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Renal perfusion changes in patients with coarctation of the aorta (REPACO trial)

DOCTORAL DISSERTATION

Medical and Health Sciences,
Medicine (M 001)

VILNIUS 2024

The dissertation was prepared between 2019 and 2024 at the Clinic of Heart and Vascular Diseases of Vilnius University, Lithuania.

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1. ABBREVIATIONS

AA – aortic arch
ABI – Ankle-Brachial Index
ACHD – adult congenital heart disease
aABP – ambulatory arterial blood pressure
aABPM – ambulatory arterial blood pressure monitoring
ACE – angiotensin-converting enzyme
AH – arterial hypertension
ANG II – angiotensin II
ARB – angiotensin receptor blocker
AT1R – angiotensin II type 1 receptor
AWI – arterial wall injury
BA – balloon angioplasty
BAV – bicuspid aortic valve
BM – bare metal
BP – blood pressure
CAMP – cyclic adenosine monophosphate
CAVI – Cardio-Ankle Vascular Index
CC – common carotid artery
CCP stent – covered Cheatham Platinum stent
CHD – congenital heart disease
CIMT – carotid intima-media thickness
CKD – chronic kidney disease
CMN – cystic medial necrosis
CoA – coarctation of the aorta
CP stent – Cheatham Platinum stent
CT – computer tomography
CVR – cerebrovascular resistance
CVD – cardiovascular diseases
DA – dorsal aorta
DB – arterial duct
DBP – diastolic blood pressure
DNA – deoxyribonucleic acid
DTPA – diethylenetriamine pentaacetic acid
EC – external carotid artery
EF – ejection fraction
FMD – fibromuscular dysplasia
HF – heart failure

IC – internal carotid artery
IMT – intima-media thickness
IPCoW – incomplete posterior circle of Willis
IVSd – Interventricular septal thickness in diastole
IVUS – intravascular ultrasound
JG – juxtaglomerular
LP – left pulmonary artery
LVDD – LV diastolic diameter
LVPWd – LV posterior wall thickness in diastole
MAS – mid-aortic syndrome
MRI – magnetic resonance imaging
mRNA – messenger ribonucleic acid
NaCl – sodium chloride
NO – nitric oxide
NOS-I – neuronal nitric oxide synthase
OD – odds ratio
PG – pressure gradients
PRA – plasma renin activity
PT – pulmonary trunk
PTFE – polytetrafluoroethylene
PWV – pulse wave velocity
PWVcf – pulse wave velocity between the carotid and femoral arteries
QCS – Quality Carotid Stiffness
RA – renal artery
RAAS – renin-angiotensin-aldosterone system
reCoA – aortic recoarctation
ROI – Region of Interest
RP – renal perfusion
RP – right pulmonary artery
RS – renal scintigraphy
RS – right subclavian artery
RVH – renovascular hypertension
SBP – systolic blood pressure
SMCs – smooth muscle cells
SNA – sympathetic nerve activity
SNS – sympathetic nervous system
TTE – transthoracic echocardiography
VA – vertebral artery
VAH – vertebral artery hypoplasia
VEGF – vascular endothelial growth factor

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2. INTRODUCTION

2.1 Background

Coarctation of the aorta (CoA) emerges as an essential congenital cardiac anomaly, the fifth in frequency among congenital heart diseases. (1–5) Characterized by a narrowing of the aorta, this condition precipitates an elevation in blood pressure in the upper extremities and proximal regions while simultaneously diminishing blood flow to areas distal to the constriction.

Historical analyses outline a grave prognosis for individuals with untreated coarctation of the aorta (CoA), indicating a mortality rate of 25% before the age of 20. During the period extending from the 1930s to the 1960s, the mortality rate increased from 1.6% per year in the first two decades of life to 6.7% per year by the sixth decade. (6) A principal risk factor for these patients, especially those not subjected to surgical intervention, is persistent arterial hypertension in the upper body while concurrently causing reduced perfusion pressure in the lower extremities.(7)

The etiology of hypertension in patients with native or post-repair CoA is multifactorial, encompassing residual narrowing, abnormal arch geometry, endothelial dysfunction, altered arterial smooth muscle reactivity, alterations in the aortic wall leading to increased arterial stiffness, and reduced baroreceptor sensitivity, which results in elevated activity of the sympathetic nervous system. (8–12)

Among the mechanisms implicated in CoA and the persistence of hypertension post-repair is the activation of the renin-angiotensin-aldosterone cascade, a phenomenon also observed in renovascular disease and mid-aortic syndrome. Captopril renal scintigraphy is a diagnostic test with the potential to identify renovascular conditions and predict treatment responses. (13–15) This diagnostic test is used to identify a functionally significant renal artery stenosis (RAS); it is not intended to detect the presence of an anatomical RAS. (13) Studies have reported that renal scintigraphy demonstrates high sensitivity (87% to 96%) and specificity (85% to 95%) in diagnosing RAS and renovascular hypertension. (13,16) Some studies suggest that improved renal scintigraphy results following renal artery revascularization may predict better outcomes in treating renovascular hypertension. (16,17)

Early detection of CoA and prompt surgical or interventional correction become critical to avert the onset of arterial hypertension. (18) Despite successful early interventions, the risk of developing cardiovascular pathologies remains significant, with systemic arterial hypertension (AH)

persisting in approximately 60% of individuals after surgical or percutaneous treatment. (7,19) Long-term observational studies indicate that arterial hypertension continues in roughly 41% of patients even 24 years post-initial repair. (20) The prevalent phenotype observed in patients with CoA is isolated systolic hypertension. (21) Notably, individuals may be classified as hypertensive even under normotensive blood pressure conditions if they are receiving antihypertensive therapy. (22)

Furthermore, longitudinal data underscore a correlation between systemic hypertension and mortality, particularly concerning the timing of corrective surgery. (20,23) Arterial blood pressure (ABP) serves as a continuous, potent, and directly causative risk factor for cardiovascular, cerebrovascular, and renal pathologies, with approximately 54% of cerebrovascular accidents (strokes) and 47% of ischemic heart disease incidents globally attributed to elevated ABP levels. (24) An increment of 20mmHg in arterial blood pressure correlates with a twofold increase in mortality rates from cardiovascular diseases. (25) Properly managing arterial blood pressure in patients with CoA, defined as maintaining office ABP below 140/90 mmHg, can be successfully achieved in 32.5% of patients undergoing pharmacological treatment for hypertension. (26)

Renal scintigraphy is not typically employed as a standard diagnostic tool for assessing the severity of stenosis in patients with CoA who are suspected of having hypertension. There is ongoing debate regarding its predictive utility in identifying individuals who may benefit from surgical or transcatheter interventions for CoA.

2.2 Study Hypothesis

This study hypothesizes that individuals with untreated native coarctation of the aorta or those who have undergone surgical repair and present with arterial hypertension demonstrate diminished renal perfusion compared to patients with native or surgically repaired coarctation who do not have arterial hypertension.

2.3 Study Aim

This study's primary aim is to investigate, for the first time in humans, the status of renal perfusion in patients with untreated native or repaired coarctation of the aorta in regard to the presence of hypertension. A secondary objective is to examine the relationship between the anatomical characteristics of the aortic arch, hypertension, and renal blood flow.

2.4 Study Objectives

1. Assess the link of arterial hypertension with the status of renal perfusion in patients with untreated native or previously repaired coarctation of the aorta.
2. Investigate the relationship between the type of aortic arch and renal perfusion in patients with coarctation of the aorta.
3. Identify factors associated with the presence of hypertension in patients with untreated native or previously repaired coarctation of the aorta.
4. To assess carotic arteries' vascular remodeling influence on renal perfusion in patients with coarctation of the aorta.
5. Analyze the effects of percutaneous interventions for coarctation of the aorta on renal blood flow.

2.5 Theses for Defence

1. Arterial hypertension in patients with coarctation of the aorta is associated with a reduction in renal perfusion.
2. The morphology of the aortic arch is correlated with alterations in renal perfusion.
3. The risk of arterial hypertension in patients with coarctation of the aorta is directly related to the severity of stenosis.
4. Increased stiffness of the carotid arteries in patients with coarctation of the aorta negatively impacts renal perfusion.
5. Reduction of the pressure gradient following percutaneous interventions in patients with clinically significant coarctation of the aorta leads to improvements in renal perfusion.

2.6 Novelty of the Study

Despite successful surgical or interventional repair of coarctation of the aorta, patients may continue to experience residual conditions, such as AH. Current clinical guidelines predominantly focus on the pressure gradient between the upper and lower limbs and minimizing residual invasive gradients. However, more research is needed on the impact of vital organ perfusion, particularly below the isthmus, and on managing arterial hypertension. This study investigates multiple factors that influence renal perfusion in this group of patients. To the best of our knowledge, this is the first study to examine renal perfusion in patients with coarctation of the aorta. Renal scintigraphy has been demonstrated to have high diagnostic accuracy

for detecting clinically significant renal artery stenosis and renovascular hypertension. This research is anticipated to provide valuable insights that will aid in more informed decision-making regarding the treatment of coarctation of the aorta and potentially enhance patient outcomes. Specifically, patients with reduced renal perfusion may benefit from earlier intervention, while those with unimpaired renal flow could be managed with a higher threshold for surgical or percutaneous treatment.

