DISFUNÇÃO VASCULAR NOS DOENTES COM COARCTAÇÃO DA AORTA TRATADA

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VASCULAR DYSFUNCTION AFTER REPAIR OF COARCTATION OF THE AORTA

Para o meu Pai.

"O conhecimento nasce da maravilha suscitada pela da contemplação da criação. (...) Sem tal assombro, o homem tornar-se-ia repetitivo e, pouco a pouco, incapaz de uma existência verdadeiramente pessoal."

São João Paulo II

In Fides et Ratio

This PhD dissertation has resulted in the following publications:

Two papers published in peer reviewed journals:

- Martins JD, Thomas B, Jalles N, Pinto FF. **Aortic arch geometry in repaired coarctation: systematic review of a consecutive series by magnetic resonance imaging.** *Rev Port Cardiol.* 2012;31(5):403-404.
- Martins JD, Zachariah MD, Selamet Tierney ES, Truong U, Morris SA, Kutty S, MD, PhD, de Ferranti SD, Guarino M, Thomas B, Oliveira D, Marinho A, António M, Gauvreau K, Jalles N, Geva T, Lock JE, Carmo MM, Prakash A, for the LOVE-COARCT Study. **Rationale and Design of LOVE-COARCT study: Long-term Outcomes and Vascular Evaluation After Successful Coarctation of the Aorta Treatment.** *Ann Pediatr Cardiol.* 201811(3):282-296

One paper, submitted to a peer review journal, currently under revision:

- Martins JD, Zachariah MD, Selamet Tierney ES, Truong U, Morris SA, Kutty S, MD, PhD, de Ferranti SD, Guarino M, Thomas B, Oliveira D, Marinho A, António M, Gauvreau K, Jalles N, Geva T, Lock JE, Carmo MM, Prakash A, for the LOVE-COARCT Study. **Impact of Treatment Modality on Vascular Function in Coarctation of the Aorta: the LOVE-COARCT study**. The results of this paper were accepted for oral presentation at the American Heart Association's Scientific Sessions 2018 (Chicago, Illinois, Noc 10-12) in the roundtable "Multi-center Studies: Latest Updates in CHD".

One paper in preparation for publication:

- Martins JD, Zachariah MD, Selamet Tierney ES, Truong U, Morris SA, Kutty S, MD, PhD, de Ferranti SD, Guarino M, Thomas B, Oliveira D, Marinho A, António M, Gauvreau K, Jalles N, Geva T, Carmo MM, Prakash A, Lock JE for the LOVE-COARCT Study. **Comparison of Vascular Function Between Transcatheter Treatments for Coarctation of the Aorta**.

Two chapters published in textbooks:

- Martins JD, Prakash A, Pereira CT, Fragata J, Geva T. **Coarctation of the Aorta.** In: da Cruz EM, Ivy DD, Jagger J, eds. *Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care.* 2nd ed. London: Springer-Verlag; 2019 (estimated release date).
- Martins JD, Pereira CT, Pinto FF. **Coartation of the Aorta.** In: Videira-Amaral JM, ed. *Tratado de Clínica Pediátrica.* Vol 2. 3rd ed. Lisbon: Abbott; 2019.

One chapter published in an exclusively on-line medical encyclopedia:

- Martins JD. **Coarctation of the Aorta.** In: Ferreira-Martins FM, Neto T, Videira-Amaral JM, Rosa FC, eds. Pepipédia, a *Enciclopédia Pediátrica Online. In* http://www.pedipedia.org/pro/artigo-profissional/coarctacao-da-aorta. 2018.

The PhD candidate was responsible for obtaining funding, conception of the research project, study design, logistic implementation and steering, database management, analysis of results, and first author of all publications.

LOVE-COARCT was a multicenter cross-sectional collaborative study. Throughout the study duration, there were 70+ regular monthly conference calls and three yearly in-person meeting with all the center principal investigators, who contributed significantly to all the items above.

All study tests were performed at each participating. LOVE-COARCT established core laboratories for each of the study tests. These were (a) Cardiac Magnetic Resonance Core Lab (responsible: Ashwin Prakash; Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA); Preventive Cardiology Core Lab (responsible: Sarah de Ferranti; Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA); Tonometry and BP Assessment Core Lab (Responsible: Justin Zachariah; Division of Pediatric Cardiology, Texas Children's Hospital, Baylor College of Medicine, Houston, USA); Endothelial Function Core Lab (Responsible: Elif Seda Selamet Tierney; Division of Pediatric Cardiology, Department of Pediatrics, Lucile Packard Children's Hospital, Stanford University, Palo Alto, USA); Biomarkers Core Lab (Responsible: Maria Guarino; CEDOC Chronic Diseases, Nova Medical School, Lisbon, PORTUGAL); Biostatistics Core Lab (Responsible: Kimberlee Gauvreau; Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA). The full list of the 29 LOVE-COARCT investigators is acknowledged in **Table 31** in the Appendix.

The study protocol was approved by the Institutional Review Board or Institutional Ethics Committee at each participating center, and informed consent and assent was obtained, depending on age, from patients and their parents/legal guardians, before study enrollment.

Thesis Mentor: Miguel Mota Carmo, MD, PhD, CEDOC Chronic Diseases, Nova Medical School, Lisbon PORTUGAL

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AAO	Ascending aorta
ABPM	Ambulatory blood pressure monitoring
ADMA	Asymmetric dimetilarginine
AIx	Augmentation index
AIx@75	Augmentation index at 75 beats per minute
BD	Balloon dilation
BMI	Body mass index
BSA	Body surface area
BP	Blood pressure
CAP	Central aortic pressure
CCISC	Congenital Cardiovascular Interventional Study Consortium
CHD	Congenital heart disease
CHLC	Centro Hospitalar de Lisboa Central
CMR	Cardiac magnetic resonance
CoA	Coarctation of the aorta
CT	Computed tomography
CV	cardiovascular
CVD	cardiovascular disease
DAO	Descending aorta
Dept	Department
DBP	Diastolic blood pressure
ECG	Electrocardiogram
Endo-PAT	Endothelial pulse amplitude testing
EST	Exercise stress test
FMD	Flow-mediated dilation
f/u	Follow up
HSM	Hospital de Santa Marta
HR	Heart rate
hs-CRP	High sensitivity C-reactive protein
HTN	Hypertension
ICVH	Ideal cardiovascular health
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
LV	Left ventricle
LVOT	Left ventricular outflow tract

MMP	Matrix metalloproteases
NO	Nitric oxide
NOx	Nitrite and nitrate
PP	Pulse pressure
PWV	Pulse wave velocity
RAA	Renin-angiotensin-aldosterone
ReCoA	Recurrent coarctation
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SSFP	Steady state free precision
TGF-β1	Transforming growth factor beta-1
TNF-α	Tumor necrosis factor alpha
VACA	Valvuloplasty and Angioplasty of Congenital Anomalies
VCAM	Vascular cell adhesion molecule

Introduction: Congenital heart disease (CHD) affects approximately 1% of liveborns and accounts for the largest proportion of infant mortality in developed countries. Coarctation of the aorta (CoA), the 6th most common CHD, consists of a narrowing of the proximal descending aorta. If left untreated, it has an unfavorable natural history. Surgery, balloon dilation (BD) or stent implantation are all current treatments that can achieve a successful long-term removal of the stenosis, and the choice is based on age, CoA anatomy, and personal or institutional preference. Coarctation is not a mere mechanical disease that is treated by removing the increased afterload. In fact, a good anatomic result does not avoid long-term cardiovascular (CV) morbidity and mortality, with late systemic hypertension (HTN) in approximately half of the patients, and reduced life expectancy, mostly due to CV complications and stroke. The abnormal blood pressure (BP) phenotype suggests that the suboptimal results are likely due to abnormal vascular function, which has been well documented in patients with repaired CoA. There are inherent changes in the arterial structure and function, impaired neuronal sensitivity or endocrinal auto-regulation, and acquired features, such as age at treatment, that contribute to vascular dysfunction in CoA. The poor long-term vascular outcome may also be impacted by the different types of repair, which likely have differing effects on the stiffness of the repaired segment and potentially compromise both the conduit and cushioning functions of the aorta. The effects of treatment modality on long-term vascular function remain uncharacterized.

Aims and Hypothesis: The goal of this study is to assess vascular function in this patient population for comparison among the treatment modalities. The central hypothesis of this study was that patients who have undergone successful BD will have better vascular function than patients who have undergone successful surgical repair or stenting since this modality is least likely to damage the integrity and biomechanical properties of the aortic wall.

Methods: Prospective assessment of vascular function using multiple non-invasive modalities, and compare the results among the three groups of CoA patients previously treated using surgery, BD or stent implantation after frequency matching for confounding variables. In successfully repaired CoA patients, we prospectively compared aortic stiffness by applanation tonometry and cardiac magnetic resonance (CMR); endothelial function by endothelial pulse amplitude testing; pulse waveform analysis by applanation tonometry and endothelial pulse amplitude testing; BP phenotype by office BP, ambulatory BP monitoring, and BP response to exercise; left ventricular (LV) mass and aortic morphometrics by CMR; blood biomarkers

of endothelial function, inflammation, vascular wall function, and extracellular matrix; and ideal cardiovascular health. In the statistical analysis, we adjusted for potential confounders.

Results: This study was done in seven, large volume centers from Portugal and the United States of America. Participants included 75 patients treated with surgery (n=28), BD (n=23), or stent (n=24). Groups had similar age at enrollment, CoA severity, residual gradient, and metabolic profile but differed by age at treatment. Systemic HTN, aortic stiffness, endothelial function, and LV mass were similar among groups. However, BD had more distensible ascending aortas, lower peak systolic BP during exercise, less impairment in diurnal BP variation, and lower inflammatory biomarkers. The results were unchanged after adjustment for potential confounders, including age at treatment.

Conclusions: Treatment modality was not associated with major vascular outcomes such as systemic HTN, global aortic stiffness, and endothelial function. However, BD patients had a better vascular phenotype profile characterized by higher ascending aorta distensibility, lower night-time BP, lower peak exercise BP and lower levels of inflammatory markers. Further studies are required to confirm if our results may contribute to refining the CoA treatment paradigm by adding to the goals of therapy the preservation of vascular function when two or more treatment techniques are applicable.

Introdução: As cardiopatias congénitas (CC) afetam aproximadamente 1% dos recém-nascidos e são responsáveis pela maior proporção de mortalidade infantil nos países desenvolvidos. A coarctação da aorta (CoA), a 6ª CC mais frequente, consiste numa estenose da aorta descendente proximal. Se não for tratada, tem uma história natural desfavorável. A cirurgia, dilatação com balão e a implantação de stent são atualmente técnicas que podem atingir o objetivo de uma remoção eficaz e duradoura da estenose ístmica, sendo a decisão baseada na idade doente, anatomia da CoA e preferência do operador ou da instituição. Contudo, um bom resultado anatómico não evita morbilidade e mortalidade de longo prazo, apresentando cerca de metade dos doentes hipertensão arterial (HTA), e registando-se mortalidade precoce, maioritariamente devido a complicações cardiovasculares e acidentes vasculares cerebrais. O perfil tensional anómalo sugere que os resultados subótimos possam ser secundários a disfunção vascular, cuja existência foi bem documentada em doentes com CoA tratada. Existem anomalias intrínsecas da estrutura arterial e função, alterações da sensibilidade neuro-hormonal ou da regulação endócrina, e fatores adquiridos, como a idade do tratamento, que contribuem para esta disfunção vascular. Os maus resultados a longo prazo podem resultar igualmente do tipo de tratamento efetuado, que provavelmente impactam de modo diverso a rigidez do istmo aórtico e potencialmente comprometem as funções da aorta. Este efeito da modalidade terapêutica não foi até ao momento estudado. A CoA não é uma simples doença mecânica que fica resolvida quando é removido o obstáculo.

Objetivos e Hipóteses: O objetivo deste estudo é comparar a função vascular entre diferentes modalidades terapêuticas de CoA. A hipótese principal é a de que os doentes submetidos a dilatação com balão têm melhor função vascular que os doentes submetidos a cirurgia ou implantação de stent, pois aquela modalidade terapêutica tem menor potencial para danificar a integridade e propriedades biomecânicas da parede da aorta do que estas.

Métodos: Avaliação prospetiva da função vascular usando múltiplas modalidades não invasivas, de modo a comparar os resultados de três grupos de doentes com CoA, tratados com dilatação com cirurgia, balão ou implantação de stent, após controle das variáveis de confusão. Em doentes com CoA tratada com sucesso, comparámos prospectivamente a rigidez da aorta com tonometria de aplanação e ressonância magnética cardíaca; função endotelial com tonometria arterial periférica endotelial; analise da onda de pulso com tonometria de aplanação e tonometria arterial periférica endotelial; massa ventricular esquerda e anatomia do arco aórtico com ressonância magnética cardíaca; marcadores

séricos de função endotelial, inflamação, função da parede arterial e matriz extracelular; e saúde cardiovascular ideal. A análises estatística incluiu ajuste para as variáveis de confusão.

Resultados: O estudo foi realizado em sete grandes centros, de Portugal e Estados Unidos da América. Foram incluídos 75 doentes, tratado por cirurgia (n=28), dilatação com balão (n=23) e implantação de stent (n=24). Os grupos tiveram idade semelhante à data de inclusão, gravidade da CoA, gradiente residual e perfil metabólico, mas eram diferentes quanto à idade à data do tratamento. A HTA, rigidez da aorta, função endotelial e massa ventricular eram semelhantes entre os grupos. Contudo, o grupo da dilatação com balão tinha mais distensibilidade regional da aorta ascendente, menor tensão arterial (TA) sistólica durante o exercício, menos alteração da variação noturna da TA, e dose menor de biomarcadores inflamatórios. Os resultados permaneceram inalterados após ajuste das potenciais variáveis de confusão, incluindo idade à data do tratamento.

Conclusões: A modalidade terapêutica não estava associada à presença de HTA, rigidez arterial global e função endotelial. Contudo, os doentes com dilatação com balão tinham um perfil de função vascular mais favorável, caracterizado por maior distensibilidade da aorta ascendente, TA noturna mais baixa, menor resposta hipertensiva no esforço e menores marcadores séricos de inflamação. São necessários mais estudos para confirmar se os nossos resultados poderão contribuir para o refinamento do paradigma de tratamento da CoA, ao adicionar ao objetivo de remoção da estenose, a preservação da função vascular, quando dois ou mais tratamentos são aplicáveis.

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I. INTRODUCTION

The most common, severe congenital anomalies are heart defects. In Portugal, the specialty of Pediatric Cardiology was established in 1969. These five decades have seen remarkable progress in the prevention, diagnosis, treatment, and rehabilitation of patients with congenital heart disease (CHD). The overall mortality has dropped from about 35% to about 3% per year and survival into adulthood is now common, even for the most complex CHD. This increasing population of adults with CHD, which already outnumber children, have given rise to new challenges. Some are specific to CHD (such as the management of the long-term complications after single-ventricle palliation or neurodevelopmental outcomes after neonatal cardiopulmonary bypass), but others are merely the effect of age on a maturing population that happens to have had been treated for CHD in infancy, including pregnancy, atherosclerosis, and acquired heart disease. The quality of a treatment is not merely obtaining survival but achieving a good long-term outcome. **The focus in CHD has shifted from mortality to morbidity.**

Improvements in CHD outcomes were based on few robust scientific data. Congenital cardiology has suffered from a lack of indisputable evidence. There have been less than 30 prospective randomized trials worldwide, and some did not reveal a clear benefit of one approach over the other. Many decisions result from individual or institutional preference, anecdotal cases or specific institutional protocols. Clinical practice guidelines for CHD are mostly class II recommendations (treatments are reasonable or may be considered) based on type C evidence (experts' consensus, case studies or standard of care). In sum, evidence-based medicine is lacking in CHD. These shortcomings result from the CHD being a group of rare diseases with diverse presentations, mostly treated in small and autonomous practices and lack of suitable research end-points. In recent years, this problem has been well recognized, and the development of evidence-based practice based on multicenter consortia is considered one of the most important future trends for CHD in the next decade.[2] **Clinical research is critical for evidence-based medicine.**

Coarctation of the aorta (CoA) is one of the most common CHD. It consists of a narrowing of the proximal descending aorta. If left untreated, most symptomatic neonates die shortly after, and even if the presentation is later and more benign, patients rarely survive beyond age 50. The repair of CoA was one of the first successful surgeries performed in CHD. Several current surgical and percutaneous treatments can achieve a successful long-term removal of the stenosis, and the choice is based on age, CoA anatomy, and personal or institutional preference. Importantly, a good anatomical result does not avoid long-term cardiovascular

morbidity and mortality remain high with late systemic hypertension (HTN) in approximately half of the patients and reduced life expectancy, mostly due to cardiovascular complications and stroke. **CoA can be "fixed but not cured".**[3]

The mechanisms responsible for the suboptimal outcomes in CoA are unclear. Patients who have been successfully treated have evidence of pre-treatment genetic modulation and neurohormonal disturbances, mild residual stenosis or arch hypoplasia that may be of more significance than it is usually accepted, and especially the persistence of vascular dysfunction in treated patients. Vascular structure and function are now recognized as a central pathological feature of cardiovascular disease (CVD). Vascular function can be described by many different functional indices, some of which are now available for use outside of a research setting and include arterial stiffness, endothelial function, pulse waveform analysis and circulating biomarkers of vascular function. One factor that compromises vascular function is the existence of stiff arteries. Preliminary evidence and biological plausibility suggest that different CoA treatment modalities may have a distinct impact on the stiffness of the isthmus. **Treatment may affect vascular function and long-term outcome.**

This thesis was designed to assess the impact of treatment modality on vascular function. To answer our study question and overcome the research challenges, we designed the Long-term Outcomes and Vascular Evaluation After Successful Coarctation of the Aorta Treatment: the **LOVE-COARCT Study** prospectivelly used multiple non-invasive modalities to perform a comprehensive assessment of vascular function and cardiovascular health. We assembled a multi-disciplinary group of investigators with established expertise in epidemiology, the conduct of clinical trials, study design, CHD, vascular function assessment, preventive cardiology and statistical analysis. A collaborative team allowed us to recruit patients at multiple centers to ensure sufficient statistical power in evaluating our hypothesis. **This study may help to refine the treatment paradigm by adding to the goals of therapy the preservation of vascular function.**

The following chapters of this PhD dissertation thesis, "Vascular Dysfunction after Repair of Coarctation of the Aorta", develop the concepts briefly aluded in this Introduction and present in detail the **LOVE-COARCT Study**.

II. BACKGROUND

1. COARCTATION OF THE AORTA

1.1. Introduction

CoA is a congenital malformation characterized by narrowing of the aorta, most commonly involving the isthmus. The term "CoA" comes from the Latin word *coarctatio*, which means narrowing.

It's first known description is in a letter written by the famous Prussian anatomist Johann Friedrich Meckel to his mentor Albrecht von Haler in 1750, reporting a case of an 18 year old patient who had an aorta in the post-mortem examination that was "so narrow that its diameter seems to be hardly one third that of the pulmonary artery".[4] Another early description of CoA can be seen in Morgagni's renowned treaty of autopsies "The Records and Causes of Death Investigated by Anatomy", written in 1760.[5] For a long time, CoA remained a mere anatomical rare curiosity discovered at autopsy. In 1928, all 200 cases known at the time were published in Abbott's classic article.[6] After surgical correction was experimentally demonstrated to be feasible,[7,8] CoA became of clinical importance when Crafoord successfully surgically corrected the lesion with an end-to-end anastomosis, in 1944.[9] Patch aortoplasty was introduced in 1961,[10] and Waldhausen introduced the subclavian flap technique to address the then high rate of reCoA.[11] The first report of a transcatheter procedure to treat CoA was balloon dilation (BD) in a neonate with a post-surgical reCoA, in 1982.[12] In the following year, BD was used to treat native CoA.[13] The first investigations with intravascular stents were done in 1986, in the aorta of animal models,[14] and preceded the widespread use of stents in coronary arteries. In 1993, animal experimental CoA was treated by stent implantation,[15] and the first human cases were published in 1995.[16]

After seven decades of treatment, Lindesmith's quote in "Review of CoA of the Thoracic Aorta", written in 1971, is still true in many aspects:[17] "Although operation for CoA has long been an accepted practice, many questions regarding this defect remain at best incompletely answered. These include indications for operation, the type of operation which should be performed, the age at which operation should be carried out, the problems of recurrence and persisting HTN, the occurrence and management of paradoxical HTN following correction, and the incidence and management of complications of operative treatment."

1.2. Epidemiology

CHD is the most common type of severe congenital malformations. It occurs in approximately 1% of liveborns and in 10% of aborted fetuses.[18] It also accounts for the largest proportion of deaths due to birth defects, which is the leading cause of infant mortality in the Western World.[19, 20] CoA is the sixth most common CHD, representing 6-8% of all cases.[21-23] In 1980, the New England Regional Infant Cardiac Program (1975-1977), a consortium of regional hospitals that pooled their data concerning ill infants admitted with heart disease, reported an incidence of 1.7 per 100,000 live births.[21] However, this study underestimated the true incidence of this disease, because it preceded the widespread use of echocardiography and did not account for patients who were not diagnosed until later in life. According to a recent review that pooled the data from 39 studies, CoA has an incidence of 4.0 per 100.000 live births and is the 6th most common congenital cardiac defect.[24] This same figure was confirmed in an on-going registry, the Metropolitan Atlanta Congenital Defects Program.[25] As with other left-sided obstructive diseases, CoA is more common (1.3 to 1.7:1) in males.[21, 26]

1.3. Etiology

1.3.1. *Genetics*

Most cases are sporadic, but there is substantial that left-sided obstructive lesions have a strong genetic component, especially when they occur in association.[27-29] Data supports a complex but most likely oligogenic pattern of inheritance,[28] but the underlying genetic etiologies are mostly unknown.[29] Recently, a few candidate genes have been described, including TBL1Y,[30] MCTP2,[31] MATR3,[32] and variants of the NOTCH1 gene,[33] thus supporting the theory that genes play an important role in CoA.[34]

There are several syndromes that have been associated with CoA. It is well-known that CoA has a high prevalence (10–20%) in Turner syndrome.[35] Other syndromes include Williams–Beuren, PHACES, congenital rubella syndromes, neurofibromatosis, and Takayasu arteritis.

1.3.2. *Embryology*

The aorta and its branches develop between the sixth to eighth week of gestation. They arise from the aortic arches, which are six paired and symmetrical embryological arteries. During development, these aortic arches lose their original symmetry, and while some enlarge

and become a part of the final aortic arch and branches, others regress and disappear: the ascending aorta arises from the ventral aorta, the aortic arch between the left common carotid artery and the left subclavian artery is formed from the left 4th aortic arch and the 3rd through the 7th segments of the left dorsal aortic root, and the thoracic descending aorta from that point onwards arises from the 6th aortic arch.[36] The precise mechanism by which CoA is produced is not clearly understood and there are two main proposed theories, which may be complementary.

1.3.2.1. Ductal Theory

The ductus arteriosus has long been recognized to play a critical role in CoA. Craigie proposed a theory in 1841,[37] later popularized by and known as Skoda Theory in 1855,[38] in which an abnormal extension of ductal tissue into the aorta created a stenosis after postnatal ductal closure. This explanation was commonly disregarded in the mid 20th century, since "such an extension of peculiar issue has never been demonstrated microscopically".[39] However, this theory has since then been abundantly demonstrated. In the 70s, histological studies confirmed that there is migration of the ductal tissue to the aortic isthmus.[40, 41] The prostaglandin E receptor EP4, a receptor in the ductus arteriosus, is abundantly expressed in human CoA segments.[42] Three-dimensional extent of ductal tissue was shown in resected human CoA segments using synchrotron radiation-based X-ray phase contrast tomography.[43] And finally, the in-vivo demonstration of this theory occurred in 1998,[44] by successfully infusing prostaglandin E1, a drug that dilates the ductus, with echocardiographic demonstration of the CoA relief in what has become a mainstay of pre-surgical neonatal medical management. It is now widely accepted the concept that CoA is associated with excessive distribution of tissue of the ductus arteriosus.

1.3.2.2. Hemodynamic Theory

However, the ductal theory does not explain all cases of CoA, especially when there is accompanying hypoplasia of the aortic arch. Early reports suggested that a reorientation of the angle at which the ductus arteriosus meets the aorta, abnormal fetal ductal flow patterns, or hemodynamic compromise of fetal aortic outflow, could be responsible for CoA.[45] In fact, the high incidence of CoA in patients with congenital heart defects that have in utero diminished antegrade aortic flow is a well-recognized association. Conversely, the paucity of CoA in patients with right-sided heart obstructions suggests that prenatal altered hemodynamics also plays a significant role in the development of CoA. The hemodynamic theory has been demonstrated in chick embryos, where alterations in intracardiac blood

flow that compromised left ventricle (LV) flow, disrupted both early cardiac morphogenesis and aortic arch development.[46] In summary, the hemodynamic theory has also become an accepted explanation of the most severe forms of CoA and arch hypoplasia. It is likely that ductal tissue migration and hemodynamic changes co-occur to produce the varied spectrum of CoA.

1.4. Natural History

Most of the patients that present in the neonatal period or infancy do not survive beyond the critical period if left untreated. The remaining patients, who present after the first year of life, have a more benign course and mostly reach adult life. However, the mean age of death for this subset of patients is 35 years old.[47] A necropsy study of patients that died beyond infancy showed that untreated patients rarely survive beyond age 50: 25% die before they reach 20yo, 50% by 32yo, 75% by 46yo, and 90% by age 58 (**Fig. 1**):

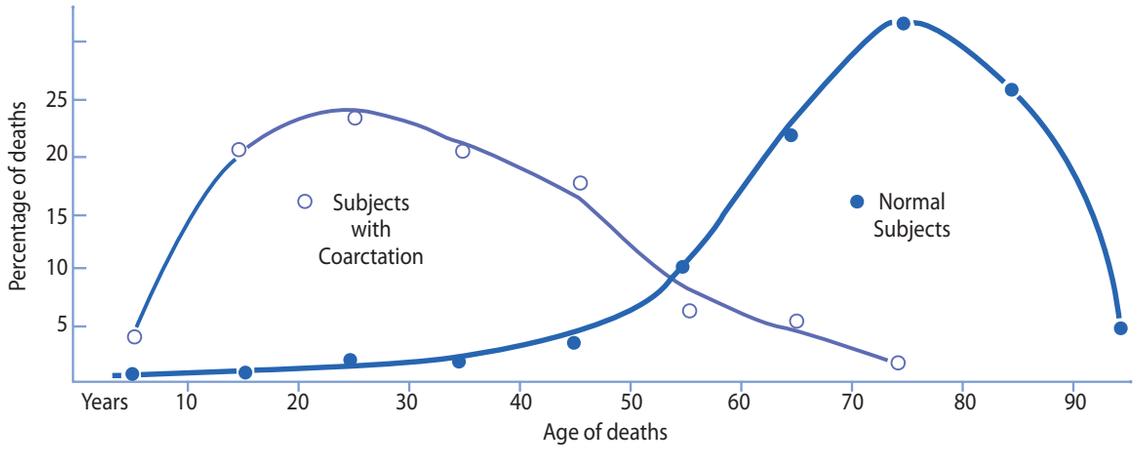

Fig. 1. The distribution of deaths by age, excluding deaths in the first year of life. *In CoA on the left and in normal subjects on the right, there is relatively little overlapping. (Reprinted from Campbell,[48] with permission from BMJ Publishing Group Ltd)*

In that same study, the most frequently reported causes of death were congestive heart failure (26%), aortic dissection (21%), bacterial endocarditis (18%), and intracranial hemorrhage (12%).

1.5. Anatomy

1.5.1. *Morphology*

CoA is an aortic narrowing nearly always localized in the isthmus, the aortic segment comprised between the origin of the left subclavian artery and the emergence of the ductus arteriosus. Rarely, it may be located after the emergence of the brachiocephalic trunk, in the descending thoracic or abdominal aorta, the latter commonly designated as abdominal CoA, and which may represent a different disease entity. The CoA itself may be a discrete and focal stenosis or shaped as a long segment isthmic hypoplasia. Additionally, there may be a wide spectrum of accompanying aortic arch hypoplasia, that can be manifested up to the extreme of aortic arch interruption. Currently, Pediatric Cardiology centers use the measurements of the arch indexed to the body surface area (BSA) and describe them in terms of z scores, where one z score which represents one standard deviation for the appropriate sex, height, and weight. Z scores less than-2 are considered to represent arch hypoplasia. Other approaches are considering that the segment between innominate and left carotid should be greater than 60% of ascending aorta, the segment between left carotid and subclavian artery 50% of ascending aorta, and the isthmus not inferior to 40% of the ascending aorta. Another rule is to consider hypoplastic arch which size is smaller than baby's weight plus one.[49]

CoA occurs in concomitance with other congenital heart defects, including ventricular septal defects and other left-sided obstructions, especially bicuspid aortic valve (BAV), which may be present in up to 60% of CoA cases (**Table 1**):[50]

Table 1. Incidence of congenital cardiac anomalies associated with CoA

Associated anomalies	Incidence
Patent ductus arteriosus	77%
Bicuspid aortic valve	46%
Ventricular septal defect	26%
Subaortic stenosis	25%
Atrial septal defect	13%
Mitral valve stenosis	10%
Transposition of great arteries	8%
Shone complex	3%

One common association is Shone syndrome, that includes supravalvar mitral ring, parachute mitral valve, discrete subaortic stenosis and CoA or other complex congenital heart diseases, such as the Taussig-Bing anomaly, univentricular heart, often with systemic outflow obstruction, and hypoplastic left heart syndromes.[51] The most important noncardiac associated anomaly is intracerebral aneurysm (berry aneurysm), present in up to 10% of all cases.[52]

1.5.2. *Histopathology*

In the site of the CoA, there is usually an infolding of aortic wall tissue. Although the aorta and ductus arteriosus are in continuity and exposed to the same hemodynamics, the ductus arteriosus has structural properties similar to those of muscular arteries rather than those of elastic arteries. A similar intimal thickening is one of the prominent histopathological changes of CoA.[53, 54] In the medial layer, light and electron microscopy of necropsy and surgical specimens showed histopathological changes including increased collagen and reduced smooth muscle content in the ascending but not the descending aorta.[55-57] The expression of the smooth muscle cell phenotype in CoA is similar to that is found in the ductus arteriosus.[58] It is interesting to note that similar changes histopathological changes are found in the ascending aorta of patients with BAV without CoA.[59] These observations suggest that CoA is not a localized disease but a diffuse arteriopathy.

1.6. Pathophysiology

In the last years, it has become apparent that CoA is not a mere focal stenosis but an inborn systemic vascular disease. The isthmic stenosis is associated not only with altered hemodynamics but also with gene modulation of the vascular phenotype, impaired neuronal sensitivity, and endocrinal auto-regulation. All these contribute to HTN and vascular dysfunction that are currently well recognized to characterize the long-term follow up of CoA.

1.6.1. *Hemodynamics*

CoA creates an obstacle that increases LV afterload and leads to a rise in BP proximal, and hypoperfusion distal to the isthmus. The hemodynamic consequences depend on the rapidity of the ductus arteriosus closure, the severity of the obstruction, the level of pulmonary vascular resistance, and associated cardiac lesions. In the neonatal and infantile presentation, post-natal ductus closure leads to an acute narrowing of the aortic lumen that results in systolic dysfunction and cardiogenic shock. In the more insidious childhood or

adolescent presentation, the closure of the ductus is better tolerated and elicits an adaptive pathophysiological adaptation that results in upper body HTN, compensatory LV hypertrophy, systolic dysfunction, and development of collateral blood flow.

The presence of collateral vessels allows for BP below the CoA to be only slightly decreased or even within normal limits.[60] However, the pulse pressure (PP) is markedly reduced below the CoA, as a result of the attenuation of the pulse in travel through the long, tortuous and narrow collateral vessels. When present in native CoA, the collateral vessels provide almost complete replacement for the abnormal aortic conduit function, but little or none for altered cushioning reservoir function and only one-third of the whole arterial system is able to act as cushion to LV ejection.[61]

Exercise further accentuates the differences described above. Previous studies have shown that physical exertion is associated with a more accentuated increase in BP above the CoA than in patients that have severe essential HTN.[62]

1.6.2. *Gene modulation*

Changes in gene expression due to the mechanical stimuli of the CoA may explain these histopathological changes. The stenosis caused by experimental CoA results in the development of differentially expressed genes that are associated with altered vascular structure or function.[63-65] In a rabbit model of CoA, immunohistochemical results showed a shift from smooth muscle to non-muscle myosin heavy chain isoform expression in the medial smooth muscle cells that reflects a long-standing change in the vascular phenotype since these changes persisted after removal of the induced CoA.[66] Human studies also revealed genetic polymorphisms in CoA patients that are associated with HTN.[67-69] Interestingly, these polymorphisms are different from those seen in patients with essential HTN[67] or abnormal BP regulation during exercise.[68] This finding reinforces the different ethiopathogenic mechanism for HTN in CoA.

1.6.3. *Neuro-endocrine system*

The renin-angiotensin-aldosterone (RAA) system may be involved in the ethiopathogenesis of CoA, especially in the systemic HTN. However, its role is unclear: while some studies provided evidence of increased RAA activity in patients with CoA,[70-72] others did not confirm these findings.[73-75] It may be that the RAA is important in the early development of, but not in the maintenance of HTN in CoA.[76]

1.6.4. *Autonomic nervous system*

The autonomic system and baroreceptor function may be altered, including enhanced sympathetic tone set to a higher value, reduced spontaneous baroreceptor reflex sensitivity and heart rate (HR) variability, and diminished sensitivity to changes in arterial pressure.[77-79] Some authors suggest that these abnormalities in neuronal mediation may be involved only in the pre-treatment HTN, which is then reset after repair.[80, 81]

1.7. Diagnosis

1.7.1. *Clinical Presentation*

1.7.1.1. Neonates and Infants

Most of the CoA cases present in neonates and infants.[82] The acute closure of the ductus arteriosus will lead to left heart failure or, in the most dramatic cases, cardiogenic shock with metabolic acidosis. Patients present with tachycardia, tachypnea, pale skin, and diaphoresis. They have radio-femoral pulse delay with diminished or absent femoral pulses and poor peripheral perfusion. The cardiac auscultation is sometimes unremarkable, but there may be a harsh systolic ejection murmur, best heard in the suprasternal notch or the interscapular area, in the back. The arm-leg BP gradient is pathognomonic of CoA but may be difficult to obtain in a moving infant or when cardiac output is diminished. The hypoperfusion of the lower body may lead to end-organ damage, including renal failure and necrotizing enterocolitis. This clinical presentation may be difficult to distinguish from neonatal sepsis without cardiovascular imaging. Rarely, there will be some infants that present with dilated cardiomyopathy.

1.7.1.2. Children, Adolescents and Adults

10-25% of patients will present later in life.[82] CoA is then suspected due to complaints related to HTN (such as headache or epistaxis), reduced exercise capacity, claudication or cold feet. Often, the diagnosis is incidental and made during routine office visits such as a physical examination that shows cuff HTN or absent femoral pulses, or pre-exercise sports assessment such as changes in the electrocardiogram (ECG) that will prompt a cardiac evaluation. Cardiac auscultation is most often normal, but an uncharacteristic systolic ejection murmur best heard in the suprasternal notch or continuous murmurs in the interscapular area or thorax (due to collateral vessels) may occur. Atypical clinical presentations that may lead to the diagnosis of CoA include retinopathy in eye assessments, infective endocarditis, aortic dissection or rupture, and intracranial hemorrhage.

This relatively uncharacteristic, mostly benign clinical picture, and the absence of a clearly abnormal cardiac auscultation are often responsible for late diagnosis. It is well documented in pediatric studies that the diagnosis is often missed by the referring doctor and this has had little improvement over the past 20 years.[83-85] Consequently, it remains critical to stress the importance of femoral pulse palpation and brachial cuff measurement of BP in routine child visits to the pediatrician or family doctor.

1.7.2. *Electrocardiogram*

In the neonatal period, the ECG of CoA patients may be indistinguishable from the findings in the normal newborn, with right ventricular dominance with positive R, and T waves in the right precordial leads and QRS angle in the right lower quadrant.[86] After ductal closure, the ECG in the neonate and infant with CoA persists with right axis deviation of the QRS axis in the frontal-plane, right ventricular hypertrophy and upright T waves in the right precordial leads, contrary to the normal newborn in whom the T wave becomes negative.[87] These ECG changes associated with CoA persist throughout infancy and, if present beyond, may suggest pulmonary HTN associated with other congenital heart diseases.

In older children, there may not be any ECG changes if there is a mild CoA. As age and severity progress, the ECG findings will reflect the HTN and LV hypertrophy, such as increased R wave amplitude in the left-sided ECG leads (I, aVL and V4-6) and increased S wave depth in the right-sided leads (III, aVR, V1-3) and ST and T-wave abnormalities in the lateral leads.[88]

1.7.3. *Chest X-Ray*

In the neonate, the chest X-ray in CoA is non-specific. If there is heart failure, there will be cardiomegaly and congested pulmonary vasculature, due to passive congestion and active fluid overload due to left-to-right shunt.

In older children and adolescents, the CoA patients have a normal or slightly enlarged heart and two characteristic findings: (a) figure-3 sign, that results from the combination of a localized indentation in the site of the isthmic stenosis with dilated proximal subclavian artery and distal descending aorta; and (b) rib notching, that results from the erosion of the inferior surface of the ribs by the prominent collateral circulation of the enlarged of intercostal arteries. Rib notching involvement is bilateral with distal coarctation, right- sided with proximal coarctation, and left-sided with distal coarctation with anomalous right subclavian artery.[89]

1.7.4. *Echocardiography*

1.7.4.1. Prenatal

Despite all the advances in fetal echocardiography, prenatal diagnosis of CoA remains a challenging diagnosis even in tertiary centers, with high false positive and false negative rates.[90-93] A recent, a large cohort study showed that CoA is one of the most commonly missed prenatal congenital heart diseases[92] and another study showed that this detection can occur in less than one third of patients.[93]

Early studies noted that most patients have indirect 2D echocardiographic signs, such as a disproportionally larger right ventricle and pulmonary artery, but only half had a direct visualization of the stenotic aortic arch.[94] Several parameters have been proposed to assist in the 2D fetal diagnosis of CoA including a ratio of the left common carotid artery to transverse aorta > 0.73 compared with < 0.62 for the normal fetuses,[95] the isthmic diameter z-scores <-2 and the ratio of isthmus to duct diameters < 0.74,[96] and the visualization of CoA shelf. Finally, the presence of other commonly associated left heart obstructive lesions may help to raise the suspicion for the presence of CoA. The Doppler assessment helps in the prenatal diagnosis of CoA, including the presence of continuous isthmic flow, detected in 50% of the patients,[91] and the inversion of flow in the ascending aorta is a pathognomonic sign.

Despite the difficulties, the prenatal diagnosis is critically important since it allows the birth to occur in an adequate institution. The timely early administration of proper neonatal care and has been shown to be associated with lower mortality and morbidity.[97]

1.7.4.2. Postnatal

Transthoracic echocardiography is the primary imaging modality for CoA. The crucial diagnostic steps are the establishment of the presence, degree, and shape of the isthmic stenosis; the size of the aortic arch; the anatomy of the aortic arch branches, namely the involvement of the left subclavian artery in the CoA and the presence of an aberrant right subclavian artery; and the patency of the arterial duct and associated cardiac lesions.

In the newborn, the presence of the ductus may mask the presence of the CoA. However, the bidirectional ductal flow with right-to-left shunt associated with hypoplasia of the isthmus is indicative of the presence of a CoA. Once the ductus closes, the echocardiographic features will be more apparent. The best echocardiographic view is the suprasternal notch view and, occasionally in newborns, the subcostal view.[98] In 2D, there will become evident a stenosis of

the aortic isthmus, and often a posterior shelf will be seen in the proximal descending aorta, opposite to the aortic end of the ductus (**Fig. 2**). In isolated CoA, the measurements of the arch show variable degrees of hypoplasia of the aortic arch.

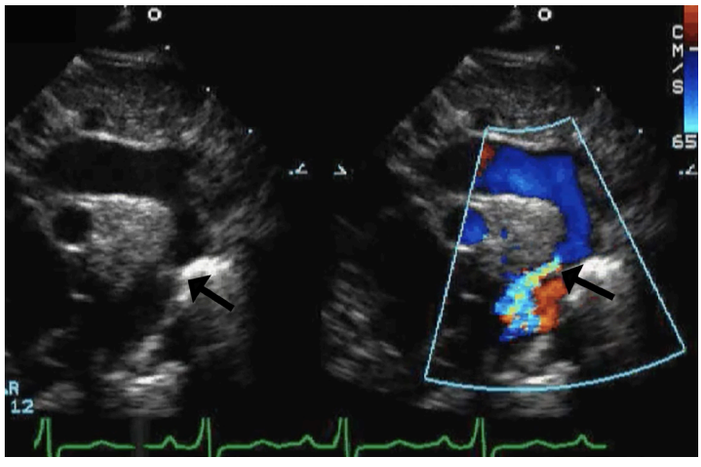

Fig. 2. Suprasternal notch view showing a CoA. *The CoA (marked with an arrow) is seen as a narrowing in 2D imaging (left panel), where there is color Doppler flow aliasing (right panel).*

Doppler assessment is an important adjunct for the diagnosis and severity assessment of CoA.[99] The best correlation between the Doppler-estimated gradients and the invasive peak-to-peak hemodynamic gradient is to use the Bernoulli equation with the post-CoA velocity minus the pre-CoA velocity.[99] The persistence of antegrade flow in diastole or diastolic run-off assessed by continuous wave Doppler is the most specific (100%) and sensitive (79%) in the diagnosis of CoA.[100] The continuous and low velocity pulsed Doppler flow in the abdominal aorta also indicates the presence of CoA (**Fig. 3**).

