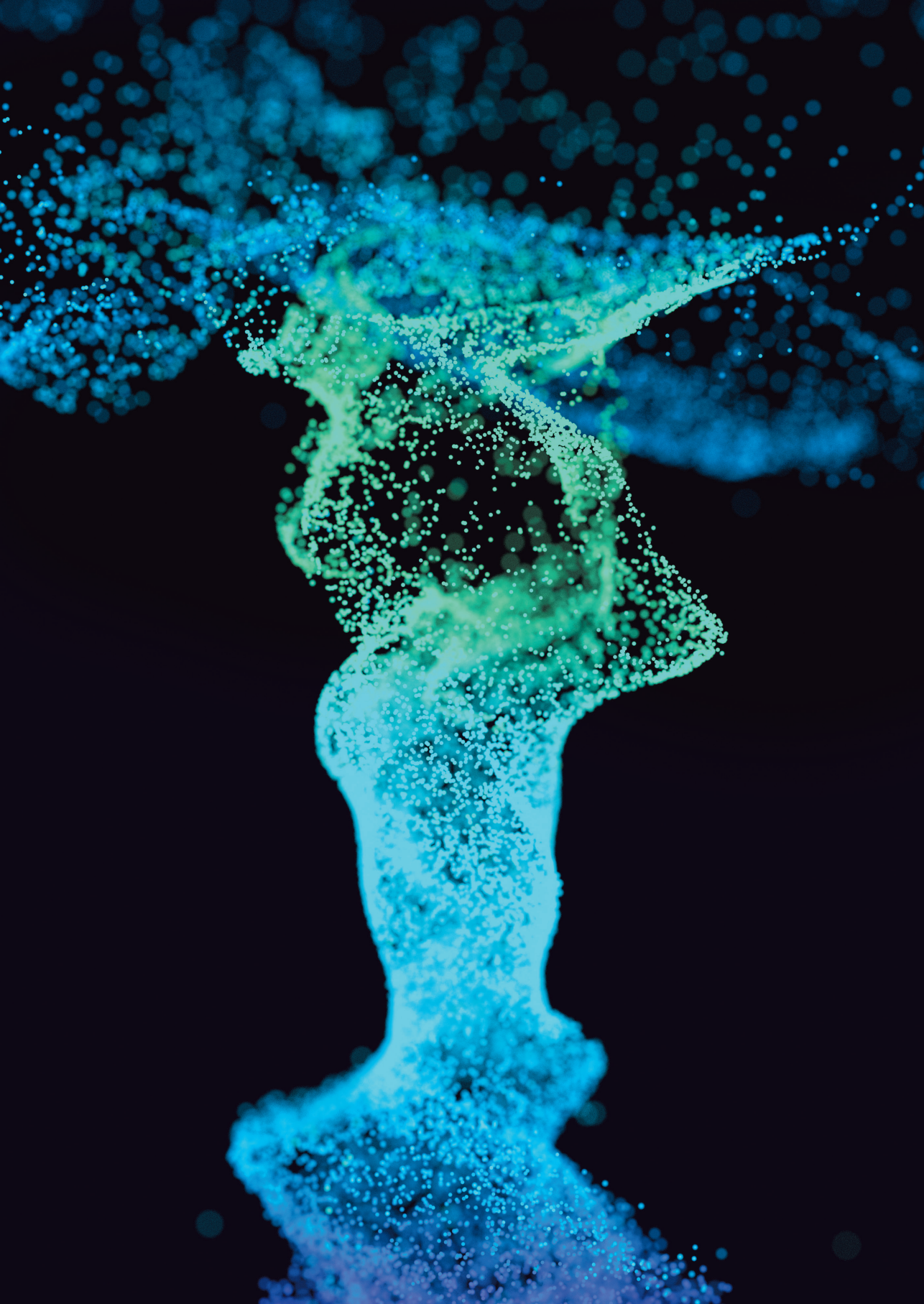

# CHAPTER 6

# Endovascular coil embolization of a complex aortic arch pseudoaneurysm following arch stenting

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Mirella M.C. Molenschot, Michiel Voskuil

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**ABSTRACT**

Pseudoaneurysm formation is a life-threatening complication of thoracic aortic stenting due to the high risk of rupture. When located in the aortic arch, anatomic features may pose difficulties in choosing the optimal treatment strategy. Here, we describe the first post-stenting aortic arch pseudoaneurysm treated by endovascular coil embolization. This approach, which we performed in a multidisciplinary setting, may be a feasible alternative in patients not considered suitable for open repair or stent-grafting. Since an acute pseudoaneurysm may develop and rapidly expand during the first days after aortic stenting, early follow-up imaging is preferable.

## INTRODUCTION

Over the last years, stent implantation has become the treatment of choice in adults with native or recurrent aortic coarctation.[1] In addition, stenting is increasingly used to correct aortic arch obstruction due to hypoplasia or aberrant geometry of the arch.[2] Although rare, stenting of the thoracic aorta may be complicated by acute aortic wall injury, including dissection and pseudoaneurysm formation.[3] In this case, we illustrate that the complex anatomy associated with aortic arch pseudoaneurysms may limit standard treatment options and may therefore require an alternative, multidisciplinary approach.

## CASE REPORT

A 36-year-old male presented with systolic hypertension despite treatment with three antihypertensive agents. He had a history of surgical repair of aortic coarctation by patch angioplasty during infancy. Balloon angioplasty and surgical aortoplasty were performed to treat recurrent coarctation at age 17 and 28, respectively. At age 35, two overlapping ev3 Max LD stents (ev3 Inc., Plymouth, MN, USA) were placed for aortic arch obstruction due to pronounced gothic geometry of the arch. Because of persistent hypertension under medication, re-catheterization was performed. In response to the blood pressure-lowering effect of conscious sedation, 40 μg of epinephrine was administered to reach a systolic blood pressure comparable to daily life. Although no pressure gradient was detected across the coarctation site, a pressure gradient of 25 mmHg was measured across the aortic arch. This gradient matched the most narrow and rigid aspect of the stented gothic arch. Balloon dilatation with a 22 x 20 mm Atlas PTA balloon (Bard Peripheral Vascular Inc., Tempe, AZ, USA) at 26 atm was ineffective, showing recoil of the previously placed ev3 stents and a residual pressure gradient of 15 mmHg. Therefore, a 45 mm non-covered Cheatham-Platinum (CP) stent (NuMED Inc., Hopkinton, NY, USA) on a 24 x 45 mm balloon-in-balloon catheter (NuMED) was implanted for additional radial strength. Although angiography showed an improved anatomical result, the elevated pressure gradient persisted. Consequently, post-dilation with a 24 x 20 mm Atlas PTA balloon at 12 atm was performed, resulting in near elimination of the pressure gradient. Final angiography showed no evidence of iatrogenic aortic wall injury.

At our institution, computed tomography angiography (CTA) is routinely performed the day after aortic stenting. This CTA revealed a 17 x 12 mm pseudoaneurysm located ventroproximally to the additionally placed CP stent. The patient was asymptomatic. Despite the severity of this complication, the acute risk of rupture was considered limited due to the presence of excessive scar tissue as a result of multiple prior surgical procedures. Therefore, initial management was conservative, consisting of serial imaging and strict heart rate and blood pressure regulation with a systolic blood pressure target below 120 mmHg. After 4 days, CTA

showed no spontaneous thrombosis of the aneurysm. Instead, it had expanded to 20 x 14 mm (Figures 1A-C). Therefore, it was decided to perform endovascular coiling of the pseudoaneurysm. Under general anesthesia, a 6 Fr sheath (Glidesheath Slender, Terumo Corp., Tokyo, Japan) was inserted into the right brachial artery. A 6 Fr RDC guiding catheter (Boston Scientific Corp., Marlborough, MA, USA) was then advanced, accommodating a 5 Fr headhunter-shaped TEMPO AQUA catheter (Cordis Corp., Fremont, CA, USA). Subsequently, a 45° PX SLIM microcatheter (Penumbra Inc., Alameda, CA, USA) was introduced, which enabled placement of 16 coils (Ruby Coil, Penumbra Inc.) in the aneurysm sac. This resulted in successful exclusion of the pseudoaneurysm from the circulation (Figures 2A,A' - B,B'). However, follow-up imaging after 1 week showed that coil impaction had caused a residual defect of 8 x 7 mm in the cranial part of the aneurysm, requiring additional coiling. Similarly to the first coiling procedure, the right brachial artery was punctured, a 6 Fr sheath was introduced (Glidesheath Slender, Terumo Corp.), and a 6 Fr RDC guiding catheter (Boston Scientific Corp.) was advanced. After the subsequent introduction of a 45° Headway 17 microcatheter (MicroVention Inc., Aliso Viejo, CA, USA), 8 additional coils (Ruby Coil, Penumbra Inc.) were placed (Figures 2C,C' - D,D'). Follow-up imaging at 6 months showed a good result with complete closure of the pseudoaneurysm (Figure 3). The patient was normotensive, although still on antihypertensive medication.

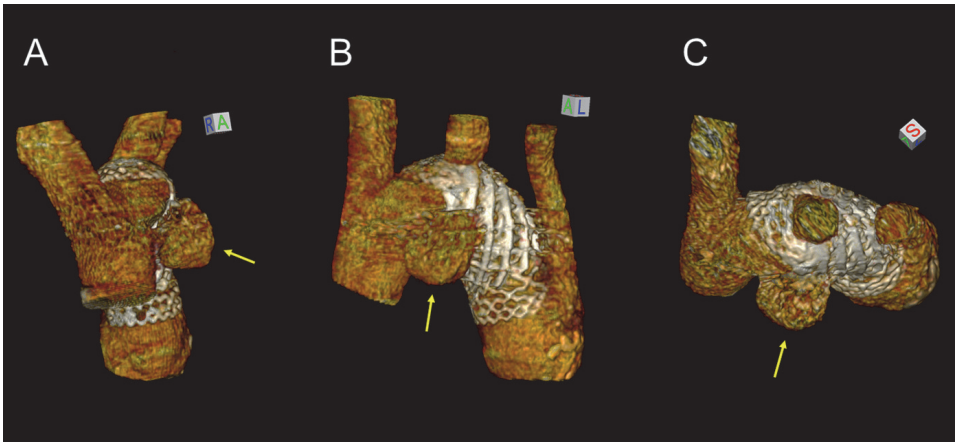


**Figure 1. Three-dimensional reconstruction of the follow-up CTA performed after additional CP stent implantation, displayed in frontal (A), lateral (B), and cranial (C) planes.** Note the 20 x 14 mm pseudoaneurysm located ventroproximally to the CP stent (yellow arrows).

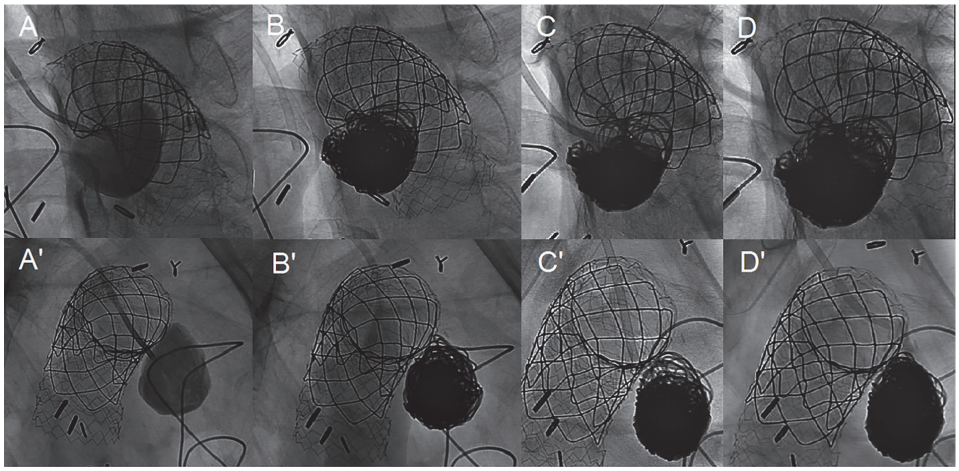


**Figure 2. Angiography showing the pseudoaneurysm before (A,A') and after (B,B') the first coiling procedure.** Due to coil impaction, an 8 x 7 mm cranial defect with residual contrast filling developed within 1 week (C,C'). Consequently, additional coiling was performed, resulting in successful closure of the pseudoaneurysm (D,D').



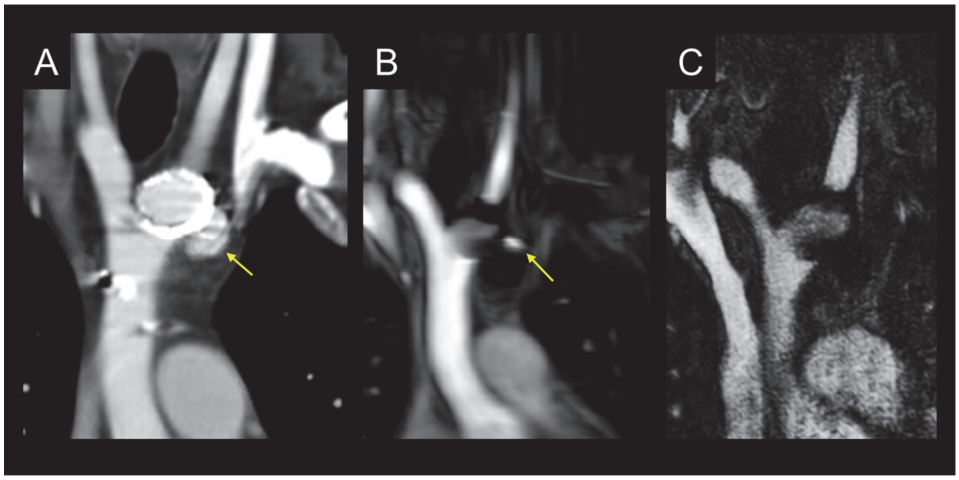


**Figure 3. Serial imaging of the proximal aorta in a coronal plane.** Part A shows the pseudoaneurysm (yellow arrow) prior to coil embolization on CTA. Magnetic resonance angiography (MRA) after the first coiling procedure (B) showed residual contrast filling in the cranial part of the aneurysm sac (yellow arrow). After additional coiling, no residual contrast filling was observed on follow-up MRA (C).

## DISCUSSION

An aortic pseudoaneurysm is defined as a disruption of all layers of the aortic wall with containment of blood by periaortic connective tissue.[4] Although pseudoaneurysms of the thoracic aorta are rare, they may be caused by blunt trauma, surgical or transcatheter interventions, infections (mycotic aneurysms), or penetrating ulcers.[5,6] Development of these aneurysms is potentially fatal due to the high risk of rupture, aortoesophageal fistula formation and compression of surrounding tissues.[6] As a consequence, early detection and treatment are of importance, particularly in a rapidly expanding aneurysm as in our case. Ascending aortic aneurysms are generally treated by open surgical repair, whereas aneurysms of the descending thoracic aorta have been increasingly managed by endovascular stent-grafting due to improved short-term survival and neurological outcomes compared to surgery.[7] However, the optimal treatment of aortic arch aneurysms is less evident. Their anatomy often presents unique challenges to avoid malperfusion of the supra-aortic branches. The choice of intervention should be determined on an individual basis, taking into account the extent and expansion of the aneurysm, location in the arch, comorbidities, and prior aortic interventions. Generally, arch aneurysms may be treated by open surgical repair, stent-grafting, or a hybrid approach.[8] Our patient was considered a poor candidate for open repair or a hybrid procedure, due to the multiple prior cardiothoracic interventions and relatively high complication rates associated with these procedures.[9] Taking into account the proximity of the left carotid artery and the large aortic arch diameter post-stenting, implantation of an additional covered stent-graft was not our preferred option either. Furthermore, the subacute setting did not allow for the fabrication of a customized branched or fenestrated stent-graft. However, we found a limited number of reports describing coil embolization as a feasible alternative treatment of arch aneurysms that developed after surgical repair of type A aortic dissection.[10-12] To our knowledge, we present the first coiling procedure of an aortic arch pseudoaneurysm following stenting. Coil embolization is frequently used by interventional radiologists in the treatment of intracranial aneurysms.[13] Complex intracranial aneurysms may even be treated by stent-assisted coiling, which has shown to reduce recurrence rates compared to standard coiling.[14] The analogy with the current case is striking and emphasizes the added value of a multidisciplinary approach to treat complex aneurysms.

Currently, the timing of follow-up imaging after aortic stenting varies widely across institutions.[15] Although AHA/ACC guidelines state that post-interventional imaging is recommended, no timing interval is provided.[1] As demonstrated by this case, aortic wall injury may not be present or recognized at the end of the stenting procedure, but instead develop during the first days after the procedure. In our opinion, this underlines the importance of routine CTA early after stent implantation, preferably before hospital discharge. Prospective studies are needed to determine the optimal timing of follow-up imaging after aortic stenting.

## CONCLUSION

An aortic arch pseudoaneurysm is a rare and anatomically challenging complication of aortic stenting. In this report, we show that endovascular coil embolization may be a feasible alternative option when the patient is not suitable for open repair or stent-grafting.

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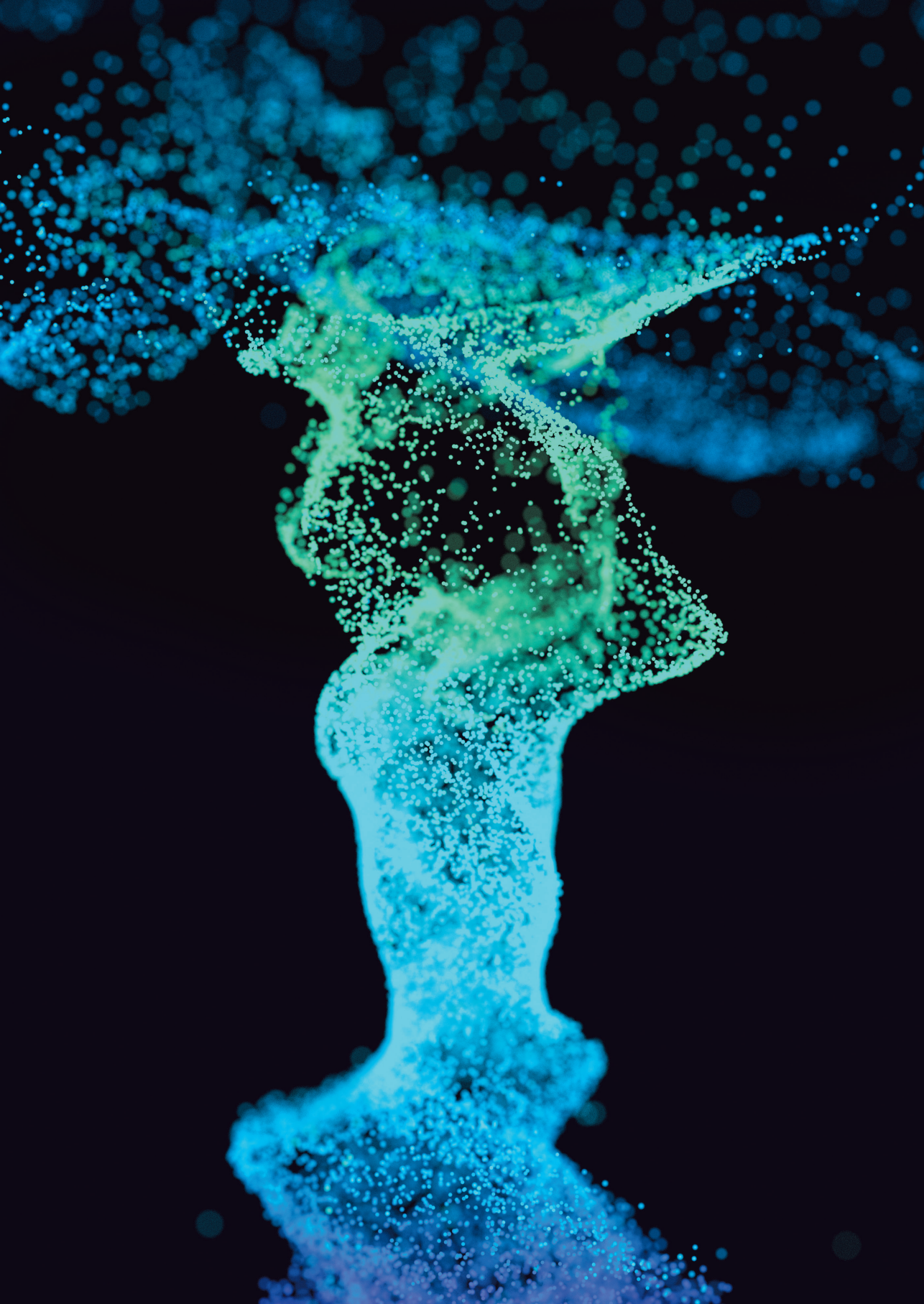
# PART II

# Long-term clinical outcome in aortic coarctation



# CHAPTER 7

# Cardiovascular morbidity and mortality in adult patients with repaired aortic coarctation

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**Journal of the American Heart Association. 2021;10(22):e023199.**

**ABSTRACT**

**Background**

The long-term burden of cardiovascular disease after repair of coarctation of the aorta (CoA) has not been elucidated. We aimed to determine the incidence of and risk factors for cardiovascular events in adult patients with repaired CoA. Additionally, mortality rates were compared between adults with repaired CoA and the general population.

**Methods and Results**

Using the CONgenital CORvitia (CONCOR) registry, patients ≥16 years with previous surgical or transcatheter CoA repair from 5 tertiary referral centers were included. Cardiovascular events were recorded, comprising coronary artery disease, stroke/transient ischemic attack, aortic complications, arrhythmias, heart failure hospitalizations, endocarditis, and cardiovascular death. In total, 920 patients (median age 24 years [range 16-74 years]) were included. After a mean follow-up of 9.3±5.1 years, 191 patients (21%) experienced at least one cardiovascular event. A total of 270 cardiovascular events occurred, of which aortic complications and arrhythmias were most frequent. Older age at initial CoA repair (HR 1.017 [95% CI 1.000-1.033]; $p$=0.048) and elevated left ventricular mass index (LVMI; HR 1.009 [95% CI 1.005-1.013]; $p$<0.001) were independently associated with an increased risk of cardiovascular events. The mortality rate was 3.3 times higher than expected based on an age- and sex-matched cohort from the Dutch general population (standardized mortality ratio: 3.3 [95% CI 2.3-4.4]; $p$<0.001).

**Conclusions**

This large, prospective cohort of adults with repaired CoA showed a high burden of cardiovascular events, particularly aortic complications and arrhythmias, during long-term follow-up. Older age at initial CoA repair and elevated LVMI were independent risk factors for the occurrence of cardiovascular events. Mortality was 3.3-fold higher compared to the general population. These results advocate stringent follow-up after CoA repair and emphasize the need for improved preventive strategies.

## INTRODUCTION

Coarctation of the aorta (CoA) is a common congenital heart defect, accounting for approximately 5-7% of all congenital heart disease.[1] Due to improved detection and management, nowadays the vast majority of patients survive into adulthood. However, the risk of adverse cardiovascular events and consequent premature death remains remarkably high. Over 70% of patients with long-term follow-up dies from cardiovascular complications.[2] Accelerated coronary artery disease was previously identified as the most common cause of death, although arrhythmias, heart failure, and aortic aneurysms are also prevalent.[3-5] Importantly, complications are not limited to the heart and aorta. Ischemic and hemorrhagic stroke occur 15.9 and 28.5 years earlier, respectively, compared to the general population, suggesting that CoA is the expression of an underlying diffuse arteriopathy.[6] However, there is limited information on the exact burden of cardiovascular disease in the adult CoA population. This knowledge gap was recognized by the NHLBI/ACHA Working Group and therefore marked as a high-priority research topic in adult congenital heart disease.[7] Furthermore, it is unclear how to identify CoA patients at the highest risk of cardiovascular complications. In addition to the suggested underlying arteriopathy, hypertension is thought to play an important role, as up to 60% of patients develops hypertension late after initial repair.[8]

To our knowledge, we present the largest prospective cohort of adults with repaired CoA to date. In this study, we aimed to determine the incidence of and risk factors for cardiovascular events in this patient population. In addition, we aimed to compare mortality rates of adults with repaired CoA to those of the general population.



## METHODS

### Study design

The study cohort consisted of adult patients with repaired CoA from 5 tertiary referral centers in the Netherlands, who were included in the CONgenital CORvitia (CONCOR) registry between 2002 and 2018. CONCOR is a prospective, nationwide registry of adults with congenital heart disease. Informed consent was obtained upon enrollment. Patients were included when they had previously undergone surgical or transcatheter repair of CoA. Exclusion criteria were a functionally univentricular circulation and transposition of the great arteries which was not repaired by an arterial switch procedure. Patients were followed until the last clinic visit, death, or the end of the study (April 2020). The study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht. The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Data collection and outcome measures**

Collected baseline data included demographics, medical history, blood pressure (BP) status, medication use, renal function, and echocardiographic parameters. BP was measured on the right arm at the outpatient clinic. When the arm was unspecified or when only the left arm BP was available, it was decided to use these values to minimize missing BP recordings. Hypertension was defined as an office systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or the use of any antihypertensive medication.[9] Cigarette smoking was regarded as current or former smoking. Left ventricular (LV) hypertrophy was assessed at baseline by echocardiography and defined as an LV mass indexed for body surface area >115 g/m2 for males and >95 g/m2 for females.[10]

Cardiovascular events that were considered clinically important in this adult CoA population were recorded. These consisted of coronary artery disease, stroke or transient ischemic attack (TIA), thoracic aortic complications (i.e. aneurysm and dissection), arrhythmias, hospitalizations for heart failure, endocarditis, and cardiovascular death. Cardiovascular events were recorded by two researchers (TAM, SCSM) based on the information provided in the medical correspondence by the treating cardiologist. Coronary artery disease comprised myocardial infarction, coronary revascularization, and medical treatment for stable angina. An aortic aneurysm was defined as a 50% diameter increase compared to the expected diameter based on aortic segment and sex, and/or surgical treatment of the aneurysm.[11] Aortic dissection included dissection, pseudoaneurysm, intramural hematoma, and rupture of the thoracic aorta. Arrhythmias were subdivided into three types of arrhythmia: supraventricular arrhythmias, ventricular arrhythmias, and conduction disturbances. Supraventricular arrhythmias included atrial fibrillation, atrial flutter, and atrioventricular (nodal) reentrant tachycardia. Ventricular arrhythmias comprised ventricular fibrillation/flutter (if survived), sustained and non-sustained ventricular tachycardia. Non-sustained ventricular tachycardia was only recorded as a cardiovascular event when subsequently medical or device treatment was initiated. Conduction disturbances included sick sinus syndrome, sinoatrial block, third-degree atrioventricular block, and Mobitz type II second-degree atrioventricular block. Subsequent episodes of the same type of arrhythmia were not recorded as a new event. Cardiovascular events occurring <30 days after an invasive procedure were considered post-procedural and were therefore excluded. Mortality was recorded regardless of any potential association with an invasive procedure and was categorized as cardiovascular or non-cardiovascular based on the definitions provided by the SCTI/FDA consensus report.[12] In case of uncertainty regarding the exact cause of death, this was discussed with a third researcher (MV) until consensus was reached.