3. LITERATURE REVIEW

3.1 Development and Embryology of the Aortic Arch

The genesis of the aorta begins in the third week of embryonic development, commencing a complex process of the formation of the endocardial tube by approximately day 21. (27) This critical period lays the groundwork for congenital aortic variations. Each primitive aorta comprises ventral and dorsal segments interconnected through the first aortic arch. The fusion of ventral aortas results in the aortic sac's formation, and the dorsal aortas' convergence forms the descending aorta along the embryonic midline. This stage involves developing six pairs of aortic arches and branchial or pharyngeal arch arteries, linking the ventral and dorsal aortae. The dorsal aorta also spawns multiple intersegmental arteries, further elaborating the embryonic vascular framework. (28)

The embryonic aortic arches evolve as follows: The first arch pair contributes to the development of the maxillary and external carotid arteries. The second pair is pivotal for the formation of stapedial arteries. The third aortic arch, known as the carotid arch, plays a crucial role in forming the internal carotid artery, with the proximal segments of this pair developing into the common carotid arteries and their distal segments, along with parts of the dorsal aortae, contributing to the internal carotid arteries. The left fourth arch is essential for forming the definitive aortic arch segment between the left common carotid and subclavian arteries. In contrast, the proximal proper subclavian artery forms from the right fourth arch, while the distal part of the right subclavian artery arises from the right dorsal aorta and the right seventh intersegmental artery. The fifth pair of arches, being rudimentary, regress early on. The left arch of the sixth pair forms the central and left pulmonary arteries and the ductus arteriosus, which closes postnatally. The right sixth arch aids in developing the right pulmonary artery. As the heart descends during the second month of fetal life, the seventh intersegmental arteries expand and ascend to form the distal subclavian arteries. The left subclavian artery emerges solely from the left seventh intersegmental artery, while the formation of the right subclavian artery involves the right fourth arch and the right dorsal aorta. Deviations in the aortic arch system may result from the preservation of segments usually doomed to regression, the disappearance of segments that should typically be preserved, or a mix of these alterations. (29)

3.2 Development of a renovascular system

The kidney, a highly vascularized organ, receives about 20% of the cardiac output in adults. The intricate spatial arrangement of each kidney arteriole with its corresponding nephron is a complex system crucial for regulating renal blood flow, glomerular filtration rate, and other specialized kidney functions that maintain homeostasis. Therefore, the proper and timely assembly of these nephron-vascular units is not just a morphogenetic event but an essential process leading to the formation of a functioning kidney necessary for independent extrauterine life. (30)

In humans, nephrogenesis of the definitive (metanephric) kidney begins about the fifth week of gestation, culminating in nearly 1 million (400,000 to 2.4 million) nephrons. (31) In humans, the production of new nephrons stops after 36–38 weeks of gestation. (30) However, significant individual variability exists, with a 10-fold difference in nephron numbers. (31) Kidney development initiates with a ureteric bud from the nephric duct, invading a cluster of mesenchymal cells at the caudal end of the nephric cord, leading to branching morphogenesis. (32) This process, crucial for the formation of nephrons and the urinary collecting system, is primarily regulated by the glial-cell-derived neurotrophic factor. (33) Nephron progenitors undergo epithelialization to form renal cysts, which then elongate into S-shaped bodies before fully maturing into nephrons. Between the 18th and 32nd weeks, there is a marked increase in nephron numbers, with nephrogenesis concluding between the 32nd and 36th weeks of gestation (31), indicating that nephrogenesis is typically complete at term. However, preterm infants, who are at risk of reduced nephron endowment, are a vulnerable population. Their nephron endowment is influenced by gestational age, intrauterine environment, and perinatal care.

In the adult mammalian kidney, cells that express renin are situated within the walls of the afferent arterioles, right at the point where they lead into the glomeruli. Due to their adjacent location, these cells are called juxtaglomerular (JG) cells. (34) JG cells act as sensors that produce and secrete the hormone enzyme renin in response to subtle changes in ABP and alterations in the composition and volume of the extracellular fluid. (35)

Renin-expressing cells are essential for survival. Over 400 million years ago, they emerged in nature and have acquired numerous defensive functions throughout evolution as perfect apparatus to ensure tissue and whole-body homeostasis. They control arterial blood pressure, fluid-electrolyte balance, vascular development, and glomerular regeneration. (36)

The contribution of renin cells to arteriolar assembly follows a distinctive, fractal-like developmental pattern. Initially, differentiating renin-expressing cells are few and randomly distributed in the stromal-interstitial compartment. As development progresses, the renin cells participate actively in the morphogenesis and branching of the renal arterial tree. (37) As a new branch is about to form, a few renin cells group as a macula, then bulge and elongate, maturing into a new arteriolar branch. (37) As the vessels mature and the cells differentiate into smooth muscle cells (SMCs), renin-expressing cells are gradually confined to the JG area, where they remain throughout adult life. (38)

Epidemiological studies have identified prematurity and low birth weight as risk factors for later-life kidney disease and hypertension (39), as well as low nephron number resulting from intrauterine growth restriction or preterm birth, leading to compensatory glomerular hyperfiltration and hypertension. (31,40) Moreover, studies have noted that prematurity correlates with elevated plasma renin levels, angiotensin II (ANG II), and angiotensin-converting enzyme (ACE) activity. (41) These changes can lead to a detrimental cycle of nephron loss, increased blood pressure, declining renal function, and potentially chronic kidney disease (CKD). Maternal use of RAAS-interfering drugs (e.g., ACEIs or ARBs) is avoided in pregnant women due to risks of fetopathy and renal maldevelopment. (42)

Currently, nephron count in living humans remains undeterminable, though advancements in using ferritin-based nanoparticles as MRI contrast agents for nephron number estimation show promise. (43)

3.3 Coarctation of the aorta

Coarctation of the aorta represents a significant congenital heart defect (CHD) encountered in clinical practice. Historical evidence indicates that CHDs were detected at a rate of approximately 4-5 per 1000 live births. (1,4) However, advancements and the widespread adoption of non-invasive diagnostic technologies, notably echocardiography, in the latter half of the last century have led to an increase in the detection of CHDs, with current incidence rates estimated at 12-14 per 1000 live births. (44) CoA accounts for 4-8% of all CHDs and is ranked fifth in prevalence. (1–5) Males have a higher incidence of CoA, with ratios ranging from 1.27:1 to 1.74:1 compared to females. Furthermore, a higher prevalence of CoA is observed among Caucasian populations compared to African American or Hispanic groups. (45)

The etiological factors contributing to the development of CoA continue to be the subject of research. While familial aggregation (46,47) and genetic mutations (48) have been identified as potential contributors, other less common factors, such as kinship among close relatives, maternal age, birth order, and season of birth, have been investigated without definitive conclusions. (45)

3.4 Pathogenesis of CoA

The pathogenesis of coarctation of the aorta encompasses a variety of theories, from hemodynamic changes to abnormalities in cellular migration during aortic arch formation, particularly the abnormal proliferation of arterial duct tissues in constricted areas. (49)

Intriguingly, research involving rabbit models with CoA has revealed an upregulation of type I and III collagen gene expression, specifically in the proximal area of the CoA. (50) This finding is consistent with observations in CoA of increased collagen and diminished smooth muscle content within the proximal regions of the aorta before narrowing, as opposed to its distal segments. (51) It may be explained by mechanical stress resulting from heightened pressure load, accelerating gene expression for collagen production. This, in turn, facilitates the structural remodeling of muscular and elastic fibers of the vessel wall, effectively mitigating the extent of aortic dilation induced by pressure. Consequently, this restructuring leads to a stiffening of blood vessels, which is implicated in the escalation of central aortic systolic pressure and the subsequent development of systolic hypertension. (52)

In an experimental framework utilizing zebrafish embryos, mutations in the hey2 gene were identified to induce alterations resembling coarctation of the aorta. (48) Notably, it has been observed that enhancing the Vascular Endothelial Growth Factor (VEGF) regulation during early developmental stages can avert modifications in the aorta. VEGF is pivotal in aortic development, serving as a chemoattractant that facilitates the migration of angioblasts toward the central axis in anticipation of aortic formation. (53) Furthermore, experiments inhibiting VEGF expression in mice have documented significant aortic developmental anomalies. (54) The causative link between the initial mutation of VEGF and potential secondary impacts on signaling pathways, which affect the distribution of fetal intramural cells leading to CoA, remains speculative. This hypothesis is subject to debate, given that growth factors exhibit systemic effects that may impair the formation of other vascular structures. Also, subsequent research challenges

this viewpoint by demonstrating the preservation of vascular structure and functionality in the lower extremities before and after the coarctation intervention. (55–57)

Several researchers advocate that the elastic properties of the ascending aorta are already compromised in newborns diagnosed with CoA, and these abnormalities persist even after successful surgical interventions. This notion interprets CoA as a localized mechanical constriction of the aorta and a systemic arterial disease affecting the arteries proximal to the CoA site. (56) The relationship between these vascular changes and reduced blood flow to the lower body or elevated intra-arterial pressure remains uncertain.

Cystic medial necrosis (CMN), characterized by the depletion and disarray of medial elastic fibers, is frequently associated with coarctation of the aorta, affecting sites both proximal and distal to the constricted segment. The etiology of CMN in CoA patients – whether a congenital or an acquired condition – remains a subject of ongoing debate, with substantial evidence supporting both viewpoints. (58) Observations of cystic medial necrosis in the aortic wall have been documented at birth or shortly after. (58,59) These observations support the hypothesis that individuals with CoA undergo morphological changes in the aortic wall during fetal development. However, the precise mechanisms driving these morphological and functional anomalies are yet to be elucidated.

