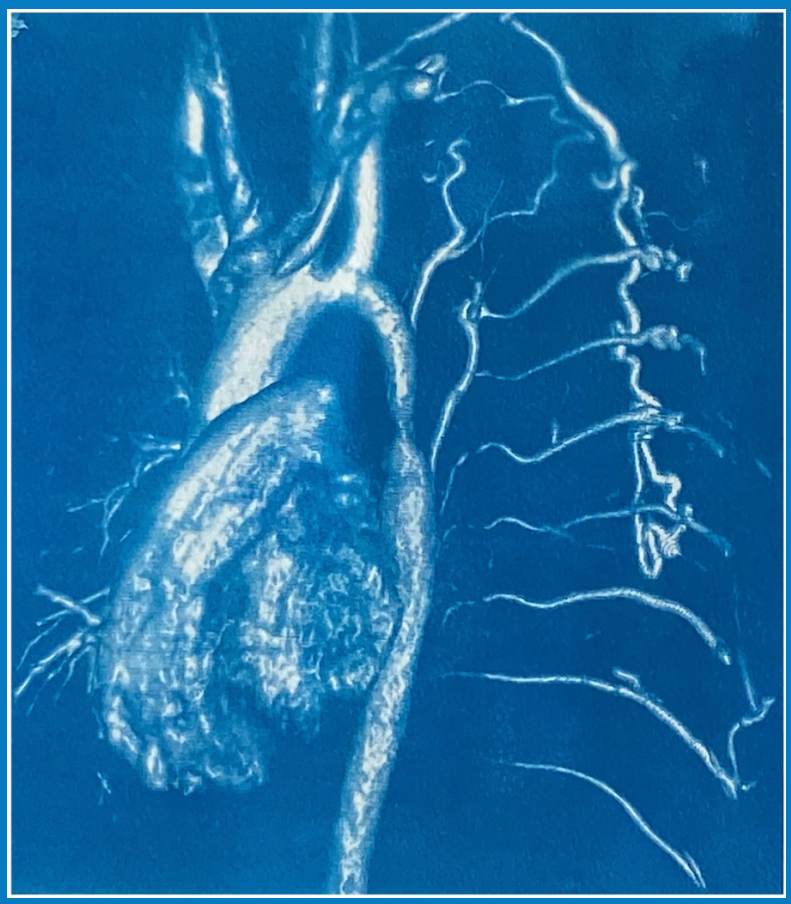
Hemodynamic Considerations after Coarctation Repair



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Hemodynamic Considerations after Coarctation Repair

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“Physician physiologists, often fall into the trap of measuring certain cardiovascular parameters because they can be measured, rather than because they should be measured.”

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Abbreviation List

A	area
ACE	angiotensin converting enzyme
AD	aortic distensibility
AHA	American heart association
ALARA	as low as reasonably achievable
ARB	angiotensin receptor blocker
AS	aortic stenosis
ASD	atrial septal defect
BA	balloon angioplasty
BAV	bicuspid aortic valve
BP	blood pressure
BRS	baroreceptor sensitivity
C	compliance
c-SBP	central aortic systolic blood pressure
CAH	central aortic hemodynamics
CCB	calcium chanel blocker
CFD	computational fluid dynamics
CHD	congenital heart disease
CI	coarctation index
CO	cardiac output
CoA	coarctation of the aorta
CoA-Repair	coarctation of the aorta repair
CVA	cerebro-vascular accident
CT	computed tomography
E	elastance
Ea	arterial elastance
EDPVR	end diastolic pressure volume ratio
Ees	ventricular elastance
ESC	european society of cardiology
ESH	european society of hypertension
ESPVR	end systolic pressure volume ratio
FCW	forward compression waves
FEW	forward expansion waves
FMD	flow mediated dilatation
FSI	fluid structure interaction
GTN	glycerltrinitrate
HAA	hypoplastic aortic arch
Hb	hemoglobin
HHb	deoxygenated hemoglobin
HG	handgrip test
HR	heartrate
HRV	heart rate variability
HT	hypertension

IMT	intima media thickness
ipCOW	incomplete posterior circle of Willis
IVC	inferior vena cava
LV	left ventricle
LVH	left ventricular hypertrophy
LVM	left ventricular mass index
MRI	magnetic resonance imaging
NIRS	near-infrared spectroscopy
O_2	oxygen
P	pressure
PDA	patent ductus arteriosus
PRSW	preload recruitable stroke work
PV	pressure volume
PWV	pulse wave velocity
Q	flow
QO2	oxygen delivery
re-CoA	re-coarctation of the aorta
R	resistance
R_p	peripheral resistance
RAAS	renin-angiotensin-aldosterone-system
RER	respiratory exchange ratio
SBP	systolic blood pressure
SV	stroke volume
TAC	total arterial compliance
TAR	total arterial resistance
TDI	tissue doppler imaging
TOI	tissue oxygenation index
TPR	total peripheral resistance
TTE	transthoracic echocardiography
VA	ventriculo-arterial
VAH	vertebral artery hypoplasia
VO2	oxygen uptake
VCO2	carbon dioxide production
VSD	ventricular septal defect
WIA	wave intensity analysis
Z_c	characteristic impedance

Chapter I General Introduction

1.1 Incidence

Coarctation of the Aorta (CoA) comprises approximately 5-8% of all structural congenital cardiac lesions. It occurs in approximately 4 out of every 10000 live births and has a male predominance [1, 2]. CoA is considered as part of a generalized arteriopathy, and not only a localized narrowing. It can occur as a solitary lesion, but is often associated with other cardiovascular lesions, such as a bicuspid aortic valve (BAV) (50%–75%), aortic arch hypoplasia (HAA), subaortic stenosis, mitral valve abnormalities, ventricular (VSD) and atrial septal defects (ASD) and patent ductus arteriosus (PDA). The most important non-cardiac associated lesion is cerebral aneurysm in 2.5%–10% of patients with CoA. Syndromal associations include Turner - and Williams-Beuren syndrome.

1.2 Clinical Presentation

CoA has a wide morphological variety, from negligible narrowing to near-complete interruption of the aorta and its location varies throughout the aorta, with most occurring para-ductal.

Due to the spectrum of severity and associated pathology the presentation is equally variable. Frequently CoA is diagnosed or suspected on pre-natal echocardiography. The condition can otherwise present clinically soon after birth or it can be found in the elderly as a coincidental post-mortem finding. If the degree of stenosis is mild or moderate, it might go unnoticed and present with hypertension (HT) later in life. It is common for patients with CoA to be treated for essential HT, sometimes for considerable time before the underlying CoA is diagnosed. Frequently the diagnosis is made after HT-related complications or cardiac decompensation.

In neonates the narrowing can be so severe that flow in the descending aorta is dependent on patency of the ductus arteriosus (a duct-dependant systemic circulation). When the duct starts closing in the first hours to days after birth, the lack of distal organ perfusion and abrupt increase of LV afterload leads to metabolic acidosis and shock. The prompt administration of prostaglandin E to keep the duct patent is usually effective in stabilizing the patient and reversing shock.

Occasionally coarctation is diagnosed on routine clinical examination in the first days of life due to the absence of femoral pulsations. Ideally, early detection and treatment can prevent decompensation and shock and therefore astute clinical

examination including the palpation of femoral pulses in neonates should be routinely performed. In older children and adults, palpation of the femoral pulsations should ideally be part of any routine clinical cardiac examination, and certainly in the presence of HT. The blood pressure (BP) can also be measured in all 4 limbs if there is any doubt.

Unfortunately, it is common that numerous visits to various physicians fail to detect CoA due to the fact that most children have no symptoms. If symptoms do occur, they can be related to HT e.g., headache or claudication. A large percentage of adult patients diagnosed with CoA have had HT for considerable time. This has severe prognostic implications as early treatment of coarctation improves the likelihood of remaining normotensive, and therefore reduces morbidity and mortality in the long-run [3, 4].

1.3 Diagnosis

CoA can be diagnosed prenatally, although it can still not be predicted in all cases [5]. Clinical examination after birth can pick up significant CoA in most cases, if femoral pulses are absent or pulse volume is diminished. Other clinical findings are more subtle and cannot be relied upon to establish the diagnosis. Although a cardiac murmur is not necessarily present, a suprasternal murmur and even a thrill can be found in older children and adults. Also, absolute BP values can be normal. A BP difference between the right arm and one of the lower limbs (or radio-femoral pulse delay) can be useful to establish the diagnosis, with a difference of ≥20mmHg indicating significant CoA [1]. The BP should always be measured in the right arm as the BP can be normal or low in the left arm in CoA with narrowing before the left subclavian artery. Chest X-Ray in adults can occasionally show rib-notching due to collaterals.

CoA is divided into pre-ductal, post-ductal and juxta-ductal type depending on the exact site of the narrowing in relation to the ductus arteriosus, but is frequently described as para-ductal. Occasionally it can occur elsewhere like the proximal transverse arch or the abdominal aorta.

Currently (at least in the paediatric population) the diagnosis is usually confirmed by transthoracic echocardiography (TTE). TTE is generally the first imaging test because of its ease of use and lack of ionizing radiation, however, not all segments of the aorta can be optimally evaluated with this modality, especially in older children and adults. TTE is highly operator dependent and coarctation is a notoriously difficult diagnosis, especially in a neonate, where the duct may still be patent. Occasionally the diagnosis remains tentative until the duct has closed. In neonates and infants, the aortic arch can usually be well visualized, allowing assessment of associated hypoplasia of the arch [6]. TTE is also useful in evaluating associated cardiac lesions. A BAV can be adequately diagnosed by TTE as well. Choudhary et al found a BAV in 66% of patients of whom 5% needed

intervention [7]. The presence of a BAV did not correlate with death or future re-coarctation.

The size of the aortic arch can also be measured with TTE (Figure 1.1). One of the most important prognostic factors in patients treated for coarctation is the presence of aortic arch hypoplasia (HAA).

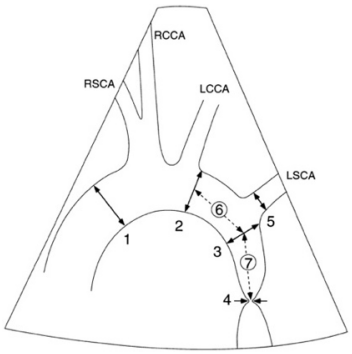
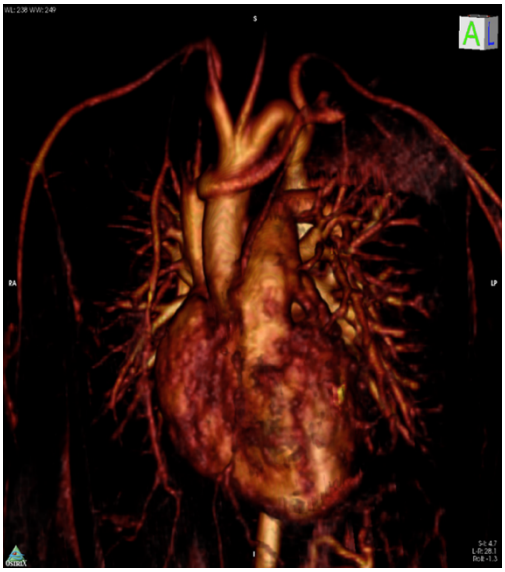


Figure 1.1: Sites of echocardiographic measurements of the aortic arch:
1, ascending aorta diameter;
2, distal transverse aortic arch diameter;
3, aortic isthmus diameter;
4, coarctation site diameter;
5, left subclavian artery diameter;
6, distal transverse aortic arch length; and
7, aortic isthmus length.
RSCA indicates right subclavian artery; RCCA, right common carotic artery; LCCA, left common carotid artery; and LSCA, left subclavian artery.

(Adapted from Kaine et al [8])

HAA can be defined as a transverse arch with a z-score of less than -2 [6]. Another commonly used method is derived from absolute echocardiographic measurements: HAA is established when the diameter of the transverse aortic arch is less than 50% of the ascending or descending aorta diameter. As a rule of thumb in neonates, the diameter of the transverse arch + 1mm should be more than the baby's weight in kilogram. Outcome is significantly worse when a hypoplastic aortic arch is present unless it can be adequately addressed during surgery [9].



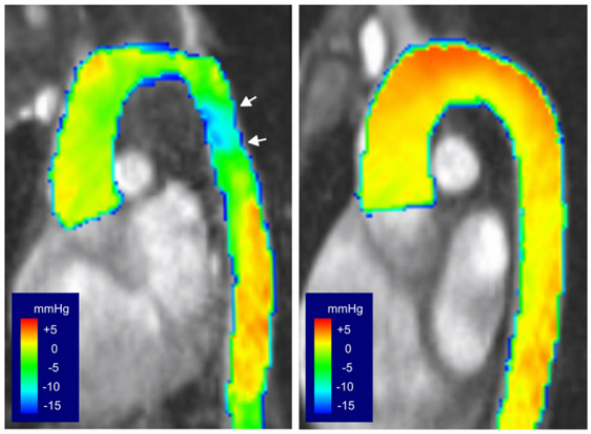
CT (computed tomography) (Figure 1.2) or MRI (magnetic resonance) are commonly used for surgical planning and follow-up of CoA in adults.

Figure 1.2: An example of a 3D reconstruction from MRI data to show arch morphology

(Own data with reconstruction by Author using Osirix®)

The diagnostic use of conventional catheter angiography has almost completely disappeared, as CT and MRI can provide excellent anatomic detail as well as direct and indirect functional data [10].

Imaging with MRI or CT is especially helpful in providing anatomical information, of the CoA itself and aortic arch morphology, prior to intervention (Figure 1.3). The measurements obtained from either CT or MRI can be used to select the interventional material, for instance stent size and stent length. Moreover, this non-invasive imaging modality provides accurate information for surgical planning and follow-up.



Color-coded pressure difference maps at mid systole in a representative patient with good result after aortic coarctation repair (**a**) and a healthy volunteer (**b**). **a** The patient shows a pressure drop at the proximal descending aorta (*arrows*). **b** The healthy volunteer shows homogenous relative pressures in the entire thoracic aorta with a small increase in the aortic arch

Figure 1.3: 4D MRI showing a pressure drop at the isthmus in repaired CoA compared to a normal aorta.

(Addapted from Rengier et al [12])

As MRI also gives functional information like pressure gradients across re-CoA, therapeutical decision-making is facilitated. The non-invasive pressure difference can be mapped with 4D flow in MRI [11]. Pressure maps are derived from flow patterns translated into different colour-codes [12].

4D Phase-contrast MRI is a promising method to investigate the hemodynamics in patient-specific analysis [13]. Another important advantage of these non-invasive imaging modalities is simultaneous evaluation of the heart for associated congenital defects. Disadvantages of MRI include technical difficulties in performing these studies, increased cost, lack of equipment and expertise availability and a lower resolution than CT scans (Figure 1.4). Furthermore, with current MRI sequences and techniques, general anaesthesia is frequently necessary in smaller children due to long breath-holds and moving artifacts.

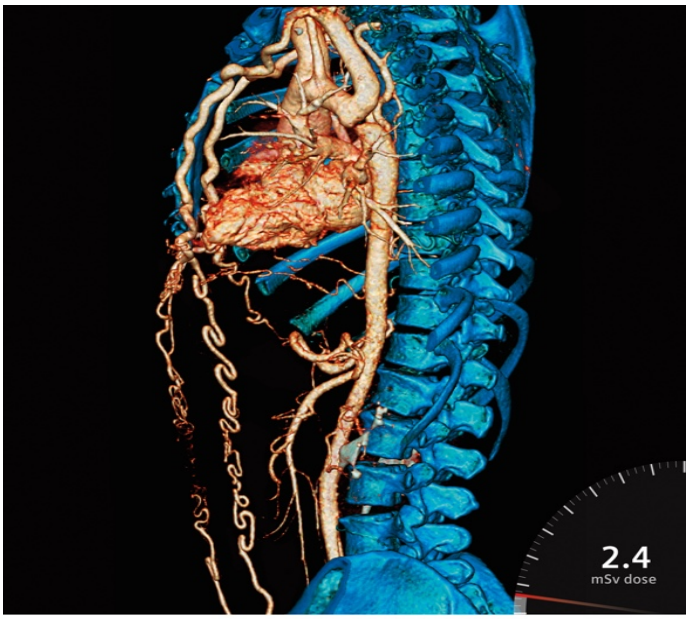


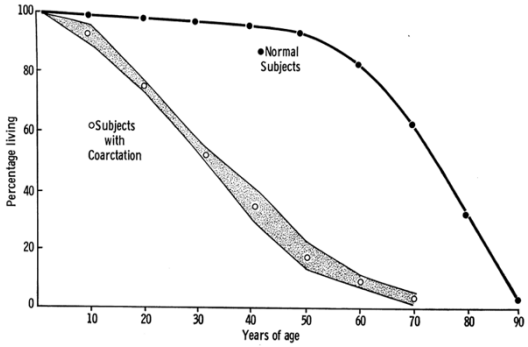
Figure 1.4: Newly diagnosed CoA in an adult

(Siemens International CT Image Contest Winner 2011. Copyright: Liz D'Arcy, Wexford General Hospital, Ireland)

In addition, 3D data from either CT or MRI is increasingly used as an overlay or road-map during interventional procedures, in order to reduce radiation and contrast-usage.

With modern scanning techniques and state-of-the-art CT scanners, the overall radiation burden has also been significantly reduced; however, considering the need for lifelong follow-up of young patients, the radiologist should still be prudent and cautious with the use of these ionizing radiation tools. Radiation remains an important consideration in the cathlab as well, when performing diagnostic or interventional procedures. We looked at diagnostic reference levels (DRL) of radiation during catheterization to monitor radiation exposure in our patients [14] undergoing catheterizations. We found a strong correlation between dose area product (DAP) and body weight x fluoroscopy time (BW x FT) and concluded that this was predictive of diagnostic reference levels (DRL). This facilitates local DRL determination in smaller centers. The most important principle remains using as little as radiation as possible: ALARA (acronym used in radiation safety for “As Low As Reasonably Achievable”) should be used. MRI may therefore be a better option than CT or diagnostic catheterization for most patients, especially for detecting complications like residual narrowing, aneurysms and re-coarctation but CT is frequently preferrable after stenting [10, 15]. The higher resolution and the ability to perform CT in neonates and small infants without anaesthetics can make this the preferred examination in selected cases, despite the burden of radiation. Local expertise and availability of the modalities are important parameters that should be taken into account before making a final decision.

1.4 Natural History



The natural history of CoA was described in the literature before the era of surgical therapy (Figure 1.5). At that time the age of death was on average between 20 and 40 years [16].

Figure 1.5
(Adapted from Crafoord et al [17])

Since 1945 surgery has become a treatment modality for coarctation. Initially it was thought that surgery offered a definitive cure for this condition and many patients were lost to follow-up presenting later with severe hypertension (HT) and heart failure.

The surgical therapy has significantly improved the long-term perspective of these patients. The 20-year survival is 95-97% for patients operated before the age of 20 years, 75% for patients operated on between 20 and 40 years, but only 50% in patients undergoing surgery after the age of 40 years.

The Mayo Clinic examined the records of 819 patients from 1946 to 2005: Actuarial survival rates were 93.3%, 86.4%, and 73.5% at 10, 20, and 30 years, respectively. Mean age of death was 34.2 ± 20.1 years [18]. Older age at repair (>20 years) and pre-operative HT were associated with decreased survival.

1.5 Treatment of Coarctation

Since the first report on surgical treatment of CoA by Crafoord, C et al. in 1947 [17], the outlook for patients with coarctation has improved drastically.

Before a specific treatment modality can be chosen, it is imperative that the general aims of treatment, timing of treatment, current recommendations and diagnostic dilemmas in diagnosing Re-CoA are considered. Only when taking these factors into account can treatment modalities be compared.

The aim of treatment is to reduce the morbidity and mortality, commonly related to the development of HT. Based on the important relationship between HT after CoA repair and age at the time of surgery, the ideal time for repair of coarctation is usually shortly after the diagnosis is made. Patients operated on before the age of 6 months have the lowest incidence of late HT after successful surgical repair [4]. However, the risk of re-CoA is higher with very early repair [19].

Recommendations for intervention in coarctation and re-coarctation of the aorta

Recommendations	Class[a]	Level[b]
Repair of coarctation or re-coarctation (surgically or catheter based) is indicated in hypertensive patients[c] 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.	I	C
Catheter treatment (stenting) should be considered in hypertensive patients[c] with ≥50% narrowing relative to the aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is <20 mmHg, when technically feasible.	IIa	C
Catheter treatment (stenting) should be considered in normotensive patients[c] with an increased non-invasive gradient confirmed with invasive measurement (peak-to-peak ≥20 mmHg), when technically feasible.	IIa	C
Catheter treatment (stenting) may be considered in normotensive patients[c] with ≥50% narrowing relative to the aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is <20 mmHg, when technically feasible.	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Right arm ambulatory blood pressure monitoring should be considered for the diagnosis of hypertension.

In adults, the current guidelines from the ESC Clinical Practice Guidelines for the Management of Adult Congenital Heart Disease 2020 state that treatment should be considered for a non-invasive gradient of 20 mmHg (confirmed by invasive measurement) even in the absence of HT (Figure 1.6 and 1.7) [1].

Figure 1.6: 2020 ESC guidelines: recommendations for intervention.

(Adapted from the European Heart Journal)

Unfortunately, echo-derived doppler gradients are barely useful for quantification of the degree of stenosis, neither in native nor repaired CoA [20]. In the presence of collaterals, gradients can be underestimated. On the other hand, even without narrowing, increased flow rates and thus doppler gradients can be seen after surgery due to decreased aortic compliance and doppler-related pressure recovery. A diastolic tail in the descending aorta and diastolic forward flow in the descending aorta are frequently present in re-CoA [1]. Early diastolic reversal is usually absent in significant coarctation and doppler gradients are low [21].

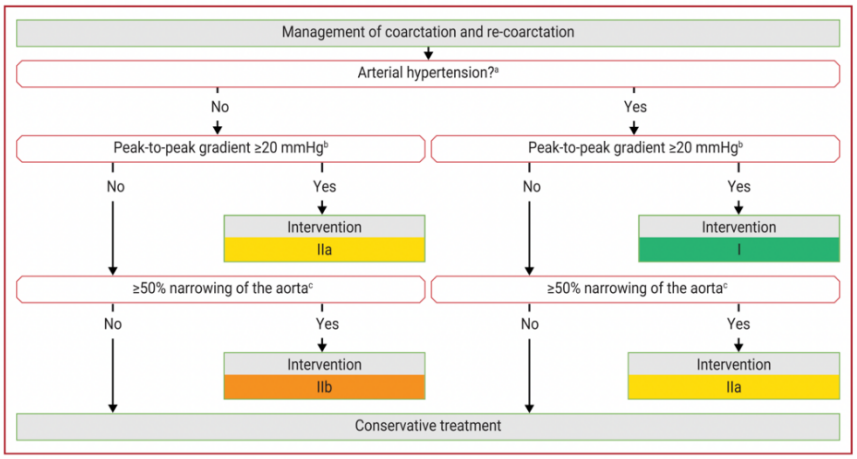


Figure 1.7: 2020 ESC guidelines: management of CoA and re-CoA

(Adapted from the European Heart Journal)

Choosing a treatment modality for CoA: surgery, Balloon Angioplasty (BA) or stenting

Currently there are various treatment options for CoA, depending on the severity, age at presentation, anatomical site and associated conditions. Each treatment option can lead to specific complications, and needs expert follow-up, to diagnose and treat complications early.

Systematic Reviews and Meta-analysis are usually preferred when comparing treatment modalities but they can be difficult to perform and interpret and can find insufficient evidence to reach robust conclusions. Furthermore surgery, stenting and BA are often applied in different patient populations, complicating direct comparison. It is therefore always necessary to make individualized treatment decisions, in a multi-disciplinary setting, taking local expertise into account.

- Comparing Stenting to Surgery:

A recent Cochrane meta-analysis looking at randomized or quasi randomized controlled clinical trials, comparing patients with CoA undergoing open surgery or stent placement, found insufficient evidence. The conclusion was that there was a need to perform further randomized controlled clinical trials [22]. One of the concerns with stenting is the risk of complications related to the large sheath sizes required to deliver them, however, recently stents have been developed requiring smaller calibre access [23].

- Comparing BA to Surgery:

In a recent systematic review and meta-analysis, surgery had a significantly lower incidence of re-coarctation, repeat intervention and residual gradient in mid- to

long-term follow-up, compared to Balloon dilatation alone without stenting. However, Balloon dilatation (BA) resulted in a significantly shorter hospitalization time. Incidence of aneurysm formation, perioperative mortality, complications and immediate residual gradient were not statistically different between surgery and BA [24].

- Comparing BA to Stenting:

Long-term data after BA and stenting is scarce, making it difficult to compare these treatment modalities [25]. A systematic review and meta-analysis found evidence to indicate that primary stenting of CoA achieves superior immediate relief of a relevant pressure gradient compared with BA. In addition, patients undergoing stenting may experience fewer severe complications during hospitalization compared to BA [26]. When carried out in a state-of-the-matter fashion, stenting of the aorta is a safe procedure [27]. It is also possible to safely re-intervene at a later stage after stenting or BA [28].

Age at presentation is another important consideration when deciding on the best treatment option. The mortality with surgical treatment of a simple coarctation in neonates approaches 0% in experienced centres but can reach 7% for the more complex surgical procedures or with associated abnormalities. After primary BA of CoA in neonates, re-intervention (repeat balloon dilatation or surgery) is almost always necessary, however in infants older than 1 year, results were comparable [29]. Therefore, surgery remains the treatment of choice for neonatal treatment of CoA. In exceptional cases interventional treatment (including stenting) can be used in neonates, including delivery via the axillary artery, if surgery is deemed to have an unacceptably high risk [30-32]. Primary stenting is not routinely advocated in small children although that is slowly changing in some centres [33, 34]. The results of BA alone are better than in adults but there is a higher incidence of iliofemoral artery injury compared to surgery and a higher rate of reintervention [25, 29, 35]. The reluctance to perform stenting in the growing child might change in future when bio-absorbable stents become available for clinical usage in CoA. Currently early stent failure with loss of radial force and sirolimus-induced systemic immunosuppression limit the use of Magmaris^{R} absorbable stents in neonates [36].

If CoA presents later, in infants, teenaged children or even adults, it is usually possible to plan an elective surgical or percutaneous repair. In infants and young children with a weight below 25 kg and a hypoplastic aortic arch, most centres prefer surgery. In fact, even in the absence of a hypoplastic aortic arch, many centres still choose surgery as their treatment of choice for these young children, although recent studies show good results of BA in infants [29,37]. In older children and adults, BA alone is associated with an increased risk of reintervention; therefore, primary stenting is considered first-line treatment if little growth of the aorta is anticipated [26, 38], despite a lack of systematic reviews comparing very long-term outcome of stenting vs surgery [1, 38].

Surgical Treatment Options

The initial surgical treatment modality must be chosen with the best long-term prognosis in mind, accounting for the prognostic impact of associated HAA. There are various surgical techniques (Figure 1.8) with resection and (extended) end-to-end anastomosis most frequently used, with or without addressing the hypoplastic aortic arch (HAA).

End-to-side or extended end-to-end repair is advocated for severe HAA or, alternatively, aortic arch reconstruction is proposed with patch enlargement, with the use of median sternotomy and extracorporeal circulation [39].

Different techniques might be necessary in select cases, for instance with the additional use of the subclavian artery, as a flap to address distal arch hypoplasia [40]. For distal Aortic Arch Hypoplasia, a repair combining carotid-subclavian angioplasty and extended end-to-end anastomosis can also be used. A carotid-subclavian anastomosis enlarges the distal arch and shows excellent long-term outcome [41]. Primary patch aortoplasty with foreign material has been abandoned due to the high incidence of aneurysm formation.

End-to-end repair remains the treatment of choice in uncomplicated coarctation without significant hypoplasia of the arch in neonates. The arch with mild distal hypoplasia can grow, especially when operated on early but growth is not always adequate [9]. When significant HAA is present, surgery is the treatment of choice, even in adolescents and adults.

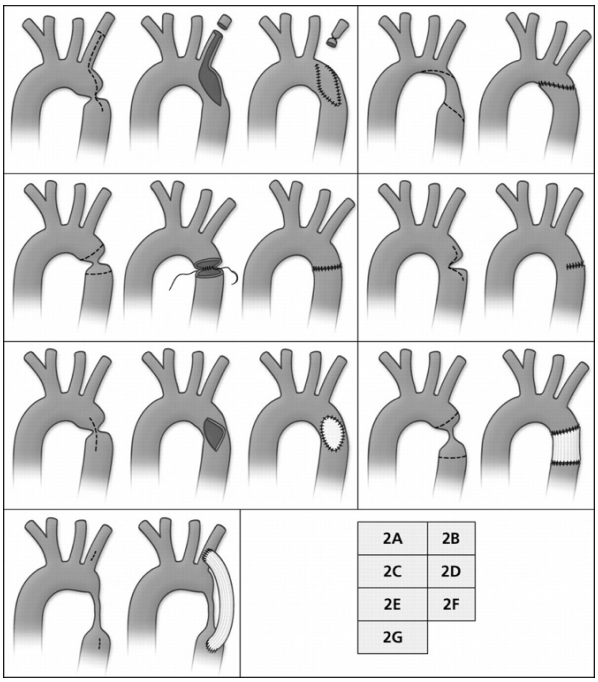


Figure 1.8: Summary of Surgical options.
(A) Subclavian flap.
(B) Resection and end-to-end anastomosis enlarged to the aortic arch.
(C) Resection and end-to-end anastomosis.
(D) Pyloroplasty type.
(E) Patch aortoplasty.
(F) End-to-end conduit interposition.
(G) Left subclavian artery to descending thoracic aorta conduit interposition.

(Adapted from Corno et al [40])

Catheter based treatment options

Percutaneous Treatment options are BA or Stent Placement (bare or covered) of the CoA.

Immediate hemodynamic results are usually comparable between BA and surgery in children older than 1 year, but BA has a higher rate of reintervention (Figure 1.9) and aneurysm formation [29].

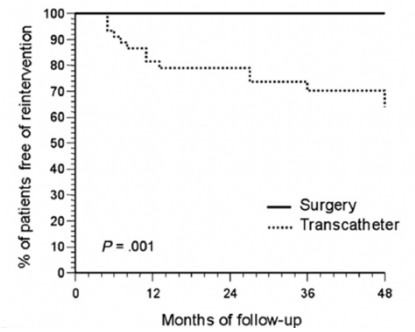


Figure 1.9: reintervention after surgery or transcatheter treatment

(Adapted from Rodes-Cabau et al [29])

Stenting (Figure 1.10 and 1.11) is advocated as primary intervention in older children and adults and can be performed with a bare-metal or a covered stent [1].

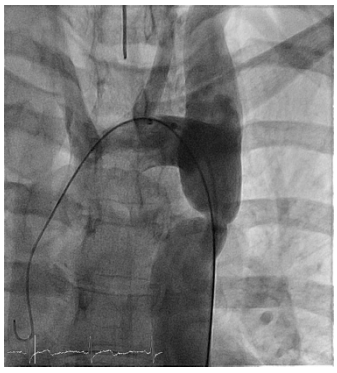


Figure 1.10: Angiography showing a CoA prior to stenting

(Authors own Data)

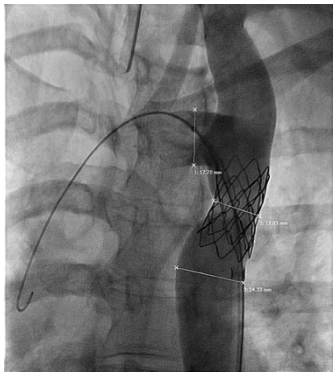
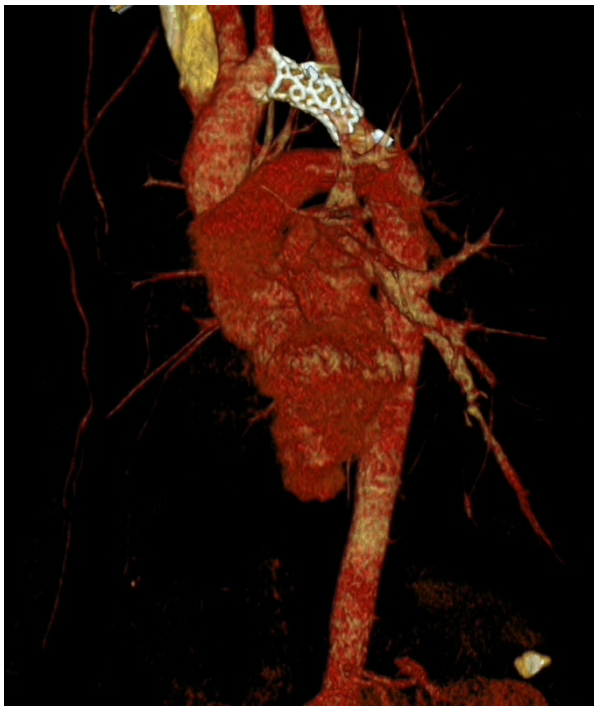


Figure 1.11: Angiography after stenting

Whether to choose a bare-metal stent or a covered stent is still unclear. Rare cases of aortic wall rupture following bare-metal stenting have raised concerns, leading to an increased usage of covered stents even though it is unknown whether covered stents mitigate effectively against rupture, as case reports of aortic rupture have been published after covered stents as well [42]. Occasionally aortic rupture can be treated interventionally with a covered stent placed in the bare-metal stent [43].

In the COAST II trial (Covered Cheatham Platinum Stents for the Prevention or Treatment of Aortic Wall Injury Associated with Coarctation of the Aorta) it was found that various complications occur at an increased rate with covered stents compared to bare-metal stents. Femoral artery injury, occlusion of the left subclavian artery leading to left-arm ischemia, and malposition of the stent which holds far more significance with covered stents [44]. Furthermore, in the extended COAST trial after 48-60 months follow-up, stent fracture occurred in 24,4% and aneurysms in 6,3% [45].

Recently, covered stents have become available which can be delivered via smaller sheaths (Bentley BeGraft^{R}), with a reduction in local complications [46]. A good case can be made for the usage of covered stents in specific situations like pre-existing aneurysm after previous BA, but routine usage of covered stents is probably not preferrable to bare-metal stents. A strategy of sequential dilatation can reduce complications especially in severe aortic narrowing [47, 48].



Regardless of the type of treatment, careful follow-up in a congenital (pediatric) cardiac centre is mandatory. Expertise is required in the various surgical and interventional catheter-based treatment modalities with the necessary equipment for imaging (including CT and cardiac magnetic resonance) (Figure 1.12) and expertise in managing complications.