**Statistical analyses**

Baseline characteristics were compared between patients who developed a cardiovascular event and patients who did not. For categorical variables the Fisher's exact test was used and for continuous variables the independent samples t-test or Mann-Whitney U test, where appropriate. The yearly risk of a cardiovascular event and specific types of cardiovascular events were estimated by smoothed estimates based on B-splines. Cox proportional-hazards regression was performed to identify factors associated with the risk of cardiovascular events. Patients were followed until the occurrence of a cardiovascular event. If no cardiovascular event occurred, they were censored at the time of the last clinic visit. Potential risk factors were included by forced entry and selected based on their clinical relevance, effect on pathophysiological mechanisms, and previous reports.[4,13-15] These included sex, age at initial CoA repair, bicuspid aortic valve, ventricular septal defect, prior coronary artery disease, prior stroke/TIA, prior arrhythmia, systolic and diastolic BP, body mass index (BMI), hypercholesterolemia, diabetes mellitus, cigarette smoking, family history of premature cardiovascular disease, and LV mass index at baseline. Of all patients, 7% had incomplete data. As deleting patients with missing information from the analysis may introduce bias in results, we used multiple imputation. Imputation included all potential risk factors in the analysis. Other factors were also incorporated based on clinical relevance, including the presence of a left-sided mechanical heart valve (MHV), antihypertensive agents, renal function, and echocardiographic parameters. Multiple imputation was performed with fully conditional specification, with logistic regression for categorical variables and predictive mean matching for continuous variables. The number of imputed datasets was based on the percentage of patients with missing data.[16] Twenty-eight imputed datasets were created, the analysis was performed in each imputed dataset, and results were subsequently pooled using Rubin's rules. To correct for left-truncated, right-censored data, a delayed entry approach was used with age as the time scale. The proportional-hazards assumption was evaluated for the multivariable model and each separate variable by graphical inspection of fitted penalized B-spline curves and the goodness-of-fit test based on scaled Schoenfeld residuals. The assumption of linearity was assessed for continuous variables using restrictive cubic splines. A sensitivity analysis was performed by adding age at baseline to the multivariable model, as the measurements of certain potential risk factors, e.g. BP and BMI, may be affected by age. Overall survival was compared to Dutch general population data from Statistics Netherlands (CBS, The Hague, Netherlands) by matching for age, sex, year of study entry, and observation time. Accordingly, there was a similar left-truncated data pattern between the study cohort and the reference population. Statistical analyses were performed using IBM SPSS Statistics 25 (Armonk NY, USA), RStudio version 1.2.5001 (packages: survival, relsurv, survminer, survexp.fr, bshazard; Boston MA, USA), and SAS version 9 (Cary NC, USA). A p-value $<0.05$ was considered statistically significant.

## RESULTS

### Patient characteristics

A total of 920 patients were included in the study, of whom 191 patients (21%) developed a cardiovascular event. Baseline characteristics are shown in Table 1. Median age at study entry was 24 years (range 16-74 years). Hypertension was more common in patients with an event compared to patients without an event (75% and 52%, respectively). Sixty patients had a left-sided mechanical heart valve, of whom 49 patients an aortic MHV, 5 patients a mitral MHV, and 6 patients both an aortic and mitral MHV. Mean follow-up duration was 9.3 ± 5.1 years and was longer in the event group (11.3 ± 4.5 vs. 8.7 ± 5.1 years; $p<0.001$).

### Incidence of cardiovascular events

Table 2 provides an overview of the observed cardiovascular events. In 191 patients (21%) at least one cardiovascular event occurred. In total, 270 events occurred, of which arrhythmias and aortic complications were most frequent. A substantially higher incidence of events was observed in patients with important comorbidity, i.e. the presence of a bicuspid aortic valve, mechanical heart valve, and/or Turner syndrome. The estimated yearly risk of developing a cardiovascular event increased from 0.8% (95% CI 0.6-1.1%) at 20 years to 8.2% (95% CI 5.5-12.1%) at 70 years (Figure 1A). Figure 1B presents a yearly risk estimation for various types of cardiovascular events, with detailed information supplied in Supplemental Table 1. Fourteen CoA site aneurysms were observed. In these patients, initial repair consisted of end-to-end anastomosis in 4 patients, patch angioplasty in 3 patients, balloon angioplasty (without subsequent surgical repair) in 2 patients, and an unknown surgical technique in 5 patients.

Among the 60 patients with a left-sided MHV at baseline, 36 patients (60%) experienced at least one cardiovascular event, as shown in Supplemental Table 2. In this group, there were 24 arrhythmias (of which 16 supraventricular arrhythmias), 11 cases of ischemic stroke or TIA, 7 cardiovascular deaths, 6 heart failure hospitalizations, 5 aortic complications, 4 cases of endocarditis, and 2 cases of coronary artery disease. Of the 4 cases of endocarditis in patients with a left-sided MHV, in 2 cases there was echocardiographic evidence of prosthetic valve endocarditis. In the 2 other cases there was a clinical suspicion for prosthetic valve endocarditis, despite the absence of evidence on cardiac imaging.

**Table 1. Baseline characteristics.**

| | All patients n = 920 | CV event n = 191 | No CV event n = 729 | *p*-value* |
|---|---|---|---|---|
| Age (y), median (range) | 24 (16-74) | 31 (17-72) | 23 (16-74) | **<0.001** |
| Female sex, n (%) | 365 (40) | 58 (30) | 307 (42) | **0.004** |
| Age at initial CoA repair (y), median (range) | 4 (0-67) | 6 (0-67) | 3 (0-61) | **<0.001** |
| Type of initial CoA repair, n (%) | | | | **0.02** |
| Surgery | 863 (94) | 173 (91) | 690 (95) | |
| Balloon angioplasty | 19 (2) | 9 (5) | 10 (1) | |
| Stenting | 38 (4) | 9 (5) | 29 (4) | |
| Type of surgical repair, n (%)† | | | | **0.005** |
| End-to-end anastomosis | 474 (55) | 87 (50) | 387 (56) | |
| Patch angioplasty | 88 (10) | 17 (10) | 71 (10) | |
| Subclavian flap angioplasty | 89 (10) | 9 (5) | 80 (12) | |
| Graft interposition | 33 (4) | 11 (6) | 22 (3) | |
| Ascending-to-descending bypass graft | 7 (1) | 2 (1) | 5 (1) | |
| Unknown | 172 (20) | 47 (27) | 125 (18) | |
| Intervention for re-CoA, n (%) | 178 (19) | 29 (15) | 149 (20) | 0.12 |
| Associated congenital defects, n (%) | | | | |
| Bicuspid aortic valve | 519 (56) | 130 (68) | 389 (53) | **<0.001** |
| Patent ductus arteriosus | 141 (15) | 25 (13) | 116 (16) | 0.37 |
| Ventricular septal defect | 208 (23) | 35 (18) | 173 (24) | 0.12 |
| Atrial septal defect | 53 (6) | 10 (5) | 43 (6) | 0.86 |
| Patent foramen ovale | 22 (2) | 3 (2) | 19 (3) | 0.60 |
| Turner syndrome | 24 (3) | 4 (2) | 20 (3) | 0.80 |
| Left-sided MHV, n (%) | 60 (7) | 36 (19) | 24 (3) | **<0.001** |
| Prior CV events, n (%) | | | | |
| Prior CAD | 10 (1) | 5 (3) | 5 (1) | **0.04** |
| Prior stroke/TIA | 20 (2) | 10 (5) | 10 (1) | **0.003** |
| Prior arrhythmia | 49 (5) | 18 (9) | 31 (4) | **0.01** |
| Systolic BP (mmHg), mean ± SD | 135 ± 19 | 140 ± 20 | 133 ± 18 | **<0.001** |
| Diastolic BP (mmHg), mean ± SD | 76 ± 11 | 79 ± 11 | 75 ± 11 | **<0.001** |
| Hypertension, n (%) | 522 (57) | 143 (75) | 379 (52) | **<0.001** |
| Use of any antihypertensive medication, n (%) | 299 (33) | 91 (48) | 208 (29) | **<0.001** |
| Other CV risk factors | | | | |
| BMI (kg/m$^2$), mean ± SD | 24.0 ± 4.5 | 25.6 ± 5.4 | 23.6 ± 4.1 | **<0.001** |
| Hypercholesterolemia, n (%) | 85 (9) | 38 (20) | 47 (6) | **<0.001** |
| Diabetes mellitus, n (%) | 21 (2) | 7 (4) | 14 (2) | 0.17 |
| Cigarette smoking, n (%) | 169 (18) | 49 (26) | 120 (17) | **0.005** |
| Family history of premature CVD, n (%) | 55 (6) | 16 (8) | 39 (5) | 0.12 |
| eGFR <60 mL/min/1.73 m$^2$, n (%) | 29 (3) | 10 (5) | 19 (3) | 0.10 |
| LVEF <40%, n (%) | 7 (1) | 4 (2) | 3 (0.4) | **0.04** |
| LV mass index (g/m$^2$), mean ± SD | 94 ± 31 | 111 ± 36 | 90 ± 28 | **<0.001** |
| LV hypertrophy, n (%) | 249 (27) | 89 (47) | 160 (22) | **<0.001** |
| Follow-up duration (y), mean ± SD | 9.3 ± 5.1 | 11.3 ± 4.5 | 8.7 ± 5.1 | **<0.001** |

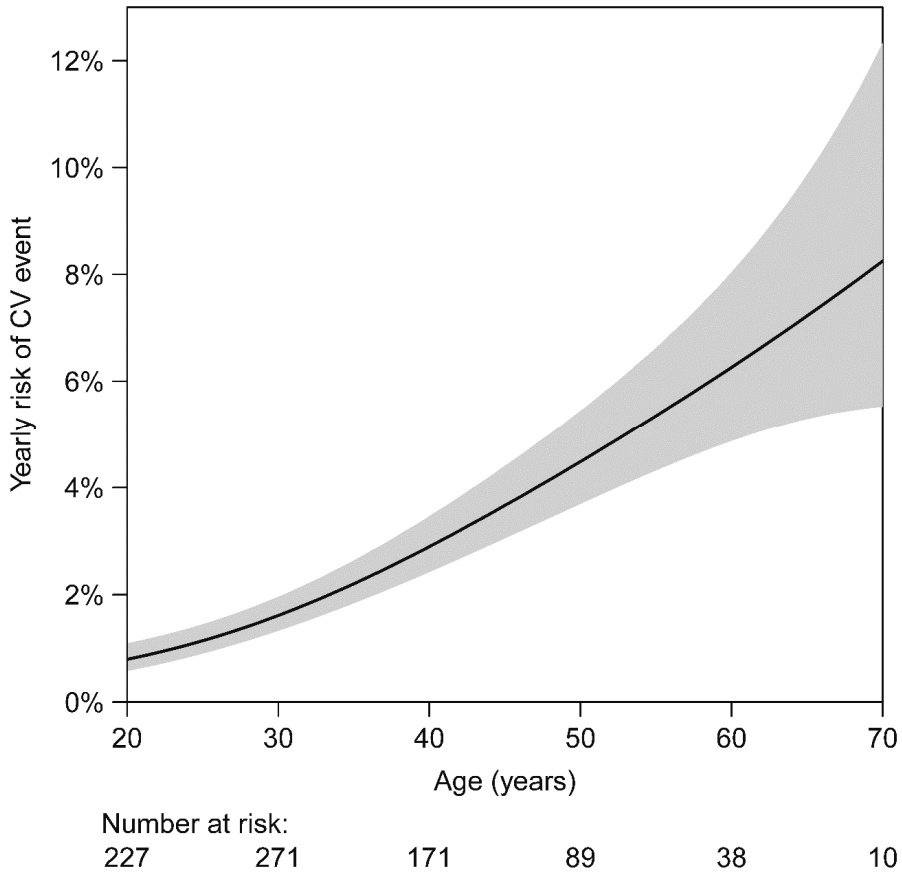
* Indicates the difference between patients who developed a cardiovascular event versus patients who did not, as determined by the independent-samples t-test, Mann-Whitney U test, or Fisher's exact test, where appropriate.
† Among patients with surgery as initial CoA repair (n = 863).
BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; TIA, transient ischemic attack; y, years.

**Table 2. Overview of cardiovascular events.**

| | All patients (n = 920) | | Low-risk CoA* (n = 376) | | High-risk CoA† (n = 544) | |
|---|---|---|---|---|---|---|
| | No. of cases | Incidence / 1,000 patient-years | No. of cases | Incidence / 1,000 patient-years | No. of cases | Incidence / 1,000 patient-years |
| **Coronary artery disease** | **14** | **1.6** | **4** | **1.3** | **10** | **1.9** |
| Myocardial infarction | 6 | 0.7 | 1 | 0.3 | 5 | 0.9 |
| Coronary revascularization | 6 | 0.7 | 2 | 0.6 | 4 | 0.7 |
| Stable angina, medically treated | 2 | 0.2 | 1 | 0.3 | 1 | 0.2 |
| **Stroke/TIA** | **34** | **4.0** | **9** | **2.8** | **25** | **4.7** |
| Ischemic stroke | 18 | 2.1 | 5 | 1.6 | 13 | 2.4 |
| Hemorrhagic stroke, intracerebral | 1 | 0.1 | 1 | 0.3 | 0 | 0 |
| Hemorrhagic stroke, subarachnoidal | 1 | 0.1 | 0 | 0 | 1 | 0.2 |
| TIA | 14 | 1.6 | 3 | 0.9 | 11 | 2.1 |
| **Aortic complication** | **84** | **9.9** | **16** | **5.1** | **68** | **12.7** |
| Aneurysm | 77 | 9.0 | 15 | 4.7 | 62 | 11.6 |
| Dissection | 7 | 0.8 | 1 | 0.3 | 6 | 1.1 |
| **Arrhythmia** | **84** | **9.9** | **22** | **6.9** | **62** | **11.6** |
| Supraventricular arrhythmia | 58 | 6.8 | 15 | 4.7 | 43 | 8.0 |
| Ventricular arrhythmia | 18 | 2.1 | 4 | 1.3 | 14 | 2.6 |
| Conduction disturbance | 8 | 0.9 | 3 | 0.9 | 5 | 0.9 |
| **Heart failure hospitalization** | **15** | **1.8** | **6** | **1.9** | **9** | **1.7** |
| **Endocarditis** | **15** | **1.8** | **2** | **0.6** | **13** | **2.4** |
| **CV death** | **24** | **2.8** | **8** | **2.5** | **16** | **3.0** |
| **Total CV events** | **270** | **31.7** | **67** | **21.1** | **203** | **38.0** |
| **No. of individual patients with CV event** | **191** | **NA** | **48** | **NA** | **143** | **NA** |

* Includes patients with isolated CoA or patients with any of the following associated lesions: closed or small ventricular septal defect, atrial septal defect, patent foramen ovale, patent ductus arteriosus.
† Includes patients with a bicuspid aortic valve, left-sided mechanical heart valve, and/or Turner syndrome.
CV, cardiovascular; NA, not applicable; TIA, transient ischemic attack.

**A**


12%
10%
8%
6%
4%
2%
0%
Yearly risk of CV event
20
30
40
50
60
70
Age (years)
Number at risk:
227
271
171
89
38
10

**B**

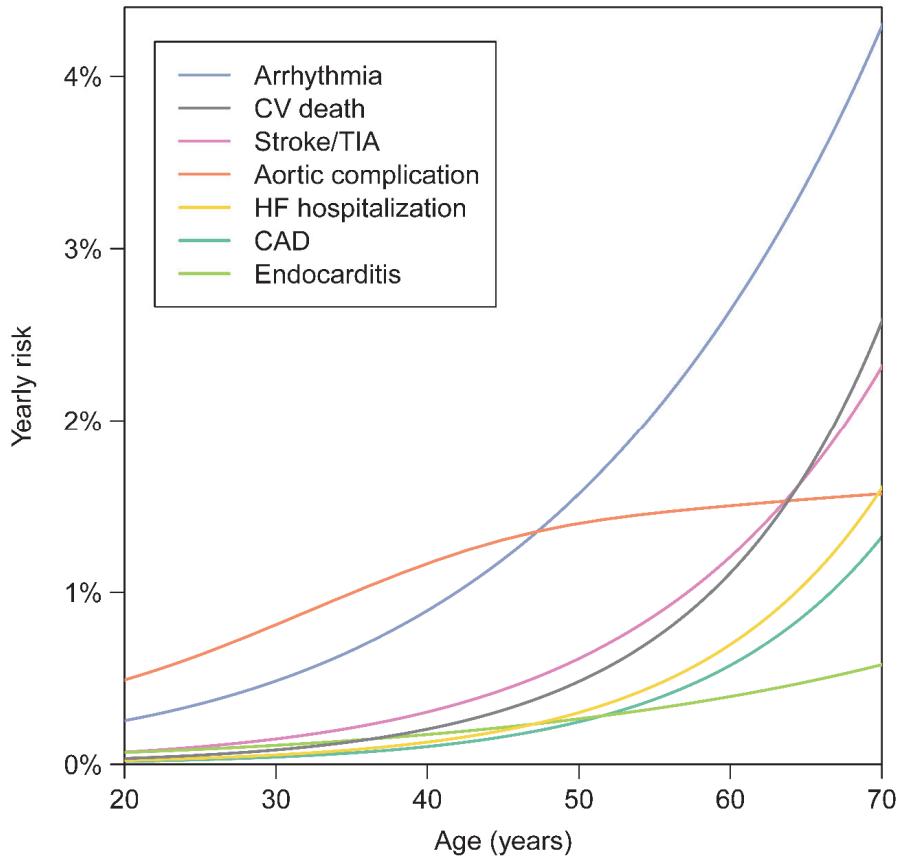



**Figure 1. Estimated yearly risk of a cardiovascular event (A) and specific types of cardiovascular events (B) by age.** Hazard functions and corresponding 95% CIs are smoothed estimates based on B-splines. Detailed information regarding the hazard of specific event types is provided in Supplemental Table 1. CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; TIA, transient ischemic attack.

**Factors associated with the risk of cardiovascular events**

The results of Cox proportional-hazards regression are presented in Table 3. In univariable analysis, factors associated with an increased risk of cardiovascular events were older age at initial CoA repair (HR 1.018 [95% CI 1.003-1.033]; *p*=0.02), bicuspid aortic valve (HR 1.45 [1.07-1.96]; *p*=0.02), increased BMI (HR 1.04 [1.01-1.07]; *p*=0.004), and elevated LV mass index (HR 1.010 [1.007-1.014]; *p*<0.001), whereas female sex (HR 0.59 [95% CI 0.44-0.81]; *p*=0.001) was associated with a decreased risk. In multivariable analysis, older age at initial CoA repair (HR 1.017 [95% CI 1.000-1.033]; *p*=0.048) and elevated LV mass index (HR 1.009 [95% CI 1.005-1.013]; *p*<0.001) were identified as independent risk factors for the occurrence of cardiovascular events. The use of restrictive cubic splines for continuous variables did not result in improvement of the model fit. Similar associations were observed when patients with a left-sided MHV were excluded from the analysis. The unadjusted difference in cardiovascular event incidence between patients with and without LV hypertrophy at baseline is graphically shown in Figure 2. The risk of cardiovascular events appeared to increase when initial repair was performed beyond 10 years of age, although not statistically significant (*p*=0.08; Supplemental Figure 1).

**Table 3. Results of Cox proportional-hazards regression to identify factors associated with the risk of cardiovascular events.**

| | **Cardiovascular event** | | | |
|---|---|---|---|---|
| | **Univariable** | | **Multivariable** | |
| | **HR (95% CI)** | ***p*-value** | **HR (95% CI)** | ***p*-value** |
| Female sex | 0.59 (0.44-0.81) | **0.001** | 0.82 (0.59-1.15) | 0.25 |
| Age at initial CoA repair (y) | 1.018 (1.003-1.033) | **0.02** | 1.017 (1.000-1.033) | **0.048** |
| Bicuspid aortic valve | 1.45 (1.07-1.96) | **0.02** | 1.34 (0.98-1.83) | 0.07 |
| Ventricular septal defect | 0.98 (0.67-1.42) | 0.92 | 1.04 (0.71-1.54) | 0.83 |
| Prior CAD | 1.98 (0.76-5.14) | 0.16 | 2.18 (0.82-5.81) | 0.12 |
| Prior stroke/TIA | 1.74 (0.88-3.41) | 0.11 | 1.74 (0.86-3.53) | 0.12 |
| Prior arrhythmia | 1.55 (0.94-2.54) | 0.09 | 1.46 (0.87-2.45) | 0.15 |
| Systolic BP (mmHg) | 1.006 (0.999-1.014) | 0.11 | 1.004 (0.995-1.013) | 0.37 |
| Diastolic BP (mmHg) | 1.012 (0.998-1.026) | 0.09 | 1.010 (0.994-1.026) | 0.21 |
| BMI (kg/m$^2$) | 1.04 (1.01-1.07) | **0.004** | 1.03 (1.00-1.06) | 0.08 |
| Hypercholesterolemia | 1.36 (0.93-2.00) | 0.11 | 1.41 (0.94-2.11) | 0.10 |
| Diabetes mellitus | 0.67 (0.30-1.51) | 0.33 | 0.51 (0.21-1.24) | 0.14 |
| Cigarette smoking | 1.30 (0.94-1.81) | 0.11 | 1.14 (0.81-1.61) | 0.46 |
| Family history of premature CVD | 1.37 (0.82-2.29) | 0.23 | 1.21 (0.70-2.11) | 0.49 |
| LV mass index (g/m$^2$) | 1.010 (1.007-1.014) | **<0.001** | 1.009 (1.005-1.013) | **<0.001** |

A total of 920 patients were included in the analysis, of whom 191 patients developed a cardiovascular event.
BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LV, left ventricular; TIA, transient ischemic attack; y, years.

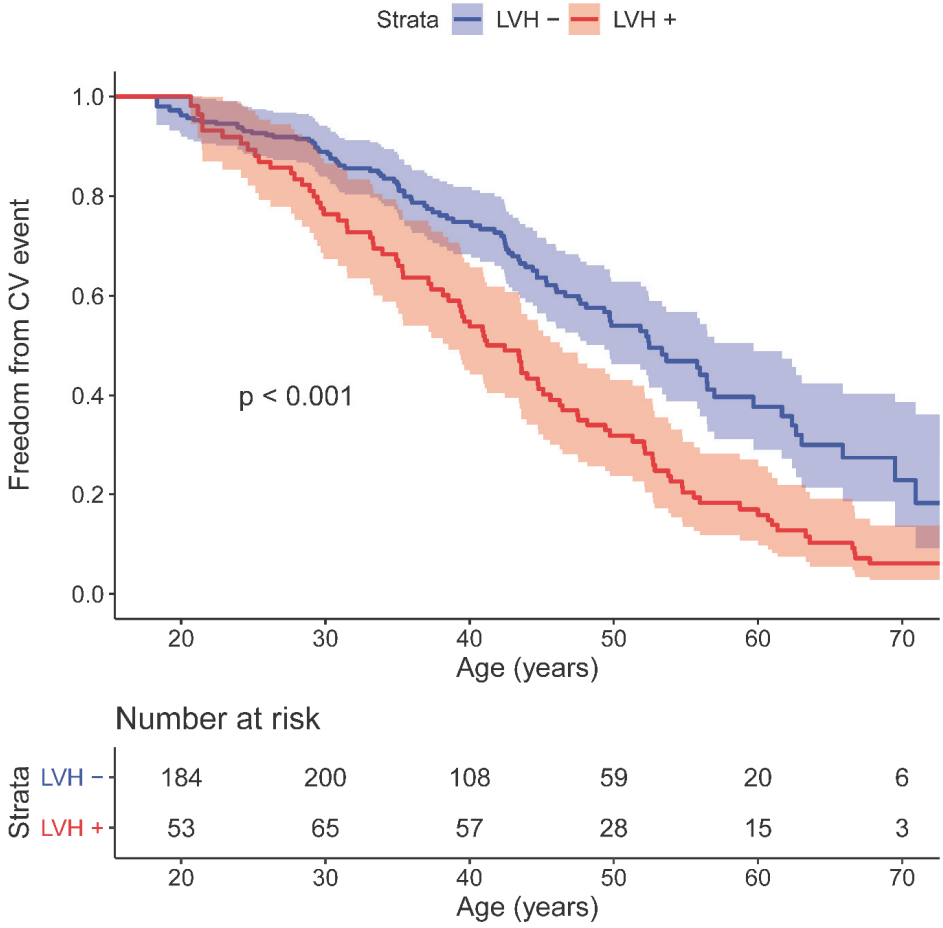



**Figure 2. Freedom from a cardiovascular event by the presence or absence of left ventricular hypertrophy at baseline.** Kaplan-Meier graph showing the freedom from a cardiovascular event in patients with and without left ventricular hypertrophy at baseline (LVH + and LVH -, respectively) with corresponding 95% CIs. CV, cardiovascular; LVH, left ventricular hypertrophy.

Sensitivity analyses showed that the addition of age at baseline did not result in substantial changes to the multivariable model (Supplemental Table 3). In this model, age at initial CoA repair (HR 1.021 [95% CI 1.004-1.039]; $p$=0.01) and LV mass index (HR 1.009 [95% CI 1.005-1.013]; $p$<0.001) remained the only factors associated with the occurrence of cardiovascular events.

**Risk of mortality**

A total of 42 patients died during the study period, of which 24 patients (57%) from a cardiovascular cause (Supplemental Table 4). As illustrated by Figure 3, all-cause mortality was 3.3 times higher than expected based on a cohort from the Dutch general population matched for age, sex, year of study entry, and observation time (standardized mortality ratio (SMR): 3.3 [95% CI 2.3-4.4]; $p<0.001$). When the analysis was limited to patients with isolated CoA (n = 215), i.e. patients without other congenital defects or left-sided MHV, the mortality difference persisted (SMR: 4.5 [95% CI 2.5-7.3]; $p<0.001$).

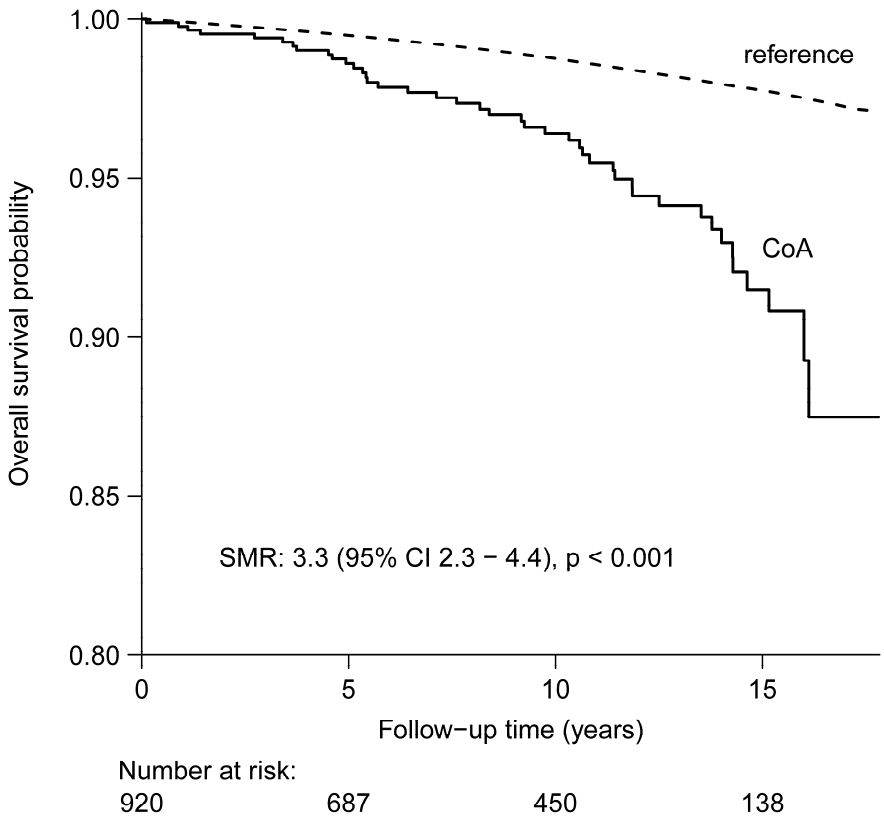



**Figure 3. Overall survival compared to a cohort from the Dutch general population (reference).** The reference cohort was matched for age, sex, year of study entry, and observation time. The standardized mortality ratio (SMR) is provided, which represents the ratio between the observed number of deaths in the CoA population and the expected number of deaths based on the reference population.