Coarctation of the aorta represents a complex arteriopathy that goes beyond a simple reduction in the diameter of the aortic passage; it manifests either as a discrete segment of stenosis or as a longitudinally hypoplastic segment within the aortic arch. Coexistence between CoA and bicuspid aortic valve (BAV) is also common. Currently, individuals with native aortic coarctation comprise approximately 70% of all patients diagnosed with BAV, which ranges from 49% to 55%. (60–63) Furthermore, CoA is intricately associated with a spectrum of cardiovascular abnormalities, as well as specific syndromic conditions such as Turner syndrome and Williams-Beuren syndrome, and vascular anomalies, including the anomalous emergence of the right subclavian artery. Additionally, collateral arterial circulation and intracerebral aneurysms, found in up to 10% of CoA cases, further illustrate the extensive impact of this condition. (64)

In significant coarctation of the aorta, symptomatic presentation often occurs early in an individual's life. In contrast, those with milder forms of CoA may not exhibit symptoms, or their symptoms may remain latent until adulthood, frequently identified during evaluations for arterial hypertension. Associated symptoms of CoA span the cardiovascular and neurological domains, including but not limited to headaches, epistaxis, vertigo, tinnitus,

dyspnea, abdominal angina, claudication, and acrocyanosis. These manifestations underscore the importance of promptly recognizing CoA and managing potential complications.

Without surgical intervention, a range of grave complications encompasses heart failure, intracranial hemorrhage due to cerebral aneurysms, infective endocarditis, aortic rupture or dissection, and the premature development of atherosclerotic disease. As a result of these potential complications, individuals with significant native CoA who reach adulthood without treatment may experience a constrained life expectancy, with a median survival age approximating 60 years. (64) Therefore, timely and effective intervention in CoA is essential to prevent these adverse health outcomes.

3.5 Invasive diagnostic criteria for CoA and reCoA

Significant native or residual coarctation of the aorta (CoA) is defined as follows:

- A systolic pressure gradient between the upper and lower limbs of >20 mmHg or an echographically measured average systolic gradient of >20 mmHg.
- A systolic pressure gradient between the upper and lower limbs of >10 mmHg or an echographically measured average systolic gradient of >10 mmHg in patients with reduced LV systolic function or aortic regurgitation (AR).
- A systolic pressure gradient between the upper and lower limbs of >10 mmHg or an echographically measured average systolic gradient of >10 mmHg in patients with significant collateral circulation.(7,60,65)

3.6 Indications for CoA repair: (64)

- For patients with hypertension and significant non-invasive gradient between the upper and lower limbs, confirmed by invasive measurement (systolic gradient ≥20 mmHg), CoA correction (either surgical or percutaneous) is recommended, with a preference for percutaneous treatment (stenting) when technically feasible. Class I, Level C
- If technically possible, percutaneous treatment (stenting) should be considered for patients with hypertension and aortic narrowing ≥50%

compared to the aortic diameter at the diaphragm, even if the invasive systolic gradient is <20 mmHg. Class IIa, Level C

- When technically feasible, percutaneous treatment (stenting) should be considered for patients with normal blood pressure and significant non-invasive gradient, confirmed by invasive measurements (systolic gradient ≥20 mmHg). Class IIa, Level C
- When technically possible, percutaneous treatment (stenting) may be considered for patients with normal blood pressure and aortic narrowing ≥50% compared to the aortic diameter at the diaphragm, even if the invasive systolic gradient is <20 mmHg. Class IIb, Level C

Since coarctation is not a localized aortic disease, associated lesions requiring structural interventions should be considered:

- Associated significant aortic valve stenosis or insufficiency.
- An aneurysm of the ascending aorta with a diameter >50 mm or rapid diameter progression.
- Aneurysms and false aneurysms at the previous CoA site.
- Symptomatic or giant Willis ring aneurysms
- Treatment should be performed in centers with extensive experience treating Cardiovascular Diseases (CVD).

3.7 Surgical repair of CoA

The significant increase in survival since the first surgical correction of aortic coarctation in 1944 is a testament to significant advances in surgical methodologies, perioperative care, and the continuous evolution of long-term management protocols. These developments have collectively improved the prognosis and quality of life for patients diagnosed with this condition. Introducing less invasive procedures, like balloon angioplasty and stenting, along with refinement of traditional surgical methods, has played a crucial role in minimizing complications and enhancing patient outcomes. (66)

This progress has led to an increase in the number of individuals with COA living into adulthood. This shift emphasizes the need for continuous monitoring and management of potential long-term complications associated with COA and its treatments, including re-coarctation, hypertension, and an increased risk of cardiovascular diseases. A multidisciplinary care strategy includes regular health evaluations, lifestyle adjustments, and timely implementation of medical or surgical interventions to address arising complications.

3.7.1 Surgery types

3.7.1.1 End-to-end anastomosis

End-to-end anastomosis was first successfully performed by Crafoord and Gross in 1945 through a left lateral thoracotomy approach. (66) This method involves the mobilization of the aorta, the application of cross clamps above and below the narrowed segment, and the excision of the stenosed isthmus and coarcted segment following aortic transections. The remaining portions of the aortic arch and descending aorta are aligned and joined through direct end-to-end anastomosis.

While this technique initially demonstrated success, long-term follow-ups indicated a relatively high incidence of re-coarctation, particularly in surgeries performed on neonates, with the prevalence being significantly influenced by the early age at the time of the procedure. The relatively high re-coarctation rates, ranging between 41% and 51%, have led to a gradual decline in the adoption of direct end-to-end anastomosis as the preferred method for CoA repair in the current surgical paradigm, prompting the development and adoption of alternative techniques that aim to minimize the risk of re-coarctation and enhance long-term outcomes. (67)

3.7.1.2 Prosthetic patch aortoplasty

Prosthetic patch aortoplasty was developed as a surgical alternative for repairing CoA. It aimed to address the significant re-coarctation rates observed with the traditional end-to-end anastomosis technique. Initiated by Vosschulte, the method involves creating a longitudinal incision in the affected aortic segment and suturing a prosthetic patch to enlarge the constricted area. (68)

Initially, using Dacron grafts for the patch was promising, showing a potential reduction in re-coarctation incidence. However, this approach was later found to have a considerable downside: a high occurrence of postoperative aortic aneurysm formation, with rates reported between 20% and 40%. (69) To decrease the risk of aneurysm development, polytetrafluoroethylene (PTFE) began to be used as the material for the patch. Although PTFE successfully reduced the rate of aneurysm formation to about 7%, it inadvertently led to an increase in re-coarctation rates, which soared to around 25%. (70)

This technique may also be indicated in older children or adults when direct end-to-end anastomosis is not feasible due to the vessel size or the severity of the coarctation.

3.7.1.3 Subclavian Flap Aortoplasty

Subclavian flap aortoplasty, introduced by Waldhausen and colleagues in 1966, represents a significant advancement in the surgical treatment of aortic coarctation. (71) The procedure involves ligating the subclavian artery close to connecting with the left vertebral artery. From there, an incision is made in the subclavian artery, extending down to the aortic isthmus and across the coarcted segment. This created flap is then folded downward and sutured into the incised part of the aorta, thereby widening the constricted area.

The subclavian flap aortoplasty technique has been widely successful in older children, showing meager re-coarctation rates ranging from 0 to 3%. (72) However, its effectiveness appears to be reduced in neonates, where re-coarctation rates have reached up to 23%. (73) A notable benefit of this method is the minimal risk of ischemia in the left arm following the subclavian artery ligation, thanks to the development of collateral circulation. However, a risk remains for long-term claudication in the affected arm due to reduced blood flow. (72) Despite these points of consideration, subclavian flap aortoplasty remains a preferred surgical option for specific demographics.

3.7.1.4 Extended end-to-end anastomosis

The extended end-to-end anastomosis technique, introduced by Amato in 1977, has become a widely adopted procedure for the surgical repair of coarctation of the aorta. (74) This method offers an advantage over traditional direct end-to-end anastomosis by modifying the placement of clamps and the extent of the aortic incision. In this procedure, the proximal aortic clamp is positioned to encompass a portion of the aortic arch, potentially extending to include the left subclavian or even the left carotid artery and the aortic arch. The distal clamp is placed below the coarcted segment, ensuring the entire area of concern is isolated. Following the ligation and division of the ductus arteriosus, the coarctation segment is excised. The aortic arch is then incised on its inferior aspect to create an opening that facilitates the end-to-end anastomosis with the descending aorta. The extended end-to-end anastomosis technique is notable for its low peri-operative mortality rates and has demonstrated comparatively low rates of re-coarctation, ranging from 4% to 13%, according to various reports. (75)

3.7.1.5 Interposition graft

The interposition graft technique, introduced by Gross in 1951, revolutionized the surgical approach to coarctation of the aorta repair by excising the coarctation segment and replacing it with a graft, typically made from Dacron tube or an aortic homograft. (76) This approach is especially beneficial when non-native tissue is considered appropriate, mainly because the graft cannot grow or expand alongside the patient. This characteristic of the graft makes it a preferred choice in situations where adaptability to growth is not a primary concern, such as in adult patients or where the potential for outgrowing the graft is minimal.

3.7.1.6 Extra-anatomical correction

The extra-anatomical correction technique offers a novel surgical strategy to address the complications associated with directly repairing the coarctation of the aorta. (77) This method sidesteps the direct manipulation of the stenosed aortic segment by maintaining it intact and instead focuses on augmenting blood flow to the distal aorta. Typically executed via a median sternotomy and utilizing cardiopulmonary bypass, the procedure establishes an alternative route for blood circulation. A prosthetic conduit is connected proximally to the ascending aorta or the subclavian artery and distally to the descending aorta. (78) This setup effectively bypasses the coarcted segment, facilitating seamless blood flow to the lower body.