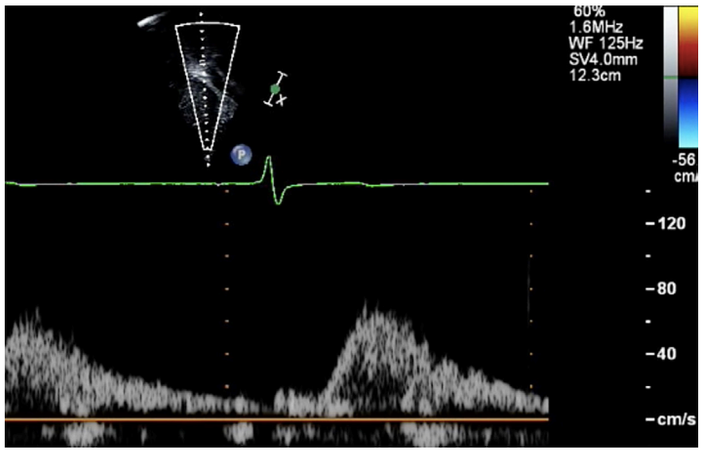

Fig. 3. Subcostal view with pulsed-wave interrogation of the abdominal aorta. *Note the typical low velocity and continuous flow of CoA.*

The color-coded Doppler study is helpful in localizing a CoA when the 2D images is suboptimal, and shows a persistence of color flow signal throughout the whole cardiac cycle. A complete echocardiographic study is also important to detail possible associated congenital heart defects.

1.7.5. *Magnetic resonance imaging*

Cardiac magnetic resonance imaging (CMR) is the preferred advanced non-invasive diagnostic tool for assessment of CoA since it allows both good anatomic and functional data of the aortic arch, which is clinically useful for both preoperative planning and post-interventional monitoring.[101, 102]

Regarding anatomy, CMR can provide excellent and detailed visualization of the entire aortic arch, the site, degree, and extent of the aortic narrowing, as well as aneurysms. Anatomic imaging allows for imaging the arch in multiple custom-made planes that assist in the accurate quantification of the vessel size along its path and quantify the LV hypertrophy, function, and fibrosis (with T1 mapping). The utilization of gadolinium-enhanced CMR permits three-dimensional reconstruction of the aortic arch as well as depicting the presence and extent of collateral vessel formation (**Fig. 4**).

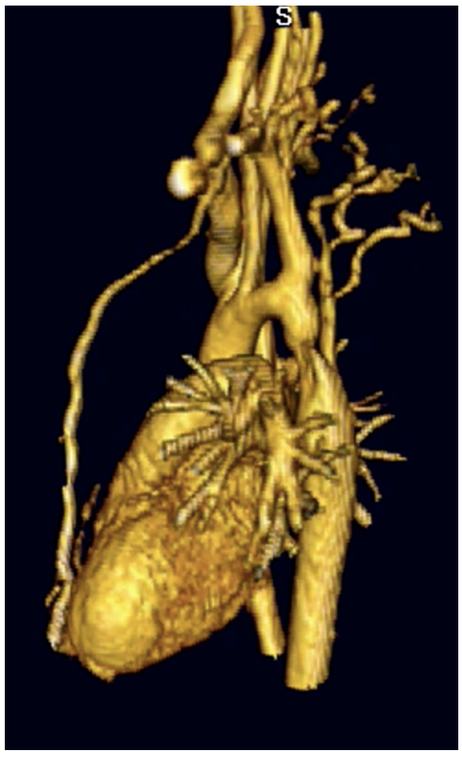

Fig. 4. 3D reconstruction of gadolinium-enhanced CMR angiography of the aorta.

CMR can also provide valuable information regarding pathophysiology.[60, 103] The severity of CoA can be inferred by quantification of hemodynamic parameters such as flow velocity and volume and estimation of pressure gradients across the CoA. The quantification of the amount of collateral flow has been shown to be associated with the degree of CoA. Recent technological developments in CMR that involve a comprehensive analysis of flow direction and its interaction with the aortic wall has been used as 4D CMR to the study the wall shear stress that is exerted in the aorta,[104] and to accurately predict the invasive hemodynamic gradient.[105]

Compared to the other techniques, CMR is limited by (a) its relatively longer time for image acquisition and need for patient cooperation, which may require sedation for patients under 6 to 8 years old; (b) its higher cost; and (c) the artifacts associated with metal stents used to treat CoA, which impede isthmus visualization. Therefore, CMR is not routinely used in infants but is recommended in in the diagnosis initial diagnosis and follow up of children, infants, and adults.

1.7.6. *Computed tomography*

Computed tomography (CT) scan provides the best non-invasive anatomic imaging, by 2D and 3D reconstructions of the aortic arch. The most important limitations of CT scan are the requirement of iodinated contrast that may worsen renal failure and the associated ionizing radiation, especially deleterious in children who may require several consecutive exams. However, the radiation risk is minimized with the recent availability of third-generation dual-source scanners, which provide high-quality imaging in a single heartbeat, thus avoiding the need for breath holding and minimizing artifact.[106, 107]

1.7.7. *Diagnostic catheterization*

It is currently very rare the need to perform an invasive cardiac catheterization with the sole purpose of a diagnostic catheterization. First, the hemodynamic significance of a CoA is well established by clinical and non-invasive methods. Second, the angiographies provide excellent imaging of the aortic arch but don't have a favorable risk/ benefit ratio compared to the non-invasive imaging modalities described above.

1.8. Treatment

1.8.1. *Indications*

All hemodynamically significant CoA should be treated once the diagnosis is made. The American Heart Association and the American College of Cardiology, the European Society of Cardiology, and the Canadian Cardiovascular Society have all issued guidelines for adults and agree that what defines a significant CoA is a gradient greater than 20 mm Hg (Class I; *Level of Evidence*: C).[108-110] There are, however, some important nuances between these recommendations: while the United States of America guidelines specify that the 20 mm Hg value corresponds to the invasive, peak-to-peak CoA gradient, the European guidelines consider that a non-invasive BP between upper and lower limbs greater than 20 mm Hg is an indication for intervention if there is associated HTN, pathological BP response during exercise, or significant LV hypertrophy.

Treatment may also be indicated in hemodynamically non-significant CoA (with a gradient less than 20 mm Hg) if there is an imaging evidence of significant CoA (defined as a greater than 50% narrowing relative to the aortic diameter at the diaphragm level) and significant collateral flow, which may mask the severity of the CoA (Class I; *Level of Evidence*: C),[109] or if the patients are hypertensive (Class IIa; *Level of Evidence*: C).[108] The guidelines above recommend that these treatment indications be the same for native CoA and reCoA.

There are no specific guidelines for asymptomatic older children, but the indications noted above are widely accepted in clinical practice and, as for adults, the timing of treatment should be after the diagnosis of significant CoA is made.[111]

In neonates and infants, even if only mildly symptomatic or asymptomatic, there is an urgent indication for treatment since they are at risk of developing heart failure. This is particularly true in the neonate with a patent ductus, that may not have a significant gradient due to the patent ductus supplying the descending aorta or ventricular dysfunction resulting in low cardiac output.

1.8.2. *Medical Management*

The mainstay of medical treatment in the neonate with CoA is prostaglandin E1 (PGE_1). Since the in vitro description of its role in the regulation of the intrinsic muscular tone of the ductus arteriosus,[112] pharmacologic manipulation of the ductus has become an important

first line palliation in ductus-dependent CHD such as the critical CoA of the newborn. If there is a prenatal diagnosis or postnatal early diagnosis, prompt institution of a PGE_1 infusion will avoid the overt heart failure that may develop in neonates with CoA. Even when a newborn presents critically ill, this drug can still effectively re-opens the ductus and improves flow into the descending aorta, which may reduce the risk of metabolic acidosis and end-organ ischemia such as necrotizing enterocolitis and renal failure.[113] Medical management of the decompensated newborn may also require other measures such as mechanical ventilation, inotropic support, and other general supportive intensive care measures. Once clinical stability is achieved, the patient should proceed to repair the CoA, as soon as possible.

1.8.3. *Surgical Management*

1.8.3.1.Introduction

The majority of patients are managed by a left posterior thoracotomy through either the 3rd or 4th intercostal space, sparing both trapezius and serratus muscles whenever possible. However, for cases with severe aortic arch hypoplasia or concomitant correction of other associated anomalies, median sternotomy is preferred. Collaterals in neonate and infants are usually not profuse, but some patients, particularly beyond infancy, and in adolescents and adults, dealing with profuse collaterals, during thoracotomy and aorta mobilization might be challenging.

At surgery, care is taken to identify nearby nerves, thoracic lymph duct area, and collaterals. Mediastinal pleura is incised longitudinally over the aorta, from thoracic operculum to mid thoracic descending aorta and structures are identified and mobilized. Typically, left subclavian, aortic arch and supra aortic trunks, aortic isthmus, ductus and descending aorta are dissected circumferentially, mobilized and encircled with silicone loops. Particular care is taken with collaterals, posteriorly and laterally placed, and some medial esophageal arterial branches. Collaterals should be gently controlled with loops, rarely being sacrificed. This mobilization process is standard, but must be individualized to each surgical technique, as simple aortoplasty and patch corrections will need far less extensive mobilization of structures, than the extended end-to-end type of procedures. Once the structures are properly dissected and fully mobilized, the surgeon will need to make technical choices based on both anatomical coarctation patterns and his surgical preference. Arch hypoplasia is probably best dealt with extended end-to-end technique, and extreme cases will best be treated under cardiopulmonary bypass, through a sternotomy. For cases with a long hypoplastic isthmus, the subclavian flap aortoplasty may still be an alternative.

1.8.3.2. End-to-End (and Extended End-to-End) Anastomosis

Resection and end-to-end anastomosis (**Fig. 5**) is the technique most commonly used.[82]

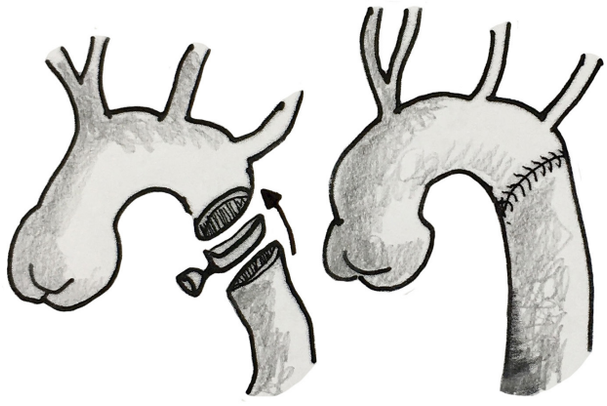

Fig. 5. End-to-end coarctectomy. *(The description of the surgery is in the text)*

It implies significant mobilization of the aortic arch and descending aorta, without sacrificing any collaterals, and ductus resection, to achieve a tension free anastomosis. An oblique anastomotic line with fine continuous or interrupted nylon sutures is typically used, to minimize circumferential stenosis at the anastomotic site, when children will grow into adolescence.

The extended end-to-end technique is the preferred method in cases when the arch is considered hypoplastic and needing augmentation (**Fig. 6**).

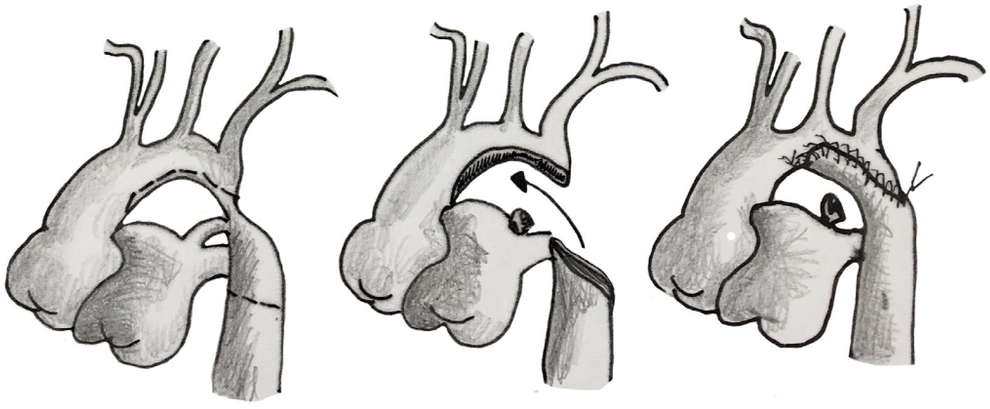

Fig. 6. Extended end-to-end coarctectomy. *(The description of the surgery is in the text)*

It consists in bringing the thoracic descending aorta to the undersurface of the aortic arch, reaching a proximal level just distal to the innominate artery. This technique requires extensive aorta and aortic arch mobilization and a critical placement of aortic arch clamp, letting

innominate artery perfusing the brain, while the arch is being excluded. The anastomosis is beveled down to increase its circumference, suturing being similar to the technique used for classical end-to-end anastomosis.[114, 115]

1.8.3.3. Subclavian Flap and Reverse Flap

This is a classical technique (**Fig. 7**), now rarely used.[82]

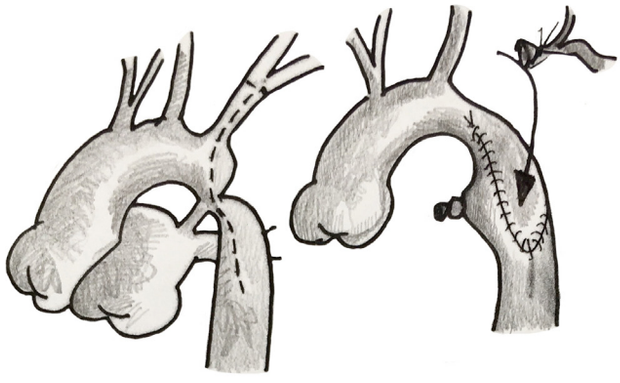

Fig. 7. Subclavian flap coarctectomy. *(The description of the surgery is in the text)*

It can be particularly suitable for neonatal coarctation with isthmus hypoplasia, as it patch enlarges the narrowed segment with a vital subclavian flap, but it implies the sacrifice of arterial supply to the arm (with few relevant consequences). Despite potentially leaving active ductus tissue in the inner wall, the propensity to reCoA is low.

This is an easy operation, also easy to learn. Structures need to be mobilized in the usual way, extending subclavian dissection to the thoracic outlet, where the vertebral artery must be ligated to prevent steal syndromes to the cerebral circulation. Using two clamps, sometimes only one curve clamp, a vertical aortotomy is performed, and a long subclavian flap is slit open, reversed and sewn over the aortotomy, taking care to bring it down, well below the coarctation shelf by at least one centimeter. Concerns regarding the growth and potential ischemic syndromes (rarely described), whenever subclavian artery was sacrificed, would lead to the introduction of some clever sliding techniques, as the one introduced by Meier,[116] that preserves the left arm blood flow, as it detached the proximal subclavian artery from the arch and slide it down to use as the aortoplasty flap.[116] Subclavian flaps have also been used, in combination with end-to-end repair, to augment the distal arch, with the advantage of using strictly autologous vital patch material, that grows with age.[117]

1.8.3.4. Patch Reconstruction

Patch reconstruction for coarctation repair was introduced earlier, to overcome two problems (**Fig. 8**). Firstly, the concerns that circumferential sutures used with end-to-end techniques would prevent growth, particularly when used in children. Secondly, to overcome issues of inadequate or non-existent conduits for interposition.[118]

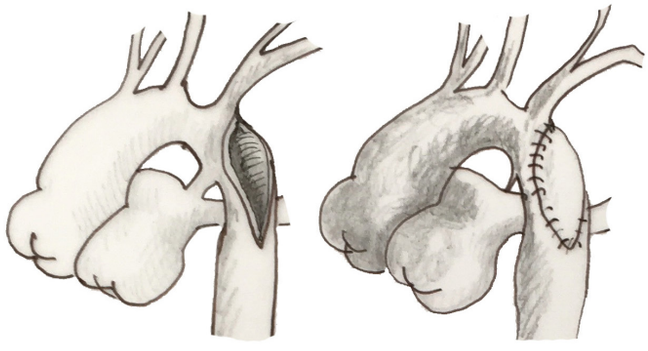

Fig. 8. Patch reconstruction technique for CoA. *(The description of the surgery is in the text)*

Patch repair for coarctation of the aorta is a technically simple procedure, typically used in older children and adults, consisting on enlarging the coarctation area with a patch of Dacron®, Gore-Tex® or heterograft pericardium. The ideal patch material has not been found, as aneurysms develop contra-laterally, particularly with classical Dacron® patches, due to the uneven rigidity of the aortic wall or direct surgical injury.[119, 120] Therefore, the use of this technique has faded down.[82] Some have used heterograft pericardium with the expectation that there is less aneurysm formation, but the patch reconstruction technique has faded in favor of other surgical approaches.[118]

1.8.3.5. Conduit Interposition

When coarctation of aorta repair was introduced, the ideal technique was end-to-end anastomosis. However, for some patients, predominantly adults, the extension of coarctation and the incapacity to mobilize adjacent aorta, warranted the use of an interposed conduit. Initially, homograft material was used, but soon synthetic material would be introduced, Dacron® or Gore-Tex®, with excellent results.[121] The use of conduits is limited by patient size, as growth is naturally limited. The use of conduits less than half of the normal adult aorta should not be used, for the risk of becoming stenotic.

Technically, the operation is simple. However, in patients with extensive collateral networks, the interposition of a graft may impose their dissection and sacrifice, with the risks of hemorrhage and eventually paraplegia, and it is rarely used today.[82]

1.8.3.6. Extra-Anatomical Conduits

Coarctation repair should, whenever possible, privilege both the physiology and the anatomy, however, the objective of a nice anatomical repair should not preclude safety, and the primary aim of getting a good hemodynamic result. Therefore, whenever local anatomical challenges, namely collaterals, a long narrow segment, or in case of any complex re-do, the option for an extra-anatomical conduit should be considered (**Fig. 9**).

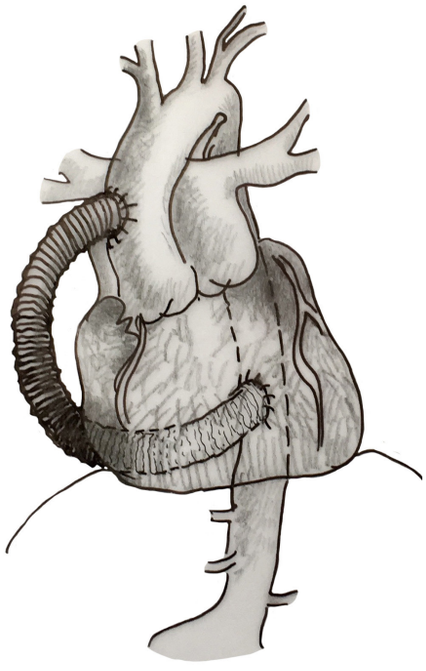

Fig. 9. Extra-anatomical conduit technique for CoA. *(The description of the surgery is in the text)*

Para-anatomical conduits are an alternative to anatomical reconstructions, whenever the direct correction is not possible or is considered too risky. Ipsilateral jump grafts, from the aortic arch or left subclavian artery to the descending aorta beyond coarctation, are easy to perform and pose few problems. However, truly extra-anatomical conduits will offer a more effective alternative to bypassing the coarctation. Typically, they are performed through a median sternotomy, the heart is luxated to the left shoulder (not rarely, extracorporeal support is recommended), exposing the aorta in a midline position before it will cross the diaphragm.[122] Mediastinal pleura is incised, the aorta is encircled and a by using a side-biting clamp, a large Dacron tube (16 or 18 mm) is anastomosed terminal-laterally to the descending aorta. The graft is brought, typically, in between the IVC and the inferior right pulmonary vein, to lie laterally in the pericardial sac, in a position that will facilitate a terminal-lateral anastomosis to the right aspect of the ascending aorta.

1.8.3.7. Postoperative Management

Post-operative strategies should be oriented taking into account the preoperative course and patient age. A newborn who presents with low-cardiac output, metabolic acidosis and renal failure should undergo a different medical approach than an older child with preoperative HTN.

As a rule, patients are usually monitored with an arterial line and an indwelling catheter to quantify urinary output. Noninvasive BP measurements in the upper and lower limbs are vital to identifying residual CoA, and somatic near-infrared spectroscopy is used to assess the systemic perfusion. Fluid management in older children is not restricted, but newborns and infants should have two-thirds restrictive fluid administration. Neonates with severe CoA and poor systolic function frequently need inotropic support. Milrinone and dopamine are the most commonly used.

Post-operative paradoxical HTN is a common feature, can present with abdominal pain, mesenteric arteritis and even bowel ischemia and requires strict BP control to prevent anastomosis leaks and bleeding. Possible explanations are neuro-hormonal elevated sympathetic nervous system activity (early HTN) and the activation of the RAA system (second phase or later HTN). There isn't a consensus about the best medical strategies to achieve that goal and variability in patient care is seen, and different pharmacological agents can be used.[123-125] Betablockers (β-blockers) act by sympathetic blockade and should be the agents of choice. Esmolol is a selective short-acting β-blocker with predominant β1-receptor selectivity, safe and effective in CoA, and the most frequent choice in the postoperative HTN.[125] It should be started with a 100 to 500µg/Kg bolus followed by a continuous infusion starting at 50 µg/Kg/m titrated as needed. Labetalol has α1 and non-selective β-blocker effect and can also be safely used. Sodium nitroprusside acts as a direct and potent vasodilator (continuous infusion 0,5-1 µg/Kg/m), and in spite of the risk of thiocyanate toxicity, it is still currently used.[123, 125] In cases of severe HTN, as seen in older children, sodium nitroprusside and β-blockers can be considered in association. Other agents can be considered as adjunctive therapy, like dexmedetomidine in a continuous infusion (0,2-0,7 µg/Kg/h). This agent is a selective α2 receptor agonist acting directly through it symphaticolytic effect, reducing HR and BP and indirectly by achieving pain control and sedation and therefore preventing HR and BP to rise.[124, 126]

Older children do not generally need ventilator support and are quickly extubated after CoA repair. Newborns that presented preoperatively with cardiogenic shock and dilated left

ventricle with poor systolic function may require mechanical ventilation for longer periods of time, at least for 24-48 hours. Ventilation weaning and extubation should be done after the cardiac output is reestablished (normal lactate levels, urinary output greater than 1 mL/Kg/h) and echocardiographic signs of LV function recovery are evident.

1.8.3.8. Acute Results

Coarctation surgical repair is a standardized procedure, known for achieving excellent outcomes.[82, 127, 128] Results for neonatal correction have been extensively reported: Two decades ago, two-year survivals were of 84%.[127] A review of the Society of Thoracic Surgeons Congenital Heart Surgery Database reported contemporary results for 2705 patients, with a mortality of 1% and complications in 25%.[82] Another recent review (343 patients; 42% neonates, 36% infants, and 23% older children) showed that mortality was only neonatal (3%), independent from surgical technique and acute outcomes were superior when coarctation was repaired earlier.[128]

The most feared but rare complication (0-0.4%) is paraplegia.[82] Risk factors are CoA with minimal collaterals, prolonged cross-clamp times, long excluded aorta segments, division of collaterals, hypotension, and hyperthermia. Protective measures such as shunt bypass or extracorporeal circulation, local hypothermia, systemic pressures in the high range, and short aortic cross-clamp periods will minimize the risk for this much-feared complication.

Recurrent laryngeal nerve injury (1.6%) with unilateral vocal cord paralysis, stridor and airway obstruction or phrenic nerve injury (0.4%) with hemidiaphragmatic paralysis, can occur and may lead to extubation failure.[82] The clinical presentation depends on the severity of the nerve damage (transient or permanently damaged) and on patient age (newborns tend to do worst). Nasal continuous positive airway pressure (CPAP) can be tried in less severe cases. Hemidiaphragmatic paralysis can spontaneously resolve but occasionally requires diaphragmatic plication, especially in cases of failure of a second extubation attempt. Chylothorax (2.1%),[82] is usually management conservatively with dietary lipid manipulation (restriction of long-chain fatty acids and supplementation with medium-chain fatty acids) or total parenteral nutrition and octreotide infusion. Surgical approach with thoracic duct ligation may be considered if the chylothorax recurs or if the previous measures do not achieve resolution.

Post-coartectomy syndrome generally occurs two or three days after surgery, rarely in neonates, and is characterized by HTN, severe abdominal pain with abdominal tenderness, vomiting, ileus and even melena. It is most likely caused by necrotizing arteritis of the small mesenteric arteries probably related to the sudden increase of BP in the mesenteric territory. It can be prevented by BP control and avoiding early enteral feeding, which should be started very slowly and after bowel sounds are present and abdominal exam normal.

1.8.3.9. Long-term Outcomes

The incidence of reCoA is 4-25% and occurs in all surgical techniques.[129, 130] Neonates have higher reintervention rates, which is not associated with the type of repair, surgical era, or arch hypoplasia.[107] In a recent study, freedom for reCoA was 93% when end-to-end anastomosis in a neonatal population (median f/u 6 years).[128]

Another concern is local aortic wall complications. Aneurysms have a high incidence after patch repair, even with more distensible patches.[119] The incidence of aneurysms after surgical repair is reported between 2-24%.[131-138] The 2017 update from the Congenital Cardiovascular Interventional Study Consortium (CCISC) prospective registry showed an aneurysm incidence of 4% with end-to-end, 17% with patch, and 9% with tube graft (results for subclavian flap not reported).[137] The incidence of aneurysms is associated with BAV and longer follow up.[138] Late complications will affect survival, including systemic HTN and cardiovascular morbidity.

1.8.4. *Balloon Dilation*

1.8.4.1. Introduction

BD has been used to treat CoA for more than three decades. Conceptually, it is a simple procedure that consists in inflating a balloon located at the tip of a catheter, advanced over a guide-wire, in the CoA (**Fig. 10**).

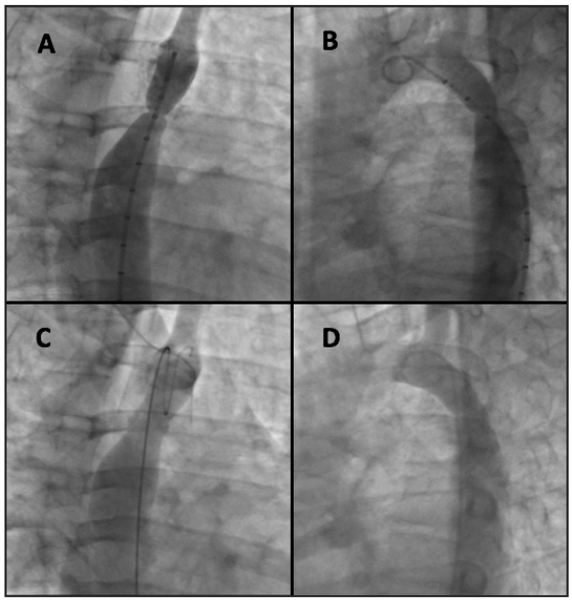

Fig. 10. Balloon dilation of a native CoA. Balloon dilation of CoA. *In panels A and B (above), biplane aortography (right anterior oblique 30°, and left anterio oblique 70°) shows a native CoA. In panels C and D (below), after balloon dilation of the CoA, there is no residual stenosis. A small endothelial tear is seen (arrow, in panel C). (image from a LOVE-COARCT patient cardiac catheterization).*

The inflation of the balloon produces a controlled tear of the aorta's intima and part of the media, meant to achieve a relief of the stenosis when the vessel heals in the newly created diameter.[139, 140] In experimental lamb coarctation, it was found that there was complete intimal healing two months after the dilation.[141]

1.8.4.2. Technique

BD is done most frequently in a retrograde fashion, via femoral artery access. It can also be performed via an antegrade approach, through a venous access, a technique useful in infants with single ventricle-type malformations that allow the aorta to be accessed in such a fashion. There are many options for balloons, including some that were purposefully designed for CHD. The balloon diameter should be two to three times the minimum diameter of the lesion without exceeding 1.2 times the diameter of the surrounding aorta. The balloon length should be long enough to completely cover the area of the coarctation and provide stability during inflation and, at the same time, short enough not to extend too far in either direction away from the coarctation in which the natural curvature of the aortic arch impedes full inflation. If the diameter of the balloon is adequately chosen, it should be inflated until full resolution of the waist or the maximum inflation pressure is achieved. The contrast should be relatively diluted to ensure fast deflation.

1.8.4.3. Results for native CoA

Several papers report that BD for native CoA is an acutely successful procedure in 80-94% of the cases.[131-134, 136, 142-145] The Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) registry published several important multicenter studies on procedural outcomes of BD of coarctation of the aorta, including one that reported the short-term results of BD in 140 patients with native CoA that showed the procedure to be safe (0.7% mortality, 17% morbidity) and effective (86% immediate procedural success) in relieving CoA.[132]

In the mid- and long-term follow up, the incidence of reCoA is variable (8-32%) and depends on the patients age.[131, 133, 134, 136, 142-144] A mid-term follow-up (median f/u 36.2 months; range 12-117 months) study of 102 patients with native CoA had an immediate success of 91% but 23% required re-intervention due to reCoA. In that study, 88% of infants > 7 months old and older children required no additional intervention but, in contrast, 71% of the neonates required reintervention, suggesting that balloon angioplasty of native CoA is effective in infants and older children but provides only effective palliation in neonates.[133] Another mid-term (mean f/u 31 ± 18 months; 67 patients) confirmed a higher incidence of reCoA in neonates (83%), compared to infants (39%) and older children (8%).[134] On the opposite end, a long-term study (median f/u 13,4 years; range 1-22 years) of older patients (58 patients; mean age 24+/-9 years) reported an immediate success of 92%, no early mortality and only 8% of the patients with initial immediate success developed reCoA and required reintervention.[131]

The risk of aneurysm formation is a significant concern after BD but its true incidence is unknown, and reported between 2 and 24%.[131-136, 142, 143] This is likely due to different definitions of an aneurysm, distinct methodologies of looking for this diagnosis, and the historical impact of the evolution of technique in retrospective series (low-pressure, progressive or stepwise BD and smaller balloon sizes). When there is late integrated imaging, the aneurysms appear to remain stable or regress and rarely require intervention.[135, 143, 146] One recent paper looked at the long-term (mean f/u 8.5 years, range 2.2-13 years) aneurysm formation in 29 adult patients who had BD of a native CoA. An angiographic intimal tear was detected in 8 (28%), without signs of dissection, and remained unchanged or diminished in a three-month follow-up angiography. MR or CT excluded late aneurysm formation, and in the latest follow-up, only 3/8 still showed a persistent irregular aortic contour without progression or an aneurysm formation.[146]

1.8.4.4. Results for reCoA

BD has an immediate success in 88-93% and 0-1% major complications in reCoA (including mortality or need for urgent surgery due to aortic rupture).[147-152] The VACA registry reported the multicenter prospective results on 200 patients (mean age 7.0 years, range 1 month to 26 years) and reported an immediate success in 79%, with a 2.5% procedure-related deaths and 8.5% vascular morbidity.[152] In the long-term follow up, different studies (with median f/u between 3.5 to 8.1 years) showed that reCoA occurred between 10 and 27% of patients, and aneurysm formation between 0 and 4%.[148-151] The surgical technique did not have an impact on acute or long-term outcomes and older age at the angioplasty was associated with a higher incidence of reinterventions.[150]

Despite the promising initial results that showed BD of native and recurrent CoA as safe and effective techniques, especially after the neonatal period, the concern about aneurysm formation inhibited BD of achieving wide popularity as a first-choice treatment for the native CoA, while it was accepted as the first choice for relief of reCoA. To address this discrepancy, a review of the VACA registry compared acute BD results of native CoA vs. reCoA from 970 procedures (422 native and 548 recurrent lesions) performed between 1982 and 1995 in 907 patients from 25 centers. The procedural success was significantly higher in native (81%) vs. reCoA (75%), and complications overall were similar for both groups, except for more reported intimal tears or flaps in the native coarctation group (native CoA 5.2% vs. reCoA 1.6%). The authors concluded that acute results and complications of balloon angioplasty of native coarctation appeared to be equivalent or slightly superior to those of recurrent aortic obstructions.[153] In that same study, there was an overall significant trend for failure with increasing age and a slightly increased risk in neonates.

1.8.5. *Stent implantation*

1.8.5.1. Introduction

After its introduction in the mid-90s, stenting of CoA (**Fig. 11**) has rapidly gained popularity,[154] because, contrary to the BD, the rigid endovascular prosthesis avoids vessel recoil, provides a sustained gradient relief and allows a more controlled dilation of the aortic wall that avoids over dilation and the potential risk of aortic rupture.

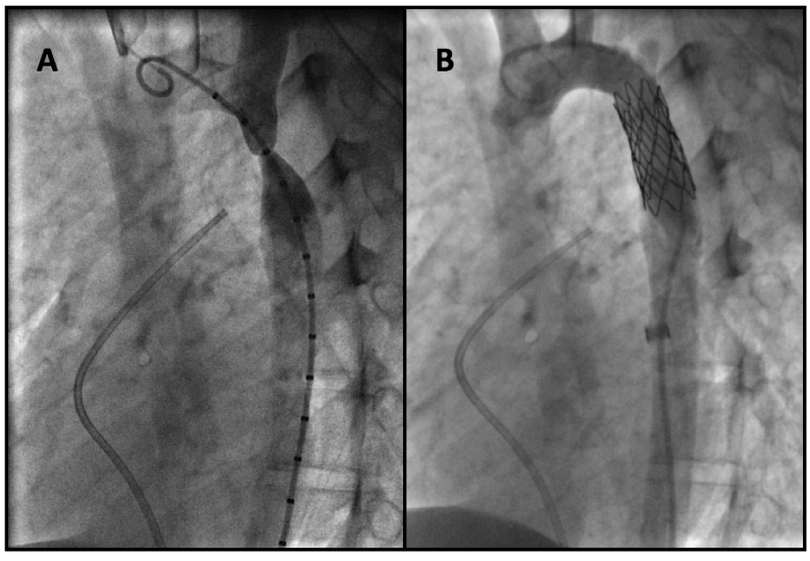

Fig. 11. Stent implantation in native CoA. *In panel A (left), the aortography in a left anterior oblique projection shows the anatomy of the CoA. In panel B (right), the aortography is performed after the stent has been implanted, showing adequate stent position and no residual stenosis. In both pictures, a venous catheter is seen, in the pulmonary artery. (image from a LOVE-COARCT patient cardiac catheterization).*

Patient weight is a major limitation for stent placement in CoA due to the risk of femoral artery injury and the aorta needs to be large enough to accommodate a stent that can be dilated up to an adult sized aorta, even if it is done in subsequent staged interventions. Although it can be feasible,[155, 156] most authors agree that it is generally not recommended to implant stent for CoA treatment in patients weighting less than 25kg.[101, 111, 154, 157]

1.8.5.2. Technique

The vast majority of CoA stenting is done retrogradely since there is a fairly direct route from the femoral artery. Stent implantation is a little more cumbersome than balloon angioplasty of the CoA but currently done as a routine procedure in most Pediatric Cardiology catheterization laboratories. The stent is mounted over a balloon-tipped catheter and advanced over a guiding-wire through a long delivery sheath. When the stent is in the optimal position, the sheath is retracted, and the balloon inflated up to the diameter of the width of the surrounding aorta. Angiographic and hemodynamic assessment are done to decide whether there is a need for further stent inflation to achieve an optimal result. If the initial CoA is very tight, staged dilation may be preferable instead of expanding the stent to the full diameter.

There are many technical tips and tricks that include the type and location were the guide-wire tip is placed, the strategy to mount the balloon and loading into the sheath (front vs.

back-loading), the use or not of balloon predilation, the use of maneuvers to diminish the blood flow and assure a proper positioning (adenosine or rapid ventricular pacing) and the way to make control angiographies during the procedure (through the sheath vs. additional venous or arterial access). The current Cath Lab armamentarium is wide in terms of stents and balloons, and operators have to choose the type stent (different brands that have different sizes, metal alloys, pre- vs. unmounted, and open vs. closed cell, balloon and also sheath and guidewire. These choices are mostly based on personal and institutional experience, and many are not guided on evidence-based medicine.

1.8.5.3. Acute Results

Numerous publications reported that stent implantation for CoA is acutely safe and effective, for both in native and reCoA.[157-169] The success of the procedure is achieved in 95-99% and most patients have a very good angiographic and hemodynamic result, with a final gradient ≤ 5 mm Hg. The mortality rate is 0-1.4% and the adverse event rate of 0-7.3%. The largest study to date reported the acute results of coarctation stenting (52% native) in 555 consecutive patients from 17 institutions.[168] The median balloon to coarctation ratio was 2 (1.1–18). A successful procedure (defined as a final gradient < 20 mm Hg or increase in post stent coarctation to descending aorta ratio (CoA:DAo) of > 0.8 was achieved in 97.9%. There were two procedure-related deaths, and 14.3% of the procedures had complications, including 3.9% aortic wall lesions (intimal tears in eight, aortic wall dissection/rupture in nine, and aortic aneurysm in six), 2.3% injury to access vessels and 8.1% technical-related complications (stent migration, balloon rupture). The risk of aortic dissection increased significantly in patients over the age of 40 years. More recently, the Coarctation of the Aorta Stent Trial (COAST), a prospective, multi-center, single-arm clinical study involving 19 pediatric cardiology centers in the United States reported their acute results of CoA bare-metal stenting (57% native CoA).[169] All procedures started with simple BD and if the balloon waist was less than 80% of the maximum balloon diameter, the aorta was labeled noncompliant and the patients ineligible for inclusion in the trial. Stent implantation diameter did not exceed 1.4 times the diameter of the balloon waist during compliance testing and was not greater than 1.1 times the lesser diameter of the distal transverse arch or the descending aorta at the level of the diaphragm. All patients achieved successful stent implantation (final gradient < 20 mm Hg and CoA:DAo 0.84 ± 0.18). There were no deaths and 7% adverse events (aortic aneurysms in 4, localized dissection in 1, stent migration in 1, injury to access vessels in 2). Covered stents were first described to treat aortic wall complications,[170, 171] but have since been used prophylactically in selected cases, to prevent the occurrence of such complications.[172-175]

1.8.5.4. Mid-term Results

There are a few mid-term results,[158, 161, 164-167, 176] and the long-term implications of stent placement in the aorta are mostly unknown.[177] CCISC reported the mid- (3-18 months, 124 patients) and long-term (> 18-60 months, 46 patients) results of their 34-center cohort.[177] Procedural success (defined as arm-to-leg systolic gradient < 20 mm Hg, lack of significant recurrent obstruction, and freedom from unplanned repeat intervention) evolved from 96% after the procedure, to 86% in the intermediate follow-up and 77% in the long-term follow-up. Advanced integrated imaging including CT scan, CMR, or catheterization, showed that 20% had reCoA and 1% had aortic wall complications, which were associated with balloon: coarctation ratio of > 4 and performance of pre-stent BD. Other adverse events occurred mainly acutely and included technical complications such as stent malposition. A significant number of the interventions (64%) were elective staged procedures. However, unplanned repeat interventions were required in 4%, due to intimal hyperplasia, stent re-stenosis, fracture, and arterial wall complications. The prospective COAST study also reported their mid-term (12- and 24-month) results: 11% had reCoA in the context of planned staged dilation or somatic growth and required stent re-dilation; some degree of stent fracture was observed in 22% but with no embolization, loss of stent integrity or necessity for re-intervention; and 4% had de novo aneurysm, rarely requiring re-intervention. The overall re-intervention rate in this cohort was 14%.

1.8.6. *Decision Making*

There are no randomized, prospective trials comparing the results of balloon angioplasty, surgery, and stent placement for the treatment of CoA. A Cochrane Collaboration® review was deemed impossible due to a lack of randomized controlled trials comparing CoA treatments and highlighted the need for prospective randomized controlled clinical trial with an emphasis on primary outcomes such as quality of life and long-term survival. The current treatment decisions are based on mostly retrospective single-treatment and a few retrospective comparison studies and metanalysis, that have selection bias concerning anatomy, age at repair, personal, and institutional preference.[178, 179] Therefore, there remains controversy and uncertainty about the best treatment modality in coarctation of the aorta.

1.8.6.1. Native CoA in the Neonate and Young Infant

In these patients, with weight usually < 10 Kg, stent treatment is not technically feasible in most, due to the size of the aorta and access vessels and is only considered as a palliative approach in exceptional circumstances. Most studies that reported a comparison between BD

and surgery in this age group showed that the acute outcomes are not significantly different, but surgery is associated with fewer re-interventions and aortic aneurysm formation than BD.[178, 180-184] Only a recent, retrospective comparison (92 patients) of BD vs. surgical repair for short-segment coarctation, found no difference in the acute and mid-term outcome.[185] Surgical repair is considered by most to be the best approach for these age groups, and BD should be reserved as a palliative strategy in high-risk patients to stabilize their condition prior to definitive correction.[178, 180, 183] Many cohort studies over 35 years comparing surgical techniques favor the choice of aortic resection and end-to-end anastomosis,[186-191] when possible, but few large cohorts still advocate the use of subclavian flap as a reliable and straightforward approach, particularly in cases with a long hypoplastic isthmus.[192, 193] Arch hypoplasia is probably best dealt by extended end-to-end technique, and extreme cases will best be treated under cardiopulmonary bypass, through a sternotomy.

1.8.6.2. Native CoA in the Older infant and Young Children

In these patients, with weight comprised between 10 and 25 Kg, the aorta's small size still constitutes a technical limitation for stent implantation, and the two viable treatment options remain BD and surgery. There are few direct comparison studies of surgery vs. BD in these ages. One interesting prospective, randomized, small single-center trial compared BD and surgery for native CoA. The acute,[194] and long-term[195] results showed no difference in gradient reduction and reCoA, but the incidence of aortic wall injury (35% vs. 0%) and need for re-intervention (50% vs. 13%) were significantly higher with BD vs. surgery. Two small, single center retrospective studies showed similar results between BD and surgery, but the former had a higher incidence of re-CoA and need for re-intervention.[183, 184] The available comparative studies favor the surgical approach vs. BD, but a review of studies, taking into consideration the favorable BD individual series results,[196] consider this technique as a primary option in this age group, which is regarded as a reasonable option in patients beyond 4 to 6 months of age (Class, *Level of Evidence*: C).[197]

1.8.6.3. Native CoA in Older Children, Adolescents and Young Adults.

In patients with weight > 25 Kg, all three treatment modalities are technically feasible. There are a few studies that compare treatment modalities, but all[135, 183, 186, 198-200] except one compare only two of the three techniques. A clinical, randomized, 5-center trial with 58 pediatric patients comparing surgery and BD showed no acute differences but a higher reCoA rate in the BD group in the short-term follow-up.[186] One multicenter retrospective study (80 patients, four centers)[183] compared the three treatments acute and mid-term results and found similar

effectiveness in acute gradient relief and again that BD was associated with a higher rate of re-intervention and aneurysm formation.[135] Smaller single center studies comparing the three modalities (9 patients),[183] surgery vs. stent (28 patients),[198] and surgery vs. BD (46 patients),[199] found no difference in acute outcome, re-intervention, and incidence of aneurysm.