## DISCUSSION

Repaired CoA is often regarded as a relatively benign condition. However, the cardiovascular burden of CoA patients in adulthood has not been well characterized, as most previous studies were small or focused on particular complications. To our knowledge, we present the long-term clinical outcome of the largest prospective cohort of this patient population to date. In our cohort, consisting of patients with a median age of 24 years who were followed for a mean of 9.3 years, the most important findings were that (1) 21% of patients developed at least one cardiovascular event with particularly high incidences of aortic complications and arrhythmias, (2) older age at initial CoA repair and elevated LV mass index were independently associated with an increased risk of cardiovascular events, and (3) all-cause mortality was 3.3 times higher compared to an age- and sex-matched cohort from the Dutch general population.

Although surgical and transcatheter techniques have improved drastically over the last decades, the observed all-cause mortality in our cohort was more than 3-fold higher than the population-based expected mortality. This is in accordance with other recent findings.[15] The majority of these deaths were of cardiovascular origin. However, increased mortality is not the only concern in this patient cohort, as cardiovascular morbidity is also frequent. The incidence of cardiovascular events rapidly increased with age, up to a yearly incidence of 8% in patients 70 years of age. This is consistent with previous results in adults with congenital heart disease, who show a substantially higher burden of morbidity beyond the sixth decade.[17] Aortic aneurysm formation was one of the most common cardiovascular complications in our study. Although aneurysms may occur at the CoA repair site, the vast majority was located in the ascending aorta, which can be largely attributed to the high prevalence of an associated bicuspid aortic valve. However, it is likely that CoA contributes to ascending aortic dilatation, as the prevalence of ascending aortic complications was previously reported to be significantly higher in patients with both a bicuspid aortic valve and CoA compared to patients with an isolated bicuspid aortic valve.[18] In addition, arrhythmias were frequently observed in this CoA cohort, particularly supraventricular arrhythmias. The impact of arrhythmias on morbidity and mortality in CoA should not be underestimated. The incidence of atrial fibrillation in the general population <50 years of age is less than 0.5 per 1,000 person-years, whereas in our CoA cohort the incidence of supraventricular arrhythmias was more than 10-fold higher (6.8 per 1,000 patient-years).[19] The frequent presence of hypertension in CoA patients may contribute to this high incidence, as a history of hypertension is strongly associated with the development of atrial fibrillation.[19] Furthermore, in CoA patients already known with supraventricular arrhythmias, hypertension may have a substantial impact on the risk of stroke and, consequently, the need for prolonged anticoagulant therapy. A previous large study showed that supraventricular arrhythmias were associated with increased all-cause and cardiovascular mortality in adults

with congenital heart disease, which emphasizes the prognostic consequences of this type of arrhythmia.[20]

Prior studies have identified coronary artery disease as the most common cause of late death in CoA patients.[4,21] However, the incidence of coronary artery disease in our cohort was significantly lower in comparison to cerebrovascular events. In particular ischemic cerebrovascular events were frequent. Interestingly, we observed only two cases of hemorrhagic stroke, even though intracranial aneurysms have been reported in approximately 10% of adults with CoA.[22] The low incidence of hemorrhagic stroke in our study suggests that intracranial aneurysms may either be less prevalent than previously thought or may carry a low risk of rupture, at least in this relatively young CoA population. Hence, our results do not support routine screening for intracranial aneurysms in CoA patients, which has been subject of debate for decades.[3] We hypothesize that the high incidence of ischemic stroke is likely related to hypertension in post-repair CoA patients, even though hypertension is a stronger predictor for hemorrhagic stroke than for ischemic stroke.[23] In the general population, the incidence of ischemic stroke is 6-7 fold higher compared to hemorrhagic stroke, which is quite similar to our findings.[24] In patients with native CoA, who often have more severe hypertension, the distribution of stroke subtypes may be different.

Considering the increased risk of acquired cardiovascular disease in adults with CoA, it is important to identify patients who are at the highest risk. Our analyses show that LV mass index is strongly associated with the occurrence of cardiovascular events, which is consistent with the known prognostic importance of LV mass index in the general population.[25] Interestingly, this association was observed irrespectively of BP. This is in line with recent findings indicating that LV mass index is elevated in CoA patients compared to controls despite similar systolic BP.[26] Perhaps, BP should not be the only measure to guide the antihypertensive regimen in these patients. Other arterial load indices, including backward compression waves and total arterial compliance, have shown to better correlate with LV mass index than systolic BP.[26,27] The BP response to exercise may also play a role in assessing the need for antihypertensive therapy.[28] However, the therapeutic and prognostic implications of a hypertensive response to exercise, particularly in patients with a normal resting BP, are not yet fully elucidated.[29] Naturally, re-coarctation should be ruled out as a cause of LV overload. Re-coarctation can be effectively treated by stent implantation, which has shown to result in substantial hemodynamic improvement during medium-term follow-up.[30] Remarkably, both systolic and diastolic BP did not correlate with the risk of cardiovascular events. This may due to the fact that office BP measurements were used, while 24-hour ambulatory BP monitoring correlates more accurately with LV afterload and remodeling indices in CoA patients and is superior in predicting cardiovascular events in the general population.[31,32] Although the importance of ambulatory BP monitoring has become widely recognized over the last years, this method was not yet routinely performed at the initiation of this study.

Older age at initial CoA repair was identified as another risk factor for the occurrence of cardiovascular events in our study. It has been previously reported that late CoA repair contributes to the development of vascular dysfunction and hypertension.[4,33,34] In contrast, another study showed no association between the time of repair and arterial wall stiffness.[35] Despite these conflicting results, several studies have highlighted the prognostic impact of age at initial repair on mortality.[4,14,21] Particularly, mortality due to coronary artery disease is frequent among patients with late CoA repair.[21] Although intervening at a young age may increase the need for subsequent re-interventions, our findings underline the importance of early repair to prevent late cardiovascular sequelae. Our data suggest a particular increase in cardiovascular risk when repair is performed beyond the age of 10 years. To ensure timely detection of CoA, careful attention should be paid to hypertension in childhood, which is still frequently undiagnosed.[36]

Besides, our results indicate that patients with CoA and a concomitant aortic and/or mitral MHV represent a group highly susceptible of cardiovascular complications, as 60% of these patients experienced at least one cardiovascular event and the events in this group accounted for 19% of all events observed in the study. In particular thromboembolic events (ischemic stroke, TIA), endocarditis, and supraventricular arrhythmias, which are complications known to be associated with left-sided MHVs, were considerably more frequent in these patients compared to patients without a left-sided MHV.[37] Interestingly, the incidence of stroke/TIA (1.8% per patient-year) and endocarditis (0.7% per patient-year) in MHV patients were comparable to those reported in the literature.[37,38] These findings suggest that the risk of complications in CoA patients with a left-sided MHV is largely determined by the MHV, whereas the additional risk associated with the repaired CoA appears to be limited.

The results of this study provide clinicians insight into the risk of (specific) cardiovascular events in the adult CoA population and how clinical characteristics of an individual patient may affect this risk. The high incidence of acquired cardiovascular disease necessitates regular follow-up after CoA repair, preferably in a specialized center for adults with congenital heart disease. Furthermore, a better understanding of the mechanisms responsible for the increased susceptibility of cardiovascular complications is needed. This may lay the foundation for improved preventive strategies.

**Limitations**

The incidence of cardiovascular events in our study may be underestimated, as patients may have presented with a cardiovascular event in a different (non-participating) medical center, which was therefore unknown to the investigators. Additionally, traditional risk factors for cardiovascular disease were extracted from the medical correspondence, which were infrequently reported in some cases. This study may also be limited by the fact that the primary endpoint was a composite of various types of cardiovascular events with differences in

pathophysiology. However, it was not considered feasible to perform analyses on specific types of cardiovascular events due to limited power and potential overfitting.

## CONCLUSIONS

A substantial burden of cardiovascular disease was observed in this large, prospective cohort of adults with prior CoA repair, which illustrates that repaired CoA is not a condition as benign as previously assumed. Aortic complications and arrhythmias were the most common cardiovascular events. Independent risk factors for the occurrence of cardiovascular events were older age at initial CoA repair and elevated LV mass index. A 3.3-fold increase in all-cause mortality was observed compared to an age- and sex-matched cohort from the general population. These results advocate stringent follow-up after repair of CoA, preferably in a specialized center for adult congenital heart disease, and underline the importance of improving preventive strategies in this high-risk patient population.

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## SUPPLEMENTAL MATERIAL

**Supplemental Table 1. Estimated yearly risk of specific types of cardiovascular events at various ages (supplemental to Figure 1B).**

| Age (y) | Arrhythmia | | CV death | | Stroke/TIA | | Aortic complication | | HF hospitalization | | CAD | | Endocarditis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. at risk | Yearly risk, % (95% CI) | No. at risk | Yearly risk, % (95% CI) | No. at risk | Yearly risk, % (95% CI) | No. at risk | Yearly risk, % (95% CI) | No. at risk | Yearly risk, % (95% CI) | No. at risk | Yearly risk, % (95% CI) | No. at risk | Yearly risk, % (95% CI) |
| **20** | 242 | 0.25 (0.16-0.40) | 243 | 0.03 (0.01-0.09) | 243 | 0.07 (0.03-0.15) | 228 | 0.49 (0.32-0.74) | 243 | 0.02 (0.01-0.07) | 243 | 0.02 (0.01-0.06) | 243 | 0.07 (0.03-0.17) |
| **30** | 287 | 0.48 (0.36-0.66) | 297 | 0.08 (0.04-0.17) | 295 | 0.15 (0.09-0.25) | 284 | 0.81 (0.62-1.06) | 296 | 0.05 (0.02-0.13) | 297 | 0.04 (0.02-0.11) | 295 | 0.11 (0.06-0.21) |
| **40** | 184 | 0.89 (0.69-1.15) | 197 | 0.20 (0.12-0.34) | 195 | 0.30 (0.20-0.46) | 187 | 1.17 (0.90-1.52) | 197 | 0.13 (0.07-0.24) | 197 | 0.10 (0.05-0.21) | 193 | 0.17 (0.10-0.29) |
| **50** | 104 | 1.57 (1.20-2.05) | 110 | 0.48 (0.32-0.75) | 107 | 0.61 (0.41-0.91) | 103 | 1.40 (1.02-1.91) | 111 | 0.30 (0.18-0.51) | 108 | 0.25 (0.14-0.44) | 109 | 0.26 (0.15-0.48) |
| **60** | 41 | 2.60 (1.87-3.62) | 46 | 1.11 (0.70-1.76) | 45 | 1.21 (0.75-1.94) | 44 | 1.50 (0.97-2.33) | 46 | 0.70 (0.39-1.24) | 44 | 0.58 (0.30-1.09) | 46 | 0.39 (0.18-0.88) |
| **70** | 14 | 4.22 (2.64-6.76) | 17 | 2.51 (1.37-4.58) | 13 | 2.27 (1.18-4.34) | 16 | 1.57 (0.79-3.13) | 17 | 1.56 (0.73- 3.36) | 16 | 1.29 (0.55-3.01) | 17 | 0.57 (0.19-1.70) |

CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; TIA, transient ischemic attack; y, years.

**Supplemental Table 2. Overview of cardiovascular events in CoA patients with and without a left-sided MHV.**

| | Left-sided MHV (n = 60) | | No left-sided MHV (n = 860) | |
|---|---|---|---|---|
| | No. of cases | Incidence / 1,000 patient-years | No. of cases | Incidence / 1,000 patient-years |
| **Coronary artery disease** | **2** | **3.4** | **12** | **1.5** |
| Myocardial infarction | 1 | 1.7 | 5 | 0.6 |
| Coronary revascularization | 1 | 1.7 | 5 | 0.6 |
| Stable angina, medically treated | 0 | 0 | 2 | 0.3 |
| **Stroke/TIA** | **11** | **18.4** | **23** | **2.9** |
| Ischemic stroke | 4 | 6.7 | 14 | 1.8 |
| Hemorrhagic stroke, intracerebral | 0 | 0 | 1 | 0.1 |
| Hemorrhagic stroke, subarachnoidal | 0 | 0 | 1 | 0.1 |
| TIA | 7 | 11.7 | 7 | 0.9 |
| **Aortic complication** | **5** | **8.4** | **79** | **10.0** |
| Aneurysm | 4 | 6.7 | 73 | 9.2 |
| Dissection | 1 | 1.7 | 6 | 0.8 |
| **Arrhythmia** | **24** | **40.2** | **60** | **7.6** |
| Supraventricular arrhythmia | 16 | 26.8 | 42 | 5.3 |
| Ventricular arrhythmia | 7 | 11.7 | 11 | 1.4 |
| Conduction disturbance | 1 | 1.7 | 7 | 0.9 |
| **Heart failure hospitalization** | **6** | **10.1** | **9** | **1.1** |
| **Endocarditis** | **4** | **6.7** | **11** | **1.4** |
| **CV death** | **7** | **11.7** | **17** | **2.1** |
| **Total CV events** | **59** | **98.9** | **211** | **26.6** |
| **No. of individual patients with CV event** | **36** | **NA** | **155** | **NA** |

CV, cardiovascular; MHV, mechanical heart valve; NA, not applicable; TIA, transient ischemic attack.

**Supplemental Table 3. Addition of age at baseline to the multivariable Cox proportional-hazards regression to identify factors associated with the risk of cardiovascular events.**

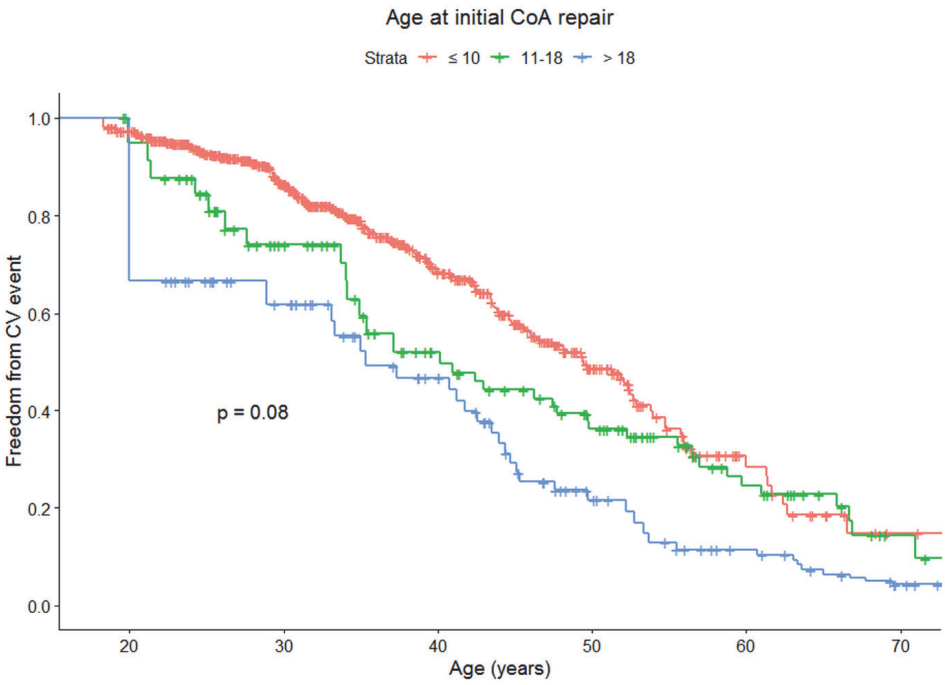
| | Cardiovascular event | |
|---|---|---|
| | **HR (95% CI)** | ***p*-value** |
| Female sex | 0.82 (0.59-1.15) | 0.25 |
| Age at baseline (y) | 0.95 (0.92-0.99) | **0.01** |
| Age at initial CoA repair (y) | 1.021 (1.004-1.039) | **0.01** |
| Bicuspid aortic valve | 1.31 (0.95-1.80) | 0.09 |
| Ventricular septal defect | 1.03 (0.70-1.52) | 0.88 |
| Prior CAD | 2.30 (0.86-6.18) | 0.10 |
| Prior stroke/TIA | 1.91 (0.93-3.92) | 0.08 |
| Prior arrhythmia | 1.61 (0.95-2.71) | 0.08 |
| Systolic BP (mmHg) | 1.004 (0.995-1.013) | 0.37 |
| Diastolic BP (mmHg) | 1.012 (0.997-1.028) | 0.12 |
| BMI ($kg/m^2$) | 1.03 (1.00-1.06) | 0.05 |
| Hypercholesterolemia | 1.50 (1.00-2.26) | 0.05 |
| Diabetes mellitus | 0.50 (0.20-1.24) | 0.13 |
| Cigarette smoking | 1.15 (0.81-1.62) | 0.43 |
| Family history of premature CVD | 1.24 (0.71-2.16) | 0.44 |
| LV mass index ($g/m^2$) | 1.009 (1.005-1.013) | **<0.001** |

A total of 920 patients were included in the analysis, of whom 191 patients developed a cardiovascular event. BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LV, left ventricular; TIA, transient ischemic attack; y, years.

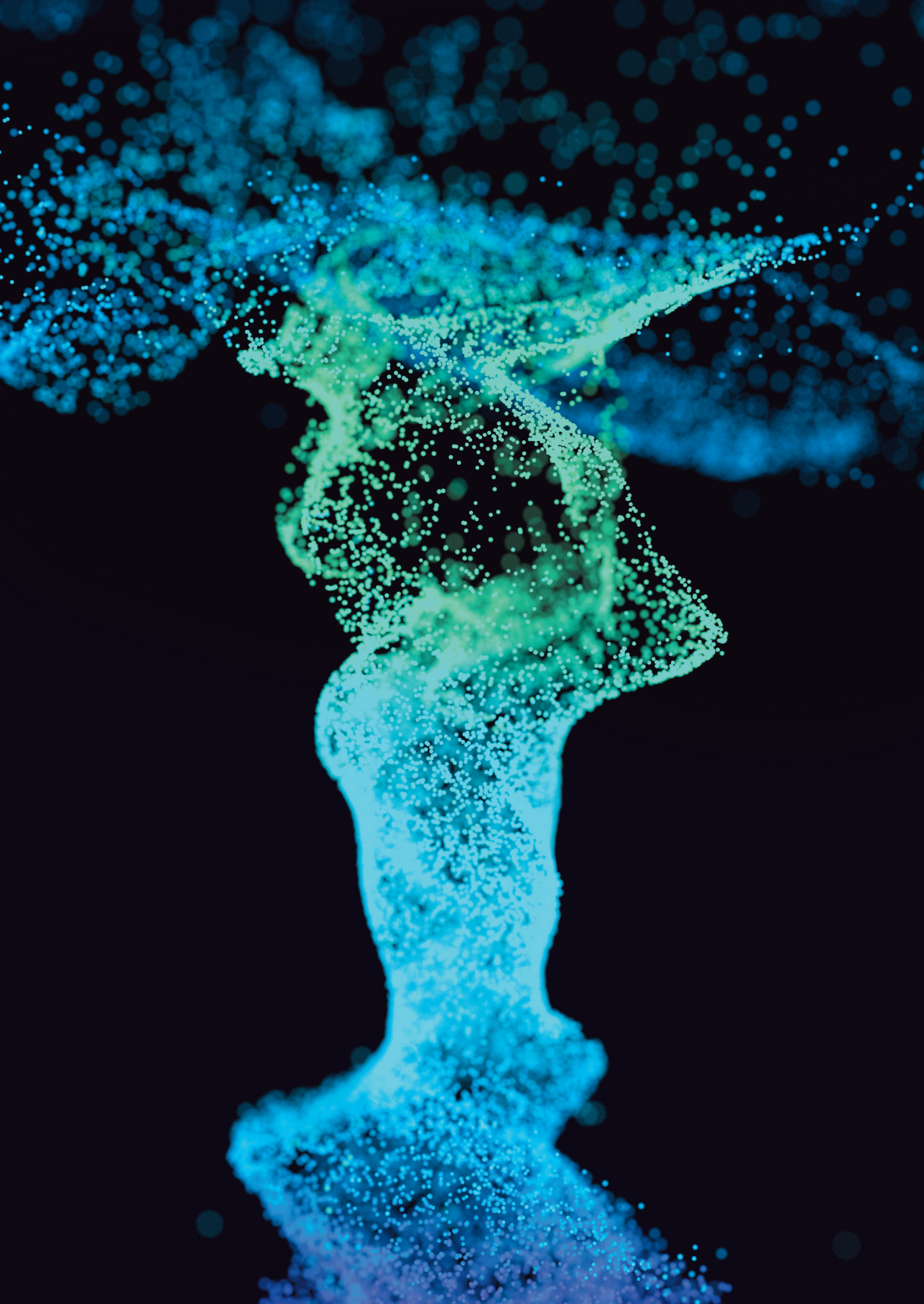
**Supplemental Table 4. Overview of causes of mortality.**

| **Cause of mortality** | **Total** n = 42 | **Age at death (y)** median (range) |
|---|---|---|
| **Cardiovascular** | **24** | **48 (25-79)** |
| Sudden cardiac death | 10 | 49 (25-77) |
| Heart failure | 8 | 54 (35-79) |
| Spontaneous thoracic aortic dissection | 2 | 62 (57-67) |
| Iatrogenic thoracic aortic dissection | 1 | 42 |
| Myocardial infarction | 1 | 40 |
| Endocarditis | 1 | 44 |
| Ischemic stroke | 1 | 45 |
| **Non-cardiovascular** | **17** | **49 (30-84)** |
| Malignancy | 6 | 35 (30-49) |
| Sepsis | 3 | 50 (33-65) |
| Gastrointestinal hemorrhage | 2 | 72 (59-84) |
| Renal hemorrhage | 1 | 51 |
| Other | 5 | 58 (30-75) |
| Unknown | 1 | 72 |

y, years.




**Supplemental Figure 1. Freedom from a cardiovascular event in subgroups based on age at initial CoA repair.**
Kaplan-Meier graph showing the freedom from a cardiovascular event in three subgroups based on the age at initial CoA repair (≤10 years, 11-18 years, and >18 years). CV, cardiovascular.



# CHAPTER 8

# Hypertensive response to exercise in adult patients with repaired aortic coarctation

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**ABSTRACT**

**Objective**

The clinical and prognostic implications of a hypertensive response to exercise after repair of coarctation of the aorta (CoA) remain controversial. We aimed to determine the prevalence of a hypertensive response to exercise, identify factors associated with peak exercise systolic blood pressure (SBP), and explore the association of peak exercise SBP with resting blood pressure and cardiovascular events during follow-up.

**Methods**

From the Dutch national CONgenital CORvitia (CONCOR) registry, adults with repaired CoA who underwent exercise stress testing were included. A hypertensive response to exercise was defined as a peak exercise SBP ≥210 mmHg in men and ≥190 mmHg in women. Cardiovascular events consisted of coronary artery disease, stroke, aortic complications, and cardiovascular death.

**Results**

Of the original cohort of 920 adults with repaired CoA, 675 patients (median age 24 years [range 16-72 years]) underwent exercise stress testing. Of these, 299 patients (44%) had a hypertensive response to exercise. Mean follow-up duration was 10.1 years. Male sex, absence of a bicuspid aortic valve, and elevated resting SBP were independently associated with increased peak exercise SBP. Peak exercise SBP was positively predictive of office SBP (β=0.11, $p$<0.001) and 24-hour SBP (β=0.05, $p$=0.03) at follow-up, despite correction for baseline SBP. During follow-up, 100 patients (15%) developed at least 1 cardiovascular event. Peak exercise SBP was not significantly associated with the occurrence of cardiovascular events (HR 0.994 [95% CI 0.987-1.001], $p$=0.11).

**Conclusions**

A hypertensive response to exercise was present in nearly half of the patients in this large, prospective cohort of adults with repaired CoA. Risk factors for increased peak exercise SBP were male sex, absence of a bicuspid aortic valve, and elevated resting SBP. Increased peak exercise SBP independently predicted hypertension at follow-up. These results support close follow-up of patients with a hypertensive response to exercise to ensure timely diagnosis and treatment of future hypertension.

## INTRODUCTION

Coarctation of the aorta (CoA) is referred to as a local stenosis of the proximal descending aorta, often at the level of the duct. While CoA was previously regarded as a simple, curable condition, it is now increasingly recognized as the expression of a complex, generalized arteriopathy that requires lifelong monitoring.[1,2] Pathological vascular mechanisms contribute to the high prevalence of resting hypertension, which should be adequately treated to avoid late cardiovascular complications.[3] In addition to resting hypertension, 19-35% of CoA patients show a hypertensive response to exercise.[4-8] This is rather inconsistently defined but is commonly referred to as a systolic blood pressure (SBP) ≥210 mmHg in men and ≥190 mmHg in women during maximal exercise.[9] Like resting hypertension, it is often observed in the absence of restenosis at the repair site.[10,11] Hence, it remains unclear which CoA patients are at high risk of a hypertensive response to exercise and may therefore require more intensive monitoring.

In the general population, a hypertensive response to exercise carries significant prognostic implications, as it is associated with an increased risk of future hypertension, cardiovascular events, and mortality.[12,13] Although some studies have identified a hypertensive response to exercise as a risk factor for chronic hypertension in CoA patients, these studies were limited by a relatively small sample size or did not correct for potentially important confounding factors, such as baseline blood pressure (BP).[14,15] In particular, the prognostic significance of this hypertensive response during exercise in the setting of a normal resting BP is subject of debate, which was recognized as a "gap in knowledge" in the recent 2020 ESC guidelines.[3] Furthermore, although it is well known that patients with repaired CoA are at increased risk to experience cardiovascular events, including coronary artery disease, stroke, and aneurysm formation, the impact of a hypertensive response to exercise on the incidence of these cardiovascular complications remains to be elucidated.[16]

Using a multicenter, prospective cohort of adults with repaired CoA, we aimed to determine the prevalence of a hypertensive response to exercise, identify factors associated with peak exercise SBP, and examine the association of peak exercise SBP with resting SBP and the occurrence of cardiovascular events during follow-up.

## METHODS

### Study design

Adult CoA patients from 5 tertiary referral centers who underwent exercise stress testing upon enrollment in the CONgenital CORvitia (CONCOR) registry were included in this study. CONCOR is a prospective registry of adult patients with congenital heart disease in the Netherlands and was founded in 2001. Patients provided informed consent at the time of study

entry. The short- and medium-term outcomes of patients in 1 participating center have been previously published.[14,17,18] Patients were only included when prior surgical or transcatheter repair of CoA was performed. Exclusion criteria comprised a functionally univentricular circulation or transposition of the great arteries not repaired by an arterial switch procedure. Patients were enrolled between 2002 and 2018 and followed until their last clinic visit or death. The study was designed and performed without patient or public involvement. Approval for this study was obtained from the Medical Research Ethics Committee of the University Medical Center Utrecht.