Figure 1.12: CT after Stenting of the transvers arch

(Own data with reconstruction by the Author using Osirix^{R})

A particularly important question regards the efficacy of applied local therapy. Ideally the treatment aims to leave the least possible residual invasive gradient. The ESC Clinical Practice Guidelines for the Management of Adult Congenital Heart Disease 2020 state that an invasive gradient of 20 mmHg should be treated in patients with CoA or re-CoA, regardless of the presence or absence of HT [1].

1.6 Complications after Treatment

Unfortunately, the idea that CoA is a simple and easily repaired lesion persists and many patients are still lost to follow-up. Various specific complications after treatment have already been discussed when comparing treatment options but it is important to realize that CoA is still associated with substantial morbidity and mortality, resulting in a reduced life expectancy with half of all patients requiring further invasive cardiovascular treatment by 50 years of age [49].

Local Complications

A major cause of reintervention is residual CoA or recurrent CoA. Residual CoA is a narrowing that is present immediately after treatment of CoA, if treatment fails to establish a normal calibre of the repaired zone and recurrent CoA is a narrowing that develops during growth, when the treated segment doesn't grow at the same rate compared to the rest of the aorta.

The severity of the recurrent or residual stenosis is quantified by the coarctation index (CI), defined as the ratio of the diameter of the coarctation zone to the diameter of the descending aorta (D_{CoA}/D_{DAo}). The higher the CI, the lower the severity of the recurrent or residual narrowing.

Re-CoA occurs more commonly in neonates with severe duct-dependent CoA, requiring early repair [19, 50].

HAA is another risk factor promoting the incidence of re-CoA, since some degree of HAA might be left untreated despite extended surgical repair.

Aneurysm-formation has been described after CoA repair by "patch" aortoplasty with the use of artificial patch materials. This complication is seen less frequently in the current era, as awareness of the usefulness of complete resection of ductal tissue has evolved. If this type of repair was performed, careful follow-up with CT/MRI is required to prevent spontaneous rupture [10, 25].

Interventional treatment of (pseudo)aneurysms is possible in selected cases [51]. BA without stenting has a higher incidence of aneurysm formation [35].

Stenting seemed to show a slightly higher chance of local complications compared to BA alone in some studies (1 to 9%) [52] but this was not confirmed [26, 53]. When stenting is performed for CoA in patients with Turner syndrome there is definitely an increased risk of local complications, which can partially be mitigated with the usage of covered stents but this remains controversial [54-56].

Systemic Complications

Hypertension is undoubtedly the most frequent systemic complication in CoA patients, and its related conditions include an increased risk of premature atherosclerosis, resulting in coronary as well as peripheral artery disease. Morbidity and mortality in CoA patients are mainly due to heart failure, aortic rupture, myocardial infarction, cerebrovascular incidents and even sudden death [57-59].

Cerebral aneurysms are found 5 times more frequently in patients with CoA compared to the general population. HT has been found to be the single best predictor of CVA after CoA repair [57]. Obviously, the long-term prognosis is also dependent on associated defects.

1.7 Hypertension

According to a recent meta-analysis the prevalence of HT after CoA repair is around 32,5% (range 25-68%) [58]. The studies with the longest follow-up found the highest incidence of HT, pointing towards a progressive nature of HT after CoA repair [7, 18, 60-62]. In the COALA study the incidence of HT increased from 23% to 53%, by following a group of 273 patients over a period of 14y [63].

Very few publications concerning CoA used the 2016 European Society of Hypertension guidelines [64] to categorize patients in blood pressure phenotypes based on both the office blood pressure and ambulatory blood pressure-monitoring results. Isolated systolic hypertension is the dominant phenotype in CoA [62].

However, the use of standardized definitions to categorize HT are important when comparing studies on HT after CoA repair. Various cut-offs have been used for the definition of HT after CoA repair, complicating comparisons [58]. Another confounding factor relates to the fact that in some studies, patients are identified as hypertensive if they are on antihypertensive medication, but had normal BP measurements. Furthermore, it is possible that some antihypertensive medications were started for indications other than HT [65].

Additional Tests to Diagnose HT

In various studies, 24h blood pressure (or exercise induced HT) is included to find the true prevalence of hypertensive patients, invariably leading to an increased incidence [62, 63, 66-69]. In one study the incidence of HT increased from 5% to 39% when 24h blood pressure measurement was included in a group of patients with repaired CoA [68]. Underestimation of HT can also be due to inconsistent measuring techniques and usage of different devices [70, 71].

The current ESC guidelines recommend 24 BP measurement to detect/confirm arterial HT (with cut-off values on 24h BP measurement of systolic >130mmHg and/or diastolic >80mmHg) [1].

Exercise Testing is an additional method to detect HT, at least during exercise [60, 63, 66-69]. The mean systolic blood pressure (SBP) at peak exercise is commonly higher in CoA. While a cut-off SBP >200 mmHg during exercise is usually indicative of exercise induced HT, this threshold may be too high in children where a value of 190mmHg might be more reasonable [68].

Factors influencing HT

Re-CoA itself can cause a high BP in the right arm with a lower BP after the narrowing. A limitation in extracting blood pressure data from studies (and finding the true prevalence) is that in most cases the blood pressure data is not separated between those with and without re-CoA and variable indications are used for reintervention. The recommended cut-off for treatment is an invasive gradient of 20mmHg [1]. In some studies, re-CoA is diagnosed by echocardiography [65], in others via MRI-based gradient [49, 60, 72] or BP gradient [61].

A clear correlation between the prevalence of HT in those with re-stenosis and those without is not always found [7, 72]. An association has been shown between an increased arm-leg BP gradient, obesity and HT [61].

It has already been reported in 1989 that the most important predictor of long-term survival and HT is the age of patients at the time of the initial repair [73]. Various studies support this finding [7, 18, 19, 62, 74], but not all [61, 63].

The type of repair might also be important. In an interesting study, two groups of patients were compared, a group with isolated CoA (148 patients) and one with complex congenital heart disease (CHD) and CoA (87). Although patients with isolated CoA were significantly younger, they had a markedly higher incidence of HT (44% vs 24%) [67], possibly related to the type of repair in the complex CHD group, resulting in less hypoplasia after repair. Some centers have increased their surgical approach with the use of median sternotomy and extracorporeal circulation to enlarge the transverse arch, after comparing patients treated in different eras and finding that catch-up growth of arch hypoplasia after end-to-end anastomosis was insufficient [9, 39]. The type of repair is not always predictive of vascular function differences and HT, when comparing surgery, BA and stenting [69]. However, a recent systematic review and meta-analysis did find surgery to be superior to BA, with a lower incidence of re-CoA, repeat intervention and lower residual gradient in the mid- to long-term follow-up [24]. A limitation of this type of meta-analysis is that patients with significant HAA usually receive a surgical intervention rather than BA.

Arch morphology should be differentiated from HAA, as morphology describes the 3D structure and is not necessarily associated with any hypoplastic segment. Although arch morphology (Gothic, Crenel and Romanesque) has been found to

be a contributing factor in various studies with a Gothic Arch having the highest risk [75], some doubt has been cast on the usefulness of this classification in predicting HT [76].

In an MRI based study it was recently shown that while there are many variations in 3D aortic shape after coarctation repair, there was only a modest association between variation in aortic radius and pathological wave reflections, but not with 3D curvature. This suggests that 3D shape is not the major determinant of vascular load following coarctation repair, calibre being more important than curvature [77].

Obesity is a well-known risk factor for HT in the general population and it has been established that there is an alarming and increasing prevalence of obesity after CoA repair, contributing to HT [61, 78].

The role of the kidneys in the development and persistence of HT after CoA remains controversial. Abnormal activation of the Renin-Angiotensin-Aldosterone system (RAAS) (Figure 1.13) has been proposed to contribute to HT pre- or post-intervention, with conflicting results.

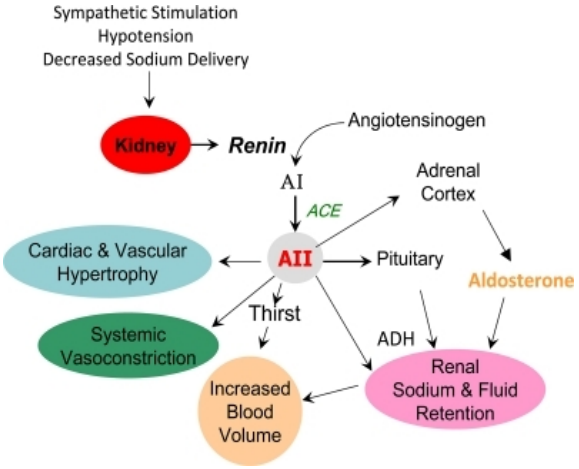


Figure 1.13: The RAAS system

AI= Angiotensin I
AII= Angiotensin II

The etiology of HT is probably multifactorial, although hemodynamic factors have been found to explain most of the HT after CoA repair since 1971 [79]. Already in 1977 Sanchez et al came to the conclusion that the RAAS showed no modifications after surgical repair for CoA and was not responsible for late HT after CoA repair [80]. However, this is not absolute proof and the RAAS might certainly contribute to HT. In addition to possible Renal damage occurring during and after catheterization and/or surgery, the kidneys might be congenitally abnormal too (e.g., dysplastic). Arterial stiffness was not found to be related to activity of the RAAS [81].

1.8 Pathophysiology of HT and Hemodynamics in CoA

The question arises why there is such a high prevalence of HT in CoA patients. The majority of clinical studies look at complications, mortality rate and residual pressure gradient rather than at the correlation of hemodynamic indices with long-term outcome [18, 22, 24, 35, 73, 82]. The role of specific hemodynamic indicators of long-term outcome is currently not well understood.

Already in 1971, O'Rourke and Cartmill suggested that morbidity in CoA patients could be explained by abnormal hemodynamics and vascular biomechanics [79]. Recent developments in experimental and computational methods seem to support this theory [83]. Factors contributing to an increased LV afterload are a residual narrowing leading to additional resistance and a less distensible aorta interfering with the buffer function of the aorta.

The proximal aortic wall in patients with repaired CoA has been shown to have different histology, containing more collagen, less elastin fibres, and less smooth muscle cells. Compliance and distensibility of the aorta are therefore impaired in comparison with healthy individuals. Increased stiffness of the ascending aorta on MRI after CoA Repair has been demonstrated with a higher central aortic BP [84]. The increased stiffness and reduced distensibility leads to stimulation of the sympathetic system through activated mechanoreceptors, changes in the endocrine system, endothelial dysfunction and progressive vascular remodelling, further increasing the peripheral vascular resistance and thus blood pressure.

In general, HT is based on measurement of the peripheral BP, being the simplest measure of afterload. However, peripheral BP can deviate from central aortic pressure in patients with repaired CoA, limiting thereby its value in assessing properly the vascular and cardiac hemodynamics after CoA repair [85]. The altered wall properties of the ascending aorta influence central aortic hemodynamics (CAH) but the characterization thereof, especially when taking wave reflections into account, is difficult and requires simultaneous measurement of aortic pressure and flow. Because of this difficulty in properly assessing central aortic hemodynamics, most studies looking at HT after CoA repair, examined vascular function in an indirect fashion:

- Increased arterial stiffness has been demonstrated in this population as well as a reduced arterial response to glyceryltrinitrate (GTN) [86, 87].

- Flow Mediated Dilatation (FMD) has been shown to be impaired [87, 88].

- Carotid Intima-Media thickness (IMT) is increased in CoA patients. Some of these findings (Elevated PWV, increased IMT) are correlated with increased cardiovascular risk in healthy subjects and there is no reason to believe that these findings are not associated with an increased risk in the treated coarctation group as well. IMT is frequently raised in patients with repaired CoA [66].

- Pulse Wave Velocity is commonly used to assess vascular hemodynamics in the clinical setting, reflecting mostly stiffness. There is a significantly higher PWV in CoA patients compared to controls [88]. Major vascular outcomes are similar in CoA patients treated with BA stenting or surgery, but segmental assessment of PWV and distensibility measures by CMR shows differences: Proximal aortic stiffness was lowest in the BA patients and highest in the stenting group [69].

Of course, factors leading to HT unrelated to the heart or the aorta itself can increase the risk of developing HT. As an interesting example, vertebral artery hypoplasia (VAH) with an incomplete posterior circle of Willis (ipCoW) occurs almost 6 times more in CoA patients and can lead to HT [90].

Normotensive children with successfully repaired CoA can exhibit reduced Heart Rate Variability (HRV) and Baroreceptor Sensitivity (BRS) [91]. This suggests a role for altered baroreceptor reflex control of cardiac autonomic modulation. Together, these results suggest that early anatomical correction of CoA may not be sufficient to ameliorate autonomic dysfunction, providing a mechanism for future development of hypertension [92].

1.9 Treatment of CoA-related hypertension

Once HT develops after CoA repair there is no clear consensus on the best treatment.

If an invasive gradient of 20mmHg is suspected with non-invasive imaging or by BP difference, this should invariable be addressed [1]. Stenting has been shown to significantly reduce BP in medium-term follow-up [82].

Once there is established HT in the absence of a significant re-CoA, recommendations are to use the same guidelines for the treatment of HT as in other patient groups [1, 93] with the ESC stating in the 2018 ESC/ESH Guidelines that HT in patients with CoA repair should follow the same treatment algorithm as other patients as there have been no formal RCTs to define optimal treatment strategies [93].

Treatment includes lifestyle changes, dietary sodium restriction, moderation of alcohol consumption, weight reduction, regular physical activity and smoking cessation. Pharmacological treatment consists of five major drug-classes: ACE (angiotensin-converting enzyme) inhibitors, ARBs (angiotensin receptor blockers), beta-blockers, CCBs (calcium channel blockers) and diuretics. These drug classes can also be combined when needed (except ACE and ARBs).

In the case of children and adolescents, the 2016 European Society of Hypertension guidelines for the management of high BP in children and adolescents can be followed. These guidelines state that the population with CoA

pose a particularly high risk and that Beta-blockers, CCBs, ARBs and ACE inhibitors can efficiently lower the BP [64].

There were no specific recommendations in the 2010 ESC guidelines for choice of first line anti-hypertensive agents in this setting [94].

In the 2008 AHA guidelines B-Blockers, ACE inhibitors and Angiotensin Receptor Blockers were suggested as first line anti-hypertensive treatments in this setting with the choice depending on the presence of aortic root dilatation and aortic valve insufficiency [95].

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Chapter II Objectives of the thesis

Despite successful treatment of CoA by surgery and endovascular techniques, haemodynamic as well as morphological sequelae of either treatment remain major determinants of later morbidity.

This thesis aims to improve the understanding of the haemodynamic factors contributing to a suboptimal long-term outcome, through combining fundamental translational research and clinical studies on the interaction between aortic and ventricular dynamics.

Objective 1

Arterial hypertension remains a common clinical concern in CoA patients. Since important new evidence has emerged on the underlying pathophysiologic mechanisms after CoA repair, leading to or preceding overt hypertension, it seemed important to re-visit the actual data through conducting a systematic review on this particular topic.

STUDY 1
Hypertension after coarctation repair - A systematic Review compared to previous data. *Panzer J, Vandekerckhove K, Bové T, De Wolf D. (Submitted)*

Objective 2

Clinical CoA studies tend to focus on the prevalence of cardiovascular complications, mortality and the post-interventional relief of the pressure drop across the coarctation zone, rather than on the contribution of hemodynamic indices to late morbidity. Consequently, the underlying role of hemodynamics in the progression of the disease is not well understood.

Through sophisticated mathematical integration of the main hemodynamic components of aortic dynamics, computational modelling has allowed a greater insight into the complex interaction between structural and hemodynamic changes. In a first in-vitro study we investigated the sequelae of CoA repair through a numerical 3D fluid-structure interaction (FSI) computational model to assess central aortic hemodynamics in relation to local stiffening and/or stenosis of an otherwise healthy aorta. In this way the hemodynamic effects of specific

morphological sequalae which commonly occur after CoA repair can be assessed.

STUDY 2
Differential impact of local stiffening and narrowing on hemodynamics in repaired aortic coarctation: an FSI study. *Taelman L, Bols J, Degroote J, Muthurangu V, Panzer J, Vierendeels J, Segers P. Med Biol Eng Comput. 2016 Mar;54(2-3):497-510. doi: 10.1007/s11517-015-1336-1. Epub 2015 Jul 5. PMID: 26142885.*

Objective 3

Aortic stiffness and residual stenosis comprising a short- to long aortic segment are current sequelae of CoA repair. Although well analysed through computational modelling, the results are limited by boundary assumptions in comparison with the real-time central aortic dynamics. Furthermore, aortic wall characteristics and LV function might additionally influence the central aortic hemodynamics. In this study we set out to confirm the in-vivo effect of CoA sequelae on aortic and ventricular hemodynamics in an animal model.

STUDY 3
Effect of aortic stiffness versus stenosis on ventriculo-arterial interaction in an experimental model of coarctation repair. *Panzer J, De Somer F, Segers P, De Wolf D, Bove T. Eur J Cardiothorac Surg. 2020 Dec 1;58(6):1206-1215. doi:10.1093/ejcts/ezaa241. PMID: 32862227.*

Objective 4

It has been shown that exercise can unmask subtle pathological findings in patients with repaired CoA prior to developing overt HT. Unfortunately, it is not possible to perform reliable imaging in children during bicycle ergonometry. This is particularly true if a detailed analysis including not only systolic, but also diastolic measurements of ventricular function such as tissue doppler indices (TDI), is required, Therefore, a set-up of echocardiographic cardiac function evaluation was investigated in children after coarctation repair, based on isometric exercise testing during handgrip loading.

STUDY 4
Echocardiography during submaximal isometric exercise in children with repaired coarctation of the aorta compared with controls. *Panzer J, Dequeker L, Coomans I, Vandekerckhove K, Bove T, De Wolf D, Rietzschel E. Open Heart. 2019 Oct 24;6(2):e001075. doi: 10.1136/openhrt-2019-001075. PMID: 31749973; PMCID: PMC6827756.*

Objective 5

Data from the literature demonstrated that exercise tolerance is lower in children after coarctation repair. The reason for this reduced exercise capacity after CoA repair is not yet fully understood. Whereas previous research focused on the relationship between aortic and ventricular hemodynamic changes after CoA repair during exercise, the purpose of this study was to assess whether the lower exercise tolerance in children is associated with alterations in peripheral tissue oxygen exchange during exercise. Hereto, the technique of near-infrared spectroscopy (NIRS) was used to study tissue oxygenation patterns at different sites of the body during periods of exercise-related changes of metabolic demand to understand the reciprocal effect between metabolic and vascular control, particularly in CoA patients.

STUDY 5

Different Patterns of Cerebral and Muscular Tissue Oxygenation 10 Years After Coarctation Repair. *Vandekerckhove K, Panzer J, Coomans I, Moerman A, De Groote K, De Wilde H, Bové T, François K, De Wolf D, Boone J. Front Physiol. 2019 Dec 11;10:1500. doi: 10.3389/fphys.2019.01500. PMID: 31920705; PMCID: PMC6917622.*

Chapter III Methods of hemodynamic assessment

Already in 1971, O'Rourke and Cartmill suggested that morbidity in CoA patients was related to abnormal hemodynamics and vascular biomechanics [1].

To study the hemodynamic factors which potentially contribute to the increased morbidity and mortality, it is useful to divide hemodynamics into Arterial Hemodynamics *(BP, Wave Travel: PWV, Waveform Analysis and Wave Intensity Analysis, Arterial Input Impedance and Transfer of pressure)* and Cardiac Hemodynamics (*Ventricular function, P-V Relation, Cardiac Oxygen consumption, and Ventriculo-Arterial Coupling)*

3.1 Arterial Hemodynamics

Peripheral BP

Measuring peripheral BP has a long and interesting history starting 4000 years ago, when the Chinese Emperor Huang-Ti was already aware that people who eat too much salt had hard pulses and tended to suffer strokes [2]. Today aneroid sphygmomanometers are used to measure blood pressure through a lever and bellows system. They are however less accurate than mercury sphygmomanometers [2].

The peripheral BP is the simplest measure of afterload. However, peripheral BP can deviate from central aortic pressure, especially in patients with repaired CoA, limiting thereby its value in assessing properly the vascular and cardiac hemodynamics after CoA repair [3]. Egbe et al. showed that (peripherally measured) SBP may underestimate the LV afterload after CoA repair since CoA patients have a higher arterial afterload compared with controls, even with similar SBP [4]. LV afterload is best described in terms of pressure-flow relations [5].

Central Aortic Pressure (c-SBP), Wave travel and reflection

Pressure and flow create travelling waves. The time delay in flow (Δtq) or pressure (Δtp) allows calculation of PWV. (PWV=distance/Δt). Pulse Wave Velocity is commonly used to assess vascular hemodynamics in the clinical setting, reflecting mostly stiffness. Luitingh et al. found significantly higher PWV in CoA patients compared to controls [6].

Central aortic systolic blood pressure (c-SBP) can be assessed non-invasively using radial or carotid artery applanation tonometry. Unfortunately, this can be difficult to perform (especially in the obese) and is uncomfortable for patients. Furthermore, radial tonometry may not accurately reflect c-SBP.

Fortunately, the arterial pressure-area relationship can be approximated mathematically and the c-SBP be estimated from area measurements with calibration to the brachial BP with MRI [7]. Quail et al demonstrated the ability to assess c-SBP non-invasively using a combination of phase-contrast magnetic resonance and oscillometric brachial artery BP [7].

Oscillatory Flow Theory is based on sinusoidal oscillations of pressure and flow. This implies that application of the theory to hemodynamics requires Fourier analysis, which allows for the representation of hemodynamic variables as a series of waves, called harmonics. It can be used to relate Pressure-Flow relations (impedance Z) by dividing their amplitudes, and subtraction of their phase angles of harmonics of the same frequency. By convention the term resistance is used for non-oscillatory flow and impedance for pulsatile flow [5]. Forward pressure and flow are related by characteristic impedance (Zc). These signals are only valid and useful in a steady state of oscillation. Oscillatory flow theory only gives a small correction over and above the use of resistance in series, but is of great importance for wall shear stress and measurements of local flow.

Wave intensity Analysis (WIA) is a technique that allows comprehensive assessment of arterial and cardiac function. Wave reflections occur at sites of bifurcations or where changes in wall properties are present (for instance scar tissue or stenting). These wave reflections cause amplification. Aortic pressure and flow waves can further be separated in their forward and reflected components (Figure 3.1 and 3.2). Reflections of pressure and flow are “inversed”.

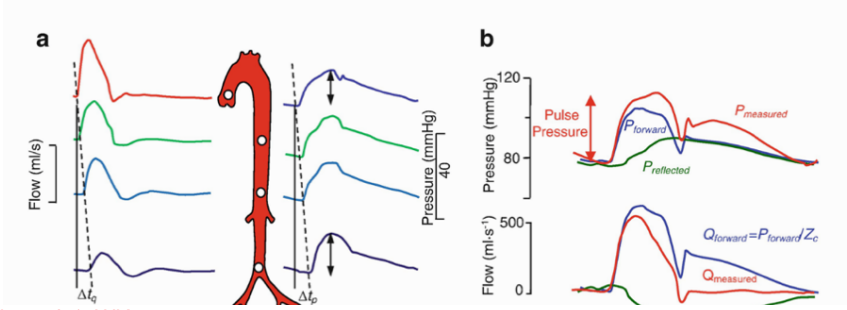
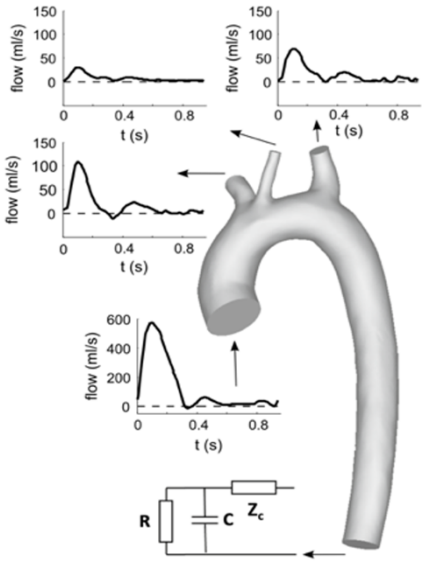


Figure 3.1: WIA (Snapshots of Hemodynamics, third edition. Published with permission Springer License ID 1129083-1)

Forward compression waves (FCW) correlate with LV contractility and Forward expansion waves (FEW) correlate with diastolic function [8]. WIA can be assessed from pressure and velocity data. The requirement of invasive pressure measurements has precluded WIA as a routine clinical test but Phase Contrast CMR can now be used to estimate WIA based on diameter (and distension) rather

than pressure. PC-CMR has the disadvantage that it takes longer to acquire and vessel wall delineation is suboptimal, but recently spiral PC-CMR sequence accelerated with sensitivity encoding (SENSE) has been used to obtain WIA in a single breath-hold [9].



Methodological figure with setup and boundary conditions

Figure 3.2: Methodological figure FSI model with boundary conditions

(*Adapted from our FSI study: Taelman et al [10].*)

Flow can also be measured directly with perivascular flow probes and invasive pressure be obtained directly in an experimental study. Aortic pressure and flow signals can then be decomposed into sinusoidal harmonics using a discrete Fourier analysis, transforming the signals from the time domain into the frequency domain. Ohms law is applied and gives a sufficiently accurate approximation of input impedance in the systemic circulation.

The Arterial system has a buffer function and can be described in terms of a Windkessel model (Figure 3.3).

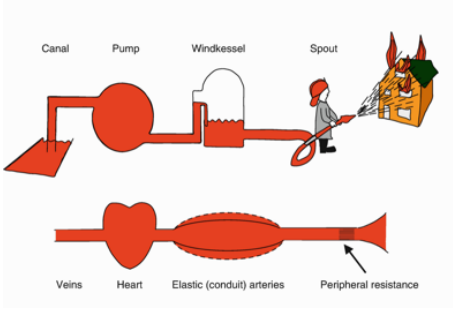


Figure 3.3: Windkessel Model

(Snapshots of Hemodynamics, third edition. Published with permission Springer License ID 1129083-1)

The distensibility of the Aorta allows it to store around 60% of the stroke volume in systole, with elastic recoil redistributing it to the periphery during diastole. Measured flow waveforms can be imposed as a boundary condition at the ascending aorta and the three side branches. At the descending aorta a three-element windkessel model can be used. The descending aortic distension waveform can be used as a substitute for pressure waveform after scaling it to the measured brachial BP. The two-element Windkessel contains total peripheral resistance (R_p) and total arterial compliance (TAC), reflecting small vessel

resistance and large artery compliance respectively. The two-element Windkessel falls short in the high frequency range. The three-element windkessel adds (aortic) characteristic impedance. (Zc). $Zc=P_{forward}/Q_{forward}$. Zc reflects pulsatile load in early systole better than TAC which reflects P-V relation of the entire arterial tree [5]. $C=\Delta V/\Delta P$ (C = compliance, V=Volume). The inverse of C is Elastance E: $\Delta P/\Delta V$ which is addressed further on page 41.

CoA and re-CoA consist of a localized narrowing in the arterial lumen and can be quantified by the ratio A_s/A_o, the area ratio (where As is the minimal cross-sectional lumen area and Ao is the unobstructed cross-sectional lumen area). The relationship between pressure drop ΔP and flow Q is quadratic. CoA consists of a converging section, a narrow section and a diverging section (Figure 3.4).

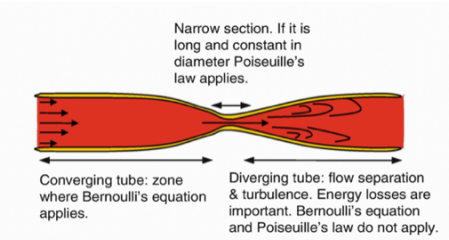


Figure 3.4: Arterial Stenosis

(Snapshots of Hemodynamics, third edition. Published with permission Springer License ID 1129083-1)

Echocardiography with doppler is routinely used to estimate the severity of a residual stenosis after CoA repair using the simplified Bernoulli equation $\Delta P = 4v^2$ (v=velocity). However, conversion of potential to kinetic energy is not perfect with viscous and turbulent losses leading to incomplete pressure recovery, which can lead to over- or underestimation. Overestimation can occur in mild CoA when the distal aorta is not enlarged. Underestimation occurs when CoA is more severe and/or "tunnel" like. [11].

Aortic distensibility (AD)

Compliance and distensibility of the aorta are different from normal individuals. After coarctation repair patients have a less compliant aorta. Schäfer et al. [12] found increased stiffness of the ascending aorta on MRI after CoA Repair. Reduced aortic distensibility was related to a higher central aortic systolic blood pressure and this might contribute to later cardiovascular disease after coarctation repair. Recently abnormal diastolic LV function on echocardiography was shown to be related to proximal aortic elasticity [13, 14]. CoA patients after surgery or stent implantation did not show significant differences of aortic elasticity on MRI [15]. Martins et al. found that major vascular outcomes were similar in CoA patients treated with balloon angioplasty (BA), stenting or surgery but through segmental assessment of PWV and distensibility measures by CMR differences emerged: Proximal aortic stiffness was lowest in the BA patients and highest in the stenting group [16]. AD can be assessed from 3D MRI Data, measuring the distensibility during the cardiac cycle but can also be evaluated by intravascular ultrasound. Quantification of AD is based on the cross-sectional aortic area change from diastole to systole and adjusted for the instantaneous pulse pressure, by the equation: $AD= (\Delta A/A)/\Delta P$ where A=area in cm^2.

3.2 Cardiac dynamics

LVH can be seen as an adaptive response to increased afterload, and is histologically characterized by increase of cardiac myocyte size and density, and enhanced interstitial fibrosis. Sendzikaite et al. found LVH in 31% of normotensive and 33% of hypertensive patients with repaired CoA [17]. Chen et al. measured LV function and mass with CMR and found a strong relation between LV mass and the risk of hospitalization [18]. Egbe et al also showed that patients with CoA had worse LV diastolic function indices and more LV hypertrophy compared to controls [19]. They also showed that peripheral SBP may underestimate LV afterload after coarctation repair since CoA patients have a higher c-SBP compared with controls, even with similar peripherally measured BP [4]. Abnormal diastolic LV function on echocardiography was shown to be related to proximal aortic elasticity [13, 14]. Cardiac Function can be measured via different modalities like echocardiography, with Cardiac MRI or with PV Loops via conductance catheter technology.

Systolic Function and Diastolic Function by TTE

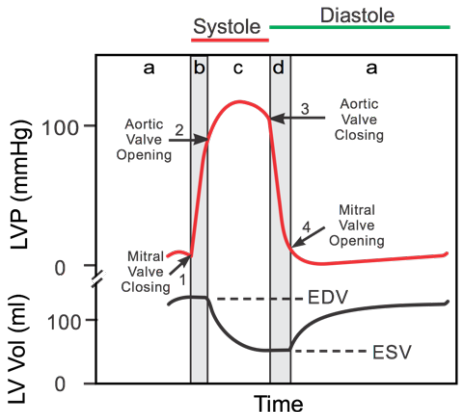
Systolic Function can be estimated by TEE, measuring fractional shortening (FS) and (EF). It can also be assessed by TDI, with the s-wave being particularly sensitive. Diastolic function of the LV can be estimated by TTE, measuring flow across the mitral valve in combination with TDI [20]. Parameters which are particularly useful are annular é-wave velocity (septal and lateral), average E/é ratio >14, maximum LA volume index >34ml/m^2 and peak TR velocity >2.8m/s at least in adults according to the ASE/EACVI [21]. Strain imaging can detect subclinical LV dysfunction.

Cardiac Function assessment with MRI

EF can be accurately measured with MRI, by measuring the ventricular volume in diastole and systole and by direct measurement of flow in the aorta with phase-contrast imaging. It is also possible to accurately assess diastolic function with MRI and peak filling rate (PFR) can also be measured [22].

Systolic and Diastolic Function by conductance

Ideally ventricular function is assessed by simultaneous and instantaneous measurement of volume and pressure [23]. P-V loops (Figure 3.5) are generated with the use of conductance technology which is frequently done in an experimental setting, but rarely in clinical practice. Both systolic and diastolic function can be accurately determined by calculating load-independent indices of systolic and diastolic ventricular function, during modulation of loading conditions through the occlusion of the IVC.



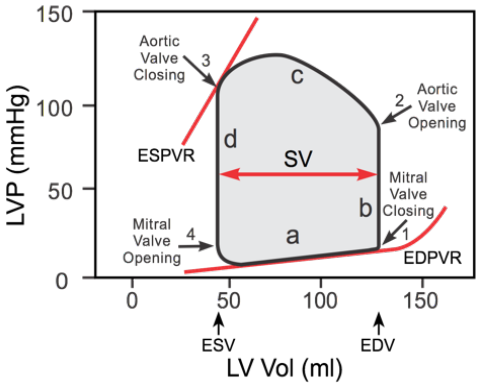


Figure 3.5: P-V loops. *(https://www.chegg.com/flashcards Digital Millenium Copyright Act)*

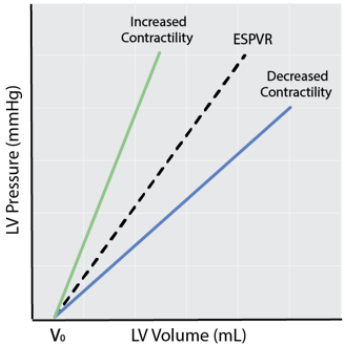


Figure 3.6: ESPVR (Published with permission ADInstruments)

Systolic function is best predicted by the end-systolic P-V relationship (ESPVR) (Figure 3.6) (instantaneous maximal P to V ratio) or by the PRSW (Figure 3.7) (preload recruitable stroke work). PRSW is determined by the linear regression between stroke work and end-diastolic volume. The slope of the PRSW relationship is an index of myocardial contractility, insensitive to preload or afterload.