The largest and most significant study is based on the Congenital Cardiovascular Interventional Study Consortium (CCISC) prospective registry, started in 2005 as an attempt to answer the lack comparative data for the three treatment modalities, for patients ≥ 10Kg. Their results comparing the treatment outcomes for native CoA were initially published in 2011[130] and recently updated (BD 85 patients, stent 422 patients, surgery 102 patients; mean f/u 36 months; 18-92).[137] The three techniques did not differ in the acute and intermediate success in achieving an adequate resolution of the stenosis. However, the stent group has significantly fewer complications in the acute and intermediate follow-up, and the complications differed in nature: the stent group has more vascular and technical-related complications, the BD group has more aortic wall injuries and the surgical group has more severe post-operative HTN, atrial fibrillation, pleural effusion, neurological/spinal cord injury and vocal cord paralysis. In the intermediate follow-up, a sub-group that had advanced aortic imaging (CT scan, CMR or catheterization) demonstrated that BD (39%) had more aortic wall injury (dissection/ intimal tear or aneurysm) than surgery (10%) or stent (5%). In contrast to surgical patients, late aneurysm formation in BD and stent patients is rare and typically occurs within the first year after the transcatheter procedure,[145, 168] and rarely requires treatment.

Despite the favorable acute BD results, only a minority of authors advocate its use as a first choice.[145] Its association with a higher rate of recurrent obstruction and aortic wall injury made the treatment choice in most centers for CoA to be between surgery or stent therapy.[111, 154, 200-202] Regarding surgical technique, the requirement for tube graft interposition or patch augmentation of the coarctation segment increased significantly, particularly in long segment CoA and only 42% of the patients > 8 years of age, 25% of patients > 12 years of age, and none > 16 years of age were able to undergo end-to-end repair of their CoA segment.[130] The European guidelines make no specific treatment recommendations but assert that in many centers, stenting has become the treatment of first choice in adults of native CoA with appropriate anatomy[108] while the North American guidelines state that the choice between the treatment techniques should be a team decision based on a case-by-case, institutional, practitioner, and patient preference. (Class I; *Level of Evidence* B[110] or C[109]). Some authors advocate specific treatment techniques but, given the lack of strong data, the decision is

ultimately based on age and weight, anatomic details, practitioners and institutional results and patient's preference.

1.8.6.4. ReCoA

Despite the lack of prospective, randomized studies, the results and complications of percutaneous treatment for reCoA compare favorably with surgical therapy, and this is accepted as the preferred treatment for all reCoA. The only Class I (level of evidence C) indications in clinical practice guidelines regarding CoA treatment are to indicate that it is reasonable to use percutaneous therapy for reCoA in children[197] and adults.[108-110] There are no studies comparing surgical vs. transcatheter approaches, and these recommendations are based in evidence that shows that mortality for surgical reoperation is higher than for primary repair (1 to 3 % versus 1%) and can be as high as 5–10% if there are significant comorbidities or LV dysfunction.[111] The choice between BD and stent is based on the same considerations made for native CoA.

1.9. Follow Up

1.9.1. *Morbidity and Mortality*

Currently available surgical and percutaneous techniques are equally effective at eliminating the gradient across the aortic isthmus in CoA patients.[130, 137, 154] However, even after a good anatomical result, patients remain to have late morbidity with high rates of late systemic HTN detected during routine office visits (12-65%),[130, 154, 166, 177, 203-215] at peak exercise (10-47%),[211-213, 216, 217] or during ABPM (30-59%).[72, 75, 213, 216-225] A recent study highlighted that mild aortic arch hypoplasia, a common finding in treated CoA patients usually considered benign in the absence of reCoA, is associated with office and exercise-induced HTN.[226] Elevated BP has long been recognized as an indicator of disease and contributes to the suboptimal long-term prognosis. There is a worldwide consensus on the need to identify and treat people with HTN before vascular or cardiac damage occurs. The abnormal BP profile may contribute to the suboptimal long-term prognosis successfully observed in repaired CoA patients.

The increased pressure afterload after repair has been shown to increase LV mass, both by echocardiogram[217, 221, 227-232] and CMR,[75, 231, 233-236] which may explain the normal or increased LV systolic function based on M-Mode or 2 Dimensional echocardiography,[221, 237-241] but not

accurately reflect myocardial performance. Recent studies, including tissue Doppler, speckle tracking and strain imaging show abnormal regional fiber shortening,[225, 229, 230, 232, 234, 235, 238, 242-246] and diastolic dysfunction.[230, 232, 238, 244, 247, 248] According to a recent study, a combination of clinical assessment and CMR is the most cost-effective approach to long-term surveillance of patients with repaired CoA.[249]

Treated patients with no clinically significant gradient have reduced life expectancy, mostly due to cardiovascular complications (such as coronary heart disease, sudden cardiac death, end-stage heart failure, and rupture of aortic aneurysms),[207, 250-253] and stroke (reported to be seen up to 13 times more frequently in patients with coarctation).[254, 255]

1.9.2. *Pregnancy*

Pregnancy is usually well tolerated in treated patients with no residual stenosis, aortic wall aneurysms and none or well controlled HTN.[256-258] The presence of HTN before pregnancy should prompt close monitoring of the BP, avoiding medication that is known to be teratogenic such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[259] A recent review of pregnancy outcomes in women with CoA (50 patients; 38% with hemodynamically significant coarctation; 118 pregnancies) reported one maternal death (due to aortic dissection in a Turner syndrome patient), 9% of miscarriages and 3% premature deliveries; the neonates had CHD in 4%, and there was one neonatal death; 30% had HTN during their pregnancy, and related to the presence of significant isthmic stenosis.[257] Therefore, timely treatment of reCoA and aneurysms is vital to ensure a safe pregnancy.

2. VASCULAR FUNCTION

2.1. Introduction

CVD represents the visible ending of a pathophysiological process called the cardiovascular continuum.[260, 261] This starts with many risk factors and progresses through numerous physiological pathways and processes to the development of end-stage heart disease. Several large studies from previous decades have identified what are now known as the traditional risk factors for CVD: age, gender, dyslipidemia, HTN, diabetes, smoking, obesity and family history (**Fig. 12**):

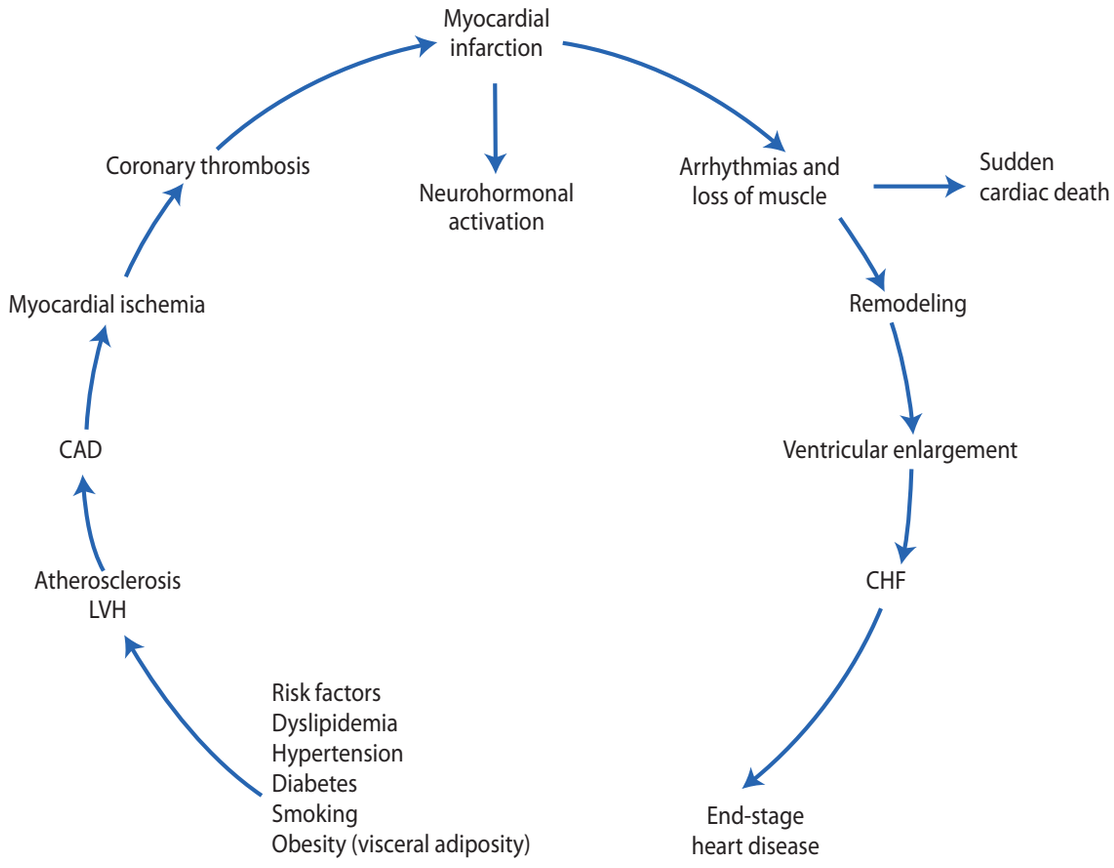

Fig. 12. The cardiovascular disease continuum. *(Reprinted from Dzau et al,[262] with permission from Elsevier).*

It is interesting that the first studies on high BP were based on recordings of the shape of the arterial pulse wave obtained with a sphygmograph, a mechanical device invented in the mid-XIX century by the German physiologist Karl von Vierordt.[263] It was only in the early XX century that the sphygmomanometer, a device that measures the BP, gained popularity as the most common approach to measure BP. In recent years, the analysis of the arterial pulse waveform regained popularity and, together with many other measurements that reflect the function of the arteries, have been grouped and are now known as indices of vascular function. These biomarkers reflect the biomechanical properties of the vascular wall and circulating biomarkers (vasoactive mediators, inflammatory responses, and vascular remodeling modulators that affect the biomolecular arterial response) and act together in a cascade of events that culminates in end-organ pathology. Man studies showed a clear association between increased arterial stiffness and risk of major cardiovascular events.[264]

The interest of vascular function to researchers and clinicians is depicted in **Fig. 13**, that shows the significant increase in publications that occurred in the XXI century that report arterial stiffness:

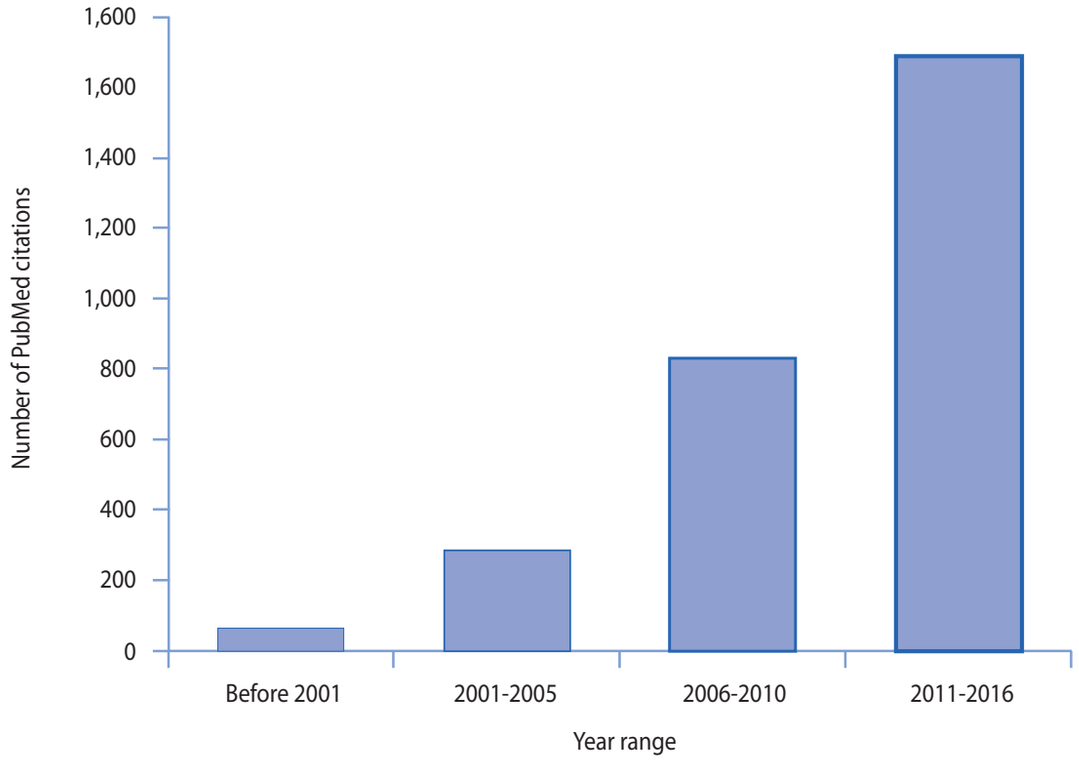

Fig. 13. The frequency of 'arterial stiffness' in the title PubMed publications. *(reprinted from Townsend[1] with permission from Karger Publications)*

2.2. The function of Arteries

The function of the systemic arterial system is to deliver blood at high pressure and in a continuous stream to peripheral vascular beds, and can be simplistically divided into three regions:[265] large arteries serve predominantly as a cushioning reservoir that stores blood during systole and expels it during diastole; muscular arteries act predominantly as conduits that distribute blood to the organs and actively modify wave propagation by changing its smooth muscle tone and diameter; and arterioles change their caliber and control peripheral resistance and affect mean arterial pressure.

Changes in the properties of large elastic arteries make them stiffer and is called arteriosclerosis (derived from the Greek word sclerosis which means hardening) and modifications in the small muscular arteries properties lead to abnormal vascular reactivity. All these biomarkers can be objectively measured and evaluated as indicators of this pathological process.

2.3. Indices of Vascular Function

The publication of the 2006 European consensus document on arterial stiffness[266] and the 2015 American Heart Association scientific statement on arterial stiffness measurements[267] have guided researchers and clinicians in the choice of methods, standardization of measurement and appraisal of results of vascular function. Most of the indices of vascular function are standardized for adults, however, measuring them in children is feasible but presents some age-related challenges and limitations, such as heart rate and body habitus.[268]

2.3.1. *Arterial Stiffness*

Arterial stiffness refers to the biomechanical properties of the arterial wall, which, in turn, affect the way pressure, blood flow, and arterial diameter change with each heartbeat. Arterial stiffness reflects the vessel resistance to deformation. A complete list of arterial indices of arterial stiffness can be found in **Table 2**.

2.3.1.1. Pulse Wave Velocity

Arterial stiffness is most often determined by measuring the velocity of pulse-wave travel in a segment of the vessel, where a higher pulse wave velocity (PWV) signifies increased aortic stiffness.[269] The arterial wall fiber elements are stretched and recoil with each ventricular contraction, and an arterial stiffening will increase the velocity of blood.

PWV can be measured in many segments of the arterial tree.[266, 267] However, **carotid-femoral PWV (cfPWV)** is the one that has been extensively validated in large studies as an independent predictor of cardiovascular morbidity and mortality.[266, 267, 270-275] cfPWV is considered the gold standard of arterial stiffness but PWV measured in other arterial segments also possesses research and clinical interest.[266, 267]

There are several methods to undertake PWV measurements, namely: (a) devices that use a probe or tonometer to record the pulse wave with a transducer;[276] devices using cuffs placed around the limbs or the neck that record arrival of the pulse wave oscillometrically;[277] ultrasonography approaches;[278] and CMR-based approaches.[279] Any of these allow the measurement of the time delay or transit time (T) between the feet of the carotid artery and femoral artery waveforms. The distance (D) between the two sites is then measured. This measurement should be done precisely and in a standardized fashion, since it may introduce a human error that affects the results. Several ways have been used to estimate the distance between the two sites, but both

the European consensus document[266] and the American Heart Association scientific statement[267] recommend measuring the suprasternal notch to the carotid pulsation site, and the suprasternal notch to the femoral pulsation site, and then subtracting the carotid from the femoral distance. PWV is calculated as PWV = D (meters) / T (seconds). (**Fig. 14**)

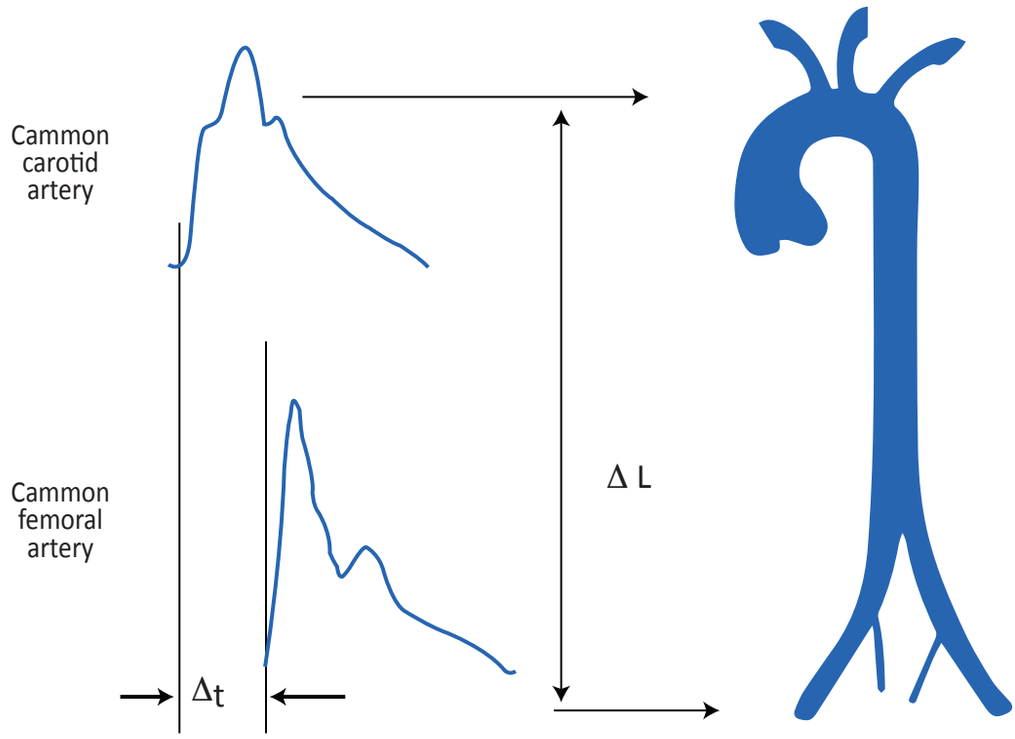

Fig. 14. Measurement of carotid-femoral PWV with the foot to foot method. *(Reprinted from Laurent et al,[266] with permission from Oxford University Press).*

PWV is influenced by the mean arterial pressure and therefore its measurement requires the patient to lie supine in a quiet and stable environment for at least 10-15 minutes to ensure hemodynamic stability and eviction of alcohol, smoking, caffeine-containing food and drinks or bouts of vigorous exercise, ideally for 12 hours. HR exerts a minimal influence on PWV in the lower range of mean pressure values and only a small but significant effect in higher values.[280] There are reference values published for cfPWV in both children[281] and adults.[282-284] Because of distinct measurement approaches, it should be emphasized that these values are applicable predominantly to measurements performed with the same methodologies.

2.3.1.2. Local Elastic Properties of the Arterial Wall

There are a host of indices that have been introduced to assess the elasticity of the aortic wall, by measuring changes in vessel diameter as a response to changes in pressure and

include aortic **strain** (relative change in diameter), **compliance** (absolute change in diameter in response to a change in pressure), **distensibility** (relative change in diameter in response to a change in pressure), and the **aortic stiffness β index** (distensibility using the logarithmic conversion of the relative pressure). These indices are measurements of local elastic properties of the arterial wall, and not measurements of regional stiffness such as PWV (**Table 2**):

Table 2. Indices of arterial stiffness

Term	Definition	Methods of measurement
Elastic modulus**	The pressure change required for theoretical 100% stretch from resting diameter $(\Delta PXD)/\Delta D$ (mmHg)	Ultrasound* MIRI
Young's modulus**	Elastic modulus per unit area $(\Delta PXD)/(\Delta DXh)$ (mmHg/cm)	Ultrasound* MRI
Arterial distensibility**	Relative change in diameter (or area) for a given pressure change; inverse of elastic modulus $(\Delta D)/(\Delta PXD)$ ($mmHg^{-1}$)	Ultrasound* MRI
Arterial compliance**	Absolute diameter (or area) change for a given pressure step $\Delta D/\Delta P$ (cm/mmHg) (or cm^2/mmHg)	Ultrasound* MRI
Pulse wave velocity	Velocity of travel of the pulse along a length of artery Distance/ Δt (cm/s)	Pressure waveform* Volume waveform Ultrasound MRI
Augmentation index	The difference between the second and first systolic peaks as a percentage of pulse pressure	Pressure waveform*
Stiffness index (β)**	Ratio of In (systolic/diastolic pressures) to (relative change in diameter) $\beta = \frac{\ln (P_s/P_d)}{(D_s - D_d)/D_d}$	Ultrasound*
Capacitative compliance	Relationship between pressure change and volume change in the arteries during the exponential component of diastolic pressure decay $\Delta V/\Delta P$ (cm^3/mmHg)	Pressure waveform*
Oscillatory compliance	Relationship between oscillating pressure change and oscillating volume change around the exponential pressure decay during diastole $\Delta V/\Delta P$ (cm^3/mmHg)	Pressure waveform*

D = diameter; d = diastolic; P = pressure; t = time; s = systolic; v = velocity; V = volume. * Most common method of measurement; ** Also requires pressure measurements (Reproduced from Mackensie et al.[285] with permission from Oxford University Press)

An advantage of these indices is that the local arterial stiffness is directly determined, from the change in pressure driving the change in volume. However, because it requires a high degree of technical expertise and takes longer than measuring PWV, they are mostly used for research purposes instead of epidemiological studies or daily clinical work. In a recent review of published studies, it was noted that several of these indices are biomarkers of CVD, but in 8 out of 11 studies at least one of the arterial parameters listed had no relationship with outcome.[267]

The imaging of the artery dimensions can be done with ultrasound and more recently with magnetic resonance imaging. Ideally, the distending pressures should be measured invasively in the same point as the dimensions were obtained, but this is often not possible, and the pressures are usually obtained non-invasively by cuff measurement.

2.3.2. *Central Pulse Wave Analysis*

The afterload imposed on the LV is determined by the arterial stiffness, arteriolar caliber and wave reflection morphology of the arterial tree.[286] No single index represents ventricular afterload. **Central aortic pressure** (CAP) and **PP** are two variables that express elements of this arterial afterload.[267] Reflected pressure waves arriving in the ascending aorta are quantified by the augmentation index (**AIx**), which is the ratio of the amplitude of the reflected wave and the PP (**Fig. 15**):

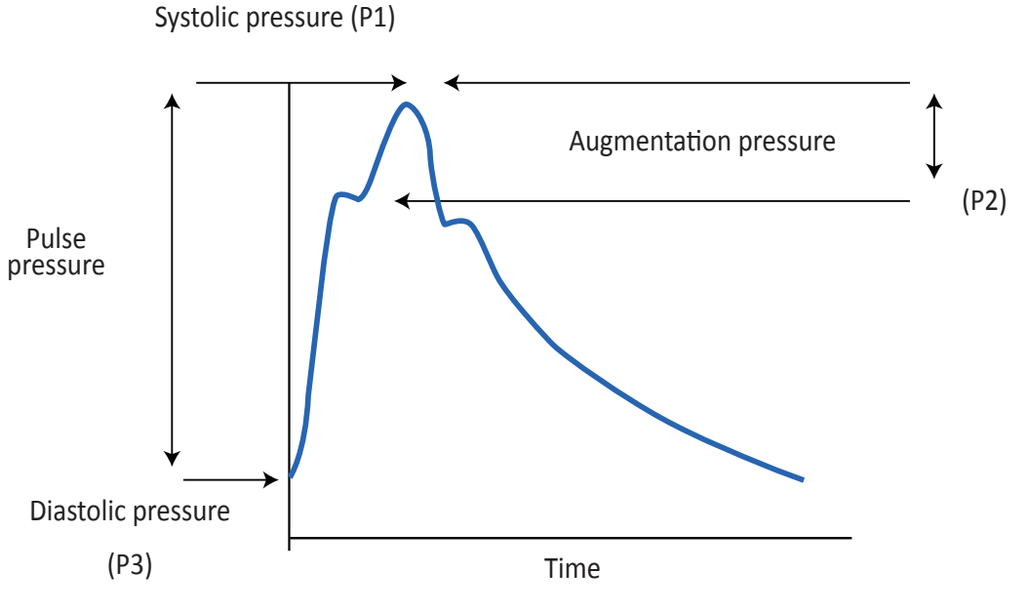

Fig. 15. Carotid pressure waveform. *(Reprinted from Laurent et al.[266] with permission from Oxford University Press)*

Normal peripheral pulse amplification means that brachial pressure should not be confused with central SBP and PP.[266] CAP is physiologically more relevant and better related to future cardiovascular events than brachial pressure.[287] Despite being more operator-dependent than PWV, the analysis of the central BP and waveform are well documented as important clinical tools for monitoring of vascular function and has an independent predictive value for CV events.[267] A recent meta-analysis of 11 longitudinal studies showed a significant increase of total CV events with a 10 mm Hg rise in CAP (1.1 relative risk), PP (1.2 relative risk) and AIx (1.3 relative risk).[264] Despite this, AIx should not be considered an absolute surrogate marker of arterial stiffness.[267] It is true that a stiffer vasculature has a higher PWV and results in reflected waves arriving earlier in systole that produces a higher AIx. However, the degree of augmentation is also related to the intensity of peripheral wave reflection, which depends on associated hemodynamic confounders and it is highly sensitive to HR.[288] For this reason, AIx is also commonly normalized for a HR of 75 beats per minute, to allow comparison between patients (**AIx@75**). This is particularly important in children, who have a higher HR, which varies significantly between different age groups

CAP is obtained invasively with cardiac catheterization. However, several non-invasive methods have been developed to estimate CAP and waveform. These include pulse waveform recordings from sites distal to the aorta, such as the carotid, radial or brachial arteries. There is a lack of consensus regarding the optimal method to estimate the CAP curve using tonometry and each has its strengths and weaknesses. The brachial and radial artery derive the CAP using a general transfer function, which has not been validated in children. Carotid pressure is most often used as the surrogate for CAP because of the close proximity of these two arterial sites.[289] Carotid pressure waveforms are recorded by applanation tonometry and then calibrated to the brachial mean and diastolic pressures obtained by sphygmomanometry, based on the principle that - unlike systolic pressure - mean and diastolic pressure do not vary markedly throughout the arterial tree.[267]

2.3.3. *Endothelial Function*

Vascular endothelium is the largest organ in the body and plays a major role in the homeostasis of the vascular tone, inflammation, and thrombosis. Endothelial function results from the balance between vasodilators and vasoconstrictors produced by (or acting on) endothelial cells. Nitric oxide (NO) is produced in the endothelium from L-arginine by the enzyme endothelial nitric oxide synthase (eNOS). NO has a very short half-life, and it is continually produced as a signaling mechanism to the arterial wall, serving to inhibit the

adhesion of platelets and leukocytes to the vessel wall and to relax the smooth muscle cells to maintain vascular patency and distensibility.[290, 291] The production of NO is stimulated by flow shear stress exerted directly on the vessel endothelium[292-294] and receptor-dependent agonists such as bradykinin, acetylcholine and adenosine triphosphate.[291] In the smooth cells, NO activates the enzyme guanyl cyclase, which produces cyclic guanosine monophosphate (cGMP) that results in smooth muscle cells relaxation and vasodilation.[290]

Endothelial dysfunction occurs when there is impairment of the endothelium-dependent vasorelaxation caused by a decline of NO bioavailability. Several human studies have shown that traditional risk factors for atherosclerosis such as HTN, diabetes, cigarette smoking, and heart failure predispose to endothelial dysfunction.[295]

Endothelial dysfunction can result from decreased NO production but is largely due to increased production of reactive oxygen species (ROS) such as superoxide that occur in the context of oxidant stress, which will accelerate NO degradation and decrease its bioavailability.[295, 296] A growing body of evidence suggests that endothelial dysfunction is associated with cardiovascular events and that it has prognostic implications in patients with established stable coronary artery disease, essential HTN, and in patients with acute coronary syndromes and peripheral artery disease.[297]

There are several methods to quantify endothelial function (**Table 3**):

Table 3. Methods to measure endothelial function.

Technique (Outcome measure)	Noninvasive	Repeatable	Reproducible*	Reflects Biology	Reversible	Predicts Outcome†
Cardiac catheterization (change in diameter, change in coronary blood flow)	–	–	+/–	+	+	+
Venous occlusion plethysmography (change in forearm blood flow)	–	+/–	+/–	+	+	+
Ultrasound FMD (change in brachial artery diameter)	+	+	+/–	+	+	+‡
PWA (change in augmentation index)	+	+	+/–	+	–	–
PCA (change in refletive index)	+	+	+/–	+	–	–
PAT (change in pulse amplitude)	+	+	+/–	+	–	–

+ indicates supportive evidence in literature; – insufficient evidence; FMD - flow-mediated dilatation; PWA - pulse wave analysis; PCA- pulse contour analysis; and PAt- pulse amplitude tonometry.

*Reproducibility or PWA, PCA, and PAT has been less extensively investigated than FMD.

†Studies that link PWA, PCA, and PAT to outcome have not yet been reported.

‡FMD is currently the standart for noninvasive assessment of conduit artery endothelial function because there is considerable clinical trial experience, validation, a firm link to biology, and association with cardiovascular events.

Reprinted from Deanfield et al,[298] with permission from Wolters Kluwer Health

Endothelial dysfunction can be assessed invasively by intracoronary injection of agonists of endothelium-dependent vasodilator acetylcholine[299] and brachial artery catheterization with venous occlusion plethysmography. In 1992, Celermajer was the first to report the use of a non-invasive ultrasound test, flow-mediated dilation (FMD), to assess vascular function in the brachial artery.[300] Since then, several additional non-invasive modalities have been described to assess vascular endothelial function, such as pulse wave analysis, pulse contour analysis, digital thermal monitoring, and peripheral artery tonometry.[301] Finger pulse amplitude tonometry (Endo-PAT)[302] has emerged as a promising technique because it is a simple method, in contrast to the more cumbersome FMD (**Fig. 16**):

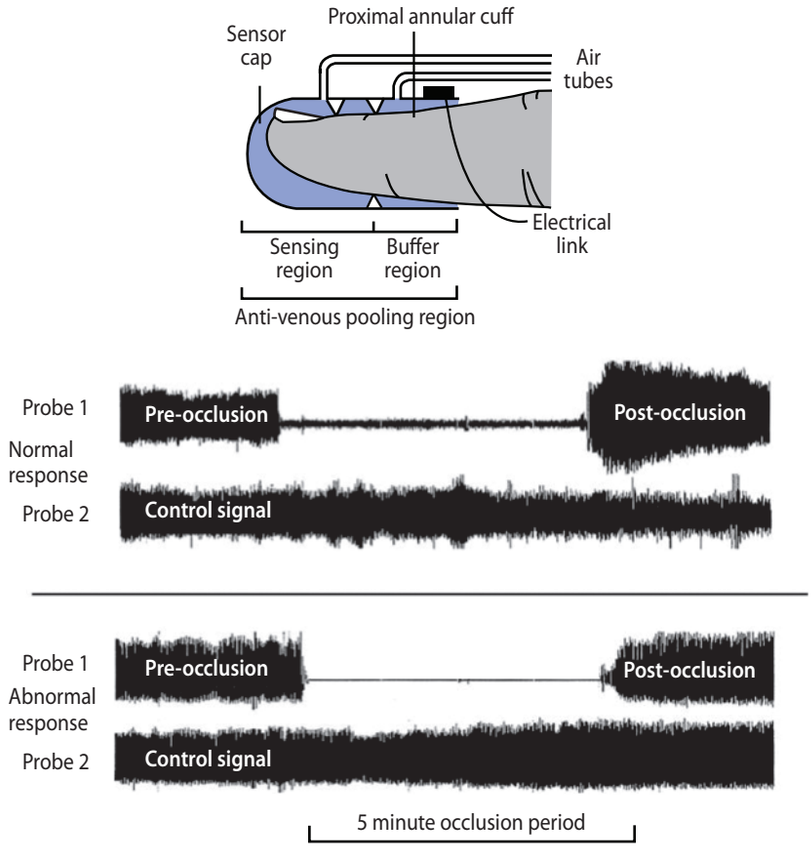

Fig. 16. Reactive hyperemia peripheral arterial tonometry recordings. *Above, is the normal reactive hyperemic response, characterized by a distinct increase in the signal amplitude after cuff release compared with baseline. Below, is the abnormal response, characterized by a blunted increase in the signal amplitude after cuff release compared with baseline (reprinted from Bonetti et al,[303] with permission from Elsevier)*

It requires insertion of one finger of each hand in peripheral tonometers and inflation of a cuff in the arm to achieve a 5-minute occlusion on one arm while the contralateral arm serves as control. The probe measures the reactive hyperemia index (RHI) that ensues after cuff deflation by measuring the increase in pulse amplitude and comparing it with the contralateral finger. Endothelial function measured by Endo-PAT can be easily performed with high reproducibility in the ambulatory clinical setting,[304, 305] has been validated as a surrogate for coronary endothelial function,[303] and is a risk factor for CVD.[303, 306, 307]

2.3.4. *Circulating Biomarkers*

There are many biochemical and molecular processes involved in vascular dysfunction. There is a growing research interest in these circulating biomarkers pathways, which constitute possible 'active' mechanisms that lead to increased arterial stiffness. Our understanding is growing but still limited.

2.3.4.1. Endothelial Function

NO is a key modulator of endothelium-dependent vasodilation, but it's rapid metabolism, and short half-life poses a considerable obstacle for the analytical assessment. However, several biochemical mediators of the NO pathway can be measured. These include L-arginine (NO's precursor), endothelial NO synthase (eNOS; NO's enzyme), asymmetric dimetilarginine (ADMA; NO's inhibitor),[308] and nitrite and nitrate (NOx, stable by-product of NO). Endothelial dysfunction leads to decreased l-arginine and increases in all other metabolites of the NO pathway.

2.3.4.2. Inflammation

Systemic and local inflammation is an important key in the process of atherosclerosis and vascular dysfunction.[309]

Pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) trigger the production systemic inflammatory markers such as C-reactive protein.[310] A large body of literature shows that high sensitivity C-reactive protein (hs-CRP) may help to estimate risk for initial cardiovascular events and may be used most effectively in people at intermediate risk for vascular events, offering moderate improvement in reclassification of cardiovascular risk.[311-313] hs-CRP is associated with other biomarkers of vascular dysfunction such as PWV.[314] Studies also show that the inflammatory cytokines may also be also markers and predictors of CVD.[315]

The pro-inflammatory cytokines also act on vascular endothelium to up-regulate the expression of several adhesion molecules such as selectins, vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and other adhesion molecules such of the selectin family, that play a crucial role in atherogenesis, since these are the receptors who mediate the cell adhesion and migration that triggers atherogenesis.[309]

2.3.4.3. Vascular Remodeling

Another critical area of understanding is the molecular mechanisms of aortic wall remodeling to hemodynamic changes. These include the role of transforming growth factor beta-1 (TGF-β1), a smooth cell growth-modulating factor, that is involved in the arterial wall response to HTN,[316] and has been suggested as having a prognostic value regarding the degree of dilation of the aorta in Marfan syndrome[317] and other dilatative pathology of ascending aorta.[318] Another aspect is the role of the matrix metalloproteases such as MMP-2

and MMP-9, a family of proteolytic enzymes responsible for protein degradation and vascular remodeling,[319] and are well documented biomarkers for the presence and risk of rupture of aortic aneurysm.[320]

2.3.5. *Ventriculo-Arterial Coupling*

The cardiovascular physiology concept of the ventricle and the arteries functioning as a coupled system is not recent,[321] is called ventriculo-arterial coupling,[322] and has been the focus of recent attention.[323]An optimal ventriculo-arterial coupling occurs when the highest energy is transferred from the LV to the aorta with a minimum amount of energy wasted to overcome resistance to ejection and blood flow. Long standing arterial stiffness leads to LV hypertrophy and stiffness, and an altered ventriculo-arterial coupling. In such circumstances, heart and arteries interact in a complex interplay to limit the cardiovascular performance and generate symptoms.[324, 325] Earlier analysis were based on detailed invasive instantaneous measurements that were used to plot pressure-flow curves. Recently, the ventriculo-arterial stiffness assessment can be done with echocardiography or CMR, by measuring the LV contractility (representing the slope of the end-systolic pressure-volume relation, the end-systolic elastance, Ees), the arterial vascular load as the ratio of ventricular end-systolic pressure to stroke volume (elastance of the arterial system, Ea), and the relationship between Ea/ Ees.[326]

3. VASCULAR DYSFUNCTION IN COA

3.1. Treatment Does Not Equal Cure

Currently available surgical and percutaneous techniques are equally effective at eliminating the gradient across the aortic isthmus in CoA patients,[130, 154] (except in infants and young children, in whom surgery is preferred). However, even after a good anatomical result, patients remain to have late morbidity with high rates of late systemic HTN detected during routine office visits (12-65%),[130, 154, 166, 177, 203-215] at peak exercise (10-47%),[210-217, 220, 327-332] or during ABPM (30-59%).[72, 75, 213, 216-225] Patients show signs of premature atherosclerotic lesions in the retina,[333] internal mammary or coronary arteries.[334]

Furthermore, treated patients have reduced life expectancy (**Fig. 17**), mostly due to cardiovascular complications[187, 250-253, 335-341] and stroke,[255] reported to be seen up to 13 times more frequently in patients with coarctation, compared to the general population.[254]

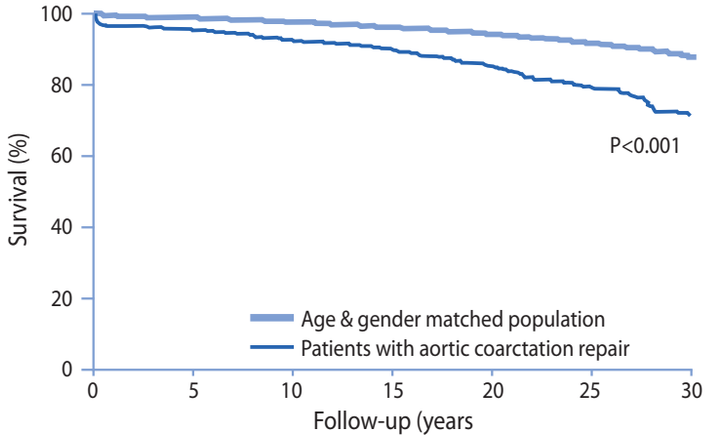

***Fig. 17. Single-center follow-up of 819 patients for over 60 years**. (reprinted from Brown et al,[207] with permission from Elsevier)*

A metanalysis showed that CoA had the highest incidence of all CHD of long-term vascular complications such as 3.2% with stroke or transient ischemic attack and 5.1% with myocardial infarction.[342] The most recent study still showed a late mortality of 5.7% at a median f/u after treatment of 31.4 years (range 14.1–39.9 years) corresponding to a lethality of 0.3% per year and estimated survival rates of 97%, 94%, 91% and 80% at 10, 20, 30 and 39 years after repair.[343] Consequently, CoA should be regarded as a complex and systemic cardiovascular syndrome involving the aorta that may not be "cured" after relief of the localized mechanical obstruction. In light of the suboptimal long-term outcomes, an editorial has recently questioned if we need to redefine the current definition of successful treatment of aortic coarctation as a gradient < 20 mm Hg.[344]

3.2. Vascular Dysfunction is Common after CoA Treatment

The amply documented abnormal resting and exercise-induced BP profile suggest that vascular dysfunction may contribute to the suboptimal long-term prognosis successfully observed in repaired CoA patients. Indeed, it has long been recognized that successfully repaired CoA patients show abnormal vascular function.

Patients show increased arterial stiffness, with higher PWV,[72, 233, 244, 345-349] and altered compliance, distensibility, or the elastic wall modulus.[228, 229, 233, 235, 242, 244, 350-356] Concerning intima media-thickness, a measure of the presence and extent of arterial atherosclerosis, there have been conflicting results as to whether it is improved[217, 230, 244, 350, 351, 354] or not[347, 348, 357, 358] after CoA repair.

Most studies have shown compromised arterial reactivity,[217, 224, 328, 345, 347, 348, 350, 359-361] while a minority failed to demonstrate impaired reactivity in retinal,[333] peripheral[362, 363] or coronary[363] arteries of repaired CoA patients when compared to controls. Repaired CoA patients show altered pulse waveforms with higher AIx,[224, 348, 364] PP,[75, 358] and CAP.[348, 358, 364]

There is imbalance of numerous biomarkers of vascular function, namely of the NO-mediated endothelial function,[347, 365, 366] systemic and local inflammation,[349, 360, 364, 367] and of the vascular wall function[349, 360, 364, 368]

Finally, the increased BP phenotype and vascular function contribute to the increase LV mass,[75, 217, 221, 227-236] impaired LV segmental systolic[225, 229, 230, 232, 234, 235, 238, 242-246] or diastolic dysfunction.[230, 232, 238, 244, 247, 248] Studies have also shown ambivalent results regarding the ventriculo-arterial coupling in CoA: some have shown that there is altered ventriculo-arterial coupling in patients with repaired CoA,[234, 244] while others did not find that the presence of HTN affected the ventriculo-arterial coupling.[369] The abnormal ventriculo-arterial stiffness may contribute to further HTN in repaired CoA.[218]

3.3. Inherent Pre-Treatment Features May Contribute to Vascular Dysfunction

The damage to the vascular wall occurs before treatment, is present at birth,[353] and persists despite neonatal treatment.[352] Inherent problems that may trigger this vascular dysfunction include genetic causes, changes in the arterial structure and function, impaired neuronal sensitivity or endocrinal auto-regulation.

The mechanical stimuli caused by an experimental CoA is responsible for the differential expression of genes associated with vascular function.[63-65] Human studies also revealed such genetic polymorphisms in CoA patients.[67-69] However, CoA patients do not show the most common genomic polymorphisms associated with essential HTN[67] or BP regulation during exercise,[68] thus suggesting a different ethiopathogenic mechanism.