**Data collection and definitions**

Patients underwent maximal exercise stress testing on a treadmill or cycle ergometer. The test was symptom-limited, unless other reasons for termination were present according to ESC guidelines.[19] Exercise workload was expressed as metabolic equivalents (METs). One MET equals an energy expenditure of 3.5 mL $O_2$/kg/min. BP was measured in upright position before the start of the test and during exercise using standardized intervals, generally every 2-3 minutes. A hypertensive response to exercise was defined as a peak exercise SBP ≥210 mmHg in men and ≥190 mmHg in women.[9] Resting BP status was determined at baseline and at last follow-up. Resting BP was measured at the right arm at the outpatient clinic. In case the BP was only measured at the left arm or it was unclear which arm was used, these values were recorded to reduce the number of missing BP readings. Resting hypertension was regarded as an office SBP ≥140 mmHg, office diastolic blood pressure (DBP) ≥90 mmHg, and/or the use of ≥1 antihypertensive agents. Additionally, 24-hour ambulatory BP monitoring (ABPM) was performed at follow-up. Left ventricular (LV) mass was assessed by echocardiography at baseline and follow-up, and was indexed for body surface area. LV hypertrophy was defined as an LV mass index >115 g/m$^2$ for men and >95 g/m$^2$ for women.[20] Other collected data included demographics, prior CoA interventions, and associated congenital defects.

**Outcome measures**

Outcomes at follow-up consisted of office SBP, 24-hour SBP as determined by ABPM, and LV mass index. Additionally, two independent researchers (TAM and SCSM) recorded cardiovascular events during the follow-up period, based on the written medical correspondence by the treating cardiologist. Cardiovascular events consisted of coronary artery disease, stroke, aortic complications, and cardiovascular death. Coronary artery disease was defined as myocardial infarction, coronary revascularization or medical therapy for angina. Aortic complications comprised thoracic aortic aneurysms and dissections. An aortic aneurysm was defined as an aortic diameter >50% larger than predicted based on sex and aortic segment, and/or surgical treatment of the aneurysm.[21] Aortic dissection also included pseudoaneurysm, intramural hematoma, and aortic rupture. The definitions of the SCTI/FDA consensus report

were used to determine whether mortality was due to a cardiovascular or non-cardiovascular cause.[22] In case of uncertainty, this was resolved by discussion with a third study member (MV).

**Statistical analyses**

Baseline characteristics were compared between patients with and without a hypertensive response to exercise using the independent-samples t-test, Mann-Whitney U test or Fisher's exact test, where appropriate. To identify factors associated with peak exercise SBP, univariable and multivariable linear regression were performed. Covariates were included when a potential association with the outcome was conceivable based on previous findings or pathophysiological mechanisms. All covariates were entered into the multivariable model without any selection based on significance. Residual analyses (normality, homoscedasticity, and linearity) were performed to assess the validity of the model. Potential multicollinearity was assessed by inspection of the variance inflation factor values. Similar linear regression models were created for the outcomes office SBP, 24-hour SBP, and LV mass index at follow-up.

A potential association between peak exercise SBP and cardiovascular events was explored by Cox proportional-hazards regression. Patients were followed until the occurrence of a cardiovascular event or censored at the time of the last follow-up visit. A delayed entry model with age as the time scale was used to correct for left-truncated, right-censored data. The model was adjusted for potential confounding factors, which were included by forced entry and consisted of sex, age at initial CoA repair, end-to-end anastomosis, prior intervention for re-CoA, bicuspid aortic valve, ventricular septal defect, aortic and/or mitral mechanical heart valve, resting SBP and DBP, and LV mass index. Fitted penalized B-spline curves and scaled Schoenfeld residuals were examined for each individual covariate and the multivariable model to determine whether or not the proportional-hazards assumption was violated. Due to a relatively low number of events per covariate, Firth's correction was applied to reduce bias associated with monotone likelihood.[23] Statistical analyses were performed using IBM SPSS Statistics 25 (Armonk NY, USA) and SAS version 9 (Cary NC, USA). A $p$-value $<0.05$ was considered to represent statistical significance.



**RESULTS**

**Baseline characteristics**

Of the original cohort of 920 adult CoA patients from the CONCOR registry, 675 patients (73%) underwent exercise stress testing and were therefore included in the current study. Of these, 299 patients (44%) showed a hypertensive response to exercise. Baseline characteristics are presented in Table 1. In the group with a hypertensive response to exercise, 195 patients (65%) had resting hypertension versus 181 patients (48%) in the group without a hypertensive response to exercise ($p<0.001$). Exercise workload was comparable between the groups (11.2

± 3.6 vs. 11.0 ± 3.9 METs, respectively; $p$=0.46). Mean follow-up duration was 10.1 ± 4.7 years. Figure 1 depicts the study cohort stratified by resting BP status and the presence or absence of a hypertensive response to exercise.

Baseline characteristics were compared to patients from the original cohort who were excluded from this study, i.e. patients who did not undergo exercise stress testing (Supplemental Table 1). Patients in the study cohort were younger at the time of initial repair, less frequently treated by graft interposition, and more likely to have LV hypertrophy.

**Factors associated with peak exercise SBP**

Table 2 displays the results of linear regression analysis to identify factors associated with peak exercise SBP. In multivariable analysis, resting SBP at baseline (β=0.53; $p$<0.001) was positively associated with peak exercise SBP. Female sex (β=-11.68; $p$<0.001) and the presence of a bicuspid aortic valve (β=-6.52; $p$=0.007) were negatively associated with peak exercise SBP.

**Change in resting SBP and antihypertensive medication from baseline to follow-up**

Supplemental Table 2 shows that office SBP and DBP remained similar during the follow-up period, both in patients with and without a hypertensive response to exercise. The proportion of patients taking any antihypertensive medication and the number of antihypertensive agents increased in both groups, although the increase in antihypertensive agents was more outspoken in patients with a hypertensive response to exercise (0.52 vs. 0.35; $p$=0.03).

**Value of peak exercise SBP in predicting resting SBP at follow-up**

As shown in Table 3, peak exercise SBP positively predicted office SBP at follow-up (β=0.11; $p$<0.001). This association was independent of resting SBP at baseline and other potential confounding factors. Resting SBP at baseline (β=0.23; $p$<0.001) and the use of any antihypertensive medication (β=0.63; $p$=0.02) were also independent positive predictors of office SBP at follow-up, whereas stent implantation as initial CoA repair (β=-9.76; $p$=0.01) was an independent negative predictor. When limiting this analysis to normotensive patients at baseline, peak exercise SBP was similarly predictive of office SBP at follow-up (β=0.08; $p$=0.002; Supplemental Table 3).

In 244 patients (36%) 24-hour ABPM was performed at follow-up. Higher peak exercise SBP was associated with increased 24-hour SBP at follow-up in a multivariable model (β=0.05; $p$=0.03; Table 3).

**Table 1. Baseline characteristics.**

| | All patients n = 675 | Hypertensive response to exercise n = 299 | No hypertensive response to exercise n = 376 | *p*-value[a] |
|---|---|---|---|---|
| Age (y), median (range) | 24 (16-72) | 25 (16-65) | 24 (16-72) | 0.66 |
| Female sex, n (%) | 272 (40) | 127 (42) | 145 (39) | 0.31 |
| BMI (kg/m$^2$), mean ± SD | 23.9 ± 4.3 | 24.1 ± 3.8 | 23.8 ± 4.6 | 0.47 |
| Age at initial CoA repair (y), median (range) | 3 (0-67) | 4 (0-54) | 2 (0-67) | 0.37 |
| Type of initial CoA repair, n (%) | | | | |
| End-to-end anastomosis | 344 (51) | 154 (52) | 190 (51) | 0.82 |
| Patch angioplasty | 72 (11) | 27 (9) | 45 (12) | 0.26 |
| Subclavian flap angioplasty | 65 (10) | 33 (11) | 32 (9) | 0.29 |
| Graft interposition | 19 (3) | 10 (3) | 9 (2) | 0.49 |
| Ascending-to-descending BG | 5 (1) | 1 (0.3) | 4 (1) | 0.39 |
| Surgery, technique unknown | 127 (19) | 58 (19) | 69 (18) | 0.77 |
| Balloon angioplasty | 15 (2) | 8 (3) | 7 (2) | 0.80 |
| Stenting | 28 (4) | 8 (3) | 20 (5) | 0.17 |
| Prior intervention for re-CoA, n (%) | 140 (21) | 69 (23) | 71 (19) | 0.21 |
| Bicuspid aortic valve, n (%) | 389 (58) | 158 (53) | 231 (61) | **0.03** |
| Ventricular septal defect, n (%) | 155 (23) | 63 (21) | 92 (24) | 0.31 |
| Aortic and/or mitral MHV, n (%) | 41 (6) | 15 (5) | 26 (7) | 0.33 |
| Resting hypertension, n (%) | 376 (56) | 195 (65) | 181 (48) | **<0.001** |
| Resting SBP (mmHg), mean ± SD | 134 ± 18 | 139 ± 18 | 130 ± 17 | **<0.001** |
| Resting DBP (mmHg), mean ± SD | 76 ± 11 | 77 ± 11 | 76 ± 11 | 0.28 |
| Resting arm-leg gradient (mmHg), mean ± SD[b] | 1 ± 17 | 3 ± 16 | -1 ± 17 | 0.06 |
| Exercise workload (METs), mean ± SD | 11.1 ± 3.8 | 11.2 ± 3.6 | 11.0 ± 3.9 | 0.46 |
| Peak exercise SBP (mmHg), mean ± SD | 196 ± 33 | 225 ± 20 | 174 ± 22 | **<0.001** |
| Use of any AHM, n (%) | 224 (33) | 111 (37) | 113 (30) | 0.06 |
| LV mass index (g/m$^2$), mean ± SD[c] | 96 ± 31 | 96 ± 30 | 95 ± 31 | 0.87 |
| LV hypertrophy, n (%)[c] | 187 (29) | 87 (29) | 100 (28) | 0.73 |

[a] Indicates the difference between patients with and without a hypertensive response to exercise, as determined by the independent-samples t-test, Mann-Whitney U test, or Fisher's exact test, where appropriate.

[b] Unavailable for 449 patients (67%), of whom 188 patients (63%) with and 261 patients (69%) without a hypertensive response to exercise.

[c] Unavailable for 26 patients (4%), of whom 4 patients (1%) with and 22 patients (6%) without a hypertensive response to exercise.

AHM, antihypertensive medication; BG, bypass graft; BMI, body mass index; DBP, diastolic blood pressure; LV, left ventricular; MET, metabolic equivalent; MHV, mechanical heart valve; SBP, systolic blood pressure; y, years.

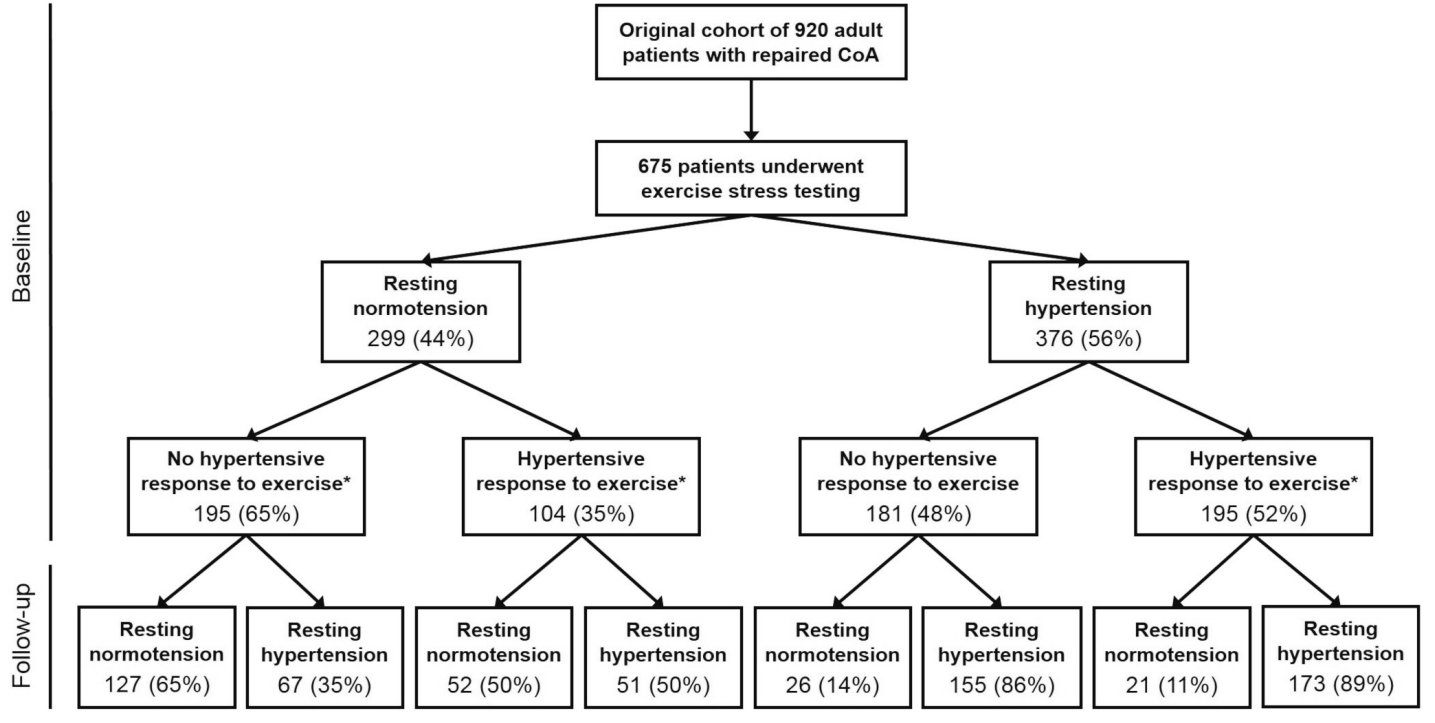


**Figure 1. Flowchart displaying the stratification of patients based on the presence or absence of resting hypertension (office) and a hypertensive response to exercise at baseline.** The prevalence of hypertension at follow-up is shown for the various subgroups. * BP status at follow-up was unknown for 1 patient in this group.

**Table 2. Factors associated with peak exercise SBP.**

| | Peak exercise SBP (mmHg) | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value |
| Age (y) | -0.13 (0.11) | 0.23 | -0.28 (0.15) | 0.06 |
| Female sex | -16.57 (2.50) | **<0.001** | -11.68 (2.69) | **<0.001** |
| BMI (kg/m$^2$) | 0.31 (0.30) | 0.30 | 0.29 (0.32) | 0.37 |
| Age at initial CoA repair (y) | -0.12 (0.14) | 0.37 | 0.25 (0.21) | 0.23 |
| Type of initial CoA repair | | | | |
| End-to-end anastomosis | 3.03 (2.53) | 0.23 | 3.89 (3.40) | 0.25 |
| Patch angioplasty | -2.74 (4.10) | 0.50 | -4.59 (4.92) | 0.35 |
| Subclavian flap angioplasty | 5.89 (4.29) | 0.17 | 8.25 (5.02) | 0.10 |
| Graft interposition | 5.78 (7.66) | 0.45 | 8.81 (8.56) | 0.30 |
| Balloon angioplasty | 2.70 (8.33) | 0.75 | -6.23 (8.89) | 0.48 |
| Stenting | -12.03 (6.45) | 0.06 | -16.32 (8.30) | 0.05 |
| Prior intervention for re-CoA | 6.58 (3.12) | **0.04** | 5.88 (3.12) | 0.06 |
| Bicuspid aortic valve | -5.42 (2.56) | **0.04** | -6.52 (2.43) | **0.007** |
| Resting SBP (mmHg) | 0.54 (0.07) | **<0.001** | 0.53 (0.07) | **<0.001** |
| Use of any AHM | 1.21 (0.54) | **0.02** | 0.56 (0.57) | 0.33 |
| LV mass index (g/m$^2$) | 0.10 (0.04) | **0.02** | 0.02 (0.04) | 0.61 |

In multivariable analysis, there was additionally adjusted for exercise workload in METs. A total of 644 complete cases were included in the multivariable model.

[a] Represents the change in peak exercise SBP per unit increase of the covariate.

AHM, antihypertensive medication; BMI, body mass index; LV, left ventricular; MET, metabolic equivalent; SBP, systolic blood pressure; SE, standard error; y, years.

Peak exercise SBP was univariably predictive of LV mass index at follow-up (β=0.10; *p*=0.006), but this association was no longer observed in multivariable analysis (β=0.04; *p*=0.23; Supplemental Table 4). Similarly, peak exercise SBP was not an independent predictor of LV mass index at follow-up when the analysis was limited to patients who were normotensive at baseline (β=0.06; *p*=0.27; Supplemental Table 5).

**Peak exercise SBP and the risk of cardiovascular events**

During follow-up, 113 cardiovascular events were observed: 12 cases of coronary artery disease, 15 strokes, 69 aortic complications, and 17 cardiovascular deaths (Supplemental Table 6). These events occurred in 100 individual patients. Peak exercise SBP was not associated with the risk of cardiovascular events in univariable (HR 0.996 [95% CI 0.990-1.002]; *p*=0.19) nor multivariable (HR 0.994 [95% CI 0.987-1.001]; *p*=0.11) Cox proportional-hazards regression (Table 4). In contrast, older age at initial repair, the presence of a bicuspid aortic valve, and elevated LV mass index at baseline were independent risk factors for the occurrence of cardiovascular events.

**Table 3. Value of peak exercise SBP in predicting office and 24-hour SBP at follow-up.**

| | Office SBP at follow-up (mmHg) | | | | 24-hour SBP at follow-up (mmHg) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | |
| | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value |
| Age (y) | 0.21 (0.05) | **<0.001** | 0.09 (0.07) | 0.18 | 0.03 (0.07) | 0.71 | -0.09 (0.09) | 0.30 |
| Female sex | -3.00 (1.28) | **0.02** | -0.004 (1.26) | 1.00 | -0.69 (1.73) | 0.69 | 0.06 (1.77) | 0.97 |
| BMI (kg/m$^2$) | 0.63 (0.15) | **<0.001** | 0.19 (0.15) | 0.20 | 0.24 (0.21) | 0.25 | 0.22 (0.21) | 0.29 |
| Age at initial CoA repair (y) | 0.15 (0.07) | **0.02** | 0.14 (0.10) | 0.15 | 0.03 (0.09) | 0.73 | 0.00 (0.15) | 1.0 |
| Type of initial CoA repair | | | | | | | | |
| End-to-end anastomosis | -2.02 (1.25) | 0.09 | -2.61 (1.62) | 0.11 | -1.21 (1.63) | 0.46 | -2.97 (2.07) | 0.15 |
| Patch angioplasty | 1.16 (2.04) | 0.57 | -1.67 (2.27) | 0.46 | -0.81 (2.64) | 0.76 | -3.07 (2.95) | 0.30 |
| Subclavian flap angioplasty | -1.00 (2.12) | 0.64 | -0.81 (2.37) | 0.73 | -3.38 (3.19) | 0.29 | -7.20 (3.40) | **0.04** |
| Graft interposition | -0.78 (3.79) | 0.84 | -6.21 (4.08) | 0.13 | 4.73 (3.92) | 0.23 | 3.08 (4.80) | 0.52 |
| Balloon angioplasty | -1.89 (4.12) | 0.65 | -8.22 (4.22) | 0.05 | -3.71 (4.87) | 0.45 | -7.61 (5.49) | 0.17 |
| Stenting | -4.97 (3.19) | 0.12 | -9.76 (3.95) | **0.01** | -1.87 (3.77) | 0.62 | -2.04 (5.05) | 0.69 |
| Prior intervention for re-CoA | 2.01 (1.54) | 0.05 | 1.27 (1.48) | 0.39 | 0.52 (1.89) | 0.79 | -0.21 (1.90) | 0.91 |
| Bicuspid aortic valve | -1.87 (1.27) | 0.14 | -0.41 (1.17) | 0.73 | 2.30 (1.66) | 0.17 | 3.58 (1.60) | **0.03** |
| Resting SBP at baseline (mmHg) | 0.35 (0.03) | **<0.001** | 0.23 (0.04) | **<0.001** | 0.22 (0.05) | **<0.001** | 0.25 (0.05) | **<0.001** |
| Use of any AHM | 1.46 (0.26) | **<0.001** | 0.63 (0.27) | **0.02** | 0.71 (0.33) | **0.03** | 0.25 (0.33) | 0.46 |
| Peak exercise SBP (mmHg) | 0.15 (0.02) | **<0.001** | 0.11 (0.02) | **<0.001** | 0.07 (0.02) | **0.003** | 0.05 (0.02) | **0.03** |
| LV mass index (g/m$^2$) | 0.06 (0.02) | **0.007** | 0.02 (0.02) | 0.47 | -0.03 (0.03) | 0.37 | -0.05 (0.03) | 0.08 |

A total of 645 (office SBP) and 239 (24-hour SBP) complete cases were included in the multivariable model.

[a] Represents the change in SBP per unit increase of the covariate.

AHM, antihypertensive medication; BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

**Table 4. Cox proportional-hazards regression to assess the association between peak exercise SBP and the risk of cardiovascular events.**

| | Cardiovascular event | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Female sex | 0.51 (0.32-0.79) | **0.003** | 0.70 (0.42-1.15) | 0.15 |
| BMI (kg/m$^2$) | 1.04 (1.01-1.08) | **0.02** | 1.02 (0.98-1.06) | 0.30 |
| Age at initial CoA repair (y) | 1.030 (1.010-1.050) | **0.004** | 1.027 (1.004-1.049) | **0.02** |
| End-to-end anastomosis | 0.72 (0.48-1.09) | 0.12 | 0.79 (0.51-1.23) | 0.30 |
| Prior intervention for re-CoA | 0.79 (0.46-1.35) | 0.39 | 0.79 (0.44-1.43) | 0.44 |
| Bicuspid aortic valve | 2.29 (1.43-3.69) | **0.001** | 2.23 (1.34-3.70) | **0.002** |
| Ventricular septal defect | 0.89 (0.52-1.52) | 0.68 | 1.16 (0.67-2.00) | 0.61 |
| Aortic and/or mitral MHV | 1.73 (0.96-3.14) | 0.07 | 1.27 (0.69-2.34) | 0.45 |
| Resting SBP (mmHg) | 1.005 (0.994-1.016) | 0.37 | 1.006 (0.993-1.020) | 0.37 |
| Resting DBP (mmHg) | 1.017 (0.997-1.036) | 0.09 | 1.015 (0.993-1.038) | 0.19 |
| Peak exercise SBP (mmHg) | 0.996 (0.990-1.002) | 0.19 | 0.994 (0.987-1.001) | 0.11 |
| LV mass index (g/m$^2$) | 1.009 (1.005-1.014) | **<0.001** | 1.009 (1.003-1.014) | **0.003** |

A total of 648 complete cases were included in the multivariable model, of whom 94 patients developed a cardiovascular event (composite of coronary artery disease, stroke, aortic complications, and cardiovascular death).

BMI, body mass index; DBP, diastolic blood pressure; HR, hazard ratio; LV, left ventricular; MHV, mechanical heart valve; SBP, systolic blood pressure; y, years.

## DISCUSSION

In this multicenter, prospective cohort of adult CoA patients, we sought to investigate the prevalence, potential risk factors and prognostic consequences of a hypertensive response to exercise. A hypertensive response to exercise occurred in 44% of patients in our cohort, which is even higher than previously reported.[4-8] Patients with an increased peak exercise SBP were more often male, had less frequently a bicuspid aortic valve, and had a higher resting SBP. Increased peak exercise SBP was predictive of elevated resting SBP at follow-up, even after correction for baseline SBP (Figure 2). These findings underline the prognostic impact of a hypertensive response to exercise in the adult CoA population. However, in this study no association between peak exercise SBP and the occurrence of cardiovascular events was demonstrated.

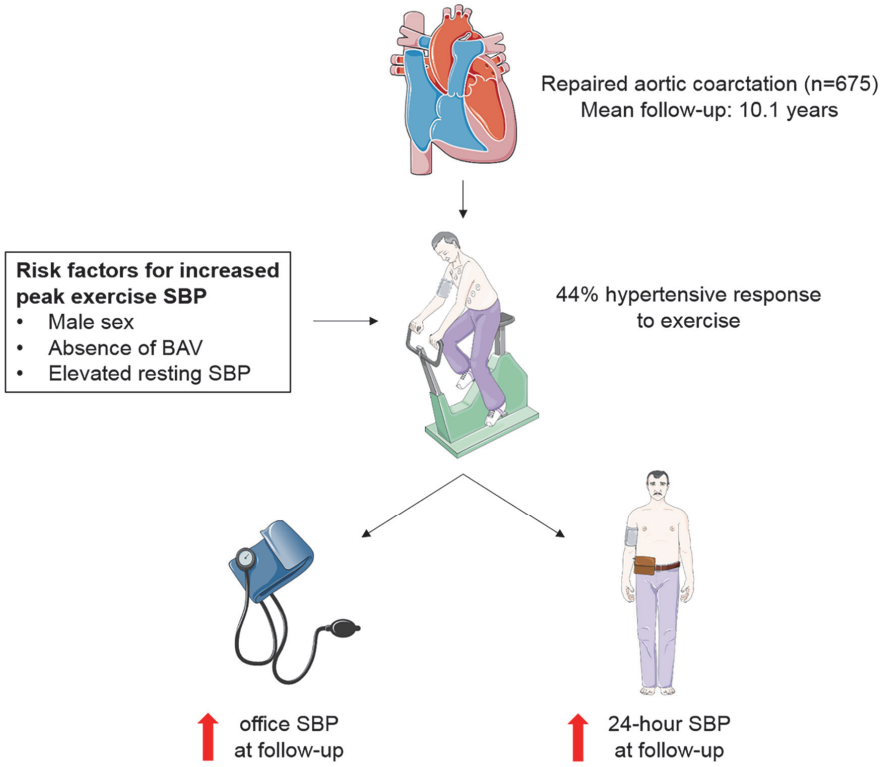


**Figure 2. Graphical summary of the main findings in this study.** Images from Servier Medical Art (smart.servier.com) were used to create this figure. BAV, bicuspid aortic valve; SBP, systolic blood pressure.