Figure 3.7: PRSW (Published with permission Creative Commons)

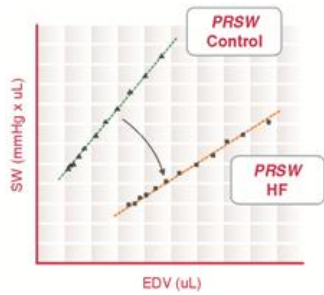
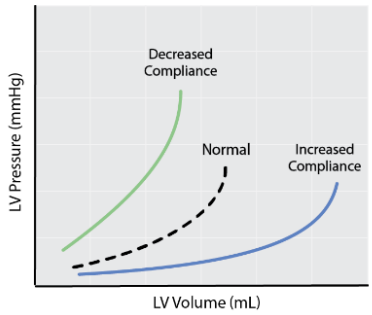


Figure 3.8: Ventricular Compliance (Published with permission ADInstruments)



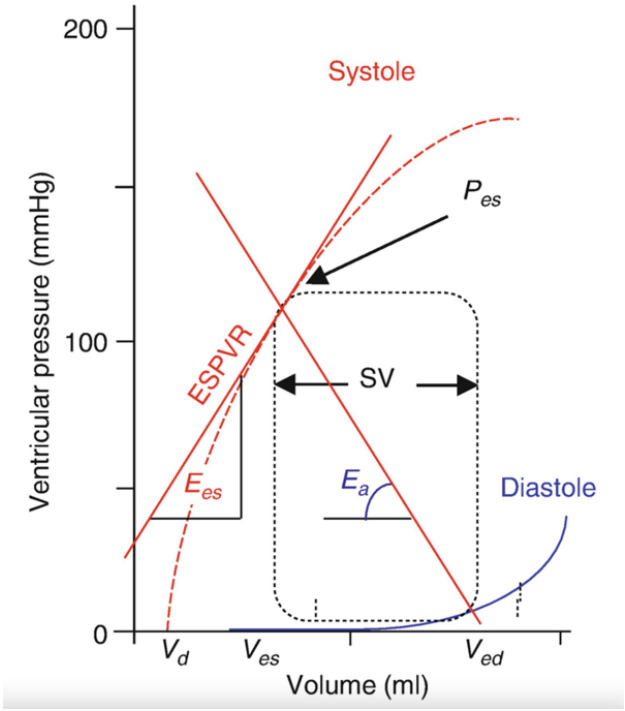
Diastolic function is reflected by the end-diastolic P-V relationship (EDPVR). EDPVR describes the passive filling curve for the ventricle and thus the passive properties of the myocardium. The slope of the EDPVR at any point along this curve is the reciprocal of ventricular compliance (or ventricular stiffness) (Figure 3.5 and 3.8).

Ventriculo-Arterial Coupling

When the heart pumps blood into the vascular system at a rate and volume that matches the capability of the arterial system, both cardiovascular performance and cardiac energetics are optimal. V-A coupling can be defined as the ratio of arterial elastance (Ea) to the ventricular elastance (Ees) (Figure 3.9). The Ea/Ees ratio has been consistently demonstrated as a reliable and effective measure of cardiovascular performance [24].

Left ventricular elastance (Ees)

The slope of the ESPVR is the LV elastance (Ees) and determines the intrinsic contractility of the heart. It is a load independent index of myocardial contractility and LV inotropic efficiency (end-systolic LV stiffness).



Arterial elastance (Ea)

The Ea represents the total afterload imposed on the left ventricle and represents the complex association of different arterial properties including wall stiffness, compliance and outflow resistance. Ea can be defined as the capability of the arterial vessels to increase pressure when LV stroke volume increases.

Figure 3.9: VA-Coupling

(Snapshots of Hemodynamics, third edition. Published with permission Springer License ID 1129083-1)

3.3 Stress Testing

Stress testing can unmask subtle early pathophysiological changes in the cardiovascular system. Different methods of exercise and pharmacological stress testing exist.

Hemodynamic changes during dynamic exercise, isometric exercise, and dobutamine stress testing have been compared in healthy subjects and in patients with aortic stenosis (AS) and aortic coarctation (CoA) (Table 3.1) [25].

Table 3.1: comparing hemodynamic parameters with various stress tests

Adapted from Runte et al [25]

Trends of changes in hemodynamic parameters in healthy individuals.

Type of stress	HR	SV	CO	SET	Utility for diagnostics
Light dynamic	↑↑	↑	↑	↓	Daily life activity
Light pharmacological	↑	↑	↑		Imitate exercise without patient motion
Light isometric	↑	⟷	↑	⟷	Ventricular adaptation to afterload
Moderate dynamic	↑↑↑	↑↑	↑↑	↓↓	Daily life exercise
Moderate pharmacological	↑↑	↑	↑↑		Imitate exercise without patient motion
High dynamic	↑↑↑↑	↑↑↑	↑↑↑	↓↓↓	Limits of exercise capacity
High pharmacological	↑↑↑	⟷	↑↑	(↓↓↓)	Ischemia, symptoms without patient motion

HR indicates heart rate; SV, stroke volume; CO, cardiac output; SET, systolic ejection time. ↑, increase; ↓, decrease; ⟷, no change. Blanks indicate that no data were available. Higher number of arrows indicates a more marked change of the respective parameter.

When comparing pharmacological stress and dynamic exercise, a lower increase of all outcome parameters was found during pharmacological stress. Moderate intensity dynamic and pharmacological stress result in similar increases in HR, SV and CO with similar effect sizes. Compared to dynamic exercise, light intensity dobutamine stress results in a similar increase in SV, but not in HR. High dose dobutamine stress does not cause an increase in SV but increases HR significantly [24].

Dynamic stress testing is generally considered the most physiological type of stress but it has limitations due to the difficulty of simultaneous acquisition of data, such as those obtained by echocardiography. The most frequently used method to assess dynamic stress testing in children with congenital heart lesions is based on bicycle ergometry. Cardiopulmonary exercise testing in children with congenital heart disease differs from adult cardiological exercise testing. There are a number of established treadmill exercise testing protocols for children. The Bruce ramped protocol is commonly used, but the incremental increases in workload may be too great for less-fit patients. The aim is 6-10 minutes of exercise in young children and 8-12 minutes in adolescents [26, 27].

Pharmacological stress testing can be useful when additional imaging is performed simultaneously. Dobutamine is widely used as a pharmacological stressor to assess the hemodynamic response in congenital heart disease [28, 29]. Dobutamine leads to a positive inotropic and chronotropic reaction with minor vasodilating effects. In CoA, a dobutamine stress can be useful to maintain adequate blood pressure and HR in patients under anaesthesia or sedated during anaesthesia (heart catheterization, animal studies), allowing reliable measurement of pressure gradients before and after altering hemodynamic states [30].

Isometric Exercise can be performed easily by squeezing a handgrip dynamometer, without causing artefacts affecting image quality. Isometric exercise differs from dynamic stress testing mainly by imposing a high afterload on the ventricle [25]. For this reason, it might be particularly useful to study the hemodynamics in children with repaired CoA.

Peripheral tissue Oxygenation. It has been shown that maximal exercise tolerance is substantially lower in patients after CoA repair, but the etiology is still unclear [6, 16, 31]. Studying oxygenation patterns in peripheral tissues during exercise may be relevant to understanding metabolic and vascular control.

Near-Infrared spectroscopy (NIRS) allows measuring the relationship between O_2 delivery (QO_2) and O_2 utilization (VO_2) at the level of the microcirculation, with changes in deoxygenated Hemoglobin (HHb) reflecting an increase in microvascular O_2 extraction, as a result of inadequate matching between O_2 supply and O_2 demand [32]. The derived parameter TOI (tissue oxygenation index: $O_2Hb/(O_2Hb + HHb)$ can be used to quantify tissue oxygenation.

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Chapter IV

STUDY 1 (SYSTEMATIC REVIEW ARTICLE)
***vHypertension after coarctation repair - A systematic Review compared to previous data*.** Panzer J, Vandekerckhove K, Bové T, De Wolf D. (Submitted)

Hypertension after coarctation repair - A systematic Review

1. Introduction

Coarctation of the Aorta (CoA) comprises approximately 5-8% of all structural congenital cardiac lesions. It occurs 3 times more commonly in males than females. CoA still leads to increased morbidity and mortality later in life despite early surgical or percutaneous treatment. Many long-term complications are related to hypertension which is a common finding late after coarctation repair.

Improved treatment and surveillance have shifted the emphasis from short-term to long-term outcome (1). Since the last systematic review on hypertension after coarctation published in 2013 by Canniffe et al (1), important new evidence has emerged on this topic. We therefore revisited a systematic review on hypertension after CoA Repair based on findings from 2012 to 2020, with additional focus on pathophysiology. The role of specific hemodynamic indicators of long-term outcome is currently not well understood. We touch on this subject with a brief discussion on ways of assessing central hemodynamics non-invasively.

The holy grail would be to identify preliminary signals of potentially harmful pathophysiologic changes, in order to find treatments that prevent the cascade ending towards established hypertension. In this way long-term complications related to hypertension (HT) in CoA patients might be anticipated.

2. Methods

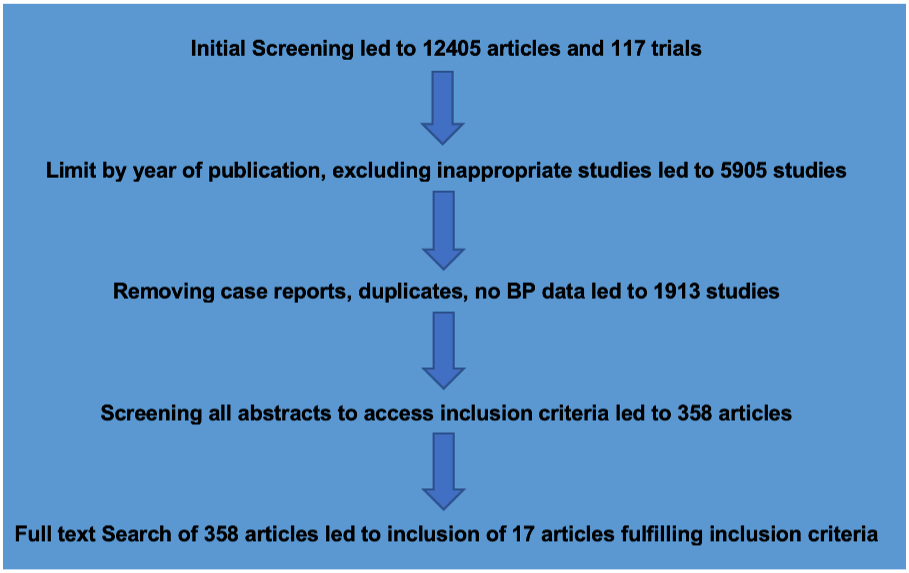
A systematic Review on the subject of hypertension after repair of aortic coarctation was performed, with emphasis on articles published in the English language from February 2012 until December 2020. PRISMA guidelines (preferred reporting items for systematic reviews and meta-analysis) were used. Systematic searches were conducted on PubMed and the Cochrane Controlled Trials Register to look for studies on hypertension after aortic coarctation repair. No restrictions were applied to the status of publication other than the above-mentioned elements. Search Terms were hypertension, blood-pressure, coarctation repair, coarctation surgery, percutaneous treatment of coarctation, coarctation stenting, age-at-repair, and pathophysiology.

Inclusion and Exclusion Criteria:

The novel data of this review was compared to these of the systematic review retrieved from 1987 to 2012 (1), based on the use of identical inclusion criteria. Studies were only included when blood pressure (BP) was an outcome measure after coarctation repair. Coarctation repair could be either surgically or via catheter-based interventions. Studies also needed to be randomized controlled trials or case-controlled or cross-sectional studies yielding at least 35 patients. Observational studies were included if the study population comprised more than 120 study subjects, with more than 20 years follow-up. The paper of Meijs et al. (2) was excluded for comparison as this meta-analysis investigated the effect of stent

therapy on blood pressure changes in the short and medium term, rather than the incidence and prevalence of HT after treatment in the long term.

Figure 1: Initial Screening



A PubMed search for articles on coarctation initially led to 12405 articles. Limiting the search to articles published since February 2012, retained 5905 articles. By excluding duplicates, case reports and systematic reviews the total was brought to 1913 articles. Of these, abstracts were read to eliminate inappropriate studies. This reduced the total to 358 articles requiring the reading of the full text to ascertain whether the inclusion criteria were fulfilled. Of the 358 articles, 352 were obtained via institutional online access. The remaining full texts were requested via our library, but only 4 published in English were used. After consulting the full content of these 356 articles, only 17 fulfilled the inclusion criteria as set out above (3-19).

Table 1: Articles meeting Inclusion Criteria

Author	Group	Standarized def. HT	Follow-up (in years)	Age at Surgery	24h BP	Exercise Test	Re-CoA or HAA data %	HT %	Surgery % vs Percutaneous	BAV %
Bambul [4]	273	yes	31.4 (14.1-39.9	9.7 (0-56)	yes	yes		70	100	48
Brown [5]	819	yes*	17.4 ±13.9	17.2 ± 13.6	no	no		40 to >70**	100	
Chen [6]	247	yes	5.9	S: 6 (0-55) I: 25 (0.5-64)	no	no	31re-CoA 25.9 HAA	69.6	81	56
Choudhary [7]	151	yes	26 ±13	5 (0-10)	no	no	31 Re-CoA	44	Mixed	66
Dijkema [8]	206	yes	12.5	0.1 (0-17)	no	no	21 HAA	20	86	39
Egbe [9]	546	yes	Age 33 ±9		no	yes		60	87	57
Giordano [10]	148	yes	13.3±4.5	0.4 (0-11.8)	yes	yes		44	100	
Lee [11]	834	yes	27 (18-36)	3 (0.1-15)	no	no	59 Re-CoA	57	83	58
Lillitos [12]	87	yes	1.9 (0-9)	0 – 5.6**	no	no	15 Re-CoA	7 – 40**	100	
Luitingh [13]	41	yes	13±3	0.03 (0.02-0.1)	yes	yes	32 HAA	39 (12 on Exercise test)	100	61
Martins [14]	75	yes	9-12 **	S 6 (1-26) BD 5 (1-17) ST 15 (7-26)	yes	yes		30 S 39 BD 45 ST	Mixed	79 S 45 B
Mery [15]	343	yes	12 (0.5-19)	0.1(0-0.75)	no	no	33 HAA	33	100	
Rinnström [16]	653	yes	27.4 ±12.8	9.5 ±11	no	no	49 Re-CoA	52.7	94	
Rog [3]	58	yes	20.39±9.8	8.7 ±8.6	yes	yes	39 Re-CoA 46 HAA	48.3	86	62
Sendzikaite [17]	90	yes	8.5 (6-11.8)	0.4(0.05-2)	yes	no		46.7	71	54
Smith-Parrish [18]	160	yes	14 (4.6-36.7		no	no		22-38**	86	
Wu [19]	2295	not stated	Age 18- 60		no	no		34.5		

*Including self-reported HT
**Data divers in cohorts
I = interventional treatment
S= surgery
BD = balloon dilatation
ST = stent

The Cochrane Controlled Trials Register was searched for trials reporting on CoA, using BP as an outcome measure. One hundred seventeen trials were initially identified but only 1 article had data on long-term CoA outcome (20). The paper of Padua et al. reported on the efficacy of surgery versus stenting as best treatment of aortic coarctation. As hypertension was not a specific outcome measure, this publication was not included.

Data Extraction:

One single reviewer extracted all data. The acquired information considered blood pressure, hypertension, age-at-repair, type of repair, duration of follow-up, control group data, vascular measurements, aortic arch geometry, journal, year of publication and first author.

3. Results

Standardized Definitions

Compared to the review by Canniffe (1), the definition of HT has meanwhile been scrutinized by classifying HT consistently for a BP value ≥140/90 mmHg or above the 95th percentile in children. All studies used this definition for HT. Significant differences have been shown when using two different 24h blood pressure devices (21) and in our included studies various devices were used. Another confounding factor relates to the fact that in some studies, patients were identified as hypertensive if they were taking medication for HT, although having normal BP measurements, as observed by Bambul et al. (4). This is logical because medication was started for hypertension, however the exact definition and cut-offs used to initiate anti-hypertensive treatment could not be retrieved from these studies. Furthermore, it is possible that some antihypertensive medications were started for

an indication other than HT, with insufficient data in the studies to test this hypothesis.

Very few publications used the 2016 European Society of Hypertension guidelines (22) to categorize patients in blood pressure phenotypes based on both the office blood pressure and ambulatory blood pressure-monitoring results. Using the recommended blood pressure registration tools, Sendzikaite et al (17) found that isolated systolic hypertension was the dominant phenotype in CoA patients, and that Left Ventricular Pressure (LVH) was prevalent even after successful repair.

Most studies agreed on the definition of re-CoA as an invasive gradient of 20mmHg but as this was not measured, it was estimated in various ways. In some studies, re-CoA was diagnosed by echocardiography (15), in others via MRI (6, 9, 11) or clinically measuring of a BP gradient (16).

Exercise induced HT with SBP > 200mmHg was considered a limiting definition in children and Luitingh et al. identified a cut-off of 190mmHg as a more suitable value to identify those with HT (13).

Prevalence of hypertension in aortic coarctation

The mean prevalence of hypertension in this systematic review was 47.3% (range 20-70%). However, the prevalence was as low as 7% in a specific cohort (12). In a previous review Canniffe et al found a prevalence of 32,5% (range 25-68%) (1). The

exact prevalence of hypertension was difficult to interpret. Obviously, the incidence of hypertension increased with longer follow-up, but also increased as more effort was undertaken to identify patients with hypertension, like 24h blood-pressure measurements and exercise induced hypertension. Mery et al (15) noted the confounding factor that BP measurement was not always standardized and the usage of cardiac medications for other cardiac conditions might also have influenced the measured blood pressure (15). In their cohort, acquisition of echocardiographic data was documented more consistently than blood pressure data, pointing thereby to time constraints in outpatient clinics and technical difficulties for measuring blood pressure in small children.

Hypertension developing in CoA patients without documented residual narrowing should be viewed separately from those with some residual obstruction. A limitation in extracting blood pressure data from these studies is that in most cases the blood pressure data does not differentiate between those with re-CoA and those without. In re-CoA, the blood pressure measured proximal to the residual narrowing (i.e., right arm) can be increased, but normal or even low when measured distal to the narrowing (leg or in some instances left arm). Some studies report on the incidence of re-coarctation or hypoplastic arches, but failed to separate the blood pressure data. However, Chaudhary et al (7) and Chen et al (6) found no clear correlation in the prevalence of hypertension in those with and without re-stenosis.

There is a progressive character of hypertension after CoA repair. In a study by Bambul et al (4), a group of 273 patients were studied previously (COALA study) and re-assessed 14 years later. All patients had ambulatory 24h blood pressure

measurements. In this study, 23% of patients were found to be hypertensive with 25% taking anti-hypertensive drugs initially. 14 years later 53% of the same patient group was found to be hypertensive with nearly half receiving antihypertensive medication. Furthermore, the studies with the longest follow-up found the highest incidence of HT (5, 7, 9, 16, 17).

Additional Tests to Diagnose HT

24h Blood Pressure data was performed in 6 studies (3, 4, 10, 13, 14, 17). It is interesting to note that Luitingh et al. compared the incidence of hypertension in patients at rest, after 24h blood pressure recording and during exercise (13). They found that of the 41 patients, 5% showed resting HT while 39% had HT on 24h blood pressure measurements. As expected, a higher prevalence of HT was found if 24h BP registration was performed but no additional cases were identified by exercise testing.

Exercise Tests were performed in 6 studies (3, 4, 9, 10, 13, 14). Luitingh et al. found an overall reduced exercise endurance in coarctation patients compared to the control group (13). The mean systolic blood pressure (SBP) at peak exercise was higher in the coarctation population (164 ± 26 mmHg vs. 148 ±19 mmHg, $p = 0.003$). Five of the 41 (12%) coarctation patients had a peak exercise SBP >200 mmHg and were therefore considered to have exercise-induced hypertension.

If only studies are included recording 24h BP recording in addition to standard BP measurements, the incidence of HT rises to 57.8%, which is 10% higher compared to only standard BP measurement.

Factors influencing HT and pathophysiology of HT

In various studies age at repair was the main determinant of hypertension, with older age at repair being associated with an increased incidence of hypertension (5, 7, 12, 17), but not in the studies of Bambul et al (4) and Rinnstrom et al (16).

The type of repair might also be important. In an interesting study, Giordano et al [10], compared a group of patients with isolated CoA (148 patients) with patients having CoA as part of a complex congenital heart disease (CHD) (87 patients). Although patients with isolated CoA were significantly younger, they had a markedly higher incidence of HT (44% vs 24%). They postulated that in the complex CHD group, the incidence of hypertension was lower because the aortic repair was more effective than in those with isolated CoA, obtained through aortic arch enlargement with a pulmonary homograft patch in most cases. Minor grades of hypoplastic aortic arch (HAA) and a reduced stimulation of baroreceptor reflex in the pre-stenotic area were hypothesized to be the reason for the distinct prevalence of HT. Dijkema et al (8) compared patients treated in different eras. They favored enlarging the transverse arch in the last period, as it has been shown that catch-up growth of arch hypoplasia after end-to-end anastomosis did not always occur (23). In contrast, Martins et al failed to demonstrate that the type of repair was predictive for vascular

function differences and hypertension when comparing surgery vs balloon dilatation vs stents (14).

Smith-Parrish et al. looked at the prevalence of obesity as a separate outcome measure in a cross-sectional study involving coarctation patients (18). They found an alarming and increasing prevalence of obesity of 26% at the age of 10 years, and 63% at the age of 20 years. There was good correlation between obesity and HT in their study. Rinnström et al (16), revealed an association between HT and obesity as well as with an increased arm-leg BP gradient a, concluding that a mild residual pressure-drop over the repaired coarctation zone is probably less benign than thought.

Wu et al (19), looked at the risk of CVA and hypertension after coarctation repair and found hypertension to be the single best predictor of cerebro-vascular accident (CVA), increasing the risk three-fold.

While the majority of all clinical studies tend to look at complications, mortality rate and residual pressure gradient rather than correlating hemodynamic indices with long-term outcome (2, 5, 20, 24-26), the role of specific hemodynamic indicators of long-term outcome is currently not well understood. In this systematic review, many of the included studies only briefly touch on the underlying vascular mechanisms involved in the pathophysiology of HT, with one exception where detailed vascular function was compared in 3 groups of CoA-repair (14). The relevance of the hemodynamic factors can be divided into arterial- and cardiac components. Various studies tried to assess arterial hemodynamic factors with pulse wave velocity (PWV),

carotid intima media thickness (IMT), endothelial function, aortic distensibility and, in one study, with central BP (14). Ventricular function was assessed with echocardiographic and occasionally cardiac magnetic resonance (CMR) measurements of systolic and diastolic function, degree of LVH and exercise testing with metabolic measurements.

Arterial Hemodynamics

PWV is commonly used to assess vascular hemodynamics in the clinical setting. Luitingh et al. found a significantly higher PWV in CoA patients compared to controls (13). However, carotid artery distensibility and arterial stiffness index were similar in both groups. They also performed exercise testing but metabolic results like VO2 max were not available due to lack of ergo-spirometry. Carotid IMT was also measured and found to be significantly raised in CoA patients even without HT (3). In a multicenter, cross-sectional, observational comparison of vascular function in CoA patients, Martins et al. (14) found that major vascular outcomes (prevalence of HT, global aortic stiffness, central BP and endothelial function) were similar in CoA patients treated with balloon dilatation (BD), stenting or surgery. Through segmental assessment of PWV and distensibility measures by CMR they revealed that proximal aortic stiffness was lowest in the BD patients and highest in the stenting group.

Cardiac hemodynamics

Selected studies measured LV hemodynamic factors, usually systolic and sometimes diastolic LV function with echocardiography (4, 9, 13, 17). Martins et al. looked at LV mass, usually derived from echo-measurements (14). There was an

important prevalence of LVH in the absence of HT. Sendzikaite et al. found a similar proportion of LVH in normotensive (31%) and hypertensive patients (33%) with repaired CoA (17). Chen et al. measured LV function and mass with CMR (6). They found a strong relation between an increased LV mass and the risk of hospitalization. Egbe et al. looked at LV diastolic dysfunction and found that the aortic isthmus ratio (ratio of the aortic isthmus diameter to the descending aorta diameter at the level of the diaphragm ≤0.5) had a strong correlation with diastolic dysfunction and exertional symptoms (9). Rog et al. found lower values of peak VO2/kg, heart rate peak, % max HR at cardiopulmonary exercise tests in CoA patients in comparison to controls (3). These differences were postulated to be related to chronotropic incompetence.

4. Discussion

Despite „successful treatment" of aortic CoA, long-term morbidity and mortality remains higher in this patient population compared to controls. Frequent problems found in the long-term follow-up of these patients are early onset of cardiovascular diseases like myocardial infarction, cardiac failure, stroke, and even sudden death, often promoted by arterial hypertension. Indeed, the incidence of HT found in this systematic review, is high, being 47.3%. Various factors influence the development of HT. Cohen and colleagues already reported in 1989 that the most important determinant of long-term survival and hypertension in CoA patients was the age of patients at the time of the initial repair (26). This finding was confirmed in many studies (5, 7, 12, 17), excepted for a few recent studies (4, 16). Rinnström et al.

followed up patients during 3 decades after CoA repair and found that the age at intervention was less important than the age at follow-up, postulating that the beneficial effect of early repair might eventually wear off as patients age (16).

Already in 1971, O'Rourke and Cartmill suggested that morbidity in CoA patients was related to abnormal hemodynamics and vascular biomechanics (27). Recent developments in experimental and computational methods seem to support this theory (28). Factors contributing to an increased LV afterload are (1) a residual narrowing leading to additional resistance and (2) a less distensible aorta interfering with the buffer function of the aorta.

The proximal aortic wall in patients with repaired CoA has been shown to have different histology, containing more collagen, less elastin fibers, and less smooth muscle cells. Compliance and distensibility of the aorta are therefore impaired in comparison with healthy individuals. Schäfer et al. found increased stiffness of the ascending aorta on MRI after CoA Repair with higher central aortic BP (29). The increased aortic wall stiffness and reduced distensibility leads to activation of the sympathetic system through activated mechanoreceptors, changes in the endocrine system, endothelial dysfunction and progressive vascular remodeling, further increasing the peripheral vascular resistance and thus BP.

In general, hypertension is based on measurement of the peripheral BP, being the simplest measure of afterload. However, peripheral BP can deviate from central aortic pressure in patients with repaired CoA, limiting thereby its value in assessing properly the vascular and cardiac hemodynamics after CoA repair [33]. The altered

wall properties of the ascending aorta influence central aortic hemodynamics (CAH) but the characterization thereof, especially when taking wave reflections into account, is difficult and requires simultaneous measurement of aortic pressure and flow.

Central aortic pressure can be predicted by using the descending aortic distension waveform as a substitute for the pressure waveform and by scaling it to the measured brachial pressure in a fluid-structure interaction (FSI) (30). Quail et al demonstrated the ability to assess central aortic systolic blood pressure (c-SBP) non-invasively using a combination of phase-contrast magnetic resonance and oscillometric brachial artery blood pressure (31). They also showed that it was possible to use the same high temporal-resolution phase-contrast magnetic resonance data to perform non-invasive wave intensity analysis (WIA) in patients with repaired CoA. Using this technique, the central aortic pressure was significantly higher in patients with repaired CoA compared to controls (31). Patients with repaired CoA had reduced total arterial compliance, increased pulse wave velocity, and larger backward compression waves, resulting in a higher LVM index. The magnitude of the backward compression waves was independently associated with variation in LVM (32). It would be interesting to correlate these parameters of central aortic hemodynamics with long-term outcome, but so far, such studies are lacking.

Egbe et al also showed that patients with CoA had worse LV diastolic function indices and more LV hypertrophy compared to controls (33). They also showed that SBP may underestimate LV afterload after coarctation repair since CoA patients have a higher arterial afterload compared with controls, even with similar SBP (34).

Recently abnormal diastolic LV function on echocardiography was shown to be related to proximal aortic elasticity (35, 36). The authors postulated that in children who had a successful CoA repair very early in life, persistently elevated aortic stiffness may lead to diastolic impairment. We also found decreased diastolic LV function in children with repaired coarctation, despite early repair and absence of residual stenosis (37).

It has long been proposed that (early) arterial reflection waves generated by scar tissue at the repair site or by a stent leads to a new pressure wave reflection, generating LVH, considered as an adaptive response to maintain wall stress. Histologically cardiomyocyte size and density increase and fibrosis ensues. This leads to changes in the viscoelastic properties and results in increased LV filling pressures. This is clinically translated in the development of LVH, regardless of HT in CoA patients (17). We showed in an experimental animal study that despite adequate relief of aortic coarctation, the Ventricular-Arterial (VA) hemodynamic relationship is compromised, depending on the sequelae of aortic treatment varying from a short residual stenosis to long non-stenotic aortic stiffening as by aortic stenting. Moreover, the impaired VA coupling is enhanced after inotropic stimulation, suggesting that the ventricular adaptation to the altered vascular dynamics may be underestimated, becoming unmasked during exercise. Although the therapeutic approach aims for complete elimination of the transaortic pressure gradient, the impact on other components of aortic hemodynamics or LV function often remains unsolved (38).

Aortic arch morphology has been found to contribute to abnormal vascular remodelling various studies, with a gothic arch having the greatest effect, Quail et al showed recently in an MRI based study that while there are many variations in 3D aortic shape after coarctation repair, there was only a modest association between variation in aortic radius and pathological wave reflections, but not with 3D curvature. This suggests that 3D shape is not the major determinant of vascular load following coarctation repair, calibre being more important than curvature (32). It is known that Aortic size mismatch between the ascending and descending aorta (D_{AAo}/D_{DAo}) can be predictive for exercise intolerance in repaired coarctation (39).

Finally, factors leading to HT unrelated to the heart or the aorta itself have also been identified. As an interesting example, Rodrigues et al showed that vertebral artery hypoplasia (VAH) with an incomplete posterior circle of Willis (ipCoW) led to an increase in cerebrovascular resistance before the onset of increased sympathetic nerve activity in borderline hypertensive humans (40). To increase cerebral blood flow, blood pressure had to rise, leading to the description “the selfish brain”. They found that CoA patients were 5.8 times more likely to have VAH+ ipCoW than controls, as identified by MRI.

5. Conclusion

A The **prevalence of HT after CoA-repair** remains substantial, and is even higher than the percentage reported by Canniffe et al.

B **Routine 24h BP measurement** is recommended yearly in patients after CoA repair as a minimal diagnostic test for HT;

C **LV diastolic dysfunction and LVH** are common in patients with repaired CoA, even in the absence of peripherally measured HT, and correlates with a worse long-term outcome.

D **Although hypertension is diagnosed based on measurement of peripheral BP, it has been shown that peripheral BP in CoA patients has a poor correlation with central aortic pressure.** Central aortic hemodynamics are significantly altered in patients with repaired CoA, and can now adequately be investigated non-invasively through echocardiography- or MRI-based wave reflection analysis methods. At the present time there are no studies linking long-term outcome with abnormal central hemodynamics in the absence of HT, but it is expected that raised central aortic pressure should have an even more deleterious effect on the heart and brain. Further studies are needed to elucidate whether it might be beneficial to treat such patients with anti-hypertensive medication.

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Chapter V

STUDY 2
Differential impact of local stiffening and narrowing on hemodynamics in repaired aortic coarctation: an FSI study. Taelman L, Bols J, Degroote J, Muthurangu V, Panzer J, Vierendeels J, Segers P. Med Biol Eng Comput. 2016 Mar;54(2-3):497-510. doi: 10.1007/s11517-015-1336-1. Epub 2015 Jul 5. PMID: 26142885.

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ORIGINAL ARTICLE

Differential impact of local stiffening and narrowing on hemodynamics in repaired aortic coarctation: an FSI study

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Abstract Even after successful treatment of aortic coarctation, a high risk of cardiovascular morbidity and mortality remains. Uncertainty exists on the factors contributing to this increased risk among which are the presence of (1) a residual narrowing leading to an additional resistance and (2) a less distensible zone disturbing the buffer function of the aorta. As the many interfering factors and adaptive physiological mechanisms present in vivo prohibit the study of the isolated impact of these individual factors, a numerical fluid–structure interaction model is developed to predict central hemodynamics in coarctation treatment. The overall impact of a stiffening on the hemodynamics is limited, with a small increase in systolic pressure (up to 8 mmHg) proximal to the stiffening which is amplified with increasing stiffening and length. A residual narrowing, on the other hand, affects the hemodynamics significantly. For a short segment (10 mm), the combination of a stiffening and narrowing (coarctation index 0.5) causes an increase in systolic pressure of 58 mmHg, with 31 mmHg due to narrowing and an additional 27 mmHg due to stiffening. For a longer segment (25 mm), an increase in systolic pressure of 50 mmHg is found, of which only 9 mmHg is due to stiffening.

Keywords Fluid–structure interaction · Stent · End-to-end anastomosis · Image-based modeling

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1 Introduction

Aortic coarctation (CoA) is a congenital disease, characterized by a narrowing of the upper descending aorta, obstructing the blood flow from the heart toward the lower part of the body. The treatment can be minimally invasive using a stent and/or a balloon catheter to dilate the coarctation zone, or the narrow section can be removed surgically. Even after a successful treatment, a high risk of cardiovascular morbidity and mortality remains with a.o. recoarctation, aortic aneurysm formation or aortic dissection, left ventricular hypertrophy, premature coronary atherosclerosis, cerebrovascular accidents and systemic hypertension [33, 44]. This suggests surgical or transcatheter treatments modify rather than correct the complex pathology of aortic coarctation [5, 10, 30] and coarctation cannot be considered an uncomplicated disease.

In 1971, O'Rourke [32] first related morbidity in CoA (repair) to adverse hemodynamics and biomechanics in the thoracic aorta and the side branches. Considering disturbed blood flow strongly affects vascular pathogenesis, and vice versa, hemodynamic information is of high clinical importance, among others to diagnose cardiovascular malfunctioning and evaluate treatment outcomes. However, the majority of the clinical CoA studies focuses on the prevalence of cardiovascular complications [8, 18, 38], the rates of mortality

[8, 18, 36] and the post-interventional relief of the pressure drop across the coarctation zone [3, 14, 19] rather than the correlation of hemodynamic indices with manifestation of late morbidity. As such, the underlying role of hemodynamics in the progression of the disease is currently not well understood. With advances in computing power, clinical imaging and segmentation software, computational simulations are nowadays an optimal tool to study the patient-specific hemodynamics and/or the biomechanics in (repaired) CoA, as they can retrieve data that are difficult to obtain in vivo.

Uncertainty exists on the factors contributing to the increased morbidity among others the presence of a residual narrowing (recurrent coarctation) and a less distensible zone, caused by the presence of a stent or scar tissue. As approximately 60 % of the buffer capacity of the aorta is located in the proximal aorta [37], this local stiffening affects the 'cushioning' function of the aorta. The local narrowing, on the other hand, leads to an additional resistance in the arterial system. In addition, a local narrowing and stiffening generate wave reflections that reach the heart fast, given the short distance to the heart [41].

The many interfering factors and adaptive physiological mechanisms present in vivo prohibit the study of the isolated impact of these individual factors. As experimental or computational studies more easily allow to mimic the alterations caused by a single parameter, these approaches are crucial in the understanding of central aortic hemodynamics following coarctation treatment. Although there is considerable literature on computational modeling of aortic coarctation, most studies do not account for the elasticity of the aorta and the fluid–structure interaction (FSI) [20, 23, 31, 40, 45] and/or have their focus on the hemodynamic impact of coarctation in patient-specific cases [21] or on arterial wall stress and remodeling [9]. The aim of this work is to develop a physiologically relevant 3D model of the aorta with a parametric model for the coarctation zone to predict the hemodynamic impact of (coexisting) stiffening and narrowing in CoA repair. Varying lengths, stiffnesses and diameter reductions of the coarctation zone are studied using fluid–structure interaction simulations, and the results are compared against the reference case of the healthy subject.