A significant merit of the extra-anatomical correction technique is its adaptability in surgeries where additional cardiac interventions are concurrently necessitated. (79) For example, in patients who need concurrent replacement of aortic valve or coronary artery bypass grafting in addition to correction of CoA, this approach allows for the combined treatment of these conditions without direct intervention on the coarcted aorta.

3.7.1.7 Surgical considerations

The selection of a surgical technique for coarctation of the aorta repair hinges on multiple critical factors, such as the length and location of the coarcted segment, its relation to the ductus arteriosus, the state of collateral circulation in the distal aorta, and the existence of atherosclerotic alterations in the aortic wall. (80) During infancy, resection followed by direct end-to-end anastomosis and subclavian flap arterioplasty are generally preferred, thanks to the more conducive anatomical conditions at this stage.

While advancements in surgical techniques for CoA correction have significantly improved outcomes, the lifespan of CoA patients remains shorter compared to individuals without the condition. Notably, late mortality remains a concern for post-CoA correction patients. Historical data from the long-term registry describe that those operated on at an average age of 16 years have a 10-year post-operation survival rate of 91%, which declines to 84% after 20 years and 72% after 30 years. (81)

Early surgical correction, especially before age 5, is recommended to enhance long-term outcomes. Nonetheless, even with early intervention, survival rates decrease, with 91% of patients living up to 20 years post-surgery and 80% up to 40-50 years. This indicates that early correction benefits longevity but does not eliminate the long-term complications associated with CoA. (82,83) Corrective surgery is still advised for older patients receiving a delayed diagnosis, as it can significantly improve blood pressure control and may reduce the risk of later cardiac and vascular complications, thereby improving survival rates. (84,85)

The surgical risk for isolated non-complex CoA remains relatively low at less than 1% but increases significantly between the ages of 30 and 40. Fortunately, complications such as spinal cord injury have become exceedingly rare (86), reflecting improvements in surgical techniques and perioperative care.

3.8 Percutaneous Treatment Strategies for CoA

Percutaneous interventions for correcting CoA have been performed for over three decades. (87) Percutaneous approaches now account for over 50% of CoA treatments in older patients. In contrast, surgery is still dominant in younger populations, particularly those requiring initial repair during infancy. It has been established that treating native aortic coarctation via percutaneous approaches is feasible, effective, and efficient when performed at a younger age. This is due to younger patients having less fibrotic and more compliant aortic tissues. Older individuals may present an unfavorable risk profile (OR 1.13 per 5-year increment) because their aortas are typically stiffer and more fibrotic. (88)

Percutaneous angioplasty, both with and without stent placement, has become widely adopted for addressing aortic recoarctation. While effective for many patients over the long term, certain conditions, such as aortic arch hypoplasia, sometimes necessitate surgical intervention. (89) However, recent advancements in percutaneous treatments have demonstrated that stent placement can effectively manage conditions involving hypoplastic aortic

arch. (90,91) Percutaneous interventions are generally suitable for patients with recoarctation, except in cases involving complex anatomical challenges or concurrent cardiac conditions, which may be better addressed through surgical methods. (92) The risk of post-operative recoarctation varies significantly by age: about 44% in newborns but decreases to 11% in older children. (93,94) This risk ranges between 0% and 9% for adults, (95,96) with the highest incidence observed following surgical procedures like superficial end-to-end anastomosis and subclavian artery flap aortoplasty. (83,97) In pediatric patients, the incidence of restenosis following balloon angioplasty for native coarctation decreases dramatically with age, from 77-83% in newborns to just 7-8% in older children and adults. (98,99)

Stent implantation presents a viable alternative for treating recurrent coarctation of the aorta (reCoA) or in patients who have relative contraindications for surgical intervention. The short- and mid-term outcomes of stent implantation are generally excellent, with technical success rates exceeding 95%, regardless of the type of stent used. (100) Nevertheless, repeated stent angioplasty might be required to achieve an aortic diameter appropriate for adult size, involving the interventional expansion of existing stents with larger ones or surgical repair using a conduit. (101)

Following stent implantation, the reduction or complete elimination of the pressure gradient across the coarctation site is achievable in more than 95% of adult patients. (90,102) Another benefit of stent implantation is its capability to address long segments of CoA, which might be inadequately treated with balloon angioplasty alone. However, the long-term outcomes of these procedures are still under evaluation.

Post-stent implantation blood pressure decreases in most patients, indicating the initial success of the procedure. However, in patients who underwent multiple interventions due to restenosis, although their BP decreased following the first intervention, it tended to increase upon the recurrence of restenosis and then reduce again after subsequent interventions once the restenosis was resolved. Some patients experienced a resurgence of hypertension even in the absence of restenosis, which underscores the critical need for ongoing long-term follow-up examinations to appropriately detect hypertension, rule out restenosis, and initiate antihypertensive medications promptly. (103)

The first fatal incident following endovascular intervention for Coarctation of the Aorta was documented in 1983 by Finley and colleagues after an attempt at balloon angioplasty (BA) in an infant. (104)

In the initial period of employing BA for treatment, it was proposed that postoperative periaortic fibrous scarring could offer protection against aortic

dissection or rupture, thereby rendering BA a safe approach for addressing recurrent coarctation of the aorta. (89) It has been speculated that the rigid fibrous tissue cannot expand with BA and may confer a risk of rupture. In support of this theory, the only reported post-rupture autopsy after BA for recurrent CoA showed a longitudinal tear crossing the suture line of intact end-to-end anastomosis. (105)

The COAST trial (Coarctation of the Aorta Stent Trial), followed by the COAST II trial, are pivotal studies in the endovascular treatment of coarctation of the aorta. (100,106) The COAST trial evaluated the safety and efficacy of the bare metal (BM) Cheatham Platinum (CP) aortic stent. This trial involved the implantation of 105 stents in as many patients, with acute aortic complications occurring in 6 patients (6%). These complications included two small aneurysms and four minor confined tears. While a tiny aneurysm did not require treatment beyond the initial CP stent placement, the others were managed with additional covered CP (CCP) stents, and these cases were subsequently included in the COAST II trial.

Notably, the COAST II trial revealed significant complications related to the vascular access site, including four critical iliac dissections. These complications are associated with the larger sheath sizes (12-14F) required for delivering the CCP stent, which poses a particular challenge given the often young patient population. (106)

Tretter et al. documented variable rates of aneurysm formation following different stent interventions: 0% and 13% after balloon angioplasty (BA), 0% to 5% after bare metal stent placement, and less than 1% after covered stent placement. (107) This variability has contributed to a recent trend favoring the use of covered stents, which is attributed to their lower associated risks of rupture (<1%) and dissection (3%). Additionally, covered stents will likely reduce long-term complications such as endothelial proliferation and restenosis. (108) Despite these benefits, data indicate that patients with uncovered stents experience a more significant mean decrease in aortic blood pressure gradient and an increase in aortic diameter following intervention than those with covered stents. However, these differences have not reached statistical significance. (109) This suggests that while covered stents offer specific advantages in terms of safety, the efficacy in improving hemodynamic parameters might be less distinct.

To reduce aortic wall injuries (AWI), Hijazi and associates advised that the diameter of the balloon or expanded stent should be, at most, the diameter of the descending thoracic aorta at the diaphragmatic level or three times the diameter of the CoA segment. (110) Duke and colleagues advocated for an initial strategy of incomplete stent expansion, followed by subsequent dilation

in a later procedure, to further mitigate the risk of pathological aortic wall injury. Although staged treatment makes sense in high-risk situations, there must be evidence that this approach is necessary or practical. (111) The progressive dilation and expansion of the CoA segment may enable the operator to detect early therapeutic tears and minor AWIs. This early detection allows for consideration of either implanting a covered stent or adopting a staged approach. In the staged approach, the initial tear or injury can heal before undertaking a second procedure to alleviate the CoA fully. (107) Heck et al. have proposed a sequential dilation strategy defined as a second planned catheterization for further dilatation after the first stent graft implantation. (112) In their study, the total complication rate was 14.7% in a median follow-up time of 31 months. Most of the patients who developed aortic complications were treated conservatively. (112)

Sohn et al. conducted an intravascular ultrasound (IVUS) study to visualize AWI better.(113) Moreover, virtual simulations of stent implantation represent a promising approach in pre-procedural planning. (114,115) They allow for predicting the suitability of various stent types for individual cases. This technological advancement enhances precision in treatment planning, potentially improving outcomes.

However, the long-term durability of percutaneous interventions remains a concern. The COAST I and COAST II trials reported a notably high incidence of stent fractures during extended follow-up. The cumulative incidence of fractures was 0% at immediate follow-up (1 month), 2.9% by early follow-up (12 months), and escalated to 24.4% by late follow-up (4860 months), predominantly in patients who were older at the time of stent implantation. (116) Earlier research highlighted a trend towards lower rates of re-coarctation and lower rates of aneurysm formation in patients treated with covered CP stents. (117) Furthermore, bare CP stents have been identified as an independent predictor of stent fractures. (116)

Innovations in bioresorbable stents are ongoing, potentially allowing aortic growth after the stent has been fully resorbed. In adults, balloon angioplasty is typically reserved for previously stented aortas.