### Prevalence and associations of a hypertensive response to exercise

In our cohort, a hypertensive response to exercise was observed in 299 out of 675 patients (44%), whereas in previous literature the reported prevalence ranged from 19% to 35%.[4-8] A possible explanation for the higher prevalence in the current study is that patients were younger (median of 24 years vs. a mean between 30 and 40 years in four previous studies) and younger patients tend to have a higher peak exercise SBP.[4-7] Only 10% of people in the general population shows a hypertensive response to exercise, as the definition of a peak exercise SBP ≥210 mmHg in men and ≥190 mmHg in women roughly corresponds to the 90th percentile.[24] The mechanisms underlying this response have not been fully elucidated, although endothelial dysfunction, increased arterial stiffness, activation of the renin-angiotensin-aldosterone system, and elevated sympathetic tone are considered key processes.[24] In CoA patients, a hypertensive response to exercise may also be a clue to the presence of re-coarctation, especially in the setting

of normal BP at rest.[7] Recently, we demonstrated that mimicking exercise by epinephrine administration during cardiac catheterization may be useful in detecting hemodynamically relevant re-coarctation.[25]

In this study, male sex was predictive of higher peak exercise SBP. This is reflected by the current definition of a hypertensive response to exercise, which applies a higher cut-off value for men compared to women (210 vs. 190 mmHg, respectively), even though some earlier studies used a cut-off value of 200 mmHg for both men and women.[14,18] Furthermore, elevated resting SBP was a predictor of increased peak exercise SBP, despite several previous studies reporting no association between resting SBP and SBP response to exercise.[4,11] Lastly, patients with a bicuspid aortic valve showed a lower BP response to exercise, which may be related to the degree of aortic valve stenosis in this specific patient subset. However, it was previously found that patients with moderate to severe aortic valve stenosis (regardless of the presence of a bicuspid aortic valve) may have a hypertensive response to exercise, even though a blunted BP response to exercise was more frequent (21% vs. 37%, respectively).[26]

**Value of a hypertensive response to exercise in predicting hypertension and LV afterload**

Although the BP response to exercise is frequently assessed in CoA patients, there is uncertainty regarding its prognostic consequences. We found that peak exercise SBP was predictive of resting SBP at follow-up, which is in line with previous findings.[14,15] Importantly, this association was observed independently of resting SBP at baseline, which suggests that the BP response to exercise may have additional value in clinical decision making besides resting BP. Our results indicate that this also applies to normotensive patients with an isolated hypertensive response to exercise. Of note, stent implantation was associated with a lower resting BP at follow-up, which is consistent with the previously reported favorable hemodynamic effects of stenting.[27] However, patients who undergo stenting as primary repair generally have less complex disease compared to those surgically treated and therefore this finding should be interpreted with caution.

**Hypertensive response to exercise and the risk of cardiovascular events**

Despite the association between a hypertensive response to exercise and late hypertension, we found no conclusive evidence that this response predisposes for cardiovascular complications in the CoA population. One possible reason is that our follow-up time was not long enough. In addition, our patients were still relatively young and perhaps CoA patients with a hypertensive response to exercise may not be at increased risk to experience cardiovascular events in early adulthood, but rather beyond the age of 50 years. In contrast, a previous study identified a hypertensive response to exercise as a risk factor for adverse cardiovascular events in CoA patients.[4] However, events occurred only in 24 patients and aortic aneurysm formation, a hypertension-related complication frequently observed in CoA, was not included as an

outcome. In our study, on the contrary, patients with a low peak exercise SBP tended to experience more events, although not statistically significant. We observed a particularly high incidence of ascending aortic aneurysms, despite correction for the presence of a bicuspid aortic valve. Obviously, aneurysm formation is a gradual process, and it is likely that these patients already had some degree of aortic dilatation at the time of the exercise stress test. It has been shown that the elasticity of the ascending aorta decreases during exercise to increase pulse wave velocity, which indicates that the ascending aorta plays a crucial role in elevating central BP during exercise.[28] It is conceivable that patients with ascending aortic dysfunction, as a result of aortic dilatation, are less capable of this adaptive BP response to exercise, which may result in a relatively low peak exercise SBP. However, further detailed study is necessary to elucidate these underlying mechanisms.

**Implications for management**

The results of this study suggest that CoA patients with a hypertensive response to exercise are prone to develop hypertension during follow-up. Therefore, close surveillance of these patients is indicated in order to adequately identify and treat future hypertension. However, it remains unclear whether to start antihypertensive medication in normotensive patients with a hypertensive response to exercise, since some of these patients may never develop hypertension but would be exposed to potential side-effects. Furthermore, a clear association between a hypertensive response to exercise and cardiovascular events has not yet been demonstrated. These questions need to be addressed in future studies to further clarify the clinical value of exercise stress testing in addition to conventional office and ABPM measurements, which have logistical advantages.

**Limitations**

This study has several limitations. As this was a multicenter study, there was a lack of uniformity in the protocols for exercise stress testing. Particularly, differences in interval duration between BP measurements may have affected peak exercise SBP. Furthermore, patients in the study cohort were more likely to have LV hypertrophy compared to patients from the original cohort who did not undergo exercise stress testing, which may have introduced selection bias. Bias may also have been caused by the fact that 24-hour ABPM at follow-up was only available in a subset of patients. In addition, the presence of aortic arch hypoplasia was not systematically assessed in this study, even though arch hypoplasia may contribute to the development of resting hypertension in patients with CoA.[29] Also, since the majority of surgical repairs was performed prior to 1990, surgical reports were frequently unavailable. Hence, determination of the surgical technique was primarily based on the correspondence by the treating cardiologist. In this correspondence, it was often not specified whether a simple or

extended end-to-end repair was performed. Furthermore, the surgical technique was unknown in a substantial number of patients (19%).

## CONCLUSIONS

In this large nationwide study involving adults with repaired CoA, the prevalence of a hypertensive response to exercise was 44%, which is higher than previously reported. Independent risk factors for increased peak exercise SBP were male sex, absence of a bicuspid aortic valve, and elevated resting SBP. Peak exercise SBP was positively predictive of resting SBP at follow-up independently of baseline SBP. Close monitoring of CoA patients with a hypertensive response to exercise is required to timely identify and treat future hypertension.

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## SUPPLEMENTAL MATERIAL

**Supplemental Table 1. Baseline characteristics in patients who underwent exercise stress testing (study cohort) versus patients who did not undergo exercise stress testing (excluded cohort).**

| | EST (study cohort) n = 675 | No EST (excluded cohort) n = 245 | *p*-value[a] |
|---|---|---|---|
| Age (y), median (range) | 24 (16-72) | 24 (16-74) | 0.45 |
| Female sex, n (%) | 272 (40) | 93 (38) | 0.54 |
| BMI (kg/m$^2$), mean ± SD | 23.9 ± 4.3 | 24.3 ± 5.3 | 0.35 |
| Age at initial CoA repair (y), median (range) | 3 (0-67) | 6 (0-61) | **0.004** |
| Type of initial CoA repair, n (%) | | | |
| End-to-end anastomosis | 344 (51) | 130 (53) | 0.60 |
| Patch angioplasty | 72 (11) | 16 (7) | 0.08 |
| Subclavian flap angioplasty | 65 (10) | 24 (10) | 1.0 |
| Graft interposition | 19 (3) | 14 (6) | **0.045** |
| Ascending-to-descending BG | 5 (1) | 2 (1) | 1.0 |
| Surgery, technique unknown | 127 (19) | 45 (18) | 0.92 |
| Balloon angioplasty | 15 (2) | 4 (2) | 0.62 |
| Stenting | 28 (4) | 10 (4) | 1.0 |
| Prior intervention for re-CoA, n (%) | 140 (21) | 38 (16) | 0.09 |
| Bicuspid aortic valve, n (%) | 389 (58) | 130 (53) | 0.23 |
| Ventricular septal defect, n (%) | 155 (23) | 53 (22) | 0.72 |
| Aortic and/or mitral MHV, n (%) | 41 (6) | 19 (8) | 0.37 |
| Resting hypertension, n (%)[b] | 376 (56) | 138 (59) | 0.36 |
| Resting SBP (mmHg), mean ± SD[b] | 134 ± 18 | 137 ± 20 | 0.05 |
| Resting DBP (mmHg), mean ± SD[b] | 76 ± 11 | 76 ± 12 | 0.97 |
| Resting arm-leg gradient (mmHg), mean ± SD[c] | 1 ± 17 | 5 ± 25 | 0.27 |
| Use of any AHM, n (%)[d] | 224 (33) | 72 (30) | 0.38 |
| LV mass index (g/m$^2$), mean ± SD[e] | 96 ± 31 | 91 ± 31 | **0.04** |
| LV hypertrophy, n (%)[e] | 187 (29) | 46 (21) | **0.04** |

[a] Determined by the independent samples t-test, Mann-Whitney U test or Fisher's exact test, where appropriate.
[b] Unavailable for 12 patients (5%) in the excluded cohort.
[c] Unavailable for 449 patients (67%) in the study cohort and 178 patients (73%) in the excluded cohort.
[d] Unavailable for 5 patients (2%) in the excluded cohort.
[e] Unavailable for 26 patients (4%) in the study cohort and 31 patients (13%) in the excluded cohort.
AHM, antihypertensive medication; BG, bypass graft; BMI, body mass index; DBP, diastolic blood pressure; EST, exercise stress testing; LV, left ventricular; SBP, systolic blood pressure; y, years.

**Supplemental Table 2. Change in office blood pressure and antihypertensive medication from baseline to follow-up.**

| | Office SBP (mmHg) mean ± SD | | | Office DBP (mmHg) mean ± SD | | | Use of any AHM n (%) | | | No. of antihypertensives mean ± SD | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **FU** | ***p*-value** | **Baseline** | **FU** | ***p*-value** | **Baseline** | **FU** | ***p*-value** | **Baseline** | **FU** | ***p*-value** | $p_{diff}$[a] |
| All patients | 134 ± 18 | 134 ± 16 | 0.43 | 76 ± 11 | 77 ± 10 | 0.06 | 224 (33) | 354 (52) | **<0.001** | 0.51 ± 0.85 | 0.93 ± 1.13 | **<0.001** | |
| Hypertensive response to exercise | 139 ± 18 | 138 ± 16 | 0.73 | 77 ± 11 | 78 ± 10 | 0.15 | 111 (37) | 173 (58) | **<0.001** | 0.56 ± 0.88 | 1.08 ± 1.19 | **<0.001** | **0.03** |
| No hypertensive response to exercise | 130 ± 17 | 130 ± 15 | 0.44 | 76 ± 11 | 77 ± 10 | 0.22 | 113 (30) | 181 (48) | **<0.001** | 0.47 ± 0.83 | 0.82 ± 1.06 | **<0.001** | |

Baseline and follow-up data were compared using the paired t-test for office SBP and office DBP, McNemar test for use of any AHM, and Wilcoxon signed rank test for no. of antihypertensives.

[a] This *p*-value indicates whether the change in no. of antihypertensives (from baseline to follow-up) was different between patients with and without a hypertensive response to exercise, as determined by the independent-samples t-test.

AHM, antihypertensive medication; DBP, diastolic blood pressure; FU, follow-up; SBP, systolic blood pressure.

**Supplemental Table 3. Value of peak exercise SBP in predicting office SBP at follow-up when the analysis is limited to normotensive patients at baseline (n = 299).**

| | Office SBP at follow-up (mmHg) | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value |
| Age (y) | 0.26 (0.09) | **0.006** | 0.06 (0.11) | 0.59 |
| Female sex | -4.64 (1.63) | **0.005** | -2.71 (1.69) | 0.11 |
| BMI (kg/m$^2$) | 0.64 (0.24) | **0.008** | 0.48 (0.23) | **0.04** |
| Age at initial CoA repair (y) | 0.10 (0.12) | **0.048** | 0.12 (0.17) | 0.46 |
| Type of initial CoA repair | | | | |
| End-to-end anastomosis | -4.42 (1.64) | **0.007** | -8.50 (2.22) | **<0.001** |
| Patch angioplasty | 1.88 (2.96) | 0.53 | -3.91 (3.30) | 0.24 |
| Subclavian flap angioplasty | 0.50 (2.46) | 0.84 | -4.99 (2.94) | 0.09 |
| Graft interposition | -3.59 (7.13) | 0.62 | -12.97 (6.74) | 0.06 |
| Balloon angioplasty | -2.08 (5.84) | 0.72 | -12.73 (5.70) | **0.03** |
| Stenting | -5.57 (5.07) | 0.27 | -17.57 (6.40) | **0.006** |
| Prior intervention for re-CoA | -1.03 (2.27) | 0.65 | -1.61 (2.17) | 0.46 |
| Bicuspid aortic valve | -1.21 (1.68) | 0.47 | 0.07 (1.55) | 0.96 |
| Resting SBP at baseline (mmHg) | 0.42 (0.08) | **<0.001** | 0.33 (0.08) | **<0.001** |
| Peak exercise SBP (mmHg) | 0.12 (0.03) | **<0.001** | 0.08 (0.03) | **0.002** |
| LV mass index (g/m$^2$) | 0.04 (0.03) | 0.18 | 0.01 (0.03) | 0.84 |

A total of 285 complete cases were included in the multivariable model.

[a] Represents the change in office SBP per unit increase of the covariate.

BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

**Supplemental Table 4. Value of peak exercise SBP in predicting LV mass index at follow-up.**

| | LV mass index at follow-up (g/m$^2$) | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value |
| Age (y) | 0.48 (0.10) | **<0.001** | 0.41 (0.13) | **0.001** |
| Female sex | -20.07 (2.19) | **<0.001** | -19.00 (2.22) | **<0.001** |
| BMI (kg/m$^2$) | 0.77 (0.29) | **0.007** | 0.40 (0.28) | 0.15 |
| Age at initial CoA repair (y) | 0.45 (0.12) | **<0.001** | 0.15 (0.18) | 0.40 |
| Type of initial CoA repair | | | | |
| End-to-end anastomosis | -3.73 (2.28) | 0.10 | 0.06 (2.99) | 0.98 |
| Patch angioplasty | 9.85 (3.63) | **0.007** | 11.16 (4.10) | **0.007** |
| Subclavian flap angioplasty | -5.51 (3.82) | 0.15 | 1.64 (4.36) | 0.71 |
| Graft interposition | -7.84 (6.89) | 0.26 | -5.96 (7.14) | 0.40 |
| Balloon angioplasty | 18.99 (7.50) | **0.01** | 14.38 (7.91) | 0.07 |
| Stenting | -1.24 (5.78) | 0.83 | -4.40 (7.17) | 0.54 |
| Prior intervention for re-CoA | -0.90 (2.81) | 0.75 | 0.23 (2.70) | 0.93 |
| Bicuspid aortic valve | 4.38 (2.30) | 0.06 | 4.22 (2.12) | **0.047** |
| Resting SBP at baseline (mmHg) | 0.12 (0.06) | 0.06 | -0.07 (0.07) | 0.27 |
| Use of any AHM | 1.97 (0.48) | **<0.001** | 0.70 (0.49) | 0.16 |
| Peak exercise SBP | 0.10 (0.03) | **0.006** | 0.04 (0.04) | 0.23 |

A total of 638 complete cases were included in the multivariable model.

[a] Represents the change in LV mass index per unit increase of the covariate.

AHM, antihypertensive medication; BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

**Supplemental Table 5. Value of peak exercise SBP in predicting LV mass index at follow-up when the analysis is limited to normotensive patients at baseline (n = 299).**

| | LV mass index at follow-up (g/m$^2$) | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | β (SE)[a] | *p*-value | β (SE)[a] | *p*-value |
| Age (y) | 0.04 (0.18) | 0.82 | 0.22 (0.21) | 0.28 |
| Female sex | -20.02 (2.76) | **<0.001** | -19.53 (2.99) | **<0.001** |
| BMI (kg/m$^2$) | 0.31 (0.45) | 0.49 | 0.25 (0.43) | 0.56 |
| Age at initial CoA repair (y) | 0.10 (0.21) | 0.64 | 0.04 (0.31) | 0.90 |
| Type of initial CoA repair | | | | |
| End-to-end anastomosis | -1.13 (3.03) | 0.71 | 2.57 (4.15) | 0.54 |
| Patch angioplasty | 9.26 (5.16) | 0.07 | 11.43 (5.93) | 0.06 |
| Subclavian flap angioplasty | -3.04 (4.49) | 0.50 | 0.38 (5.48) | 0.95 |
| Graft interposition | 12.44 (12.67) | 0.33 | 21.25 (12.42) | 0.09 |
| Balloon angioplasty | 14.27 (10.36) | 0.17 | 11.25 (10.50) | 0.29 |
| Stenting | -5.29 (9.03) | 0.56 | -4.78 (11.79) | 0.69 |
| Prior intervention for re-CoA | 3.15 (4.09) | 0.44 | 1.65 (3.96) | 0.68 |
| Bicuspid aortic valve | 5.96 (3.06) | 0.05 | 6.64 (2.85) | **0.02** |
| Resting SBP at baseline (mmHg) | 0.25 (0.14) | 0.08 | -0.01 (0.14) | 0.97 |
| Peak exercise SBP (mmHg) | 0.15 (0.05) | **0.002** | 0.06 (0.05) | 0.27 |

A total of 282 complete cases were included in the multivariable model.

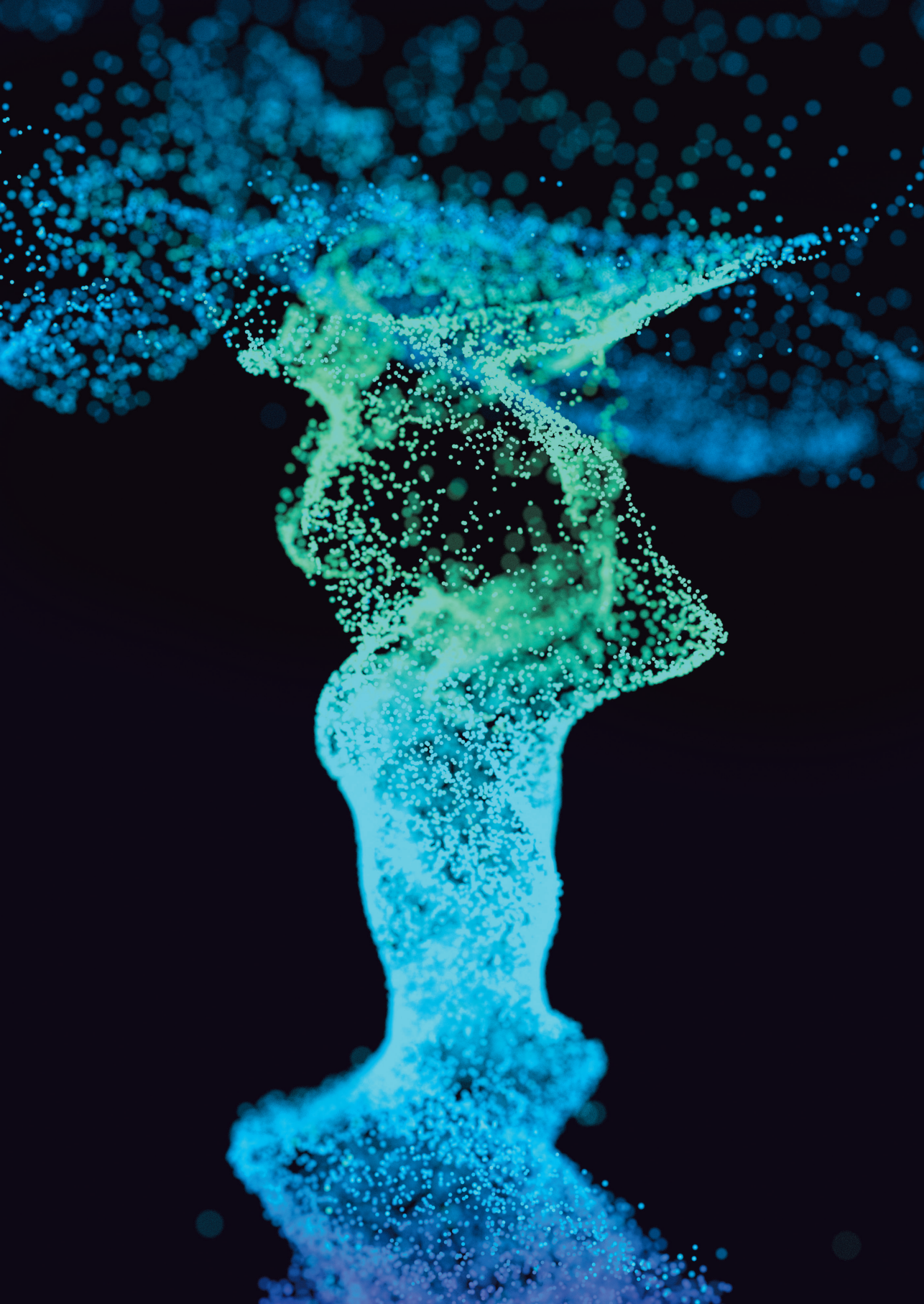
[a] Represents the change in LV mass index per unit increase of the covariate.

BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

**Supplemental Table 6. Overview of cardiovascular events.**

| | No. of cases |
|---|---|
| **Coronary artery disease** | **12** |
| Myocardial infarction | 6 |
| Coronary revascularization | 5 |
| Medical treatment for angina | 1 |
| **Stroke** | **15** |
| Ischemic stroke | 14 |
| Hemorrhagic stroke, intracerebral | 0 |
| Hemorrhagic stroke, subarachnoidal | 1 |
| **Aortic complication** | **69** |
| Aneurysm | 64 |
| Dissection | 5 |
| **CV death** | **17** |
| **Total CV events** | **113** |
| **No. of individual patients with CV event** | **100** |

CV, cardiovascular.



# CHAPTER 9

# Assessment of aortic and cerebral hemodynamics and vascular brain injury with 3T and 7T MRI in patients with aortic coarctation

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**Submitted.**

**ABSTRACT**

**Background**

Coarctation of the aorta (CoA) is characterized by a central arteriopathy resulting in increased arterial stiffness. The condition is associated with an increased risk of stroke. We therefore aimed to assess the aortic and cerebral hemodynamics and the presence of vascular brain injury in patients with CoA.

**Methods**

Twenty-seven CoA patients ≥12 years with previous surgical repair and 25 age- and sex-matched controls underwent 3 tesla (cardiac, aortic, and brain) and 7 tesla (brain) MRI scans. Hemodynamic parameters were measured using 2D phase-contrast images of the ascending and descending aorta, internal carotid artery (ICA), basilar artery (BA), middle cerebral artery (MCA), and perforating arteries in the basal ganglia and centrum semiovale. Vascular brain injury was assessed by rating white matter hyperintensities, cortical microinfarcts, lacunes, and microbleeds.

**Results**

CoA patients had a median age of 22 years (range 12-72) and controls of 24 years (range 12-64). Pulse wave velocities in the aortic arch (5.9±2.2 vs. 4.9±1.1 m/s, $p$=0.04) and descending aorta (5.7±2.0 vs. 4.6±1.6 m/s, $p$=0.03) were increased and ascending aortic distensibility was decreased ($6.1 \cdot 10^{-3} \pm 4.1 \cdot 10^{-3}$ vs. $8.5 \cdot 10^{-3} \pm 3.6 \cdot 10^{-3}$ $mmHg^{-1}$, $p$=0.03) in CoA patients versus controls. CoA patients showed a higher mean flow velocity in the right ICA, left ICA, and BA, and a reduced distensibility in the right ICA, BA, and left MCA. Hemodynamic parameters in the perforating arteries, total cerebral blood flow, and intracranial volumes were similar between the groups. The prevalence of vascular brain injury in CoA patients was low and not substantially different from controls.

**Conclusions**

Patients with CoA show an increased flow velocity and reduced distensibility in the aorta and proximal cerebral arteries, which suggests the presence of a generalized arteriopathy that extends into the cerebral arterial tree. Reassuringly, no substantial vascular brain injury was observed in this relatively young CoA population.

## INTRODUCTION

Coarctation of the aorta (CoA) is a congenital, focal stenosis of the aortic isthmus, affecting approximately 4 of 10,000 newborns.[1] Nowadays, most patients undergo surgical repair in the first months after birth, sometimes preceded by balloon angioplasty in case of critical CoA. CoA is characterized by a central arteriopathy resulting in increased arterial stiffness of the prestenotic aorta, even after anatomically successful repair.[1,2] Microscopic evaluation has revealed that this is caused by pronounced elastin fragmentation and accumulation of collagen.[3] Increased arterial stiffness may induce several pathological changes. It augments the left ventricular (LV) afterload, resulting in LV hypertrophy and potentially fibrosis. Furthermore, the dampening of the arterial pulse wave, also known as the Windkessel effect, is impaired.[4] Deterioration of this protective mechanism may result in end organ damage.[5] Increased arterial stiffness is also associated with hypertension, which is frequently observed in patients with repaired CoA and predisposes for vascular brain injury.[1]

Importantly, CoA patients are at increased risk of hemorrhagic and ischemic stroke, despite successful CoA repair.[6-8] According to a recent study, CoA patients experience hemorrhagic and ischemic stroke on average 29 and 16 years earlier, respectively, than non-CoA patients.[9] In particular subarachnoid hemorrhage is frequent.[7] This may be partly related to the high prevalence of intracranial aneurysms, which are present in approximately 10% of adults with CoA as opposed to 2% in the general population.[10-12] Despite the high incidence of stroke, little is known about the characteristics of the cerebral circulation in this specific patient population and its role in the pathogenesis of stroke. In this exploratory case-control study, we used 3 tesla (3T) and 7 tesla (7T) MRI to evaluate hemodynamic parameters in the aorta and the proximal and distal segments of the cerebral arterial tree in CoA patients. Furthermore, we assessed the presence and extent of vascular brain injury.

## METHODS

### Study population

In this study, patients ≥12 years of age with previous surgical repair of CoA were included. Controls, defined as subjects with no history of cardiovascular disease, were frequency-matched by age and sex in a 1:1 ratio to patients. Exclusion criteria for CoA patients and controls were a history of stroke or intellectual disability, current pregnancy, and the presence of a contraindication for MRI. All subjects completed the Questionnaire for Verifying Stroke-Free Status (QVSFS).[13] A specific exclusion criterion for CoA patients was the presence of an associated congenital defect or syndrome other than a bicuspid aortic valve (BAV), closed/small ventricular septal defect, atrial septal defect, patent foramen ovale, or patent ductus arteriosus. CoA patients were also excluded when they had a history of aortic stent implantation

(due to potential MRI artifacts) or when there was currently evidence of recoarctation, defined as hypertension in combination with either an arm-leg systolic blood pressure (BP) gradient >20 mmHg or >50% aortic narrowing relative to the aorta at diaphragm level.[14] Written informed consent was provided by all subjects. The study was reviewed and approved by the institutional review board of the University Medical Center Utrecht (number 19-417).

**Study procedures**

In all subjects, BP measurements were performed on the right arm and right leg. Hypertension in subjects >16 years was defined as a systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, and/or the use of any antihypertension medication.[15] In subjects ≤16 years, reference values were based on the 95th percentile for age, sex, and height.[16] CoA patients additionally underwent 24-hour ambulatory BP monitoring, which was classified according to ESC guidelines for subjects >16 years and ESH guidelines for subjects ≤16 years.[15,16] Clinical data, including comorbidities, prior interventions and use of antihypertensive medication, were extracted from medical records.

All subjects underwent two MRI scans: a combined cardiac, aortic and brain MRI scan on a 3T Philips Ingenia Elition scanner (Philips Healthcare, Best, The Netherlands) and a brain MRI scan on a 7T Philips Achieva scanner (Philips Healthcare). The imaging parameters of these MRI scans are provided in Supplemental Table 1. The maximal duration between both scanning sessions was 6 months.

***Cardiac and aortic imaging***

Cardiac and aortic evaluation was performed with 3T MRI to assess LV volumes, LV ejection fraction, aortic pulse wave velocity (PWV), and aortic distensibility. The cardiac cines were analyzed using Qmass (Medis Medical Imaging, Leiden, Netherlands). The cardiac-gated 2D phase-contrast images were analyzed on the scanner console using the Philips scanner software (R5.1.7). Based on these analyses, aortic PWV was calculated (1) between the ascending and proximal descending aorta, both measured at the level of the pulmonary bifurcation (PWV aortic arch), (2) between the proximal descending aorta and the aorta at diaphragm level (PWV descending aorta), and (3) between the ascending aorta and the aorta at diaphragm level (PWV total thoracic aorta), as previously described.[2,17] Ascending aortic distensibility was calculated according to the following formula: $(A_{max}–A_{min}) / (A_{min} \times (BP_{systolic}–BP_{diastolic}))$.[2] In this formula, $A_{max}$ and $A_{min}$ refer to the maximal and minimal lumen area ($mm^2$) and the right arm BP measurement was used as proxy for the local intraluminal pulse pressure. Cardiac and aortic analyses were performed independently by two trained operators (T.A.M. and R.J.T.).