2 Methods

To obtain the geometric model of the aorta, MR images of a healthy 39-year-old male volunteer were taken. The protocol was approved by UK's national research ethics committee, and written informed consent was obtained from the volunteer. Semi-automatic segmentation (Mimics, Materialise) resulted in a 3D reconstruction of the aortic arch and thoracic aorta. At the boundaries of the computational domain, the flow rates were measured with phase-contrast

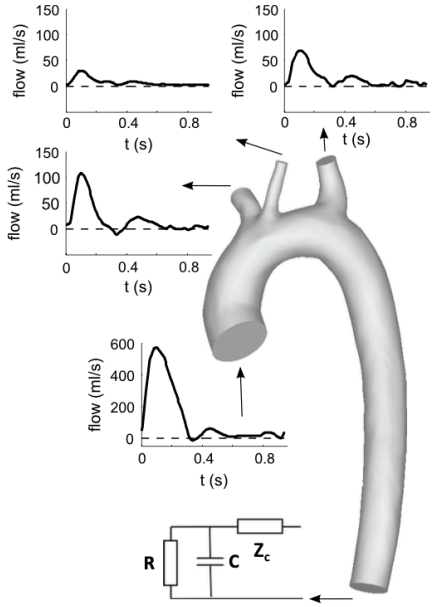

Fig. 1 Methodological figure with setup and boundary conditions

MRI and processed using Osirix. The PCMR data were encoded in one direction (through plane) to acquire volumetric flow with the encoding velocities optimized to the peak through plane velocity in the vessel of interest. These measured flow waveforms are imposed as a boundary condition at the ascending aorta and the three side branches (see Fig. 1) assuming a flat velocity profile. Mean aortic inflow was 129.8 ml/s, while mean outflow via the right brachiocephalic, left common carotid and left subclavian artery was 18.9, 7.6 and 15.9 ml/s, respectively. At the descending aorta, a three-element windkessel model is implemented, for which the parameters are defined such that physiological pressure variations are retrieved ($Z_c = 0.08$ mmHg/(ml/s), $R = 1.024$ mmHg/(ml/s), $C = 2.0$ ml/mmHg). These values were obtained by fitting a three-element windkessel model to the data, imposing the measured descending aorta flow as input and minimizing the difference between model-predicted pressure and a "measured" pressure waveform. The latter was generated by using the descending aortic distension waveform as a substitute for the pressure waveform, and scaling it to the measured brachial diastolic (80 mmHg) and systolic (115 mmHg) blood pressure. The subject's heart rate was 64 beats/min.

As computational fluid dynamics (CFD) simulations with rigid walls fail to capture some physiological patterns (such as wave propagation and reflection), the fluid–structure interaction (FSI) between the blood flow and the deformation of the arterial wall is taken into account. The governing equations for the blood flow and the deformation of the structure are solved with two separate codes (Ansys, Fluent and Simulia, Abaqus/Standard resp.), which are strongly coupled. This approach allows the flow equations and the structural equations to be solved with different techniques that are particularly suited to solve the respective equations. In this work, a quasi-Newton algorithm with an approximation for the inverse of the Jacobian (IQN-ILS) is used to solve the coupled problem [12]. This algorithm influences only the interface displacement; all remaining variables in the fluid and solid domain are considered as internal variables. It thereby treats both the flow and the structural solver as a black box which allows the use of commercial software packages. In [12], the IQN-ILS technique is compared with other partitioned schemes, such as Aitken relaxation and Interface-GMRES(R). This comparison indicates that fewer coupling iterations per time step are required if the IQN-ILS algorithm is used. To obtain an accurate calculation of the stress on the fluid–structure interface, the flow equations are solved in the Arbitrary Lagrangian–Eulerian formulation on a deforming mesh.

To create a geometric model of the aortic tissue, the aortic lumen was extended such that a diameter-to-thickness ratio of 10 % was obtained. At the boundaries, only radial displacement is allowed. The material behavior of the aortic tissue is described using a polynomial hyperelastic model (hyperelastic constants: $C_{10} = 18.9$ kPa, $C_{01} = 2.75$ kPa, $C_{20} = 400$ kPa, $C_{11} = 847.2$ kPa [35]) with the value of C_{20} obtained in an iterative way, such that the deformations of the descending aorta in the FSI simulation corresponded to the deformations measured with MRI (9 %).

Using the extended Treemesh method [2], an automated high-quality hexahedral mesh was generated in both the fluid and solid domains. Hexahedral meshes are superior to tetrahedral/prismatic meshes as they converge better, and require less computational time for the same accuracy [11]. This method furthermore allowed to create an additional refinement in the flow region distal to the coarctation where vortices develop. A mesh sensitivity study eventually led to a grid with 216 and 51k linear cells in the fluid and solid domains, respectively. A time step size of 2 ms is used to resolve the flow field in time. Details on the mesh and time step sensitivity study are provided in "Appendix". No explicit turbulence model has been used which means that small turbulent structures if present are dissipated by the numerical scheme itself (second-order upwind scheme) or resolved and dissipated by the molecular viscosity if the mesh is fine enough. This way of turbulence modeling is called ILES (implicit Large Eddy Simulation) [1].

The structural model, the flow model and the interaction between both, allow to predict the central hemodynamics in a healthy aorta. These results will be used as a reference for the other simulations. To model the functional impact of repaired CoA, a segment with varying length (L), stiffness (E_{CoA}) and diameter (D_{CoA}) is included (indicated by the colored zone in Fig. 2) using the software 3-matic (Materialise). Two types of intervention are considered. (1) Resection by end-to-end anastomosis, resulting in circular scar tissue at the location where both ends of the aorta are sutured together. In [42], local elasticity properties of the aortic wall (such as the elasticity modulus E and stiffness-index β) indicate local increase in stiffness in the region of the surgical scar. Based on the stiffness indices and dimensions reported in this article, the elasticity modulus of the coarctation region in our model (E_{CoA}) is chosen to be equal to 5 or 20 times stiffer than the unaffected aortic tissue (E_{Ao}). A length (L) of, alternately, 10 and 25 mm is thereby selected (see top left of Fig. 2). (2) Relief of the obstruction by stent deployment. In [13], a review on different stent types used in coarctation treatment is given and considerations to achieve successful stent implantation are discussed. The segment lengths applied in our research (20 and 50 mm) are chosen to cover the range of stent lengths currently used in coarctation repair. The presence of the noncompliant stent increases aortic stiffness. We arbitrarily assumed a 100 times stiffer material to mimic the wall behavior in the stented section (see top right of Fig. 2).

The severity of the residual stenosis is quantified by the coarctation index (CI), defined as the ratio of the diameter of the coarctation zone to the diameter of the descending aorta ($D_{\mathrm{CoA}}/D_{\mathrm{DAo}}$). The higher the CI, the lower the severity of the recurrent narrowing. Two gradations of severity are considered: an index of 0.5 indicating a severe stenosis which requires treatment and an index of 0.65, mimicking a mild narrowing, which does not necessitate intervention [4] (see Fig. 2 bottom).

2.1 Impact of rigid wall modeling

In a first study, the impact of a rigid wall assumption in the assessment of coarctation severity is considered. For this purpose, both a rigid wall (CFD) and a flexible wall (FSI) simulation are performed for the case of a severe stenosis ($L = 25$ mm, $E_{\mathrm{CoA}} = E_{\mathrm{Ao}}$ and CI $= 0.5$). The aortic geometry used in the CFD study corresponds to the one extracted from MR images. The same boundary conditions were used in both simulations.

2.2 Impact of repaired CoA

Next, the effect of repaired aortic coarctation on the central hemodynamics is studied for the parameter models shown

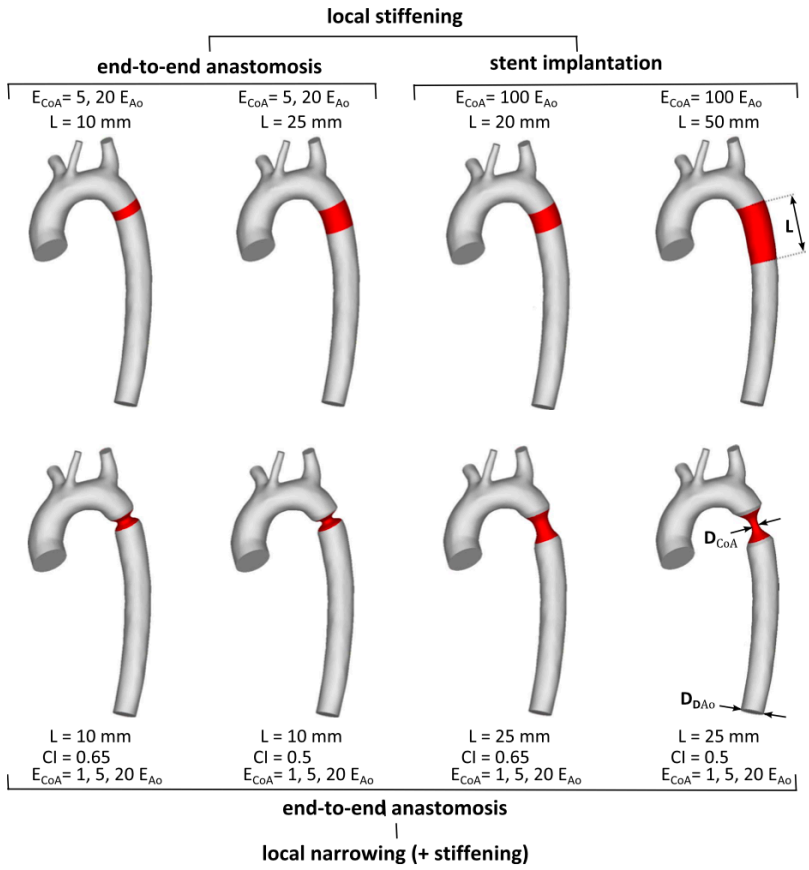

Fig. 2 Parameter models of repaired CoA used in this research

in Fig. 2. In particular, the pressure at the ascending aorta, the pressure drop across the coarctation region and the flow patterns are discussed.

3 Results

3.1 Impact of rigid wall modeling

Figure 3 compares the pressure drop and the velocity along the centerline of the aorta obtained with a rigid wall and a flexible wall simulation. For the rigid wall simulation, results are shown at peak systole. For the FSI simulation, the red curve is obtained at peak systolic inflow ($t = 0.094$ s), whereas the black curve is retrieved at the time point where the flow at the constriction site and thus the pressure gradient becomes maximal ($t = 0.174$ s). The CFD simulation strongly overestimates CoA severity as both the pressure drop across the coarctation (101 vs 57 mmHg) and the pressure difference between the ascending and descending aorta (62 vs 44 mmHg) are amplified.

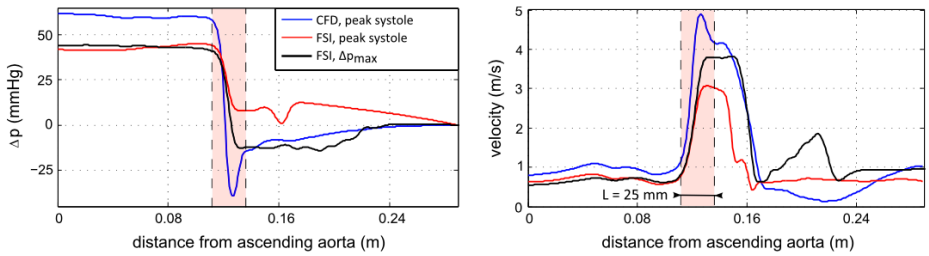

Fig. 3 Comparison of the pressure drop (viewed from the descending aorta) and velocity along the aortic arch centerline obtained with a rigid wall simulation (CFD) and a flexible wall model (FSI) of recurrent coarctation ($L = 25$ mm, $E_{CoA} = E_{Ao}$ and CI $= 0.5$). The *blue* and *red curves* are obtained at peak systole (i.e., maximal inlet flow), and the *black curve* is generated at a time point for which the pressure drop across the aortic arch reaches its maximum (color figure online)

3.2 Impact of repaired CoA on proximal pressure

Figure 4 depicts the impact of a local stiffening and/or narrowing on the pressure at the ascending aorta (i.e., the inlet of the model), averaged over the cross section. In the top left panel, the effect of an isolated stiffening is shown for the two worst cases: circular scar tissue with a length of 25 mm (20 times stiffer than the unaffected aortic tissue; black curve) and a 50-mm long stent (red curve). Only a small pressure build-up around peak systole is found, rising up to 8 mmHg with increasing stiffening and length.

The effect of a residual narrowing is illustrated in the right top panel of Fig. 4. Here, a more pronounced impact covering the whole systolic phase is observed. A coarctation index of 0.65 increases peak systolic pressure by 10 mmHg (red and green curves), independent of the length of the coarctation zone, whereas an index of 0.5 elevates the load on the heart up to 31 and 41 mmHg for a segment with a length of 10 (black curve) or 25 mm (magenta curve), respectively.

The combined effect of a narrowing (CI $= 0.5$) and a stiffening is shown in the charts at the bottom of Fig. 4. For a short segment ($L = 10$ mm), an additional stiffening will have a significant impact on the pressure evolution (up to 27 mmHg), whereas the impact of stiffening for a longer segment is relatively limited (up to 9 mmHg).

3.3 Impact of repaired CoA on pressure drop

The time-averaged pressure along the aorta is depicted in Fig. 5, in which the location of the coarctation segment is indicated by the colored zone. In a normal aorta, the mean pressure decrease is limited to 0.8 mmHg. The inclusion of a local stiffening hardly affects this pressure reduction. A sharp fall of the mean pressure near the constriction is retrieved if a narrowing is present. For a coarctation index of 0.65, the mean pressure reduces by 3.8 mmHg across the stenosis. This value further increases up to 9.1 and 11.3 mmHg for a more severe stenosis degree with a length of 10 and 25 mm, respectively. This pressure drop is accompanied by pressure recovery, persisting through a larger part of the distal aorta. Severe coarctation (CI $= 0.5$) is characterized by a smaller pressure recovery of 25 and 21 % for a length of 10 and 25 mm, whereas mild coarctation results in a recovery of 31 %.

The comparison of the pressure distribution along the aorta between the reference case and the most severe case of repaired CoA ($L = 10$ mm, $E_{CoA} = 20\,E_{Ao}$ and CI $= 0.5$) is made in Fig. 6 at the time of maximal instantaneous pressure drop (Δp_{max}) between the ascending and descending aorta (indicated in blue and red, respectively). This pressure difference is also indicated in the charts on top of this figure and differs from the peak-to-peak pressure difference (Δp_{ptp}) often reported in the literature, which is a nonphysiological measurement as the maxima at the ascending and descending aorta occur at different points in time. This last pressure difference is thus never experienced by the patient. For the normal aorta, a gradual decrease in pressure along the aortic length can be observed. For the case with recurrent coarctation, pressures falls sharply as the constriction is approached. At the distal end of the coarctation, flow deceleration is accompanied by pressure recovery which, on the other hand, takes place over the entire descending aorta.

3.4 Impact of repaired CoA on the flow patterns

Figure 6 shows the velocity contour images of the aortic arch at the time point for which the pressure gradient between the ascending and descending aorta becomes maximal. Comparison is made between the reference case and the worst case (in terms of pressure gradient across

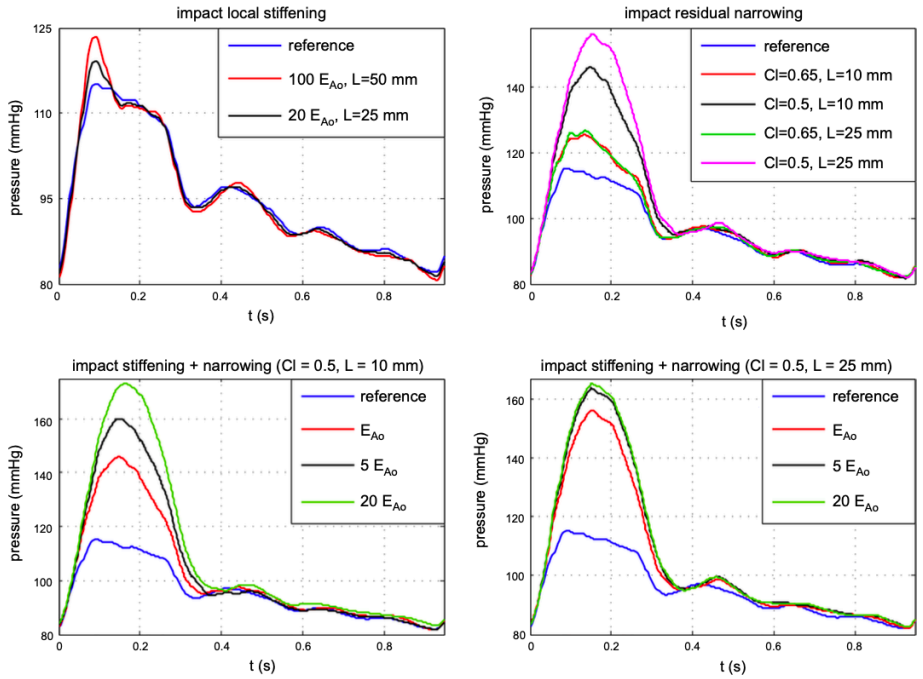

Fig. 4 Impact of a local stiffening and/or narrowing on the pressure evolution at the ascending aorta as a function of time

the CoA zone) of repaired CoA (CI = 0.5, L = 10 mm, E_{CoA} = 20 E_{Ao}). In Fig. 7, the corresponding velocity vectors at four locations along the descending aorta are shown. As reported in [20, 25], blood acceleration across the coarctation region generates complex flow distal to the stenosis. The shear layer around the flow jet, leaving the coarctation zone, is marked by a rapid growth of instabilities.

Downstream vortices and swirling are produced especially in the deceleration phase in the expansion zone. The maximal velocity increases from a value of 1.07 m/s in the normal aorta to a value of 4.7 m/s in the repaired CoA, and a shift toward the right outer wall is found. Distally, this magnitude decreases and distribution alteration results in a skewed axial velocity profile, characterized by a loss of symmetry and eventually a flow jet impacting on the posterior right outer wall. Compared with the effect of a narrowing, the impact of a local stiffening is thus fairly limited.

4 Discussion

4.1 Impact of rigid wall modeling

An important feature of the aorta is its capacity to buffer blood during systole and sustain blood flow to the rest of the body during diastole. As approximately 60 % of the buffer capacity of the healthy aorta is located in the proximal aorta [37], the presence of (repaired) CoA might affect this property. Inclusion of this characteristic hallmark in the numerical model is thus necessary in order to quantify the disease severity correctly. Most CoA studies [20, 22, 28, 31, 40, 45] are, however, performed under a rigid wall assumption. That this oversimplification may corrupt insights and provide an incorrect diagnosis of CoA severity is illustrated by Fig. 3. This substantial mismatch is related to the lack of compliance in the CFD simulation, which is responsible for the buffering and damping of the pressure pulse in the proximal aorta. Accordingly, velocities in the

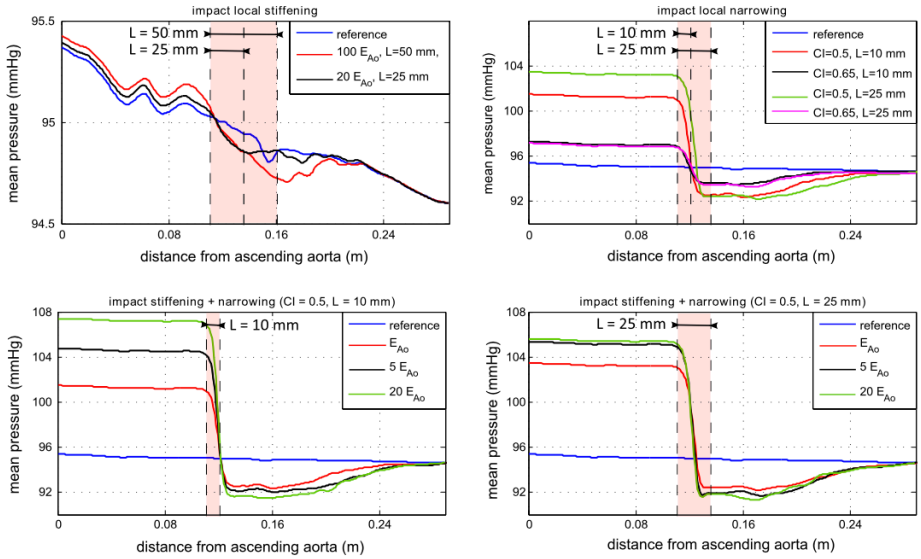

Fig. 5 Impact of a local stiffening and/or narrowing on the mean pressure evolution as a function of the distance from the model inlet (i.e., the ascending aorta)

coarctation zone and the associated pressure drop exceed the ones reported in the FSI simulation. Increased aortic compliance will enhance this buffering effect as it results in an enlarged dilation of the proximal aorta in systole and a further accumulation of stored upstream energy, which is released downstream in diastole. The diminished losses during pressure recovery downstream of the CoA partially compensate the overestimation of the pressure drop across the CoA in the CFD simulation. This might explain the moderate agreement between measured pressure differences and the ones retrieved with rigid wall models [40]. Overall, the results shown in Fig. 3 call for a fluid–structure interaction approach in the determination of pressure drops across the CoA using computational models.

4.2 Impact of repaired CoA on proximal pressure

As reported in [39], in which a physiological pressure pulse was imposed as a boundary condition to a straight, flexible tube including a local stiffening, no significant alteration of the proximal pressure is retrieved. This limited impact is comprehended by the analysis of the wave reflections induced by the stiffening. The backward compression wave generated at the transition from the flexible artery to the rigid segment is roughly canceled out by the expansion waves created at the distal end of the coarctation zone. As such, only local changes in pressure are found, related to the time delay between the backward waves. This finding is in agreement with the 1D studies performed in [6, 15] and the 3D FSI study published in [9], reporting negligible clinical consequences of a local stiffening on cardiac workload and aortic pressure. In [34], an experimental porcine model was developed to investigate the effect of a noncompliant stent. This study supports the conclusions from previous numerical studies.

Regarding the threshold for intervention, a peak-to-peak pressure difference of 20 mmHg between the upper and lower limbs is often used as an intervention criteria. This threshold compromises between the risks and benefits associated with treatment. Patients with mild coarctation are subjected to long-term hypertension or may require lifelong antihypertensive treatment. In addition, the blood pressures emerging during exercise will be much more pronounced than the ones appearing at rest. The success of noninvasive stent implantation in patients with more severe CoA, conjoined with the limited impact on the hemodynamic response, may call for a revision of the threshold for intervention [27].

For the models with recurrent coarctation, the progressive increase in proximal pressure with coarctation length

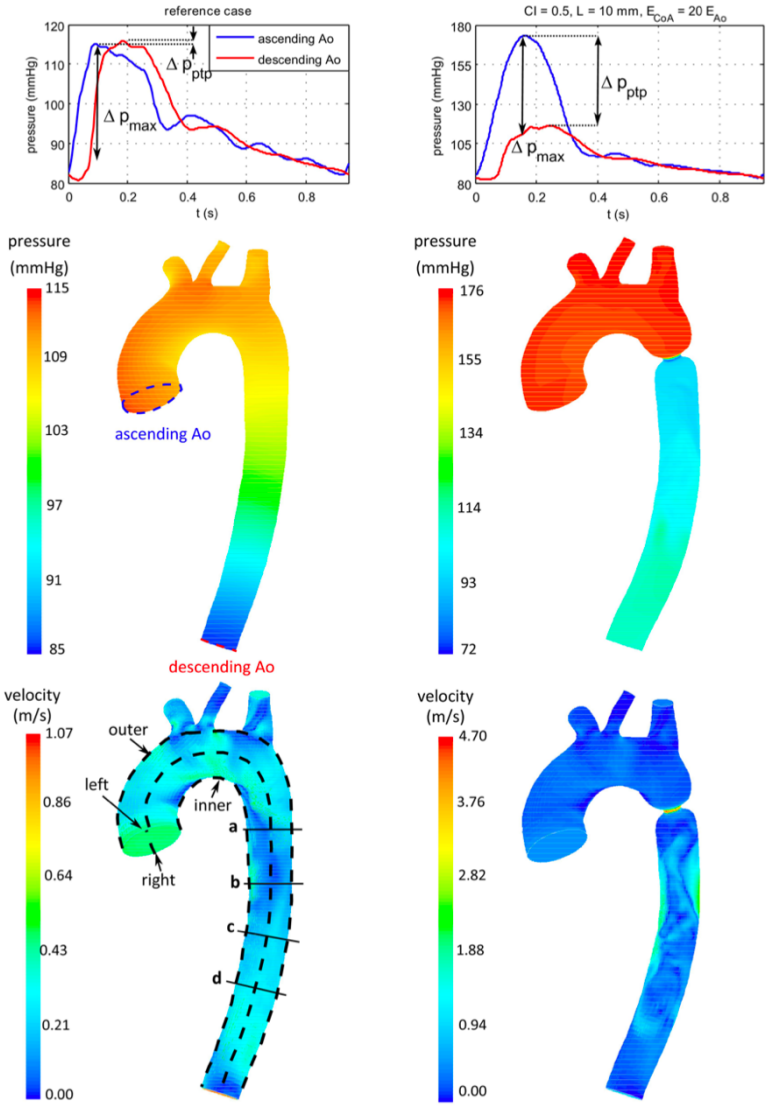

Fig. 6 Comparison of (*top*) the maximal pressure gradient in the reference case and in repaired CoA ($L = 10$ mm, $E_{CoA} = 20\ E_{Ao}$ and CI $= 0.5$) and (*bottom*) contour plot of the corresponding velocity magnitude

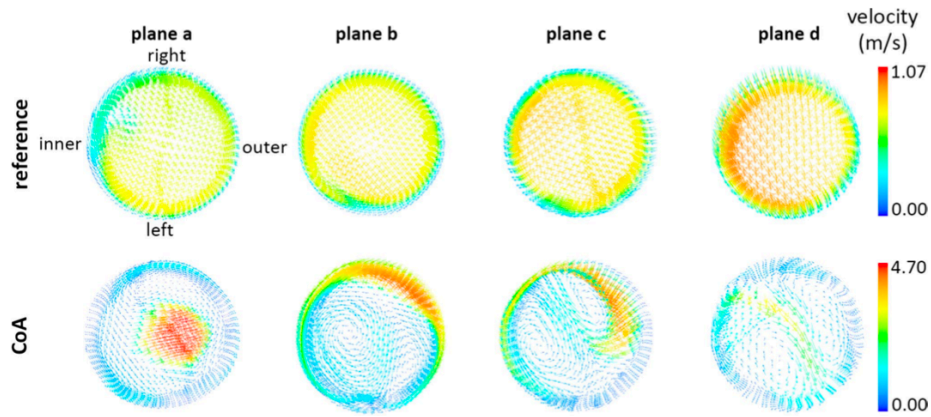

Fig. 7 Comparison of the velocity vectors along the descending aorta (planes corresponding to the ones shown in Fig. 6) in the reference case and in repaired CoA ($L = 10$ mm, $E_{CoA} = 20\ E_{Ao}$ and CI $= 0.5$)

might be explained by (1) the viscous losses which are proportional to stenosis length and inversely related to the coarctation diameter and (2) the pressure losses due to the unsteady acceleration, which become more pronounced in the stenosis due to the increased velocities and the corresponding accelerations. Remark that the pressure losses due to the unsteady acceleration should manifest in the slope of the pressure curves, as they are present during systole but become negligible around peak systole. As the slopes of the pressure curves are more or less equal in all cases, we can conclude that the additional pressure drop due to the unsteady acceleration is very small.

Considering a coexisting stiffening and narrowing, the different response between a short and a long segment might be explained by the difference in wall deformations. In the absence of a local stiffening, the short narrowed segment will experience pronounced deformations up to 29 % as it is pulled apart by the proximal and distal part of the aorta. Conversely, for a long segment, these deformations are restricted to 12 %. The smaller cross section in the latter case will result in a higher blood velocity and, as a result, in an elevated pressure drop across the coarctation. For a local stiffening ($E_{CoA} = 20\ E_{Ao}$), the distentions of the local narrowing become significantly smaller. A deformation of 3 % is retrieved for the short segment and 2.5 % for the long segment. The difference in pressure evolution in this case can be explained by the difference in shape of the constriction rather than the difference in cross section (which is nearly equal in both cases). The smaller the divergence of the streamlines distal to the stenosis, the better the pressure recovery will be. As such, a smaller pressure difference between the ascending and descending aorta is found in the case of a long stiffening which is characterized by a more gradual change in diameter.

4.3 Impact of repaired CoA on pressure drop

For a normal aorta, the dominant factor determining the value of Δp_{max} in the reference case is the inertia of the blood related to the temporal blood acceleration during the systolic phase. In case of recurrent coarctation, the (unsteady) pressure drop adds to a convective acceleration term, caused by an increase in velocity at the transition from the aorta to the stenosis and is proportional to the velocity gradient. This convective acceleration obscures the unsteady acceleration and causes the pressure to fall sharply as the constriction is approached. Distally, the conversion of kinetic energy into pressure is accompanied by energy losses related to turbulence development in the descending aorta. These losses together with the viscous losses explain the enlarged pressure drop (up to 36 mmHg) in case of repaired CoA.

Note that apart from the stenosis severity and geometry, the pressure drop and recovery furthermore depend on flow rate. For exercise conditions, for example, an even more distinctive pressure drop will be found and question remains which pressure difference is most clinically relevant: the one that is present during daily life or the worst case pressure drop, only temporary arising during exercise [7]. This suggests that an assessment of stenosis severity cannot be based on the pressure drop alone, but an additional measurement of blood flow is required. As a second

remark, we like to point out that, in this research, a circular symmetrical stiffening and narrowing are applied, mimicking stent implantation or resection by end-to-end anastomosis. Treatment outcomes of other procedures, such as patch aortoplasty or Waldhausen repair will, however, result in an asymmetrical stenosis and stiffening. This feature will manifest in an even larger pressure difference across the stenosis and a worsened pressure recovery in the posterior descending aorta [26].

5 Limitations

It is import to keep in mind that this is a parametric study where the structural and functional alterations of the coarctation zone were induced in a model entirely based on data obtained from a healthy volunteer. Patients with (repaired) aortic coarctation might have intrinsic structural defects in extracellular matrix proteins due to genetic defects [43], and their aorta has been subjected to growth and remodeling [17, 24] with adaptions in shape and material properties. In particular, for the case of aortic coarctation, wall thickening is often observed along with a decrease in compliance of the proximal aorta due to prolonged hypertension [9, 28]. As such, neither the 3D geometry, nor the assumed material constants in this paper can be considered representative for patients with (repaired) aortic coarctation. This also impacts on the demonstrated differences between the CFD and FSI results, which will be less pronounced when accounting for the reduced distensibility of the proximal aorta in the patient case.

Also, the same boundary conditions were imposed in all cases, regardless of coarctation severity. This approach, however, allows to isolate the hemodynamic alterations caused by the presence of repaired CoA and approximates the autoregulatory mechanisms of the cardiovascular system which keeps the downstream boundary conditions relatively constant. The assumption of a constant cardiac output in CoA implies an increased workload on the heart and is justified by the findings reported in [16], stating that the cardiac output and the heart rate barely change after surgically induced stenosis. We, however, believe that, due to the elevated resistance at the coarctation site, an early redistribution of flow will take place, manifesting as an increased flow through the subclavian and carotid arteries and a reduction in the descending aortic flow [9]. This was not accounted for in this study. Application of reduced order models at the distal boundaries of the fluid domain might resolve this problem [9, 21]. Since the pressure drop across the CoA is proportional to the flow rate through the constriction, the flow distribution adopted in our models represents the worst case distribution, associated with the highest pressure gradients. Similarly, disregarding the collateral network, bypassing part of the flow through the coarctation, will result in an overestimation of the actual pressure drop.

Another limitation of this research involves the lack of (viscoelastic) tissue surrounding the aorta [29]. As such, no physiological mechanism is present to damp the high-frequency oscillations of the vessel wall.

6 Conclusions

In conclusion, we have used 3D fluid–structure interaction simulations to assess the hemodynamic impact of a narrowing and/or stiffening in an otherwise healthy aorta as a parametric model of (repaired) aortic coarctation. The hemodynamic impact of an isolated stiffening is, albeit, limited. Aortic constriction, on the other hand, induces a pronounced increase in blood pressure in the proximal aorta, with buffering of the stroke volume proximal to the aortic narrowing. For short constrictions, additional stiffening will have a significant impact on the pressure evolution, whereas the impact is relatively limited for longer constricted segments. Comparison with CFD simulations highlighted the importance of accounting for the elasticity of the aorta to correctly capture the buffering of the proximal aorta.

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Appendix: Mesh and time step sensitivity study

Given the focus of the study on pressure, the criterion for the grid convergence and time step dependency study was the accuracy of the predicted pressures along the aortic arch. The case used for the analysis was the case with the shortest stenosis length (1 cm) and highest degree of stenosis (coarctation index 0.5).

Mesh sensitivity analysis

Four different, full hexahedral uniform meshes (R1, R2, R3 and R4) with an increasing number of elements in the boundary layer (ranging from 4 to 8 layers), the transversal and axial direction were constructed, with R4 considered as reference. A conforming mesh was applied in the fluid and solid domain. The number of cells is depicted in Table 1, together with the calculation time required to compute one cardiac cycle (on two 10-core Intel Xeon E5-2680v2 processors).

Table 1 Grid refinement study of the pressure in an FSI model of aortic coarctation

Grid	No. of fluid cells (k)	No. of solid elements (k)	Calc. time/cycle	Mean error (%)							
				Asc	*p1*	*p2*	Coa	*d1*	*d2*	*d3*	Desc
R1	42	21	12 h 29 min	1.44	1.42	1.42	1.72	1.61	1.56	1.33	0.77
R2	105	37	17 h 29 min	1.01	0.98	0.98	1.26	1.54	1.88	1.26	0.71
R3	281	74	30 h 55 min	0.38	0.34	0.34	0.75	1.22	1.07	0.94	0.64
R4	408	102	40 h 38 min	Reference grid							
R5	216	51	23 h 38 min	0.5	0.47	0.47	0.86	1	1.15	0.98	0.6

As the flow distal to the stenosis is complex and highly disturbed (Reynolds numbers up to 11,139), a high mesh density is required in this region to resolve the flow field in space. This is realized by locally adapting the fluid mesh. The resulting fluid mesh (R5) has, compared to the finest mesh (R4), a higher mesh density in the coarctation zone, but a coarser grid proximal to the stenosis and in the lower part of the descending aorta (see Fig. 8).