Light and electron microscopy of pre-coarctation aorta surgical specimens showed histopathological changes including increased collagen and reduced smooth muscle content.[55-57] Recent findings have demonstrated molecular mechanisms that elicit phenotypic modulation of smooth muscle cells, accumulation of excessive collagen and inborn impaired arterial elasticity in patients with CoA.[370] The pattern of histopathological[55, 57] or functional[233] vascular changes localized in the ascending but not the descending aorta is also found in patients with BAV,[59] themselves present in half to two thirds of CoA patients.[50, 252] Finally, some groups found that a gothic-shaped arch is associated with a worse BP profile.[208, 350, 371-373]

The role of the RAA system is unclear in the high BP in CoA. Some studies provided evidence of the significance of increased RAA activity in patients with CoA,[70-72] while others did not.[73-75] It may be that this neuroendocrine system is important in the early development but not in the maintenance of coarctation HTN.[76]

The autonomic system and baroreceptor's function may be altered, including an enhanced sympathetic tone, reset of the baroreflex to a higher value and diminished sensitivity to changes in arterial pressure.[77-79, 374] However, some evidence suggests that the neuronal mediation may be involved only in the pre-treatment HTN and then normalizes after repair.[80, 81]

All the above suggest that CoA is not just a localized isthmic stenosis but also an inborn systemic vascular disease of the pre-CoA arteries.

3.4. Acquired and Treatment-Related Factors may also Contribute to Vascular Dysfunction

Age of repair is the best document treatment-related factor that affects vascular function.[207, 216, 227, 229, 230, 242, 345, 349, 356, 375-378] Length of follow-up,[337, 343] and mild residual narrowing may also contribute to vascular dysfunction[217, 379-381]

Medical management also impacts on vascular function, including studies that show the favorable impact of angiotensin-converting enzyme inhibitors,[382] β-blockers,[73] and atorvastatin[383] on endothelial function or vascular function biomarkers in patients with repaired CoA.

3.5. Treatment Modality may Affect Vascular Function

The hemodynamic impact of a focal vascular stiffness was shown five decades ago.[384] Different types of treatment may have varying effects on the stiffness of the repaired arterial segment.[154] Surgical repair results in a focal scar in the site of the surgical anastomosis; stenting creates a short, rigid aortic segment; and BD produces a controlled tear of the aorta's intima and part of the media without affecting the adventitia. It is possible that different treatments translate into differences in vascular dysfunction. However, the effect of treatment modality on vascular function has not been systematically compared, and management is often guided by physician or institutional preference with the primary goal of alleviating the anatomic narrowing.

The largest (350 patients, 36 institutions), albeit observational and non-randomized, comparison between the three different modalities showed a significantly lower BP in patients treated with BD vs. those treated with a stent or surgery.[130] Similarly, another small retrospective study showed less frequent exercise-induced HTN in patients who underwent BD, compared with those who were treated with stent implantation or surgery.[378] Among surgical techniques, those who undergo resection with end-to-end anastomosis have a lower prevalence of systemic HTN and arterial stiffness compared to other surgical techniques.[385-387] Another small study demonstrated a lower carotid intima-media thickness in patients who had undergone subclavian flap repair compared to those who had stent implantation, but PWV was similar between groups.[230] Conclusions drawn from these prior studies are hampered by methodological limitations, small sample size, heterogeneous population, and limited focus.

III. AIMS AND HYPOTHESIS

The current management paradigm of CoA is often guided by personal or institutional preference, with the primary goal of alleviating the stenosis by optimizing the anatomy. However, the suboptimal long-term outcomes in apparently successfully treated patients with CoA stresses the importance that further research is needed to improve the management of this common CHD. The evidence that (a) patients with treated CoA have long-term vascular dysfunction and the recognition that (b) vascular dysfunction leads to CV events in the general population motivated this study.

CoA may also be a useful physiological model of HTN that occurs exclusively in the upper body and lessons learned in this study may also contribute to the knowledge about the impact of segmental stiff arteries on BP and the pathophysiology of HTN in the general population.[381]

There is a gap between clinical research and clinical practice has been well identified as one a critical challenge that requires addressing and fewer than half of all the medical treatments delivered today are supported by evidence.[388] Furthermore, data shows that in the United States, only about half of the effective clinical practices are adopted.[389] There are several challenges to clinical research, including cost, small incentives for physician participation, administrative and regulatory requirements, lack of clinically oriented institutions, diversity of clinical presentation of diseases and difficulty in recruitment and retention of patients. This is particularly true of CHD, that deals with rare diseases with a varied presentation, and especially in CoA patients, who feel mostly well and are seen in spaced clinical visits, despite having suboptimal long-term morbidity and mortality. LOVE-COARCT is an attempt to bridge this gap of knowledge, by exploring the causes of these late outcomes.

The **aim of this study is to determine whether three different treatment modalities for CoA** (surgery, BD, and stenting) **are associated with differences in arterial stiffness**. **The central hypothesis of this study was that patients who have undergone successful BD will have better vascular function** than patients who have undergone successful surgical repair or stenting since this modality is least likely to damage the integrity and biomechanical properties of the aortic wall.

1. PRIMARY AIM AND HYPOTHESIS

The primary aim of LOVE-COARCT's Study was to compare arterial stiffness assessed with carotid-femoral PWV (**cfPWV**) between BD, surgery and stent. We hypothesized that BD was superior to surgical repair and stenting in preserving vascular function measured by carotid-femoral PWV (**cfPWV**) after repair of CoA.

2. SECONDARY AIMS AND HYPOTHESIS

The secondary aims of LOVE-COARCT's Study were to use other well-established indices of vascular function to compare BD, surgery, and stent, namely:

a. **Carotid-femoral PWV** measured with arterial tonometry and other segmental aortic PWV measured with CMR.
b. **Indices of focal arterial stiffness measured with CMR:** aortic strain, distensibility, compliance and aortic stiffness β index.
c. **Endothelial function** determined by endothelial pulse amplitude testing (Endo-PAT) and circulating biomarkers (NOx, ADMA).
d. **Central pulse wave analysis** using arterial tonometry and Endo-PAT.
e. **BP phenotype** at rest, during ambulatory measurement, and at peak exercise.
f. **Circulating Biomarkers** of vascular function including high sensitivity C-reactive protein (**hs-CRP**) and interleukin 1 beta (**IL-1β**), local cytokines of vascular wall function (vascular adhesion molecule 1, **VCAM-1**) and vascular remodeling (matrix metalloproteases **MMP-2** and **MMP-9;** and transforming growth factor beta-1, **TGF-β1**). NOx was determined by chemiluminescence (Sievers NOAnalyzer 280i), and all remaining measurements were performed with appropriate enzyme-linked immunosorbent assay (ELISA) kits
g. **LV mass** and systolic function.
h. Prevalence of **ideal cardiovascular health** (ICVH) in patients late after treatment of CoA overall and by treatment modality.

We hypothesized that BD was superior to surgical repair and stenting in preserving vascular function measured by other secondary indices of vascular function.

We have considered the alternative hypothesis, namely the possibility that the results of this study may not support our primary and secondary hypothesis. First, it is possible that no significant differences are seen in vascular function between the treatment groups. A second possibility is that either stenting or surgery results in less stiff arteries than BD. Both alternative scenarios would add important considerations to the literature and guide clinical practice for the choice of treatment modality.

IV. METHODS

1. STUDY OVERVIEW

LOVE-COARCT was a multicenter cross-sectional prospective observational study of patients with CoA previously treated using one of three treatment modalities to identify if treatment type is associated with differences in vascular function.

1.1. LOVE-COARCT Participant Centers

We assembled a multi-disciplinary group of investigators with established expertise in epidemiology, clinical trial design, CHD, non-invasive imaging, interventional cardiology, vascular function assessment, preventive cardiology and statistical analysis. The rationale for using a multicenter design was fourfold: (a) to ensure sufficient statistical power in evaluating our hypothesis; (b) recruiting at several high-volume pediatric cardiac centers allowed us to overcome anticipated recruitment challenges; (c) it helped mitigate the impact of center-specific preferences for particular treatment modalities, and (d) we were able to leverage the broad range of expertise available at the recruiting centers to help create Core Laboratories for each test.

There were seven recruiting centers in the LOVE-COARCT study, two from Portugal and five from the United States of America. Their choice was based on center quality, large volume, and availability for study participation:

- Department of Pediatric Cardiology, **Hospital de Santa Marta** CHLC, Centro Hospitalar de Lisboa Central, EPE, Lisbon, PORTUGAL (the dissertation author's center) (Centro de Referência para a área das Cardiopatias Congénitas em Portugal)
- Department of Cardiology, **Boston Children's Hospital**, Harvard Medical School, Boston, USA
- Division of Pediatric Cardiology, **Texas Children's Hospital**, Baylor College of Medicine, Houston, USA
- Division of Pediatric Cardiology, Department of Pediatrics, **Lucile Packard Children's Hospital**, Stanford University, Palo Alto, USA
- Division of Pediatric Cardiology, **Children's Hospital Colorado**, Aurora, USA
- Joint Division of Pediatric Cardiology, Children's Hospital and Medical Center **University of Nebraska** College of Medicine Omaha, USA

- Pediatric Cardiology Department, **Hospital Pediátrico de Coimbra**, Coimbra, PORTUGAL (Centro de Referência para a área das Cardiopatias Congénitas em Portugal)

The LOVE-COARCT study was registered in the **Clinical Trial Registration** site (URL: https://www.clinicaltrials.gov) with the unique identifier NCT03262753

1.2. LOVE-COARCT Core Laboratories

To ensure data fidelity and minimize multicenter-derived errors, core laboratories (core labs) were established. This strategy allowed to leverage the broad range of expertise available at the recruiting centers. The core labs had the following tasks: (a) designing the formal Manual of Operations for the tests under its supervision, which was then strictly followed by all recruitment centers; (b) support data collection and provide counselling on procedural questions; (c) ensure quality control by reviewing all collected data; and (d) perform further data analysis, as per protocol. This was particularly true of the CMR core lab, where all CMR images were reviewed and further calculations were done. Here is the list of all core labs:

- **Cardiac Magnetic Resonance Core Lab** (responsible: Ashwin Prakash): Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA
- **Preventive Cardiology Core Lab** (responsible: Sarah de Ferranti): Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA
- **Biostatistics Core Lab** (Responsible: Kimberlee Gauvreau): Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA
- **Tonometry and BP Assessment Core Lab** (Responsible: Justin Zachariah): Division of Pediatric Cardiology, Texas Children's Hospital, Baylor College of Medicine, Houston, USA
- **Biomarkers Core Lab** (Responsible: Maria Guarino): CEDOC Chronic Diseases, Nova Medical School, Lisbon, PORTUGAL
- **Endothelial Function Core Lab** (Responsible: Elif Seda Selamet Tierney): Division of Pediatric Cardiology, Department of Pediatrics, Lucile Packard Children's Hospital, Stanford University, Palo Alto, USA

2. SELECTION CRITERIA

The medical records of potentially eligible patients were screened by a local study investigator using a pre-specified screening form to ensure that they satisfied our selection criteria.

2.1. Inclusion Criteria

We included patients with (a) diagnosis of isthmic CoA; (b) current age between 8 (to allow cooperation with study procedures, including EST test and non-sedated CMR) and 35 years (to avoid confounding by the age-related vascular dysfunction that ensues);[390] (c) treatment for CoA after 1994 (after which all three modalities were in clinical use); and (d) treatment at least 6 months after enrollment (to allow completion of the healing and fibrosis associated with treatment) (**Table 4**):

Table 4. LOVE-COARCT Inclusion Criteria

Criteria	Definitions
CoA	Isolated, isthmic CoA
Current age 8-35 years	
Treatment for CoA after 1994	
Treatment > 6 months before enrollment	

CoA = coarctation of the aorta

2.2. Exclusion Criteria

We excluded patients with (a) ReCoA defined by a systolic upper-to-lower extremity BP gradient > 20 mm Hg (which is a confounder since it impacts vascular function); (b) Co-morbidities that could independently affect vascular function, including associated significant CHD, history of known vasculopathy, genetic syndromes (such as Turner syndrome) or other cardiovascular risk factors; (c) History of two treatment types for CoA, or surgical techniques

other than the most commonly used end-to-end surgical anastomosis (to avoid confounding with other factors that may impact on the biomechanics of the isthmus); and (d) CoA types likely representing a different entity or patients amenable to one single treatment type (surgery), including atypical CoA site (such as mid-thoracic or abdominal), severe hypoplasia of the aortic arch, and an age of treatment < 1 year of age (which is a more severe disease subset that is essentially treated with only one of the three treatment types). The details of the exclusion criteria are shown in **Table 5**:

Table 5. LOVE-COARCT exclusion criteria

Criteria	Definitions
ReCoA	Systolic upper-to-lower extremity BP gradient> 20 mm Hg*
Atypical CoA	Mid-thoracic or abdominal CoA.
Severe transverse aortic arch hypoplasia	Transverse arch diameter z-score at initial echocardiogram <-4 †
Treatment of CoA at age <1y	
Clinically significant associated cardiac defects	Mitral stenosis (echocardiographic mean inflow Doppler gradient >6 mm Hg) aortic stenosis (echocardiographic mean Doppler gradient >20 mm Hg); ventricular septal defect (>3 mm in diameter); atrial septal defect (required surgical or percutaneous closure other than a patent foramen ovale); other cardiac lesions that required medical, surgical or interventional treatment
Use of two treatment modalities for CoA	This does not include BD and subsequent stent placement at the same catheterization procedure
History of known vasculopathy with vascular dysfunction	Examples: Kawasaki disease, Takayasu's arteritis, Raynaud's disease
Genetic syndromes with diffuse arteriopathy	Examples: Williams syndrome, juvenile rheumatoid arthritis
Known traditional cardiovascular risk factors	Severe obesity (body mass index >95% for age and sex in children and >40 Kg/m^2 for adults); diabetes (fasting plasma glucose ≥126mg/dl or random (non-fasting) glucose ≥200 mg/dl); hyperlipidemia (triglycerides ≥250 mg/dl; fasting LDL ≥190 mg/dl; HDL≤ 30 mg/dl, currently taking statins or first-degree relatives with familial hypercholesterolemia); smoking

BP = blood pressure; BD = balloon dilation; CoA = coarctation of the aorta; reCoA = residual coarctation of the aorta

2.3. Recruitment Challenges

Despite CoA being one of the most common congenital heart defects, we anticipated that recruitment for this study would be arduous due to three reasons. First, our focus on a comparison of treatment-associated vascular function outcome required restrictive inclusion and exclusion criteria and matching treatment groups for potential confounders. This meant establishing a lower treatment age limit of 1 year, therefore excluding a large majority of CoA patients, who present in infancy, and are almost always managed by surgery. We also used lower current age cutoff of 8 years to facilitate the completion of the study tests and a higher age limit of 35 years to avoid overlap with aging-related vascular dysfunction. Although treatment for CoA has been available for five decades, we would only include patients who had undergone treatment after 1994, after which all three treatment modalities became available. We would exclude patients who received treatment using more than one modality.

Second, recruitment could be challenging because treatment in our patient population occurred many years ago making loss to follow up more likely, especially when in asymptomatic patients without reCoA, as our enrollment criteria specified. And third, we anticipated that our one to two-day visit to the enrolling center could deter some patients to accept participate in the study for patients who feel mostly well and have spaced clinic visits.

3. OVERVIEW OF THE STUDY WORKFLOW

Study procedures occurred in a one- or two-day visit and were performed at each recruiting site, except for patients from Hospital Pediátrico de Coimbra, who were tested in Hospital de Santa Marta. All the CMR from both Portuguese centers were done in Caselas, Ressonância Magnética, S.A. Lisbon, PORTUGAL (Responsible, Nuno Jalles, MD).

Upon arrival for testing, formal consent for participation were obtained. Assessment of arterial stiffness, endothelial function, and blood sampling for biomarkers was done while fasting. Cardiopulmonary stress test was performed on the same day. CMR and ambulatory blood pressure monitoring (ABMP) were arranged for the same or for the following day (**Fig. 18**). When the study tests could not be exceptionally completed on the first visit, they were completed within 3 months of the first visit.

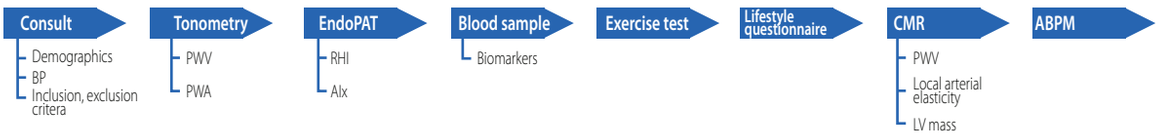

Fig. 18. LOVE-COARCT study workflow. *ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CMR = cardiac magnetic resonance imaging; PWA = pulse wave analysis; PWV = pulse wave velocity; RHI = reactive hyperemia index.*

4. RECRUITMENT

The study protocol was approved by the Institutional Review Board or Institutional Ethics Committee at each participating center, and informed consent and assent were obtained, depending on age, from patients and their parents/legal guardians before trial enrollment. A retrospective review of the patient database at each participating institution was performed to assemble a cohort of patients with CoA who had previously undergone treatment with BD, surgery or stenting. The recruitment started in June 2013 and ended in March 2017. Study data were collected and managed using REDCap electronic data capture tools hosted at Boston Children's Hospital.[391]

5. MEDICAL HISTORY

A retrospective chart review was performed to collect demographic and clinical data including severity of CoA, type and details of CoA treatment and presence of associated conditions. The main study variables from medical history are depicted in **Table 6**:

Table 6. Medical history variables

Variables	Comments or Definitions
Minimum transverse arch diameter Z-score on initial echo	Using published normative values[392]
Isthmus z score on initial echo	Using published normative values[392]
Initial Doppler CoA gradient	mm Hg
Bicuspid/Bicommisural Aortic Valve?	Yes/No
Initial arm-leg systolic BP gradient	mm Hg

BP = blood pressure; CoA = coarctation of the aorta

6. STUDY PROCEDURES

6.1. Arterial Stiffness

6.1.1. *Measurements*

Carotid-femoral PWV **(cfPWV)** was measured using applanation tonometry. Segmental PWV was measured using CMR. Segmental measures of arterial distensibility were be measured using CMR. The full list of arterial stiffness variables are in **Table 7** and **Table 8**.

Table 7. Applanation tonometry variables

Variables	Units
Central systolic BP	mm Hg
Central PP	mm Hg
Carotid-femoral PWV	meters/second
AIx (%)	%
AIx@ 75	%

AIx = augmentation index; AIx@75 = augmentation indez at 75 beats per minute; BP = blood pressure; HR = heart rate, PP = pulse pressure; PWV = pulse wave velocity

Table 8. CMR variables

Variables	Formulas and units
LV mass indexed to BSA	g/m^2
Ascending Ao- Descending Ao PWV (Ascending Ao to proximal, mid	meters/second
Type of arch	Romanesque; Gothic; Crenel
Diameter of ascending aorta, proximal and distal transverse arch,	mm; indexed to BSA
Aortic strain (Ascending, Proximal, Mid and Distal Ao)	
Aortic compliance (Ascending, Proximal, Mid and Distal Ao)	cm^2/mm Hg
Aortic Distensibility (Ascending, Proximal, Mid and Distal Ao)	mm Hg-1
Aortic beta stiffness index (Ascending, Proximal, Mid and Distal Ao)	

Ao = aorta; BSA = body surface area; LV = left ventricle; PWV = PWV

6.1.2. *Manual of Operations for Tonometry*

For applanation tonometry, some centers used the NIHem system (Cardiovascular Engineering, Inc., Norwood, MA USA) and others the SphygmoCor device (AtCor Medical, West Ryde, NSW, Australia). The technology is similar and the results comparable.[267]

The patient demographics and brachial BP were entered into the system. First, the tonometer was placed over the right carotid artery, just lateral to the thyroid cartilage. The location was adjusted, and pressure applied as needed to optimize waveform. After ensuring that the tracings are optimal, the tracing was recorded. The carotid site was marked. Then, the tonometer was placed over the right femoral artery, and the same process for obtaining an optimal curve recording was followed. The femoral site was marked. Finally, in the centers that used the SphygmoCor device, a third recording of the radial artery was performed, in the same fashion. A caliper was used to measure the distance from the suprasternal notch to the carotid site and from the suprasternal notch to the femoral site. Both distances were entered in the system.

For PWV and AIx calculation, both systems analyzed the curves and the data was supplied with the proprietary software package, without any input from the examiner.

For pulse wave analysis (CAP, PP) the analysis procedure differed slightly between systems. The system's software did the analysis from the NIHem system. In the centers that used SphygmoCor, the signal averaged carotid pulse wave was digitalized and calibrated (by the same operator, D.O.) according to a published approach:[393, 394] The brachial diastolic and mean pressures was used, and the same diastolic and mean pressures were assigned to the averaged carotid pulse. Moreover, the radial pressure waveform was used to retrieve the correspondent time instants of diastolic and mean pressures. Given the two pressure values and the correspondent time instants, it is possible to calibrate each averaged carotid pressure waveform. This process allowed a quantitative analysis of the pulse waveform.

6.1.3. *Manual of Operations for CMR*

CMR was performed using commercially available whole-body 1.5 T scanners (Achieva; Philips Healthcare, Best, the Netherlands; Signa 1.5T or GE Medical Systems, Milwaukee, WI, USA). ECG-gated steady state free precision (SSFP) localizers were used in sagittal, coronal and axial planes during free breathing. Ventricular function was assessed from short axis stack to cover ventricles from base to apex, acquired using the following imaging parameters: slice

thickness 5-8 mm, slice gap 0-1 mm, slice number 12-14, cardiac phases 30, retrospective gating with breath-holding. In patients unable to breath-hold 3 signal averages during free-breathing were used. SSFP cine imaging was also performed in two orthogonal long-axis planes of the left ventricular outflow tract (during breath-hold), short axis of the ascending aorta (AAO), and in the long axis of the aortic arch (free-breathing, used as reference for PWV measurements), proximal descending aorta (DAO, 2-3 cm distal to the isthmus, sufficiently distal to dephasing jets), mid DAO (diaphragmatic level) and distal DAO (just above iliac bifurcation). ECG-gated through-plane phase-contrast flow measurements were performed at the AAO (5 mm distal to the sinotubular junction), and in proximal, mid and distal DAO segments (matched to location of the cine SSFP acquisitions) using the following imaging parameters: signal averages = 2, cardiac phases 100 (TFE factor/views per segment/ = 1 (to maximize temporal resolution), velocity encoding 200-250 cm/s (higher if needed to avoid aliasing (**Fig. 19**). ECG and respiratory navigator-gated 3-D SSFP MRA of the aortic arch was performed in the sagittal plane.

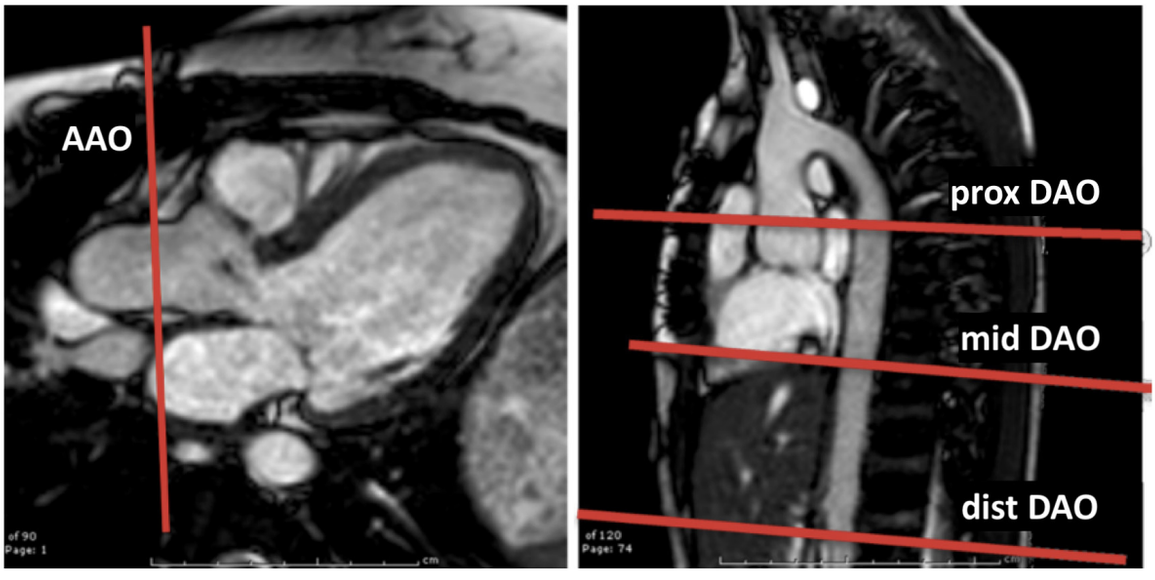

Fig. 19. ECG-gated through-plane phase-contrast flow assessment. *The global PWV is measured from the AAo to prox DAO, and segmental PWV is measured for the arch (AAO to prox DAO), mid aorta (prox to mid DAO), and distal aorta (mid to dist DAO)AAO = ascending aorta; DAO = descending aorta.*

The patient's right arm BP while on scanner table and length of time since last meal and content of last meal were recorded. Images were analyzed by a single observer (A.P.) in

the CMR core lab using a commercial computer workstation (Extended Workstation; Philips Healthcare) and using commercially available analysis software (QMass and QFlow, Medis, The Netherlands). We used CMR, by measuring area change during the cardiac cycle, paired with brachial and central BP measurements to allow quantification of local arterial **strain** (relative change in diameter), **compliance** (absolute change in diameter in response to a change in pressure), **distensibility** (relative change in diameter in response to a change in pressure) and the **aortic stiffness β index** (distensibility using the logarithmic conversion of the relative pressure). Ventricular function and mass were calculated using standard techniques. Cross-sectional areas of the AAO, and proximal, mid and distal DAO were directly planimetered at peak systole and mid diastolic frames to calculate parameters of segmental aortic stiffness as previously described.[395] PWV was measured using the transit-time method.[233] PWV was calculated for the entire aorta (AAO to distal DAO), as well as in the following segments: AAO to proximal DAO, proximal DAO to mid DAO, and mid DAO to distal DAO. Aortic arch shape was classified, and the aortic arch index calculated as previously described.[371]

6.1.4. *Rationale*

The CoA treatment affects the elasticity of the isthmus, and this may alter global aortic stiffness. Arterial stiffness is often assessed by PWV, which measures the speed of the arterial pulse propagation through the arterial system. There are several approaches to measuring PWV.

In LOVE-COARCT, we used two methods to measure PWV. The first was applanation tonometry, the most widely accepted method for estimating PWV, which uses a probe or tonometer to record the pulse wave with a transducer. Both the NIHem (Cardiovascular Engineering, Inc., Norwood, MA USA) and the SphygmoCor (AtCor Medical, West Ryde, NSW, Australia) devices have been validated in large cohort trials.[267] We used both devices, based on local availability.

A potential pitfall of this technique is that it assumes a homogenous stiffness across the aortic length and does not take into consideration vessel stenosis or distortion causing incorrect estimation of true carotid to femoral artery length. Therefore, in LOVE-COARCT we also used CMR to measure PWV. This technique enables the detection of more subtle changes in segmental stiffness, above vs. below the CoA site and with the use of real aortic travel paths to circumvent these issues. CMR has been validated against noninvasive[279] and invasive[396] techniques to calculate PWV,[397] including the ascending-to-descending aorta PWV.[233]

The measurement of the diameter vs. pressure relationships requires direct visualization of the artery, by echo-tracking or CMR. We chose the latter, since this was our chosen approach for PWV measurement. The choice of echography would require that our patients performed an additional exam in an already lengthy study protocol.

6.2. Endothelial Function

6.2.1. *Measurements*

Endothelium-dependent **RHI** and **AIx** were measured using the Endo-PAT 2000 system (Itamar Medical, Caesarea, Israel) (**Table 8**)

Table 9. Endo-PAT variables

Variables	Formulas and units
RHI	
AIx	%
AI@75	%

AIx = augmentation index; AIx@75 = augmentation index at 75 beats per minute; RHI = reactive hyperemia index

6.2.2. *Manual of Operations for Endothelial Function*

The testing room was arranged to provide a quiet, restful environment with a comfortable temperature of 22 to 24°C. Before testing, subjects were asked to fast overnight for 12 hours, except for the consumption of water. Unless the patients were taking a daily vitamin, they were asked to refrain from taking vitamin pills and over-the-counter medications; in the case that an over-the-counter medication was used, it was documented.

The Endo-PAT (Itamar Medical Ltd, Caesarea, Israel) testing protocol,[304] was performed in the morning (starting time between 8 and 11:00 am) and fasting. Any restrictive clothing that could interfere with blood flow to the arms or fingers was removed, including heavy coats or clothes with thick sleeves, watches or rings or other jewelry on the hands and fingers, and long fingernails shortened with a fingernail clipper.

Non-invasive pneumatic probes were placed on the index fingers of both hands. The pulse wave amplitude was recorded continuously from both index fingers. Reactive hyperemia was performed by achieved by occlusion of the brachial artery of one arm with a BP cuff for 5 minutes (to 200-220 mm Hg). The tracing in the non-occluded arm will serve as a control for changes in overall physiologic state. The Endo-PAT data was analyzed with the proprietary software package, without any input from the examiner. The Endo-PAT index is defined as the ratio of the average pulse amplitude during the 1-minute period beginning after exactly 90 seconds of reactive hyperemia compared with the average pulse amplitude during the 210-second pre-occlusion baseline period.

6.2.3. *Rationale*

In LOVE-COARCT, we used Endo-PAT because analysis of the pulse waveform allows for an automated calculation of flow-dependent, endothelium-mediated vasodilation in one arm, while the contra-lateral serves as a control. Therefore, this is a patient standardized method, which is important in children, in whom normative are beginning to be established.[301] It is also an easy to perform method, with reliable results. Nevertheless, few studies have been performed in congenital heart disease.[395,396] A potential pitfall of this technique is that the associated vasodilation is not entirely NO-dependent and there is an interaction with autonomic nervous system. Our research protocol included measures to minimize the influence of the autonomic nervous system, including fasting and avoidance of food with high NO content.

6.3. Pulse Waveform Analysis

6.3.1. *Measurements*

CAP and **PP** were measured using applanation tonometry). **AIx** was measured using applanation tonometry and Endo-PAT (**Table 7** and **Table 9**).

6.3.2. *Manual of Operations*

Please refer to Methods, sections 6.1.2 and 6.2.2.

6.3.3. *Rationale*

In CoA, the stiff ascending aorta and the repaired aortic isthmus may be important reflecting sites and thus impact the pulse waveform. The non-invasive analysis of the pulse waveform by tonometry and Endo-PAT have been shown to be reliable in prior studies.[267] There is a lack

of consensus regarding the optimal method to estimate the CAP curve using tonometry. The NIHem system assumes that carotid artery pulse waveform accurately reflects the central aortic waveform and therefore, the pulsed wave analysis is automatically calculated from the carotid waveform. The SphygmoCor device uses a generalized transform function to generate a central aortic PP curve from the radial or carotid pressure tracings. This transfer function has not been validated in children. To maintain consistency between data acquired on each device in our largely pediatric group, we didn't use the transfer analysis and used the non-processed, signal-averaged carotid tracing as the central aortic tracing. This tracing was digitized to calculate the CAP, following a previously published approach (**Fig. 20**):[393, 394]

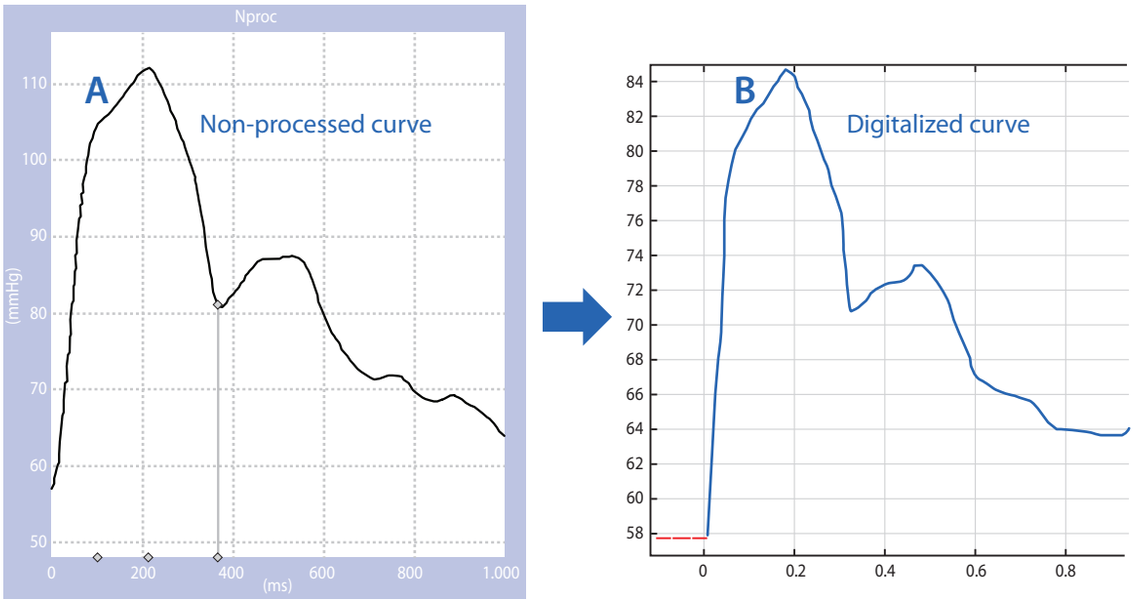

Fig. 20. Process to obtain central aortic pressure from SphygmoCor. *Panel A (left) depicts a pressure curve that was obtained with from the transducer placed in the carotid artery and exported directly from the SphygmoCor software. This tracing is a non-processed (Nproc) curve (no generalized transfer function was applied to transform it into a mathematically generated central aortic pressure curve). This curve is digitalized, point by point, and calibrated with the mean and diastolic blood pressure, which is shown in Panel B (left). Note that the pressure scale is distinct between the two curves. (images from one of LOVE-COARCT's patients).*

6.4. BP Phenotype

6.4.1. *Measurements*

The BP phenotype was measured using several techniques including auscultatory **right arm BP measurement**, measurement of **BP gradient between arm and leg**, BP response during treadmill **exercise stress test** (EST) and **ABPM.** (**Table 9**)

Table 10. BP profile variables

Variables	Formulas and units
Office BP	
Residual SBP gradient	Supine and automated; mm Hg
Right arm BP	Seated and manual; mm Hg
ABPM	
24h average systolic and diastolic BP	mm Hg
Daytime average systolic and diastolic BP	mm Hg
Nighttime average systolic and diastolic BP	mm Hg
24h systolic and diastolic load	%
Diurnal systolic and diastolic dipping	%
Exercise test	
Exercise duration	minutes
Pre-Exercise SBP gradient	mm Hg
Pre-Exercise SBP gradient	mm Hg
Peak exercise BP	mm Hg
Exercise HTN	If systolic BP is ≥220 mm Hg

ABPM = ambulatory blood pressure monitor; BP = blood pressure; DBP = diastolic blood pressure; HTN = hypertension; SBP = systolic blood pressure

6.4.2. *Manual of operations for BP Phenotype*

For **measurement of the right arm, auscultatory BPs**, the patient was seated with the feet flat on the floor, with the knees at 90-degree angle and the back supported. After 5 minutes of resting quietly, with no conversation or television, the auscultatory BP was obtained in the right arm. For cuff choice, the length of the Bladder encircled no less than 80% and no more than 100%, of the bicep and the width of Bladder encircled no less than 40% and no more than 50%, of the circumference of patient's arm circumference, measured at the widest area of bicep, midway between the tip of the patient's shoulder and the tip of the patient's elbow. The patient's right arm was placed at heart level, supported at the level of the nipple by resting arm on a table or chair arm or propped on a pillow. The stethoscope's bell was

placed over the patient's brachial pulse. The cuff was inflated up to 140 mm Hg and deflated slowly while listening for the Korotkoff sounds, systole being number when the sound is first heard consistently and diastole when the last pulsation is heard, or when it muffles. If pulsations were immediately audible, the cuff was deflated entirely, and the patient allowed to sit quietly for one minute. Then, the cuff was again inflated to 160 mm Hg (or higher) and the steps above were followed. This procedure was repeated until the BP is not immediately audible. Three BP were obtained, allowing one minute between deflation and re-inflation of the cuff for each measurement. The average of the 2nd and 3rd measurements was considered the final right arm BP and interpreted according to the published guidelines for children[400] and adults.[401]

While the patient was supine, two sets of **four extremity, automated BPs, were measured with the automated BP monitor (Dinamap)**. The BP pressure gradient was registered, between the second systolic right arm measurement and the highest of the two legs systolic second measurements.

For the **ABPM measurement**, the choice of the cuff followed the same guidelines described for manual auscultation of right arm BP. Cuff inflation was programmed for 15 to 20-minute intervals. During nighttime, intervals were wider, but not fewer than one per hour and preferably more. The patient recorded the sleep time, wake time, and any periods of vigorous exercise. The patient was instructed to avoid direct contact of the monitor with water and participation in activities that could damage it. The study was considered adequate if there was a record of at least one reading per hour, i.e. no more than 1 hour between consecutive readings for a full 24-hour study. If less than 12 hours were recorded, the ABPM data was considered inadequate. The diurnal pattern was determined by the patient diary. Vigorous exercise periods were excluded. Patients were staged as having ambulatory HTN, masked HTN, white coat HTN or normotensive, according to the age-based normative tables based on statements for children and adolescents[402] and adults.[403] Patients currently on antihypertensive medication were also classified into the hypertensive group (**Table 11**):

Table 11. Classification of BP phenotype by ABPM

Classification	Office BP SBP or DBP *	24h Mean ABPM SBP or DBP †
Non-hypertensive	Pediatric: <95th %tile Adults: <140/90 mm Hg	Pediatric: <95th %tile Adults: <135/85 mm Hg
White Coat HTN	Pediatric: ≥95th %tile Adults: >140/90 mm Hg	Pediatric: <95th %tile Adults: <135/85 mm Hg
Masked HTN	Pediatric: <95th %tile Adults: <140/90 mm Hg	Pediatric: >95th %tile Adults: >135/85 mm Hg
Ambulatory HTN	Pediatric: >95th %tile Adults: >140/90 mm Hg	Pediatric: >95th %tile Adults: >135/85 mm Hg

AMBP = Ambulatory blood pressure monitoring; BP = Blood Pressure; ABPM = Ambulatory Blood Pressure Monitoring; Pediatric patients have age < 18yo and adult patients age ≥ 18yo; %tile = percentile; BP = blood pressure; DBP = diastolic blood pressure; HTN = hypertension; SBP = systolic blood pressure.

* For pediatric patients, based on the National High Blood Pressure Education Program Task Force normative data[400]; for adult patients, based on the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure report.[401]

† For pediatric patients, based on normative pediatric ABPM values from the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young; [402] for adult patients, based on the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research report.[404]

Before the **exercise stress test** (EST), for patient safety issues, medical history, medications, activity level and symptoms were reviewed, and the EST protocol explained. Antihypertensive medications were continued the day of testing. The patient was asked to lay supine, and a right arm and right or left leg BP measured using a commercial oscillometric and appropriately sized cuff-bladders were recorded as pre-exercise BP values and gradient. The patient then stepped onto the treadmill and instructed to hold the handlebar throughout the test. We used the standard Bruce treadmill protocol and, when available, a Met Cart. As the patient exercised, their symptoms and ECG were continuously monitored. At 2-mins of each stage, a BP was taken in the right arm by having the patient take their hand off the treadmill and hold onto the arm of the person performing the test. The test was terminated when the patient could longer continue the exercise, reached a systolic BP higher than 240mm Hg, had clinically relevant

symptoms or ECG changes. Immediately after the exercise ended, BP in the right arm and the left leg was recorded in a supine position. For the recovery period, the patient set upright in a chair, and right arm BP was recorded at 1, 3, 5, and 7 mins of recovery, at which time the test is ended. When available, cardiorespiratory physiological data was documented.

6.4.3. *Rationale*

It is well known that the BP phenotype is abnormal despite successful treatment of CoA. We were careful to implement a thorough assessment in LOVE-COARCT. Based on the auscultatory BP and ABPM results, we used the appropriate children and adult guidelines to classify our patients, according to **Table 11**. Patients currently on antihypertensive medication were also classified as hypertensive. Comparing BP values between children and adults is difficult, because the definition of HTN in the former is based on normative values that depend on somatic measurements, while the latter use pre-defined cutoff values. This challenge was present in the design of the LOVE-COARCT protocol, since there is a diverse current age in the enrolled patients. However, it was possible to create discrete categories for the office and ABPM HTN definitions, since the office pediatric[400] and adult[400] reports, and the ABPM pediatric[402] and adult[404] reports are harmonized and use the same definitions. However, there are no such documents for the EST in children and adults, and we could not create discrete categories to compare exercise-induced HTN in different age groups, and therefore limited our analysis to the continuous variables.

6.5. LV Mass and Aortic Morphometrics

6.5.1. *Measurements*

LV mass, the size of the aorta and aortic arch shape were measured by CMR.

6.5.2. *Manual of Operations fo LV Mass and Aortic Morphometrics*

Please refer to Methods, section 6.1.3.

6.5.3. *Rationale*

The altered BP phenotype that persists after CoA treatment represents an increase in afterload that leads to LV hypertrophy. CMR is a well-established method for calculation of LV mass, volumes and function. Our CMR protocol included sequences that allowed this quantification. The aortic size and shape can also be accurately measured with CMR.

6.6. Biomarkers

6.6.1. *Measurements*

We measured biomarkers of endothelial function (total oxides of nitrogen- **NOx** and **ADMA**), inflammation (**hs-CRP**), vascular wall function (**VCAM-1** and **IL-1β**) and vascular remodeling (**MMP-2**; **MMP-9** and **TGF-β1**). NOx was determined by chemiluminescence (Sievers NOAnalyzer 280i) and all remaining measurements were performed with appropriate enzyme-linked immunosorbent assay (ELISA) kits: ADMA (Sunred Biological Technology, Shanghai, China); hs-CRP (BoosterBio, Pleasanton, USA); VCAM-1; IL-1β; MMP-9; MMP-2 and TGFβ-1 (RayBiotech, Inc. Norcross, USA) (**Table 12**):

Table 12. Biomarkers variables

Variable	Units
NOx	ug/ml
ADMA	ng/L
High Sensitivity CRP	mg/L
VCAM-1	ng/ml
IL-1β	pg/ml
TFG-β	ng/mL
MMP-2/Gelatinase A	ng/ml
MMP-9/Gelatinase B	ng/ml

ADMA = Asymmetric Dimetilarginine; HDL = High-density lipoprotein cholesterol; hs-CRP = High sensitivity C-Reactive Protein; IL-1β = Interleukin 1 beta; LDL = Low-density lipoprotein cholesterol; MMP-2 = Matrix Metalloproteinase-2; MMP-9 = Matrix Metalloproteinase-9; NOx = Nitric Oxide; TFG-β = Transforming Growth Factor beta; VCAM-1 = Vascular Cell Adhesion Molecule 1

6.6.2. *Manual of Operations for Biomarkers*

The patients followed a low-nitrate diet for three days before the blood sample collection, which avoided of a list of foods with a high content in nitrites that influence nitric oxide determination, including bacon, beets, broccoli, canned food, cauliflower, celery, Chinese cabbage, corned beef, ham, hot dogs, lettuce, old cheese, radish, salami, sausages, smoked

fish, spinach and turnip. After an overnight fast (for 12h), samples were collected by venipuncture from catheters maintained with saline only, since heparin interferes with the accuracy of the biomarkers assessed. The first 5-10mL of blood were discarded and 2.7 ml of venous blood were collected into 3.2% sodium citrate (light-blue) tubes (BD Vacutainer®), and into plastic microtubes (Safe-Lock Eppendorf). Within 3 hours of collection, samples were centrifuged for 20 minutes at 3000g (4°C). Aliquots of 250µl of the supernatant were collected into 14 labeled microtubes of 1.5ml and immediately stored at-80ºC until shipping to the Biomarkers Core Laboratory.