***Brain imaging***

Cerebral hemodynamic parameters were assessed from the 3T and 7T 2D phase-contrast images in the following cerebral arteries: the C3 segment of the right and left internal carotid artery (ICA), the basilar artery (BA), the M1 segment of the right and left middle cerebral artery (MCA), and the perforating arteries in the basal ganglia and centrum semiovale. For analysis of the ICA (3T), BA (3T), and MCA (7T), vessel contours were automatically detected and propagated over the cardiac cycle using Qflow (Medis Medical Imaging), as illustrated in Figure 1. Correct contour propagation was individually verified and, if necessary, manually adjusted blinded to the presence of CoA. Measurements were excluded when the quality criteria were not met, i.e. the slice planning was not perpendicular to the arteries and/or the contour was unstable over the cardiac cycle. For analysis of the perforating arteries (7T), in-house developed software was used, as previously described.[18,19] These analyses were conducted independently by two trained operators (T.A.M. and R.J.T.). The following parameters were assessed in the examined arteries: mean flow velocity, velocity pulsatility index (PI), mean flow, and distensibility. Velocity PI was calculated by dividing the difference between maximal and minimal flow velocity by the mean flow velocity over the cardiac cycle.[19]

Arterial spin labeling (ASL) and T1-weighted images were used to quantify total white matter and grey matter cerebral blood flow (CBF). CBF was estimated using BASIL software and corrected for partial volume effects.[20] Volumes of grey matter, white matter, cerebrospinal fluid and cortical thickness were measured by voxel-based morphometry on 3T T1-weighted images using CAT12 software.[21] Vascular brain lesions were assessed by experienced raters. White matter hyperintensity burden was determined on the FLAIR sequence using the Fazekas scale (N.A.W.).[22] The presence of lacunes (on 3T T1-weighted and FLAIR images) and microbleeds (on 7T T2* images) was rated according to the STRIVE criteria (H.B.).[23] Cortical microinfarcts were rated on 3T T1-weighted, FLAIR and SWI images according to previously published rating criteria (H.B.).[24]

**Statistical analyses**

Velocity PI at 7T MRI was used for sample size calculation. Recently, this was assessed in patients with lacunar stroke or intracerebral hemorrhage (mean velocity PI: 1.045 ± 0.12) and in controls (mean velocity PI: 0.94).[19] Based on these data, we expected to need 21 subjects per group ($\alpha$=0.05; $\beta$=0.20). Taking into account a margin of error, we decided to include 25 CoA patients and 25 controls in the study.

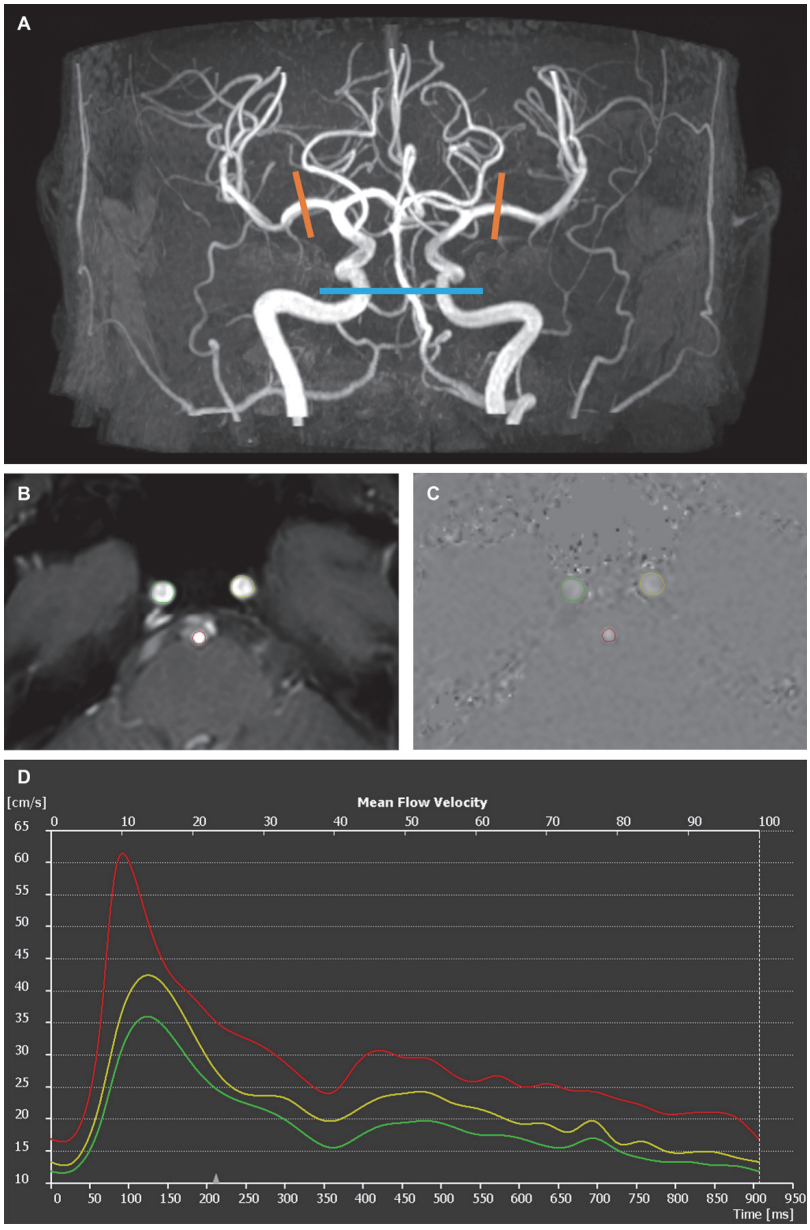


**Figure 1. Planning and contour detection for hemodynamic measurements of the internal carotid arteries, basilar artery, and middle cerebral arteries.** (A) Phase-contrast angiography (coronal view) showing the slice planning used for measurements of the internal carotid arteries and basilar artery at C3 level (blue) and the middle cerebral arteries at the M1-segment (orange). (B and C) Contours were automatically detected and propagated over the cardiac cycle (green = right internal carotid artery, yellow = left internal carotid artery, red = basilar artery). (D) Corresponding flow velocity curves in the three cerebral arteries mentioned above.

Baseline characteristics and cardiac/aortic parameters were compared between CoA patients and control subjects using the unpaired t-test, Mann-Whitney U test or Fisher's exact test, where appropriate. Multiple linear regression was performed to examine potential associations between CoA and hemodynamic parameters in the cerebral arteries. These potential associations were adjusted for age, sex, and the presence of hypertension, since these variables may impact hemodynamic measurements based on physiological concepts and/or prior reports.[25] Residual analyses were conducted to evaluate whether the assumptions of linearity, normality, and homoscedasticity were met. Variance inflation factor values were reviewed to detect potential multicollinearity. A similar regression model was created for the association between CoA and intracranial volumes. All analyses were performed using IBM SPSS Statistics 25 (Armonk NY, USA). A two-tailed $p$-value <0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics

Of the 25 included CoA patients, two patients had incomplete datasets: in one patient the 3T MRI demonstrated extensive artifacts, while in another patient the 7T MRI could not be performed due to logistical reasons. As prespecified in the study protocol, these patients were replaced but their available data were used for analysis. Therefore, a total of 27 CoA patients and 25 controls were included. Baseline characteristics of all participants are displayed in Table 1. Median age was 22 years (range 12-72) in CoA patients and 24 years (range 12-64) in controls. CoA patients were more frequently hypertensive and more likely to use antihypertensive medication when compared to controls.

### Cardiac and aortic parameters

In Table 2, cardiac and aortic parameters are presented. There were no significant differences in LV volumes and ejection fraction between the groups. PWV in the aortic arch (5.9 ± 2.2 vs. 4.9 ± 1.1 m/s, $p$=0.04), descending aorta (5.7 ± 2.0 vs. 4.6 ± 1.6 m/s, $p$=0.03), and total thoracic aorta (5.6 ± 1.5 vs. 4.7 ± 1.1 m/s, $p$=0.02) were increased in CoA patients versus controls. Inversely, distensibility of the ascending aorta was reduced in the patient group ($6.1 \cdot 10^{-3}$ ± $4.1 \cdot 10^{-3}$ vs. $8.5 \cdot 10^{-3}$ ± $3.6 \cdot 10^{-3}$ $mmHg^{-1}$, $p$=0.03).

**Table 1. Baseline characteristics.**

| | CoA n = 27 | Control n = 25 | *p*-value |
|---|---|---|---|
| Age (years) | 22 (12-72) | 24 (12-64) | 0.65 |
| Female sex | 10 (37) | 7 (28) | 0.56 |
| BMI (kg/m²) | 22.9 ± 3.8 | 22.1 ± 2.9 | 0.39 |
| Hypertension | 17 (63) | 6 (24) | **0.006** |
| Use of any AHM | 6 (22) | 0 | **0.02** |
| SBP (mmHg) | 136 ± 13 | 127 ± 15 | **0.04** |
| DBP (mmHg) | 81 ± 8 | 79 ± 10 | 0.32 |
| Pulse pressure (mmHg) | 54 ± 13 | 48 ± 13 | 0.12 |
| Arm-leg SBP gradient (mmHg) | -5 ± 14 | | |
| Age at initial CoA repair (years) | 0 (0-28) | | |
| Type of initial CoA repair | | | |
| End-to-end anastomosis | 19 (70) | | |
| Patch angioplasty | 5 (19) | | |
| Subclavian flap angioplasty | 1 (4) | | |
| Surgery, technique unknown | 2 (7) | | |
| Intervention for recurrent CoA | 5 (19) | | |
| Bicuspid aortic valve | 13 (48) | | |
| Ventricular septal defect | 6 (22) | | |

Data are presented as mean ± SD, median (range) or number (percentage).
AHM, antihypertensive medication; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

**Table 2. Cardiac and aortic parameters.**

| | CoA n = 27 | Control n = 25 | *p*-value |
|---|---|---|---|
| LV ejection fraction (%) | 57 ± 3 | 57 ± 5 | 0.56 |
| LV mass index (g/m$^2$) | 46 ± 11 | 48 ± 11 | 0.48 |
| LV end-diastolic volume (ml/m$^2$) | 96 ± 12 | 103 ± 17 | 0.10 |
| LV end-systolic volume (ml/m$^2$) | 41 ± 7 | 45 ± 10 | 0.12 |
| PWV aortic arch (m/s) | 5.9 ± 2.2 | 4.9 ± 1.1 | **0.04** |
| PWV descending aorta (m/s) | 5.7 ± 2.0 | 4.6 ± 1.6 | **0.03** |
| PWV total thoracic aorta (m/s) | 5.6 ± 1.5 | 4.7 ± 1.1 | **0.02** |
| Distensibility ascending aorta ($\cdot 10^{-3}$ mmHg$^{-1}$) | 6.1 ± 4.1 | 8.5 ± 3.6 | **0.03** |

Data are presented as mean ± SD.
LV, left ventricular; PWV, pulse wave velocity.

**Hemodynamic parameters in the cerebral arteries**

Table 3 provides the association of CoA with hemodynamic parameters in various segments of the cerebral arterial tree, corrected for age, sex, and the presence of hypertension. Mean flow velocity was higher in the right ICA (β=6.1 cm/s, $p$=0.02), left ICA (β=6.8 cm/s, $p$=0.006), and BA (β=5.2 cm/s, $p$=0.007) in CoA patients compared to controls, whereas the distensibility was lower in the right ICA (β=-2.3·$10^{-3}$ $mmHg^{-1}$, $p$=0.048) and BA (β=-6.4·$10^{-3}$ $mmHg^{-1}$, $p$<0.001). Similarly, in the right and left MCA a higher mean flow velocity and lower distensibility were observed in CoA patients, although only the lower distensibility in the left MCA reached statistical significance (β=-1.8·$10^{-3}$ $mmHg^{-1}$, $p$=0.001). CoA was not associated with altered velocity PI or mean flow in the ICA, BA, and MCA. In the perforating arteries, no significant differences between CoA patients and controls were found in mean flow velocity and velocity PI. Additionally, CoA patients and controls were comparable with regard to the number of detected perforating arteries in the basal ganglia (25 ± 8 vs. 25 ± 6, respectively; $p$=1.0) and centrum semiovale (72 ± 15 vs. 74 ± 16, respectively; $p$=0.64).

Subgroup analyses in CoA patients showed no difference in mean flow velocity and distensibility in the ICA and BA between patients with and without BAV, although patients with BAV tended to have a lower mean flow velocity in the right ICA (β=-6.2 cm/s, $p$=0.07), left ICA (β=-6.3 cm/s, $p$=0.07) and BA (β=-4.2 cm/s, $p$=0.11) (Supplemental Table 2). Similarly, hypertension status and age at initial CoA repair were not significantly associated with hemodynamic parameters in the ICA and BA (Supplemental Table 3 and Supplemental Table 4, respectively).

**Total cerebral blood flow**

White matter CBF was 25.6 ± 5.1 ml/100 g/min in CoA patients and 24.3 ± 5.9 ml/100 g/min in controls ($p$=0.42). Grey matter CBF values were 50.4 ± 10.6 and 51.4 ± 10.4 ml/100 g/min, respectively, for CoA patients and controls ($p$=0.74). When corrected for age, sex, and the presence of hypertension, CoA diagnosis was not associated with altered white matter CBF nor grey matter CBF.

**Presence of vascular brain injury**

The prevalence of white matter hyperintensities, cortical microinfarcts, lacunes, and microbleeds was low in CoA patients and controls with no substantial differences between the groups (Table 4). No patient had an occlusive lesion of the carotid arteries. As an incidental finding, a 9 mm left ICA bifurcation aneurysm was detected on a 7T T1-weighted image in a 43-year-old male CoA patient (Figure 2). Due to the substantial risk of rupture as determined by the consulted neurologist, the patient underwent successful surgical clipping of the aneurysm.

**Table 3. Association between CoA and hemodynamic parameters in the cerebral arteries.**

| | Mean flow velocity (cm/s) | | Velocity PI | | Mean flow (ml/s) | | Distensibility ($\cdot 10^{-3}$ mmHg$^{-1}$) | |
|---|---|---|---|---|---|---|---|---|
| | β (SE) | *p*-value | β (SE) | *p*-value | β (SE) | *p*-value | β (SE) | *p*-value |
| Right ICA | 6.1 (2.4) | **0.02** | -0.10 (0.06) | 0.10 | -0.38 (0.57) | 0.50 | -2.3 (1.1) | **0.048** |
| Left ICA | 6.8 (2.3) | **0.006** | -0.14 (0.07) | 0.06 | -0.22 (0.56) | 0.70 | -2.5 (1.4) | 0.08 |
| Basilar artery | 5.2 (1.8) | **0.007** | -0.08 (0.06) | 0.18 | -0.25 (0.23) | 0.28 | -6.4 (1.3) | **<0.001** |
| Right MCA, M1 segment | 2.1 (2.1) | 0.32 | -0.004 (0.03) | 0.90 | 0.06 (0.19) | 0.76 | -0.7 (0.4) | 0.09 |
| Left MCA, M1 segment | 2.4 (2.3) | 0.30 | 0.01 (0.04) | 0.80 | -0.03 (0.17) | 0.87 | -1.8 (0.5) | **0.001** |
| Perforating arteries BG | -0.1 (0.2) | 0.68 | -0.02 (0.03) | 0.46 | NA | NA | NA | NA |
| Perforating arteries CS | 0.1 (0.1) | 0.62 | 0.01 (0.03) | 0.81 | NA | NA | NA | NA |

The unstandardized regression coefficient (β) indicates the absolute change of a parameter in CoA patients relative to controls. All analyses were adjusted for age, sex, and the presence of hypertension.

BG, basal ganglia; CS, centrum semiovale; ICA, internal carotid artery; MCA, middle cerebral artery; NA, not applicable; PI, pulsatility index; SE, standard error.

**Table 4. Presence of vascular brain injury, i.e. white matter hyperintensities, cortical microinfarcts, lacunes, and microbleeds.**

| | CoA | Control |
|---|---|---|
| **Fazekas score for periventricular WMH** | n = 26 | n = 25 |
| 0 | 23 (88) | 22 (88) |
| 1 | 2 (8) | 3 (12) |
| 2 | 1 (4) | 0 |
| 3 | 0 | 0 |
| **Fazekas score for deep WMH** | n = 26 | n = 25 |
| 0 | 21 (81) | 21 (84) |
| 1 | 4 (15) | 4 (16) |
| 2 | 1 (4) | 0 |
| 3 | 0 | 0 |
| **No. of cortical microinfarcts** | n = 24 | n = 25 |
| 0 | 24 (100) | 24 (96) |
| 1 | 0 | 1 (4) |
| 2 | 0 | 0 |
| **No. of lacunes** | n = 26 | n = 25 |
| 0 | 26 (100) | 25 (100) |
| 1 | 0 | 0 |
| 2 | 0 | 0 |
| **No. of cerebral microbleeds** | n = 25 | n = 25 |
| 0 | 23 (92) | 25 (100) |
| 1 | 1 (4) | 0 |
| 2 | 1 (4) | 0 |

Data are presented as number (percentage).
WMH, white matter hyperintensities.

### Intracranial volumes

No association was observed between CoA diagnosis and intracranial volumes (Table 5). However, although non-significant, CoA patients tended to have a lower white matter volume (β=-21.4 $cm^3$, $p$=0.08), lower grey matter volume (β=-16.1 $cm^3$, $p$=0.28), and higher cerebrospinal fluid volume (β=11.0 $cm^3$, $p$=0.40).



## DISCUSSION

In this study, we performed a detailed assessment of the aortic and cerebral hemodynamics and the presence of vascular brain injury in patients with CoA. The combination of two complementary high-field strength MRI scans (3T and 7T) allowed for a unique analysis of the entire arterial vascular tree from central aorta to the proximal and distal cerebral arteries. Our results indicate that CoA patients have an increased flow velocity and decreased distensibility

in the aorta and proximal cerebral arteries. In this relatively young cohort of CoA patients, no substantial vascular brain injury was observed.

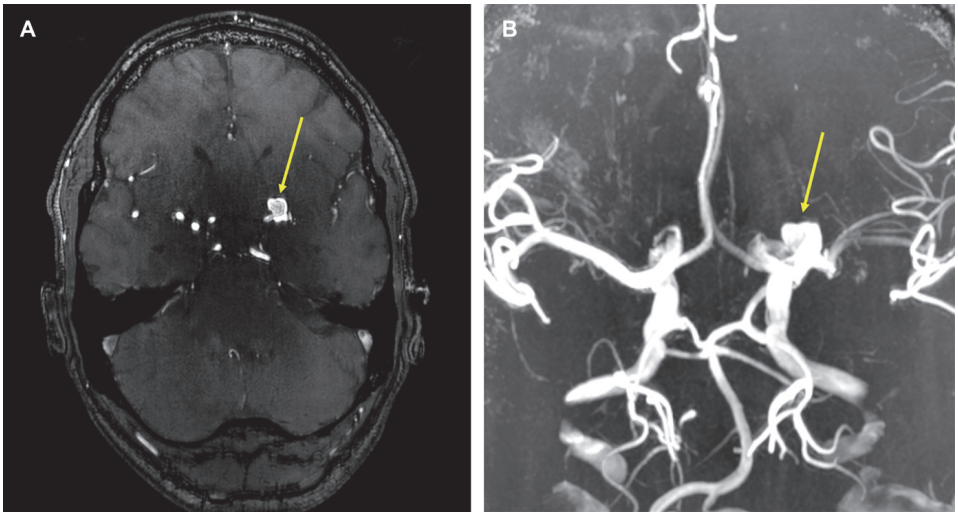


**Figure 2. A 9 mm bifurcation aneurysm of the left internal carotid artery in a 43-year-old male CoA patient.** (A) The aneurysm was incidentally detected on a 7T T1-weighted image (transversal view). (B) Subsequently, phase-contrast angiography was performed (coronal view). The aneurysm is indicated by the yellow arrows. The patient underwent successful neurosurgical clipping of the aneurysm.

**Table 5. Association between CoA and intracranial volumes.**

| | β (SE) | *p*-value |
|---|---|---|
| CSF volume ($cm^3$) | 11.0 (12.9) | 0.40 |
| WM volume ($cm^3$) | -21.4 (12.1) | 0.08 |
| GM volume ($cm^3$) | -16.1 (14.6) | 0.28 |
| TIV ($cm^3$) | -26.3 (28.0) | 0.35 |
| CSF/TIV (%) | 1.0 (0.7) | 0.15 |
| WM/TIV (%) | -0.8 (0.5) | 0.12 |
| GM/TIV (%) | -0.2 (0.6) | 0.74 |
| Average cortical thickness (mm) | -0.002 (0.030) | 0.94 |

The unstandardized regression coefficient (β) indicates the absolute change of a parameter in CoA patients relative to controls. All analyses were adjusted for age and sex.
CSF, cerebrospinal fluid; GM, grey matter; SE, standard error; TIV, total intracranial volume; WM, white matter.

**Proximal to distal cerebral hemodynamics**

Over the last decades, we have learned that CoA is not an isolated condition but should rather be considered as a central arteriopathy. Multiple studies have reported on the structural and hemodynamic abnormalities in the aorta proximal of the CoA.[2,3,26] Elastin fiber fragmentation and extensive collagen deposition result in increased aortic stiffness and increased pulse wave velocity.[2,3] Distal vascular beds are also affected. The brachial arteries were found to be less responsive to flow and nitroglycerine and the retinal arteries show pronounced corkscrew-shaped tortuosity.[27,28] Although involvement of the cerebral arteries seemed likely, especially in light of the increased risk of stroke, no detailed assessment of the cerebral arterial tree had been performed in this patient population.[7,8] In this study, we combined two MRI field strengths to evaluate various segments of the cerebral circulation. We found an increase in mean flow velocity and a decrease in distensibility in the ICA and BA. These findings suggest that these proximal cerebral arteries are involved in the complex, generalized arteriopathy observed in CoA. In the MCA, a similar increase in mean flow velocity and decrease in distensibility was observed, although not all associations reached statistical significance. These findings are in line with the higher resistive index found in the MCA of CoA patients in a previous study.[29] Interestingly, the perforating arteries appeared unaffected. This may be largely attributable to the cerebral autoregulation, which ensures adequate and constant blood flow in these small cerebral arteries. However, as the perforating arteries are too small to reliably assess the arterial wall characteristics (e.g. distensibility), the presence of a local vasculopathy cannot be excluded.

The etiology of the altered cerebral hemodynamics in the proximal cerebral arteries remains unclear. An important question is whether this is inborn or acquired. Specifically, it is unknown whether these changes are inherent to the structural condition of CoA and thus already present during prenatal development, or attributable to secondary processes such as chronic hypertension, or a combination of both. Increased aortic stiffness has already been identified in the neonatal phase and could not be resolved by adequate early surgical repair, which suggests an inborn etiology.[26] On the other hand, the impaired elasticity that we observe in the proximal cerebral arteries is also seen in individuals with chronic hypertension.[30] Additionally, an important role of hypertension is suggested by the increased carotid intima-media thickness found in CoA patients and the high incidence of hemorrhagic stroke relative to ischemic stroke in this patient population.[7,8] Our subgroup analyses showed that the extent of altered cerebral hemodynamics was not dependent on age of initial repair nor on the presence of hypertension, although the study was not adequately powered for these analyses. Interestingly, patients with an associated BAV tended to have a lower flow velocity in the ICA and BA. This finding is likely attributable to the eccentric blood flow and resulting energy loss within the ascending aorta in patients with BAV.[31]

**Vascular brain injury**

It is plausible that the altered cerebral hemodynamics in CoA patients could contribute to vascular brain injury, as increased carotid stiffness is strongly associated with cardiovascular risk and atherosclerosis.[32,33] However, in contrast to previous studies we observed no substantial vascular brain injury (including small vessel disease) compared to controls. This is an important finding, since recent data indicate that the hazard of hemorrhagic and ischemic stroke in CoA patients is 12.5-17.3 and 4.0 times higher, respectively, in comparison to the general population.[7,8] Furthermore, stroke occurs approximately 20 years earlier in CoA patients compared to non-CoA patients.[9] However, there may be an important effect of era. CoA patients from these previous studies generally underwent surgical repair with less sophisticated techniques and at a later age, thus being exposed longer to the adverse effects of CoA with increased blood pressure proximal to the aortic narrowing. In contrast, most patients in our study underwent early and technically advanced repair. This may partly explain the low incidence of vascular brain injury observed in our study, which is a reassuring finding for the current generation of CoA patients. Preserved cerebral autoregulation may also (partly) prevent vascular brain injury in this relatively young cohort. However, hypertension, diabetes mellitus, and hypercholesterolemia are known risk factors for a future decline in cerebral autoregulation.[34-36] This illustrates the importance of reducing the cumulative effects of (modifiable) risk factors other than CoA during lifetime follow-up. Alternative causes of stroke in CoA patients should also be considered, such as thromboembolic complications from atrial arrhythmias. Although none of the patients in this study had documented atrial arrhythmias, we previously showed that the prevalence of supraventricular tachycardia is more than 10-fold higher in CoA patients compared to individuals <50 years from the general population.[37] Importantly, considering the normal LV dimensions and function in our patients, there was no evidence of adverse arterio-ventricular interaction.

**Future directions**

Since this is the first exploratory study that provides a comprehensive overview of the aortic and cerebral hemodynamics and the presence of vascular brain injury in CoA patients, several aspects remain to be addressed in future studies. Ideally, a longitudinal study is performed to evaluate how cerebral hemodynamics change over time and to identify the potential cumulative effects of cardiovascular risk factors like hypertension, diabetes, and hypercholesterolemia, which may occur later in life. Furthermore, the growing population of older adults with CoA could enhance the possibilities of including patients aged >40 years. Additionally, it would be informative to study CoA patients who experienced a stroke or transient ischemic attack. For instance, the presence of carotid occlusions and atrial arrhythmias in these patients could increase our understanding of the pathophysiological mechanisms involved.

**Limitations**

One of the limitations of this study is that no systematic assessment of intracranial aneurysms was performed due to the relatively small sample size. Additionally, although mean flow velocity and distensibility in the ICA and BA were statistically different between CoA patients and controls, our study may have been underpowered to detect statistically significant differences in these parameters in the MCA. Another limitation is that the study population consisted mainly of children and young adults, which limits the conclusions that can be drawn regarding CoA patients of older age. Furthermore, our findings cannot be directly extrapolated to patients who underwent stent implantation for native or recurrent CoA, as these patients were excluded from this study.

## CONCLUSIONS

In this exploratory study using 3T and 7T MRI, patients with CoA showed altered aortic and cerebral hemodynamics, mainly expressed by an increased flow velocity and reduced distensibility in the aorta and proximal cerebral arteries. These findings support the hypothesis that CoA is characterized by a generalized arteriopathy that extends into the cerebral arterial tree. Reassuringly, we found no evidence of substantial vascular brain injury in this relatively young CoA population. However, due to the large hypertensive burden and the increased risk of stroke demonstrated by previous studies, close follow-up and adequate risk factor control remain of the utmost importance.