Figure 9 depicts the pressure along the centerline of the aorta at peak systole, with Table 1 tabulating the mean error of the pressure in different cross sections (indicated by the dashed lines in Fig. 9). These errors are defined with respect to the reference grid R4 and relative to the pressure amplitude in the corresponding cross section. The mean error thereby denotes the error averaged over one cardiac cycle and over the respective cross section. From the results in Table 1, it can be seen that even for meshes with a low

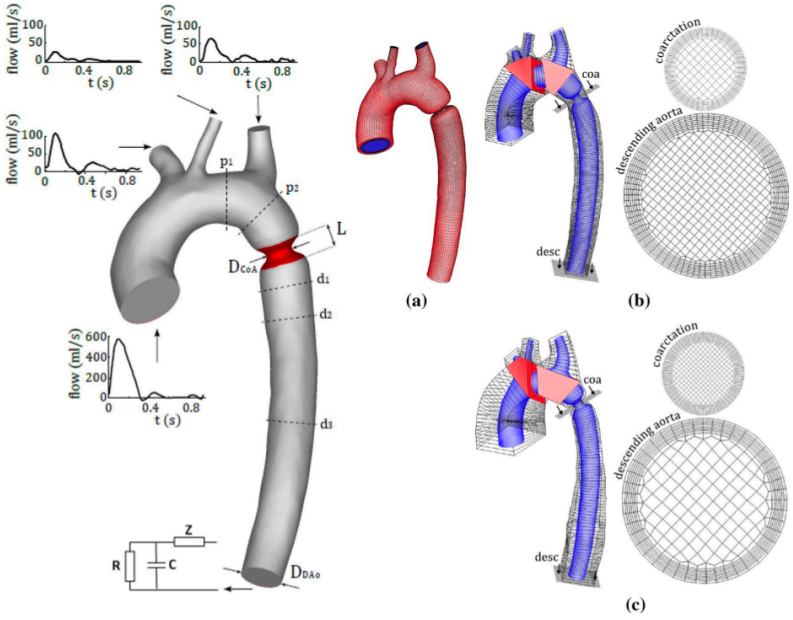

Fig. 8 *Left* indication of sections where pressure was calculated (*p* proximal; *d* distal). *Right* **a** mesh for the fluid domain (*blue*) and the arterial wall (*red*) of an aortic arch with aortic coarctation. Note the axial coarsening toward the descending aorta (R5). **b**, **c** The cross-sectional grids of the fluid mesh at the coarctation (coa) and the descending aorta (desc), which result from multiblock structures R4 (uniform grid refinement) and R5 (local grid refinement) (color figure online)

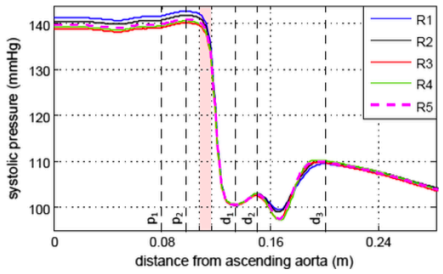

Fig. 9 Pressure along the centerline at peak systole for increasing mesh densities (R1–R4) and a grid with a local refinement at the coarctation region and a gradual coarsening toward the descending aorta (R5)

cell density, the mean errors proximal, halfway and distal to the coarctation zone remain low (<2 %). When comparing the locally refined grid R5 with the uniformly refined grids R3 and R4, an important reduction in computation time is gained (23 h 38 min per cardiac cycle vs 30 h 33 min and 40 h 38 min) without a loss in accuracy. The mean error obtained with the mesh R5 stays below 1.15 %, and comparable errors are found as for the mesh R3.

Time step sensitivity analysis

Figure 10 illustrates the impact of the time step size on the pressure evolution at different cross sections along the aorta. It can be observed that the results in the proximal part and at the coarctation zone are more or less time step independent, whereas the small pressure oscillations in the distal part are not captured with a large time step size (of 4 or 5 ms). Moreover, the oscillations developing in d3 are not even resolved properly with a time step size of 1 ms. As such, the time step size was further decreased to 0.5 and 0.25 ms and the results are shown in Fig. 11. An unstable behavior was found if a small time step size was applied. The observed oscillations responsible for this behavior were indeed not resolved for the simulations using larger time step sizes. Because the oscillations itself are resolved by multiple time steps and the frequency of the oscillations is more or less time step independent, it is presumed that these oscillations do not arise from a numerical instability but have a physical origin, triggered by the disturbed blood flow. In a physiological setting, this oscillation would, however, be cushioned by the damping nature of the surrounding tissue. We believe that the lack of physical damping in our model resulted in the observed oscillations that eventually got unstable when using a time step size smaller than 1 ms.

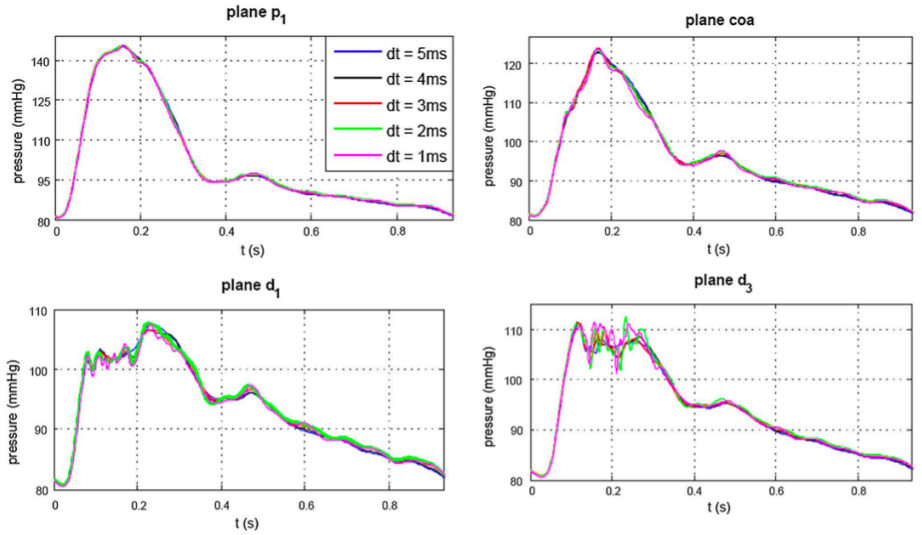

Fig. 10 Influence of the time step size on the pressure evolution at proximal cross section *p1*, halfway the coarctation zone (coa) and at two distal cross sections (*d1* and *d3*). See Fig. 8 for an indication of these plane locations

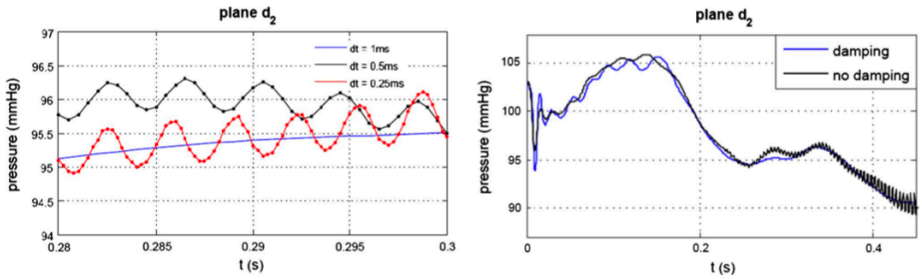

Fig. 11 *Left* detail of the pressure evolution, illustrating the temporal resolution of the oscillations. *Right* influence of Rayleigh damping on the pressure evolution at cross section *d2*. Inclusion of Rayleigh damping prevents the simulation from unstable behavior

To test this hypothesis, Rayleigh damping was added to the structural model and the simulation using a time step size of 0.5 ms was repeated. The Rayleigh damping coefficients α and β were selected such that 1 % damping of the waves with a 1-Hz frequency (close to the frequency of the cardiac cycle) was obtained and 20 % damping for the 250-Hz waves (i.e., the frequency of the observed oscillations). These constrictions resulted in a value of 0.116 for the mass proportional damping parameter α and 0.000255 for the stiffness proportional damping β. It is demonstrated in Fig. 11 that the unstable behavior indeed disappears with the use of Rayleigh damping.

The larger pressure oscillations at the start of the simulation ($t < 0.2$ s) for the case with Rayleigh damping is explained by the temporal discretization schemes used at the start. The simulation without damping is started with a first-order scheme, to facilitate the startup. After 0.2 s, the accuracy is improved by switching to a second-order scheme. For the case with damping, a second-order scheme can be used from the start on. In this study, a time step size of 2 ms has been used as a compromise between accuracy and computation time. The error obtained with this time step size is sufficiently smaller than the mutual differences in results.

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Chapter VI

STUDY 3
***Effect of aortic stiffness versus stenosis on ventriculo-arterial interaction in an experimental model of coarctation repair*.** Panzer J, De Somer F, Segers P, De Wolf D, Bove T. Eur J Cardiothorac Surg. 2020 Dec 1;58(6):1206-1215. doi:10.1093/ejcts/ezaa241. PMID: 32862227.

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Effect of aortic stiffness versus stenosis on ventriculo-arterial interaction in an experimental model of coarctation repair

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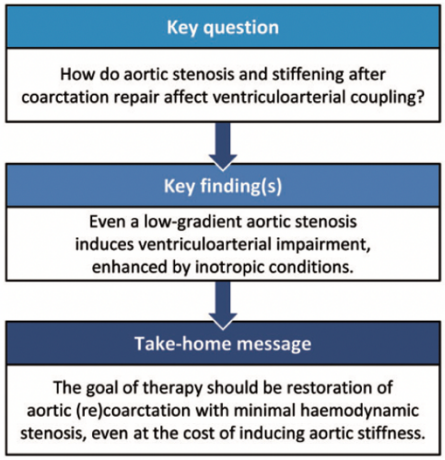

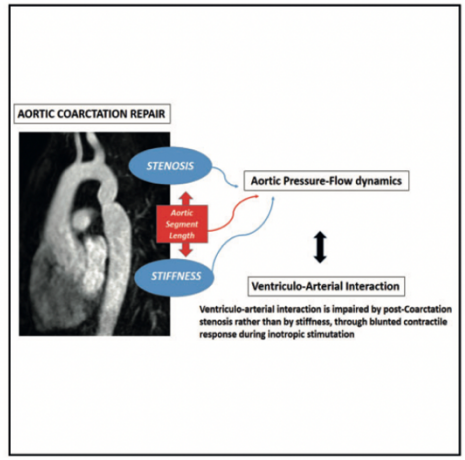

Abstract

OBJECTIVES: The aim of this study was to investigate the effect of short- versus long-segment aortic stiffness and stenosis on ventriculo-arterial interaction in a porcine model of coarctation repair.

METHODS: Short–long aortic stiffness was created by transection/suture [coarctation (CoA) suture, $n = 6$] and stenting (stent, $n = 5$) of the proximal descending aorta. Short–long aortic stenosis was achieved by wrapping a prosthetic graft around the aorta to 1/3-circumference reduction, over a segment length of 1 cm (CoA suture stenosis, $n = 5$) and 4.5 cm (stent stenosis, $n = 6$). After 3 months, aortic pressure-flow haemodynamics, aortic distensibility by intravascular ultrasound and left ventricular performance by pressure–volume loops were compared to a Sham group ($n = 5$) at baseline and during dobutamine administration.

RESULTS: The aortic impedance increased with 30.3 (12.6%) and 41.3 (20.9%) ($P < 0.001$) in CoA stenosis and stent stenosis during inotropic response. Impaired haemodynamic aortic compliance was associated with lower aortic distensibility by intravascular ultrasound, specifically in long-segment stenosis. The ventriculo-arterial coupling was disturbed in both groups with stenosis, with blunted contractile response [Sham 140.3 (19.8%), CoA suture 101.3 (14.5%), CoA suture stenosis 75.0 (8.4%), stent 115.5 (12.7%), stent stenosis 55.1 (14.6%), $P < 0.001$] and increased myocardial stiffness during dobutamine in the long-segment aortic stenosis group [Sham -26.0 (12.9%), CoA suture -27.5 (15.9%), CoA stenosis -9.5 (8.6%), stent -23.4 (4.8%), stent stenosis 19.9 (23.1%), $P < 0.001$].

CONCLUSIONS: This animal study on the sequelae of coarctation repair demonstrated that aortic stiffness had little effect on aortic pressure-flow characteristics in the absence of stenosis. However, the negative chronic effect of stenosis on aortic haemodynamics—especially a longer segment—leads to the rapid impairment of ventriculo-arterial interaction, which is accentuated by inotropy. Therefore, therapeutical management needs to focus on improving aortic remodelling after coarctation repair, preferably by minimizing residual stenosis, even at the cost of inducing aortic stiffness.

Keywords: Coarctation • Aortic haemodynamics • Ventriculo-vascular coupling

ABBREVIATIONS

AD	Aortic distensibility
CI	Coarctation index
LV	Left ventricular
MRI	Magnetic resonance imaging
PTFE	Polytetrafluoroethylene
VA	Ventriculo-arterial

INTRODUCTION

Despite successful treatment, coarctation patients remain at increased risk of cardiovascular morbidity and mortality, due to systemic hypertension, left ventricular (LV) hypertrophy, premature coronary atherosclerosis and cerebrovascular accidents [1–3]. Investigation of predisposing features has mainly been performed on patient data showing a wide variation in morphological sequelae after coarctation repair, which are often further confounded by factors such as age at the time of surgery, duration of exposure to pathophysiological loading of residual lesions and/or interplay of coexisting cardiac diseases with an impact on the adaptive response to unfavourable aortic haemodynamics.

Treatment mainly focused on the maximal elimination of the transaortic pressure gradient [4]. Although this objective can be achieved by surgery such as by endovascular stenting, clinical studies have reported residual hypertension and myocardial dysfunction in some patients, raising the suspicion that a localized aortic stiffening might affect aortic haemodynamics [5, 6]. Computational modelling studies have been designed to quantify the individual impact of various anatomical sequelae of coarctation repair on aortic haemodynamics. These data are, however, based on theoretical assumptions retrieved from magnetic resonance imaging (MRI) data of a healthy volunteer or 1 single example patient with coarctation and yield restrictive boundary conditions with regard to aortic wall properties and ventricular interaction [7, 8].

The aim of this study was to analyse the late differential effect of post-surgical or interventional lesions of coarctation therapy on aortic haemodynamics in relation to the LV adaptation in an *in vivo* animal model. Hereto, residual aortic stenosis and stiffness over short and long segments are investigated at baseline and inotropic conditions, to highlight the ventriculo-arterial (VA) interaction as observed during exercise.

METHODS

The study protocol was performed according to the standards of 'the Guide for the Care and Use of Laboratory Animals' published by the National Institutes of Health (publication 85-23, revised 1996) and approved by the ethics committee for animal research of the Ghent University Hospital (ECD 14/53).

Study protocol

Animals were sorted into 5 groups to investigate the differential effect of a short- versus long-segment aortic stiffness versus stenosis, compared to a Sham-operated control group. The study included 27 (out of 29) surviving animals divided into groups: group Sham ($n = 5$), group CoA Suture ($n = 6$), group CoA Stenosis ($n = 5$), group STENT ($n = 5$) and group STENT Stenosis ($n = 6$).

Preparation of the surgical procedure. Preparation of the animals and conduct of anaesthesia have been described in a previous work [9]. In pigs aged 4–5 months and weighing 55–65 kg, the proximal descending aorta was dissected through left lateral thoracotomy. A short-segment stiffness without stenosis (group CoA Suture) was created by aortic transection followed by unobstructed end-to-end anastomosis, and a short-segment stiffness with stenosis (group COA Stenosis) was obtained by wrapping the aortic segment with a 1-cm-long vascular polytetrafluoroethylene (PTFE) prosthesis (GORE-TEX, Gore & Ass, Newark, DE, USA), to reduce the aortic circumference by one-third. A long-segment stiffness without stenosis (group STENT) was obtained by stent implantation in the proximal descending aorta. A 4.5-cm-long bare CP stent premounted on a balloon catheter (Numed Inc., Hopkinton, NY, USA) was introduced via a 9-Fr sheath in the left carotid artery and anchored in the aorta under fluoroscopic control, facilitated by first creating a localized temporary and reversible stenosis with a removable snare. The stent was then fixed by 1 surgical suture to avoid migration. A long-segment stenosis (group STENT Stenosis) was achieved by wrapping a 4.5-cm-long PTFE prosthesis around the aorta, aiming for a 1/3 circumferential reduction. Sham-operated animals underwent a left thoracotomy without aortic procedure. Technical aspects of each procedure are shown in Fig. 1. At the end of the procedure, animals were extubated and treated with intramuscular buprenorphine 0.03 ml/kg and intercostal block with levobupivacaine 5 mg/kg.

Haemodynamic assessment. Invasive haemodynamic investigation was performed 3 months after surgery. Vascular access

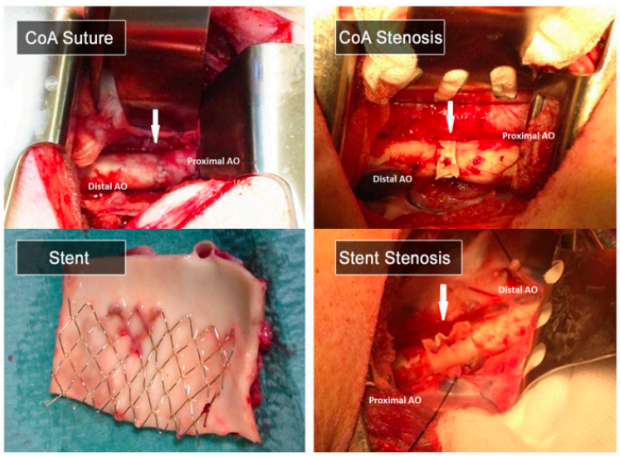

Figure 1: Coarctation repair sequelae per group: CoA suture, CoA stenosis, stent and stent stenosis (arrow indicates the study lesion at the proximal descending aorta obtained through left thoracotomy). Ao: aorta; CoA: coarctation.

was obtained by inserting a 9-Fr sheath in the right carotid artery and external jugular vein. A redo-left thoracotomy was performed to access the proximal descending aorta, after deliberate dissection of the pleural adhesions. A 16-mm perivascular flow probe (Transonic Systems, Ithaca, NY, USA) was placed around the aorta at an equal distance of ∼3–5 cm, proximally and distally to the lesion. Then, the animal was put into dorsal decubitus for heart exposure in a pericardial cradle via sternotomy. The infradiaphragmatic inferior vena cava was dissected for transient occlusion to measure preload independent indices of LV function.

Aortic pressure and flow measurements. Aortic pressure was recorded continuously through a 5-Fr fluid-filled catheter, connected to a dedicated data-acquisition platform. Catheter positioning was guided by fluoroscopy. Aortic flow into the proximal and distal aorta was recorded via the perivascular flow probes as mentioned previously. Pressure and flow recordings were integrated into the Sigma-M module (CD Leycom, Zoetermeer, Netherlands) and digitized at 250 Hz for analysis with the Conduct NT-CFL-512 software (CD Leycom). Data analysis was performed using a custom-made track programmed in MATLAB (MATLAB, Mathworks, Natick, MA, USA).

The aortic pressure was measured in the descending aorta proximally and distally from the study lesion and presented by the systolic and diastolic pressure values expressed in mmHg. The pulse pressure is calculated as the systolic–diastolic pressure difference. The pressure gradient across the lesion was obtained by subtracting the distal from proximal systolic pressure. The aortic flow is presented by the maximum value expressed in ml/s. The flow gradient is calculated by the difference in maximum flow recorded between the proximal and distal flow probe. The aortic compliance was computed using the stroke volume (ml) over the pulse pressure (mmHg), using the integral of the positive deflection of the flow measurement to calculate the stroke volume.

Aortic pressure and flow signals were then decomposed into sinusoidal harmonics using a discrete Fourier analysis, transforming the signals from the time domain into the frequency domain. The pressure and flow waves are thus considered simultaneously to represent sinusoidal waves (harmonics) with frequencies that are natural multiples of heart frequency. For a given frequency, Z_{in} is then calculated as the ratio of the pressure and flow harmonics at that frequency. Aortic characteristic impedance Z_0 was estimated in the frequency domain (Z_0-FD) as the average of the moduli of the 5th–10th harmonics.

The pressure P and flow Q signals were synchronized such that the early systolic upstroke of the Q–P relation becomes linear, with a slope as close as possible to the frequency-domain impedance Z_0-FD. The slope of the linear Q–P relationship was recorded as the time-domain characteristic impedance Z_0-TD. All data are represented by the mean value of 5–10 consecutive cycles with adequate signal registration (Fig. 2).

Aortic distensibility. Aortic distensibility (AD) was evaluated by intravascular ultrasound with the use of an 8.5-Fr PV 0.035 catheter connected to an S5 imaging system (Philips Volcano, Eindhoven, NL, USA). The intravascular ultrasound catheter was positioned via the carotid artery in the thoracic aorta distally from the aortic lesion and progressively pulled back across the lesion to the proximal aorta during recording, allowing instantaneous measurement of aortic area after manually contouring of the aorta during systole and diastole (Fig. 3). Quantification of AD is based on the cross-sectional aortic area change from diastole to systole and adjusted for the instantaneous pulse pressure, by the equation:

$$\mathrm{AD} = \text{maximum area–minimum area/minimum area} \times \text{in cm}^2 \times 1/\Delta\mathrm{P} \times 100(\text{expressed as \% area} \times \text{change/mmHg}).$$

AD was calculated at the aorta distally from the lesion and proximally at the aortic segment between the aortic arch and the

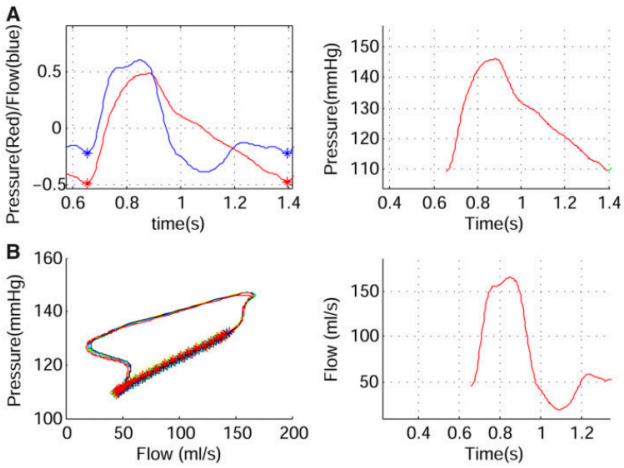

Figure 2: (**A**) Registration of simultaneous pressure (P in red)–flow (Q in blue) wave signals. (**B**) Signal synchronization is performed based on the early systolic upstroke of Q–P relationship to obtain a linear slope, for the calculation of characteristic impedance.

lesion. A similar measurement was done at the level of the surgical lesion or stent to quantify the extent of vascular stenosis, expressed as coarctation index (CI), using the distal thoracic aorta as reference. A lower CI corresponded to a higher stenosis.

Left ventricular haemodynamics. LV dynamics were assessed with a 7-Fr conductance catheter positioned into the LV and connected to the Sigma-M module and digitized at 250 Hz for on-line analysis with the Conduct NT-CFL-512 software (CD Leycom). Volume calibration was performed by the integration of slope factor α for cardiac output through a flow probe at the ascending aorta, and for parallel conductance during the injection of 0.02 ml/kg hypertonic saline. LV dynamics focused on preload independent indices of myocardial function, via transient inferior vena cava occlusion. Ventricular contractility was established based on the determination of the preload recruitable stroke work, given by the linear regression slope of stroke work during preload modulation. Diastolic LV function was determined by exponential fitting of the end-diastolic volume–pressure relationship, expressed as myocardial stiffness coefficient β. VA coupling was defined by the E_a/E_{es} ratio, with E_{es} derived from the linear regression slope of end-systolic pressure–volume points during preload decrease, and E_a by the ratio of end-systolic aortic pressure to stroke volume. Only slope values were accounted for a linear regression achieving a correlation coefficient r of >0.90, and covering at least 15 consecutive beats.

Measurements. All data were acquired during end-expiratory ventilatory arrest, at baseline and after the administration of 5 µg/kg/min dobutamine. The inotropic response was calculated as the difference between the dobutamine-induced and baseline value, normalized to the baseline value, expressed as % difference.

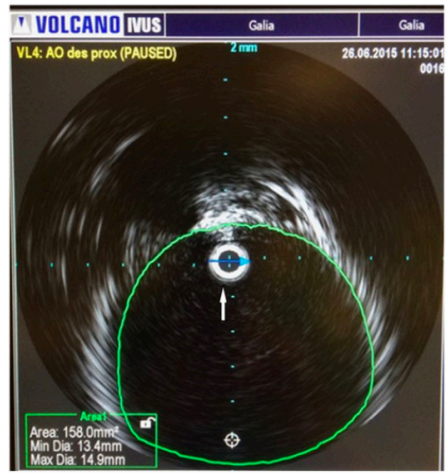

Figure 3: Intravascular ultrasound-derived method of aortic distensibility measurement: manually delineation of aortic wall contours of the aorta proximally and distally from the study lesion allows instantaneously automated calculation of intravascular area change between systole and diastole (arrow indicates the intraluminal intravascular ultrasound probe into the proximal aorta).

Histology

At the end of the procedure, animals were euthanized with the intravenous administration of embutramide 200 mg,

Table 1: Aortic haemodynamic data

	SHAM	CoA Suture	CoA Stenosis	STENT	STENT Stenosis	ANOVA *P*-value
Number	5	6	5	5	6	
Weight (kg)	130.0 (2.1)	124.5 (1.3)	121.2 (6.3)	125.6 (1.5)	124.7 (2.8)	0.103
Coarctation index	1.00 (0.06)	0.96 (0.05)	0.52 (0.05)[a]	0.85 (0.04)[b]	0.48 (0.08)[a]	<0.001
Systolic Ao pressure (mmHg)						
Baseline	127.3 (13.9)	110.9 (19.5)	108.3 (5.9)	119.8 (25.7)	109.5 (17.6)	0.611
Dobutamine	169.8 (17.4)	142.8 (17.4)	138.2 (10.6)	144.3 (30.2)	137.2 (22.1)	0.083
% Difference	34.8 (12.8)	32.7 (19.2)	27.8 (9.2)	22.8 (9.3)	26.3 (9.3)	0.340
Diastolic Ao pressure (mmHg)						
Baseline	92.6 (15.5)	76.6 (23.3)	70.3 (12.0)	85.8 (16.7)	75.3 (25.3)	0.463
Dobutamine	131.3 (12.9)	106.9 (18.6)	80.9 (11.1)[a]	109.9 (20.6)	90.7 (25.8)[a]	0.002
% Difference	43.9 (20.6)	44.3 (28.1)	12.4 (17.4)	27.3 (14.1)	23.3 (13.4)	0.065
Pulse pressure (mmHg)						
Baseline	33.7 (6.5)	32.6 (4.4)	38.0 (8.5)	33.8 (9.0)	36.2 (7.8)	0.750
Dobutamine	38.3 (10.9)	35.2 (6.1)	60.6 (15.2)[c]	35.2 (13.2)	47.9 (8.5)	0.006
% difference	14.1 (28.6)	7.9 (9.6)	51.4 (43.2)[c]	3.7 (26.3)	35.3 (16.3)	0.014
Peak pressure gradient (mmHg)						
Baseline	1.9 (0.6)	1.3 (1.6)	15.0 (3.3)[c]	3.8 (3.4)	20.5 (7.2)[d]	<0.001
Dobutamine	2.7 (3.4)	5.8 (4.8)	27.1 (8.0)[c]	8.0 (4.6)	30.4 (13.4)[d]	<0.001
% difference	88.5 (80.5)	342.8 (384.5)	94.5 (99.7)	388.8 (515.7)	48.1 (46.1)	0.334
Maximum Ao flow (ml/s)						
Baseline	184.2 (27.3)	209.1 (34.4)	185.7 (16.9)	207.2 (42.3)	148.6 (45.3)[e]	0.012
Dobutamine	297.5 (40.3)	301.2 (15.3)	234.3 (28.7)	287.8 (55.3)	174.6 (44.5)[f]	<0.001
% difference	61.9 (13.1)	48.3 (27.5)	26.5 (8.3)[g]	41.9 (11.7)	15.3 (10.5)[d]	0.001
Flow gradient (ml/s)						
Baseline	-2.2 (6.1)	-2.4 (11.3)	21.0 (14.8)[a]	9.4 (10.9)	22.1 (6.6)[a]	<0.001
Dobutamine	-9.3 (5.7)	-4.1 (6.0)	38.6 (20.1)[a]	28.6 (15.8)	46.2 (30.5)[a]	<0.001
% difference	14.2 (37.5)	6.6 (14.5)	73.9 (19.6)	46.0 (29.7)	88.0 (18.3)	0.064
Stroke volume (ml)						
Baseline	58.0 (9.1)	59.4 (7.5)	67.4 (7.4)	64.0 (15.1)	48.9 (14.8)	0.112
Dobutamine	62.2 (8.3)	58.7 (7.4)	53.2 (14.7)	61.4 (12.5)	41.0 (11.7)[d]	0.022
% difference	7.5 (5.1)	-0.5 (12.4)	-13.5 (15.2)[h]	-3.2 (7.5)	-15.7 (2.9)[i]	0.004
Impedance Z_{cFD} (mmHg/ml/s)						
Baseline	0.22 (0.05)	0.20 (0.07)	0.29 (0.07)	0.21 (0.11)	0.43 (0.12)[d]	<0.001
Dobutamine	0.16 (0.05)	0.16 (0.07)	0.38 (0.15)	0.17 (0.11)	0.56 (0.17)[d]	<0.001
% difference	-27.4 (26.4)	-24.0 (26.2)	30.3 (12.6)	-15.4 (35.4)	41.3 (20.9)[j]	<0.001
Impedance Z_{cTD} (mmHg/ml/s)						
Baseline	0.18 (0.04)	0.15 (0.03)	0.23 (0.05)	0.17 (0.04)	0.26 (0.10)[d]	0.027
Dobutamine	0.14 (0.04)	0.13 (0.05)	0.27 (0.10)	0.15 (0.08)	0.41 (0.18)[d]	<0.001
% difference	-21.4 (23.6)	-18.7 (26.4)	21.3 (24.3)	-17.9 (26.4)	55.6 (44.4)[d]	0.001
Aortic compliance (ml/mmHg)						
Baseline	0.63 (0.14)	0.78 (0.21)	0.60 (0.12)	0.74 (0.20)	0.39 (0.17)[e]	0.007
Dobutamine	0.59 (0.20)	0.65 (0.21)	0.26 (0.17)[a]	0.66 (0.25)	0.17 (0.09)[a]	<0.001
% difference	-5.7 (28.1)	-17.4 (9.8)	-59.8 (18.3)[a]	-12.5 (13.4)	-54.3 (26.5)[a]	<0.001

[a]$P < 0.05$ between STENT Stenosis/CoA Stenosis and other groups.
[b]$P < 0.05$ between STENT and Sham–CoA Suture.
[c]$P < 0.05$ between CoA Stenosis and Sham–CoA Suture–STENT.
[d]$P < 0.05$ between STENT Stenosis and Sham–CoA Suture–STENT.
[e]$P < 0.05$ between STENT Stenosis and CoA Suture–STENT.
[f]$P < 0.05$ between STENT Stenosis and all other groups.
[g]$P < 0.05$ between CoA Stenosis and Sham.
[h]$P < 0.05$ between CoA Stenosis/STENT Stenosis and Sham.
[i]$P < 0.05$ between STENT Stenosis and CoA suture.
[j]$P < 0.05$ between STENT Stenosis and Sham–CoA Suture.
Ao: aorta; CoA: coarctation.

mebenzoniumiodide 200 mg, tetracaine hydrochloride 5 mg and dimethylformamide 1 mg (T61) at a dose of 0.3 ml/kg. The heart was harvested and the LV was isolated by the excision of right ventricular free wall and adjacent atrial and vascular structures, to obtain the LV mass weight. At random LV tissue samples were fixed in 4% formaldehyde and embedded in paraffin. Haematoxylin–eosin and Masson's trichrome staining were used for the delineation of interstitial fibrosis defined as perimysial and perivascular fibrosis. Extent of collagen infiltration was estimated semi-quantitatively as grade 0 (= poor), 1 (= mild), 2 (= moderate) and 3 (= severe). Samples of the thoracic aorta distally and proximally from the study lesion were analysed for visual quantification of the collagen–elastin distribution across the aortic wall.

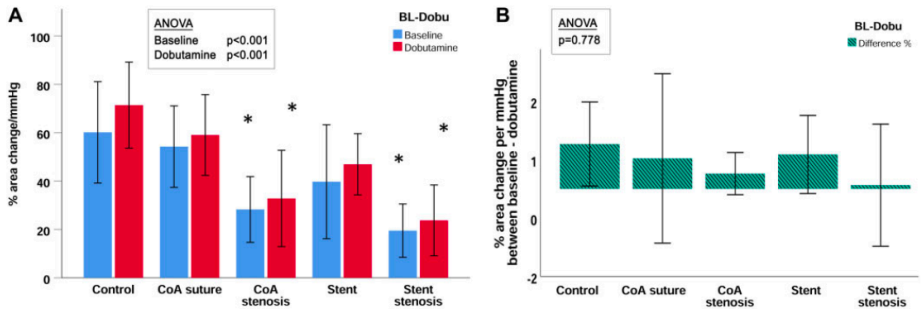

Figure 4: Proximal aortic distensibility. Bars represent mean values and standard deviation. *P < 0.05 between STENT Stenosis–CoA Stenosis and Sham–CoA Suture. CoA: coarctation.