3.9 Recoarctation of the aorta definition and diagnosis

The frequency of aortic recoarctation (reCoA) varies significantly and highly depends on the patient's age at the correction time and the definition used. ReCoA is commonly defined as a condition where the invasive systolic gradient across the CoA is ≥ 20mmHg. (118–120) The definition of reCoA using other non-invasive imaging methods is more complicated. Based on the

Bernoulli equation, gradients measured during echocardiography are unreliable for determining the significance of reCoA post-correction. (121) This is related to the geometry of the aortic arch (i.e., hypoplastic arch), the complex dynamics of aortic arch blood flow, and the difficulties in adequately positioning the Doppler beam along the direction of blood flow. (121,122) During echocardiography, the presence and degree of antegrade diastolic flow ("sawtooth phenomenon") in the descending thoracic aorta are considered very specific for hemodynamically significant recoarctation.

The definition of recoarctation using magnetic resonance imaging varies widely. Bogaert and colleagues define reCoA when the aortic diameter ratio between the CoA and the aorta at the diaphragm is <0.9. (123) Other authors have defined re-coarctation as >50% narrowing of the aorta. (124,125) Patients with low residual gradients (<20mmHg), which are considered insufficient indications for re-intervention, may still have slightly increased blood pressure and, thereby, elevated risk of cardiovascular diseases. (102,126) After surgical correction or stenting, the increased systolic flow may occur even without significant narrowing due to decreased aortic compliance and the pressure recovery determined by Doppler, potentially overestimating the gradient. Diastolic tail in the descending aorta and antegrade diastolic flow in the abdominal aorta indicate significant reCoA. In the presence of extensive collateral arteries, gradient measurements may need to be more accurate, as the collateral vessels can divert some of the pressure that would otherwise be recorded across the coarctation.

Right arm ambulatory blood pressure measurement is recommended for diagnosing/confirming arterial hypertension (24-hour average systolic >130 mmHg and/or diastolic >80 mmHg). Other findings may be observed, such as a suprasternal thrill (proximal) or notching of the third and fourth (to eighth) ribs on chest X-ray due to collateral vessels. Measuring arterial blood pressure in the upper and lower limbs is a fundamental examination for all patients with CoA. The blood pressure gradient between the upper and lower limbs (systolic ≥20 mmHg) indicates significant CoA. A weak pulse or absence of pulse in the lower limbs or a delay in the radio femoral pulse also suggests significant coarctation.

3.10 Imaging role in CoA and reCoA patient's management

Even after a successful CoA correction, the risk of late complications such as recoarctation, aneurysm, pseudoaneurysm, and dissection remains. Long-term follow-ups after successful surgical CoA correction reveal that

11% of patients may require repeat interventions due to restenosis identified by MRI or CT during routine examinations. (127)

Patients who underwent surgical correction with patch aortoplasty have a higher risk of aneurysm formation, which an MRI or CT scan can assess. After successful percutaneous intervention (balloon angioplasty or stenting), a subsequent MRI or CT examination is recommended to check for possible late complications such as the formation of aneurysms, stent fractures, or stent migration. (127)

MRI and CT scans, including 3D reconstruction, are the most suitable non-invasive methods for evaluating the entire aorta in adolescents and adults. Both methods can depict the location, extent, and degree of aortic narrowing, the aortic arch, head and neck vessels, the aorta before and after stenosis, and collaterals. Both methods are capable of identifying complications such as aneurysms, pseudoaneurysms, restenosis, or residual stenosis.

CoA is defined based on computed tomography (CT) scans, which show a difference of ≥50% in diameter between the isthmus and the descending aorta at the diaphragm level.(64,65)

Imaging of intracerebral vessels is indicated in the presence of symptoms and (or) clinical manifestations of aneurysms/rupture.(128)

The invasive gradient measured during heart catheterization (systolic gradient ≥20mmHg) indicates hemodynamically significant CoA without well-developed collaterals. However, the measurement may be underestimated in patients under general anesthesia.

3.11 Hemodynamically like coarctation lesions

Numerous vascular abnormalities, such as mid-aortic syndrome and fibromuscular dysplasia, can affect hemodynamics similar to those observed in CoA.

Fibromuscular dysplasia (FMD) is a known cause of renovascular hypertension (RVH). It has been reported in 4.4% of prospective renal donors and is recognized as the second most common cause of RVH after atherosclerotic disease. (129) The prevalence of FMD among patients, particularly women with early-onset, accelerated, malignant, or resistant hypertension, may be as high as 7.5% in hypertensive women under 50 years of age. (130) FMD primarily affects medium-sized arteries, including the renal arteries (RAs), carotid, and vertebral arteries.

Mid-aortic syndrome (MAS) represents a rare but significant condition characterized by the narrowing of the abdominal aorta and the ostial stenosis of its major branches, including the renal arteries. If left untreated, significant

MAS can result in hypertensive encephalopathy, congestive heart failure, and stroke, typically manifesting in the third or fourth decade of life. (131,132)

MAS is linked to genetic and phenotypic conditions, such as neurofibromatosis type I, William's syndrome, Alagille syndrome, and mucopolysaccharidosis. Potential etiologies include failure of the two dorsal aortas to fuse during embryonic development (133), rubella infection (134), or abnormal kidney migration, as suggested by the high incidence of multiple renal arteries observed in 70% of cases in one series. (135) It was suggested that in patients with Alagille syndrome, MAS or renal artery (RA) stenosis might be associated with the progression of vascular abnormalities, leading to occlusion of the unilateral RA. (136,137) The location of the aortic lesion in idiopathic MAS is inter-renal in 19–52% of cases, supra-renal in 11–40%, infra-renal in 19–25%, and diffuse in 12%. (135,138)

The most common histological finding in the aorta and visceral vessels in idiopathic MAS is fibroplasia of the intima and variable distortions of the internal elastic lamina with a lack of inflammatory changes. The fibrotic proliferation of the media and adventitia has also been described. These lesions are similar to those found in isolated renal artery stenosis and some forms of fibromuscular dysplasia. (139)

Surgical correction of idiopathic MAS remains the definitive treatment when technically feasible. However, with effective anti-hypertensive treatment, conservative therapy is often possible before surgery. In cases where the level of operative risk is deemed unacceptable or in the very young, medical treatment is sometimes the only option. The exact timing of surgery should be individualized based on the severity of symptoms, the response to medical treatment, the age and size of the patient, and the consideration of surgical risks. (140,141) In cases where medical management is effective, it may be preferable to wait until total adult growth and adult vascular size are reached. Conversely, others suggest that effective surgical treatment with the option of future surgical revision is more appropriate. (141)

Clinical case collection and report of one of the most extensive MAS patient data (96 pts) treated surgically with aortoaortic bypass. Patch aortoplasty was performed for 10% of cases and was best for short-segment stenoses (142) and very young patients, leaving the possibility of the bypass at an older age. Other interventions, such as percutaneous transluminal balloon angioplasty and stent placement, were unsuccessful in the long term and were accompanied by many complications. (132,143) Of the 96 surgical cases, 73% of BP was normalized, and 27% had decreased blood pressure. (142) Onat and Zeren found that 42% (46 out of 91) of patients presented with hypertensive encephalopathy, and 45% (49 out of 91) died before 34 years of age. (6)

3.12 Coarctation of the aorta and arterial hypertension

Historically, untreated coarctation of the aorta exhibited a grave prognosis. In the mid-1960s, the annual mortality rate of native CoA escalated from 1.6% in the first two decades to 6.7%. This trend likely continued to rise gradually until the sixth decade of life. (6) Expanded diagnostic capabilities and diverse therapeutic options have subsequently improved the survival rate to 87.4% by the mean age of 40. (144)

Arterial hypertension at rest might not be detectable; thus, ambulatory arterial blood pressure (aABP) monitoring can help to identify and adequately treat patients with arterial hypertension. (65) Evidence in the adult literature shows that 24-hour arterial blood pressure predicts end-organ damage and provides a better measure of ABP than casual readings. (145) Some studies measured 24-hour ABP, but there was no standardization of the type of BP devices. Significant differences have been shown when using two different 24-hour BP devices. (146) In a study by Bambul Heck et al., 273 patients were studied (COALA study) and reassessed 14 years later. (22) All patients had ambulatory 24 h BP measurements. In this study, 23% of patients were found to have arterial hypertension, with 25% taking antihypertensive drugs. Fourteen years later, 53% of the same patient group were found to have AH, with nearly half receiving antihypertensive medication. (147)

Despite early and successful corrective surgeries for coarctation of the aorta, these patients continue to exhibit a heightened early cardiovascular risk. Regardless of successful interventions, hypertension remains a prevalent complication among these individuals, thereby raising significant clinical concerns. With the advent of endovascular interventions, this approach has been established as a guideline-supported therapeutic modality (2018 AHA/ACC guidelines CLASS I LEVEL B-NR). (65)

The prevalence of arterial hypertension and mortality among post-surgery patients in longitudinal studies correlates with age at the time of surgical intervention and the duration of postoperative observation. (18,20,23,82,83,148–150) A higher age than nine years old at the time of repair is linked to an elevated incidence of hypertension (relative risk: 4.1; 95% CI: 2.1 to 8.4; $p < 0.001$) (21,151–153). However, this association was not observed in the studies conducted by Bambul Heck et al. and Rinnström et al. (22,154) Rinnström et al. conducted a follow-up of patients over three decades after CoA repair. They found that the age at intervention was less critical than the age at follow-up in AH development, suggesting that the benefits of early repair may diminish over time. (154) It is crucial to acknowledge that adults undergoing coarctation repair exhibit a lower long-

term survival rate than a matched average population, with an increased decline at the beginning of their thirties. (8) An independent correlation has been identified between left ventricular mass and age during CoA correction, suggesting that early correction not only preserves myocardial structure and function but also reduces the likelihood of subsequent hypertension. (155)