Aliquots for NOx analysis were deproteinized using cold ethanol precipitation methodology. Ethanol was refrigerated to 0°C and added to the plasma sample in a 1:3 proportion. After letting it stand at 0°C for 30 minutes, the sample was centrifuged at 14000rpm for 10 minutes. The supernatant was then removed for analysis. The quantification of plasma NO levels was carried out using a nitric oxide analyzer, the Sievers Instruments NOA 280i™, a high sensitivity detector of that allows determination of NO based on a chemiluminescence reaction between NO and ozone.

Plasma ADMA; VCAM-1; hs-CRP; IL-1β; MMP-2 and MMP-9 were quantified using the following double-antibody sandwich enzyme-linked immunosorbent assay ELISA kits: Human asymmetrical dimethylarginine, ADMA (Sunred Biological Technology, Shanghai, China); high-sensitivity C Reactive Protein (hs-CRP, BoosterBio, Pleasanton, USA); vascular cell adhesion molecule 1 (VCAM-1); interleukin-1-Beta (IL-1β); MMP-9/Gelatinase A ; MMP-2/Gelatinase B and transforming growth factor beta (TGFβ-1) (RayBiotech, Inc. Norcross, USA).

6.6.3. *Rationale*

We chose a wide variety of biomarkers, to encompass several pathways that may be involved in the genesis or maintenance of vascular dysfunction in patients with treated CoA, namely the NO-dependent endothelial function, systemic and local wall inflammation, and aortic wall remodelling. All of these tests were obtained from a single, fasting blood sample, that was collected at the beginning of the study visit, for patient convenience.

6.7. Cardiovascular Health Assessment

6.7.1. *Measurements*

We assessed health factors (BP, total cholesterol, plasma glucose), behaviors (smoking, body mass index BMI, physical activity and diet) and family history of cardiovascular disease and risk factors.

6.7.2. *Manual of Operations for Cardiovascular Health Assessment*

The following questionnaires were used as a lifestyle questionnaire (**Table 12**) and family history questionnaire (**Table 13**):

Table 13. Lifestyle questionnaire questions

Lifestyle Questionnaire
On an average weekday, how many hours do you watch TV?
On an average weekday, how many hours do you play video/computer games or use a computer for something that is not school/work related?
In the past week, how many days were you/was your child physically active for a total of at least 30 minutes per day?
In the past week, how many days did you/your child eat breakfast? In the past week, how many days did you/your child eat food from a fast food restaurant?
In the past week, how many days did all or most of your family sit down and eat dinner at home?
On an average weekday, how many hours of sleep do you get a night?
Have you smoked one or more cigarettes in the past month? If yes, please quantify.
Were you previously a smoker?
Do you live in a household with a smoker?

Table 14. Family history questionnaire

Family History Questionnaire
Biological relatives of you/your child with Overweight/Obesity
Biological relatives of you/your child with Type 2 Diabetes
Biological relatives of you/your child with High Blood Pressure
Biological relatives of you/your child with High Cholesterol
Biological relatives of you/your child with Heart Disease/Stroke
(all answers had the following options: No/ Parents/ Siblings/ Grandparents/ Aunts)

6.7.3. Rationale

Cardiovascular health is very important in patients with CoA, who experience early CVD (please refer to Background, section 1.9.1). We implemented a simple questionnaire to assess family history of CV disease and ICVH according to the procedures and recommendations of the American Heart Association.[405]

7. STATISTICAL ANALYSIS

The statistical analysis was done in the Biostatistics Core Lab (Responsible: Kimberlee Gauvreau) from the Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, USA. Analyses were performed in SAS (version 9.4, Cary, NC, USA).

7.1. Adjustment for Confounders

Since several known factors other than treatment modality can influence vascular function, we will frequency-match our treatment groups for documented confounders. The confounding variables included: (a) age at treatment; (b) current age; and (c) BAV as it is associated with impaired aortic elasticity.[406] Because of the relatively large number of matching variables and three treatment groups, matching individual subjects was not feasible. During recruitment,

we attempted to frequency match the three treatment groups. During analysis, the treatment groups were compared for each of these confounding variables and appropriate adjustments were made using multivariable modeling, as needed. Age at treatment and presence of a BAV were thought to be possible confounding variables and were observed to differ by treatment group; therefore, linear and logistic regression models were used to adjust for confounding when comparing selected outcome variables across treatment groups. In these models, the surgical group was used as the reference category against which BD and stent were compared. Each model adjusted for age at treatment as a continuous variable, and presence of a BAV as a binary variable.

7.2. Analytic Plan.

Categorical patient characteristics, clinical variables, and outcomes were summarized as frequencies and percentages and compared across the three treatment groups using Fisher's exact test. Continuous variables that which were approximately normally distributed were summarized using means and standard deviations and compared using one-way analysis of variance; continuous variables which were not normally distributed were summarized using medians and ranges and compared using the Kruskal-Wallis test.

Our primary outcome variable was cfPWV assessed by tonometry. Differences in cfPVW across groups were explored using one-way analysis of variance. When differences in matching variables were detected among the groups, adjustments were made using analysis of covariance. Post-hoc analyses were performed as necessary.

Sample size estimates were obtained based on prior data that showed that ascending-descending PWV measured by CMR is 3.3±0.6 m/s in normal subjects and 4.7±1.1 m/s after CoA surgery.[233, 407] Sample size estimates for comparison of PVW between three equal-sized treatment groups (assuming overall significance level=0.05 and power=0.8) are shown in **Table 15**. We planned on recruiting 24 to 30 patients in each group for a total sample size of 72 to 90:

Table 15. Sample size calculation

Smallest Mean PWV (m/s) Among Groups	Largest Mean PWV (m/s) Among Groups	Standard Deviation	Sample Size for Each Group	Total Sample Size
4.0	4.8	1.0	30	90
4.0	4.8	1.1	36	108
4.0	4.8	1.2	43	129
4.4	5.3	1.0	24	72
4.4	5.3	1.1	29	87
4.4	5.3	1.2	34	102

PWV = pulse wave velocity; m/s = meters per second

7.3. Choice of the Primary Outcome Variable

There is no single, universally accepted marker of vascular dysfunction. Therefore, we chose cfPWV as our primary outcome variable because: (a) it has been validated as a simple, accurate and reproducible measure of arterial stiffness with a proven association to hard cardiovascular outcomes and (b) it can be reliably measured by two different techniques, applanation tonometry, and CMR.

7.4. Choice of the Secondary Outcomes Variables

No single parameter encompasses all aspects of vascular function. Therefore, including other parameters such as other measures of arterial stiffness, endothelial function, pulse waveform analysis, BP phenotype, blood biomarkers and LV mass allowed us to perform a comprehensive assessment of vascular function in small and large arteries.

V. RESULTS

Below is **Fig. 21 (central illustration)**, that shows in one figure a comparison of the key vascular function parameters from the LOVE-COARCT study between the three groups:

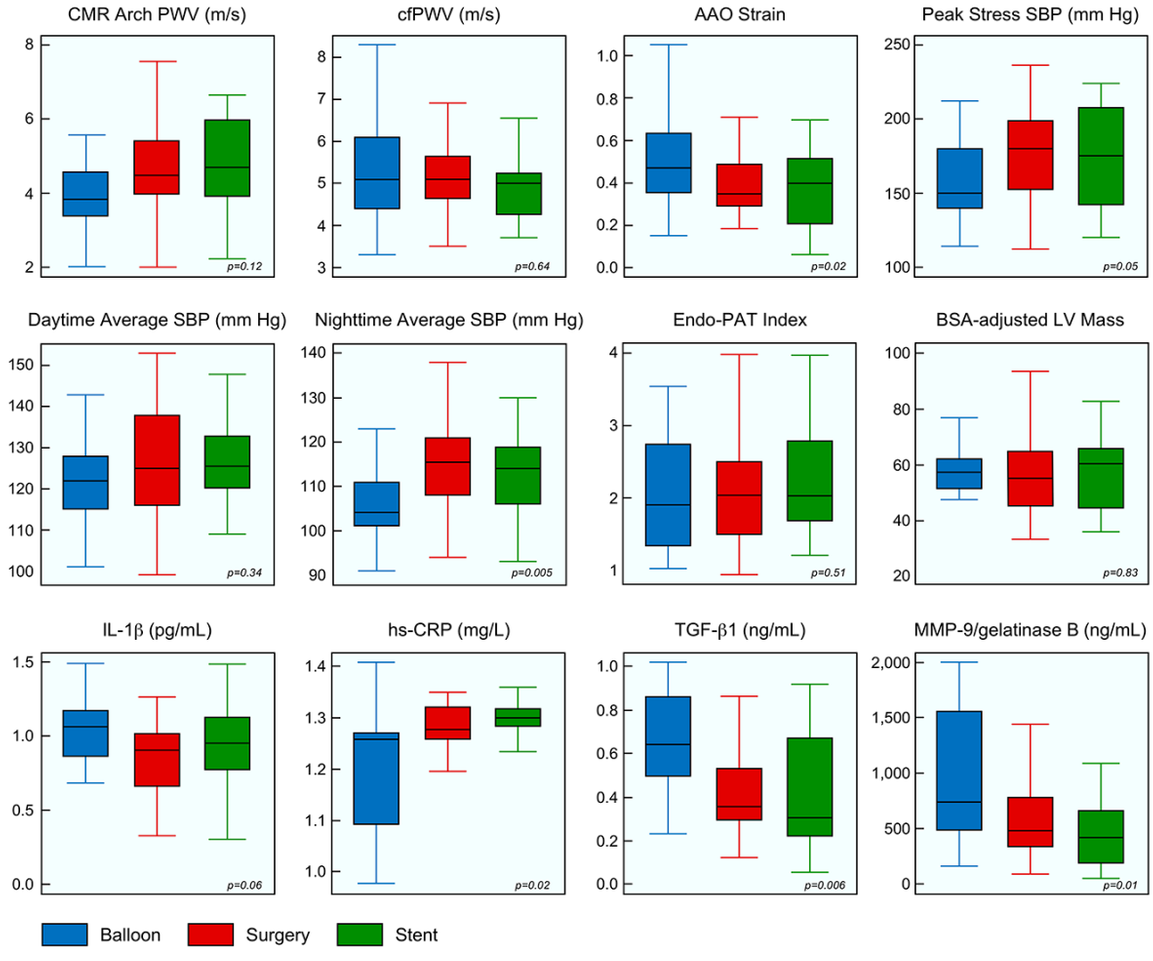

Fig. 21. Comparison of key vascular function parameters between groups (Central Illustration).

BD in blue; Surgery in red; and Stent in green. AAO = ascending aorta; BSA = body surface area; CMR = cardiac magnetic resonance; Endo-PAT = endothelial pulse amplitude testing; hs-CRP = high sensitivity C-reactive protein; IL-1β = interleukin 1 beta; LV = left ventricle; MMP-9 = matrix metalloprotease 9; PWV = pulse wave velocity; SBP = systolic blood pressure; TGF- β1 = transforming growth factor beta-1

A detailed presentation of the LOVE-COARCT results is presented in the follow pages.

1. STUDY SUBJECTS

Patient characteristics by treatment group are summarized in **Table 16**.

Table 16. Patient characteristics at treatment

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p Value
Age at treatment (years)	**6 (1, 26)**	**5 (1, 17)**	**15 (7, 26)**	**<0.001**
SBP gradient (mm Hg)	43.7 ± 19.3	34.6 ± 15.0	38.4 ± 21.0	0.29
TAA diameter z-score	-1.9 ± 1.0	-1.5 ± 1.4	-1.9 ± 0.8	0.38
Isthmus diameter z-score	-3.59 ± 1.21	-3.92 ± 0.89	-3.31 ± 1.37	0.32
Initial Doppler gradient (mmHg)	48.0 ± 14.7	47.9 ± 14.8	52.5 ± 20.3	0.60
Male sex	79%	74%	75%	0.94
Bicuspid aortic valve	71%	45%	50%	0.13

Values are mean ± standard deviation, median (minimum, maximum), or percent. SBP = systolic blood pressure; TAA = transverse aortic arch

Among pre-treatment characteristics, the treatment groups were similar with respect to CoA severity, sex distribution, and the prevalence of BAV. However, patients treated with a stent were older at the time of treatment compared to those treated with surgery or BD.

Table 17. Patient characteristics at enrollment

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p Value
Age at enrollment (years)	15 (8, 33)	17 (11, 26)	20 (9, 33)	0.12
BMI at enrollment	22 (15, 32)	21 (16, 33)	23 (16, 38)	0.69
SBP gradient at enrollment (mm Hg)	-7.1 ± 14.0	-3.0 ± 12.3	-3.7 ± 14.5	0.52
NYHA class at enrollment				0.37
Class I	89%	100%	92%	
Class II	11%	0%	8%	
Metabolic profile at enrollment				
Total cholesterol, mg/dL	159 (112, 210)	153 (123, 229)	152 (108, 227)	0.59
LDL, mg/dL	86 (53, 145)	81 (59, 179)	85 (44, 130)	0.66
HDL, mg/dL	53 (34, 90)	48 (31, 90)	51 (32, 88)	0.99
Triglycerides, mg/dL	76 (29, 224)	52 (29, 149)	74 (29, 167)	0.07
Plasma glucose, mg/dL	82 (74, 98)	81 (59, 93)	86 (63, 108)	0.15
Insulin, uIU/mL	6 (3, 44)	6 (3, 17)	7 (2, 20)	0.86
Hemoglobin A1c, %	5.3 (4.1, 5.7)	5.3 (4.4, 5.7)	5.3 (4.8, 5.9)	0.60
Anti-HTN Medication	14%	26%	33%	0.14
β-blockers	2 (7)	5 (22)	4 (17)	0.12
ACE inhibitors	5 (18)	2 (9)	3 (13)	0.88
ARBs	0 (0)	0 (0)	1 (4)	0.94

Values are mean ± standard deviation, median (minimum, maximum), or percent. ACE inhibitors = angiotensin-converting-enzyme blockers; ARBs = angiotensin II receptor blockers; β-blockers = betablockers; BSA = body surface area; BMI = body mass index (weight (kg)/ height (m)2); HTN = hypertension; LDL = low density lipoprotein; HDL = high density lipoprotein; NYHA = New York Heart Association; SBP = systolic blood pressure; TAA = transverse aortic Arch

The mean age (min, max) of our entire cohort was 18 (8, 33) and 76% were male. At study enrollment, the treatment groups were similar with respect to baseline characteristics including age and body mass index at enrollment, reCoA severity, and metabolic profile.

2. AORTIC STIFFNESS

Results of aortic stiffness assessment by CMR and applanation tonometry are summarized in **Table 18**, **Table 19** and in the **Fig. 21**.

Table 18. Aortic stiffness results by CMR

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p Value
PWV (m/s)				
Global (AAO to Distal DAO)	4.0 ± 0.5	4.2 ± 0.9	4.2 ± 0.7	0.72
Arch (AAO to prox DAO)	4.7 ± 1.5	4.0 ± 1.2	5.5 ± 3.8	0.12
Prox to Mid DAO	3.8 ± 0.9	4.0 ± 1.3	3.9 ± 1.4	0.87
Mid to Distal DAO	4.4 ± 1.6	4.8 ± 1.7	4.5 ± 1.5	0.70
Strain				
AAO	**0.38 ± 0.14**	**0.51 ± 0.25**	**0.36 ± 0.19**	**0.02**
Proximal DAO	0.27 ± 0.09	0.31 ± 0.13	0.30 ± 0.15	0.47
Mid DAO	0.37 ± 0.11	0.36 ± 0.10	0.36 ± 0.16	0.97
Distal DAO	**0.37 ± 0.14**	**0.40 ± 0.12**	**0.30 ± 0.12**	**0.04**
Distensibility (10-3mm Hg-1)				
AAO	**7.8 ± 3.6**	**9.8 ± 5.2**	**6.6 ± 4.3**	**0.05**
Proximal DAO	5.6 ± 2.1	6.1 ± 3.3	5.6 ± 2.7	0.71
Mid DAO	7.5 ± 2.5	6.9 ± 3.3	6.8 ± 3.4	0.67
Distal DAO	7.8 ± 4.1	7.5 ± 3.1	5.9 ± 3.2	0.15
Compliance (mm2 mm Hg-1)				
AAO	**2.23 (1.21, 4.08)**	**2.90 (1.61, 5.93)**	**2.35 (1.15, 7.35)**	**0.02**
Proximal DAO	1.05 (0.65, 2.83)	1.24 (0.19, 2.82)	1.26 (0.64, 2.84)	0.15
Mid DAO	1.16 (0.54, 2.54)	0.91 (0, 2.28)	1.07 (0.50, 2.02)	0.58
Distal DAO	0.63 (0.27, 1.85)	0.74 (0, 1.66)	0.51 (0.08, 1.83)	0.09
β stiffness index				
AAO	**1.76 ± 0.73**	**1.59 ± 1.15**	**2.49 ± 1.48**	**0.02**
Proximal DAO	2.53 ± 1.59	2.63 ± 1.89	2.50 ± 0.96	0.96
Mid DAO	1.75 ± 0.76	1.93 ± 0.75	2.15 ± 1.11	0.26
Distal DAO	1.84 ± 0.91	1.72 ± 0.68	2.98 ± 3.70	0.11

Values are mean ± standard deviation. AAO = ascending aorta; AI = augmentation index; aortic arch PWV = AAO to proximal DAO pulse wave velocity; DAO = descending aorta; Endo-PAT = endothelial pulse amplitude testing; HR = heart rate; m/s = meters per second; PP = Pulse pressure; SBP = Systolic blood pressure; total PWV = AAO to distal DAO pulse wave velocity.

Combining the three treatment groups, the results for PWV (in m/s) were 4.1 ± 0.7 for global PWV, 4.8 ± 2.5 for arch PWV, 3.9 ± 1.2 for mid aorta, and 4.5 ± 1.6 for distal aorta.

Table 19. Aortic stiffness results by applanation tonometry

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p Value
cfPWV (m/s)	5.2 ± 0.9	5.3 ± 1.1	5.0 ± 0.9	0.64
AIx at HR 75 bpm (%)	-14 ± 13	-13 ± 21	-6 ± 18	0.24
Central SBP (mm Hg)	114 ± 18	109 ± 14	112 ± 21	0.60
Central PP (mm Hg)	50 ± 20	46 ± 13	45 ± 19	0.49

Values are mean ± standard deviation. AIx = augmentation index; cfPWV = carotid-femoral pulse wave velocity; DAO = descending aorta; HR = heart rate; PP = Pulse pressure; SBP = Systolic blood pressure

The combined cfPWV of the three treatment groups is 5.2 ± 1.0 m/s. At comparable distending pressures (**Table 20**), overall PWV was similar among the treatment groups by both CMR and applanation tonometry (**Fig. 21**). In segmental PWV measurements by CMR, aortic arch PWV was lowest in the BD group, but the difference did not reach statistical significance (**Fig. 21**). Among CMR segmental aortic stiffness parameters, BD patients had the most distensible AAO, while stent patients had the least distensible AAO, with surgical patients demonstrating intermediate values (**Fig. 21**). Compared to stent patients, BD patients showed 48% higher AAO distensibility and 27% lower aortic arch PWV. Segmental stiffness parameters were mostly similar across treatment groups at the DAO (proximal, mid, and distal), except for distal DAO strain, which was lowest in the stent group.

To assess for potential confounding by age at treatment or BAV (known to be associated with impaired aortic elasticity)[406] on the relationship between treatment modality and aortic stiffness, we used multivariable modeling for key stiffness parameters. The univariate relationships shown in **Table 18** and **Table 19** remained unchanged in the multivariable models after adjustment for the potential confounding variables (age at treatment, and BAV) (details in **Table 30**).

3. ENDOTHELIAL FUNCTION

Endothelial function assessed using the Endo-PAT index was similar across treatment groups (**Table 20** and **Fig. 21**).

Table 20. Endo-PAT results

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p Value
Endo-PAT index (RHI)	2.15 ± 0.77	2.00 ± 0.78	2.25 ± 0.68	0.51
AIx @ 75 bpm	-6 ± 12	-4 ± 14	2 ± 11	0.14

Values are mean ± standard deviation. BPM = beats per minute; Endo-PAT = endothelial pulse amplitude testing; RHI = reactive hyperemia index.

The combined RHI of the three treatment groups was 2.14 ± 0.74. The univariate relationships remained unchanged in the multivariable models after adjustment for the potential confounding variables (age at treatment, and BAV) (details in **Table 30**).

4. PULSE WAVEFORM ANALYSIS

The pulse waveform analysis (central SBP and PP measured with applanation tonometry, and AIx measured with both applanation tonometry and Endo-PAT) did not show any differences between the three treatment groups (**Table 19** and **Table 20**).

5. BP PHENOTYPE

Results of office BP measurements are summarized in **Table 21**, ABPM results are in **Table 22**, and EST results are in **Table 23**. There were no significant differences across treatment groups concerning the prevalence of HTN by office measurements or ABPM, and average systolic and diastolic BP by ABPM. However, the BD group showed lower nighttime BP and less impairment in diurnal variation, compared to the stent and surgery groups (**Fig. 21**).

Table 21. Office BP results

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
Office BP				0.20
Normal	15 (54%)	13 (57%)	7 (29%)	
Pre-HTN	10 (36%)	8 (35%)	15 (63%)	
Stage 1 HTN	3 (11%)	2 (9%)	1 (4%)	
Stage 2 HTN	0 (0%)	0 (0%)	1 (4%)	

Values are mean ± standard deviation, or number (percent). BP = blood pressure; HTN = hypertension

Combining the three treatment groups, the office BP in LOVE-COARCT shows that 44% of the patients had pre-HTN and 9% had either stage 1 or stage 2 office HTN, and the ABPM results show that 36% have either HTN/masked HTN, or anti-HTN medication.

Table 22. ABPM results

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
24-hr average SBP (mm Hg)	123 ± 13	118 ± 9	124 ± 10	0.19
24-hr average DBP (mm Hg)	68 ± 8	66 ± 6	68 ± 8	0.77
Day average SBP (mm Hg)	125 ± 13	122 ± 10	127 ± 10	0.34
Day average DBP (mm Hg)	69 ± 9	69 ± 7	71 ± 9	0.82
Night average SBP (mm Hg)	116 ± 12	106 ± 10	113 ± 10	**0.005**
Night average DBP (mm Hg)	**60 ± 7**	**56 ± 5**	**59 ± 4**	**0.05**
% SBP readings above diurnal threshold	32 ± 29	19 ± 19	30 ± 27	0.19
% DBP readings above diurnal threshold	16 ± 20	13 ± 14	14 ± 16	0.72
Diurnal systolic variation (%)	**7 ± 7**	**13 ± 6**	**11 ± 6**	**0.01**
Diurnal diastolic variation (%)	13 ± 10	19 ± 6	16 ± 7	0.06
Non-dippers (%)	17 (65%)	7 (32%)	12 (55%)	0.08
Classification by ABPM				0.76
No HTN	16 (59%)	18 (82%)	15 (68%)	
White coat HTN	3 (11%)	1 (5%)	1 (5%)	
Masked HTN	6 (22%)	2 (9%)	5 (23%)	
HTN	2 (7%)	1 (5%)	1 (5%)	
Classification including medication use				
HTN/masked HTN, or anti-HTN medication	8 (30%)	9 (39%)	10 (45%)	0.49
No HTN/ white coat HTN	20 (70%)	14 (61%)	14 (55%)	

Values are mean ± standard deviation, or number (percent). ABPM = ambulatory blood pressure measurement; BP = blood pressure; DBP = diastolic blood pressure; Dippers = night-time BP dipping ≥10%, non-dippers = night-time BP dipping <10%; HTN = hypertension; SBP = systolic blood pressure

On EST, there were no significant differences between the treatment groups with respect to exercise duration, peak VO2, VE/VCO2 slope, or upper-lower extremity SBP gradient. (**Table 23**):

Table 23. EST results

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
Exercise duration (minutes)	12 (7,21)	11 (9, 21)	13 (5,17)	0.45
Pre-exercise SBP gradient (mm Hg)	-3 ± 21	1 ± 9	6 ± 18	0.17
Peak-exercise SBP gradient (mm Hg)	32 ± 30	33 ± 22	26 ± 27	0.64
Peak right arm SBP (mm Hg)	**177 ± 35**	**157 ± 27**	**177 ± 33**	**0.05**
Peak right arm DBP (mm Hg)	71 ± 13	75 ± 9	73 ± 11	0.50
VO2 Max (ml/Kg/min)	41 ± 11	32 ± 27	41 ± 11	0.30
VE/CO2 slope	26 ± 4	26 ± 5	26 ± 6	0.98

Values are mean ± standard deviation, or median (minimum, maximum). DBP = diastolic blood pressure; SBP systolic blood pressure; VO2 Max = peak exercise oxygen consumption; VE/CO2 = relationship between ventilation and CO2 output

However, the peak SBP during exercise was lower in the BD group (**Fig. 21**) and this relationship persisted after adjustment for potential confounding variables (age at treatment, and BAV) (details in **Table 30**).

6. LV AND AORTIC MORPHOMETRICS

The treatment groups were similar with respect to LV size, ejection fraction, and mass (**Table 24** and **Fig. 21**):

Table 24. LV measurements by CMR

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
EDV indexed to BSA (ml/m^2)	71 ± 13	76 ± 17	73 ± 18	0.64
Ejection fraction (%)	63 ± 6	61 ± 5	62 ± 5	0.52
Mass indexed to BSA (g/m^2)	56 ± 13	58 ± 9	57 ± 13	0.83

Values are mean ± standard deviation. EDV = end-diastolic volume

Aortic dimensions, including those of the transverse aortic arch, were similar between the treatment groups. Isthmic dimensions were slightly smaller in the BD group compared to the surgical group but could not be measured in stented patients due to ferromagnetic artifact from the stent. Arch shape distribution was also similar between the treatment groups, assessed both qualitatively and quantitatively (using the arch shape index)[408] (**Table 25**):

Table 25. Aortic dimensions and shape by CMR

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
Aortic Diameters (mm indexed to BSA)				
Ascending aorta	19.1 ± 3.0	20.6 ± 3.2	20.7 ± 3.4	0.18
Proximal transverse arch	12.6 ± 1.2	12.8 ± 1.8	12.7 ± 2.9	0.96
Distal transverse arch	11.5 ± 1.7	11.2 ± 1.6	11.9 ± 2.1	0.45
Isthmus	12.6 ± 3.7	10.4 ± 2.8	N/A*	0.03
Descending aorta	12.4 ± 1.1	12.6 ± 1.8	12.5 ± 1.6	0.95
Arch Shape				0.33
Romanesque	11 (39%)	10 (43%)	10 (42%)	
Crenel	2 (7%)	5 (22%)	2 (8%)	
Gothic	14 (50%)	6 (26%)	12 (50%)	
Arch Shape Index	0.64 ± 0.14	0.65 ± 0.11	0.68 ± 0.13	0.64

Values are mean ± standard deviation, or number (percent). * N/A = not available, due to presence of stent artifact. Arch shape index = aortic arch height divided by width; BSA = body surface area

7. BLOOD BIOMARKERS

Patients in the BD group had lower levels of hs-CRP, and higher levels of MMP-9 and TGF-β1 (**Table 25** and **Fig. 21**):

Table 26. Blood biomarkers results

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
NOx (ug/mL)	18 (12, 31)	20 (12, 37)	20 (10, 34)	0.18
ADMA (ng/L)	6 (1, 45)	7 (1, 51)	3 (0, 31)	0.20
hs-CRP (mg/L)	**1.28 (0.74, 1.49)**	**1.26 (0.66, 1.41)**	**1.30 (0.95, 1.46)**	**0.02**
VCAM-1 (ng/mL)	133 (66, 203)	134 (61, 206)	128 (66, 168)	0.42
IL-1β (pg/mL)	0.91 (0.04, 1.26)	1.06 (0.68, 1.98)	0.95 (0.06, 1.49)	0.1
TGF- β1 (ng/mL)	**0.35 (0.12, 1.24)**	**0.64 (0.23, 3.21)**	**0.31 (0.05, 2.07)**	**0.006**
MMP-2/gelatinase A (ng/mL)	1.14 (0.10, 3.37)	1.53 (0.00, 4.93)	0.62 (0.00, 3.62)	0.26
MMP-9/gelatinase B (ng/mL)	**474 (91, 3157)**	**738 (158, 4453)**	**421(487, 1739)**	**0.01**

Values are median (minimum, maximum). ADMA = asymmetric dimethylarginine; hs-CRP = high sensitivity C-reactive protein; IL-1β = interleukin 1 beta; MMP **=** matrix metalloprotease**;** NOx = nitrite/nitrate; TGF- β1 = transforming growth factor beta-1; VCAM-1 = vascular adhesion molecule 1

These differences persisted after adjustment for potential confounders (details in **Table 30**). Levels of other blood biomarkers were similar across the treatment groups.

8. IDEAL CV HEALTH

The only difference between the three treatment groups are in the number of days that the family ate dinner at home together (**Table 27**).

Table 27. Ideal CV Health

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
Hours of TV on average weekday	1.5 (0.5, 6)	2 (0, 5)	1.8 (0, 5)	0.58
Hours of video/computer games on average weekday	1 (0, 6)	2 (0, 5)	1 (0, 5)	0.34
Days physically active for ≥30 minutes in past week	5 (0, 7)	2 (0, 7)	4 (0, 7)	0.13
Days ate breakfast in past week	7 (0, 7)	7 (0, 7)	7 (0, 7)	0.30
Days ate food from a fast food restaurant in past week	0 (0, 7)	0 (0, 7)	1 (0, 7)	0.06
Days family ate dinner at home in past week	4 (0, 7)	7 (4, 7)	5 (0, 7)	0.001
Hours of sleep per night on average week	7.5 (5.5, 10)	8 (7, 11)	7.4 (4, 10)	0.07
Smoked ≥1 cigarette in past month	2 (7)	2 (9)	1 (4)	0.86
Previously a smoker	2 (7)	3 (13)	1 (4)	0.66
Live in household with smoker	7 (25)	6 (26)	2 (8)	0.21
Biological relatives overweight/obese				0.26
Parents/siblings	4 (14)	8 (35)	3 (13)	
Grandparents/aunts/uncles	6 (21)	4 (17)	2 (8)	
Both	5 (18)	2 (9)	4 (17)	
No	11 (39)	9 (39)	15 (63)	
Unknown	2 (7)	0 (0)	0 (0)	
Biological relatives with type 2 diabetes				0.37
Parents/siblings	2 (7)	5 (22)	4 (17)	
Grandparents/aunts/uncles	10 (36)	8 (35)	5 (21)	
Both	1 (4)	0 (0)	0 (0)	
No	13 (46)	10 (43)	15 (63)	
Unknown	2 (7)	0 (0)	0 (0)	

Biological relatives with high blood pressure				0.18
Parents/siblings	5 (18)	3 (13)	7 (29)	
Grandparents/aunts/uncles	13 (46)	11 (48)	5 (21)	
Both	2 (7)	1 (4)	5 (21)	
No	6 (21)	8 (35)	7 (29)	
Unknown	2 (7)	0 (0)	0 (0)	
Biological relatives of with high cholesterol				0.16
Parents/siblings	7 (25)	7 (30)	8 (33)	
Grandparents/aunts/uncles	6 (21)	4 (17)	5 (21)	
Both	5 (18)	6 (26)	0 (0)	
No	8 (29)	6 (26)	11 (46)	
Unknown	2 (7)	0 (0)	0 (0)	
Biological relatives with heart disease/stroke				0.85
Parents/siblings	1 (4)	2 (9)	1 (4)	
Grandparents/aunts/uncles	12 (43)	8 (35)	9 (38)	
Both	0 (0)	1 (4)	0 (0)	
No	13 (46)	11 (48)	14 (58)	
Unknown	2 (7)	1 (4)	0 (0)	

Values are median (minimum, maximum). CV = cardiovascular.

9. ADJUSTMENT FOR POTENTIAL CONFOUNDERS

As seen in **Table 16**, despite efforts at frequency matching, there were differences between the treatment groups with respect to potential confounding variables including age at treatment and the presence of a BAV (known to be associated with impaired aortic elasticity).[406] Analyses to assess the impact of these confounding variables are summarized in **Table 28**, **Table 29** and **Table 30**.

As seen in **Table 28**, age at treatment was significantly associated with AAO strain, Endo-PAT index, right arm diastolic BP, and 24-hour diastolic BP but not with other key outcome variables:

Table 28. Assessment for confounding by age at treatment

	1-3	4-9	10-14	≥15	p Value
MRI proximal PWV (m/s)	4.8 ± 2.1	4.2 ± 1.1	5.6 ± 4.4	4.9 ± 1.3	0.35
AAO strain (%)	**0.48** ± 0.24	**0.44 ± 0.16**	**0.45 ± 0.24**	**0.28 ± 0.15**	**0.02**
cfPWV (m/s)	5.4 ± 1.1	4.8 ± 0.8	5.4 ± 1.1	5.3 ± 0.9	0.13
AI (%)	-12 ± 14	-14 ± 20	-7 ±18	-3 ± 19	0.21
Endo-PAT index	**1.85** ± 0.55	**1.89** ± 0.72	**2.50 ± 0.73**	**2.34** ± 0.75	**0.02**
Right arm SBP (mm Hg)	121 ± 14	117 ± 12	124 ± 13	123 ± 12	0.34
Right arm DBP (mm Hg)	**61 ± 5**	**63 ± 9**	**69 ± 11**	**68 ± 11**	**0.05**
24-hour average SBP (mm Hg)	119 ± 14	120 ± 11	124 ± 8	126 ± 10	0.20
24-hour average DBP (mm Hg)	**66 ± 8**	**64 ± 7**	**69 ± 7**	**71 ± 8**	**0.04**
HTN Classification					0.14
No HTN	7 (58%)	19 (70%)	9 (53%)	6 (35%)	
White coat HTN	1 (8%)	1 (4%)	2 (12%)	1 (6%)	
HTN/Masked HTN/Anti HTN meds	4 (33%)	7 (26%)	6 (35%)	10 (59%)	
Peak exercise right arm SBP (mm Hg)	161 ± 34	169 ± 35	170 ± 27	180 ± 33	0.47
hs-CRP (mg/L)	127 (104, 146)	127 (66, 143)	129 (86, 149)	128 (98, 146)	0.67
MMP-9/gelatinase B (ng/mL)	707 (246, 4228)	411 (91, 2004)	515 (487, 3157)	409 (150, 4453)	0.15

Values are mean ± standard deviation, number (percent), or median (minimum; maximum). AAO = Ascending aorta; AI = Augmentation index; cfPWV = carotid-femoral pulse wave velocity; DBP = Diastolic blood pressure; Endo-PAT = Endothelial pulse amplitude testing; hs-CRP = High sensitivity C-reactive protein; HTN = Hypertension; MMP = matrix metalloprotease; MRI = Magnetic resonance imaging; PWV = Pulse wave velocity; SBP = Systolic blood pressure.

As seen in **Table 29**, the presence of BAV was not signifcanlty associated with any outcome variables:

Table 29. Assessment for confounding by presence of BAV

	BAV	No BAV	p Value
MRI proximal PWV (m/s)	5.2 ± 3.1	4.2 ± 1.1	0.07
AAO strain (%)	0.37 ± 0.19	0.46 ± 0.21	0.07
cfPWV (m/s)	5.2 ± 0.8	5.1 ± 1.2	0.75
AI (%)	-7 ± 18	-14 ± 19	0.14
PAT index	2.13 ± 0.75	2.17 ± 0.75	0.79
Right arm SBP (mm Hg)	122 ± 12	119 ± 13	0.21
Right arm DBP (mm Hg)	66 ± 10	64 ± 9	0.47
24-hour average SBP (mm Hg)	121 ± 12	123 ± 10	0.54
24-hour average DBP (mm Hg)	68 ± 8	67 ± 7	0.68
HTN Classification			0.86
No HTN	22 (55%)	18 (58%)	
White coat HTN	3 (7%)	1 (3%)	
HTN/Masked HTN/Anti HTN meds	15 (38%)	12 (39%)	
Unknown	2	1	
Peak exercise right arm SBP (mm Hg)	174 ± 32	166 ± 34	0.29
High sensitivity CRP (mg/L)	128 (74, 149)	128 (66, 146)	0.98
MMP-9/gelatinase B (ng/mL)	488 (91, 4228)	546 (49, 4453)	0.45

Values are mean ± standard deviation, number (percent), or median (minimum; maximum). AAO = Ascending aorta; AI = Augmentation index; cfPWV = carotid-femoral pulse wave velocity; DBP = Diastolic blood pressure; Endo-PAT = Endothelial pulse amplitude testing; hs-CRP = High sensitivity C-reactive protein; HTN = Hypertension; MMP = matrix metalloprotease; MRI = Magnetic resonance imaging; PWV = Pulse wave velocity; SBP = Systolic blood pressure.

Table 28 summarizes the results of multivariable modeling comparing key outcome variables between treatment groups while adjusting for these confounding variables (age at treatment and presence of BAV). Adjusted and unadjusted models did not differ significantly for these key outcome variables, suggesting that the impact of these potential confounding variables on our study measurements was not significant.

Table 30. Adjustment for potential confounders

	Unadjusted Model		Adjusted Model	
	Coefficient	**p value**	**Coefficient**	**p value**
CMR proximal PWV (m/s)				
Balloon dilation	-0.76	0.29	-0.49	0.50
Stent	0.77	0.26	0.87	0.28
AAO strain (%)				
Balloon dilation	0.14	**0.02**	0.12	**0.04**
Stent	-0.02	0.73	0.03	0.68
cfPWV (m/s)				
Balloon dilation	0.05	0.84	0.07	0.79
Stent	-0.20	0.46	-0.54	0.09
AIx (%)				
Balloon dilation	8.65	0.08	10.6	**0.04**
Stent	18.3	**0.001**	18.0	**0.003**
Endo-PAT index				
Balloon dilation	-0.15	0.48	-0.12	0.59
Stent	0.11	0.62	-0.12	0.64
24-hour average SBP (mm Hg)				
Balloon dilation	-4.99	0.12	-5.24	0.11
Stent	0.42	0.89	-2.30	0.36
24-hour average DBP (mm Hg)				
Balloon dilation	-1.15	0.60	-0.26	0.91
Stent	0.48	0.83	-2.57	0.29
Peak exercise right arm SBP (mm Hg)				
Balloon dilation	-20.1	**0.03**	-19.3	**0.04**
Stent	-0.28	0.97	-3.28	0.76
Log hs-CRP (mg/L)				
Balloon dilation	-0.07	0.07	-0.07	0.10
Stent	0.02	0.65	0.03	0.54
Log MMP-9/gelatinase B (ng/mL)				
Balloon dilation	0.53	**0.02**	0.64	**0.01**
Stent	-0.27	0.22	-0.29	0.28

Multivariable linear models adjusted for age at treatment and presence of bicuspid aortic valve. For each comparison, the surgical group is the reference group. AAO = ascending aorta; AI = augmentation index; CMR = cardiac magnetic resonance imaging; DBP = diastolic blood pressure; hs-CRP = high sensitivity C-reactive protein; MMP-9 = matrix metalloprotease 9; PWV = pulse wave velocity; SBP = systolic blood pressure

VI.DISCUSSION

In this multicenter, prospective comparison of optimally treated patients with CoA treated with surgery, BD, or stenting, we found that the treatment groups were similar with respect to several parameters of vascular function including the prevalence of systemic HTN, global aortic stiffness, CAP, endothelial function, and LV mass. However, despite adjustment for potential confounding variables (including age at repair), the BD group showed a better vascular phenotype characterized by a more distensible AAO, a lower peak SBP during exercise, and less impairment in diurnal BP variation.

1. STUDY SUBJECTS

Our study groups differed by age at treatment, with older stent patients than surgical and BD patients. This is not surprising, considering that LOVE-COARCT was designed to include patients with more than one year old (yo) at treatment, and that stent patients usually have more than 6 yo at this time (please refer to Background, section 1.8.6.). However, this was also likely unavoidable: an earlier draft of the study design specified that the lower limit for recruitment was patients older 6 yo at time of treatment, however a preliminary review of the participating center's databases showed that this would exclude a significant part of the BD and surgical patients and render recruitment nearly impossible. To address this, our approach was therefore to implement a careful adjustment for potential confounding by age at treatment and other variables and found to have no impact on our results (please refer to Methods, section 7.1).