Table 2: LV haemodynamic results

	Sham	CoA Suture	CoA Stenosis	STENT	STENT Stenosis	ANOVA P-value
Heart rate (bpm)						
Baseline	82.6 (6.6)	79.8 (5.7)	75.6 (12.1)	79.8 (3.8)	81.3 (18.9)	0.191
Dobutamine	106.6 (13.5)	102.0 (10.5)	110.8 (12.1)	99.4 (4.4)	118.5 (21.6)	0.164
% difference	28.7 (6.9)	28.6 (18.5)	48.2 (18.8)	24.8 (9.9)	36.3 (6.4)	0.083
ES-LV pressure (mmHg)						
Baseline	109.2 (11.9)	92.8 (20.0)	97.6 (10.4)	107.0 (11.4)	103.5 (20.2)	0.436
Dobutamine	147.6 (9.5)	130.7 (20.7)	148.0 (7.1)	140.6 (23.7)	132.0 (19.6)	0.340
% difference	36.2 (14.8)	42.7 (15.1)	52.5 (12.1)	30.9 (9.8)	28.6 (8.9)[a]	0.032
ED-LV pressure (mmHg)						
Baseline	12.8 (3.9)	8.8 (4.1)	9.4 (3.0)	12.6 (2.7)	19.3 (7.2)[b]	0.004
Dobutamine	15.6 (2.7)	11.0 (4.9)	10.7 (3.3)	17.0 (5.1)	23.5 (5.9)[c]	0.001
% difference	25.9 (19.4)	24.6 (24.6)	24.0 (13.2)	35.3 (24.3)	28.9 (36.1)	0.951
PRSW-slope (mW/s/ml)						
Baseline	47.2 (3.2)	49.3 (8.2)	51.7 (4.2)	50.4 (4.4)	46.1 (13.5)	0.780
Dobutamine	113.0 (7.1)	99.3 (12.2)	87.3 (7.0)[d]	108.5 (10.1)	71.6 (19.8)[e]	<0.001
% difference	140.3 (19.8)	101.3 (14.5)	75.0 (8.4)[f]	115.5 (12.7)	55.1 (14.6)[e]	<0.001
Myocardial stiffness β (ml^{-1})						
Baseline	0.17 (0.04)	0.18 (0.05)	0.22 (0.03)	0.26 (0.11)	0.17 (0.08)	0.120
Dobutamine	0.12 (0.02)	0.13 (0.05)	0.19 (0.02)	0.20 (0.09)	0.21 (0.08)	0.118
% difference	-26.0 (12.9)	-27.5 (15.9)	-9.5 (8.6)	-23.4 (4.8)	19.9 (23.1)[g]	<0.001
E_a/E_{es}						
Baseline	1.40 (0.38)	1.12 (0.18)	1.31 (0.13)	1.03 (0.33)	0.99 (0.18)	0.061
Dobutamine	2.11 (0.51)	2.05 (0.53)	3.32 (0.42)[h]	1.80 (0.42)	3.07 (0.48)[h]	<0.001
% difference	53.9 (22.6)	82.6 (44.8)	150.9 (30.3)[h]	77.3 (22.9)	171.1 (35.1)[h]	<0.001

[a] P < 0.05 between STENT Stenosis and CoA Stenosis.
[b] P < 0.05 between STENT Stenosis and CoA Suture.
[c] P < 0.05 between STENT Stenosis and CoA Suture–CoA Stenosis.
[d] P < 0.05 between CoA Stenosis and Sham–STENT.
[e] P < 0.05 between STENT Stenosis and Sham–CoA Suture–STENT.
[f] P < 0.05 between CoA Stenosis and Sham–CoA Suture–STENT.
[g] P < 0.05 between STENT Stenosis and other groups.
[h] P < 0.05 between STENT Stenosis–CoA Stenosis and other groups.
bpm: beats per minute; CoA: coarctation; E_a: arterial elastance; E_{es}: ventricular elastance; ED: end-diastolic; ES: end-systolic; LV: left ventricular; PRSW: preload recruitable stroke work.

Statistical analysis

Sample size calculation was based on a hypothetical difference of 10% between at least 2 of the study groups, accounting for a 5% standard deviation and aiming for a power >80% and $\alpha = 0.05$. Using a one-way ANOVA statistical method for comparison between 5 groups, a number of 6 animals per group were required, resulting in an actual power of 0.91 (SAS sample size calculator 3.1).

All data are expressed as mean value and standard deviation. Assuming normality of the data distribution, one-way ANOVA

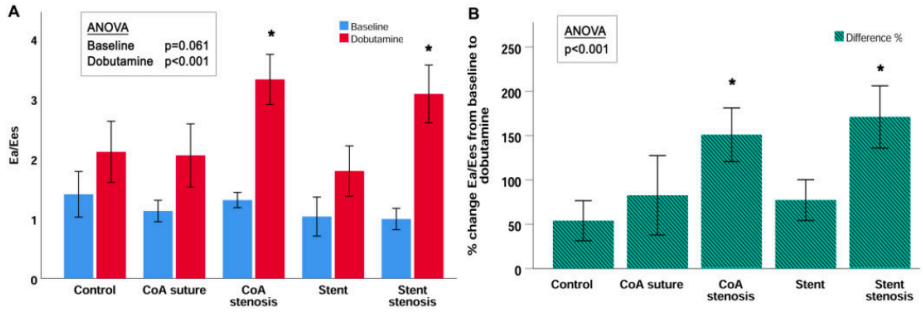

Figure 5: Ventriculo-arterial coupling at baseline and inotropic stimulation. Bars represent mean values and standard deviation. *P < 0.05 between STENT Stenosis–CoA Stenosis and other groups. CoA: coarctation.

was used for between-group comparison with *post hoc* correction for multiple comparisons based on, respectively, Tukey or Dunnett-T3 correction, depending on the homogeneity of variance. This analysis was done for measurements at baseline and during dobutamine administration, as well as for the percentage change from baseline to inotropic response among the study groups. Semi-quantitative histological comparison of myocardial fibrosis was based on the Kruskal–Wallis testing followed by Mann–Whitney tests with Bonferroni correction for 2 × 2-group comparisons. Statistical testing was performed with SPSS version 25 (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 was considered as statistically significant.

RESULTS

Twenty-nine animals were operated on, 6 per study group and 5 as control. Two animals died: 1 in group STENT due to stent dislocation and 1 in group CoA Stenosis due to pulmonary infection and septicaemia.

Aortic flow and pressure haemodynamics

A significantly lower CI was measured in both groups with induced aortic stenosis, whereas group STENT showed a CI lower than groups Sham and CoA Suture (Table 1). Consequently, the pressure gradient at baseline was significantly elevated in groups CoA Stenosis and STENT Stenosis and further accentuated during dobutamine stimulation. This was associated with an increased peak flow gradient in these groups at baseline as well as during inotropy. The pulse pressure was higher in groups CoA Stenosis and STENT Stenosis, mainly related to a proportionally lower rise of the diastolic blood pressure during dobutamine administration [CoA Stenosis: 12.4 (17.4%)–STENT Stenosis: 23.3 (13.4%) vs Sham: 43.9 (20.6%)].

The characteristic impedance expressed as Z_{cFD} and Z_{cTD} was significantly higher in group STENT Stenosis in comparison with other groups at baseline and during inotropy, except for the comparison with CoA Stenosis. Aortic compliance based on the stroke volume-to-pulse pressure ratio was lower in group STENT Stenosis at baseline but decreased significantly in both groups with stenosis during inotropy, whereas compliance remained grossly unchanged in the absence of stenosis.

Aortic distensibility

Data are represented graphically in Fig. 4. Groups STENT Stenosis and CoA Stenosis showed a decreased AD compared to groups Sham and CoA Suture at rest and during inotropy (ANOVA P < 0.001). The difference in group STENT was not significant (baseline: STENT Stenosis–STENT, P = 0.205, and CoA Stenosis–STENT, P = 0.739; dobutamine: STENT Stenosis–STENT, P = 0.124, and CoA Stenosis–STENT, P = 0.588).

Left ventricular haemodynamics

LV contractility based on preload recruitable stroke work slope was comparable in between the groups at baseline but was significantly depressed in group STENT Stenosis compared to other groups (except to CoA Stenosis) during dobutamine. LV contractility during inotropy was also lower in group CoA Stenosis compared to group Sham [mean difference 25.7 (3.6%), P = 0.029] (Table 2). Consequently, the inotropic response was significantly blunted in both groups with stenosis, illustrated by a mean difference of, respectively, 85.2 (10.6%) and 65.3 (6.1%) between group STENT Stenosis and group CoA Stenosis versus Sham. This was associated with decreased LV compliance during dobutamine administration, comparing group STENT Stenosis to other groups. Diastolic LV function appeared to be unaffected by a short-segment stenosis.

In addition, the group differences in E_a/E_{es} ratio were not significant at baseline, but E_a/E_{es} increased significantly in groups STENT Stenosis and CoA Stenosis compared to other groups during dobutamine stimulation, resulting in a significant impairment of VA coupling during inotropy in both groups with stenosis (Fig. 5).

Histology

The LV mass was, respectively, 279.4 (4.8), 284.7 (17.7), 315.6 (24.5), 308.4 (10.5) and 378.7 (22.2) g in groups Sham, CoA Suture, CoA Stenosis, STENT and STENT Stenosis (ANOVA P < 0.001) and

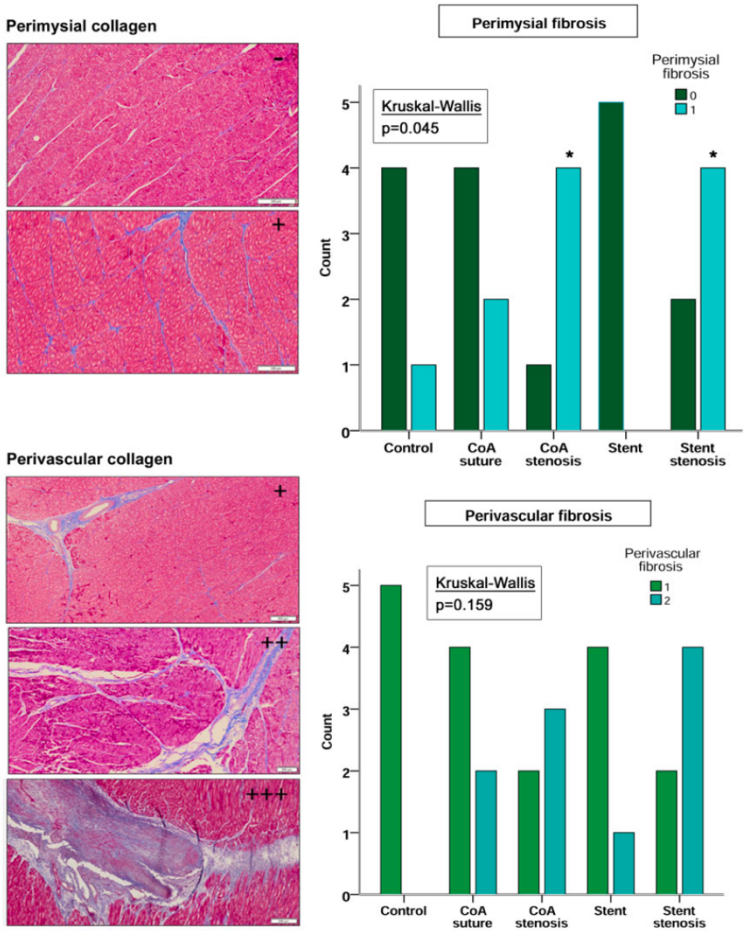

Figure 6: Histological left ventricular tissue analysis: quantification of interstitial fibrosis content. Bars represent cumulative counts. *$P < 0.05$ between STENT Stenosis–CoA Stenosis and Sham. CoA: coarctation.

was significantly increased in group STENT Stenosis compared to all other groups ($P < 0.001$), and in group CoA Stenosis compared to Sham ($P = 0.029$). A significantly greater extent of especially perimysial fibrosis was found in groups CoA Stenosis ($P = 0.041$) and STENT Stenosis ($P = 0.038$) compared to Sham, whereas differences in perivascular fibrosis were not significant ($P = 0.159$). The total amount of myocardial fibrosis reached no statistically significant difference in between the groups ($P = 0.085$) (Fig. 6). Histological tissue examination showed no changes in the proximal and distal aortic wall composition.

DISCUSSION

Despite adequate relief of aortic coarctation, the late VA haemodynamic relationship stays compromised, depending on the sequelae of aortic treatment varying from a residual stenosis to local aortic stiffening. Although the therapeutic approach aims for complete elimination of the transaortic pressure gradient, the impact on other components of aortic haemodynamics or LV function remains often unsolved [6]. Recently, the role of localized aortic stiffness due to surgical scarring or aortic stent

implantation has been investigated but revealed to have only a modest effect on cardiac workload or aortic haemodynamics [8].

In this animal study, the chronic effect of each type of rest lesion after coarctation repair is assessed in terms of aortic pressure–flow interference, aortic compliance and VA coupling. Creation of a moderate stenosis resulted in a peak pressure gradient ranging from 15 to 20 mmHg at rest, which increased significantly to 27.1 (8.0) and 30.4 (13.4) mmHg for, respectively, a short- and long-segment stenosis during dobutamine stimulation. Aortic impedance increased with, respectively, 30.3 (12.6%) and 41.3 (20.9%) in short- and long-segment stenosis from baseline to inotropic condition. Compliance and distensibility of the proximal aorta were equally impaired. Hence, even such moderate, low gradient stenosis, raising the impedance with 30–40%, had an adverse effect on myocardial performance, with blunted contractile response to dobutamine administration, increased myocardial stiffness and VA uncoupling.

The effect of the stenosis length on vascular haemodynamics has been examined via computational modelling and revealed that the pressure evolution was most impacted by a long stenosis compared to a short stenosis, whereas stiffening on top of the stenosis had only an additive contribution for a short constriction [7]. By investigating the effect of various types of aortic arch hypoplasia, Coogan *et al.* [10] found that the cardiac workload increased proportionally with the length of aortic hypoplasia, being even higher for diffuse hypoplasia at a lower degree of stenosis than for a short coarctation of 75% stenosis. Our study confirmed similarly that a long-segment stenosis resulted in a greater afterload increase than a short-segment stenosis, with a worse effect on cardiac function.

The emergence of endovascular stenting as an effective treatment of aortic (re)coarctation has initiated research on the effect of localized aortic stiffness on vascular and cardiac dynamics. Besides alterations in laminar flow at the transition between the stent and native aorta, stenting usually enables obstruction relief without residual pressure gradient, at least at rest. In a porcine model, stenting had no impact on aortic compliance in the short term [11]. Accordingly, in a long-term assessment of aortic stenting at 12 months after implantation, Maschietto *et al.* [12] were not able to show any haemodynamic alteration but identified an increase in the expression of genes associated with oxidative stress and endothelial dysfunction, suggesting a susceptibility for increased stiffness of the proximal aorta, despite the absence of histological aortic wall deformation. Based on a computational fluid dynamic simulation retrieved from MRI data of a young coarctation patient, virtual stent therapy was shown to have a negligible effect on cardiac workload and aortic pressure compared with surgical resection and anastomosis [8]. In our study, aortic and cardiac haemodynamics due to short-segment stiffening such as that obtained after surgical coarctation repair without residual stenosis were comparable to those in Sham-operated animals. The effect of stenting on aortic pressures and characteristic impedance and on ventricular interaction remained equally futile, regardless of whether a 15% reduction in aortic diameter measured by intravascular ultrasound was induced.

Clinical implications

The decision for active treatment of a residual stenosis is usually based on the transaortic pressure gradient, commonly measured at rest, although the threshold value is a matter of debate. Despite complete alleviation of the pressure gradient, Keshavarz-Motamed *et al.* [6] found no improvement in LV function and only a modest change in aortic haemodynamics in 34 adults with mild coarctation causing a pressure gradient of <20 mmHg. These results need to be interpreted while keeping in mind that some functional alterations were long-standing and perhaps irreversible in a cohort with a mean age of 40 years and that functional assessment was performed immediately after stent implantation. Otherwise, Wendell *et al.* [13] proposed that the threshold of 20 mmHg pressure gradient should be maintained by demonstrating an amelioration of LV function and mass regression in a rabbit model of coarctation repair.

Our study confirmed the unfavourable effect of even moderate stenosis on aortic and LV haemodynamics, together with adverse myocardial tissue remodelling. Its effect is enhanced by the length of the stenosis and further accentuated during inotropic stimulation. Although the measured pressure gradient might be acceptable, it is conceivable that the chronic effect on VA relationship is underestimated in view of its stronger impact during stress conditions as perceived during altering periods of adrenergic stimulation related to daily-life activities. In contrast, as a long-segment aortic stiffness alone has limited effect, stenting for even a moderate residual aortic constriction seems appropriate. Our results argue for supplementary haemodynamic investigation wherein, besides the baseline pressure gradient, the impact of other components such as the length and morphology of the stenotic rest lesion is taken into account. Moreover, the use of dynamic conditions during haemodynamic testing might give additional information of its true impact on VA interaction.

Limitations

This study is performed on pigs with an healthy aorta, which is clearly different from the aorta of coarctation patients, and might therefore not account for the effect of intrinsic structural aortic wall changes in aortic compliance. Aortic pressure-flow measurements were made at the proximity of the lesion and can slightly differ from registrations at the ascending aorta to reflect the VA afterload more properly. This becomes important when wave intensity analysis of pressure and flow wave reflections is included to understand more precisely the contribution of altered aortic haemodynamics on cardiac workload.

This coarctation model was performed intentionally on pigs at an age that growth of the descending aorta was deemed to be minimal, aiming to avoid growth-induced accentuation of the aortic stenosis after 3 months, and the expected increase in pressure gradient to a clinically significant level.

Although the number of animals might be too small to highlight a statistical significance of some between-group differences, we feel confident with the validity of the *in vivo* measures to support the translational message of this study.

CONCLUSION

This animal study on the haemodynamic assessment of current sequelae of aortic coarctation repair demonstrated that short- or long-segment aortic stiffening without stenosis had a limited effect on aortic pressure-flow characteristics and cardiac function. However, the negative chronic effect of even a moderate stenosis on aortic haemodynamics—certainly when it concerns a longer segment—leads to rapid impairment of VA interaction, which is

accentuated during inotropic stimulation. Therefore, therapeutic strategies should focus on effective haemodynamic restoration of the aortic lesion with minimal residual stenosis, even if it is at the cost of inducing a long-segment aortic stiffness as by stent implantation. It also opens a window for supplementing the assessment of aortic recoarctation with dobutamine-induced stress testing to objectify the exact contribution of a residual constriction in relation to its length variation in aortic haemodynamics.

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Conflict of interest: none declared.

Author contributions

Joseph Panzer: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft. **Filip De Somer:** Data curation; Formal analysis; Investigation; Writing—review & editing. **Patrick Segers:** Formal analysis; Methodology; Software; Supervision; Validation. **Daniel De Wolf:** Formal analysis; Supervision; Writing—review & editing. **Thierry Bove:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing.

Reviewer information

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Chapter VII

STUDY 4

Echocardiography during submaximal isometric exercise in children with repaired coarctation of the aorta compared with controls. Panzer J, Dequeker L, Coomans I, Vandekerckhove K, Bove T, De Wolf D, Rietzschel E. Open Heart. 2019 Oct 24;6(2):e001075. doi: 10.1136/openhrt-2019-001075. PMID: 31749973; PMCID: PMC6827756.

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Echocardiography during submaximal isometric exercise in children with repaired coarctation of the aorta compared with controls

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ABSTRACT

Objective Patients with repaired coarctation (RCoA) remain at higher risk of cardiac dysfunction, initially often only detected during exercise. In this study, haemodynamics of isometric handgrip (HG) and bicycle ergometry (BE) were compared in patients with RCoA and matched controls (MCs).

Methods Case–control study of 19 children with RCoA (mean age 12.9±2.3 years; mean age of repair 7 months) compared with 20 MC. HG with echocardiography followed by BE was performed in both groups.

Results During HG (blood pressure) BP increased from 114±11/64±4 mm Hg to 132±14/79±7 mm Hg, without significant differences. During HG as well as BE, HR increased less in patients with RCoA. There were no significant differences in (left ventricle) LV dimensions or LV mass.

The RCoA group had diastolic dysfunction: both at rest and during HG they had significantly higher transmitral E and A velocities and lower tissue Doppler E′ and A′ velocities. E/E′ was higher, reaching statistical significance during HG ($p<0001$).

Conventional parameters of systolic function (FS and EF) were similar at rest and HG. More sensitive tissue Doppler S′ was significantly lower at rest in CoA subjects (5.1±1.5 cm/s vs 6.5±1±1 cm/s; $p<0.01$), decreasing further during HG by 5% in the CoA group (NS) while unchanged in controls.

Conclusions We provide first evidence that HG with echocardiography is feasible, easy and patient-friendly. A decreased systolic (tissue Doppler) and impaired diastolic LV function was measured in the RCoA group, a difference that tended to increase during HG.

Key questions

What is already known about this subject?

- Haemodynamics as measured by echocardiography (and blood pressure) during isometric exercise have been studied in adults but not in children with repaired coarctation of the aorta.
- We know that cardiac problems and hypertension occur frequently after successful repair of coarctation. Initially, cardiac dysfunction may only be present during exercise.

What does this study add?

- Our study shows that it is feasible and easy to do echocardiography during a child-friendly stress-test.
- We show that a decreased systolic and diastolic function is present in the repaired coarctation group and tended to increase during handgrip test.

How might this impact on clinical practice?

- We believe that echocardiography during isometric exercise is feasible and easy and adds to the haemodynamic understanding of patients with repaired coarctation. Future studies will hopefully elucidate where this technique has added value in routine follow-up.

INTRODUCTION

Coarctation of the aorta (CoA) is a type of congenital heart disease characterised by stenosis in the aorta, typically juxta-ductal. The incidence is 1 in 2000 live births,[1–3] representing 5%–8% of the congenital cardiovascular malformations.[1–6] It can occur with other congenital lesions, most commonly bicuspid aortic valve (BAV) and ventricular septum defect.[2 3]

Severe CoA results in hypertension proximal to the stenosis and leads to significant pressure differences between the right arm and leg.[1 3 6 7]

Treatment of CoA consists of surgical resection of the narrowing or balloon dilatation with or without stenting.[2 6] Even after successful repair, considerable morbidity and increased mortality remains in these patients and is related to complications like recoarctation, aortic aneurysm or dissection, premature coronary atherosclerosis, coexisting BAV and endocarditis.[8 1 5 9–11] Hypertension is the most important determinant for adverse outcomes.[12]

Many recent studies have shown that the precoarctation vascular wall is

abnormal.[5 9 12–16] This results in vascular and ventricular abnormalities in coarctation patients, especially after late repair.[9 10 16 17] Early repair of the aortic obstruction cannot change the intrinsic structural abnormalities of the aortic wall.[3 9 12 13 16] CoA should be considered a complex cardiovascular syndrome rather than an isolated stricture.[7 9 10 17]

Exercise-induced hypertension is common in these patients and is assumed to be a predictor of arterial hypertension.[18 12 19 20]

Pharmacological stress testing (eg, dobutamine) is generally used when exercise testing is not possible or when additional tests have to be performed, like echocardiography. Being invasive, it is not ideal in children.[21]

Currently, routine follow-up in most centres includes blood pressure measurements and bicycle exercise testing, as well as echocardiography (at rest but not during exercise).[3 10 22]

Isometric handgrip test is a sustained submaximal stress test.[23] The fact that this test causes limited movement of the body implies that a simultaneous echocardiography is possible.[24] The complementary use of echocardiography during exercise may aid in the early detection of abnormalities in patients with a repaired coarctation.[15 25]

STUDY OBJECTIVES

In this study, the effect of isometric exercise on the cardiovascular system of patients with a successfully repaired CoA is investigated. To enhance our understanding of haemodynamic changes in these patients, sustained submaximal isometric exercise and maximal dynamic exercise were executed. We performed an explorative investigation with prospective evaluation of 19 patients with isolated coarctation who underwent surgery at Ghent University Hospital and compared their results with healthy matched controls.

The aims of this study are: (1) to compare blood pressure and cardiac ultrasound measurements during isometric exercise of patients with a repaired coarctation with healthy controls and (2) to compare blood pressure during isometric exercise with blood pressure during dynamic exercise in children with a repaired CoA and healthy controls.

METHODS

This study was designed as a case–control study where patients with repaired coarctation are compared with age-matched and sex-matched controls.

Patients with coarctation were identified from Ghent University Hospital's database. Inclusion criteria for this database were: patients aged 9–16 years with CoA repaired with end-to-end anastomosis at this institute. This resulted in a group of 113 patients. We studied CoA patients who were operated without: (1) major associated cardiovascular abnormalities, (2) evidence of recoarctation (limit was set up at >20 mm Hg pressure gradient in the aortic arch by echocardiography) and (3) other serious concomitant disorders (one patient was excluded due to a syndrome affecting multiple organs). This left 39 patients suitable subjects. Nineteen children agreed to participate in this prospective study (figure 2). All patients were clinically well and taking no medication.

Twenty healthy normotensive children of similar age and matched for weight, height and sex served as control subjects. They were recruited by poster recruitment from local schools.

All subjects and their parents gave written informed consent.

Exercise testing

Each study started by obtaining blood pressure and heart rate (HR) at rest. The first exercise test performed by every participant was isometric handgrip. After a period of rest (30 min), patients underwent bicycle ergometry until exhaustion.

Baseline data

Demographic data, including, age, interventions and associated diseases were extracted from medical records. Height and weight were measured. Blood pressure and HR were obtained at rest, during isometric exercise and during bicycle exercise testing. Blood pressure was measured in the supine position with the cuff positioned on the right arm (to avoid operation-related disturbances) using an automatic blood pressure monitor (Spot Vital Signs LXi, Welch Allyn, Skaneateles Falls, USA). Average was taken from at least two separate readings.

Isometric handgrip

A handgrip dynamometer (Biometrics G200/H500 Modified Jamar Dynanometer) connected to an X4-InterX interface (Biometrics Ltd, GWENT, UK) was held in the left hand while lying on a hospital bed. First, the participant performed three efforts of maximum grip strength with the highest noted as maximum voluntary contraction (MVC). Then the subject was asked to sustain isometric exercise at 25% of MCV with the same instrument. A display of a seesaw was positioned at eye level to provide visual feedback. In that way the participants and observer knew if enough grip strength was provided. During exercise, they were watched carefully to avoid a Valsalva manoeuvre.

Participants were instructed to state when they thought that they would only be able to sustain the exercise for a further 60 s. At this point, blood pressure and echocardiography were performed. To compare these measurements with values at rest, blood pressure and echocardiography were noted before and after exercise.

Echocardiography was performed with a Vivid 7 ultrasound imaging system, using a 3S transthoracic probe (GE Healthcare, Norway).

All echocardiographic examinations were performed by the same experienced paediatric cardiologist. The echocardiographic analyses were done with EchoPAC software (GE Healthcare) by another blinded investigator. In

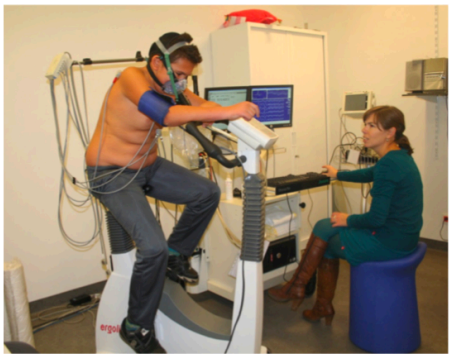

Figure 1 Bicycle Ergometer Exercise Test (stock photograph reproduced with permission from UZ Gent).

the statistical analyses, means of the echocardiographic parameters derived from three cardiac cycles were used.

Bicycle ergometer exercise test

After the isometric test all study participants underwent a dynamic maximal stress test on a fully automated ergospirometry system with integrated 12-lead ECG and cyclo-ergometer (Ergoline Ergoselect 100K, Bitz, Germany). Ramp protocol was used: at start, workload was set at 0W, and during the exercise, workload increased ramp wise with 0.25W/kg in a linear way. Participants cycled at constant speed of 60 rotations per minute (rpm) and were verbally encouraged to achieve maximum effort.(figure 1) The exercise was terminated when the patient reached its self-determined point of full exhaustion or was unable to maintain a cycling frequency of 60 rpm. This was followed by a recovery period of 6 min.

HR was calculated from the 12-lead ECG (Marquette, GE Healthcare, UK). Blood pressure was obtained every 3 min during exercise and every 2 min during recovery by using an integrated blood pressure device (Tango, SunTech Medical, USA). During the test, breath-by-breath analysis of expiratory gases was performed with a metabolic measuring system (Oxycon Pro, Jaeger, CareFusion Corporation, vs) in order to retrieve respiratory data to define peak VO2.

Statistical analysis

Data were statistically analysed with SPSS V.25. The values of both stress tests were compared between the coarctation cohort and controls. Included in the analysis were clinical data (age, sex, BMI and age at repair) and echocardiographic indexes. Results, unless stated otherwise, are expressed as mean±SD. The normality Shapiro-Wilk test with visual support of histograms was performed to determine whether continuous variables were normally distributed. If so, the differences between groups were evaluated by unpaired Student's t-test. Otherwise, data were compared using the Mann-Whitney U test. The χ^2 test was used to compare categorical variables between groups. The variables of the same cohort were evaluated using the paired Student t-test or the Wilcoxon signed-ranks test. The relation between variables was assessed by determination of the Pearson or Spearman coefficient. A probability value of $p<0.05$ was considered to be statistically significant.

RESULTS

Clinical data

In the coarctation cohort 5 female and 14 male patients, mean age 13.0 years, were included. No significant differences were observed between patients and controls with respect to sex, age, weight and length. However, the ratio girls/boys was higher in the control cohort, although this did not reach statistical significance ($p=0.23$). Aortic repair had been performed at a median age of 1.5 months (0.1–47.7), with 78% of the subjects undergoing surgery within the first 6 months of life. Forty-two per cent of the included patients had a BAV and 47% had a hypoplastic arch. Clinical characteristics of the study group are given in table 1.

Blood pressure and HR data

The systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR before (baseline), during (exercise) and immediately after (recovery) the stress tests are shown in table 2.

There were no differences in resting BP or HR before the isometric handgrip test or before the bicycle ergometry.

When performing bicycle ergometry, the SBP and DBP increased with, respectively, 33% and 3% in coarctation patients. There was no difference in SBP (baseline, exercise, recovery and Δ) between the coarctation and the control group. The peak DBP and ΔDBP were significantly lower in coarctation patients compared with controls ($p<0.05$), because DBP remained unchanged in patients with repaired coarctation (2±14 mm Hg), wheras in increased with 13±14 mm Hg in the controls. HR almost doubled in both cohorts, although the coarctation group achieved a statistically 11 bpm lower maximal HR than controls ($p<0.05$).

During isometric handgrip, SBP and DBP increased with, respectively, 16% and 25%, without a significant differences in response between the coarctation patients and the control group. During handgrip test HR increased in coarctation patients and in controls with, respectively, 16% and 31%. As was the case during bicycle ergometry, the degree of increase in HR test was significantly higher in controls compared with the coarctation cohort ($p<0.05$).

When comparing the adynamic responses during bicycle ergometry and isometric handgrip, as expected, the maximum SBP and HR responses were, respectively, 21.2% and 101% higher during bicycle ergometry (both

Table 1 Basic clinical data

	CoA	Controls
No.	19	20
Sex ♀–♂	5–14	9–11
Mean age (years)	13.0±2.3	12.7±2.1
Weight (kg)	47.9±17.3	44.5±13.0
Length (cm)	155±13	156±15
BMI (kg/m^2)	19.4±4.6	17.9±2.5
BSA (m^2)	1.4±0.3	1.4±0.3
Age at operation (mo, median)	1.5 (0.1–47.7)	
Bicuspid valve	8	
Hypoplastic arch	9	

Data are expressed as mean±SD; median (minimum, maximum). BMI, body mass index; BSA, body surface area; CoA, coarctation of the aorta.

p<0.01). The SBP was also significantly higher during recovery when performing bicycle ergometry (p<0.01). In contrast, as DBP increased significantly during handgrip, but not during bicycle ergometry, DBP was significantly higher when executing the isometric handgrip test (p=0.001).

Echocardiographic data

The echocardiographic measurements of LV mass and function were compared between the coarctation cohort and controls and are summarised in table 2 and in figure 2.

There were no significant differences in LV dimensions or LV mass between the study groups.

The diastolic function of CoA patients was significantly different from controls: they had significantly higher transmitral E and A velocities and significantly lower tissue doppler E′ and A′ velocities. During exercise, in coarctation patients, the E wave velocity decreased by 3.6% (p=0.21) and the A wave increased by 20.5% (p<0.05) resulting in an E/A ratio decrease of with 26.3% during exercise (p<0.05). The increase of the A wave can be explained by the importance of atrial contraction during exercise. These effects were mirrored in the tissue Doppler data with a decrease of the E′ wave by 4.7% (p=0.13), an increase of the A′ wave with 33.1% (p<0.01) during handgrip exercise.

The E/E′ ratio, a marker of diastolic filling pressure was higher in CoA than controls, although this difference only reached statistical significance during handgrip exercise. Except for the latter, there were no big differences in haemodynamic response during handgrip between CoA and controls.

Conventional parameters of systolic function (fractional shortening (FS) and ejection fraction (EF)) were similar between CoA and controls, at rest and during handgrip. The more sensitive tissue Doppler S′ was however significantly lower already at rest in CoA subjects (5.1±1.5 cm/s vs 6.5±1.1 cm/s). This difference at rest enlarged further during handgrip as the S′ amplitude decreased by 5% in the CoA group (NS) while remaining unchanged in the controls.

No demonstrable differences were found in stroke volume (SV) and EF when performing isometric exercise (insignificant increase with 0.6%). Due to the increase in HR, cardiac output (CO) was significantly increased with 19.6% (p<0.01). Interestingly, stroke volume (indexed for body surface area) decreased in controls but remained unchanged in CoA subjects (ΔSVI; p=0.043). Because of the larger HR increase in controls, no differences were found in CO among the study groups.

Exercise capacity

Oxygen consumption at maximal exercise is considered to be the gold standard parameter to assess exercise capacity.

When performing bicycle ergometry, VO2max was lower in CoA patients (36.2 (±11.8 mL/min/kg) compared with controls (45.7 (±6.1 mL/min/kg; p<0.01).

BMI and VO2 max

Explorative analyses suggested that the relation between BMI and VO2 max might be different in the control group compared with the coarctation group. To be able to compare the subjects, we used the BMI charts developed for Flemish children to determine the BMI percentile for age and sex.[26] In figure 3, we see that VO2max correlates negatively with increasing BMI percentiles in both groups. Although the decrease in VO2max with increasing BMI seems more pronounced in the coarctation group, this did not reach statistical significance in our small sample.

DISCUSSION

The present research is to the best of our knowledge the first time that isometric exercise in conjunction with echocardiographic examination is used in children with repaired coarctation.

Our main findings are that in patients with repaired CoA diastolic function and systolic function (the latter only when measured using more sensitive tissue Doppler methods) are decreased compared with controls. These relative differences were not strongly influenced when remeasured at a higher operating pressure (during isometric handgrip). Although during handgrip in coarctation subjects E/E′, a marker of elevated LV filling pressures became significantly higher than in controls and S′ tended (non-significantly) to decrease further while remaining unchanged in control subjects.