Longitudinal data indicate that 41% of patients are diagnosed with arterial hypertension 24 years post-primary correction of coarctation of the aorta. (155) Other investigations report an even higher persistence rate of hypertension post-repair, ranging from 44% to 60%. (19) A systematic review presented a mean prevalence of arterial hypertension of 47.3%, with a variability ranging from 20% to 70%). (147) Sendzikaite et al. reported isolated systolic hypertension as the predominant phenotype among CoA patients. (21) Furthermore, some studies classify individuals as hypertensive if they are under previously prescribed medical treatment for hypertension, (154) regardless of their regular blood pressure measurements, as noted by Bambul Heck et al.. (22)

De Divitiis et al. reported that early surgical intervention in the coarctation of the aorta helps to preserve the elastic properties of the aortic arch branches. However, a diminished reactivity to stimulation persists. (156) Current medical guidelines recommend prompt correction upon diagnosis to mitigate the risk of persistent or emergent hypertension (Class 1, level C). (64,65) The advantages of early intervention outweigh the risks of re-coarctation associated with procedures in early infancy. Notably, a high prevalence of hypertension is still observed in children, including those who underwent surgery in early childhood (mean age one year), even with no significant aortic arch obstruction. (18)

Findings from Giordano's study documented the lower incidence of hypertension in cases of complex CoA compared to simple CoA in surgical patients. (157) The discrepancy in hypertension incidence between simple and complex CoA might not solely depend on the surgical technique but could also be influenced by other physiological factors. It can be explained that the reduced rate of late hypertension in complex CoA could stem from diminished stimulation of the baroreceptor reflex in the pre-stenotic area, likely due to decreased systemic blood flow and pressure before intervention—a condition not present in simple CoA cases. (158,159)

On multivariable Cox regression analysis, specific factors such as the nature of the coarctation (simple vs. complex CoA) and the age at the time of stenting significantly influenced the likelihood of hypertension at the last follow-up. The odds of developing Hypertension were substantially higher in patients with complex CoA compared to simple CoA, with an odds ratio (OR)

of 4.01 and a 95% confidence interval (CI) ranging from 1.30 to 12.41 (P=0.016). Additionally, older age at the time of the first stent implantation was associated with an increased incidence of hypertension during follow-up, indicated by an odds ratio of 1.81 and a 95% CI of 1.15 to 2.84 (P=0.01). (103)

The aortic arch morphology can be categorized into three distinct shapes: Crenel, Romanesque, and Gothic arches. These classifications are based on qualitative assessment, emphasizing the height of the aortic arch and the distance between the ascending and descending aorta (width). The width (W1) is markedly reduced in the Gothic arch configuration, and the height (H1) needs to be preserved. In the Crenel arch configuration, while the height (H2) is maintained, the width (W2) must be narrowed sufficiently. In contrast, the Romanesque arch configuration is characterized by both the preservation of height (H3) and a moderate reduction in width (W3) ($H1 < H2 = H3$, $W1 < W3 < W2$). (160) In one of the small studies, multiple logistic regression analysis revealed the only independent factor significantly associated with hypertension status was the Gothic arch geometry ($P = 0.02$) when the independent variables included in the model were age at operation, age at the time of the study, weight, height, arm-leg systolic blood pressure gradient, and the geometry category. However, when the continuous variable representing the aortic arch height-to-width ratio (H/W) was substituted for the geometry category in the model, H/W emerged as the sole independent factor associated with hypertension status ($P = 0.04$).(19)

3.13 Pathogenesis of Arterial Hypertension

The regulation of ABP is maintained through both short-term and long-term mechanisms. Short-term regulation is achieved by modulating cardiac output and peripheral arterial resistance, allowing the body to adapt quickly to changes in physiological demand. Conversely, long-term regulation of ABP involves controlling blood volume and vascular capacity through mechanisms influenced by the renal system, hormonal signals, and vascular remodeling. This comprehensive explanation of blood pressure regulation underscores the complex physiological orchestration required to maintain vascular health and prevent target organ damage associated with arterial hypertension.

Current population-representative studies primarily report the prevalence of arterial hypertension in older adults, as the prevalence is relatively low before the age of 30. According to data from 2019, the global age-standardized average prevalence of hypertension among adults aged 30 to 79 was 34% in men and 32% in women. (161,162)

Arterial hypertension (AH) has a systemic impact, affecting multiple target organs, including the brain, heart, eyes, kidneys, and blood vessels. The pathogenesis of organ damage in AH associated with vascular damage is complex. The damage to the heart and other target organs involves multifaceted mechanisms that extend beyond hemodynamic stress, encompassing the activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and inflammatory pathways. (163) This condition reflects functional and structural changes within the vasculature, acting as both a precipitant and a result of elevated blood pressure. The pathophysiological process is linked to arteriosclerosis and atherogenesis. Arteriosclerosis describes the hardening of large arteries due to non-inflammatory changes in the medial vessel wall layer, leading to increased arterial stiffness. Atherogenesis, on the other hand, involves the formation of intimal plaques that narrow and obstruct blood flow, an inherently inflammatory process. These processes collectively contribute to atherosclerosis, a condition that affects blood vessels of varying calibers throughout the body. The emergence of arterial hypertension results from a complex interplay of various factors, which can differ significantly across individuals. Central to the development of arterial hypertension are the activation of neurohumoral systems, lifestyle influences such as obesity and high salt consumption, and genetic predispositions.

The RAAS primarily influences the long-term regulation of ABP by modulating NaCl excretion and fluid balance, actions mediated through angiotensin II and aldosterone. This impact of the system on fluid volume and vascular resistance is pivotal in maintaining or altering blood pressure levels. (164) Meanwhile, the SNS affects ABP through direct mechanisms like vasoconstriction and increased cardiac output, facilitated by activating sympathetic vasoconstrictor fibers in the vasculature and kidneys. (165)

The afferent sympathetic pathways from the kidneys play a pivotal role in conveying information to the central nervous system, utilizing pressure-sensitive receptors in the renal pelvis, which regulate the sympathetic response through the reno-renal reflex. (166) This intricate communication underscores the significant influence of renal sympathetic innervation on ABP regulation and the development of AH. (167) The activation of renal sympathetic nerves leads to substantial physiological outcomes, including sodium retention, increased secretion of renin, and a reduction in the kidney's ability to excrete sodium (impaired natriuresis) effectively. This activation process is particularly pronounced in the proximal tubules of kidneys, densely innervated by SNS fibers. (168) The role of SNSs in modulating sodium

reabsorption in these tubules is crucial to the mechanisms involved in arterial hypertension.

Under normal conditions, an increase in renal perfusion triggers a decrease in sodium reabsorption in the proximal tubules, promoting natriuresis. However, in the context of hypertension, this adaptive mechanism is compromised. This compromise leads to a decrease in sodium excretion, contributing to the development of hypertension. (168)

Understanding the potential early-life origins of arterial hypertension and kidney disease is crucial, particularly concerning the renin-angiotensin-aldosterone system (RAAS) and its developmental influence. In humans, nephron development ceases post 36–38 weeks of gestation. (30) Epidemiological studies highlight prematurity, low birth weight, and maternal use of RAAS-interfering drugs as risk factors for later-life kidney disease and hypertension. (39,42) Speculating on the influence of coarctation of the aorta prenatally, it's essential to consider that the arterial duct predominantly maintains fetal hemodynamics until birth. Upon closure of the arterial duct post-birth, when renal cells are already formed and operational, CoA might reduce arterial pressure to the lower body and diminish renal perfusion. This reduction in perfusion could affect renal baroreceptors, which regulate arterial blood pressure by suppressing renin release. (169) This mechanism has been well-documented in the context of baroreceptors' "dose" (pressure)–response relationships. (170) Additionally, the reduced sensitivity of baroreceptors, coupled with discrepancies in the growth of the aortic arch—especially if the arch remains hypoplastic—may predispose individuals to hypertension. (51,156,171,172)

3.14 Arterial hypertension risk factors

The unique morphology of the aortic arch significantly influences hemodynamic forces and blood flow distribution, which can lead to variations in blood pressure. Specifically, the recurrence or persistent presence of CoA may exacerbate arterial hypertension and associated complications. (173)

The ongoing prevalence of AH following CoA stenting is likely multifactorial, involving variables such as arch morphology, patient age, arterial compliance, and the effects of recurrent CoA. (174) Persistent hypertension in patients with native CoA or reCoA is commonly attributed to several interconnected factors: endothelial dysfunction, abnormal reactivity of the arterial smooth muscle, changes in the material properties of the aorta, leading to increased arterial stiffness, and decreased baroreceptor sensitivity, which triggers heightened sympathetic activity. (8–10)

Obesity has also been highlighted as a significant issue in patients with CoA and hypertension. In a cross-sectional study by Smith-Parrish et al., an alarming increase in the prevalence of obesity was noted—26% at age 10, escalating to 63% by age 20—with a strong correlation found between obesity and hypertension. (175) Similar associations between hypertension and obesity were reported by Rinnström et al. (154)