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## SUPPLEMENTAL MATERIAL

**Supplemental Table 1. Imaging parameters of the 3T cardiac/aortic, 3T brain, and 7T brain MRI scans.**

| **3T cardiac/aortic imaging** | | |
|---|---|---|
| **Sequence** | **Imaging parameter** | **Value** |
| bTFE cine | FOV, mm | 270 x 270 |
| | Acquired voxel size, mm | 2.0 x 2.0 x 8.0 |
| | Flip angle, º | 45 |
| | TR, ms | 2.7 |
| | TE, ms | 1.4 |
| | Acquired temporal resolution, ms* | 50 – 84 |
| | Acquisition time, min:s† | 0:08 |
| 2D phase-contrast | FOV, mm | 320 x 260 |
| | Acquired voxel size, mm | 2.5 x 2.5 x 8.0 |
| | Flip angle, º | 10 |
| | TR, ms | 4.7 |
| | TE, ms | 2.8 |
| | Acquired temporal resolution, ms | 9.4 |
| | Acquisition time, min:s | 1:59 (HR 51) |
| **3T brain imaging** | | |
| **Sequence** | **Imaging parameter** | **Value** |
| 3D T1 | FOV, mm (FHxAPxRL) | 256 x 232 x 192 |
| | Acquired voxel size, mm | 1.0 x 1.0 x 1.0 |
| | Flip angle, º | 7 |
| | TR, ms | 8.2 |
| | TE, ms | 4.5 |
| | TI, ms | 1161 |
| | Acquisition time, min:s | 5:39 |
| 2D phase-contrast | FOV, mm | 256 x 256 |
| | Acquired voxel size, mm | 1.1 x 1.1 x 5.0 |
| | Flip angle, º | 10 |
| | TR, ms | 9.1 |
| | TE, ms | 5.5 |
| | Acquired temporal resolution, ms | 18.2 |
| | Venc (cm/s) | 220 |
| | Acquisition time, min:s | 2:33 (HR 54) |
| ASL (pCASL) | FOV, mm | 240 x 240 |
| | Acquired voxel size, mm | 3.0 x 3.0 x 7.0 |
| | Flip angle, º | 90 |

| | | |
|---|---|---|
| | TR, ms | 4400 |
| | TE, ms | 15.5 |
| | Number of label-control pairs | 40 |
| | Acquisition time, min:s | 6:00 |
| 3D FLAIR | FOV, mm (FHxAPxRL) | 250 x 250 x 180 |
| | Acquired voxel size, mm | 1.0 x 1.0 x 1.0 |
| | Flip angle, º | 90 |
| | TR, ms | 5000 |
| | TE, ms | 292 |
| | TI, ms | 1700 |
| | Acquisition time, min:s | 6:15 |
| SWI | FOV, mm | 320 x 320 |
| | Acquired voxel size, mm | 0.78 x 0.78 x 2.0 |
| | Flip angle, º | 13 |
| | TR, ms | 45.0 |
| | TE, ms | 31.0 |
| | Acquisition time, min:s | 1:21 |
| **7T brain imaging** | | |
| **Sequence** | **Imaging parameter** | **Value** |
| 3D T1 | FOV, mm (FHxAPxRL) | 350 x 250 x 190 |
| | Acquired voxel size, mm | 1.0 x 1.0 x 1.0 |
| | Flip angle, º | 5 |
| | TR, ms | 4.2 |
| | TE, ms | 2.0 |
| | TI, ms | 1292 |
| | Acquisition time, min:s | 2:00 |
| 2D phase-contrast BG | FOV, mm | 250 x 250 |
| | Acquired voxel size, mm | 0.30 x 0.30 x 2.0 |
| | Flip angle, º | 50 |
| | TR, ms | 28.0 |
| | TE, ms | 14.8 |
| | Acquired temporal resolution, ms | 112 |
| | Venc, cm/s | 20 |
| | Acquisition time, min:s | 5:28 (HR 61) |
| 2D phase-contrast CSO | FOV, mm | 250 x 250 |
| | Acquired voxel size, mm | 0.30 x 0.30 x 2.0 |
| | Flip angle, º | 65 |
| | TR, ms | 29.1 |
| | TE, ms | 16.9 |
| | Acquired temporal resolution, ms | 116 |
| | Venc, cm/s | 4 |

| | | |
|---|---|---|
| | Acquisition time, min:s | 5:04 (HR 59) |
| 3D T2*w EPI | FOV, mm (FHxAPxRL) | 230 x 230 x 120 |
| | Acquired voxel size, mm | 0.57 x 0.57 x 0.6 |
| | Flip angle, º | 24 |
| | TR, ms | 70.0 |
| | TE, ms | 20.0 |
| | Acquisition time, min:s | 3:36 |

* Depending on heart rate, range for 80 – 50 bpm.

† Independent of heart rate.

ASL, arterial spin labeling; BG, basal ganglia; bTFE, balanced turbo-field-echo; CSO, centrum semiovale; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; HR, heart rate; pCASL, pseudo-continuous arterial spin labeling; SWI, susceptibility-weighted imaging; TE, echo time; TI, inversion time; TR, repetition time.

**Supplemental Table 2. Association between the presence of a bicuspid aortic valve and mean flow velocity and distensibility in the ICA and basilar artery in CoA patients.**

| | Mean flow velocity (cm/s) | | Distensibility ($\cdot 10^{-3}$ mmHg$^{-1}$) | |
|---|---|---|---|---|
| | β (SE) | *p*-value | β (SE) | *p*-value |
| Right ICA | -6.2 (3.2) | 0.07 | 0.3 (1.1) | 0.79 |
| Left ICA | -6.3 (3.3) | 0.07 | 0.5 (1.2) | 0.72 |
| Basilar artery | -4.2 (2.5) | 0.11 | 0.3 (1.0) | 0.74 |

The unstandardized regression coefficient (β) indicates the absolute change of a parameter in CoA patients with a bicuspid aortic valve relative to CoA patients without a bicuspid aortic valve. All analyses were adjusted for age, sex, and the presence of hypertension.
ICA, internal carotid artery; SE, standard error.

**Supplemental Table 3. Association between hypertension (as assessed by 24-hour ABPM) and mean flow velocity and distensibility in the ICA and basilar artery in CoA patients.**

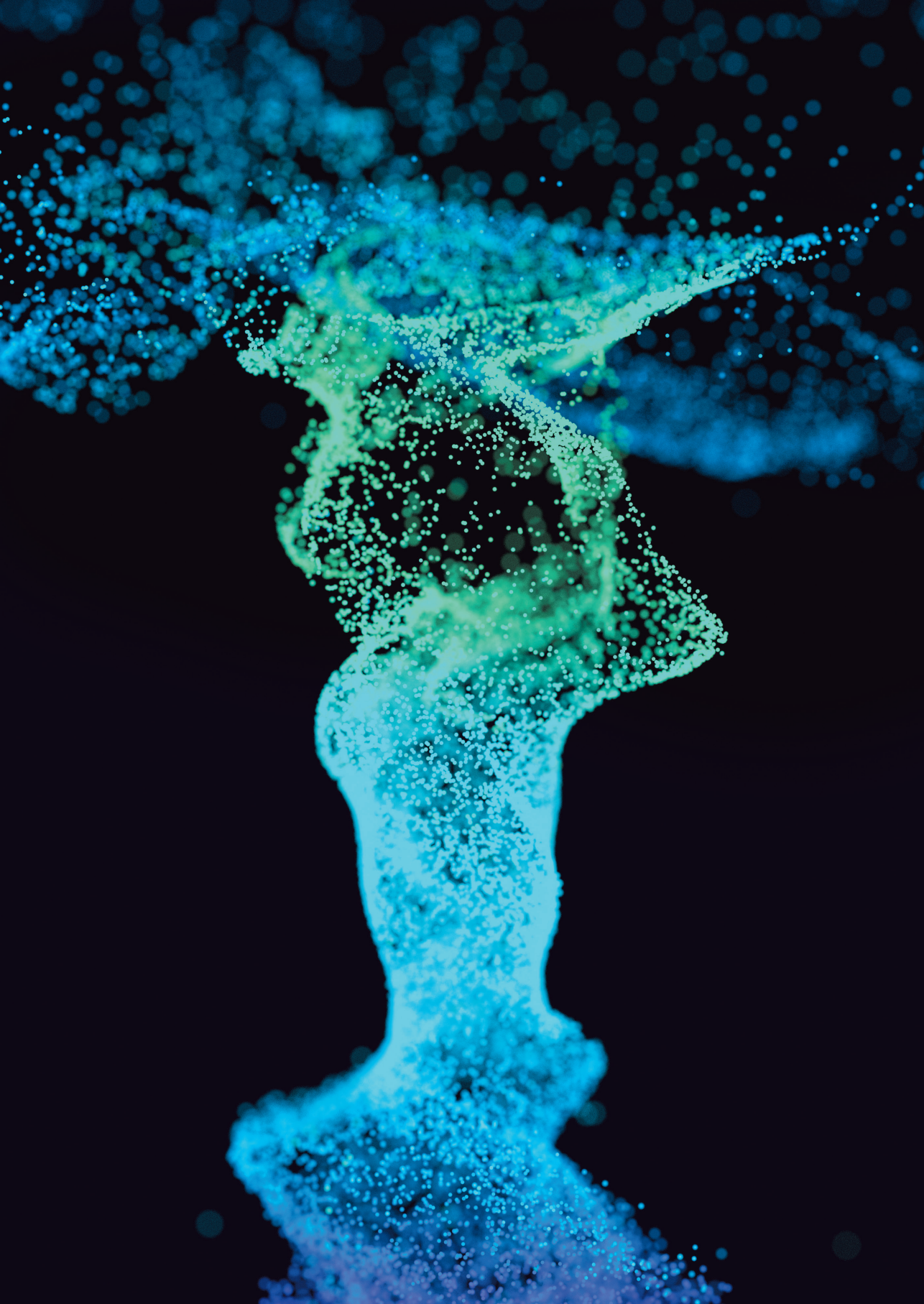
| | Mean flow velocity (cm/s) | | Distensibility ($\cdot 10^{-3}$ mmHg$^{-1}$) | |
|---|---|---|---|---|
| | β (SE) | *p*-value | β (SE) | *p*-value |
| Right ICA | -0.8 (3.9) | 0.84 | -1.3 (1.3) | 0.31 |
| Left ICA | 1.9 (4.0) | 0.64 | -0.5 (1.5) | 0.72 |
| Basilar artery | 2.8 (3.0) | 0.36 | -0.7 (1.2) | 0.55 |

The unstandardized regression coefficient (β) indicates the absolute change of a parameter in hypertensive CoA patients relative to normotensive CoA patients. All analyses were adjusted for age and sex.
ICA, internal carotid artery; SE, standard error.

**Supplemental Table 4. Association between age at initial CoA repair and mean flow velocity and distensibility in the ICA and basilar artery in CoA patients.**

| | Mean flow velocity (cm/s) | | Distensibility ($\cdot 10^{-3}$ mmHg$^{-1}$) | |
|---|---|---|---|---|
| | β (SE) | *p*-value | β (SE) | *p*-value |
| Right ICA | 0.04 (0.47) | 0.94 | 0.07 (0.15) | 0.66 |
| Left ICA | 0.59 (0.55) | 0.30 | 0.13 (0.20) | 0.52 |
| Basilar artery | 0.48 (0.32) | 0.16 | 0.01 (0.13) | 0.92 |

The unstandardized regression coefficient (β) indicates the absolute change of a parameter with one year increase in age at initial CoA repair. All analyses were adjusted for age, sex, and the presence of hypertension.
ICA, internal carotid artery; SE, standard error.



# CHAPTER 10

## General discussion and future perspectives

## GENERAL DISCUSSION

The survival of patients with congenital heart disease (CHD) has drastically improved over the last six to seven decades, which is largely attributable to advances in surgical and percutaneous treatment. Currently, nearly 90% of patients with CHD survive into adulthood.[1] As the population of adults with CHD is rapidly growing, it has become evident that long-term complications frequently occur. Patients with coarctation of the aorta (CoA), previously regarded as a relatively benign and easily repaired lesion, show signs of generalized vascular dysfunction leading to various cardiovascular sequelae, including hypertension, aortic aneurysm formation, and premature atherosclerotic disease.[2,3] Early correction of CoA is critical, as it is associated with improved survival and may counteract the development of vascular dysfunction.[4,5] Although surgery is the preferred treatment for neonates, infants, and young children with CoA, stent implantation is nowadays the treatment of choice in older children and adults.[6,7] In this thesis, we study the indications for and outcomes of stent implantation, as well as the long-term clinical outcome in patients with CoA.

In **chapter 2**, we provide an overview of the epidemiology, clinical findings, and therapeutic modalities in CoA. The significance of early detection is illustrated by a patient whose CoA diagnosis was delayed until adulthood despite several years of difficult-to-control hypertension. Since most children and young adults with hypertension initially present to the general practitioner, we focused primarily on the specific clinical findings during physical examination that may suggest the presence of CoA.

### Part I: Evaluation and optimization of stent implantation for aortic coarctation

Stent implantation for CoA has shown to effectively relief the obstruction with little or no residual pressure gradient.[8] However, aortic wall injury may occur, resulting in dissection, rupture, or (pseudo)aneurysm formation. Therefore, post-interventional aortic imaging by CT or MR angiography is indicated.[6,7] Additionally, regular follow-up imaging is recommended to assess stent integrity and to rule out late (pseudo)aneurysms or recurrent CoA.[6,7] It has been proposed that the use of covered stents could decrease the risk of (pseudo)aneurysms in comparison to bare metal stents, although this is not substantiated by previous research.[9] Importantly, compared with balloon angioplasty, the risk of (pseudo)aneurysm formation is lower after stent implantation.[10] Furthermore, the stent prevents recoil of the arterial wall, resulting in a decreased incidence of recurrent CoA.[11,12] Despite the successful relief of the obstruction and the relatively low risk of complications associated with stenting, insufficient evidence exists regarding late clinical outcome. In **chapter 3**, we investigated the effect of stenting on arterial blood pressure after medium-term follow-up (≥12 months) by performing a systematic review and meta-analysis. After pooling the results of 26 studies with a median follow-up duration of 26 months, stenting was associated with a systolic and diastolic blood

pressure reduction of 20 and 8 mmHg, respectively. These findings suggest that the favorable short-term outcomes of stenting are sustained at medium-term follow-up. It is conceivable that this blood pressure reduction may attenuate the future risk of cardiovascular events, although this has not been demonstrated yet. This chapter also shows that the largest reduction in systolic blood pressure (SBP) is observed in patients with native CoA and patients with a higher SBP and peak systolic gradient at baseline.

The current ESC guideline for adult congenital heart disease states that "repair of coarctation or re-coarctation is indicated in hypertensive patients with an increased non-invasive gradient between upper and lower limbs confirmed with invasive measurement (peak-to-peak ≥20 mmHg) with preference for catheter treatment (stenting), when technically feasible (Class I recommendation, Level of evidence C)".[6] The invasive peak systolic gradient also plays an important role in case of contradictory or inconclusive clinical findings, such as hypertension with a non-invasive gradient <20 mmHg. However, since the blood pressure is generally lower during cardiac catheterization due to the vasodilatory effects of general anesthesia or conscious sedation, the invasive peak systolic gradient may be underestimated.[13,14] This may mask the hemodynamic relevance of CoA. Consequently, intervention may not be performed despite the presence of a significant CoA. Therefore, in **chapter 4**, we introduce a novel technique called epinephrine stress testing, in which we administer epinephrine intravenously during cardiac catheterization to counteract the hypotensive effects of anesthesia. Almost half of the patients with a baseline peak systolic gradient ≤20 mmHg had an epinephrine peak systolic gradient >20 mmHg. Most of these patients (88%) underwent intervention, whereas the majority of patients with an epinephrine peak systolic gradient ≤20 mmHg (77%) were treated conservatively. At medium-term follow-up, patients with a high epinephrine peak systolic gradient who underwent intervention showed a substantial reduction in blood pressure and required less antihypertensive medication compared to patients with a low epinephrine peak systolic gradient treated conservatively. These results suggest that epinephrine stress testing may aid in determining the hemodynamic relevance of CoA during cardiac catheterization. However, the potential benefit of intervention in these patients should always be evaluated against the background of the potential harms. Although complications were rare in this study, the risk-benefit ratio of epinephrine stress testing should be further assessed in future (preferably prospective) studies.

Prior to surgical repair, hypoplasia of the aortic arch is observed in up to 75% of patients with CoA.[15] Depending on the surgical technique and subsequent growth of the arch, aortic arch hypoplasia may persist after repair.[16,17] Other aberrant morphologies of the aortic arch, such as a gothic- or crenel-shaped arch, may also be observed in this patient population. It has been shown that aortic arch morphology may be a substrate for hypertension in patients with CoA.[18] Although stent implantation could prove beneficial in these patients, it is theoretically associated with higher risks than CoA stenting, which is mainly related to the proximity of the

supra-aortic conduit arteries. Until now, only small retrospective studies have been performed, with contradictory results. In one study no peri-procedural complications occurred.[19] In two other studies the incidence of adverse events was substantial (10-31% of patients).[20,21] However, these adverse events mostly occurred in small patients (<10 kg), patients with a functional univentricular circulation, or in case no rapid pacing was used during the procedure. In **chapter 5**, we present our experiences with aortic arch stenting in 12 patients. The arch diameter and area significantly increased with successful reduction of the pressure gradient. A concomitant reduction in blood pressure and antihypertensive medication was observed after a mean follow-up of 14 months. Importantly, no major complications occurred peri-procedurally or during follow-up. These data suggest that aortic arch stenting can be safely performed with favorable short- and medium-term efficacy. However, it is imperative that the operators have a thorough understanding of the anatomy of the aortic arch by means of a pre-procedural CT or MR angiography. Preferably, 3D rotational angiography is performed during the procedure. Other factors that may positively influence procedural outcome are balloon interrogation and rapid pacing. Potential complications of arch stenting are similar to those of CoA stenting, although the anatomical location may pose unique challenges. This is illustrated by **chapter 6**, in which we describe the case of a CoA patient with four prior aortic interventions and two stents in situ in the aortic arch. Due to persistent hypertension and a significant pressure gradient, a third stent in the aortic arch was placed and post-dilated. Despite no signs of aortic wall injury at the end of the procedure, CT angiography was performed the next day, which is standard protocol in our center. This showed a 17x12 mm pseudoaneurysm ventral to the additionally placed stent. Pseudoaneurysm formation is a life-threatening complication of aortic stenting, as the risk of rupture is high.[22] The patient was no candidate for open repair due to the prior interventions and placement of an additional covered stent was not considered feasible. Hence, endovascular coil embolization was performed. Despite its frequent use by interventional radiologists in the treatment of intracranial aneurysms, this was the first post-stenting aortic pseudoaneurysm treated by endovascular coil embolization, to our knowledge. This chapter illustrates that although a pseudoaneurysm may not be present or visible intra-procedurally, it may quickly develop and expand during the first days after stenting. Therefore, we propose CT angiography before hospital discharge in all patients undergoing stenting for CoA or aortic arch hypoplasia.

**Part II: Long-term clinical outcome in aortic coarctation**

Despite improvements in detection, repair techniques and follow-up of CoA, patients remain at increased risk of mortality at the adult age.[23] The majority of these patients die from a cardiovascular cause.[24] Coronary artery disease, heart failure, and sudden cardiac death have previously been identified as the most common causes of mortality.[3] However, other cardiovascular complications, including stroke, aortic aneurysms, and arrhythmias, also

frequently occur and may have a negative impact on quality of life. As most previous studies were either small or focused on specific complications, it is difficult to determine the exact burden of cardiovascular disease in adult patients with CoA. In **chapter 7**, we provide an overview of the cardiovascular morbidity and mortality in a cohort of 920 adult patients with prior CoA repair. Despite a young median age of 24 years, 191 patients (21%) experienced at least one cardiovascular event during a mean follow-up of 9.3 years. These data illustrate the high cardiovascular burden in adults with CoA. Although the highest incidences were observed for aortic complications and arrhythmias, 34 cases of stroke or transient ischemic attack occurred. Especially in this young population, this may have a detrimental effect on quality of life. The highest risk of cardiovascular events was observed in patients with late initial repair and patients with an elevated left ventricular (LV) mass index. This emphasizes the importance of early detection and treatment of CoA, as already addressed in chapter 2, to minimize the harmful effects associated with untreated CoA. These effects include severe hypertension, increased LV afterload, and adverse LV remodeling. In addition to the observed morbidity, all-cause mortality was 3.3-fold increased in comparison to a cohort from Dutch general population matched for age and sex. In summary, the data in this chapter do not support the previous assumption that CoA is a relatively benign condition after successful repair. Instead, this patient population is at increased risk of a variety of major cardiovascular complications, which requires lifetime monitoring. A better understanding of the pathophysiology of late cardiovascular complications in CoA is needed, as this may lead to improvements in risk stratification and prevention.

The occurrence of cardiovascular complications is thought to be largely attributable to the high prevalence of hypertension in CoA patients.[3,25] As described in the introduction of this thesis, multiple factors may play a role in het etiology of hypertension. However, accumulating evidence suggests that hypertension in these patients is mainly caused by the presence of a diffuse arteriopathy and resulting vascular dysfunction.[26] This is in contrast to the prior general belief that CoA is a localized lesion. In particular, CoA patients are found to have a stiffer, less compliant ascending aorta due to elastic fiber fragmentation, as well as a dampened response of the brachial arteries to chemical and flow-mediated stimuli.[27,28] Vascular adaptation to exercise may also be impaired, since a hypertensive response to exercise is present in 19-35% of patients with CoA.[29-33] Although there is a consensus regarding the therapeutic and prognostic consequences of resting hypertension, the implications of a hypertensive response to exercise are less clear. In **chapter 8**, we examined 675 patients with repaired CoA who underwent exercise stress testing. Nearly half of these patient (44%) had a hypertensive response to exercise, which is an even higher proportion compared to previous studies. In this chapter, we identified factors associated with an increased SBP during peak exercise, which were male sex, absence of a bicuspid aortic valve, and increased resting SBP. Additionally, we show that peak exercise SBP correlates with resting SBP at follow-up, both when measured in

office and with 24-hour ambulatory blood pressure monitoring. This association is particularly of importance, since it was corrected for resting SBP at baseline. This suggests that the blood pressure response during exercise provides clinically relevant information in addition to conventional resting blood pressure measurements. In contrast, we found no association between peak exercise SBP and cardiovascular complications. This may be partly due to the demographic characteristics of the study population. Possibly, a hypertensive response to exercise does not predispose for cardiovascular events at this relatively young age, but instead from the fifth or sixth decade. Furthermore, the mean follow-up duration of 10.1 years may not be long enough to detect significant differences between patients with and without a hypertensive response to exercise.

As previously described, chapter 7 showed that long-term follow-up was frequently complicated by stroke, despite the young median age of the study population (24 years). Previous studies have also demonstrated an increased risk of stroke in CoA patients in comparison to the general population, with a hazard ratio of 4.0 for ischemic stroke and a rate ratio of 12.5 to 17.3 (depending on the subtype) for hemorrhagic stroke.[34,35] The pathophysiology of stroke in these patients is not fully elucidated. Intracranial aneurysms have been detected in up to 10% in of adult patients by CT or MR angiography.[36-38] Although these tend to be small, the rate of progression and risk of rupture have not yet been investigated.[38] As previously discussed, CoA is characterized by a diffuse arteriopathy affecting the pre-stenotic aorta and large conduit arteries. However, it is unclear whether and how the cerebral arterial tree is affected. Therefore, in **chapter 9** we examined the hemodynamics from the aorta to the proximal and distal cerebral circulation in CoA patients and age- and sex-matched controls. Especially the small perforating arteries are difficult to visualize with conventional MR imaging. Hence, we used a combination of 3 tesla and 7 tesla MRI to assess the entire arterial tree ranging from the aorta and carotid arteries to the perforating arteries in the basal ganglia and centrum semiovale. We demonstrated that CoA patients have an increased flow velocity and decreased arterial distensibility in the aorta and proximal cerebral arteries when compared to control subjects. These data suggest that the (proximal) cerebral arterial tree is involved in the diffuse arteriopathy observed in CoA patients. In contrast, we found no differences in hemodynamic parameters in the small perforating arteries, which may be due to preserved cerebral autoregulation. In this contemporary cohort of CoA patients with relatively early repair, we observed no substantial vascular brain injury. Although this is a favorable finding, it implies that stroke likely occurs at a later age, considering the increased risk of stroke demonstrated by previous studies. It also suggests that the risk of stroke in patients with CoA may be reduced by adequate control of cardiovascular risk factors, most notably hypertension. However, this association should be further explored in longitudinal studies.

## FUTURE PERSPECTIVES

CoA is a complex disease, characterized by a diffuse arteriopathy resulting in vascular dysfunction and premature atherosclerosis. Patients may experience a wide variety of cardiovascular complications during adulthood, which requires lifelong follow-up. Although notable progress has been made in the surgical and percutaneous treatment of CoA, improving long-term prognosis through prevention of late cardiovascular complications will remain an important area of focus. This may be achieved by further optimization of therapeutic strategies and improved management during follow-up, which will be discussed in this section.

### Optimization of therapeutic strategies

When technically feasible, stenting is the preferred treatment of native and recurrent CoA in adult patients.[6] Stent implantation leads to excellent short-term outcomes and a lower rate of complications compared to surgery and balloon angioplasty.[8,11,39] Furthermore, in chapter 3 we show that stenting is associated with a 20 mmHg SBP reduction at medium-term follow-up. In light of these favorable outcomes, it is important to carefully evaluate the indications for stenting. The recent ESC guideline recommends intervention in patients with hypertension and a non-invasive and invasive gradient ≥20 mmHg.[6] However, the cut-off value of 20 mmHg is rather arbitrary and was proposed in the era before stent implantation was widely performed.[40] Given the contemporary efficacy and safety of stenting, one may argue that in patients with a gradient between 15 and 20 mmHg, or perhaps even lower, the benefit of stenting may outweigh the potential risks. It is sensible that the ESC guideline adheres to the cut-off value of 20 mmHg for the simple reason that there is no sufficient data to support a lower cut-off value. Future research efforts may be focused on determining the optimal cut-off value, taking into account the anticipated benefit in terms of blood pressure, LV afterload, and cardiovascular risk, versus the risks associated with intervention.

Important developments in stent implantation for CoA are expected for the upcoming 10 to 15 years. First, improvement of the stent design is imperative. The optimal stent has sufficient radial strength, a suitable cover, and is compliant enough to be used for aortic arch stenting as well. It is also desirable that the stent can be pre-mounted on balloons of different sizes and that the sheath size is as small as possible to reduce the risk of groin complications. Second, treatment and control of the CoA site is currently the main focus, whereas less attention is paid to the anatomy of the aortic arch. Clinicians should routinely assess patients for the presence of aortic arch obstruction (e.g. secondary to a gothic or hypoplastic arch). In case of supporting clinical and radiographic findings, the possibility of aortic arch stenting should be considered. It is also important to address aortic arch hypoplasia during initial CoA repair in young children, which has become more widely recognized over the last years.[41] Third, reduction of radiation exposure during stenting is of main interest, especially since a substantial

proportion of stenting procedures is performed in children. Interventions guided by MRI in CHD patients were previously found to be feasible and were associated with less radiation exposure compared to fluoroscopically-guided interventions.[42,43] Additionally, a pilot study in five CoA patients showed promising results.[44] Another novel technique using Fiber Optic RealShape (FORS) technology was recently developed and implemented in our center for abdominal and peripheral endovascular procedures, although its applicability may be expanded to cardiovascular procedures in the near future. Early results indicate adequate feasibility and safety and suggest potential benefit in reducing radiation exposure.[45] Another advantage of both MRI- and FORS-guiding is the intra-procedural 3D visualization of the arterial anatomy. Fourth, a better understanding of aortic flow patterns may contribute to improved patient selection and timing of stent implantation. Advanced imaging modalities like 4D flow MRI and computational fluid dynamics (CFD) are currently being investigated and have the potential to be incorporated in clinical care in the upcoming years.[46,47] Fifth, patient selection may be improved by using pharmacological stress testing, which has shown to be useful in determining the hemodynamic relevance of CoA in chapter 4. However, the choice of pharmacological agent and the desired increase in cardiac output remain to be addressed in future studies.