Our conventional measures of systolic function (EF and SF) were similar in CoA compared with controls. Despite the fact that some studies found an increased systolic function, the absolute values of these variables corresponded to those in this study.[14 27–29] However, the conclusion that LV systolic function is usually preserved in patients with repaired coarctation without stenosis

Table 2 Echocardiographic data

	Baseline		Exercise		Δ	
	CoA	Controls	CoA	Controls	CoA	Controls
M-mode variables						
LVM (g)	106.5±34.3	105.9±44.5				
LVMI (g/ m^2)	73.8±192	76.4±27.3				
IVSd (mm)	9.1±2.1	8.9±1.8				
LVEDD (mm)	39.0±7.9	37.8±7.2				
PWd (mm)	8.9±2.4	9.3±2,0				
IVSs (mm)	11.7±1.7	11.1±2.1				
LVESD (mm)	23.1±5.8	23.8±6.4				
PWs (mm)	12.0±3.01	12.3±3.3				
Diastolic variables						
E (cm/s)	124.2±28.2*	103.1±15.1*	119.8±20.7*	100.9±13.6*	−4.4±14.3	−3.3±19.6
A (cm/s)	69.7±42.3*	44.9±11.1*	84.0±34.4*	54.4±16.9*	14.3±24.2	14.4±16.5
E/A	2.2±0.90	2.45±0.8	1.6±0.5	2.1±1.0	−0.6±0.9	−0.6±1.4
E' (cm/s)	9.8±1.7*	12.5±1.4*	9.4±1.6*	11.5±2.0*	−0.4±1.0	−1.1±1.7
A' (cm/s)	2.6±1.2*	4.1±1.2*	3.5±1.3	4.3±1.7	0.9±1.0	0.2±1.9
E/E'	13.1±4.1	8.4±1.6	13.2±3.3*	8.8±2.2*	−0.0±2.4	0.6±1.9
Systolic variables						
S (cm/s)	5.1±1.5*	6.5±1.1*	4.8±0.9*	6.5±1.4*	−0.2±0.9	0.0±1.0
SV (mL)	67.5±38.4	60.4±14.9	67.9±37.0	53.9±15.9	0.4±11.4	−7.0±9.6
SVI (mL/m^2)	45.1±17.7	44.4±12.0	45.8±17.6	40.8±11.7	0.6±7.6*	−5.2±7.2*
EF (%)	60.8±23.6	56.9±18.8	59.5±23.9	52.9±12.2	−1.1±14.8	−6.8±15.2
CO (l)	5.1±3.3	4.3±1.1	6.1±3.3	5.0±1.5	0.9±0.9	0.7±1.0
CI (l/m^2)	3.4±1.6	3.2±0.9	4.1±1.8	3.8±1.3	0.7±0.6	0.6±0.8
PWV (m/s)	2.9±0.3	3.2±0.5	3.4±0.7	3.7±0.5	0.4±0.5	0.3±0.4
PP (mm Hg)	49.6±2.6	50.0±1.9	52.6±3.5	52.7±2.1	3.0±1.9	2.7±1.3
SV/PP (mL/mm Hg)	1.4±0.2	1.2±0.1	1.3±0.1	1.0±0.1	−0.1±0.1	−0.2±0.1

Data are expressed as mean (±SD). It was verified whether the difference between CoA and controls was significant (*p<0.05).
CI, Cardiac Index; CO, Cardiac Output; CoA, coarctation of the aorta; EF, Ejection Fraction; IVSd, Interventricular Septum diastolic; IVSs, Interventricular Septum systolic; LVEDD, Left Ventricular End-Diastolic Diameter; LVM, Left Ventricular Mass; LVMI, Left Ventricular Mass Index; PP, Pulse Pressure; PWd, Posterio Wall diastolic; PWs, Poster Wall systolic; PWV, Pressure Wave Velocity; SV, Stroke Volume; SVI, Stroke Volume Index; SV/PP, Stoke Volume/Pulse Pressure.

might need revisiting in the light of the decreased S′ we observed. In many disease conditions (such as hypertrophic cardiomyopathy), a decrease in S′ is a sensitive and early marker of declining systolic function, preceding a decrease in EF.[30]

In our data, children with CoA repair at young age show abnormalities of the LV diastolic function at rest and during exercise. Compared with controls, they have significantly higher E and A waves and reduced E/A ratio, indicating a greater dependence on atrial contraction in coarctation patients. Present at rest, there was no further deterioration during isometric exercise, although the E/E′ ratio, an approximation of the LV filling pressure, became significantly increased in coarctation patients. Generally our findings (at rest) are in agreement with various studies.[13 31]

As in other studies, no significant differences were found in resting blood pressure and HR between coarctation patients and controls.[13 16 32] The responses in SBP during isometric HG and bicycle ergometry was similar in both groups. In contrast, maximal HRs (in both exercises) and peak DBP and change in DBP were significantly lower in coarctation patients compared with controls during isometric handgrip but not during bicycle ergometry. The response to an isometric stress test differs in children compared with adults, and the increase of HR in children surpasses the very subtle increase in HR in adults when executing the isometric handgrip test[33] (E Rietzschel, personal data, 2019, using a similar protocol in >2000 healthy volunteers aged 56 years on average, HR increased only slightly by 7±5 beats/min; unpublished data; manuscript in preparation).

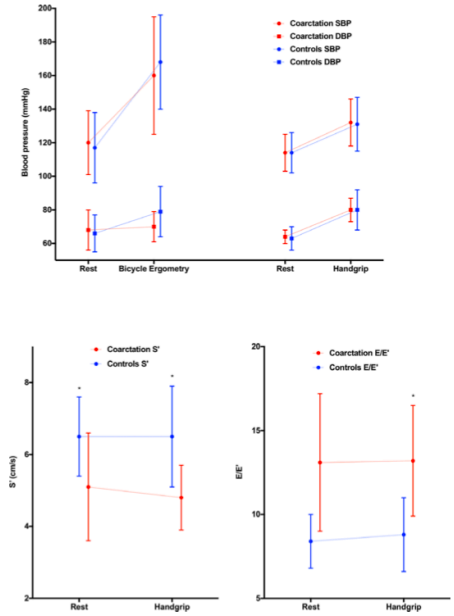

Figure 2 BMI percentile and VO2/kg (ml/min/kg) compared in RCoA patients and controls.

The increase in SBP and HR were much higher during bicycle ergometry than during handgrip. The first is a dynamic stress test of maximal effort with increases in CO giving volume load on the LV, while the latter is a submaximal static contraction against resistance resulting in an increased pressure load on the LV.[22]

Functionally, as in other studies, exercise capacity as assessed by VO2max was clearly lower in CoA patients compared with controls.[20 34] This is consistent with the lower peak HR found in patients with repaired coarctation. Since isometric handgrip is a submaximal stress test, no conclusions in terms of exercise capacity can be reached when performing this stress test. The lower VO2max seemed more pronounced with increasing BMI percentiles in the coarctation group, although this needs to be confirmed in a larger cohort as this did not reach statistical significance on our small sample.

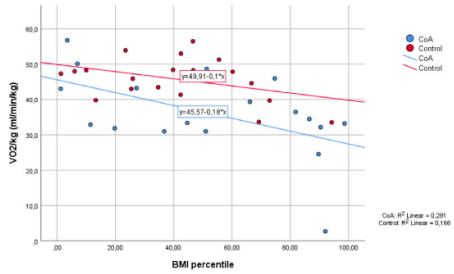

Figure 3 Bicycle exercise test with ergospirometry.

In our study, no increase in LV dimensions or LV mass was observed in CoA patients. In contrast, several studies have shown an increased LVM in patients with repaired coarctation.[12 13 15 28 29 32] In comparison with these investigations, our patients were younger and underwent surgical repair at lower age. This potentially suggests that early repair reduces the risk of an increased LVM in coarctation patients. Tantengco *et al*[15] demonstrated a positive correlation between LVMI and hypertension in patients with repaired coarctation. Nevertheless, it has been shown that an increase of LVM occurs even in normotensive patients with repaired coarctation.[12 28] LV hypertrophy is an independent risk factor for cardiovascular morbidity and mortality.[28]

Patients with repaired CoA remain at higher risk of developing cardiovascular complications.[3 9 12] Currently, follow-up includes blood pressure measurements and echocardiography at rest, completed with bicycle ergometry.[10] Exercise testing plays an essential role because haemodynamic parameters may be normal at rest but changes may appear first during exercise.[5 19 24] Exercise-induced hypertension is assumed to be a predictor of arterial hypertension.[12 19 35] Even without hypertension, abnormal diastolic and systolic LV function can be found in patients with repaired coarctation.[27 28 31] This suggests that LV dysfunction appears before patients become hypertensive.[35] To detect LV dysfunction, echocardiography was used. Images of good quality are easy to obtain during isometric stress testing but next to impossible during bicycle ergometry.[24] In cardiovascular disorders with increased afterload, like CoA, isometric handgrip test could be interesting in unmasking latent LV dysfunction.

Evaluating the cardiac response to an increased pressure load is useful to estimate the cardiac reserve.[22 36]

Although in our study the peak SBP was similar to controls, many previous studies reported higher peak SBP.[19 20 34 37] This discrepancy can be explained by differences in study populations, where often the age at repair was much higher. Furthermore, when studying coarctation patients after puberty, the influence of hormones should be taken into account, in addition to the genetic and haemodynamic factors.[12]

Strengths and weaknesses

Comparison of our haemodynamic responses during isometric handgrip with other studies was not possible since this is the first study that reports the influence of isometric exercise in children with repaired coarctation. The major limitation of this study relates to the number of patients studied. This relatively small patient cohort has limited the statistical power to identify risk factors.

Nonetheless, this study has provided new insights on the LV function in this population and should be seen more as a proof of concept and feasibility testing. Another shortcoming is the possibility that patients perform a Valsalva manoeuvre during isometric handgrip. This could be avoided by carefully observing and instructing the patient during exercise (and by engaging the in conversation). Another limitation is the fact that simultaneous blood pressure measurements were not performed in the arm and legs during exercise. This could have given additional information about a change in gradient across the repaired coarctation during exercise.

We believe that isometric exercise in conjunction with echocardiography could be useful in children with repaired coarctation. The fact that no further deterioration in diastolic function was found in this study during exercise could possibly be related to early good repair. This does not preclude the possibility that diastolic function could show significant changes during exercise in other patients where repair was at later age or other possible factors are present, like recoarctation. Therefore, the potential usefulness use of isometric handgrip test should be further investigated in the follow-up of patients with repaired coarctation.

CONCLUSIONS

We showed for the first time that echocardiography is feasible in children with repaired coarctation during isometric stress testing.

Both diastolic function and systolic function are significantly decreased compared with controls.

Further studies in adults (who have had a longer period since repair of coarctation) or in children with later repair might show more pronounced changes from controls.

The long-term clinical impact (if any) of the subtle systolic and diastolic dysfunction we documented remains to be elucidated.

Highlights

- Submaximal isometric handgrip test (HG) is feasible and easy in children aged 9–15 years.
- Chilen after coarctation repair have impaired systolic and diastolic function
- There is a tendency for the impaired systolic and diastolic dysfunction to deteriorate further during HG test.

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Chapter VIII

STUDY 5

Different Patterns of Cerebral and Muscular Tissue Oxygenation 10 Years After Coarctation Repair. Vandekerckhove K, Panzer J, Coomans I, Moerman A, De Groote K, De Wilde H, Bové T, François K, De Wolf D, Boone J. Front Physiol. 2019 Dec 11;10:1500. doi: 10.3389/fphys.2019.01500. PMID: 31920705; PMCID: PMC6917622

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Different Patterns of Cerebral and Muscular Tissue Oxygenation 10 Years After Coarctation Repair

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The purpose of this study was to assess whether the lower exercise tolerance in children after coarctation repair is associated with alterations in peripheral tissue oxygenation during exercise. A total of 16 children after coarctation repair and 20 healthy control subjects performed an incremental ramp exercise test to exhaustion. Cerebral and locomotor muscle oxygenation were measured by means of near infrared spectroscopy. The responses of cerebral and muscle tissue oxygenation index (cTOI, mTOI), oxygenated (O_2Hb), and deoxygenated hemoglobin (HHb) as a function of work rate were compared. Correlations between residual continuous wave Doppler gradients at rest, arm-leg blood pressure difference and local oxygenation responses were evaluated. Age, length, and weight was similar in both groups. Patients with aortic coarctation had lower peak power output (Ppeak) (72.3 ± 20.2% vs. 106 ± 18.7%, $P < 0.001$), VO_2peak/kg (37.3 ± 9.1 vs. 44.2 ± 7.6 ml/kg, $P = 0.019$) and %VO_2peak/kg (85.7 ± 21.9% vs. 112.1 ± 15.5%, $P < 0.001$). Cerebral O_2Hb and HHb had a lower increase in patients vs. controls during exercise, with significant differences from 60 to 90% Ppeak (O_2Hb) and 70% to 100% Ppeak (HHb). Muscle TOI was significantly lower in patients from 10 to 70% Ppeak and muscle HHb was significantly higher in patients vs. controls from 20 to 80% Ppeak. Muscle O_2Hb was not different between both groups. There was a significant correlation between residual resting blood pressure gradient and ΔmuscleHHb/ΔP at 10–20W and 20–30W ($r = 0.40$, $P = 0.039$ and $r = 0.43$, $P = 0.034$). Children after coarctation repair have different oxygenation responses at muscular and cerebral level. This reflects a different balance between O_2 supply to O_2 demand which might contribute to the reduced exercise tolerance in this patient population.

Keywords: coarctation aortae, near infrared spectroscopy, exercise test, children, muscle oxygenation

INTRODUCTION

Repair of coarctation of the aorta (CoA) has been performed for more than 50 years (Cohen et al., 1989; Corno et al., 2001). Although this surgical intervention aims to restore the functional capacity of these patients, exercise performance in this patient group remains impaired in adults (Trojnarska et al., 2007) as well as in children (Rhodes et al., 2010). However, pulmonary gas exchange responses,

which should be considered as "whole-body" measurements, obtained during cardiopulmonary exercise tests cannot provide a sufficient insight into the origins of the lower exercise performance. In this context, residual coarctation, left ventricular dysfunction, and hypertension have all been proposed as possible underlying causes. In 1981, Eriksson et al. (Eriksson and Hanson, 1981) observed a disturbed blood flow regulation and impaired blood flow to the working leg muscles during exercise in adults after CoA repair. Johnson et al. (1995) studied blood flow measurements by duplex ultrasound and found an impaired lower limb blood flow in response to strenuous dynamic exercise, even without significant residual stenosis at rest. These studies indicate that also the relationship between O_2 delivery and O_2 utilization might be altered in CoA.

Near-infrared spectroscopy is a technique that measures the (changes in) concentration of oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin (i.e., tissue oxygenation) during exercise in a non-invasive way. Together with the derived parameter TOI (i.e., tissue oxygenation index: O_2Hb/(O_2Hb + HHb) these parameters quantify the overall oxygenation at the level of the tissues. It has been suggested that HHb is a reflection of arterio-venous O_2 difference (DeLorey et al., 2003; Grassi et al., 2003). According to the principle of Fick, in this context HHb can provide information on the dynamic balance between O_2 delivery (QO_2) and O_2 utilization (VO_2) at the level of the tissues. In non-steady state conditions there are substantial changes in the ratios between QO_2 and VO_2 in different body regions (active/non-active muscles, brain, heart, and other organs, etc.). Therefore, studying the oxygenation patterns at different sites of the body during periods of changing metabolic demand is highly relevant to understanding key aspects of metabolic and vascular control.

At the level of the locomotor muscles HHb increases following a sigmoid pattern as exercise intensity increases during incremental ramp exercise (Boone et al., 2016; Vandekerckhove et al., 2016). The initial slow increase in HHb at the onset of the incremental exercise indicates faster QO_2 kinetics vs. VO_2 kinetics at the level of the muscle. In a second phase HHb increases more rapidly revealing an increased fractional O_2 extraction due to a relative slowing of QO_2 vs. VO_2. Finally, a leveling-off in HHb occurs, at an intensity closely corresponding to the respiratory compensation point. Although it has been suggested that fractional O_2 extraction reaches its limits at this intensity, more recent studies (Inglis et al., 2017; Iannetta et al., 2018) suggest that a local redistribution of blood causes a matching between QO_2 and VO_2 with a leveling off in HHb as a consequence.

Also the oxygenation responses at the level of the brain might provide insights into the factors limiting exercise tolerance. It has been shown during incremental ramp exercise that cerebral O_2Hb increases up to a point at high intensity exercise where a breakpoint occurs and a decline in O_2Hb is initiated (Bhambhani et al., 2007; Rooks et al., 2010). Cerebral HHb remains stable during submaximal exercise but then shows a rapid increase from hard (>60% $\dot{V}O_{2max}$) to maximal intensity (Rooks et al., 2010). These typical O_2Hb and HHb response patterns indicate that cerebral blood flow increases in accordance with the increase in work rate during incremental exercise (Panerai et al., 1999; Jorgensen et al., 2000; González-Alonso et al., 2004). In a recent study in Fontan patients it was shown that cerebral O_2Hb did not increase during incremental exercise, which resulted in a progressive decrease in cerebral saturation (i.e., cerebral TOI), as HHb increased during the exercise (Vandekerckhove et al., 2019). These results confirm the potential role of brain oxygenation as a limiting factor to exercise tolerance, especially in patient populations (Brassard and Gustafsson, 2016).

Given the unknown etiology of the lower exercise tolerance in CoA patients after repair, assessing local oxygenation responses (O_2Hb, HHb, and TOI) during incremental exercise could provide important insights into the underpinning mechanisms. In the past (Eriksson and Hanson, 1981; Johnson et al., 1995) it has been shown that tissue blood flow was affected in individuals following repair of aortic coarctation. Therefore, it can be expected that local oxygenation responses (brain, muscle) during incremental exercise differ from those of healthy controls. Thus, the purpose of the present study was to investigate oxygenation responses at the level of the brain and locomotor muscles during incremental exercise in children after CoA repair. We hypothesize first, that these children will have a lower exercise tolerance compared to healthy children. Second, we hypothesize altered oxygenation responses at the level of the brain and muscle that will be related to residual lesions in the patient group.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the local ethical committee (Ghent University Hospital, Ghent, Belgium) and followed the ethical recommendations for the study of humans as suggested by the Declaration of Helsinki. All participants gave written informed consent prior to the start of the study.

Participants

Sixteen children post aortic coarctation repair (13 boys, 3 girls) (CoA patients) and twenty healthy children (9 boys, 11 girls) volunteered to take part. The age and anthropometric characteristics of the two groups are presented in **Table 1**. The groups did not differ significantly for these characteristics. All patients were operated under the age of 4 years, with the majority operated under 1 year (12/16, median 6 weeks, 1 day – 4 years). Most patients (15/16) underwent resection of the coarctation site with end-to-end anastomosis, 1 patient underwent extended arch repair. CoA patients were in stable follow-up. They had normal blood pressures at rest, good left ventricular function (fractional shortening >28% in all patients), and no significant LV hypertrophy on echocardiography. All patients and controls were attending normal school and sports activities.

Experimental Procedure

An incremental exercise test was performed on an electromagnetically braked cycle ergometer (Ergoline Ergoselect

TABLE 1 | Age and anthropometric characteristics for coarctation aortae patients and healthy controls.

	Coarctation	Controls	*P*-value
Age (years)	13.0 ± 2.2	12.0 ± 1.8	*P* = 0.137
Body weight (kg)	47.5 ± 17.2	41.1 ± 11.0	*P* = 0.104
Body height (m)	1.57 ± 0.13	1.52 ± 0.11	*P* = 0.256
Type of surgery	End to end 15/16 Extended end to end 1/16		
Age at surgery (median, min-max)	6 weeks (1 day – 4 years)		
Residual gradient (mm Hg)	26.6 ± 7.3		
LV function (fractional shortening, %)	36.8 ± 5		
Septal thickness (diast)	8.25 ± 1.29		
(*Z*-value)	0.67 ± 0.70		
Posterior wall thickness	7.31 ± 1.49		
(diast) (*Z*-value)	0.55 ± 0.94		

Values are mean ± SD. LV, left ventricle; diast, diastole.

100K, Bitz, Germany). Following a 3 min warm-up at unloaded cycling, the work rate increased in a linear and continuous way (i.e., ramp exercise). The ramp slope (i.e., the increase in work rate per minute) was individualized and determined by dividing the individual body weight by 4 and rounding off to the closest natural number [0 Watt + (body weight/4) Watt.min^{-1}]. This internally validated protocol leads to an optimal exercise duration of 8 – 12 min in healthy children, with reference values equal to the values of Wasserman et al. (Wasserman, 2012). Participants were asked to maintain a pedal rate of 60 revolutions per minute (rpm) and the test was terminated when they reached their self-determined point of full exhaustion or were unable to maintain the required pedal rate despite strong verbal encouragement. Echocardiographic measurements were reviewed and the residual doppler gradient (continuous wave) over the aortic coarctation zone at rest (mmHg) was defined.

Experimental Measures

During the exercise tests, pulmonary gas exchange (VO_2, oxygen uptake; VCO_2, carbon dioxide production; VE, ventilation) was measured continuously on a breath-by-breath basis by means of a computerized O_2-CO_2 analyzer-flowmeter combination (Jaeger Oxycon Pro, Germany). Respiratory exchange ratio (RER) was calculated by expressing VCO_2 relative to VO_2 (VCO_2/VO_2).

Blood pressure in the arm was measured every 3 min during the exercise phase and every 2 minduring the recovery phase with an integrated blood pressure monitor (SunTech Tango) that uses 3D K-Sound Analysis. At the start and at maximal exercise, blood pressure was measured at the leg using the same technique. The difference between systolic pressure arm compared to leg was analyzed at rest and at maximal exercise. This is proven to be an important parameter for the degree of residual obstruction at the aortic arch (Dijkema et al., 2017).

Muscle and cerebral oxygenation (O_2Hb and HHb) were measured by means of near infrared spectroscopy technology (NIRO-200NX, Hamamatsu Photonics K.K., Hamamatsu, Japan). This system consists of an emission probe emitting near-infrared light at three wavelengths (735, 810 and 850 nm) and a photon detector which measures the intensity of incident and transmitted light at a frequency of 2 Hz. For measurements of oxygenation, the probe was positioned longitudinally over the distal section of the left M. Vastus Lateralis and adhered to the skin. For measurements of cerebral oxygenation, the probe was placed over the left pre-frontal lobe, approximately 3 cm from the midline and just above the supra-orbital ridge (Kleinschmidt et al., 1996; Bhambhani et al., 2007). This device measures TOI as a reflection of mixed arterio-venous O_2 saturation (in%) at the location of the probe. Additionally, relative changes to baseline values in the concentration of O_2Hb and HHb (in μmol) are recorded. Baseline cycling at 0 Watt was used as baseline values for O_2Hb and HHb and were set to 0 μmol.

Data Analysis

Cardiopulmonary Exercise Test

The breath-by-breath data from the gas exchange responses were filtered upon exportation based on the following criteria: tidal volume < 0.2 and >10 l·min^{-1}; fraction of expired CO_2 <1 and >10% (Fontana et al., 2015). The VO_2peak was calculated as the highest 30s average (i.e., moving average) VO_2 throughout the test. Since a leveling-off in VO_2 is often not reached in children (Armstrong and Welsman, 1994), the term VO_2peak will be used throughout to avoid erroneous conclusions on maximal effort. The peak power output (Ppeak) was determined as the work rate attained at the termination of the exercise phase. The VO_2peak and Ppeak were expressed relative to the norm values (predVO_2peak, predPpeak), based on age and anthropometrics (Wasserman, 2012).

The gas exchange threshold (GET) was determined using the criteria of a disproportionate increase in carbon dioxide production (VCO_2) to VO_2 (Beaver et al., 1986), a first departure from the linear increase in minute ventilation (VE) and an increase in VE/VO_2 with no increase in VE/VCO_2. The disproportionate increase in VCO_2 is related to an increase in the buffering of H^+ due to an increased production of pyruvate from glycolytic processes in the cytosol of muscle fibers. The peak Respiratory Exchange Ratio (RERpeak) was determined as the highest 30s RER throughout the test, the peak heart rate (HRpeak) as the highest value obtained throughout the test.

Cerebral and Muscle Oxygenation

The changes in TOI and in the concentration of cerebral and muscle O_2Hb and HHb from baseline values (i.e., baseline cycling at 0 Watt) of each individual were expressed as a function of Ppeak by calculating the mean TOI, O_2Hb and HHb response at 10%, 20%, 30%, . . ., 100% Ppeak. The values at these% Ppeak were calculated as the average of the O_2Hb and HHb values 10s prior and 10s following the relative intensity.

Additionally, to quantify the relationship between muscle O_2 supply and O_2 demand, the change in muscle HHb

(Δmuscle HHb) as a function of the change in work rate (ΔP) (Δmuscle HHb/ΔP) for each 10% Ppeak interval (i.e., from 0 to 10%, 10 to 20%, *etc*) was calculated.

To quantify the sudden changes in the pattern of the NIRS responses, breakpoints (BP) were determined. Therefore, the studies of Miura et al. (1998) and Spencer et al. (2012) were used as examples of typical responses in muscle O_2Hb (BP at moderate and high intensity demarcating the point of an accelerated and attenuated decrease, respectively) and HHb (BP at high intensity at which muscle HHb levels off), respectively. The studies of Rooks (Rooks et al., 2010) and Bhambani (Bhambhani et al., 2007) served as examples of the typical responses in cerebral O_2Hb (BP at high intensity at which O_2Hb starts to decrease) and HHb (BP demarcating the point of an accelerated increase). In case the determination of the breakpoints was not possible with the two-segment linear piecewise model of curve fitting in Sigmaplot (Systat Software Inc., San José, CA, United States), two experienced researchers analyzed the oxygenation responses visually to detect the BPs. When the analysis did not correspond between the two researchers, the data were re-evaluated together with a third researcher until a consensus was reached.

Finally, the amplitude of the NIRS responses was calculated as the difference between the NIRS value at baseline cycling and the highest (or lowest) obtained value throughout the test (i.e., either at the BP or Ppeak).

Statistical Analysis

The statistical analysis was performed in SPSS 21.0 (IBM Corp., Armonk, NY, United States). The pulmonary gas exchange (VO_2, VCO_2) and NIRS (TOI, O_2Hb, HHb) data were normally distributed, and therefore the data are presented as mean values ± SD and parametric statistical analyses were performed. The parameters quantifying exercise tolerance (Ppeak, VO_2peak, and GET) were compared between the CoA patients and healthy controls by means of Independent Samples *T*-tests. The predPpeak and predVO_2peak in both patients and controls were compared to a reference value of 100% (Wasserman, 2012) by means of One Sample *T*-tests. The cerebral and muscle TOI, O_2Hb, and HHb responses at the 10% Ppeak intervals (between 0% and 100% Ppeak) were compared between the CoA patients and healthy controls and between the intensities by means of Two-way Anova (Group x Intensity). Additionally, the Δmuscle HHb/ΔP values were compared at each relative intensity (% Ppeak) between patients and controls by means of Two-way Anova. In case of significant interaction or main effects *post hoc* Tukey tests were performed. Statistical significance was set at $P < 0.05$.

RESULTS

Exercise Tolerance

In **Table 2** the parameters quantifying exercise tolerance, obtained from the incremental ramp exercise, are presented. When expressed relative to body weight, the CoA subjects had significantly lower Ppeak (Watt.kg^{-1}) ($P = 0.010$), VO_2peak (ml.min^{-1}.kg^{-1}) ($P = 0.019$), and GET (ml.min^{-1}.kg^{-1}) ($P = 0.002$). Also, the CoA patients had significantly lower Ppeak and VO_2peak values compared the expected values for age, gender, stature and weight ($P < 0.001$).

TABLE 2 | Exercise tolerance (Ppeak, VO_2peak, RERpeak, HRpeak, GET, and blood pressure) in coarctation aortae patients and healthy controls,

	Coarctation	Controls	*P*-value
Ppeak (Watt)	119 ± 49	125 ± 41	$P = 0.723$
Ppeak/kg (Watt.kg^{-1})	2.42 ± 0.65	3.04 ± 0.59	$P = 0.010$*
% Predicted Ppeak (%)	72.3 ± 20.2	106 ± 18.7	$P < 0.001$*
VO_2peak (ml.min^{-1})	1792 ± 581	1790 ± 459	$P = 0.991$
VO_2peak/kg (ml.min^{-1}.kg^{-1})	37.3 ± 9.1	44.2 ± 7.6	$P = 0.019$*
% Predicted VO_2peak (%)	85.7 ± 21.9	112.1 ± 15.5	$P < 0.001$*
RERpeak	1.14 ± 0.10	1.09 ± 0.06	$P = 0.382$
HRpeak (bts.min^{-1})	179 ± 19	193 ± 9	$P = 0.188$
GET (ml.min^{-1})	933 ± 371	964 ± 289	$P = 0.657$
GET/kg (ml.min^{-1}.kg^{-1})	19.0 ± 4.7	23.6 ± 3.9	$P < 0.002$*
Blood pressure rest (sys/dias) (mm hg)	121 ± 19/ 68 ± 12	110 ± 16/ 63 ± 16	$P = 0.561$/ $P = 0.624$
Blood pressure max (sys/dias) (mm hg)	175 ± 22/ 69 ± 10		

*Values are mean ± SD. Ppeak, peak power output; $\dot{V}O_2$peak, peak oxygen uptake; RERpeak, peak respiratory exchange ratio; HRpeak, peak heart rate; GET, gas exchange threshold; BP, blood pressure. *Indicates a significant ($P < 0.05$) difference between coarctation and controls.*

Cerebral and Muscular Oxygenation

In **Figures 1**, **2**, the cerebral and the muscular TOI, HHb and O_2Hb patterns are presented as a function of intensity in 10% Ppeak intervals. For cerebral TOI there were no differences between patients and controls ($P > 0.05$) at any intensity. However, the BP in cerebral TOI (at which TOI starts to decrease) occurred at a significantly lower absolute (78 ± 33 Watt vs. 93 ± 37 Watt, respectively, $P = 0.027$) and relative intensity (65.5 ± 9.7% Ppeak vs. 74.4 ± 11.2% Ppeak, respectively, $P = 0.014$) in patients compared to controls.

For the cerebral O_2Hb ($P = 0.038$) and HHb ($P = 0.045$) a significant interaction effect (Intensity x Group) was demonstrated, indicating that the response pattern differed between CoA patients and healthy controls. For cerebral O_2Hb, *post hoc* tests revealed that cerebral O_2Hb was significantly lower ($P < 0.05$) from 60 to 90% Ppeak in patients vs. controls. Also the BP occurred at a significantly lower absolute (89 ± 36 Watt vs. 101 ± 35 Watt, respectively, $P = 0.027$) and but not relative intensity (74.8 ± 12.1% Ppeak vs. 80.8 ± 9.4% Ppeak, respectively, $P = 0.102$) in patients compared to controls. For cerebral HHb, *post hoc* tests showed that the increase in cerebral HHb was more pronounced in healthy controls from 70 to 100% Ppeak. The BP did not occur at a different absolute (78 ± 36 Watt vs. 78 ± 32 Watt, respectively, $P = 0.027$) and relative intensity (66.0 ± 11.8% Ppeak vs. 66.8 ± 10.4% Ppeak, respectively, $P = 0.862$) in patients and controls.

For muscle TOI a significant main effect ($P = 0.021$) of Group was found. *Post hoc* analysis showed that muscle TOI was significantly ($P < 0.05$) lower in patients compared to controls

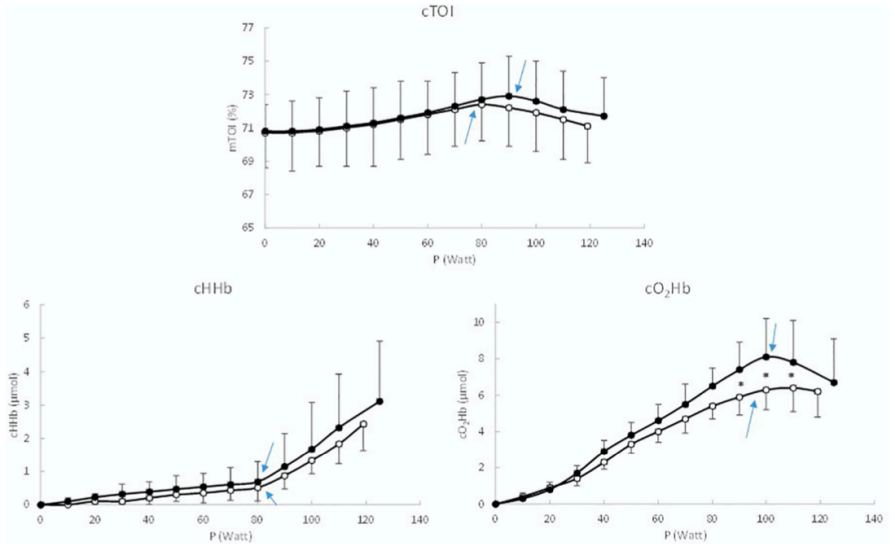

FIGURE 1 | Response pattern of cerebral TOI, HHb, and O_2Hb as a function of work rate, expressed in 10% Ppeak intervals. Black circles represent the healthy controls, white circles represent the coarctation aortae patients, and * indicate significant differences between patients and controls.

from 10 to 70% Ppeak. The total amplitude of the decrease in muscle TOI did not differ significantly ($P = 0.739$) between both groups ($-11.7 \pm 4.6\%$ vs. $-11.6 \pm 5.5\%$ in patients and controls, respectively) and also the muscle TOI at Ppeak ($56.8 \pm 4.0\%$ vs. $58.4 \pm 5.1\%$ in patients and controls, respectively did not differ significantly ($P = 0.372$). Also for muscle HHb a significant ($P = 0.010$) main effect of Group was found. Muscle HHb was significantly ($P < 0.05$) higher in patients compared to controls from 20 to 70% Ppeak. The BP in muscle HHb occurred at a significantly lower absolute (92 ± 33 Watt vs. 105 ± 36 Watt, respectively, $P = 0.031$) and relative intensity ($77.1 \pm 9.1\%$ Ppeak vs. $84.4 \pm 9.7\%$ Ppeak, respectively, $P = 0.039$) in patients compared to controls, whereas the maximal amplitude of the muscle HHb response (7.6 ± 3.6 µmol vs. 6.8 ± 3.6 µmol, respectively, $P = 0.466$) did not differ significantly between patients and controls.

In **Figure 3** ΔmuscleHHb is presented for each 10 Watt increase. It was observed that ΔmuscleHHb was significantly higher in CoA patients compared to healthy controls for the 0–10, 10–20, and 20–30, 30–40 Watt intervals ($P < 0.05$). Muscle O_2Hb did not differ significantly ($P > 0.05$) between CoA patients and controls over the entire intensity range and at Ppeak (-4.3 ± 1.4 µmol vs. -4.4 ± 2.0 µmol, respectively, $P = 0.792$). A clear BP could only be found in 4 of 16 CoA patients and 7 of 20 controls, therefore the BP in muscle O_2Hb was not considered.

Finally, it was also found that some NIRS variables were correlated to clinical indices. ΔMuscle HHb for the 10–20 and 20–30 Watt intervals (10–20 Watt: $r = 0.40$; $P = 0.039$ and 20–30 Watt: $r = 0.43$; $P = 0.034$) showed a weak but significant correlation with the residual gradient over the coarctation zone (**Figure 4**). The total amplitude of muscle HHb (i.e., the change between 0% Ppeak and 100% Ppeak) was significantly correlated ($r = 0.61$, $P = 0.017$) to the blood pressure difference between the arm and leg at maximal exercise.