The pathophysiological underpinnings of hypertension in post-CoA patients include residual narrowing, enhanced aortic stiffness, hyperactivity of the renin-angiotensin system, impaired baroreflexes, and peripheral vascular dysfunction compounded by abnormal arch geometry. (11,12) Moreover, older age at the time of CoA repair has been linked to a higher incidence of late hypertension. (81) Furthermore, hypertension is recognized as a significant risk factor for aortic wall injury (AWI) and consequent mortality, both in native and postoperative cases of CoA. (81)

In the COALA study, the utilization of prosthetic material during surgical or catheter interventions was identified as a significant risk factor for hypertension in patients without evident restenosis. This was attributed to increased aortic stiffness and the non-compliant nature of the prosthetic materials used. (7)

3.15 Association between residual stenosis and arterial hypertension

The impact of residual stenosis in the descending aorta on the development of arterial hypertension remains a contentious issue. Researchers advocate for applying percutaneous interventions, such as stent implantations, in cases of minor stenosis due to its potential association with recoarctation and the subsequent presence of arterial hypertension. (26,102)

A Swedish National Registry (SWEDCON) suggests that incomplete stenosis correction could precipitate hypertension, (176,177) underlining the necessity for timely clinical and imaging evaluations of CoA. Previous research has also demonstrated that even mild residual descending aortic stenosis compared with no stenosis in patients with repaired CoA independently correlates with mean daytime blood pressure (178) and is associated with LV hypertrophy. (176) Residual narrowing contributes to hypertension irrespective of treatment outcomes. (154)

One study examined blood pressure outcomes following percutaneous stent implantation, revealing no significant differences in systolic blood pressure (SBP) between patients categorized into significant CoA (invasive peak gradient >25mmHg) and non-significant CoA (invasive peak gradient <25mmHg) groups, both six weeks (141 mmHg vs. 135 mmHg; $P = 0.21$) and

9—12 months post-intervention (139 mmHg vs. 139 mmHg; P = 0.96). (179) This study also highlighted that neither absolute nor percentage changes in pressure gradients (PG) after stenting correlated significantly with reductions in SBP at subsequent follow-ups. The antihypertensive treatments included beta-blockers, ACEI, and calcium channel blockers. (179)

Research conducted by Choudhary et al. and Chen et al. did not establish a definitive correlation between the prevalence of arterial hypertension and the presence or absence of re-stenosis. (151,180) However, a reduced threshold for re-intervention in cases of aortic narrowing may be advantageous. (181) It is critical to recognize that the previous 2010 ESC guidelines were established when most re-interventions for coarctation of the aorta were surgical, carrying the inherent risks of thoracic surgery, uncertain impacts on minor gradients, and the frequent requirement for prosthetic materials. (182) Considering recent evidence and the current dominance of catheter-based techniques, re-evaluating the risk-benefit ratio might lead to different recommendations.

The implications of current CoA management strategies, particularly the alleviation of central aortic obstruction, on cerebral perfusion merit careful consideration, especially in individuals with pre-existing vascular anomalies such as vertebral artery hypoplasia (VAH). Interestingly, the reduction in central aortic pressure anticipated from CoA corrective interventions might paradoxically impair cerebral perfusion in those with vulnerable vascular systems. This concern is echoed in research findings indicating that individuals who received treatment for hypertension post-CoA repair displayed significantly reduced cerebral perfusion when compared to non-treated controls. (183) Furthermore, observations of diminished cerebral blood flow in CoA patients support this hypothesis. (128) If this theory is accurate, CoA interventions might predispose specific individuals to increased neurogenic-mediated sympathetic nerve activity, a condition supported by documented cases of heightened SNA in patients following CoA repair. Additionally, the occurrence of hypertension after CoA treatment underscores the complex interplay between CoA correction, vascular anomalies, and the regulation of blood pressure, indicating a need for a more nuanced approach to post-repair management and monitoring to mitigate the risk of developing hypertension. (184,185)

Consequently, there might be grounds to consider re-intervention at smaller systolic arm-leg blood pressure gradients than currently advised. Clinical observations have identified a considerable subset of patients who exhibit hypertension post-coarctation repair despite the absence of residual aortic obstruction, especially with Gothic arch anatomy. (19,186–188)

Nonetheless, additional studies are necessary to substantiate such adjustments in clinical practice. (176)

3.16 Arterial hypertension and exercise test in CoA

A significant proportion (20-35%) of patients following CoA correction display normal arterial blood pressure at rest but exhibit a hypertensive response during physical exertion. Research involving healthy, normotensive individuals has shown that those with exercise-induced hypertension are at an elevated risk of developing arterial hypertension in later years compared to those with typical blood pressure responses to physical stress. (192,193) In routine clinical practice, exercise tests are generally not recommended due to the absence of significant differences in blood pressure responses during physical exertion between patients who have undergone CoA correction and healthy subjects. (194) Consequently, the relevance of exercise testing in this context and the clinical importance of exercise-induced hypertension remain controversial.

Following the correction of CoA, exercise-induced hypertension may be attributed to increased stiffness and diminished elasticity of the arterial walls. Additional contributing factors might include reduced sensitivity of baroreceptors and mismatches in the growth of the aortic arch, particularly if the arch remains hypoplastic. (51,156,171,172) In adults undergoing CoA correction, the maximum systolic blood pressure during exercise correlates strongly with average daytime systolic blood pressure, as recorded during 24-hour ambulatory monitoring. Nevertheless, maximum exercise systolic blood pressure was not a prognostic indicator for left ventricular mass. (26) No significant association was observed between left ventricular mass and exercise blood pressure variables. (155,195) Additionally, research showed no difference in indexed left ventricular mass between patients with normotension and those exhibiting exercise-induced hypertension.

In a comprehensive analysis, no variables—from patient demographics and surgical specifics to echocardiography and exercise testing outcomes—proved predictive of arterial hypertension progression in long-term follow-ups. (22)

The long-term single-center study encompassed 115 individuals with available blood pressure records over an average follow-up duration of 12.7 years. The findings did not support the hypothesis that exercise-induced hypertension could act as a precursor to chronic hypertension in adults who have undergone coarctation repair. (22) These results underscore the complexity of the mechanisms that lead to hypertension post-repair and

highlight the challenge of predicting such outcomes using the factors typically considered in clinical evaluations.

3.18 Experimental animal models of coarctation of the aorta and renal perfusion

Goldblatt et al. (196) proposed that renal ischemia may serve as the initiating factor in the pathogenesis of hypertension associated with nephrosclerosis. In 1938, Rytand (197), inspired by this foundational research, introduced the hypothesis that coarctation of the aorta leads to decreased renal blood flow, prompting the release of a renal pressure substance in canine models. Additional evidence highlights the importance of a decrease in renal perfusion and glomerular filtration rate in dogs with CoA, which is more prominent in salt restriction settings. (198) Experiments in dogs with neonatally induced chronic aortic coarctation revealed that salt restriction results in renal hypoperfusion and an abnormal increase in plasma renin activity, suggesting the activation of a renin-mediated mechanism similar to those seen in other hypertensive states characterized by renal underperfusion. (198)

The further observation of heightened renin reactivity, such as an abnormality, is shared across various hypertensive conditions, underlining the role of the renal system in the pathogenesis of hypertension associated with CoA. Similar evidence highlighting the altered hemodynamics of renal role in arterial hypertension development emerged from experimental studies in a canine model. In these investigations, one kidney was transplanted to a site proximal to the coarctation, and the contralateral kidney was excised in dogs with CoA, resulting in a notable decrease in blood pressure to normotensive levels. (199,200) This effect demonstrated the profound impact of renal positioning and perfusion on blood pressure regulation. Subsequently, the surgical technique was changed to rerouting the total renal blood flow to a position proximal to the coarctation using a prosthetic vascular graft (Dacron) anastomosed to an isolated segment of the abdominal aorta that included both renal arteries, allowing the kidneys to stay in place with their venous and ureteral drainage intact. (201) This pivotal evidence of a renal component contributing to hypertension seen in the coarctation of the aorta marked the beginning of a deeper exploration into the physiological mechanisms behind this phenomenon. (199) Despite this insight, the exact roles of mechanical factors and the potential influences of other organs located distal to the coarctation of the aorta on the development of arterial hypertension continue to be debated. These findings underscore the intricate nature of AH associated

with CoA, highlighting the interplay between renal hemodynamics and vascular anatomy in its pathogenesis. (201)

The findings from this study elucidate two distinct forms of AH associated with CoA, delineating the complexities involved in its pathophysiology. The first form is characterized by increased arterial blood pressure proximal to the coarctation and decreased pressure distal, which remained consistent. This scenario, observed in dogs from which the renal factor was eliminated, epitomizes the direct mechanical impact of coarctation: the elevated pressure proximal to the coarctation arises from the augmented vascular resistance due to the aortic narrowing. This mechanical effect necessitates the surgical removal of the coarctation itself.

The second form of hypertension manifests as progressive generalized hypertension in dogs whose renal blood flow was situated distal to the coarctation, activating renal humoral mechanisms. Although the pattern of hypertension observed mirrors that of previous studies, a unique aspect of this condition was the absence of a stable pressure (plateau) phase; (184,199,200,202) instead, hypertension escalated progressively throughout the study period. (201) Currently, there is no available data on human models.