Many retrospective studies showed a correlation between older age of treatment and worse BP phenotype and vascular function.[207, 216, 227, 229, 230, 242, 251, 335, 338, 345, 349, 356, 375-378] Early studies reporting the outcome of large cohorts of surgical patients showed that late HTN and CV mortality were strongly related to age at surgery.[251, 335, 338] The first study designed to specifically assess the impact of early surgery on BP showed that patients operated in infancy had less HTN (4%) than those treated later (27%).[377] The first report demonstrating that the timing of operation has a selective impact on specific measures of vascular function was a cohort of 64 surgical patients (median age at operation 4 months old), where it was shown that patients who underwent surgical repair of CoA < 4 months of life had normal PWV (measured by photoplethysmography) but impaired brachial artery reactivity (measured by NO-dependent FMD and NO-independent nitroglycerin infusion).[345] Another cohort of older surgical patients confirmed these findings, and showed that persistent

impairment of arterial reactivity after repair of coarctation was more likely to be present in patients treated > 9 yo, than in those treated < 9 yo, when compared to controls.[375] Since these publications, other indices of vascular dysfunction have also been associated with older age of repair or transcatheter treatment.[207, 216, 230, 242, 409]

A few papers that studied the impact of repair in vascular function prospectively, found that the elastic properties remain impaired after repair.[66, 224, 228, 352, 354, 355] One interesting study reported the results of an experimental model of CoA in rabbits, that was created with silk (permanent) or Vicryl (degradable) suture. 12 weeks beyond the time for the biodegradable suture and hence the induced CoA to disappear, these animals remained with altered BP and endothelial function.[66] In humans, prospective assessment of vascular function was reported in three small studies, after stent implantation (one with 12 patients,[224] and another with 13 patients)[228] or BD (13 patients).[355] The results showed that the ascending aortic elastic properties and other indices of vascular function remained abnormal after repair. Another small study (15 patients) reported similar finding in the mid-term follow up, after stent implantation.[354] Finally, a study found that, even after neonatal repair (15 patients), patients remain with impaired elastic properties of the aorta, at a mean age of 3.0 ± 1.0 years.[352]

All these studies concurred to demonstrate that age at operation is a strong, independent variable associated with impaired vascular properties of the aorta. To address this difference in age at treatment between the three treatment groups- which we anticipated that could occur, in the study design phase- our approach was two-fold: at the recruitment stage, we attempted to frequency match the three treatment groups for what we considered the main confounding variables, age at treatment, current age and BAV; at the analysis stage, we implemented a careful adjustment for potential confounding by age at treatment (please refer to Methods, section 7.1). Our statistical analysis for the possible effect of confounding by age (and the other variables, which did not differ) showed that this had no impact on our results.

Importantly, LOVE-COARCT's three treatment groups had no difference in any other confounding variables. Current age did not differ between the three treatment groups. The mean age of our cohort is 18. Length of follow up is an important determinant of late vascular dysfunction and abnormal BP profile, as is demonstrated by a large study in which an immediate decrease of BP after treatment was followed by an increasing incidence

of HTN after five years of follow up.[337] In our cohort, there were no differences in the severity of native CoA (BP gradient, echocardiographic dimensions of arch and isthmus, and Doppler estimated gradient). Several studies showed that the severity of the CoA, the presence of reCoA or even a mild residual narrowing at the site of CoA repair predisposed to late HTN[379, 380] and impaired vascular function,[217, 381] but this was not confirmed in other studies, who found no impact of reCoA on vascular function.[214, 348]

There were no differences between the incidence of BAV between the three treatment groups. As previously stated in the Background (please refer to Background, section 1.5.1), about half of the patients with CoA have this associated anomaly, which has been associated with impaired arterial stiffness.[406] Despite observing no differences, we performed a statistical analysis, and found that the presence of BAV had no impact in LOVE-COARCT results.

76% of our cohort were male patients, which is in accordance to what has been described in previous studies of patients with CoA.[21, 26]

2. AORTIC STIFFNESS

2.1. Global Assessment of the Aortic Wall

In LOVE-COARCT, global aortic stiffness assessed using cfPWV by applanation tonometry with the NIHem system (**Fig. 22**), or the SphygmoCor (**Fig. 23**), and using AAO to distal DAO PWV by CMR, did not show any differences between the three treatment groups. Segmental aortic stiffness of the aortic arch (AAO to prox DAO), mid (prox to mid DAO), and distal (mid to dist DAO) aorta did not also reveal any differences between treatment groups.

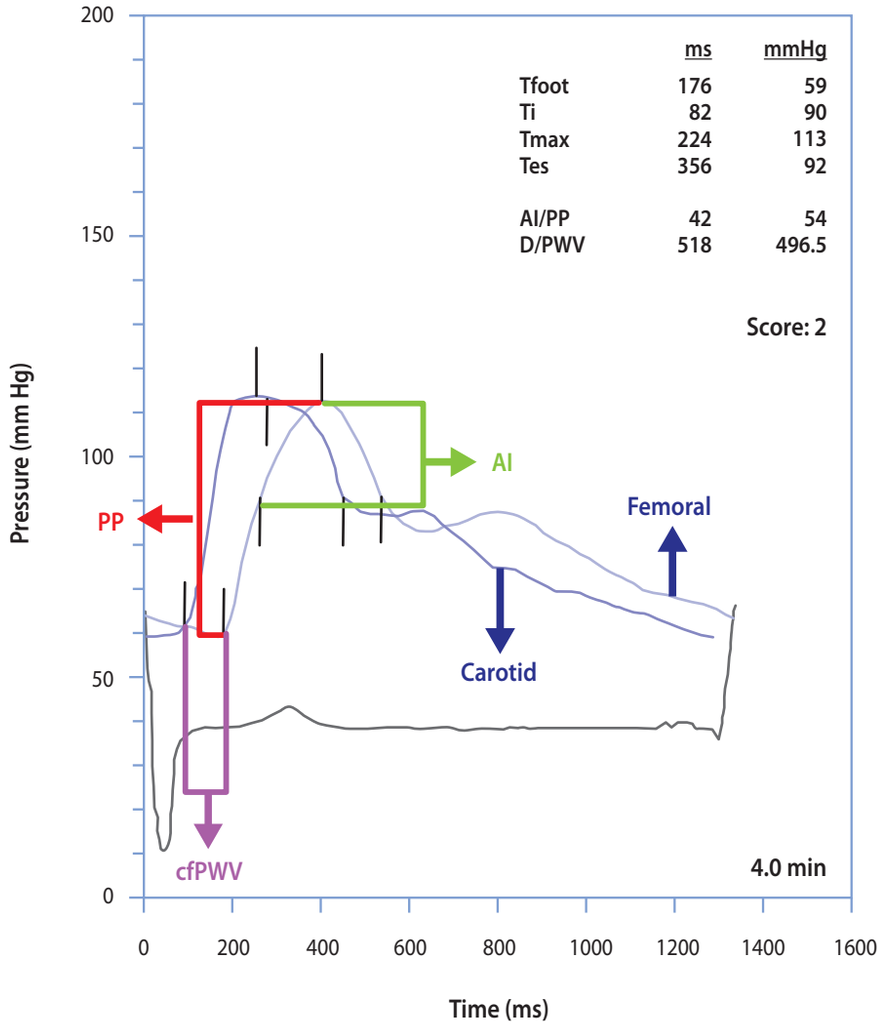

Fig. 22. Arterial tonometry with NIHem. *Both carotid and femoral curves are superimposed in the same graphic, calibrated with blood pressure and time. The proprietary software analyses the pulse wave contour and automatically marks the critical points with a spike and measures the distances, to calculate the carotid-femoral pulse wave velocity (purple), pulse pressure (red) and augmentation index (green). (Image from a LOVE-COARCT patient)..*

It is of note that, despite the non-significance of any of these results, the values of the arch PWV, the segmental measure that is mostly focused on the treated segment of the aorta, are the ones that suggest a potential difference (BD 4.0 ± 1.2 m/s, surgery 4.7 ± 1.5 m/s, and stent 5.5 ± 3.8 m/s) but do not reach statistical significance in our sample (0.12). This difference is effaced when healthier segments of the aorta are involved in the PWV estimation.

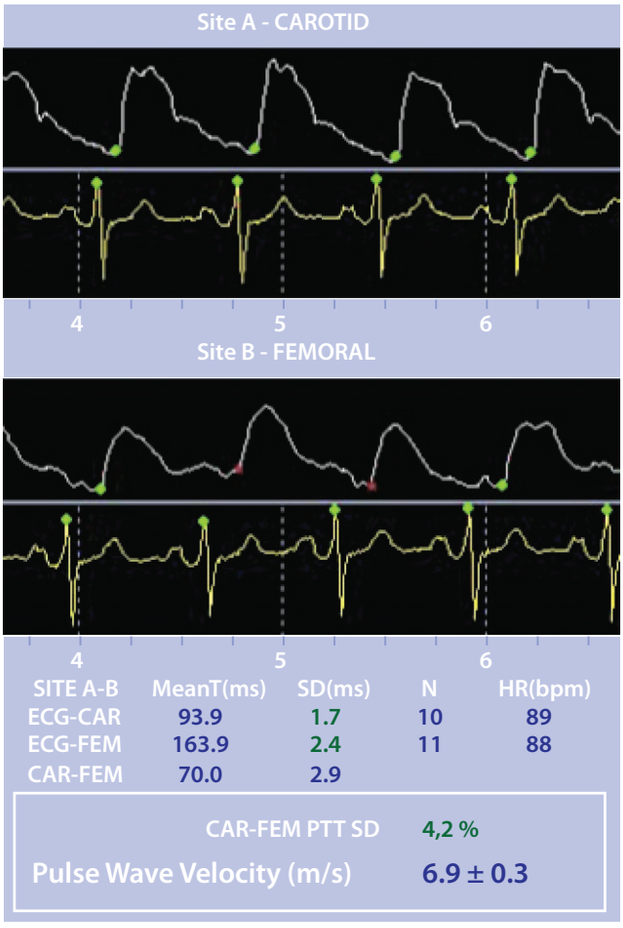

Fig. 23. Arterial tonometry with SphygmoCor. *The foot of both carotid (Site A) and femoral (Site B) tracings are automatically detected with the proprietary software and the time delay between them is divided by the carotid to femoral distance to calculary the carotid-femoral pulse wave velocity. (Image from a LOVE-COARCT patient).*

There are no previous studies that compared the three different treatments for CoA with regard to global or segmental PWV, and three papers reported comparisons of arterial stiffness outcomes between different surgical techniques. One publication compared a small sample of 20 patients treated with end-to-end anastomosis and subclavian flap surgical, and found that right arm PWV was higher in the subclavian flap compared to end-to-end anastomosis patients, while the latter did not differ from controls.[386] Another study, with 39 patients, found similar results.[387] However, a third study, comparing these same two surgical techniques, found no difference in carotid to radial PWV.

There are several publications that reported comparisons between patients with CoA and healthy controls, which show that PWV is increased in arterial segments above (carotid-radial or brachial-radial)[233, 345-349] but not across (carotid-femoral or brachial-ankle)[72, 244, 349] or below (femoral-dorsalis pedis)[345] the coarctation site. These studies have used different

techniques, including photoplethysmography,[345-347] applanation tonometry[244, 348, 349] or, more recently, by CMR.[233]

Regarding the healthy population, there are now a few pediatric studies, and a large number of large studies with adult populations that have reported data on applanation tonometry assessment of cfPWV.[283, 410-412] Nevertheless, considering the number of covariates that are known to influence PWV in children, it is recommended that these 'normal' values be interpreted only for the specific device used.[267] Therefore, we did not pursue any comparisons between the combined results of our three treatment groups as a whole, and those values.

CMR has an excellent spatial and temporal resolution, and low interobserver error,[413] but only a few studies have used it to characterize AAO to DAO PWV. Therefore, despite the well standardized protocols that were used for measuring CMR PWV, we did not have a control group and therefore these comparisons need be read carefully.

2.2. Segmental Assessment of the Aortic Wall

In LOVE-COARCT, this was done with CMR. The segmental assessment of the aortic wall with PWV and other distensibility measures of arterial stiffness that relate arterial dimensions vs. pressure by CMR (strain, distensibility, compliance and β stiffness index), differences emerged between treatment groups. Proximal aortic (AAO and aortic arch) stiffness was lowest in BD patients and highest in stent patients. Surgical patients had intermediate values of stiffness. AAO distensibility in BD patients was similar to values reported in normal controls, while patients in the stent and surgery groups had lower values.[414]

There are no studies that compare the treatment techniques with regard to the assessment of segmental arterial function, but there are a few albeit small reports that compare patients with CoA and healthy controls, and this assessment was made using vascular ultrasound,[228, 244, 350-354] transthoracic,[229] intracardiac,[355] or transesophageal echocardiogram,[242, 356] and, more recently, with CMR.[233, 235] The older of these studies (23 patients), used transesophageal echocardiography, and found that patients with CoA treated with surgery have less distensible ascending aortas but normal descending aorta.[356] More recently, two studies used CMR (one with 50 patients,[235] another with 40 patients)[233] to report that strain, distensibility, or β stiffness index were altered in the pre, but not the post-CoA aorta. A recent study used

M-mode echocardiography to described similar findings in 17 neonates, who presented with impaired elastic properties of the ascending aorta.[353] Finally, an increased proximal aortic stiffness evidenced by an elevated PWV and lower distensibility was reported in the largest study of the lot (64 patients) that were focused on surgical treatment for CoA, in comparison to healthy controls.[353] We were careful to use simultaneous BP measurements with the CMR, for the calculations of compliance and other variables. We acknowledge the limitation of using brachial artery BP instead of invasive aortic pressure measurements, but, for ethical and practical reasons, this was not feasible.

Segmental values of normal arch PWV obtained by CMR for adolescents have been published.[414] The combined result of our three treatment groups have values that appear higher than those.

All of these previous data point to the presence of an altered vascular function in the segments above, but not below, CoA. This is even more significant when one considers that in normal subjects, the elastic properties of the aorta decrease as distance from the aortic root increases,[415] which is precisely the inverse of what we and the previous studies found. LOVE-COARCT's results are in line with these works.

However, our study is the first to systematically compare aortic stiffness across treatment modalities and, more importantly, observing a difference between them. This significant result supports the LOVE-COARCT's study hypothesis. However, the mechanism leading to a more distensible proximal aorta in BD patients remains unclear and our study was not designed to answer that question. It is possible that the absence of a surgical scar or rigid stent at the isthmus contributes to a lower stiffness at the CoA site. We acknowledge that the BD group underwent treatment at a younger age, however differences in AAO stiffness persisted after adjustment for age at treatment.

3. ENDOTHELIAL FUNCTION

In LOVE-COARCT, we measured endothelial function with Endo-PAT, which is a novel non-invasive and reproducible technique that assesses changes in pulsatile arterial volume with a fingertip probe (**Fig. 24**):

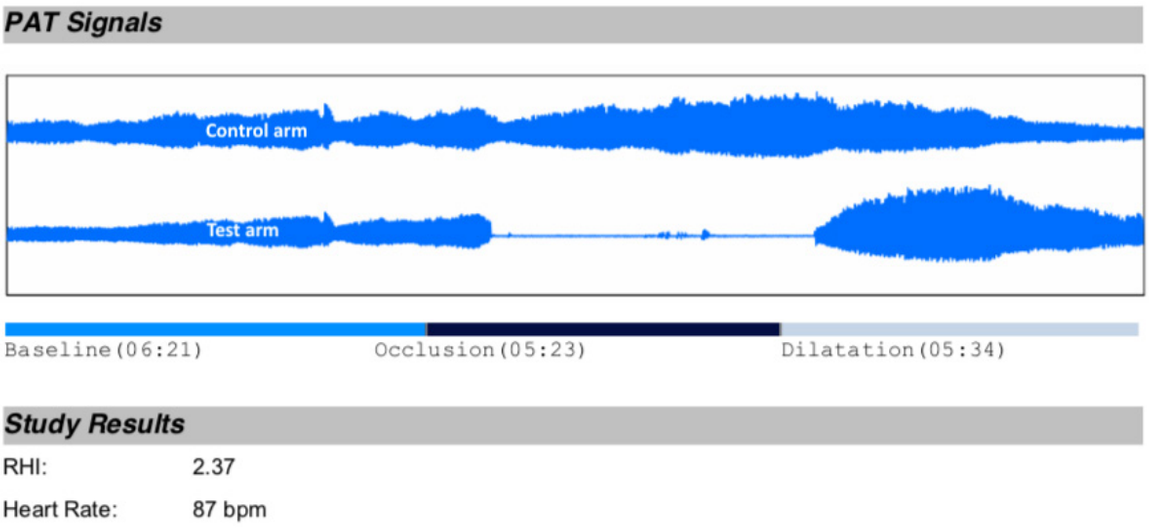

Fig. 24. Endo-PAT of a LOVE-COARCT patient. *The upper tracing is control finger and the lower tracing depicts the test finger, in the contralateral arm. After a baseline period, there is a temporary cuff occlusion, followed by cuff deflation. The dilation in pulse amplitude is measured automatically by the proprietary software, to calculate the reactive hyperemia index, shown in the lower tracing. (Image from a LOVE-COARCT patient).*

Our results did not show a difference between the three treatment groups with regard Endo-PAT's index, RHI. To the best of our knowledge, the effect of treatment type on endothelial function has not been previously studied in CoA. Our results are therefore the first to report Endo-PAT's RHI index in patients with CoA, similar across treatment groups.

There are, however, a significant number of studies that reported the arterial reactivity in patients with CoA and compared it to normals. The majority of these studies show that both vascular flow-mediated (endothelium-mediated) and glyceryltrinitrate-mediated (endothelium-independent) dilation are impaired in successfully repaired CoA patients.[217, 224, 328, 345, 347, 348, 350, 359-361] The oldest of these studies is a 25 yo study, that is remarkable for having been done only two years after the first clinical report of the FMD technique, by the same group, merely two years before.[300] It is of note that, only a minority of studies failed to demonstrate impaired reactivity in retinal,[333] peripheral[362, 363] or coronary[363] arteries of repaired CoA patients when compared to controls. The majority of these studies were done with either photoplethysmography or echo-measured changes in the brachial artery mediated by flow (FMD), but a minority was done with Endo-PAT.[362, 374]

Our RHI results, either individually for each treatment type, or combining them as a single group, suggest that endothelial function is preserved after CoA treatment in our LOVE-COARCT patients. This comparison is done with the seminal study that established normal

values in healthy children and adolescents, which is less than a decade-old.[304] Our protocol was designed and implemented by the authors of this study. In CoA, the loss of central aortic pulsatility, which buffers systole, generates chronic shear stress downstream in smaller arteries, adversely affecting endothelial function. Therefore, we expected to measure an impaired endothelial function with Endo-PAT. There are only two publications that used Endo-PAT to study endothelial function in CoA.[362, 374] And, interestingly, the values obtained in our cohort are comparable to those reported using a similar technique in a small cohort (20 patients), comprised of mostly end-to-end surgically repaired CoA.[362] However, the other existent study (23 patients) described an impaired endothelial function in another group of surgical patients, the majority repaired by subclavian flap. The age and follow up is similar in these two studies and one possible, but speculative explanation, could be the different surgical techniques.

4. PULSE WAVEFORM ANALYSIS

In LOVE-COARCT, there were no differences in the results of pulse waveform analysis between treatment groups, both with applanation tonometry and Endo-PAT results. The lack of difference in calculated central aortic pressure is in line with our findings of BP profile, presented in the following section 5. We anticipated that the presence of an undistendable metallic stent could translate into more reflected waves and higher AIx than in the other two treatment groups. However, despite a tendency for a higher AIx@75 calculated with both applanation tonometry and Endo-PAT in the stent group, this did not reach statistical significance in our results.

The analysis of the pressure waveform is an important clinical tool for monitoring of vascular function and its indices are independent markers, and predictors of cardiovascular events.[287] It is also an important instrument to assess response to treatment, as the large Conduit Artery Function Evaluation (CAFE) study showed that the differential impact of BP–lowering drugs was only detected on pulse wave analysis and not on office BP measurements.[416] Peripheral reflected pulse waves return to the aortic root rapidly via stiffer arteries, which can augment systolic pressure leading to increased central pulse pressure. There are no previous studies that compared results of pulse wave analysis between treatment types. There are, however, several studies showing that repaired CoA patients have altered functional parameters of the pressure waveform, such as a higher AIx,[224, 348, 364] a wider PP,[75, 358] or an increased central aortic pressure.[348, 358, 364] The most significant of these studies, specifically designed to assess

the pulse waveform morphology, showed an increased PP but not a higher AIx in 46 surgical patients, as compared to healthy controls.[358] There is one study that has mostly surgical but a few stent patients,[364] one reporting only stent patients,[348] and the remainder are based on patients with CoA that were treated with different surgical techniques.

There are several reasons for a careful comparison between these studies and our LOVE-COARCT results: all of these studies were done in adults, and the mean age of their patients (from 25 to 41 yo) is higher than in our LOVE-COARCT cohort (18 yo); all of the above were done with tonometry and ours included both tonometry and Endo-PAT; it is well known that the pulse waveform changes with age, so comparisons between our study should be done with care; and finally, even if central BP and AIx do not depend upon any distance measurements, they are somewhat operator-dependent and require a tonometric skill set of the operator,[268] which should be underlined in comparison with our results, which were obtained from multiple centers and different operators. Having stated this, one example of a comparison that should be done with care is the finding of negative AIx, such as we had in LOVE-COARCT, is common in children, but not in adults.[417]

5. BP PHENOTYPE

To achieve a detailed characterization of the BP profile, we assessed BP with four different approaches. We used the manual auscultation technique to measure the right arm office BP while the patient is resting and sitting. This was followed by supine four extremity oscillometric BP measurement to assess for reCoA (section 1). Subsequently, we used ABPM to measure the circadian BP profile. And finally, our patients performed an EST to assess the BP response to exercise and exercise-induced arm to leg BP gradient, exercise tolerance, HR response to exercise, and functional capacity parameters.

5.1. Office BP

In LOVE-COARCT, we found no differences of office BP measurements between treatment groups. A pilot, retrospective study from our group, compared the BP response to EST

between the three CoA treatment types, BD (12 patients), stent implantation (8 patients) and surgery (4 end-to-end, and 8 subclavian flap), and found that BD patients had a less exaggerated BP response and less arm to leg gradient, in comparison with the other two types of treatment.[378] There is only one prior study that reported a comparison between the three treatment types (350 surgery, BD, and stent patients; 36 institutions) of BP phenotype long-term outcomes.[130] Here, it was described that, in the intermediate follow up, there may be more normotensive patients treated by BD (72%) vs. surgery (96%) and stent (82%), but this falls short of reaching statistical significance (p = 0.09); and in a subgroup analysis (age 6 to 12 yo), the short term results show that patients have less anti HTN medication, however the values of SBP do not differ between the three groups. These values need to be interpreted with care, since this is a retrospective study with 36 contributing institutions, distinct methods to acquire BP, and a different definition of office HTN than the one we used in LOVE-COARCT. Three retrospective studies compared the influence of surgical technique on BP outcomes: a small study (10 end-to-end anastomosis; 11 subclavian flap);[386] a mid-sized study (21 end-to-end anastomosis; 22 subclavian flap),[385] and a large study (137 end-to-end anastomosis; 118 polytetrafluoroethylene patch aortoplasty).[119] All reported that end-to-end anastomosis, has less HTN than the other surgical approaches.

Overall, 44% of our patients had pre-HTN and 9% had either Stage 1 or Stage 2 office HTN. The prevalence of HTN on office measurement were within the range of prior reports (12-65%).[130, 154, 166, 177, 203-215] Most studies do not publish the methodology of the measurement of BP (seated or lying down, method to choose the size of cuff, the number of measurements taken, and in how many clinic visits). Consequently, comparisons need to be done carefully. Additionally, these reports differ significantly in their definition of HTN, which can be in children from a SBP > 90 percentile (in older studies),[205] SBP or DBP ≥ 95 percentile,[207] or SBP ≥ 97.5 percentile of normal subjects (age and sex adjusted);[130] in adults a value of SBP > 140 or DBP > 90;[207] and in any age group, the use antihypertensive drug treatment, HTN at ABPM, or during exercise.[213] This latter study is, in fact, the largest, single center study on HTN in CoA (Coarctation Long-term Assessment (COALA) Study), which reports that only 43% of 404 patients had a normal BP profile. Another factor to take into consideration when comparing our overall results with other studies is the length of follow up, because, age (in the general population) and time from treatment (in patients with CoA)[89] are both associated with increased incidence of HTN. Our cohort has a younger age than most of the above mentioned studies. Despite all existent epidemiologic data on BP in repaired CoA, we still don't fully understand the mechanisms underlying HTN in these patients.[418] One study

described that HTN, and not CoA itself, was an independent risk factor for CV complications in these patients.[419]

5.2. ABPM

In LOVE-COARCT, there were no differences between treatment groups with respect to the prevalence of HTN on ABPM, or the average 24-hour systolic or diastolic BP. However, we did find that BD patients demonstrated lower night-time systolic and diastolic BP, and more physiologic nighttime dipping in BP, compared to the surgery and stent groups. This improved BP phenotype in the BD group, in comparison to the other two treatment groups, has not been previously reported and is in line with our study hypothesis. The only previous comparison of ABPM results between treatment types are a two small studies (one with 43,[385] and another with 39 patients)[230] that showed end-to-end anastomosis to have better 24-hour SBP and DBP, and daytime and nighttime SBP during ambulatory monitoring than patients repaired with subclavian flap technique). Our finding of blunted nighttime dipping and lower nighttime BP has been previously linked to the development and progression of end-organ disease in patients with essential HTN, diabetes mellitus, obesity, and black race.[420] Nevertheless, the impact of this finding on long-term outcomes in CoA patients deserves further study.

Overall, 36% of the LOVE-COARCT patients were either on an anti-hypertensive medication or had HTN/masked HTN based on ABPM results. ABPM may be superior to office BP measurement in its ability to distinguish patients at the highest risk for target-organ damage,[402] and identifies patients with vascular disfunction such as increased arterial stiffness[421] and endothelial dysfunction.[422] In prior studies in patients with CoA, the diagnosis of HTN based on ABPM was between 30-59%.[72, 75, 213, 216-225] As was said for office HTN, the definitions of HTN on ABMP studies vary between studies and therefore, and therefore any detailed comparisons between LOVE-COARCT and these studies should be done with care.

5.3. EST

In LOVE-COARCT, the EST results showed that the BD group showed a less exaggerated BP elevation to exercise, compared to the surgery and stent groups. There is only one study

that compared CoA treatments with regard to EST, already mentioned above. It reported exclusively on two surgical techniques, and showed that end-to-end anastomosis has less systolic BP at peak exercise when compared to subclavian flap.[385] In the general population, exercise-induced HTN has been shown to be predictive of future development of resting HTN,[423] and an independent risk factor for cardiovascular events and mortality.[424] This finding also aligns with our study hypothesis and requires further study to assess its clinical impact, currently unknown in a population of treated CoA patients.

We did not calculate overall measurements for the entire LOVE-COARCT cohort (please refer to Methods, section 6.4.3). However, the abnormal BP profile with exercise that persists after treatment for CoA has been abundantly demonstrated in the last decades, with all treatment techniques, with exercise-induced HTN (10-47%) [210-217, 220, 327-332] or intolerance [332, 425, 426] and exaggerated BP response to exercise correlated with LV mass.[427] However, a few studies were unable to show HTN response compared to controls.[214, 221, 428] As previously stated, comparisons need to be done carefully, due to different methodologies applied in different studies. For example, HTN during exercise can be defined when the peak SBP is greater than two standard deviations more than the age- and work load–dependent reference value,[213] when the peak SBP higher than 220 mmHg in men and higher than 190 mmHg in women,[216] or if the SBP has an increase higher than the 95th percentile for their age and sex.[215]

6. LV MASS AND AORTIC MORPHOMETRICS

6.1. LV Mass

In LOVE-COARCT, despite some differences in BP phenotype and other indices of vascular function, we found that LV end-diastolic volume, LV mass and LV ejection fraction were similar across treatment groups. Furthermore, these values were normal when compared to previously reported values in healthy subjects.[429] There are no studies comparing treatment types with regard to LV volumes, mass, and function. However, The increased pressure afterload after repair has been shown to increase LV mass, both by echocardiogram[217, 221, 227-232] or CMR,[75, 231, 233-236] which may justify the finding of a normal or increased global LV function based on echocardiography,[221, 237-241] or CMR[369, 430] but not accurately reflect myocardial

performance. Recent studies, including tissue Doppler, speckle tracking and strain imaging have also shown abnormal regional fiber shortening[225, 229, 230, 232, 234, 235, 238, 242-246] and diastolic dysfunction.[230, 232, 238, 244, 247, 248] The Framingham Study has shown that the incidence of left ventricular hypertrophy is strongly related to high BP and carries a grave prognosis for cardiac events.[431]

Overall, our results contrast with this evidence of previously reported increased LV mass values in patients with repaired CoA.[233] In effect, our LV mass values were lower compared to this prior report but are similar to the values reported in a more recent publication, which had a similar age at enrollment as our sample.[226] One possible explanation for the absence of significant LV hypertrophy in LOVE-COARCT may be related to the relatively young age of our patients, and good blood-pressure control in our population, in comparison to most of the studies that were previously published, in adult populations, with more HTN. To prove this point, there is one previous work that studied a group of treated children with a young age (mean age 6.4 ± 3.0) who had compromised elastic properties of the ascending aorta after successful surgical coarctoplasty compared to controls, but similar LV mass compared to our LOVE-COARCT study.[432]

6.2. Aortic Morphometrics

In LOVE-COARCT, we did not see any difference in the size or shape of the aortic arch between the three treatment groups. Several papers, mostly from the same research group, have described that the shape of the aortic arch impacts the vascular function, namely age-related decrease in curvature[433] or (conversely) a gothic arch is a predictor of both resting[208, 371] and exercise-induced HTN[372] as well as increased aortic stiffness.[350, 373] However, these later results were unconfirmed in studies from different groups.[434, 435] Despite these controversial findings, the congenital heart community is now aware that the arch shape may impact blood flow hemodynamics and potentially vascular function.[436]

7. BIOMARKERS

7.1. Endothelial function

In LOVE-COARCT, there were no differences in NOx or ADMA levels between treatment groups, consistent with the lack of difference in endothelial function using Endo-PAT. NOx and ADMA are biomarkers related to endothelial function, and their levels have been correlated with the risk of atherosclerosis due to endothelium-dependent NO regulation of smooth muscle-derived vascular tone, in the general population.[437] There are no studies comparing treatment types, but recent insights are being gained regarding these biochemical and molecular pathways in repaired CoA patients. However, studies are small and often present contradictory results. Biomarkers of the nitric oxide-mediated endothelial function were found to be altered in animal models[365] and patients with repaired CoA, including evidence of enhanced NO inactivation,[347, 366] and increased ADMA levels. [347]A different study did not find altered NO in CoA patients.[347]

7.2. Inflammation

In our study, BD patients had lower levels of hs-CRP, which supports our initial hypothesis. Inflammation is a second aspect that relates to vascular dysfunction.[309] There are numerous markers of systemic inflammation, such as interleukins and hs-CRP, which act on the vascular endothelium to upregulate a number of adhesion molecules that reflect vascular wall function such as VCAM, with a crucial role in atherogenesis.[315, 438] There are no comparisons of inflammation biomarkers between treatment types, and prior results of inflammatory biomarkers in patients with CoA are inconclusive. Inflammatory biomarkers such as TNF-α[367], IL-1β,[360] IL-6[349, 367, 439] and IL-10[364, 367] or e-selectin are increased in repaired CoA. However, other studies showed no change in TNF-α,[364] IL-6,[360, 364] e-selectin,[367, 368] or high sensitivity C reactive protein (hs-CRP) in CoA patients.[367, 368]

Three interesting studies, from the same group of investigators, explored the role of inflammation and its response to medication, in patients with repaired CoA. A randomized, cross-over, controlled trial study reported that, after treatment with ramipril for 4 weeks in 20 patients, there was an improvement in endothelial function and decrease in serum levels

of IL-6 and sVCAM-1, which was independent of the BP lowering.[382] A similar study, from the same group of investigators, showed that after 4 weeks of atorvastatin, CoA patients had reduced circulating levels of IL-1b and sVCAM-1, but no change in IL-6 levels.[383] A third, and very recent study, performed an innovative assessment of the aortic wall inflammation with positron emission tomography/computed tomography with 18F-fluorodeoxyglucose,[428] which is the gold-standard imaging modality to noninvasively assess vascular inflammation in vivo. In this pilot study (15 patients), they found that patients with surgically repaired CoA have increased aortic wall inflammation.

There is a strong association between hs-CRP and risk of cardiovascular disease, but, despite multiple larger population trials, there remains a lack of consensus regarding its clinical use, namely the cutoff value for increased risk, since this protein is influenced by sex, traditional CV risk factor such as HTN and lipids.[440]

7.3. Vascular remodeling

The third set of biomarkers that we assessed were the ones involved in aortic wall remodeling. In LOVE-COARCT, values of both TFG-β1 and MMP-9 were elevated in the patients with CoA treated with BD, in comparison to the two other treatment types. There are no previous studies comparing CoA treatments in respect to vascular wall remodeling biomarkers in CoA, but patients with repaired CoA have altered biomarkers of the vascular wall function such as increased TGF-β,[349] or adhesion molecules (sICAM-1, sVCAM-1).[360, 364, 368] However, these results were unconfirmed in a different study where it was found, in contrary, that sICAM-1 and sVCAM-1 did not differ between CoA patients vs. controls.[367] A recent study explored the expression of genes of aortic wall remodeling and stiffness, as well as the pathological examination of the aortic wall itself, in an animal model of experimental stent treatment for CoA.[441] They found that an increased expression of MMP-9 genes in the ascending, but not the descending, aorta which points to molecular mechanisms of aortic wall remodeling in stented CoA. TGF-β1, and the family of metalloproteinases (such as MMP-2, and MMP-9) are biomarkers related to fibrotic remodeling such as the aortic remodeling that occurs in response to hemodynamic changes.[442] Elevated circulating levels have been reported in dilated aortas in patients with inherited aortopathy,[317] and are biomarkers for the presence and risk of rupture of an aortic aneurysm.[320] Experimental studies showed that increased aortic wall motion is associated with a higher risk of aneurism formation.[443] This may explain

our results in BD, who have an increased AAO strain and higher MMP-9 values The clinical implications of these findings are unclear and further research is needed to evaluate whether these biomarkers are related to the risk of aneurysm formation in the BD group, which has been a concern in this patient group.[111, 154, 200-202]

8. IDEAL CV HEALTH

In LOVE-COARCT, there were no differences in the lifestyle characteristics of our three treatment groups (eating habits, exercise, smoking) or in the hereditary risk factors for CV disease (HTN, diabetes, obesity). The baseline metabolic assessment was also not different between the three treatment groups. The only minor finding was that BD patients ate more at home with the family than the other two treatment groups. Cultural differences may explain this finding, but our study was not designed to answer that question. Overall, these results are important to exclude the contribution of well-known risk factors in our LOVE-COARCT cohort and underline the validity of our other findings reported above. A growing body of literature in the general population has demonstrated that risk of cardiometabolic disease and accelerated atherosclerosis is mitigated by ideal cardiovascular health (ICVH),[405] defined as having optimal levels of health factors (BP, total cholesterol, plasma glucose) and behaviors (smoking, body mass index, physical activity, and diet). All these factors have been well documented as risk factors for CV events, such as BMI (strongly linked to CV events in, as has been shown in a metanalysis of 239 prospective studies),[444]or lipid metabolism.[445]

To the best of our knowledge, the prevalence of ICVH in patients late after repair of coarctation, including the composite ICVH score and individual elements of ICVH, in unknown. LOVE-COARCT is the first study to report on ICVH in patients with CoA. This is important, since these patients experience increased CVD compared to the general population. Therefore, the control of traditional cardiovascular risk factors and knowledge of family history is particularly important.

9. STUDY LIMITATIONS

As previous authors have noted, research in CoA is challenging. [446, 447] There are several limitations to our study.

The first limitation of our study is related to the patient selection criteria. CoA is a heterogeneous disease, ranging from a simple discrete stenosis to a long tubular narrowing accompanied by aortic arch hypoplasia, and can occur as an isolated anomaly or coexist with other congenital heart defects. The choice of treatment modality is dictated by the age of presentation, the morphology of the CoA, the anatomy of the arch, the initial response to treatment (valid for percutaneous BD vs stent), and the associated anomalies. Some of these factors may play a role in vascular function outcome. Our restrictive inclusion and exclusion criteria excluded a significant subset of patients, namely those that required treatment in infancy or have anatomies that were not amenable to all treatment with all techniques. Therefore, our results reflect vascular function in isolated, discrete CoA and may not be representative of the population of CoA as a group. Specifically, our results may not be generalizable to neonatal and infantile CoA, which is on the one hand more severe at presentation but also on the other has an earlier treatment.

Our plan was to compare three treatment modalities, and, despite our attempted frequency-matching to balance the treatment groups with respect to key confounding variables, our groups were not perfectly matched for age at treatment. However, surprisingly, multivariable analyses (**Table 28**, **Table 29**, and **Table 30**) showed that these potential confounding variables (including age at repair) did not significantly affect the comparison of key variables between treatment groups.

Despite a multicenter design, our study is limited by a relatively low sample size. However, based on sample size estimates, the study had sufficient statistical power to detect group differences in CMR PWV. The multicenter design carries some other limitations. Retrospectively gathered data from medical records (e.g., surgical notes, original anatomy) of multiple centers makes it more likely that data may be missing for some participants. Variation in antihypertensive medication protocols between different institutions may also affect vascular parameters. Because some centers did not have a cycle ergometer, we chose the treadmill for the exercise test, which hinders the acquisition of metabolic data associated with anaerobic metabolism and makes the measurements of exercise BPs less reliable than those obtained with the cycle ergometer.

We recognize that there is no single marker of vascular dysfunction and that large vessel and small vessel functions interact mechanistically and in terms of outcomes. Additionally, the study of the impact of treatment on the aortic wall in patients with CoA is challenging because these patients show a congenitally altered aortic wall compliance. Therefore, we studied both small and large arteries, BP phenotype, biomarkers and cardiovascular health status to comprehensively model cardiovascular event risk feature differences among the three treatment groups. This wide approach carried the intrinsic limitations of each specific test. To overcome this limitation, we standardized all methodologies, to reduce the variability of the study testing measures, and institute Core Laboratories where a single researcher is responsible for the interpretation and sometimes, as for the biomarkers, the execution of the technique. We prescribed a low-NO diet and non-smoking indication for participants but had no way of measuring the compliance with this diet other than the patient's assertion.

And, finally, we compared the vascular function after treatment but have no such pre-treatment assessment of our patients. Consequently, despite our best efforts to create three treatment groups that do not differ with regard to the main confounders, the vascular function assessment of our patients does not take into consideration the baseline vascular dysfunction of each patient.

VII. CONCLUSIONS

CoA, a narrowing of the proximal descending aorta, is one of the most common congenital heart defects. There are several percutaneous and surgical techniques that may be equality effective ate relieving the stenosis. The persistence significant late cardiovascular morbidity and mortality showed that CoA is not a simple lesion that is "cured" with the relief of the anatomic narrowing but as a complex arterial syndrome that requires lifelong follow-up. As a recent editorialist wrote, "Simple CoA is an example of a disease process requiring us as clinicians to understand the interaction of inherent risk (genetic determinants, intrinsic arteriopathy) with superimposed anatomic (native and intervened aortic), physiological (compliance, BP, flow) and environmental (smoking, overweight, diabetes, sedentary lifestyle) modifiers, in a longitudinal construct".[381]

With this quote as background, it was highlighted the emphasis has been placed in recent years on the long-term morbidity due to systemic vascular dysfunction in successfully treated CoA patients. The association between vascular dysfunction and cardiovascular events is well established in the general population. There is ample evidence to suggest that CoA is a systemic arterial disease and not merely a focal stenosis of the aortic isthmus. Despite this, the current management paradigm is often guided not only by CoA anatomy and patient age but often by anecdotal, personal and institutional preference, with the primary goal of alleviating the anatomic stenosis.

We aimed to clarify if the treatment modality could contribute to the well-known vascular dysfunction that exists late after CoA treatment. It was hypothesized that BD would be associated with the best vascular outcome since it is the approach that best preserves the arterial wall integrity. The LOVE-COARCT study was designed as a multicenter, prospective, observational trial to answer this question and constitutes the bulk of the present PhD dissertation thesis written by the candidate. This work will be the first systematic, focused and comprehensive comparison of vascular function between three different treatment modalities in CoA patients.

This PhD thesis dissertation compared the three treatments with well-established indices of vascular health. It was found that there was no difference between the three treatment groups in the most robust indices vascular function including the prevalence of systemic HTN, global aortic stiffness, endothelial function, and LV mass. However, we did find that the BD group showed a somewhat better vascular function phenotype with more physiologic nocturnal dipping in BP, a more distensible AAO and aortic arch, a lower peak SBP during

exercise, and lower blood levels of pro-inflammatory biomarkers. These results may be viewed as hypothesis generating basis for a randomized control trial, or a prospective, pre- and post-treatment vascular function assessment. The LOVE-COARCT database holds potential for several secondary analysis that may be performed in further studies.

To conclude, the LOVE-COARCT results suggest that the treatment modality may impact on (at least some indices) of vascular function and some merit to our initial hypothesis, that the introduction of a non-distensible stent or surgical scar may have more deleterious effects on late vascular function than simple BD. A lot needs to be clarified, including if the hard vascular outcomes, which were unchanged in our young sample will be affected in the long-term and what is the compromise in the conduit and cushioning aortic function in CoA. Further studies are required to confirm these results and to confirm that LOVE-COARCT may contribute to refining the CoA treatment paradigm by adding to the goals of therapy the preservation of vascular function when two or more treatment techniques are applicable.

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X. APENDIXES

1. PUBLISHED PAPERS

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IMAGE IN CARDIOLOGY

Aortic arch geometry after aortic coarctation repair: Systematic magnetic resonance study in a consecutive series of patients☆

Geometria do arco aórtico em coartações da aorta corrigidas: estudo sistemático por ressonância magnética numa série consecutiva de doentes

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Systemic hypertension at rest or during exercise persists in a significant number of patients after early repair of coarctation of the aorta (CoA). Recoarctation explains only a small percentage of these cases, and recent studies have suggested intrinsic anomalies in aortic arch geometry (''gothic arch'') as a possible cause, irrespective of whether the repair was surgical or percutaneous.[1,2]

We retrospectively assessed all magnetic resonance imaging (MRI) studies in a consecutive series of patients followed in our institution, analyzing the prevalence of the various types of aortic arch geometry: gothic, romanesque and crenel. All the studies were performed using a Signa 1.5T (GE Medical Systems, Milwaukee, WI, USA). Anatomical types were classified by two physicians experienced in MRI (>1500 exams between them), based on images acquired using black blood, cine or angiographic techniques.

The type of aortic arch could be classified in 59 of the 77 consecutive patients with corrected CoA. Those with recoarctation or other significant aortic arch abnormalities, such as arch hypoplasia in the context of hypoplastic left heart syndrome, were excluded. The results showed the following distribution of types: romanesque (n = 22; Figure 1), gothic (n = 20; Figure 2) and crenel (n = 17; Figure 3), which is similar to the distribution described for international series reported in the literature.