DISCUSSION

To the best of our knowledge, this is the first study to report the patterns of cerebral and muscular tissue oxygenation during incremental exercise in children with aortic coarctation. It was found that children with CoA had a lower exercise tolerance, as can be deducted from a lower VO_2peak, Ppeak and GET, expressed relative to body weight. Additionally, there are different oxygenation patterns at the cerebral and muscle level compared to healthy children. More specifically, children with CoA had a less pronounced increase in cerebral O_2Hb at high intensities, whereas muscle TOI and HHb showed a more rapid decrease and increase, respectively, especially at low to moderate exercise intensities. Also the breakpoints in cerebral TOI and

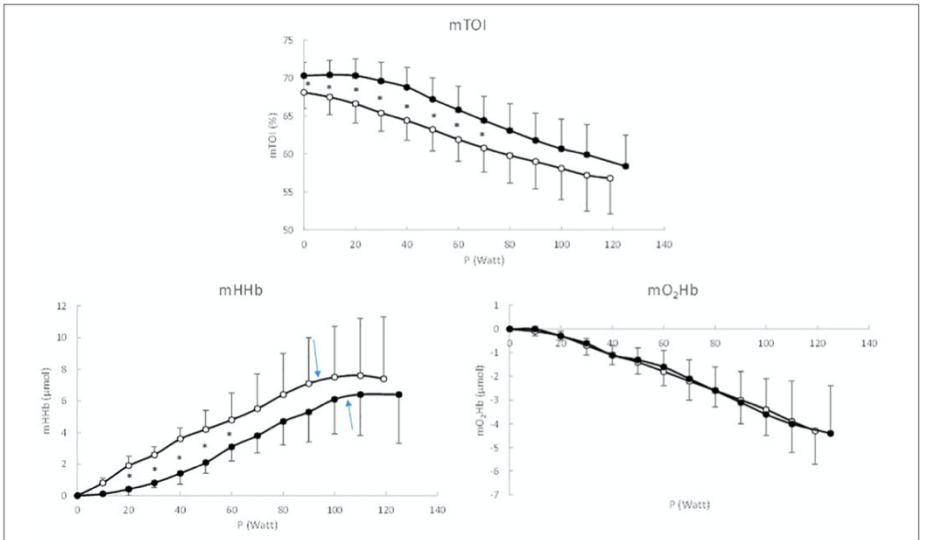

FIGURE 2 | Response pattern of muscle TOI, HHb, and O_2Hb as a function of work rate, expressed in 10% Ppeak intervals. Black circles represent the healthy controls, white circles represent the coarctation aortae patients, and * indicate significant differences between patients and controls.

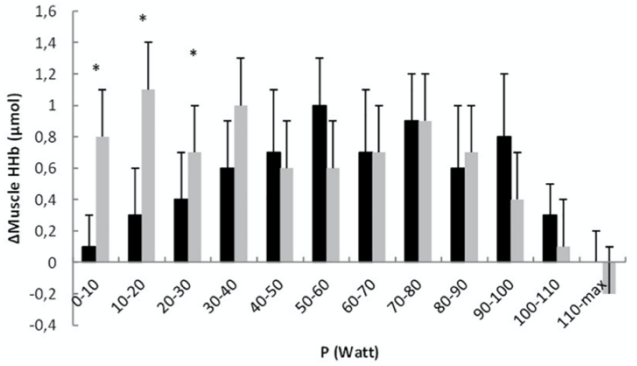

FIGURE 3 | Change in muscle HHb (Δmuscle HHb) relative to the change in work rate (Δ*P*) for each 10 Watt interval in healthy controls (black bars) and coarctation aortae patients (gray bars). * indicate significant differences between the groups.

muscle HHb occurred at a lower absolute and relative intensity, indicating that peripheral oxygenation might contribute to the lower physical fitness levels observed in CoA patients compared to healthy controls.

Exercise Performance

In accordance with previous studies (Trojnarska et al., 2007; Hager et al., 2008), we found a lower exercise performance in patients after CoA repair. The CoA patients reached only

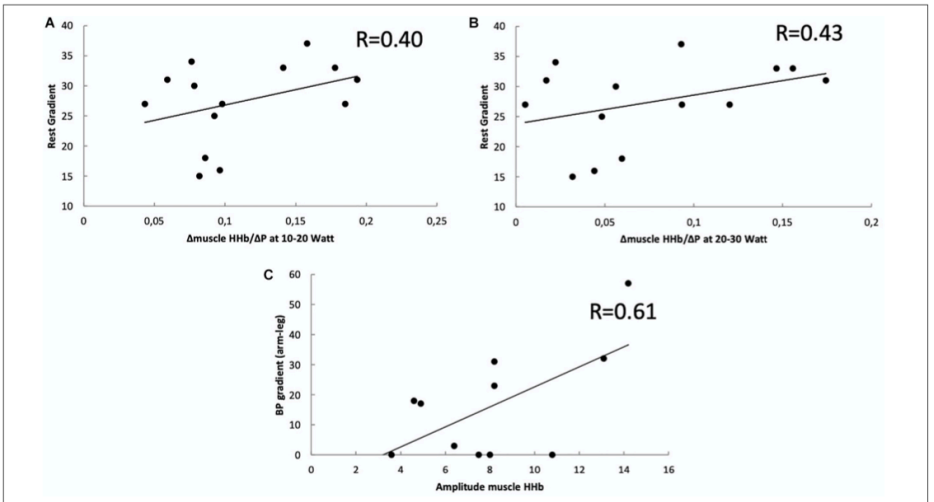

FIGURE 4 | Correlation between the change in muscle HHb (Δmuscle HHb) and residual echocardiographic **(A,B)** or blood pressure gradient **(C)**. **(A)** Relative to the change in work rate (ΔP) for 10–20 Watt. **(B)** Relative to the change in work rate (ΔP) for 20–30 Watt **(B)** Ppeak and the residual gradient using echocardiography in coarctation patients. **(C)** The correlation between the total amplitude of muscle HHb (difference between 0% Ppeak and 100% Ppeak) and blood pressure difference between arm and leg at maximal exercise.

72.3 ± 20.2% of the predicted Ppeak and 85.7 ± 21.9% of the predicted VO_2peak, which was significantly lower compared to the healthy subjects. The GET, quantifying aerobic exercise tolerance, was also lower in CoA patients.

With regards to the potential underpinning mechanisms of lower exercise performance in CoA patients is has been suggested that there might be a reduced aortic compliance after CoA repair (Hager et al., 2008). Additionally, also a reduced cardiac output could potentially contribute to the reduced exercise performance. Left ventricular hypertrophy in patients with residual CoA can disturb diastolic function with a decreased cardiac output at high intensities. However, at the moment there is no scientific evidence of an affected cardiac output in CoA patients. The present study indicates that different flow distribution patterns and local changes in oxygenation could also contribute to diminished exercise performance (see below). The observation that children after CoA repair appear to have an earlier reliance on the anaerobic metabolism (Wong et al., 2017) supports the suggestion of a reduced functional capacity of the aerobic metabolism. However, at the moment the main origin of the limitation (i.e., convective O2 supply, O_2 diffusive capacity) is unknown.

Additionally, it should be noted that next to underlying pathophysiological factors also deconditioning in relation to lower physical activity (due to an overprotective environment) might be a possible contributing factor to the lower exercise performance. However, a recent study of Stone et al. (2015) showed that the physical activity levels of CoA children after repair were similar to those of healthy children.

Cerebral Oxygenation

The lower exercise tolerance in CoA patients could at least in part be explained by a different oxygenation pattern at the peripheral level. Similar to healthy subjects (Rooks et al., 2010; Vandekerckhove et al., 2016) cerebral O_2Hb increased from low to high intensities, where a breakpoint occurred at which cerebral O_2Hb levels off or even decreased. Cerebral HHb showed a slow initial increase with a progressive speeding as work rate increased (>60% Ppeak). In comparison to the healthy controls the amplitude of the responses was less pronounced for cerebral O_2Hb. The combination of both a lower cerebral O_2Hb and a similar HHb in CoA patients vs. controls at high intensity explains the lower cerebral TOI (i.e., mixed arterio-venous saturation) in CoA patients at high intensities. It is unclear what might be at the origin of this different oxygenation pattern at cerebral level. One study, although not in coarctation patients, reported that cerebral hemodynamics adapt very rapidly to changes in tension when hypertensive adult patients received antihypertensive medication (Zhang et al., 2007). A recent study described an increased intracranial arterial stiffness and decreased responsiveness to hypercapnic stimuli in adult CoA patients (Wong et al., 2017).

Patients after coarctation repair might suffer from residual narrowing and/or arterial stiffnes distal from the origin of the

arteries supplying blood flow to the brains. This leads to a higher pressure and hypertension at the level of the brain. How the brain copes with higher pressures during exercise, and if an (over)protective mechanism is more active in children with CoA, is not known.

The results of the present study show a less pronounced increase in O_2 supply (as reflected in the O_2Hb response), in combination with an earlier onset of the decrease (i.e., the breakpoint) in cerebral O_2Hb which resulted in an earlier decrease in cerebral TOI in CoA patients compared to controls. It can be speculated that this affected the "activity" of the motor cortex as such that the firing rate to the locomotor muscles was reduced which might have resulted in an earlier termination of the exercise test. In a recent study in our laboratory, it was observed that Fontan children had a fast decrease in cerebral TOI from the onset of the incremental ramp exercise (Vandekerckhove et al., 2019) and terminated the test with a reduced cerebral TOI compared to healthy controls. In this population it was speculated that the cerebral oxygenation might have been the main contributing factor to exercise termination. Whether this is also the case in the CoA children is questionable since cerebral TOI at Ppeak was similar to the rest values and did also not differ with the controls.

Muscle Oxygenation

Also, the oxygenation at the locomotor muscles showed a different pattern in the two study groups. In the CoA patients, muscle HHb showed a more pronounced increase in the low to moderate intensity domain in combination with a lower TOI compared to healthy controls. As HHb is often considered as the most valuable NIRS parameter since it is a reflection of fractional O_2 extraction (McNarry et al., 2015), this different pattern of HHb might reflect a disturbed relationship between O_2 supply and O_2 demand. In healthy subjects the HHb response to incremental ramp exercise shows a sigmoidal pattern (Carano et al., 1999; Boone et al., 2009; Vandekerckhove et al., 2016) with a rather slow increase in HHb at the onset of the incremental ramp exercise. This typical pattern in the HHb response at low to moderate intensities indicates that the blood flow to the locomotor muscles has increased to such an extent that the fractional O_2 extraction does not need to increase (Ferreira et al., 2007; Boone et al., 2009). In the CoA patients however, this "sigmoidal" pattern is not present and the HHb response shows an immediate increase at the onset of exercise (**Figure 2**). This more pronounced increase in HHb in CoA patients is also expressed in **Figure 3**. This indicates that the balance between O_2 supply and O_2 demand might be altered at low to moderate intensities, highly likely related to a disturbed convective O_2 delivery. This disturbed balance at low intensities is also reflected in the lower mTOI values during unloaded cycling.

Interestingly, we found a correlation between residual arch gradient and ΔmuscleHHb/ΔP and between the total muscle HHb amplitude and blood pressure difference arm-leg at maximal exercise. The CoA children with higher residual obstruction at the descending aorta, have more pronounced increase in muscle HHb per increase in work rate and thus a more disturbed balance between O_2 supply and O_2 demand. Exercise testing has been shown to be a useful tool for evaluation of residual coarctation after surgery (Carano et al., 1999; Das et al., 2009). Correia et al. (2013) showed that patients with higher residual gradient can develop hypertension during exercise, despite normal tension control at rest. A difference in exercise capacity between adults with higher residual gradient or normal gradient could not be shown (Trojnarska et al., 2007), although exercise capacity is generally decreased in patients after CoA repair. The different mechanisms at the level of the muscles are unknown. Our findings demonstrate that there might also be metabolic differences at the muscular level in children after CoA repair, even more pronounced in children with higher residual stenosis. Surprisingly, this study also showed that CoA patients have a higher total amplitude of the muscle HHb response compared to healthy subjects, indicating a greater O_2 extraction capacity in this patient population. It is highly likely that the greater reliance on O_2 extraction, due to the disturbed balance between O_2 supply and O_2 demand even at low to moderate intensities, results in the greater capacity of the locomotor muscles to extract O_2.

Although the limited number of patients should be considered a limitation of the present study, the results shed a new light on the exercise tolerance of CoA patients. The evaluation of cerebral and peripheral oxygenation in this patient population provides useful information on the physical condition of the subjects and the efficacy of treatments and rehabilitation programs. Larger patient trials are needed to explore the influencing factors and causes which can possibly explain the different patterns in CoA patients. In this context, it would be useful to integrate NIRS measurements to assess whether the oxygenation patterns could provide a more comprehensive insight into the exercise performance of CoA patients.

Conclusion

Children after coarctation repair have diminished exercise capacity in combination with different patterns of oxygenated and deoxygenated hemoglobin at the level of the brains and at the muscular level. This points toward diminished blood flow and oxygen transport at the level of the brains and increased oxygen extraction at the level of the muscles during exercise. The increased muscular deoxygenation is more pronounced in children with higher residual coarctation gradient and blood pressure gradient. The measurement of peripheral oxygenation during exercise might provide useful information with regards to the disease state of the individual patient.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ghent University Hospital. Written informed

consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KV, IC, DD, and JB contributed to the study design. KV, IC, JP, AM, KD, and TB contributed to the data collection. KV, IC, AM, TB, HD, KF, and JB contributed to the data analysis. KV, IC, TB, DD, AM, and JB contributed to the data interpretation. KV, IC, JP, KD, and JB contributed to the writing of the manuscript. AM, KD, TB, JP, HD, and KF contributed to the revision of the manuscript.

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Chapter IX Discussion

Although CoA is a well-known clinical entity, the definitive diagnosis of CoA demands a high degree of expertise, being frequently delayed to older childhood and even adulthood. Awareness of subtle clinical signs, such as diminished femoral pulse volume, (which are especially important to illicit in the context of HT), among General Practitioners, Pediatricians and Adult Cardiologists, should be improved through targeted education and teaching. After all, diagnosing CoA as early as possible has important prognostic implications, both in the short term for duct-dependent neonatal CoA, and in the long term, to reduce the prevalence of HT after CoA repair. Furthermore, diagnosing a significant re-CoA after repair is equally important, as addressing re-CoA improves the long-term prognosis. Streamlining referral patterns to pediatric cardiologists and adult cardiologists, with expertise in congenital heart lesions, should be optimized.

Once the diagnosis has been established, follow-up should include careful surveillance to address problems such as re-CoA or HT timely, in a center with the necessary expertise in pediatric and adult congenital heart disease. There is convincing evidence from the literature showing that these measures improve the long-term outcome positively. Nevertheless, the long-term morbidity and mortality remain a concern despite successful treatment of CoA. Frequent problems are early onset of cardiovascular diseases like myocardial infarction, cardiac failure, a three-fold risk of stroke and even sudden death, all related to arterial hypertension [1].

By conducting a systematic review of recent data, we have shown that the average prevalence of HT after CoA repair is 47.3% (range 20-70%) (**Chapter IV**). It is conceivable that HT still remains underdiagnosed, as the prevalence increases to 57.8% if studies are included where 24h BP monitoring (or exercise testing) was performed. In addition, HT after CoA repair shows a progressive character [2], since studies with the longest follow-up have the highest incidence of hypertension [3-7]. Moreover, obesity was found to have an increasing prevalence in patients with repaired CoA, additionally contributing to the increased incidence of HT in more recent studies [8].

The development of HT in CoA patients is influenced by various factors:

1. The age of patients at the time of the initial repair is an important determinant of long-term survival and HT in CoA patients [3, 4, 7, 9, 10]. The age at follow-up was found to be equally important, with the beneficial effect of early repair possibly wearing off as patients age. [6].

2. The type of repair can also influence the incidence of HT, especially in relation to correction of associated HAA [11, 12]. Currently surgical techniques aim at minimizing residual hypoplastic segments, in part

because of evidence that aortic catch-up growth is frequently insufficient [12, 13].

3. The aortic arch morphology has been found to contribute to abnormal vascular dynamics in various studies, with a gothic arch having the greatest effect. However, 3D shape might not be the major determinant of vascular load following CoA repair, as caliber seems more important than curvature [14].

One of the problems in comparing data on HT from different studies is the usage of various BP devices, especially for 24h BP measurement, influencing results [15]. A further limitation was that the recommended cut-off for the definition of exercise-induced HT of SBP>200mmHg was found to be high in children, with a suggested value of >190mmHg probably being more suitable [16]. We believe routine 24h BP measurement should be recommended yearly in patients after CoA repair as a minimal diagnostic test for HT, seeing as the prevalence of HT increased in all studies adding 24h BP measurements; ideally exercise testing should be added to identify patients at increased risk of developing HT.

Even though HT is probably the cause of most complications after CoA repair, the holy grail would be to identify preliminary signals of potentially harmful pathophysiologic changes before overt HT is present, in this way long-term complications related to HT in CoA patients might be anticipated. Peripheral BP is the easiest parameter to measure but has limitations in predicting afterload, furthermore peripheral BP can differ from central BP. Afterload is composed of the following parameters: myocardial wall stress, arterial BP, arterial resistance and arterial impedance.

The role of specific hemodynamic indicators of long-term outcome is currently not well understood. In our systematic review, many of the included studies only briefly touched on possible underlying vascular mechanisms.

CoA repair can lead to various sequelae, whether the treatment be surgical or percutaneous. Common sequelae include a short stiffened and/or narrowed segment (surgery) or a long stiffened and/or narrowed segment (stenting).

We studied the quantitative effects of these sequelae (narrowing and stiffness in short and long segments) in Chapter V [17] and Chapter VI [18].

In our fluid-structure interaction (FSI) study (**Chapter V**), we assessed central hemodynamics with the introduction of an isolated narrowing or stiffening in an otherwise normal aorta. Mostly, in computational modeling of CoA, studies do not account for aortic wall properties [19-21]. Comparison with Computational Fluid Dynamics (CFD) highlighted the importance of accounting for the elasticity of the aorta to correctly capture the buffering capacity of the proximal aorta. This parametric model simulated a setting after CoA-repair with a coarctation zone to predict the hemodynamic impact of (coexisting) stiffening and narrowing in CoA repair.

c-SBP could be predicted by using the descending aortic distension waveform as a substitute for the pressure waveform and by scaling it to the measured brachial pressure with our FSI model.

We found that the hemodynamic impact of an isolated stiffening is limited. Aortic constriction, on the other hand, induces a pronounced increase in c-SBP (proximal aorta), buffering the stroke volume proximal to the aortic narrowing. For short constrictions, additional stiffening was shown to have a significant impact on the pressure evolution, whereas the impact is relatively limited for longer constricted segments.

The most important limitation includes the fact that the model was based on a healthy aorta, ignoring the possibility of intrinsic abnormalities of the aortic wall in CoA patients. Besides vascular remodeling interference, the impact of ventriculo-arterial (V-A) interaction was ignored.

We therefore examined the effect of aortic stiffness and narrowing in vivo, not only on central aortic hemodynamics, but also on V-A interaction in an experimental porcine model (**Chapter VI**). Comparing a short and a long stiffening and a short and long narrowing to a control group at rest, and during inotropic stimulation, allowed us to assess the effects on central hemodynamics and V-A interaction in vivo.

Our findings were very similar effects to our FSI modelling study [17], again concluding that the hemodynamic impact of an isolated stiffening is limited, but that any narrowing, especially a longer narrowed segment has important consequences on central hemodynamics as well as on ventricular adaptation.

We showed in both the FSI modelling study and in our porcine CoA study that alterations of central aortic pressure differ clearly from peripheral BP. In addition, we showed that despite adequate relief of CoA, the VA hemodynamic relationship is compromised, depending on the sequelae of aortic treatment varying from a short residual stenosis to long non-stenotic aortic stiffening (as after aortic stenting). Moreover, the impaired VA coupling is enhanced after inotropic stimulation, suggesting that the ventricular adaptation to the altered vascular dynamics may be underestimated, becoming unmasked during exercise.

We concluded therefore that therapeutical management needs to focus on improving aortic remodeling after CoA repair, preferably by minimizing residual stenosis, even at the cost of inducing aortic stiffness. However, the data obtained from this in-vivo experiment still extrapolates from a pre-existing “healthy” porcine aorta, even though a time delay of 3 months was used to expose the animals to the pathological lesion of interest.

The contribution of additional stress testing, as conducted in this animal model, helped to better delineate the effect of pathological aortic dynamics on LV function.

So far, stress testing has been poorly validated to quantify the exact significance of a residual aortic gradient on arterial-ventricular interaction. We therefore studied a group of children after surgical repair for CoA (**Chapter VII**) in order to establish whether differences in systolic and diastolic heart function are already present, prior to the onset of HT, compared to controls. Hereto, a method of isometric exercise testing, based on sustained submaximal handgrip, was devised.

We provided first evidence that HG testing with simultaneous echocardiography was feasible, easy and patient-friendly. A decreased systolic (tissue Doppler) and impaired diastolic LV function was found in the repaired CoA group, a difference that tended to increase during HG. We have known for quite a while that diastolic function is one of the most important cardiac findings in essential HT in adults [22].

These findings in children after CoA repair without HT, confirmed that the altered aortic dynamics affect the diastolic function, characterized by increased LV hypertrophy and myocardial fibrosis [18]. The fact that diastolic dysfunction develops early-on after CoA repair, before the onset of (peripheral) HT or even LVH, confirms that HT can be a late finding while peripheral BP at rest can be normal for an extended latent period despite abnormal central hemodynamics.

Exercise tolerance has been found to be substantially lower in children after CoA repair [5, 16, 23]. Based on bicycle ergometry testing in CoA patients without re-CoA, maximal exercise capacity was reduced compared to the controls. It has been shown that lower limb blood flow can be diminished in response to strenuous exercise even in the absence of a residual stenosis at rest [24] but the exact etiology of the diminished exercise tolerance after CoA repair remains unknown. Our findings on echocardiographic assessment of LV function during exercise showed important diastolic dysfunction. From this perspective, one can postulate that the necessary increase of cardiac output during exercise is hampered by an inappropriate capacity to increase stroke volume, partly because of chronotropic incompetence. Another contributory mechanism concerns blood flow regulation to the peripheral muscles during exercise in CoA patients [25].

We decided to assess whether the lower exercise tolerance in children is associated with alterations in peripheral oxygen exchange during dynamic exercise [26] (**Chapter VIII**), once more in children after CoA repair without HT. Children after CoA repair were found to have diminished exercise capacity in combination with different patterns of oxygenated and deoxygenated hemoglobin at the level of the brains and at the muscular level. This points toward diminished blood flow and oxygen transport at the level of the brain and increased oxygen extraction at the level of the muscles during exercise. The increased muscular deoxygenation is more pronounced in children with higher residual CoA gradient and BP gradient pointing to residual aortic obstruction. The measurement of peripheral oxygenation during exercise might provide useful information with regards to the disease state of the individual patient.

Conclusions

- Awareness needs to increase of the importance of early diagnosis of CoA, in order to improve long-term outcome.
- HT is an important and progressive problem after CoA repair, even with anatomically good repair without important re-CoA. 24h BP is necessary, at least annually, to improve early detection of HT after CoA repair.
- After CoA repair, the true afterload cannot be adequately assessed by measuring peripheral BP. Additional parameters like c-SBP, arterial resistance and aortic impedance can now be evaluated non-invasively and could be useful in identifying pathological changes prior to the onset of HT.
- Important therapeutic goals in CoA repair are the prevention of residual hypoplastic segments in primary repair and maximally eliminating localized residual gradients, even at the cost of inducing a segment of stiffness.
- Modelling and invasive measurements show that stenosis is more important than rigidity, with V-A dynamics affected more by a longer narrowing than a short narrowing.
- Invasive aortic hemodynamic measurements show that the V-A relationship is impaired after CoA repair and decouples further during inotropic stimulation.
- Diastolic (and systolic) function is already impaired in children after CoA repair, even without re-CoA or HT, and declines further during exercise.
- Isometric exercise with simultaneous echocardiography is a child-friendly and easy way to perform a “stress-echo” in children with CoA.
- Children after CoA repair have diminished exercise capacity, which is partially related to disturbed diastolic LV function and chronotropic incompetence, as well as to disproportionally increased peripheral muscular oxygen extraction.

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Chapter X Future Perspectives

Keeping in mind that at least 60% of patients will go on to develop peripheral HT after CoA repair, with on top of that an increasing prevalence by ageing, it could be argued that it might be beneficial to treat all CoA patients with anti-hypertensive medication prior to developing overt HT. Benefits would most likely outweigh side-effects and risks. Hereto, agents acting on the altered renin-angiotensin system and eventually on aortic and vascular wall compliance are interesting pathways for research, in analogy to the drug trials conducted in patients with hereditary aortopathy.

At the present time there are no studies linking abnormal central hemodynamics and diastolic LV function in the absence of evident peripheral HT to long-term outcome. It is now possible to assess c-SBP non-invasively. Probably c-SBP is even more likely to be associated with increased long-term morbidity and mortality than peripheral HT although this has not been studied or proven at present. An important question is whether those who are found to have a raised c-SBP should be treated in the absence of peripheral HT. A case could be made to consider those patients with raised c-SBP as having HT and possibly at higher risk of complications from HT. I believe this presents ample opportunities for further prospective trials. However, there is no reason, other than a lack of local expertise, that MRI scans which are conducted routinely in most centres in CoA patients during adolescence, don't include parameters of central hemodynamics in future. As a bare minimum, c-SBP could be acquired during MRI scans in patients with repaired CoA. This data can be collected prospectively and would add non-significantly to scan duration.

The clinical utility of computational modelling in quantifying central aortic hemodynamics for residual aortic lesions is promising. This method might be helpful in identifying individual patient-specific parameters in order to predict the effect of various treatment options (for instance stenting vs surgery) based on their own aorta anatomy and boundary conditions. This would allow better treatment planning for reconstruction of the aortic arch, to optimize local treatment as well as central aortic hemodynamics. At present individual computational modelling is limited by the substantial time needed to analyse data and the need for additional detailed data from scans, not routinely acquired. This might change as more user-friendly analysis software and faster scans become available.

The field of exercise testing in children with heart diseases remains largely open for exploration. However, the standard approach of exercise stress testing via bicycle ergonometry is limited to older and collaborative children, and simultaneous echocardiographic investigation is usually difficult. However, isometric stress testing allows simultaneous echocardiography in children. This technique can be applied to other study groups, for instance in children with

chemotherapy-induced cardiopathy. In these children a non-invasive stress-echo might unmask subtle changes of ventricular function not detectable at rest.

In children and adults after CoA repair, a “stress-echo” with isometric exercise might also be useful during routine follow-up, to identify apparently non-critical residual aortic lesions prematurely. During the isometric stress-echo, BP gradient could be assessed. However, to anticipate early appropriate therapy, the role of exercise stress testing in CoA patients needs to be better elucidated.

The exact role of tissue oxygenation after CoA repair has so far not been adequately studied. Larger patient trials are needed to explore the influencing factors and causes which might explain the different tissue oxygenation patterns in CoA patients. Repeating the NIRS measurements during exercise, after a specific intervention - for instance treatment with antihypertensive medication or a revalidation program, will allow studying whether the treatment attenuates the different response between central and peripheral tissue oxygenation.

Chapter XI Summary

CoA repair has been performed successfully since 1945. However, long-term morbidity and mortality are still an important concern, mostly related to HT.

Besides the impact of variable clinical factors, greater insight into the aortic and ventricular hemodynamics before and after CoA repair is essential to improve the long-term perspective.

Via a systematic review (**Chapter IV**), we added to the knowledge-base on HT after CoA repair by establishing that the prevalence is currently higher than previously thought, depending on the definitions to categorize HT and the methods of BP registration.

There is increasing recommendation to include 24h BP measurements to the annual follow-of CoA patients to improve the sensitivity in diagnosing HT. The review also revealed an increased incidence of obesity in CoA patients, promoting HT.

Analysis demonstrated that peripheral BP as the simplest measure of afterload has limited value in predicting central aortic hemodynamics and the real magnitude of afterload. We highlighted novel non-invasive ways of estimating c-SBP.

In our FSI study (**Chapter V**) we added to previous modelling studies by incorporating the elasticity of the aorta. Comparison with CFD simulations highlighted the importance of accounting for the elasticity of the aorta to correctly capture the buffering capacity of the proximal aorta.

We found that the hemodynamic impact of an isolated stiffening is limited. Aortic constriction, on the other hand, induces a pronounced increase in blood pressure in the proximal aorta, buffering the stroke volume proximal to the aortic narrowing.

We concluded that for short constrictions, additional stiffening has a significant impact on the pressure evolution, whereas the impact is relatively limited for longer constricted segments. This helps us prioritize where different treatment options are available.

Taking the boundary restrictions of computational models into account, a porcine model of CoA (**Chapter VI**) allowed us to study the in-vivo effect of residual lesions after CoA repair on ventriculo-arterial interaction.

The aortic hemodynamic findings of the former study were mostly confirmed, with the addition that even a low gradient stenosis is associated with V-A impairment,

which is further enhanced by inotropic stimulation. We concluded that the goal of CoA repair is to pursue complete aortic remodelling with minimal hemodynamic stenosis, even at the cost of inducing aortic stiffness.

In children after CoA repair**,** we found that diastolic dysfunction (and early systolic dysfunction) is already present prior to developing HT. Exercise testing is a method to identify alterations of ventricular and aortic hemodynamics early. In **Chapter VII**, we validated the use of isometric exercise in children with CoA repair based on handgrip loading, which allowed simultaneous evaluation of LV function by echocardiography.

Finally, we went on to study cerebral and muscular tissue oxygenation with NIRS technology during incremental exercise in children with aortic CoA (**Chapter VIII**). We found diminished blood flow and oxygen transport at the level of the brain and increased oxygen extraction at the level of the muscles during exercise. It is highly likely that there is a greater reliance on O2 extraction because of the disturbed balance between O2 supply and O2 demand even at low to moderate exercise intensities.

Chapter XII Samenvatting

Coarctatio Aortae wordt al sedert 1945 efficiënt behandeld door middel van chirurgie. Desalniettemin gaat het herstel van CoA -ondanks het weghalen van het vernauwde segment- nog steeds gepaard met een verhoogde morbiditeit en mortaliteit, gewoonlijk ten gevolge van complicaties gerelateerd aan hypertensie. Een beter inzicht in de hemodynamische veranderingen voor en na CoA herstel ter hoogte van de aorta en het linkerventrikel, is van groot belang om de lange termijn prognose van deze patiënten te verbeteren.

Aan de hand van een systematische review (**Hoofdstuk IV**), waarbij de nieuwste bevindingen aangaande CoA en HT werden geïncludeerd, hebben wij kunnen vaststellen dat de eigenlijke prevalentie van HT in deze patiëntengroep hoger is dan tot nu toe algemeen in de literatuur werd aangenomen.

Er gaan dan ook steeds meer stemmen op om een 24h BP-bepaling te includeren in de jaarlijkse opvolging van CoA patiënten, om aldus vroegtijdig de diagnostische sensitiviteit van HT te verhogen. Bovendien hebben wij aangetoond dat obesitas steeds vaker voorkomt binnen deze patiëntengroep, gelijktijdig met een toenemende prevalentie van HT.

Bijkomende analyse suggereert verder dat de perifeer gemeten bloeddruk, die eigenlijk de eenvoudigste weergave van “afterload” is, weinig invloed heeft in het voorspellen van centrale aorta hemodynamiek. Verschillende nieuwe technieken om c-SBP te bepalen werden aangehaald.

In ons FSI-studie (**Hoofdstuk V**) hebben we getracht voorgaande modellerende studies te verbeteren door het toevoegen van de eigenschappen van de aorta elasticiteit. In vergelijking met meer voor de hand liggende CFD-simulaties werd duidelijk dat de inbreng van aorta elasticiteit in het model van belang is om een correcte voorspelling te maken van de buffercapaciteit van de proximale aorta om het linkerventrikel slagvolume op te vangen.

Dit model heeft verder aangetoond dat de hemodynamische impact van geïsoleerde lokale stijfheid ter hoogte van het restletsel na CoA herstel beperkt is. Een vernauwing van de aorta daarentegen induceert een belangrijke verhoging van de BP in de proximale aorta, met buffering van het slagvolume proximaal tot de vernauwing. We konden vaststellen dat een toegenomen stijfheid bij een korte vernauwing een belangrijk effect heeft op de drukcurve, terwijl de impact hiervan op een langer vernauwd segment relatief minder uitgesproken blijkt. Deze bevindingen kunnen hulp bieden bij het vastleggen van een keuzestrategie in het geval van meerdere behandelingsopties.

Dergelijke wiskundige modellen hebben echter hun beperkingen. Daarom werden de in-vivo effecten van residuele letsels na CoA herstel op de ventriculo-arteriële interactie gemodelleerd in dierexperimenteel model van CoA (**Hoofdstuk VI**). In deze studie hebben wij aangetoond dat zelfs een lage gradiënt stenose de VA koppeling nadelig beïnvloedt, dit wordt nog versterkt door inotrope stimulatie. Bovendien blijkt dat het negatief hemodynamisch effect van een stenose belangrijker is dan een segmentaire aortastijfheid, zeker wanneer het een langer segment betreft. Ons conclusie is dat het finale doel van de behandeling van CoA een optimale anatomische en functionele remodelering van de aorta moet beogen, liefst met minimale residuele gradiënt, zelfs indien deze therapie ten koste is van een lokaal toenemende aortastijfheid.

Het effect van inspannings-gerelateerde veranderingen op de hemodynamiek werd onderzocht in een klinische studie bij kinderen geopereerd van een CoA (**Hoofdstuk VII**). Hier hebben wij aangetoond dat diastolische dysfunctie (alsook vroegtijdige systolische dysfunctie) reeds aanwezig is voor de ontwikkeling van HT. Deze studie heeft bovendien aangetoond dat de submaximale isometrische handgreep-test een gemakkelijke en haalbare methode is om bij kinderen echocardiografische opnames en metingen tijdens inspanning te verrichten.

Als laatste onderzoek (**Hoofdstuk VIII**) werd bij kinderen na CoA herstel de zuurstofvoorziening ter hoogte van de hersenen en het spierweefsel tijdens toenemende inspanning onderzocht met behulp van de NIRS-technologie,. Bij deze kinderen hebben we een verminderde bloedtoevoer en zuurstoftransport ter hoogte van de hersenen vastgesteld, en een verhoogde zuurstof extractie in de spieren, welke toeneemt tijdens inspanning. Deze verhoogde zuurstofextractie kan hoogstwaarschijnlijk verklaard worden door een verstoord evenwicht tussen O_2 aanvoer en O_2 behoefte, zelfs bij matige inspanning.

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The Backpage

“Another Chapter Ends
All Targets Met
All Systems Working
All Patients Satisfied*
All Staff Eager and Enthusiastic
All Pigs Fed and Ready to Fly”

*(*quote adapted to medicine by the author)*