**Management during follow-up**

Management of CoA patients during follow-up is primarily focused on the early detection of restenosis and aneurysm formation, assessment of associated lesions such as a bicuspid aortic valve, and guideline-directed medical therapy for hypertension. Early diagnosis and treatment of hypertension is crucial, as hypertension already contributes to the development of atherosclerotic disease during childhood in CoA patients.[48] Early antihypertensive treatment may attenuate the process of arterial remodeling. Of children between 7 and 16 years with prior CoA repair, 30% has hypertension.[49] However, hypertension is often not adequately recognized in children with CoA.[50] This may be partly due to a subset of patients with masked hypertension during office measurements. Ambulatory blood pressure measurements have shown to be more sensitive than office measurements in detecting hypertension in the pediatric and adult CoA population.[18,51] Therefore, it is imperative that the use of ambulatory measurements is expanded in the upcoming years. One of the reasons why ambulatory measurements may identify masked hypertension is the exaggerated rise in blood pressure during daily activities (including exercise) observed in CoA patients.[31] In chapter 8, we show that 44% of adult CoA patients have a hypertensive response to exercise, which predisposes for future hypertension at rest. However, the question whether normotensive patients with an isolated hypertensive response to exercise should receive antihypertensive therapy remains unanswered and may be investigated in subsequent studies.

LV mass index is associated with the occurrence of cardiovascular complications in CoA patients, as shown in chapter 7. Interestingly, LV mass index was previously found to be

increased in patients with CoA compared to controls despite similar SBP.[52] Therefore, it has been questioned whether blood pressure is the most adequate measure of LV afterload in patients with CoA. Due to the abnormal structure and function of the aortic wall, larger backward compression waves are observed in CoA patients.[53] Importantly, the correlation between the magnitude of these backward compression waves and LV mass appears to be stronger than the correlation between SBP and LV mass.[53] Also echocardiographic indices like elastance index and total arterial compliance were superior to SBP in predicting LV mass.[52] In the near future, these parameters may play a role in determining the optimal antihypertensive strategy for individual patients. Due to the generalized vascular dysfunction and high burden of atherosclerotic disease in patients with CoA, statin therapy may be considered. However, a previous randomized study with 3 years of follow-up showed no effect of atorvastatin on carotid intima media thickness nor cardiovascular events, despite a reduction in LDL cholesterol.[54] As hypertension was the strongest determinant of progression of carotid intima media thickness in this study, blood pressure has remained the main target in the prevention of long-term cardiovascular complications.

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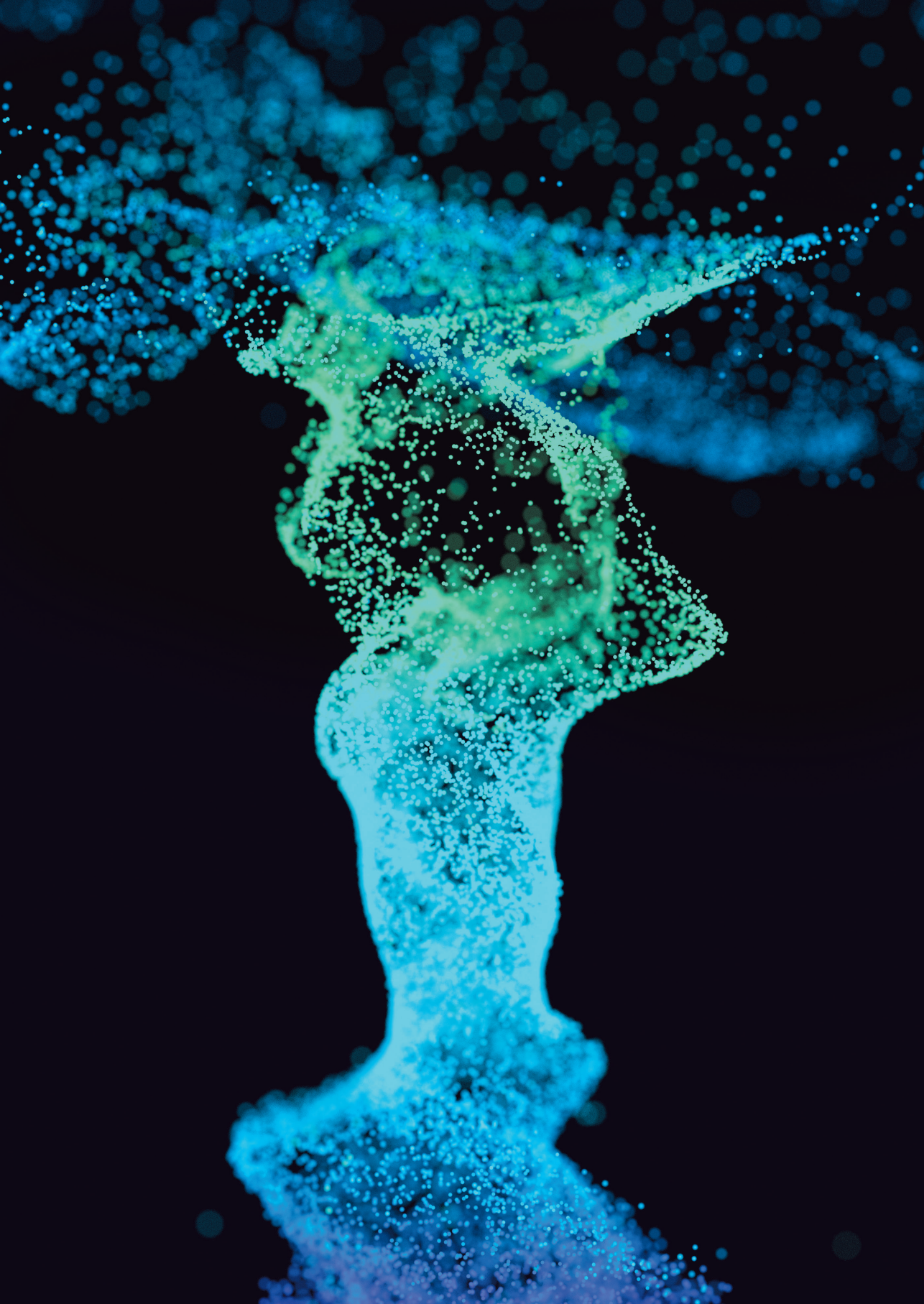

# APPENDIX

## NEDERLANDSE SAMENVATTING

Coarctatio aortae (CoA) is een aangeboren hartafwijking die voorkomt bij 3 tot 4 op de 10.000 levendgeborenen. Daarmee vormt het 5-6% van alle aangeboren hartafwijkingen. De aandoening kenmerkt zich door een vernauwing van het proximale gedeelte van de aorta descendens, ter hoogte van de insertie van de ductus arteriosus. Hoewel CoA kan voorkomen als een geïsoleerde aandoening, heeft ruim de helft van de patiënten tevens een bicuspide aortaklep. Als CoA niet behandeld wordt, is de prognose slecht met een gemiddelde levensverwachting van 32 jaar. De mogelijkheid om CoA chirurgisch te corrigeren heeft geleid tot een drastische verbetering van de overleving. Daarnaast zijn de laatste decennia minder invasieve, percutane technieken ontwikkeld, namelijk ballondilatatie en stentimplantatie. Uit eerdere studies is gebleken dat stentimplantatie is geassocieerd met een lager risico op recidieven (re-coarctaties) en lokale aneurysmata vergeleken met ballondilatatie. Stentimplantatie is echter minder aantrekkelijk bij kinderen <30 kg, aangezien bij deze patiënten vaak re-dilataties van de stent nodig zijn om te compenseren voor de somatische groei. Voor neonaten, zuigelingen en jonge kinderen met CoA is derhalve chirurgische correctie nog steeds de aangewezen therapie. Bij oudere kinderen en volwassenen heeft stentimplantatie de voorkeur.

Ondanks de vooruitgang in chirurgische en percutane behandelmogelijkheden, hebben CoA patiënten op de lange termijn na correctie een verhoogd risico op complicaties. Zo kunnen re-interventies nodig zijn vanwege een re-coarctatie of lokale aneurysmavorming. Tevens is hypertensie een belangrijk probleem tijdens de follow-up. Vijftien jaar na de initiële correctie heeft ongeveer twee derde van de patiënten hypertensie. Het merendeel van deze patiënten heeft geen aanwijzingen voor een re-coarctatie als oorzaak van de hypertensie. Derhalve blijft de origine vaak onbekend en lijkt deze multifactorieel bepaald te zijn. Eén van deze factoren is een toegenomen stijfheid van de aorta proximaal van de vernauwing. Daarnaast tonen ook de brachiale arteriën tekenen van vasculaire dysfunctie. Deze bevindingen hebben ertoe geleid dat CoA niet langer wordt beschouwd als een lokale stenose, maar als een meer diffuse arteriopathie. Andere factoren die mogelijk bijdragen aan hypertensie bij deze patiëntengroep zijn een verhoogde activatie van het renine-angiotensine-aldosteron systeem, baroreceptor dysfunctie en een afwijkende morfologie van de aortaboog. Patiënten met CoA hebben een verhoogd risico om op relatief jonge leeftijd hypertensie-gerelateerde complicaties te ontwikkelen, waaronder ritmestoornissen, coronairlijden en cerebrovasculaire accidenten (CVA's). Hoewel de groep volwassen CoA patiënten in omvang toeneemt door betere detectie en behandeling op de kinderleeftijd, is er nog veel onduidelijk over de incidentie, ontstaansmechanismen en preventie van deze late cardiovasculaire complicaties.

In **hoofdstuk 2** van dit proefschrift wordt aan de hand van een casus het belang van vroege detectie van CoA besproken. Daarnaast wordt een overzicht gegeven van de

epidemiologie, diagnostiek en behandelopties van deze aandoening. Aangezien kinderen en jongvolwassenen met hypertensie zich vaak initieel bij de huisarts presenteren, wordt voornamelijk ingegaan op de kenmerkende bevindingen bij het lichamelijk onderzoek die wijzen op het bestaan van een CoA. De overige inhoud van dit proefschrift bestaat uit twee delen. Het eerste deel is gewijd aan het evalueren van de effectiviteit en veiligheid van stentimplantatie en het optimaliseren van de indicatiestelling voor deze behandeling. In het tweede deel wordt getracht meer inzicht te krijgen in de lange termijn uitkomsten bij volwassen CoA patiënten.

**Deel I: Evaluatie en optimalisatie van stentimplantatie voor coarctatio aortae**

Stentimplantatie is bewezen effectief gebleken in het opheffen van de anatomische vernauwing en het verlagen van de bloeddrukgradiënt. Daarnaast leidt het op korte termijn tot een significante reductie van de bloeddruk. Het is echter niet duidelijk of dit gunstige effect op de bloeddruk behouden blijft tijdens de follow-up. Derhalve hebben wij in **hoofdstuk 3** een meta-analyse uitgevoerd, waarin werd gekeken naar het beloop van de bloeddruk vanaf pre-implantatie tot een follow-up van minimaal 12 maanden na de procedure. De gepoolde resultaten van 26 studies met een mediane follow-up van 26 maanden toonden een systolische en diastolische bloeddrukreductie van respectievelijk 20 en 8 mmHg. Deze substantiële reductie suggereert dat de gunstige hemodynamische effecten van stentimplantatie behouden blijven tijdens de follow-up, wat mogelijk kan bijdragen aan een vermindering van het aantal toekomstige cardiovasculaire complicaties. Daarnaast werd bekeken welke factoren het sterkst geassocieerd zijn met een bloeddrukreductie na stentimplantatie. De meest uitgesproken bloeddrukdaling werd geobserveerd bij patiënten met een natieve coarctatie en patiënten met een hogere bloeddruk en bloeddrukgradiënt voorafgaand aan de procedure.

De invasief gemeten bloeddrukgradiënt speelt een belangrijke rol bij de indicatiestelling voor stentimplantatie. Deze gradiënt is voornamelijk van belang in het geval van tegenstrijdige of onduidelijke klinische bevindingen, zoals hypertensie in combinatie met een non-invasieve bloeddrukgradiënt onder de afkapwaarde van 20 mmHg. De invasieve gradiënt kan echter onderschat worden tijdens een hartkatheterisatie vanwege de bloeddrukverlagende effecten van algehele anesthesie en sedatie. Dit kan ertoe leiden dat een hemodynamisch relevante CoA niet als zodanig wordt opgemerkt en dus onbehandeld blijft. In **hoofdstuk 4** hebben wij een nieuwe techniek geïntroduceerd, waarbij naast de conventionele invasieve bloeddrukgradiënt ook de bloeddrukgradiënt na intraveneuze toediening van adrenaline wordt gemeten. Bijna de helft van de patiënten met een lage conventionele bloeddrukgradiënt bleek een hoge bloeddrukgradiënt (>20 mmHg) onder adrenaline te hebben. Het merendeel van deze patiënten (88%) onderging stentimplantatie, terwijl de meeste patiënten met zowel een lage conventionele als adrenaline bloeddrukgradiënt (77%) conservatief werden behandeld. De interventiegroep had na een gemiddelde follow-up van 25 maanden een significant lagere bloeddruk en gebruikte minder

antihypertensiva vergeleken met de conservatief behandelde groep. Deze uitkomsten suggereren dat de adrenaline stress test van toegevoegde waarde kan zijn bij het bepalen van de hemodynamische relevantie van CoA. Prospectieve vervolgstudies zijn echter nodig om een zorgvuldige inschatting te maken van de voordelen en risico's geassocieerd met deze techniek.

Voorafgaand aan chirurgische correctie van CoA heeft tot 75% van de patiënten enige mate van hypoplasie van de aortaboog. Afhankelijk van de chirurgische techniek en de groei van de aortaboog, kan deze hypoplasie persisteren na de operatie. Tevens worden frequent andere aberrante vormen van de aortaboog gezien, zoals een gotische boog. Een afwijkende morfologie van de aortaboog is een substraat voor hypertensie, wat potentieel kan worden opgeheven door middel van stentimplantatie. Er is echter theoretisch een hoger risico verbonden aan stentimplantatie in de aortaboog, voornamelijk vanwege de nauwe samenhang met de supra-aortale arteriën. Enkele retrospectieve studies hebben tegenstrijdige resultaten laten zien, wat gedeeltelijk verklaard kan worden door de grote verschillen in patiënt-karakteristieken en toegepaste technieken tussen deze studies. In **hoofdstuk 5** delen wij onze ervaringen met deze procedure bij 12 patiënten. Stentimplantatie in de aortaboog leidde tot een substantiële toename van de diameter en een afname van de bloeddrukgradiënt. Na een gemiddelde follow-up van 14 maanden hadden patiënten een lagere bloeddruk en gebruikten zij minder antihypertensiva. Er traden geen majeure complicaties op. Hoewel deze uitkomsten doen vermoeden dat stentimplantatie in de aortaboog veilig kan worden uitgevoerd met een goede effectiviteit op korte en middellange termijn, zijn meerdere factoren in de voorbereiding en uitvoering van essentieel belang. Door middel van een pre-procedurele computertomografie (CT) of magnetische resonantie (MR) angiografie en een per-procedurele 3-dimensionele rotationele angiografie kan gedetailleerd inzicht worden verkregen in de anatomie van de aortaboog. Daarnaast kunnen balloninterrogatie en snelle pacing tijdens de procedure bijdragen aan een goede uitkomst. Stentimplantatie in de aortaboog kan echter leiden tot moeilijk behandelbare complicaties. Dit wordt geïllustreerd in **hoofdstuk 6**, waarin een casus wordt beschreven van een CoA patiënt met vier eerdere aorta-interventies en twee stents in situ in de aortaboog. Bij deze patiënt werd een derde stent bijgeplaatst vanwege persisterende hypertensie en een significante bloeddrukgradiënt. Hoewel er aan het einde van de procedure geen aanwijzingen waren voor schade aan de aortavaatwand, werd de volgende dag volgens protocol een CT angiografie verricht, waarop een pseudoaneurysma (17x12 mm) ventraal van de bijgeplaatste stent werd gezien. Een pseudoaneurysma is een potentieel levensbedreigende complicatie van stentimplantatie, waarvoor op korte termijn een operatie of interventie noodzakelijk is. Deze patiënt was echter geen kandidaat voor een open procedure en implantatie van een bedekte (covered) stent was technisch niet mogelijk. Derhalve werd besloten tot embolisatie van het pseudoaneurysma met coils. Dit is een techniek die frequent wordt gehanteerd door interventieradiologen in de behandeling van intracraniële aneurysmata, maar het was voor zover bekend de eerste keer dat dit werd toegepast voor een pseudoaneurysma

ontstaan na stentimplantatie in de thoracale aorta. Een belangrijke boodschap van dit hoofdstuk is dat ondanks het feit dat een pseudoaneurysma niet aanwezig of zichtbaar is direct na stentimplantatie, deze zeer snel kan ontstaan en uitbreiden tijdens de eerste dagen na de procedure. Om die reden adviseren wij om bij alle patiënten na stentimplantatie voor aortabooghypoplasie of CoA een CT angiografie te verrichten, uiterlijk voor ontslag uit het ziekenhuis.

**Deel II: Klinische uitkomsten op de lange termijn bij patiënten met coarctatio aortae**

De afgelopen decennia is grote vooruitgang geboekt in het vroeg detecteren en optimaal corrigeren van CoA, waardoor de meeste CoA patiënten in goede gezondheid de volwassen leeftijd bereiken. Het is echter gebleken dat volwassen CoA patiënten een verhoogd risico hebben op cardiovasculaire complicaties en vroegtijdig overlijden. De meest voorkomende oorzaken van overlijden zijn coronairlijden, hartfalen en plotse hartdood, hoewel andere complicaties zoals CVA's, aortale aneurysmata en ritmestoornissen ook frequent optreden. De exacte incidentie van deze complicaties blijft echter onduidelijk, mede vanwege het gebrek aan grote cohortstudies. In **hoofdstuk 7** geven we een overzicht van de cardiovasculaire morbiditeit en mortaliteit in een cohort van 920 volwassen CoA patiënten uit vijf academische centra in Nederland. Ondanks een relatief jonge mediane leeftijd van 24 jaar, trad bij 191 patiënten (21%) een cardiovasculaire complicatie op tijdens een gemiddelde follow-up van 9,3 jaar. De meest voorkomende complicaties waren aneurysmata van de thoracale aorta en ritmestoornissen. Patiënten met een late CoA correctie en een verhoogde linker ventrikel massa index hadden het hoogste risico op cardiovasculaire complicaties. De mortaliteit was 3,3 keer zo hoog als in een voor leeftijd en geslacht gecorrigeerd cohort van de Nederlandse bevolking. Deze resultaten illustreren dat CoA, ook na succesvolle correctie, geen onschuldige aandoening is, maar geassocieerd is met een hoge morbiditeit en mortaliteit. Derhalve is levenslange monitoring vereist. Daarnaast is het van belang om een beter begrip te krijgen van de pathofysiologie van deze complicaties, zodat preventieve strategieën hier in de toekomst op kunnen worden aangepast.

Het wordt verondersteld dat de hoge prevalentie van hypertensie een rol speelt bij het ontstaan van late cardiovasculaire complicaties. Naast hypertensie in rust, tonen CoA patiënten ook vaak een hypertensieve respons op inspanning. Een dergelijke respons wordt gerapporteerd bij 19-35% van de patiënten en kan ook optreden terwijl de bloeddruk in rust normaal is. Er is echter nog geen consensus over de therapeutische en prognostische implicaties van een hypertensieve respons op inspanning. In **hoofdstuk 8** hebben wij 675 volwassen CoA patiënten geanalyseerd die een inspanningstest hebben ondergaan. Van hen bleek 44% een hypertensieve respons op inspanning te hebben, wat zelfs een hoger percentage is dan eerder beschreven. Risicofactoren voor een verhoogde systolische bloeddruk (SBD) tijdens piekinspanning waren het mannelijk geslacht, de afwezigheid van een bicuspide aortaklep en een verhoogde SBD in

rust. Een verhoogde SBD tijdens piekinspanning was geassocieerd met een verhoogde SBD in rust tijdens follow-up, zowel bij een meting op de polikliniek als bij een 24-uurs meting. Deze associatie bleef zichtbaar na correctie voor de rust-SBD gemeten voorafgaand aan de inspanningstest. Dit onderstreept de toegevoegde prognostische waarde van een hypertensieve respons op inspanning in de latere ontwikkeling van hypertensie. Daarentegen was een verhoogde SBD tijdens piekinspanning niet gerelateerd aan het risico op cardiovasculaire complicaties. Dit zou gedeeltelijk verklaard kunnen worden door de demografische karakteristieken van de studiepopulatie. Hoewel het op deze jonge leeftijd nog geen risicofactor was voor cardiovasculaire complicaties, zou dit wel het geval kunnen zijn op oudere leeftijd. Daarnaast is de follow-up duur van 10,1 jaar mogelijk te kort om significante verschillen in cardiovasculaire complicaties vast te stellen.

Ondanks een relatief jonge mediane leeftijd van 24 jaar in het cohort beschreven in hoofdstuk 7, werd bij 34 van de 920 patiënten (4%) een CVA of transient ischemic attack vastgesteld. Deze hoge incidentie wordt bevestigd in andere studies. CVA's komen bij CoA patiënten 4 tot 15 keer vaker voor dan bij de algemene bevolking en tevens op een 15 tot 30 jaar jongere leeftijd. De pathofysiologie van deze CVA's is echter nog niet opgehelderd. Het is bekend dat intracraniële aneurysmata aanwezig zijn bij ongeveer 10% van de volwassen CoA patiënten. Hoewel deze in het algemeen relatief klein zijn, is de snelheid van progressie en het risico op ruptuur nog niet onderzocht. Zoals eerder beschreven, wordt CoA gekenmerkt door een diffuse arteriopathie van de pre-stenotische aorta en de grote aftakkende arteriën, hoewel het niet bekend is of ook de cerebrale arteriën zijn aangedaan. Derhalve hebben wij in **hoofdstuk 9** de hemodynamiek van de aorta en de proximale en distale cerebral arteriën onderzocht bij CoA patiënten en voor leeftijd en geslacht gematchte controles. Aangezien de distale perforerende arteriën moeilijk te visualiseren zijn middels conventionele MR imaging (MRI), hebben we een combinatie van 3 tesla en 7 tesla MRI gebruikt om de volledige arteriële vaatboom vanaf aorta en carotiden tot aan de perforerende arteriën te kunnen analyseren. In dit hoofdstuk laten we zien dat CoA patiënten een verhoogde flowsnelheid en een verminderde distensibiliteit hebben in de aorta en de proximale cerebrale arteriën vergeleken met controles. Dit suggereert dat de proximale cerebrale arteriën betrokken zijn in het diffuse vasculaire ziekteproces dat CoA kenmerkt. In tegenstelling tot deze proximale arteriën, werden geen aanwijzingen gevonden voor afwijkingen in de kleine perforerende arteriën. Daarnaast werd geen substantiële vasculaire hersenschade geobserveerd in deze relatief jonge patiëntengroep. Hoewel dit een gunstige bevinding is, impliceert het dat vasculaire hersenschade waarschijnlijk op een latere leeftijd optreedt, gezien het hoge CVA risico gerapporteerd in eerdere studies. Daarnaast suggereert het dat het adequaat behandelen van cardiovasculaire risicofactoren, in het bijzonder hypertensie, een belangrijke rol kan spelen bij het voorkomen van CVA's, hoewel deze potentiële associatie verder onderzocht dient te worden in longitudinale studies.

**Conclusies**

Coarctatio aortae is een veelvoorkomende maar complexe congenitale hartaandoening. Ondanks vroege chirurgische correctie recidiveert de vernauwing vaak op latere leeftijd, wat behandeld kan worden middels stentimplantatie. In dit proefschrift wordt de effectiviteit van stentimplantatie geëvalueerd en worden nieuwe strategieën belicht die de indicatiestelling en uitkomsten van stentimplantatie kunnen verbeteren. Non-invasieve beeldvormende technieken en aortaboog-stenting zullen naar verwachting een belangrijke rol gaan spelen in de toekomstige ontwikkeling van stentimplantatie. Daarnaast wordt in dit proefschrift inzicht gegeven in het optreden van cardiovasculaire complicaties op de lange termijn en worden potentiële risicofactoren onderzocht. Een beter begrip van de pathofysiologie van deze complicaties is nodig om verdere stappen te zetten op het gebied van risico-inschatting en preventie.

## LIST OF PUBLICATIONS

### Thesis

**Meijs TA**, Warmerdam EG, Slieker MG, Krings GJ, Molenschot MMC, Meijboom FJ, Sieswerda GT, Doevendans PA, Bouma BJ, de Winter RJ, Mulder BJM, Voskuil M. Medium-term systemic blood pressure after stenting of aortic coarctation: a systematic review and meta-analysis. *Heart*. 2019;105(19):1464-1470.

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Assessment of Aortic and Cerebral Hemodynamics and Vascular Brain Injury with 3T and 7T MRI in Patients with Aortic Coarctation. *Submitted.*

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## CURRICULUM VITAE

Timion Amos Meijs was born on February 15, 1991 in Utrecht, the Netherlands. He grew up in Bunnik and attended high school at Openbaar Zeister Lyceum, where he graduated cum laude. During this time, he was ranked among the nation's best youth tennis players. After graduation he chose to move to the United States for two years to combine a study in Human Biology with playing for the men's tennis team at the University of North Carolina, Greensboro.

In 2011, Timion started medical school at Utrecht University. He obtained both the Bachelor's and Master's degree with a cum laude distinction. During medical school, he gained specific interest in medical research during the Honours Programme Bachelor and a scientific internship at Massachusetts General Hospital and Harvard Medical School in Boston, United States. After his return to the Netherlands, he joined the research group of prof. dr. Chamuleau to develop scientific skills in clinical and experimental cardiology. This experience inspired him to pursue a career in the field of cardiology.

After graduating from medical school, Timion decided to first obtain clinical experience in cardiology as a resident not-in-training (ANIOS) at the Diakonessenhuis in Utrecht. In 2018, he started his PhD track in congenital cardiology at the University Medical Center Utrecht, where he was supervised by dr. Voskuil, dr. Krings, and prof. dr. Doevendans. During this track, he had the opportunity to collaborate with cardiologists, pediatric cardiologists, radiologists, neurologists, and researchers from various academic centers. The work presented in this thesis is the result of these multidisciplinary and multicenter efforts. In 2022, Timion has started as a resident in training (AIOS) at the cardiology department of the Amsterdam UMC under supervision of dr. Vis and dr. Robbers-Visser.