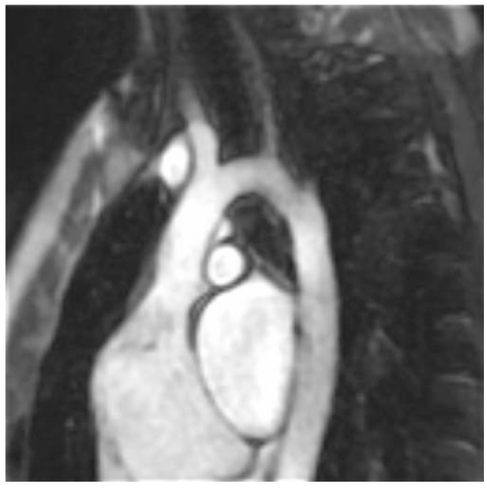

Figure 1 Romanesque arch geometry.

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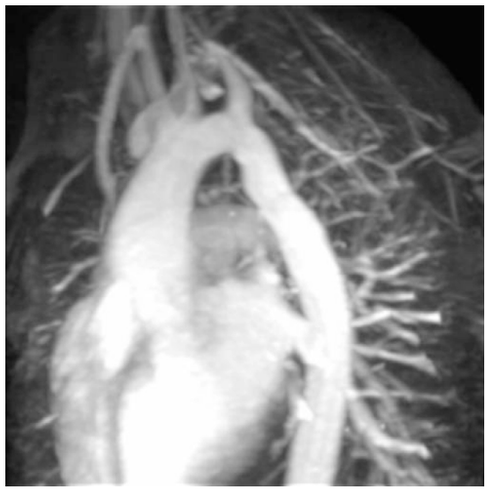

Figure 2 Gothic arch geometry.

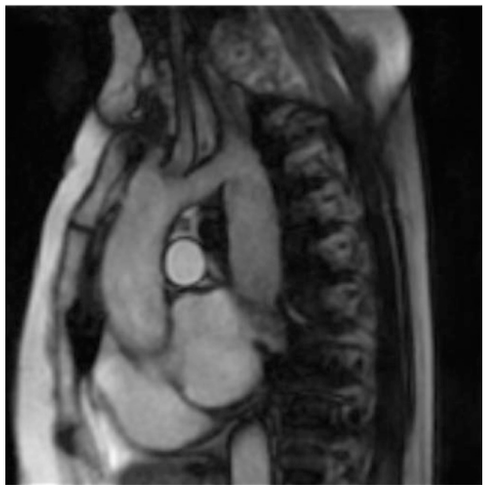

Figure 3 Crenel geometry.

A significant proportion of our series of patients with corrected CoA had aortic arch geometry that predisposes to hypertension at rest or during exercise. Besides screening for anatomical and physiological signs of recoarctation, magnetic resonance study after aortic coarctation repair should also assess aortic arch geometry, since this has a significant impact on the management and prognosis of these patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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2. PAPERS ACCEPTED FOR PUBLICATION

APC_64_18R2

MISCELLANEOUS

Rationale and design of Long-term Outcomes and Vascular Evaluation after Successful Coarctation of the Aorta Treatment study

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ABSTRACT

Background : **Coarctation of the aorta (CoA) can be treated using surgery, balloon angioplasty, or stent implantation. Although short-term results are excellent with all three treatment modalities, long-term cardiovascular (CV) morbidity and mortality remain high, likely due to persistently abnormal vascular function. The effects of treatment modality on long-term vascular function remain uncharacterized. The goal of this study is to assess vascular function in this patient population for comparison among the treatment modalities.**

Methods : **We will prospectively assess vascular Afunction in large and small arteries fusing multiple noninvasive modalities and compare the results among the three groups of CoA patients previously treated using surgery, balloon angioplasty, or stent implantation after frequency matching for confounding variables. A comprehensive vascular function assessment protocol has been created to be used in 7 centers. Our primary outcome is arterial stiffness measured by arterial tonometry. Inclusion and exclusion criteria have been carefully established after consideration of several potential confounders. Sample size has been calculated for the primary outcome variable.**

Conclusion : **Treatment modalities for CoA may have distinct impact on large and small arterial vascular function. The results of this study will help identify the treatment modality that is associated with the most optimal level of vascular function, which, in the long term, may reduce CV risk.**

Keywords : Arterial stiffness, cardiac magnetic resonance imaging, coarctation of the aorta, long-term outcomes, pulse wave velocity, vascular function

INTRODUCTION

Current treatment techniques are equally effective at eliminating the stenosis in CoA patients.[1] However, a

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good anatomical result does not preclude late systemic hypertension in office visits (12%–65%),[1-6] at peak exercise (10%–47%),[3-5,7,8] or during ambulatory blood pressure (BP) monitoring (30%–59%).[7-10] Furthermore, treated patients have reduced life expectancy [Figure 1],[2] mostly due to cardiovascular (CV) complications[2,11-14] and stroke.[15]

Successfully treated CoA patients have stiffer large arteries[16-21] and compromised vascular reactivity in small arteries,[8,10,22-26] their arterial pressure waveform is altered,[9,10,23,27,28] have imbalances in vascular function biomarkers,[24,25,27,2925,27,29,30] and increased left ventricular (LV) mass.[8,9,19-21,26,31,32] Vascular dysfunction is associated with older age at treatment,[2,19,22,29,31,33] but early treatment does not guarantee normal vascular function.[16,22]

Different treatment modalities may have varying effects on the stiffness of the repaired arterial segment:[34] Surgical repair results in a focal scar in the anastomosis; stenting creates a short, rigid segment; and balloon dilation (BD) produces a controlled tear of the intima and part of the media. Although it is possible that these differences translate into differences in vascular dysfunction, this has not been systematically compared. The largest, albeit observational and nonrandomized, comparison between the three modalities showed a lower BP in patients treated with BD versus those treated with stenting or surgery.[1] A small retrospective study showed less frequent exercise-induced hypertension in BD patients compared with other treatment types.[33] Conclusions drawn from these prior studies are hampered by methodological limitations and limited focus. In the general population, arterial stiffness is associated with major CV events.[35] Thus, choosing the CoA treatment option that optimizes vascular function is crucial for long-term outcomes in CoA.

Aim and hypothesis

The Long-term Outcomes and Vascular Evaluation after Successful Coarctation of the Aorta Treatment study aims to determine whether surgery, BD, and stenting are associated with differences in arterial stiffness in optimally treated patients. Our hypothesis is that patients who underwent successful BD will have better vascular function than patients who underwent successful surgical repair or stenting since this modality may least likely damage the biomechanical properties of the aortic wall.

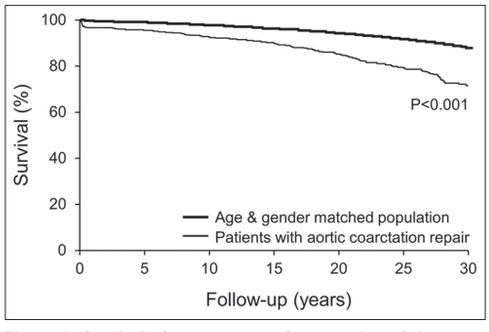

Figure 1: Survival after treatment of coarctation of the aorta. Survival curves of 819 surgical patients for over 60 years (reprinted with permission from Elsevier, license number 4131890880395)

METHODS

Study overview

This study is a cross-sectional prospective observational study of patients with CoA previously treated using one of three treatment modalities. Patients will be recruited at seven large pediatric cardiac centers from Europe and the United States of America [Appendix 1]. The study procedures will occur in a 1- or 2-day visit [Figure 2].

Recruitment

Selection criteria are depicted in Table 1. The study protocol was approved by Institutional Review Boards. Recruitment occurred between June 2013 and December 2017. The study data are collected and managed using REDCap software, hosted at Children's Hospital Boston.[36]

Study procedures

A list with the main clinical and study tests variables are depicted in Tables 2 and 3. The comprehensive list of study variables is in Appendix 7

Arterial stiffness

CoA treatments alter the biomechanics of the isthmus and may increase arterial stiffness. The velocity of the pulse wave velocity (PWV) travel in the arterial tree increases with arterial stiffness. Carotid–femoral PWV (cfPWV) is extensively validated in large studies a marker of aortic stiffness, and an independent predictor of CV events.[37] We will measure cfPWV with applanation tonometry, using either the NIHem (CV Engineering, Inc., Norwood, MA USA) or the SphygmoCor (AtCor Medical, West Ryde, NSW, Australia) devices.[37] This technique assumes a homogenous stiffness across the aorta and may potentially not accurately estimate the true carotid-to-femoral artery length. Cardiovascular magnetic resonance (CMR) measurements of PWV, on the other way, enables the detection of more subtle changes in segmental aortic PWV, above versus below the CoA site, and uses real aortic travel paths.[38] We will also use CMR to measure aortic area change during the cardiac cycle, paired with BP measurements, to quantify local arterial strain, compliance, distensibility, and the β-stiffness index [Appendix 2a and b].

Endothelial function

In CoA, the loss of central aortic pulsatility, which buffers systole, generates chronic shear stress

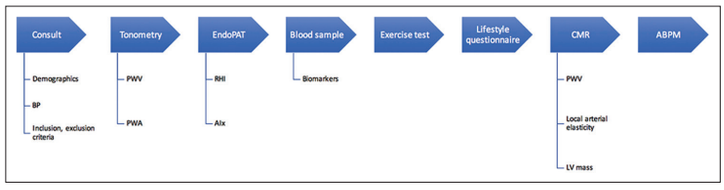

Figure 2: Long-term Outcomes and Vascular Evaluation after Successful Coarctation of the Aorta Treatment study workflow. ABPM: Ambulatory blood pressure monitoring, AIx: Augmentation index, BP: Blood pressure, CMR: Cardiac magnetic resonance imaging, PWA: Pulse wave analysis, PWV: Pulse wave velocity, RHI: Reactive hyperemia index

Table 1: Inclusion and exclusion criteria

Criteria	Definitions and comments
Inclusion criteria	
Coarctation of the aorta	
Current age 8-35 years	Lower age to allow facilitate the completion of the study tests and higher age to avoid overlap with aging-related vascular dysfunction) years 58
Treatment for CoA after 1994	Date after which all three modalities were in clinical use.
Exclusion criteria	
Residual CoA	Systolic upper-to-lower extremity BP gradient >20 mmHg.* Residual gradient is a confounder since it impacts vascular function. 8
Atypical CoA	Mid-thoracic or abdominal coarctation.
Severe transverse aortic arch hypoplasia	Transverse arch diameter z-score at initial echocardiogram <-4†
Treatment of CoA at age <1y	A more severe disease subset, essentially amenable to surgery
Clinically significant associated cardiac defects that may affect independently vascular function	Mitral stenosis (echocardiographic mean inflow Doppler gradient >6 mmHg) aortic stenosis (echocardiographic mean Doppler gradient >20 mmHg); ventricular septal defect (>3 mm in diameter); atrial septal defect (required surgical or percutaneous closure other than a patent foramen ovale); other cardiac lesions that required medical, surgical or interventional treatment
Use of two treatment modalities for CoA	This does not include balloon dilation and subsequent stent placement at the same catheterization procedure
History of known vasculopathy with vascular dysfunction	Examples: Kawasaki disease, Takayasu's arteritis, Raynaud's disease
Genetic syndromes with diffuse arteriopathy	Examples: Williams syndrome, juvenile rheumatoid arthritis
Known traditional cardiovascular risk factors	Severe obesity (body mass index >95% for age and sex in children and >40 Kg/m^2 for adults); diabetes (fasting plasma glucose ≥126 mg/dl or random (non-fasting) glucose ≥200 mg/dl); hyperlipidemia (triglycerides≥250 mg/dl; fasting LDL ≥190 mg/dl; HDL ≤30 mg/dl, currently taking statins or first degree relatives with familial hypercholesterolemia); smoking

Legend: y=years; BP=blood pressure; CoA=coarctation of the aorta; LDL=low-density lipoprotein cholesterol; HDL=high-density lipoprotein cholesterol; *using highest lower extremity systolic blood pressure; †using previously published normative values[57]

Table 2: List of main clinical variables

Variables	Comments or definitions
Medical history	
Minimum transverse arch diameter Z-score on initial echo	Using published normative values*
Isthmus z score on initial echo	Using published normative values*
Initial Doppler coarctation gradient	mmHg
Bicuspid/Bicommisural Aortic Valve?	Yes/No
Initial arm-leg systolic BP gradient	mmHg
Visit BP	
Residual systolic BP gradient	Supine and automated mmHg
Right arm BP	Seated and manual mmHg

Legend: BP=blood pressure; *using previously published normative values[57]

downstream in smaller arteries, creating endothelial dysfunction, which is associated with CV events.[39] We will measure endothelial function with the reactive hyperemia index using endothelial pulse amplitude tonometry (endo-PAT), a novel noninvasive and reproducible technique that measures changes in pulsatile arterial volume with a fingertip probe.[40] Analysis of the pulse waveform allows for automated calculation of endothelial function in one arm, while the contralateral serves as control, making this is a patient standardized method [Appendix 3].

Pulse waveform analysis

In CoA, the stiff aorta and repaired isthmus may be important reflecting sites that impact the pulse waveform. Its analysis is an important clinical tool for monitoring of vascular function and predicting CV events.[37] We will measure three variables that express pulse waveform: central aortic pressure (CAP), pulse pressure (PP), and augmentation index (AIx; ratio of the amplitude of the reflected wave in the ascending aorta and the PP).[37] CAP, PP, and AIx can be measured noninvasively using applanation tonometry (and Endo-PAT for AIx), calibrated by the peripheral diastolic and mean arterial pressure.[37] There is a lack of consensus regarding the optimal method to estimate the CAP with tonometry. The NIHem system assumes that carotid artery pulse waveform accurately

Table 3. List of main study test variables

Variables	Comments or definitions
Applanation tonometry	
Central systolic blood pressure	mmHg
Central pulse pressure	mmHg
Carotid-femoral PWV	meters/second
Augmentation index at HR75	%
CMR	
Left ventricular mass indexed to BSA	g/m^2
Ascending Ao - Descending Ao PWV (Ascending Ao to proximal, mid and distal descending Ao)	Meters/second
Type of arch	Romanesque; Gothic; Crenel
Aortic strain (Ascending, Proximal, Mid and Distal Ao)	
Aortic Distensibility (Ascending, Proximal, Mid and Distal Ao)	mmHg-1
Endo-PAT	
Reactive hyperemia index (RHI)	
Augmentation index at 75 bpm	%
ABPM	
24 h Average systolic and diastolic BP	mmHg
24 h systolic and diastolic load	%
Exercise test	
Pre-Exercise SBP gradient	mmHg
Peak exercise BP	mmHg
Biomarkers	
NOx	ug/ml
ADMA	ng/L
High Sensitivity CRP	mg/L
VCAM-1	ng/ml
IL-1β	pg/ml
TFG-β	
MMP-2/Gelatinase A	ng/ml
MMP-9/Gelatinase B	ng/ml

Legend: ADMA=Asymmetric Dimetilarginine; Ao=Aorta; BP=blood pressure; BP=Blood Pressure; BSA=Body Surface Area; CMR=Cardiac magnetic resonance; DBP=Diastolic Blood Pressure; HDL=High-density lipoprotein cholesterol; Hs-CRP=High sensitivity C-Reactive Protein; IL-1β = Interleukin 1 beta; LDL=Low-density lipoprotein cholesterol; MMP-2=Matrix Metalloproteinase-2; MMP-9=Matrix Metalloproteinase-9; NOx=Nitric Oxide; PWV=Pulse Wave Velocity; LV=Left Ventricle; SBP=Systolic Blood Pressure; TFG-β = Transforming Growth Factor beta; VCAM-1=Vascular Cell Adhesion Molecule 1; * using previously published normative values[57]

reflects the central aortic waveform and the pulsed wave analysis is automatically calculated from the carotid waveform. The SphygmoCor device uses a generalized transform function to generate a central aortic PP curve from the radial or carotid pressure tracings, which has not been validated in children. Considering our largely pediatric group and need to maintain consistency between data acquired on each device, we use the nonprocessed, signal-averaged SphygmoCor carotid tracing as the central aortic tracing which will be then digitized to calculate the CAP, following previously published approach [Appendixes 2a and 3].[41]

Blood pressure phenotype

BP phenotype is abnormal despite successful treatment of CoA. Office hypertension is a known risk factor for CV disease and the BP response during the ET is predictive of future development of resting hypertension in the general population.[42] Ambulatory blood pressure monitoring (ABPM) is superior to the office measurement in its ability to distinguish patients at the highest risk for target-organ damage.[43] We will assess BP phenotype with the manual auscultation technique to measure the right arm office BP; supine four extremity oscillometric BP measurement to assess for residual coarctation; ABPM to measure the circadian BP profile; and ET to assess the BP response to exercise and exercise-induced arm to leg BP gradient. Based on the office BP and ABPM results, we will classify our patients according to Table 4 [Appendix 4].

Biomarkers

We will measure asymmetric dimetilarginine (ADMA; NO's inhibitor),[44] and nitrite and nitrate (NOx, stable by-product of NO), biomarkers of endothelial function. Arterial stiffness is associated with increased systemic inflammation markers, which we will quantify with high-sensitivity C-reactive protein (hs-CRP) and local inflammatory cytokines of vascular wall function vascular adhesion molecule 1 (VCAM-1) and interleukin-1 beta (IL-1β).[25,45] We will finally assess the molecular mechanisms of aortic wall response to vascular dysfunction, with matrix metalloproteases (MMP-2 and MMP-9),[46] and transforming growth factor beta-1 (TGF-β1, a smooth cell growth-modulating factor involved in the arterial wall response to hypertension).[30] NOx will be determined by chemiluminescence (Sievers NOAnalyzer 280i) and all remaining measurements will be performed with enzyme-linked immunosorbent assay kits: ADMA (Sunred Biological Technology, Shanghai, China); hs-CRP (BoosterBio, Pleasanton, USA); VCAM-1; IL-1β; matrix metalloproteases (MMP)-9; MMP-2; and TGFβ-1 (RayBiotech, Inc. Norcross, USA) [Appendix 5].

Left ventricular mass

The altered BP phenotype that persists after CoA treatment represents an increase in afterload that leads to LV hypertrophy, strongly related to high BP and carrying a grave prognosis for cardiac events.[47] We will quantify LV mass by CMR, a well-established method for its calculation [Appendix 2b].

Cardiovascular health assessment

Patients with CoA experience increased CV disease compared to the general population. Literature in the general population has demonstrated that risk of cardiometabolic disease and accelerated atherosclerosis is mitigated by ideal CV health (ICVH),[48] defined as having optimal levels of health factors (BP, total cholesterol, and plasma glucose) and behaviors (smoking, body mass index, physical activity, and diet). We will implement a questionnaire to assess family history of CV disease and ICVH according to the guidelines of the American Heart Association [Appendix 6].[48]

Table 4: Classification of BP Phenotype by ABPM

Classification	Office BP SBP or DBP*	24h Mean ABPM SBP or DBP†
Non-hypertensive	Pediatric: <95th %tile Adults: <140/90 mmHg	Pediatric: <95th %tile Adults: <135/85 mmHg
White Coat Hypertension	Pediatric: ≥95th %tile Adults: >140/90 mmHg	Pediatric: <95th %tile Adults: <135/85 mmHg
Masked Hypertension	Pediatric: <95th %tile Adults: <140/90 mmHg	Pediatric: >95th %tile Adults: >135/85 mmHg
Ambulatory Hypertension	Pediatric: >95th %tile Adults: >140/90 mmHg	Pediatric: >95th %tile Adults: >135/85 mmHg

Legend: AMBP=Ambulatory blood pressure monitoring; BP=Blood Pressure; ABPM=Ambulatory Blood Pressure Monitoring; Pediatric patients have age <18yo and adult patients age ≥18yo; %tile=percentile; BP=blood pressure; DBP=diastolic blood pressure; and SBP=systolic blood pressure. *For pediatric patients, based on the National High Blood Pressure Education Program Task Force normative data[54]; for adult patients, based on the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure report.[55] †For pediatric patients, based on normative pediatric ABPM values from the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young;[43] for adult patients, based on the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research report[59]

Statistical considerations

Adjustment for confounders

We will adjust our treatment groups for three main documented confounders: (a) age at treatment; (b) current age; and (c) bicuspid aortic valve (associated with impaired aortic elasticity).[49] During recruitment, we will attempt to frequency match the three treatment groups. During analysis, the treatment groups will be compared for each of these three confounding variables and adjustments will be made using multivariable modeling with linear and logistic regression models.

Analytic plan

Our primary outcome variable will be cfPWV assessed by tonometry. Differences across groups will be explored using one-way analysis of variance. If differences in matching variables are detected among the groups, adjustment will be made using analysis of covariance. *Post hoc* analyses will be performed as necessary. Sample size estimates were obtained based on prior data that show that arch PWV measured by CMR is 3.3 ± 0.6 m/s in normal patients and 4.7 ± 1.1 m/sec after CoA surgery.[20,50] Sample size estimates for comparison of PVW between three equal-sized treatment groups (assuming overall significance level = 0.05 and power = 0.8) are shown in Table 5. We plan on recruiting 24–30 patients in each group for a total sample size of 72–90.

DISCUSSION

Methodological considerations

We chose a multicenter design to overcome recruitment challenges secondary to restrictive enrollment criteria (particularly the lower treatment age limit of 1 year, which excludes a majority of CoA patients that present in infancy, mostly managed by surgery) and need for matching treatment groups for confounders.

cfPWV is our primary outcome variable because it is validated as an accurate and reproducible measure of arterial stiffness with proven association to hard CV outcomes that can be reliably measured by applanation tonometry and CMR. We chose other parameters to complete a complementary and comprehensive assessment of vascular function in small and large arteries.

Importance of knowledge to be gained

This work will be the first systematic and comprehensive comparison of vascular function between three different treatment modalities in CoA patients. We postulate that the integrity of the arterial wall is best preserved with balloon dilatation, compared to stenting or surgery. We are aware that our population is highly selected, but believe that this is the only way to compare the three treatment types. The results of our selected population may be relevant when several modalities are applicable to one patient. Currently, the preservation of vascular function is not considered when choosing between treatment modalities. Ultimately, the results of our study may help clinicians choose treatment modalities based not only on relief of anatomic stenosis but also on their ability to preserve long-term vascular health.

Study limitations

Our results will reflect vascular function in a selected group of optimally treated CoA patients and may not be generalizable to all CoA patients. We will compare vascular function after treatment but not before the treatment. Variation in antihypertensive medication protocols between different institutions may affect vascular parameters.

CONCLUSION

There is ample evidence to suggest that CoA is a systemic arterial disease and not merely a focal stenosis of the aortic isthmus. However, the current management paradigm continues to focus on alleviating the anatomic stenosis. Our study aims to refine this treatment paradigm by adding the preservation of vascular function to the goals of successful treatment. The strengths of this study include its multicenter design and the use of multiple noninvasive modalities to perform a comprehensive and prospective assessment of vascular function and CV health.

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Table 5: Sample size estimation

Smallest mean PWV (m/s) among groups	Largest mean PWV (m/s) among groups	Standard deviation	Sample size for each group	Total sample size
4.0	4.8	1.0	30	90
4.0	4.8	1.1	36	108
4.0	4.8	1.2	43	129
4.4	5.3	1.0	24	72
4.4	5.3	1.1	29	87
4.4	5.3	1.2	34	102

Legend: PWV=Pulse wave velocity

Conflicts of interest

There are no conflicts of interest.

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AQ1: Kindly provide reference citation58 in text part.

APPENDICES

Appendix 1: Core laboratories, clinical sites, investigators for the LOVE-COARCT atudy, funding

Study Principal Investigators

Institution	Name
Department of Pediatric Cardiology Hospital de Santa Marta Centro Hospitalar de Lisboa Central Lisbon, PORTUGAL	José D. Martins, MD
Department of Cardiology Boston Children's Hospital Harvard Medical School, Boston, MA USA	Ashwin Prakash, MD

Site Investigators of the LOVE Pediatric Consortium

Institution	Name
Department of Pediatric Cardiology Hospital de Santa Marta Centro Hospitalar de Lisboa Central Lisbon, PORTUGAL	José D. Martins, MD (Study PI, Site PI) Fátima F. Pinto, MD, PhD (Study Advisor) Marta António, MD Lurdes Medroa Teresa Mateus Mafalda Selas, RN
Department of Cardiology Boston Children's Hospital Harvard Medical School Boston, USA	Ashwin Prakash, MD (Study PI, Site PI) Sarah de Ferranti, MD Kimberlee Gauvreau, ScD Tal Geva, MD Jonathan Rhodes, MD Cara Hass, BS (Study Coordinator) Jeffrey Reichman (Study Coordinator) James E. Lock, MD (Study Advisor) Jane Newburger, MD, MPH (Study Advisor)
Joint Division of Pediatric Cardiology Children's Hospital and Medical Center University of Nebraska College of Medicine Omaha, USA	Shelby Kutty, MD (Site PI)
Division of Pediatric Cardiology Department of Pediatrics Lucile Packard Children's Hospital Stanford University Palo Alto, USA	Elif Seda Selamet Tierney, MD (Site PI) Angela Chen
Division of Pediatric Cardiology Children's Hospital Colorado Aurora, USA	Uyen Truong (Site PI)
Serviço de Cardiologia Pediátrica Hospital Pediátrico de Coimbra Coimbra, PORTUGAL	António Marinho, MD (Site PI) Eduardo Castela, MD
Division of Pediatric Cardiology Texas Children's Hospital Baylor College of Medicine Houston, USA	Shaine Morris, MD (Site PI) Justin Zachariah, MD
CEDOC Chronic Diseases Nova Medical School Lisbon PORTUGAL	Miguel Mota Carmo, MD PhD (Director) Maria Guarino, MD PhD
Ressonância Magnética, S.A. Lisbon, Portugal	Nuno Jalles Tavares (Director) Marta António, MD Boban Thomas, MD
Biomedical Engineering Department Instituto Superior Técnico Lisbon, Portugal	Diana Cruz Oliveira, MPH

Core Laboratories

Core Lab	Institution
Cardiac Magnetic Ressoance (Ashwin Prakash) Preventive Cardiology (Sarah de Ferranti) Biostatistics (Kimberlee Gauvreau)	Department of Cardiology Boston Children's Hospital Harvard Medical School Boston, USA

Contd...

Appendix 1: Contd...

Core Laboratories	
Institution	**Name**
Tonometry and BP Assessment (Justin Zachariah)	Division of Pediatric Cardiology Texas Children's Hospital Baylor College of Medicine Houston, USA
Biomarkers (Maria Guarino)	CEDOC Chronic Diseases Nova Medical School Lisbon PORTUGAL
Endothelial Function (Elif Seda Selamet Tierney)	Division of Pediatric Cardiology Department of Pediatrics Lucile Packard Children's Hospital Stanford University Palo Alto, USA
Data Coordination	
Data Coordination (Jose Martins, Ashwin Prakash, Cara Hass, Jeffrey Reichman)	Department of Pediatric Cardiology Hospital de Santa Marta Centro Hospitalar de Lisboa Central Lisbon, PORTUGAL and Department of Cardiology Children's Hospital Boston Harvard Medical School Boston, USA

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Appendix 2a: Applanation tonometry manual of operations

For applanation tonometry, some centers will use the NIHem system (Cardiovascular Engineering, Inc., Norwood, MA USA) and others the SphygmoCor device (AtCor Medical, West Ryde, NSW, Australia). The technology is similar and the results comparable.

The patient demographics and brachial blood pressure (BP) are entered into the system. First, the tonometer is placed over the right carotid artery, just lateral to the thyroid cartilage. The location is adjusted and pressure applied as needed to optimize waveform. After ensuring that the tracings are optimal, the tracing is recorded. The carotid site is marked. Then, the tonometer is placed over the right femoral artery and the same process for obtaining an optimal curve recording is followed. The femoral site is marked. Finally, in the centers that use the SphygmoCor device, a third recording of the radial artery is performed, in the same fashion. A caliper is used to measure the distance from the suprasternal notch to the carotid site and from the suprasternal notch to the femoral site. Both distances are entered in the system.

For pulse wave velocity and augmentation index calculation, both systems analyze the curves and supply the data with the proprietary software package, without any input from the examiner.

For pulse wave analysis (central aortic pressure and pulse pressure), the analysis procedure differed slightly between systems. The analysis from the NIHem system is done by the system's software. In the centers that used SphygmoCor, the signal averaged carotid pulse wave is digitalized and calibrated according to a published approach:[41,51] The brachial diastolic and mean pressures are used and the same diastolic and mean pressures are assigned to the averaged carotid pulse. Moreover, the radial pressure waveform is used to retrieve the correspondent time instants of diastolic and mean pressures. Given the two pressure values and the correspondent time instants, it is possible to calibrate each averaged carotid pressure waveform. This process allows a quantitative analysis of the pulse waveform.

Appendix 2b: Cardiac magnetic resonance imaging manual of operations

Cardiac magnetic resonance (CMR) will be performed using commercially available whole-body 1.5 T scanners (Achieva; Philips Healthcare, Best, the Netherlands; Signa 1.5T or GE Medical Systems, Milwaukee, WI, USA). Electrocardiography (ECG)-gated steady-state free precision (SSFP) localizers will be used in sagittal, coronal, and axial planes during free breathing. Ventricular function will be assessed from short-axis stack to cover ventricles from base to apex, acquired using the following imaging parameters: slice thickness 5–8 mm, slice gap 0–1 mm, slice number 12–14, cardiac phases 30, retrospective gating with breath-holding. In patients unable to breath-hold 3 signal

averages during free-breathing will be used. SSFP cine imaging will also be performed in two orthogonal long-axis planes of the left ventricular outflow tract (during breath-hold), short axis of the ascending aorta (AAO), and in the long axis of the aortic arch (free-breathing, used as reference for pulse wave velocity measurements), proximal descending aorta (DAO, 2–3 cm distal to the isthmus, sufficiently distal to dephasing jets), mid-DAO (diaphragmatic level), and distal DAO (just above iliac bifurcation). ECG-gated through-plane phase-contrast flow measurements will be performed at the AAO (5 mm distal to the sinotubular junction) and in proximal-, mid-, and distal-DAO segments (matched to location of the cine SSFP acquisitions) using the following imaging parameters: signal averages = 2, cardiac phases 100 (TFE factor/views per segment/ = 1 [to maximize temporal resolution]), and velocity encoding 200–250 cm/s (higher if needed to avoid aliasing). ECG and respiratory navigator-gated three-dimensional SSFP MRA of the aortic arch will be performed in the sagittal plane.

The patient's right arm BP while on scanner table and length of time since last meal and content of last meal will be recorded. Images will be analyzed by a single observer (A.P.) in the CMR core lab using a commercial computer workstation (Extended Workstation; Philips Healthcare) and using commercially available analysis software (QMass and QFlow, Medis, The Netherlands). Ventricular function and mass will be calculated using standard techniques. Cross-sectional areas of the AAO and proximal, mid, and distal DAO will be directly planimetered at peak systole and mid-diastolic frames to calculate parameters of segmental aortic stiffness as previously described.[52] Pulse wave velocity will be measured using the transit-time method.[20] Pulse wave velocity will be calculated for the entire aorta (AAO to distal DAO), as well as in the following segments: AAO to proximal DAO, proximal DAO to mid-DAO, and mid-DAO to distal DAO. Aortic arch shape will be classified and the aortic arch index calculated as previously described.[53]

Appendix 3: Endothelial pulse amplitude testing manual of operations

The testing room will be arranged to provide a quiet, restful environment with a comfortable temperature of 22°C to 23°C. Before testing, patients will be asked to fast overnight for 12 h, except for the consumption of water. Unless the patients are taking a daily vitamin, they will be asked to refrain from taking vitamin pills and over-the-counter medications; in the case that an over-the-counter medication is used, it will be documented.

The Endo-PAT (Itamar Medical Ltd, Caesarea, Israel) testing protocol[40] will be performed in the morning (starting time between 8 and 11 am) and fasting. Any restrictive clothing that could interfere with blood flow to the arms or fingers will be removed, including heavy coats or clothes with thick sleeves, watches or rings or other jewelry on the hands and fingers, and long fingernails shortened with a fingernail clipper.

Noninvasive pneumatic probes will be placed on the index fingers of both hands. The pulse wave amplitude will be recorded continuously from both index fingers. Reactive hyperemia will be performed by achieved by occlusion of the brachial artery of one arm with a BP cuff for 5 min (to 200–220 mmHg). The tracing in the nonoccluded arm will serve as a control for changes in overall physiologic state. The Endo-PAT data will be analyzed with the proprietary software package, without any input from the examiner. The Endo-PAT index is defined as the ratio of the average pulse amplitude during the 1 minute period beginning after exactly 90 s of reactive hyperemia compared with the average pulse amplitude during the 210-s preocclusion baseline period.

Appendix 4a: Right arm, auscultatory blood pressures measurement manual of operations

The patient will be seated with the feet flat on the floor, with the knees at 90° and the back supported. After 5 min of resting quietly, with no conversation or television, the auscultatory BP will be obtained in the right arm. For cuff choice, the length of the bladder encircled no <80% and no more than 100%, of the bicep and the width of bladder encircled no <40% and no more than 50%, of the circumference of patient's arm circumference, measured at the widest area of bicep, midway between the tip of the patient's shoulder and the tip of the patient's elbow. The patient's right arm will be at placed at heart level, supported at the level of the nipple by resting arm on a table or chair arm or propped on a pillow.

The stethoscope's bell will be placed over patient's brachial pulse. The cuff will be inflated up to 140 mmHg and deflated slowly while listening for the Korotkoff sounds, systole being number when the sound is first heard consistently and diastole when the last pulsation is heard or when it muffles. If pulsations are immediately audible, the cuff will be deflated entirely and the patient allowed to sit quietly for 1 minute. Then, the cuff will be again inflated to 160 mmHg (or higher) and the steps above will be followed. This procedure will be repeated until the blood pressure (BP) is not immediately audible.

Three BPs will be obtained, allowing 1 min between deflation and reinflation of cuff for each measurement. The average of the 2nd and 3rd measurements will be considered the final right arm BP and interpreted according to the published guidelines for children[54] and adults.[55]

Appendix 4b: Four extremity, automated blood pressures (Dinamap) measurement manual of operations

While the patient is supine, two sets of four extremity blood pressure (BP) will be measured, with the automated BP monitor (Dinamap).

The BP pressure gradient will be registered, between the second systolic right arm measurement and the highest of the two legs systolic second measurements. In the presence of an aberrant right subclavian artery that originates distal to the Coarctation of the aorta site, seen by cardiovascular magnetic resonance, we will use the second left systolic arm measurement for the residual gradient.

Appendix 4c: Ambulatory blood pressure (BP) monitor methods of operations

The patient data will be recorded. The choice of the cuff will follow the same guidelines described for manual auscultation of right arm BP. Cuff inflation will be programmed for 15–20-min intervals. During nighttime, intervals are wider, but not fewer than one per hour and preferably more. The patient will record the sleep time, wake time, and any periods of vigorous exercise. The patient will be instructed to avoid direct contact of the monitor with water and participation in activities that could damage it.

The study will be considered adequate if there is a record of at least 1 reading per hour, i.e., no more than 1 h between consecutive readings for a full 24-h study. If less than 12 h are recorded, the ambulatory blood pressure monitoring data will be considered inadequate. Diurnal pattern will be determined by the patient diary. Vigorous exercise periods will be excluded.

The data on 24-h systolic BP load, 24-h diastolic BP load, diurnal systolic dipping, diastolic dipping and 24 h, daytime and nighttime mean systolic BP, and mean diastolic BP will be recorded. Patients will be staged as having ambulatory hypertension, masked hypertension, white coat hypertension or normotensive, according to the age-based normative tables based on statements for children and adolescents[43] and adults.[56] Patients currently on antihypertensive medication are also classified into the hypertensive group [Table 4].

Appendix 4d: Exercise test: Manual of operations

The patient information will be entered per equipment specification and the study identifier on the datasheet and the date of the test. For patient safety issues, medical history, medications, activity level, and symptoms will be reviewed and the exercise stress test protocol wil be explained. Antihypertensive medications will be continued the day of testing.

The patient will be asked to lay supine, and a right arm and right or left leg blood pressure measured using a commercial oscillometric and appropriate sized cuff bladders and recorded as preexercise blood pressure (BP) values and gradient. The patient then will step onto the treadmill and instructed to hold the handlebar throughout the test. We will use the standard Bruce treadmill protocol and, when available, a Met Cart. As the patient exercises, their symptoms and electrocardiography (ECG) will be continuously monitored. At 2-min of each stage, a BP will be taken in the right arm by having the patient take their hand off the treadmill and hold onto the arm of the person performing the test. The test will be terminated when the patient can no longer continue the exercise, reaches a systolic BP higher than 240 mmHg, has clinically relevant symptoms or ECG changes. Immediately after the exercise ended, BP in the right arm and the left leg will be recorded in a supine position. For the recovery period, the patient will sit upright in a chair, and right arm BP will be recorded at 1, 3, 5, and 7 min of recovery, at which time the test is ended.

The data on exercise duration, baseline and exercise right arm BP, pre- and post-exercise systolic BP gradient, patient symptoms, ECG changes and, when available, cardiorespiratory physiological data will be documented. We will label exercise-induced hypertension when the systolic BP is ≥220 mmHg.

Appendix 5: Biomarkers manual of operations

The patients will follow a low-nitrate diet for 3 days before the blood sample collection, which avoids of a list of foods with a high content in nitrites that influence nitric oxide determination, including bacon, beets, broccoli, canned food, cauliflower, celery, Chinese cabbage, corned beef, ham, hot dogs, lettuce, old cheese, radish, salami, sausages, smoked fish, spinach, and turnip. After an overnight fast (for 12 h), samples will be collected by venipuncture from catheters maintained with saline only, since heparin interferes with accuracy of the biomarkers assessed. The first 5–10 mL of blood will be discarded and 2.7 ml of venous blood will be collected into 3.2% sodium citrate (light-blue) tubes (BD Vacutainer®), and into plastic microtubes (Safe-Lock Eppendorf). Within 3 h of collection, samples will be centrifuged for 20 minutes at 3000g (4ºC). Aliquots of 250 µl of the supernatant will be collected into 14 labeled microtubes of 1.5 ml and immediately stored at – 80ºC until shipping to the Biomarkers Core Laboratory.

Aliquots for NOx analysis will be deproteinized using cold ethanol precipitation methodology. Ethanol will be refrigerated to 0ºC and added to the plasma sample in a 1:3 proportion. After letting it stand at 0ºC for 30 min, the sample will

be centrifuged at 14,000 rpm for 10 min. The supernatant will be then removed for analysis. The quantification of plasma NO levels will be carried out using a nitric oxide analyzer, the Sievers Instruments NOA 280i™, a high sensitivity detector of that allows determination of NO based on a chemiluminescence reaction between NO and ozone.

Plasma asymmetric dimetilarginine (ADMA); vascular cell adhesion molecule 1 (VCAM-1); high-sensitivity C-reactive protein (hs-CRP) interleukin-1-beta (IL-1β); MMP-2 and MMP-9 will be quantified using the following double-antibody sandwich enzyme-linked immunosorbent assay ELISA kits: Human asymmetrical dimethylarginine, ADMA (Sunred Biological Technology, Shangai, China); hs-CRP (BoosterBio, Pleasanton, USA); VCAM-1; IL-1β; MMP-9/Gelatinase A; MMP-2/Gelatinase B; and transforming growth factor beta (RayBiotech, Inc. Norcross, USA).

Appendix 6: Cardiovascular health assessment manual of operations

The following questionnaires will be used.

Lifestyle questionnaire:

- On an average weekday, how many hours do you watch TV?
- On an average weekday, how many hours do you play video/computer games or use a computer for something that is not school/work related?
- In the past week, how many days were you/was your child physically active for a total of at least 30 min/day?
- In the past week, how many days did you/your child eat breakfast? In the past week, how many days did you/your child eat food from a fast food restaurant?
- In the past week, how many days did all or most of your family sit down and eat dinner at home?
- On an average weekday, how many hours of sleep do you get a night?
- Have you smoked one or more cigarettes in the past month? If yes, please quantify.
- Were you previously a smoker?
- Do you live in a household with a smoker?

Family history questionnaire:

For all the following questions, the possible answers will be "no," "parents/siblings," "grandparents/aunts/uncles," and "both"

- Biological relatives of you/your child with overweight/obesity
- Biological relatives of you/your child with type 2 diabetes
- Biological relatives of you/your child with high blood pressure
- Biological relatives of you/your child with high cholesterol
- Biological relatives of you/your child with heart disease/stroke
- All answers had the following options: Parents/siblings/grandparents/aunts/uncles.

Appendix 7. Comprehensive List of Study Variables

	Variables	Comments or Definitions
Medical History	BSA at Initial Echocardiogram	using Haycock's Formula; m^2
	Minimum Transverse Arch Diameter Z-score on Initial Echo	Calculated with Boston z-scores
	Isthmus z score on Initial Echo	Calculated with Boston z-scores
	Initial Doppler coarctation gradient	mmHg
	Bicuspid/Bicommisural Aortic Valve?	Yes/No
	Initial arm-leg systolic BP gradient	mmHg
	Type of Initial Treatment	Balloon/Stent/Surgery
	Currently daily medications?	Yes/No. If yes, please specify.
Local blood results	Total Cholesterol	mg/dL
	LDL	mg/dL
	HDL	mg/dL
	Triglycerides	mg/dL
	Plasma Glucose	mg/dL
	Insulin	uIU/mL
	Hemoglobin A1C	%
Applanation tonometry	Central Systolic Blood Pressure	mmHg
	Central Pulse Pressure	mmHg
	Heart Rate	bpm
	Carotid Femoral PWV	meters/second
	Augmentation Index (%)	%
	Augmentation Index at HR75	%

Contd...

Appendix 7. Contd...

	Variables	Comments or Definitions
CMR	LV End-Diastolic Volume indexed to BSA	ml/m^2
	LV End-Systolic Volume indexed to BSA	ml/m^2
	LV Ejection Fraction	%
	LV Mass indexed to BSA	g/m^2
	Ascending Ao - Descending Ao PWV (Ascending Ao to proximal, mid and distal descending Ao)	$\frac{\text{Distance (Asc Ao to Desc Ao)}}{\text{Time Delay (Asc Ao to Desc Ao)}}$ meters/second
	Type of arch	Romanesque; Gothic; Crenel
	Aortic diameter (Ascending, Proximal, Mid and Distal Ao)	mm/mm^2
	Aortic strain (Ascending, Proximal, Mid and Distal Ao)	$\frac{\text{Sistolic Area - Diastolic Area}}{\text{Diastolic Area}}$
	Aortic compliance (Ascending, Proximal, Mid and Distal Ao)	$\frac{\text{Ao Area Sist - Ao Area Diast}}{\text{SBP} - \text{DBP}}$ cm^2/mmHg
	Aortic Distensibility (Ascending, Proximal, Mid and Distal Ao)	$\frac{\text{Ao strain}}{\text{SBP} - \text{DBP}}$ mmHg-1
	Aortic stiffness β index (Ascending, Proximal, Mid and Distal Ao)	$\frac{\ln(\text{SBP} / \text{DBP})}{\text{Strain}}$
	Loss of pulse amplitude	$100 \times \frac{\text{flow (AscAo} - \text{DescAo)}}{\text{flow (AscAo)}}$
	Aorta Young's modulus (Ascending, Proximal, Mid and Distal Ao)	$\frac{(\text{SBP - DBP})\,\text{Ao diameter diastole}}{\text{Ao diameter}\,(\text{systole - diastole})\,\text{Ao wall thickness}}$
	Arterial elastance (Ea)	$\frac{\text{End Systolic Pressure}}{\text{Sroke Volume}}$ mmHg/ml
	LV end-systolic elastance (Ees)	$\frac{\text{End Systolic Pressure}}{\text{LV end Systolic Volume}}$ mmHg/ml
Endo-PAT	Reactive Hyperemia Index (RHI)	
	Augmentation Index	%
	Augmentation Index at 75 bpm	%
BP during the patient's visit	Residual SBP gradient (between right arm and highest of the legs)	Supine. Automated. Two sets of measurements; mmHg
	Right arm BP	Seated. Manual. Three sets of measurements; mmHg
ABPM	24 Average Systolic BP	mmHg
	24 Hour Average Diastolic BP	mmHg
	Daytime Average Systolic BP	mmHg
	Daytime Average Diastolic BP	mmHg
	Nighttime Average Systolic BP	mmHg
	Nighttime Average Diastolic BP	mmHg
	24h systolic load	%
	24h diastolic load	%
	Diurnal Systolic Variation	%
	Diurnal Diastolic Variation	%
Exercise test	Exercise Duration	Minutes
	Pre-exercise right arm BP	mmHg
	Pre-exercise leg BP	mmHg
	Pre-Exercise SBP gradient	mmHg
	Post-exercise right arm BP	mmHg
	Post-exercise leg BP	mmHg
	Pre-Exercise SBP gradient	mmHg
	Peak exercise BP	mmHg
Biomarkers	NOx	ug/ml
	ADMA	ng/L
	High Sensitivity CRP	mg/L
	VCAM-1	ng/ml
	IL-1beta	pg/ml

Contd...

Appendix 7. Contd...

Variables	Comments or Definitions
TFG-Beta	
MMP-2/Gelatinase A	ng/ml
MMP-9/Gelatinase B	ng/ml

Legend: ADMA = Asymmetric Dimetilarginine; Ao = Aorta; BP = blood pressure; BP = Blood Pressure; BSA= Body Surface Area; CMR = Cardiac magnetic resonance; DBP = Diastolic Blood Pressure; HDL = High-density lipoprotein cholesterol; Hs-CRP = High sensitivity C-Reactive Protein; IL-1β = Interleukin 1 beta; LDL = Low-density lipoprotein cholesterol; MMP-2 = Matrix Metalloproteinase-2; MMP-9 = Matrix Metalloproteinase-9; NOx = Nitric Oxide; PWV = Pulse Wave Velocity; LV = Left Ventricle; SBP = Systolic Blood Pressure; TFG-β = Transforming Growth Factor beta; VCAM-1 = Vascular Cell Adhesion Molecule 1; † using previously published normative data.[57]

3. PAPERS SUBMITTED FOR PUBLICATION

Martins JD, Zachariah MD, Selamet Tierney ES, Truong U, Morris SA, Kutty S, MD, PhD, de Ferranti SD, Guarino M, Thomas B, Oliveira D, Marinho A, António M, Gauvreau K, Jalles N, Geva T, Carmo MM, Prakash A, Lock JE for the LOVE-COARCT Study. **Comparison of Vascular Function Between Transcatheter Treatments in Coarctation of the Aorta** [submitted for publication].

TITLE PAGE

Full title: Impact of Treatment Modality on Vascular Function in Coarctation of the Aorta: the LOVE-COARCT study

First author's surname: Martins

Short title: Vascular function after CoA treatment

Authors: Jose D. Martins, MD, MSc,[1] Justin Zachariah MD, MPH,[2] Elif Seda Selamet Tierney, MD,[3] Uyen Truong, MD,[4] Shaine A. Morris,[2] MD, MPH, Shelby Kutty, MD, PhD, MHCM[5] Sarah D. de Ferranti, MD, MPH,[6] Maria Guarino MD, PhD,[7] Boban Thomas, MD,[8] Diana Oliveira, MSc,[9] António Marinho, MD[10] Marta António, MD[1] Kimberlee Gauvreau, ScD,[6] Nuno Jalles, MD,[8] Tal Geva, MD,[6] James E. Lock, MD,[6] Miguel M. Carmo, MD, PhD,[7] and Ashwin Prakash, MD[6] for the LOVE-COARCT Study.

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ABSTRACT

Background: Optimally treated patients with coarctation of the aorta (CoA) remain at risk for late vascular dysfunction. The effect of treatment modality on vascular function is unknown. We compared vascular function in patients with CoA treated with surgery, balloon dilation (BD) or stent implantation.

Methods: In successfully repaired CoA patients, we prospectively compared aortic stiffness by applanation tonometry and cardiac magnetic resonance (CMR); endothelial function by endothelial pulse amplitude testing; blood pressure (BP) phenotype by office BP, ambulatory BP monitoring, and BP response to exercise; left ventricular (LV) mass by CMR; and blood biomarkers of endothelial function, inflammation, vascular wall function, and extracellular matrix.

Results: Participants included 75 patients treated with surgery (n=28), BD (n=23), or stent (n=24). Groups had similar age at enrollment, CoA severity, residual gradient, and metabolic profile but differed by age at treatment. Systemic hypertension, aortic stiffness, endothelial function, and LV mass were similar among groups. However, BD had more distensible ascending aortas, lower peak systolic BP during exercise, less impairment in diurnal BP variation, and lower inflammatory biomarkers. The results were unchanged after adjustment for potential confounders, including age at treatment.

Conclusions: Treatment modality was not associated with systemic hypertension, global aortic stiffness, and endothelial function. However, BD patients had a better vascular phenotype profile characterized by higher ascending aorta distensibility, lower night-time BP, lower peak exercise BP and lower levels of inflammatory markers. Further research on the association of our findings with long-term clinical outcomes may help improve treatment guidelines.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT03262753

KEYWORDS: Coarctation of the aorta (CoA), long-term outcomes, vascular function, arterial stiffness, pulse wave velocity, cardiac magnetic resonance imaging.

Current surgical and percutaneous techniques for treatment of coarctation of the aorta (CoA) are equally effective at eliminating the narrowing of the aortic isthmus (except in infants and young children, in whom surgery is preferred) [1]. However, despite optimal anatomical results, late morbidity is significant with high rates of systemic hypertension.[1] Secondary abnormalities including increased left ventricular (LV) mass,[2-5] and impaired systolic[3, 5] and diastolic function[6] have also been reported. Furthermore, treated patients have reduced life expectancy, due to premature cardiovascular complications and stroke.[7-9] Vascular dysfunction is common after CoA treatment and may contribute to these adverse outcomes.10, 11 Patients with successfully treated CoA have been reported to have stiffer large arteries,[3-5, 11] impaired endothelial function,[2, 10, 12, 13] and imbalances in biochemical and molecular pathways associated with vascular function.[12-17] Although vascular dysfunction is driven by important pre-treatment factors including abnormalities in the renin-angiotensin system[18] and baroreceptor function,[19] several treatment-related factors have been associated with worse vascular dysfunction, such as older age at treatment,[3, 10, 15] longer length of follow-up, and residual narrowing at the site of CoA repair.[2]

It is possible that treatment modality affects vascular function by different effects on the stiffness of the repaired arterial segment: surgical repair creates a focal scar at the site of the surgical anastomosis; stenting creates a rigid, noncompliant aortic segment; and balloon dilation (BD) produces a controlled tear of the aortic intima and part of the media without affecting the adventitia.[20] However, the effect of treatment modality on vascular function has not been systematically compared, and management is often guided by physician or institutional preference with the primary goal of alleviating the anatomic narrowing. Our study aims to refine this treatment paradigm by adding to the goals of therapy the preservation of vascular function. We hypothesized that patients with CoA treated using balloon dilation will demonstrate the most optimal level of vascular function because this modality is least likely to impact the biomechanical properties of the aortic wall. Using a prospective observational study design, we compared patients treated with surgery, balloon dilation, or stent implantation to examine whether treatment modality is associated with parameters of vascular function and LV remodeling after repair.

METHODS

STUDY DESIGN AND SUBJECTS

This was a multicenter cross-sectional prospective observational study. Patients were recruited at 7 large pediatric cardiac centers in Europe and North America between June 2013 and April 2017. We included patients with (a) isthmic CoA; (b) age at recruitment 8-35 years, and (c) CoA treatment after 1994. We excluded patients with (a) residual CoA defined as a systolic upper-to-lower extremity systolic BP (SBP) gradient >20 mm Hg; (b) co-morbidities including complex congenital heart disease (such as tricuspid atresia), vasculopathy, or genetic syndrome; (c) CoA treatment using > 1 modality; (d) severe hypoplasia of the transverse aortic arch (z-score <-4); (e) other cardiac defects requiring intervention (such as ventricular or atrial septal defect, valvar mitral or aortic stenosis); and (f) treatment under 1 year of age (because these patients are treated almost exclusively with surgery). We attempted to frequency-match the 3 treatment groups on age at initial repair, and age at enrollment. Study data was collected and managed centrally using REDCap electronic data capture tools.[21] The study protocol was approved by the Institutional Review Board or Institutional Ethics Committee at each participating center. Written consent was obtained from each participant or parent, as appropriate.

STUDY TESTS

All study tests occurred during a one- or two-day visit. Vascular function was assessed comprehensively by several modalities. Testing included assessment of (a) arterial stiffness by applanation tonometry and cardiac magnetic resonance imaging (CMR), (b) endothelial function by endothelial pulse amplitude testing (Endo-PAT), and (c) BP phenotype using office BP measurement, ambulatory BP monitoring (ABPM) and BP response during peak exercise, and blood biomarkers related to endothelial function, systemic inflammation and vascular remodeling.

APPLANATION TONOMETRY

Studies were performed using the NIHem (Cardiovascular Engineering, Inc., Norwood, MA USA) or the SphygmoCor device (AtCor Medical, West Ryde, NSW, Australia) to calculate carotid-femoral pulse wave velocity (PWV) using standard technique as previously described.[22] The NIHem system determines central aortic pressure as equivalent to measured carotid pulse waveform as calibrated by the brachial waveform to the brachial diastolic and mean BP. For tracings obtained using the SphygmoCor device, the signal averaged carotid pulse wave was digitalized and calibrated according to a previously published approach to allow a quantitative analysis of the pulse waveform.[23] Comparability of the two approaches as described above has been previously established.[24]

CMR

Examinations were performed using commercially available whole-body 1.5 T scanners (Achieva; Philips Healthcare, Best, the Netherlands; Signa 1.5T or GE Medical Systems, Milwaukee, WI, USA). Images were analyzed by a single observer (A.P.) in the CMR core lab using a commercial computer workstation (Extended Workstation; Philips Healthcare) and commercially available analysis software (QMass and QFlow, Medis, The Netherlands). Right brachial artery BP was measured before the examination in the supine position by using commercial oscillometric BP recorders. LV function and mass were measured using ECG-gated steady state free precision image in the ventricular short axis as previously described.[22] Segmental aortic stiffness (strain, distensibility, and β stiffness index) were calculated using cine steady state free precision images in the short axis of the ascending aorta (AAO), proximal descending aorta (DAO, 2-3 cm distal to the isthmus, sufficiently distal to dephasing jets), mid DAO (diaphragmatic level) and distal DAO (just above iliac bifurcation) using previously described methodology.[22] Global and segmental PWV were calculated using the transit-time method using ECG-gated through-plane phase-contrast flow measurements at the AAO, and proximal, mid and distal DAO segments (matched to location of the cine steady state free precision acquisitions) as previously described.[22] Temporal resolution was maximized by reconstructing 100 cardiac phases and using a turbo factor/views-per-segment setting of 1. ECG and respiratory navigator-gated 3-D steady state free precision magnetic resonance angiography of the aortic arch was performed in the sagittal plane. Aortic arch shape and the aortic arch index were obtained as previously described.[22]

ENDOTHELIAL FUNCTION

Flow-dependent, endothelium-mediated vasodilation was assessed using endothelial pulse amplitude testing (Endo-PAT; Itamar Medical, Caesarea, Israel) as previously described.[22] Endo-PAT is a novel non-invasive and reproducible technique that measures changes in pulsatile arterial volume with a fingertip probe. Analysis of the pulse waveform allows for automated calculation of endothelial function in one arm, while the contra-lateral serves as control.

BP PHENOTYPE

The seated right arm office BP was measured after 5 minutes of quiet rest using the manual auscultation technique with arm supported and feet flat on the floor. Three recordings were obtained, allowing one minute between deflation and re-inflation of the cuff. The BP was recorded as the average of the 2nd and 3rd measurements. BP was classified according to the 4th Task Force report for children[25] and the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for adults (Table I in the online-only Data Supplement).[26] Supine, oscillometric four extremity BP was used to assess for residual coarctation defined as the difference between the right arm SBP and the highest SBP in either leg.

Home ABPM was performed using previously described technique.[22] The examination was considered adequate if the recording lasted > 12 hours. BP averages and proportion of elevated readings (load) were calculated and categorized according to the age-based normative guidelines previously established for children[27] and adults[28] and patients were staged as having ambulatory hypertension, masked hypertension, white coat hypertension or normotensive (Table II in the online-only Data Supplement).

Patients performed an exercise stress test using the standard Bruce treadmill protocol to assess the BP response to exercise, as previously described.[22] Baseline and peak arm-leg SBP differences and the increase in right arm BP with peak exercise were recorded. Gas-exchange during exercise was assessed in a subset of patients, when feasible.

BLOOD BIOMARKERS

The patients followed a low-nitrate diet for three days and fasted for 12 hours prior to sample collection. We measured biomarkers of nitrate metabolism as regulators of endothelial function (nitrite/nitrate, NOx; and asymmetric dimethylarginine, ADMA);[29, 30] systemic inflammation (high sensitivity C-reactive protein, hs-CRP; and interleukin 1 beta, IL-1β);[31, 32] vascular wall function (vascular adhesion molecule 1, VCAM-1);[31] and extracellular matrix remodeling (matrix metalloproteases MMP-2 and MMP-9; and transforming growth factor beta-1, TGF-β1).[33] NOx was determined by chemiluminescence (Sievers NOAnalyzer 280i) and all remaining measurements were performed using commercial enzyme-linked immunosorbent assay kits: ADMA (Sunred Biological Technology, Shanghai, China); hs-CRP (BoosterBio, Pleasanton, USA); VCAM-1; IL-1β; MMP-9; MMP-2 and TGFb-1 (RayBiotech, Inc. Norcross, USA). All measurements were performed as previously described,[22] at the central biomarker laboratory in Lisbon.

STATISTICAL ANALYSIS

Sample size estimates were obtained based on prior reports of arch PWV measured by CMR in normal subjects (3.3±0.6 m/s) and in patients with CoA (4.7±1.1 m/s).[4, 34] Sample size estimates for comparison of CMR PWV between three equal sized treatment groups (assuming an overall significance level of 0.05 and power of 0.8) are shown in Table III in the online-only Data Supplement). Using these estimates, we planned on recruiting 24-30 patients in each treatment group.

Categorical patient characteristics, clinical variables, and outcomes were summarized as frequencies and percentages, and compared across the three treatment groups using Fisher's exact test. Continuous variables which were approximately normally distributed were summarized using means and standard deviations and compared using one-way analysis of variance; continuous variables which were not normally distributed were summarized using medians and ranges and compared using the Kruskal-Wallis test. Age at treatment and presence of a bicuspid aortic valve were thought to be possible confounding variables and were observed to differ by treatment group; therefore, linear and logistic regression models were used to adjust for confounding when comparing selected outcome variables across treatment groups. In these models, the surgical group was used as the reference category against which balloon dilation and stent were compared. Each model adjusted for age at

treatment as a continuous variable, and presence of a bicuspid aortic valve as a binary variable. Analyses were performed in SAS (version 9.4, Cary, NC, USA)

RESULTS

STUDY SUBJECTS

Patient characteristics by treatment group are summarized in Table 1. At study enrollment, the treatment groups were similar with respect to baseline characteristics including age and body mass index at enrollment, residual coarctation severity, and metabolic profile. Among pre-treatment characteristics, the treatment groups were similar with respect to coarctation severity (including size of the aortic arch and isthmus, non-invasive BP and echoDoppler estimated gradient), sex distribution, and the prevalence of bicuspid aortic valve. However, patients treated with a stent were older at the time of treatment compared to those treated with surgery or balloon dilation.

AORTIC STIFFNESS

Results of aortic stiffness assessment by CMR and applanation tonometry are summarized in Table 2 and Figure 1. At comparable distending pressures (Table 3), overall PWV was similar among the treatment groups by both CMR and applanation tonometry (Figure 1). On segmental PWV measurements by CMR, aortic arch PWV was lowest in the balloon dilation group, but the difference did not reach statistical significance (Figure 1). Among CMR segmental aortic stiffness parameters, balloon dilation patients had the most distensible AAO, while stent patients had the least distensible AAO, with surgical patients demonstrating intermediate values (Figure 1). Compared to stent patients, balloon dilation patients showed 48% higher AAO distensibility and 27% lower aortic arch PWV. Segmental stiffness parameters were mostly similar across treatment groups at the DAO (proximal, mid, and distal), except for distal DAO strain, which was lowest in the stent group. No differences were seen across treatment groups in measurements of central SBP or central pulse pressure by tonometry. Augmentation index at heart rate 75 bpm was similar among groups.

To assess for potential confounding by age at treatment or bicuspid aortic valve (known to be associated with impaired aortic elasticity)[35] on the relationship between treatment modality and aortic stiffness, we used multivariable modeling for key stiffness parameters. The univariate relationships shown in Table 2 remained unchanged in the multivariable models after adjustment for the potential confounding variables (age at treatment, and bicuspid aortic valve) (Supplemental Table VI).

ENDOTHELIAL FUNCTION

Endothelial function assessed using the Endo-PAT index was similar across treatment groups (Table 2 and Figure 1). The univariate relationships shown in Table 2 remained unchanged in the multivariable models after adjustment for the potential confounding variables (age at treatment, and bicuspid aortic valve) (Supplemental Table VI).

BP PHENOTYPE

Results of office BP measurements and ABPM are summarized in Table 3. There were no significant differences across treatment groups with respect to the prevalence of hypertension by office measurements or ABPM, and average systolic and diastolic BP by ABPM. However, the balloon dilation group showed lower nighttime BP and less impairment in diurnal variation, compared to the stent and surgery groups (Figure 1). On exercise stress test (Table 4), there were no significant differences between the treatment groups with respect to exercise duration, peak VO_2, VE/VCO_2 slope, or upper-lower extremity SBP gradient. However, the peak SBP during exercise was lower in the balloon dilation group (Figure 1) and this relationship persisted after adjustment for potential confounding variables (age at treatment, and bicuspid aortic valve) (Supplemental Table VI).

LV AND AORTIC MORPHOMETRICS

The treatment groups were similar with respect to LV size, ejection fraction, and mass (Table 5 and Figure 1). Aortic dimensions, including those of the transverse aortic arch were similar between the treatment groups. Isthmic dimensions were slightly smaller in the balloon di-

lation group compared to the surgical group but could not be measured in stented patients due to ferromagnetic artifact from the stent. Arch shape distribution was also similar between the treatment groups, assessed both qualitatively and quantitatively (using the arch shape index).[36]

BLOOD BIOMARKERS

Patients in the balloon dilation group had lower levels of hs-CRP, and higher levels of MMP-9 and TGF-β1 (Table 6 and Figure 1). These differences persisted after adjustment for potential confounders (Table VI in the online-only Data Supplement). Levels of other blood biomarkers were similar across the treatment groups.

ADJUSTMENT FOR POTENTIAL CONFOUNDERS

As seen in Table 1, despite efforts at frequency matching, there were differences between the treatment groups with respect to potential confounding variables including age at treatment and the presence of a bicuspid aortic valve (known to be associated with impaired aortic elasticity).[35] Analyses to assess the impact of these confounding variables are summarized in the Supplemental Tables IV, V and VI. As seen in Table IV in the online-only Data Supplement, age at treatment was significantly associated with AAO strain, Endo-PAT index, right arm diastolic BP, and 24-hour diastolic BP but not with other key outcome variables. As seen in Table V in the online-only Data Supplement, the presence of bicuspid aortic valve was significantly associated with AAO strain but not with other outcome variables. Table VI in the online-only Data Supplement summarizes the results of multivariable modeling comparing key outcome variables between treatment groups while adjusting for these confounding variables (age at treatment and presence of bicuspid aortic valve). Adjusted and unadjusted models did not differ significantly for these key outcome variables, suggesting that the impact of these potential confounding variables on our study measurements was not significant.

DISCUSSION

In this multicenter, prospective, comprehensive comparison of optimally treated patients with CoA treated with surgery, balloon dilation, or stenting, we found that the treatment groups were similar with respect to several parameters of vascular function including the prevalence of systemic hypertension, global aortic stiffness, central BP, endothelial function, and LV mass. However, despite adjustment for potential confounding variables (including age at repair), the balloon dilation group showed a better vascular phenotype characterized by a more distensible AAO, a lower peak SBP during exercise, and less impairment in diurnal BP variation.

AORTIC STIFFNESS

Global aortic stiffness assessed using cfPWV by tonometry, or using total aortic PWV by CMR, was higher than published normal values but was similar among treatment groups.[37] However, in segmental assessment of PWV and other distensibility measures by CMR (strain, distensibility and β stiffness index), differences emerged between treatment groups. Proximal aortic (AAO and aortic arch), stiffness was lowest in balloon dilation patients and highest in stent patients. Surgical patients had intermediate values of stiffness. AAO distensibility in balloon dilation patients was similar to values reported in normal controls, while patients in the stent and surgery groups had lower values.[38] These findings were limited to the AAO, which is in line with previous studies that show that the aortic elastic properties have been found to be altered above, but not below, the CoA site, compared to normals.[5] Increased proximal aortic stiffness evidenced by an elevated PWV and lower than normal distensibility have been previously reported in patients with CoA.[4, 10, 11] However, our study is the first to systematically compare aortic stiffness across treatment modalities. The mechanism leading to a more distensible proximal aorta in balloon dilation patients remains unclear. It is possible that the absence of a surgical scar or rigid stent at the isthmus contributes to a lower stiffness at the CoA site. We acknowledge that the balloon dilation group underwent treatment at a younger age, however differences in AAO stiffness persisted after adjustment for age at treatment.

ENDOTHELIAL FUNCTION

Flow-dependent, endothelium-mediated vasodilation was assessed using Endo-PAT. Results of prior studies of endothelial function in patients with CoA have been mixed. Some studies showed impaired endothelium-dependent vascular reactivity,[10, 39, 40] while others showed preserved vascular reactivity.[41, 42] Our results showed that the Endo-PAT index was similar across treatment groups, and suggest that endothelial function is preserved after CoA treatment, compared to previously reported values in healthy controls.[43] Values obtained in our cohort are comparable to those reported using a similar technique in patients with CoA.[41]

BP PHENOTYPE

The prevalence of hypertension on office measurement and ABPM were similar to prior reports.[1, 44-46] On office BP measurements, 44% patients had pre-hypertension and 9% had hypertension. Overall, 33% were either on an anti-hypertensive medication or had hypertension. On ABPM, 36% patients were either on an anti-hypertensive medication, or had hypertension/masked hypertension. There were no differences between treatment groups with respect to the prevalence of hypertension (on office measurements and ABPM), or the average 24-hour systolic or diastolic BP. However, balloon dilation patients demonstrated lower night-time systolic and diastolic BP, and more physiologic nighttime dipping in BP, compared to the surgery and stent groups. Our results are consistent with a prior report which found lower BP in balloon dilation patients.[1] Blunted nighttime dipping in BP has been previously linked to the development and progression of end-organ disease in patients with essential hypertension, diabetes mellitus, obesity, and black race.[47] The impact of this finding on long-term outcomes in CoA patients deserves further study.

The balloon dilation group showed a less exaggerated BP elevation to exercise, compared to the surgery and stent groups. Exercise induced hypertension has been previously documented in patients with treated CoA,[48] and exaggerated BP response to exercise correlated with LV mass.[49] In the general population, exercise-induced hypertension has been shown to be predictive of future development of resting hypertension,[50] and an independent risk factor for cardiovascular events and mortality.[51]

LV MASS

Despite differences in BP phenotype, LV mass was similar across treatment groups and values were normal compared to previously reported values in healthy subjects.[52] Increased LV mass has been previously reported in patients with CoA.[4] Our LV mass values were lower compared to this prior report but are similar to a more recent publication.[46] The absence of significant LV hypertrophy may be related to the relatively young age of our patients, and good blood-pressure control in our population.

BLOOD BIOMARKERS

NOx and ADMA are biomarkers related to endothelial function and their levels have been correlated with the risk of atherosclerosis due to endothelial dependent nitric oxide regulation of smooth muscle-derived vascular tone.[29] There were no difference in NOx or ADMA levels between treatment groups, consistent with the lack of difference in endothelial function using Endo-PAT. Prior studies in patients with CoA found increased ADMA but unchanged NOx in CoA, compared to controls.[12]

IL-1β and hs-CRP are biomarkers of systemic inflammation, which act on the vascular endothelium to upregulate a number of adhesion molecules such as VCAM, with a crucial role in atherogenesis.[31, 32] Prior results of inflammatory biomarkers in patients with CoA are inconclusive.[53, 54] In our study, balloon dilation patients had lower levels of hs-CRP.

TFG- β1, MMP-2, and MMP-9 are biomarkers related to fibrotic remodeling such as the aortic remodeling that occurs in response to hemodynamic changes.[33] Elevated circulating levels have been reported in dilated aortas in patients with inherited aortopathy,[55] and are biomarkers for the presence and risk of rupture of aortic aneurysm.[56] As previously reported in patients with CoA, values of both TFG-β1and MMP-9 were elevated in our study.[15, 57] Balloon dilation patients showed the highest levels of these biomarkers. The clinical implications of these findings are unclear and further research is needed to evaluate whether these biomarkers are related to the risk of aneurysm formation in the BD group.

STUDY LIMITATIONS

There are several limitations to our study. Firstly, despite a multicenter design, our study is limited by a relatively low sample size. However, based on sample size estimates, the study had sufficient statistical power to detect group differences in CMR PWV. Secondly, although we attempted to perform frequency-matching to balance the treatment groups with respect to key confounding variables, our groups were not perfectly matched for these variables (especially age at treatment). However, surprisingly, multivariable analyses (Table VI in the online-only Data Supplement) showed that these potential confounding variables (including age at repair) did not significantly affect the comparison of key variables between treatment groups. Finally, we only included adequately treated CoA patients and these results are not generalizable to patients with significant residual CoA.

CONCLUSIONS

In this comprehensive multicenter prospective comparison of vascular function in patients with CoA adequately treated with surgery, balloon dilation, or stenting we found that the treatment groups were similar with respect to several indicators of vascular function including the prevalence of systemic hypertension, global aortic stiffness, endothelial function, and LV mass. However, the balloon dilation group showed a somewhat better vascular function phenotype with more physiologic nocturnal dipping in BP, a more distensible AAO and aortic arch, a lower peak SBP during exercise, and lower blood levels of pro-inflammatory biomarker. A possible explanation of these findings is that the introduction of a non-distensible stent or surgical scar may have deleterious effects on late vascular function. In particular, our results may suggest a cautious approach when considering aggressive primary stenting in a patient with other available treatment options, since stented patients had the worse vascular profile in our cohort. However, the benefits of a slightly improved vascular function profile after balloon dilation will need to be balanced against a higher risk of aneurysm formation and reintervention.[58, 59] Further research is needed to study whether these findings are associated with long-term clinical outcomes and if the treatment paradigm focused on gradient reduction should be refined by adding the goal of preservation of vascular function to the goals of treatment. To our knowledge, these results represent the most comprehensive prospective comparison of late vascular function between treatment modalities for CoA.

Further research is needed to study whether these findings are associated with long-term clinical outcomes.

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DISCLOSURES

None

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FIGURES

Figure 1:

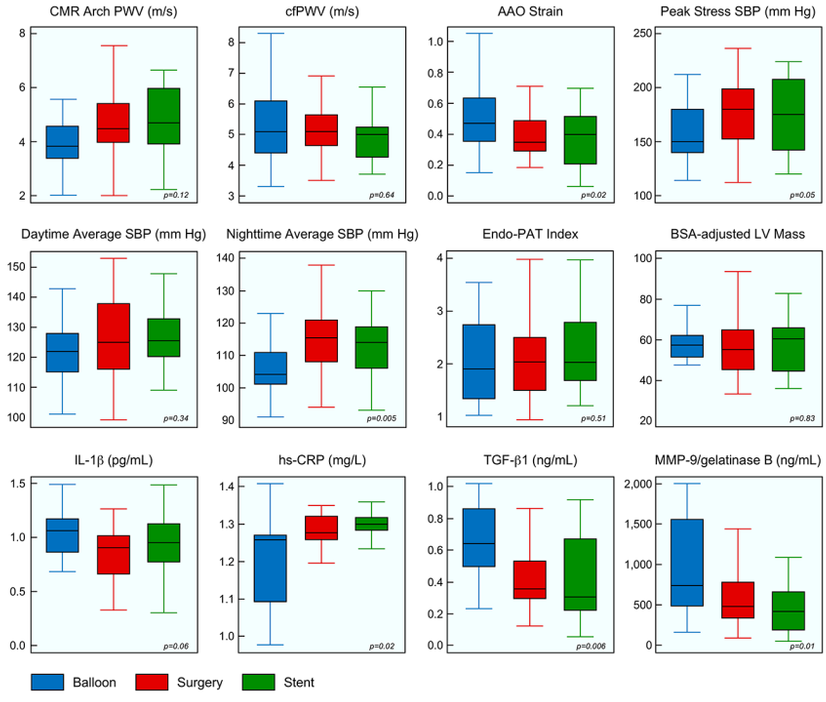

FIG. 1. COMPARISON OF KEY VASCULAR FUNCTION PARAMETERS BETWEEN GROUPS

AAO = ascending aorta; BSA = body surface area; CMR = cardiac magnetic resonance; Endo-PAT = endothelial pulse amplitude testing; hs-CRP = high sensitivity C-reactive protein; IL-1β = interleukin 1 beta; LV = left ventricle; MMP-9 = matrix metalloprotease 9; PWV = pulse wave velocity; SBP = systolic blood pressure; TGF- β1 = transforming growth factor beta-1

TABLES

TABLE 1. PATIENT CHARACTERISTICS

	Surgery (n=28)	BD (n=23)	Stent (n=24)	p Value
Pre-treatment data				
Age at treatment (years)	6 (1, 26)	5 (1, 17)	15 (7, 26)	**<0.001**
SBP gradient (mm Hg)	43.7 ± 19.3	34.6 ± 15.0	38.4 ± 21.0	0.29
TAA diameter z-score	-1.9 ± 1.0	-1.5 ± 1.4	-1.9 ± 0.8	0.38
Isthmus diameter z-score	-3.59 ± 1.21	-3.92 ± 0.89	-3.31 ± 1.37	0.32
Initial Doppler gradient (mmHg)	48.0 ± 14.7	47.9 ± 14.8	52.5 ± 20.3	0.60
Male sex	79%	74%	75%	0.94
Bicuspid aortic valve	71%	45%	50%	0.13
Age at enrollment (years)	15 (8, 33)	17 (11, 26)	20 (9, 33)	0.12
BMI at enrollment	22 (15, 32)	21 (16, 33)	23 (16, 38)	0.69
SBP gradient (mm (Hg)	-7.1 ± 14.0	-3.0 ± 12.3	-3.7 ± 14.5	0.52
NYHA class				0.37
Class I	89%	100%	92%	
Class II	11%	0%	8%	
Metabolic Profile				
Total cholesterol, mg/dL	159 (112, 210)	153 (123, 229)	152 (108, 227)	0.59
LDL, mg/dL	86 (53, 145)	81 (59, 179)	85 (44, 130)	0.66
HDL, mg/dL	53 (34, 90)	48 (31, 90)	51 (32, 88)	0.99
Triglycerides, mg/dL	76 (29, 224)	52 (29, 149)	74 (29, 167)	0.07
Plasma glucose, mg/dL	82 (74, 98)	81 (59, 93)	86 (63, 108)	0.15
Insulin, uIU/mL	6 (3, 44)	6 (3, 17)	7 (2, 20)	0.86
Hemoglobin A1c, %	5.3 (4.1, 5.7)	5.3 (4.4, 5.7)	5.3 (4.8, 5.9)	0.60
Anti-HTN Medication	14%	26%	33%	0.14

Values are mean ± standard deviation, median (minimum, maximum), or percent. BSA = body surface area; BMI = body mass index (weight (kg)/ height $(m)^2$); HTN = hypertension; LDL = low density lipoprotein; HDL = high density lipoprotein; NYHA = New York Heart Association; SBP = systolic blood pressure; TAA = transverse aortic arch

TABLE 2. AORTIC STIFFNESS AND ENDOTHELIAL FUNCTION

	Surgery (n=28)	Balloon dilation (n=23)	Stent (n=24)	p value
CMR Parameters				
PWV (m/s)				
Total	4.0 ± 0.5	4.2 ± 0.9	4.2 ± 0.7	0.72
Aortic arch	4.7 ± 1.5	4.0 ± 1.2	5.5 ± 3.8	0.12
Mid DAO	3.8 ± 0.9	4.0 ± 1.3	3.9 ± 1.4	0.87
Distal DAO	4.4 ± 1.6	4.8 ± 1.7	4.5 ± 1.5	0.70
Strain				
AAO	0.38 ± 0.14	0.51 ± 0.25	0.36 ± 0.19	**0.02**
Proximal DAO	0.27 ± 0.09	0.31 ± 0.13	0.30 ± 0.15	0.47
Mid DAO	0.37 ± 0.11	0.36 ± 0.10	0.36 ± 0.16	0.97
Distal DAO	0.37 ± 0.14	0.40 ± 0.12	0.30 ± 0.12	**0.04**
Distensibility (10^{-3}mm Hg^{-1})				
AAO	7.8 ± 3.6	9.8 ± 5.2	6.6 ± 4.3	**0.05**
Proximal DAO	5.6 ± 2.1	6.1 ± 3.3	5.6 ± 2.7	0.71
Mid DAO	7.5 ± 2.5	6.9 ± 3.3	6.8 ± 3.4	0.67
Distal DAO	7.8 ± 4.1	7.5 ± 3.1	5.9 ± 3.2	0.15
β stiffness index				
AAO	1.76 ± 0.73	1.59 ± 1.15	2.49 ± 1.48	**0.02**
Proximal DAO	2.53 ± 1.59	2.63 ± 1.89	2.50 ± 0.96	0.96
Mid DAO	1.75 ± 0.76	1.93 ± 0.75	2.15 ± 1.11	0.26
Distal DAO	1.84 ± 0.91	1.72 ± 0.68	2.98 ± 3.70	0.11
Applanation Tonometry				
cfPWV (m/s)	5.2 ± 0.9	5.3 ± 1.1	5.0 ± 0.9	0.64
AI at HR 75 bpm (%)	-14 ± 13	-13 ± 21	-6 ± 18	0.24
Central SBP (mm Hg)	114 ± 18	109 ± 14	112 ± 21	0.60
Central PP (mm Hg)	50 ± 20	46 ± 13	45 ± 19	0.49
Endo-PAT				
Endo-PAT index	2.15 ± 0.77	2.00 ± 0.78	2.25 ± 0.68	0.51

Values are mean ± standard deviation. AAO = ascending aorta; AI = augmentation index; aortic arch PWV = AAO to proximal DAO pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; DAO = descending aorta; Endo-PAT = endothelial pulse amplitude testing; HR = heart rate; PP = Pulse pressure; SBP = Systolic blood pressure; total PWV = AAO to distal DAO pulse wave velocity

TABLE 3. BLOOD PRESSURE PHENOTYPE

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
Office BP				0.20
Normal	15 (54%)	13 (57%)	7 (29%)	
Pre-HTN	10 (36%)	8 (35%)	15 (63%)	
Stage 1 HTN	3 (11%)	2 (9%)	1 (4%)	
Stage 2 HTN	0 (0%)	0 (0%)	1 (4%)	
ABPM				
24-hr average SBP (mm Hg)	123 ± 13	118 ± 9	124 ± 10	0.19
24-hr average DBP (mm Hg)	68 ± 8	66 ± 6	68 ± 8	0.77
Day average SBP (mm Hg)	125 ± 13	122 ± 10	127 ± 10	0.34
Day average DBP (mm Hg)	69 ± 9	69 ± 7	71 ± 9	0.82
Night average SBP (mm Hg)	116 ± 12	106 ± 10	113 ± 10	**0.005**
Night average DBP (mm Hg)	60 ± 7	56 ± 5	59 ± 4	**0.05**
% SBP readings above diurnal threshold	32 ± 29	19 ± 19	30 ± 27	0.19
% DBP readings above diurnal threshold	16 ± 20	13 ± 14	14 ± 16	0.72
Diurnal systolic variation (%)	7 ± 7	13 ± 6	11 ± 6	**0.01**
Diurnal diastolic variation (%)	13 ± 10	19 ± 6	16 ± 7	0.06
Non-dippers (%)	17 (65%)	7 (32%)	12 (55%)	0.08
Classification by ABPM				0.76
No HTN	16 (59%)	18 (82%)	15 (68%)	
White coat HTN	3 (11%)	1 (5%)	1 (5%)	
Masked HTN	6 (22%)	2 (9%)	5 (23%)	
HTN	2 (7%)	1 (5%)	1 (5%)	
Classification including medication use				
HTN/masked HTN, or anti-HTN medication	8 (30%)	9 (39%)	10 (45%)	0.49

Values are mean ± standard deviation, or number (percent). ABPM = ambulatory blood pressure measurement; BP = blood pressure; DBP = diastolic blood pressure; Dippers = night-time BP dipping ≥10%, non-dippers = night-time BP dipping <10%; HTN = hypertension; SBP = systolic blood pressure

TABLE 4. EXERCISE STRESS TEST

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
Exercise duration (minutes)	12 (7,21)	11 (9, 21)	13 (5,17)	0.45
Pre-exercise SBP gradient (mm Hg)	-3 ± 21	1 ± 9	6 ± 18	0.17
Peak-exercise SBP gradient (mm Hg)	32 ± 30	33 ± 22	26 ± 27	0.64
Peak right arm SBP (mm Hg)	177 ± 35	157 ± 27	177 ± 33	**0.05**
Peak right arm DBP (mm Hg)	71 ± 13	75 ± 9	73 ± 11	0.50
VO2 Max (ml/Kg/min)	41 ± 11	32 ± 27	41 ± 11	0.30
VE/CO2 slope	26 ± 4	26 ± 5	26 ± 6	0.98

Values are mean ± standard deviation, or median (minimum, maximum). DBP = diastolic blood pressure; SBP systolic blood pressure; VO2 Max = peak exercise oxygen consumption; VE/CO2 = relationship between ventilation and CO2 output

TABLE 5. CMR LV AND AORTIC MEASUREMENTS

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
LV Measurements				
EDV (ml/m^2)	71 ± 13	76 ± 17	73 ± 18	0.64
Ejection fraction (%)	63 ± 6	61 ± 5	62 ± 5	0.52
Mass (g/m^2)	56 ± 13	58 ± 9	57 ± 13	0.83
Aortic Diameters (mm/BSA$^{0.5}$)				
Ascending aorta	19.1 ± 3.0	20.6 ± 3.2	20.7 ± 3.4	0.18
Proximal transverse arch	12.6 ± 1.2	12.8 ± 1.8	12.7 ± 2.9	0.96
Distal transverse arch	11.5 ± 1.7	11.2 ± 1.6	11.9 ± 2.1	0.45
Isthmus	12.6 ± 3.7	10.4 ± 2.8	N/A*	0.03
Descending aorta	12.4 ± 1.1	12.6 ± 1.8	12.5 ± 1.6	0.95
Arch Shape				0.33
Romanesque	11 (39%)	10 (43%)	10 (42%)	
Crenel	2 (7%)	5 (22%)	2 (8%)	
Gothic	14 (50%)	6 (26%)	12 (50%)	
Arch Shape Index	0.64 ± 0.14	0.65 ± 0.11	0.68 ± 0.13	0.64

Values are mean ± standard deviation, or number (percent). * N/A = not available, due to presence of stent artifact. Arch Shape Index = aortic arch height divided by width; BSA = body surface area; EDV = end-diastolic volume

TABLE 6. BLOOD BIOMARKERS

	Surgery (n=28)	Balloon Dilation (n=23)	Stent (n=24)	p value
NOx (ug/mL)	18 (12, 31)	20 (12, 37)	20 (10, 34)	0.18
ADMA (ng/L)	6 (1, 45)	7 (1, 51)	3 (0, 31)	0.20
hs-CRP (mg/L)	1.28 (0.74, 1.49)	1.26 (0.66, 1.41)	1.30 (0.95, 1.46)	**0.02**
VCAM-1 (ng/mL)	133 (66, 203)	134 (61, 206)	128 (66, 168)	0.42
IL-1β (pg/mL)	0.91 (0.04, 1.26)	1.06 (0.68, 1.98)	0.95 (0.06, 1.49)	0.1
TGF- β1(ng/mL)	0.35 (0.12, 1.24)	0.64 (0.23, 3.21)	0.31 (0.05, 2.07)	**0.006**
MMP-2/gelatinase A (ng/mL)	1.14 (0.10, 3.37)	1.53 (0.00, 4.93)	0.62 (0.00, 3.62)	0.26
MMP-9/gelatinase B (ng/mL)	474 (91, 3157)	738 (158, 4453)	421(487, 1739)	**0.01**

Values are median (minimum, maximum). ADMA = asymmetric dimethylarginine; hs-CRP = high sensitivity C-reactive protein; IL-1β = interleukin 1 beta; MMP **=** matrix metalloprotease**;** NOx = nitrite/nitrate; TGF- β1 = transforming growth factor beta-1; VCAM-1 = vascular adhesion molecule 1

4. LIST OF LOVE-COARCT INVESTIGATORS

Table 31. LOVE-COARCT investigators

Institution	Name
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