3.19 Renin – angiotensin – aldosteron (RAAS) system

The kidney emerges as a focal point for the multifaceted constituents of the Renin-Angiotensin-Aldosterone System (RAAS), which includes prorenin/renin, angiotensin II (ANG II), angiotensin III (ANG-(2–8)), angiotensin-(1–7), angiotensin IV (ANG-(3–8)), angiotensin-(1–9), and aldosterone. (203)

Upon reaching the circulation, renin initiates an enzymatic cascade that culminates in the production of angiotensin II, a potent vasoconstrictor that elevates BP and extracellular fluid volume. Renin cells are sensors that receive constant mechanical, neurohumoral, and biochemical signals from other cell types and the extracellular matrix where they reside. (204)

Renin cells, despite their small number in adult mammals (0.01 % of the kidney cells), play a pivotal role in maintaining homeostasis. (205) They can synthesize and release renin in response to threats such as hypotension, dehydration, sodium depletion, or treatment with RAAS blockers. This ability ensures the restoration of BP, extracellular fluid volume and composition, tissue perfusion, and oxygen delivery to critical organs, thereby ensuring survival. The three primary mechanisms that control renin synthesis and release (the renal baroreceptor, the macula densa, and the β-adrenergic receptors) are activated and potentiate each other during such homeostatic

threats. The regulation of cyclic adenosine monophosphate (cAMP) generation, the principal intracellular effector of renin expression, renin release, and renin cell identity, is central to the operation of these mechanisms. (204)

ANG II is thought to exert direct negative feedback on renin secretion by the so-called "short loop feedback inhibition." Renin secretion from isolated perfused kidneys without nerve input and variation in perfusion pressure is highly sensitive to ANG II infusion. (206) In addition to mechanisms that increase the number of renin cells, ANG II negatively affects the amount of renin released into the circulation, thereby preventing hypertension. Although, in vitro, angiotensin II directly affects the number of cells secreting renin, the ability of angiotensin II to suppress renin cell recruitment and renin release depends heavily on the BP levels. (207) As discussed below, this process has no proliferation or cell migration. Smooth muscle cells along the arterioles, sometimes mesangial cells, and interstitial peritubular pericytes are transformed to synthesize renin. (36)

It has been established that whole-body sodium chloride content negatively affects renin secretion through the macula densa mechanism. (208) Macula densa cells selectively express neuronal nitric oxide synthase (NOS-I). (209) NOS-I expression in the macula densa correlates to renin expression. (210) NO synthase inhibition reduces renin secretion and renin mRNA level under acute (211) or chronic (212) low renal perfusion pressure, under a low dietary NaCl intake, under furosemide treatment, and under ANG II receptor blockade. (210)

In high salt conditions, the opposite is observed: a decrease in the number of renin-expressing cells. Whether this can be linked to the release of adenosine by macula densa cells affecting intracellular cAMP in nearby cells of the renal arterioles remains to be determined. (207) How a decrease in pressure induces the recruitment of renin cells has yet to be delineated. Tobian and Skinner et al. (169) suggested that a renal baroreceptor regulates arterial blood pressure by negatively controlling renin release. The baroreceptor has been extensively characterized concerning "dose" (pressure)–response relationships (170) and calcium dependence. (206,213) Renin mRNA abundance and release are tonically stimulated through a β-adrenoceptor mechanism independent of tubular function or glomerular filtration rate. Renin release and renin mRNA abundance are decreased by renal denervation (214), while α1-adrenoceptor agonists have the opposite effect in vivo.

The process of renin cell recruitment, often referred to as "JG cell hyperplasia," is a reversible phenomenon that does not involve cell migration. (215) A small percentage of renin-expressing cells may also be generated by

denominated neogenesis, defined as the denovo expression of renin by cells that have never expressed it. (215)

Although the evolutionary conserved ability to recruit renin-producing cells (via the transformation of SMCs to renin cells) serves the organism well in response to physiological challenges, it can result in arterial pathology when homeostatic balance is not achieved. (216)

3.20 “The Programmed Kidney”

The concept of "The Programmed Kidney" posits that adult hypertension and kidney disease may stem from early-life renal programming influenced by the renin-angiotensin-aldosterone system (RAAS) and its role across developmental stages.

For instance, a maternal low-protein diet in a rat model led to reduced renal angiotensin II type 1 receptor (AT1R) expression at birth, which then increased by the time the offspring were four weeks old. (217) Another study on placental insufficiency in Sprague Dawley rats found that adult offspring exhibited hypertension, elevated renin and angiotensinogen mRNA levels, and increased angiotensin-converting enzyme (ACE) activity at 16 weeks. However, these levels were reduced at birth. (218) These findings suggest a biphasic response in renal programming models: an initial downregulation of classical RAAS components during the neonatal stage, which tends to normalize as the organism ages. However, early-life disturbances might hinder this normalization process, potentially leading to the inappropriate activation of the classical RAAS axis, subsequent hypertension, and kidney disease in adulthood. (42)

3.21 Renal scintigraphy

The pathophysiological processes observed in renovascular disease employ captopril renal scintigraphy as a diagnostic tool to detect such conditions as renal hypertension. (13,14) Renal scintigraphy has a high degree of diagnostic accuracy for renal artery stenosis and renovascular hypertension, evidenced by sensitivity rates ranging from 87% to 96% and specificity rates from 85% to 95%. (13,16) Other studies reveal renal scintigraphy sensitivity of 73% or 85% and a specificity of 90% or 83%, depending on the chosen "positive test" criterion (captopril-induced changes between baseline and post-captopril studies or abnormality on the post-captopril research only). Therefore, employing the alterations induced by captopril as a benchmark for a "positive test" outcome, the diethylenetriamine pentaacetic acid - renal

scintigraphy (DTPA-CRS) exhibits a high specificity (along with a high negative predictive value). Nevertheless, it demonstrates a sensitivity of only 76%. This suggests that a negative test result does not conclusively eliminate the possibility of some blood pressure improvement following revascularization.

On the other hand, an abnormal post-captopril renal scintigraphy (without comparison with a baseline test) has quite good sensitivity but an unacceptably low specificity (66%). These parameters include 20-minute/peak uptake, time to maximum concentration, and relative uptake. (219)

Technetium-99m mercaptoacetyltriglycine (MAG3) usage has increased significantly since its introduction in 1986. (220,221) Because of its favorable imaging characteristics and the more efficient renal extraction of 99mTc MAG3 compared with 99mTc diethylenetriaminepentaacetic acid (DTPA), 99mTc MAG3 has become the radiopharmaceutical of choice in many clinical contexts, particularly for patients with suspected obstruction or impaired renal function. (220,222,223)

The scan results in several measurements being calculated. The time to peak, referred to as T_{max}, represents the duration from the radiopharmaceutical injection to the point where the renogram curve reaches its maximum height. 99m Tc-MAG3 renograms typically peak around 5 minutes after injection and decrease to half of their peak height within 15 minutes. Prolonged T_{max} reflects delayed renal perfusion, indicating that the kidneys take longer to process and filter blood.

The 30-min/T_{max} ratio is calculated by comparing the kidney counts 30 minutes after injection to the T_{max} counts obtained during the renal scintigraphy. This ratio serves as an indicator of both the transit time and parenchymal function of the kidneys.

The ratio of count in the whole kidney ROI at 20 min to count at 3 min (20min/3min) was also determined. This ratio has been proposed as a valuable parameter for evaluating clearance and excretion simultaneously. Elevated ratios suggest slower renal clearance following ACEI administration, which indicates impaired kidney function. (224)

There are no criteria to evaluate renal perfusion in CoA patients. For this reason, the same interpretive criteria for diagnosing renovascular hypertension of Tc-99m MAG3 scintigrams are used in this study. (225) These diagnostic criteria include:

- Unilateral parenchymal retention following ACE inhibition is a critical indicator in Tc-99m MAG3 scintigraphy, suggesting a high probability (>90%) of RVH.

- Parenchymal retention can be identified by a change in the 30-minute/T_{max} uptake ratio of 0.15 or more, a notably prolonged transit time, or a shift in the scintigraphic grade.
- Additionally, parenchymal retention may manifest as a delay in the excretion of the tracer into the renal pelvis exceeding 2 minutes post-ACE inhibitor administration or an increase in the T_{max} (time to maximum concentration) by at least 2 minutes or 40%.
- While a greater than 10% change in the relative uptake of Tc-99m MAG3 following ACE inhibition is rare, it, too, indicates a high likelihood of RVH.

4. METHODS

This study was conducted using a prospective methodology. It was performed at the Vilnius University Hospital Santaros Klinikos (VUL SK). Permission for the biomedical research was granted by the Vilnius Regional Biomedical Research Ethics Committee (No. 2019/5-1113-61). In this prospective cohort study, adult individuals diagnosed with either native or post-repair coarctation of the aorta were enrolled. Before being included in the study, an informed and signed patient consent form consent was obtained.

Doctoral candidate Sigitas Cesna developed the study inclusion and observation protocol. The doctoral candidate also selected patients for the study, performed invasive procedures, and monitored patients.

4.1 Study population

Inclusion criteria:

1. Adult patients (> 18 years old)
2. Patients with native coarctation of the aorta and post-surgical or percutaneous coarctation treatment.

Exclusion criteria:

1. Patients with complex congenital diseases involving left-sided lesions (such as residual aortic valve stenosis or regurgitation, mitral valve disease, or Shone syndrome)
2. Pregnant patients or those planning pregnancy during the study.

The potential candidates for inclusion in our study were identified from our database of adult congenital heart disease (ACHD) clinic patients (Figure 1). For initial screening, we considered individuals who had previously undergone surgical or interventional treatment for coarctation at our institution or those with native coarctation.

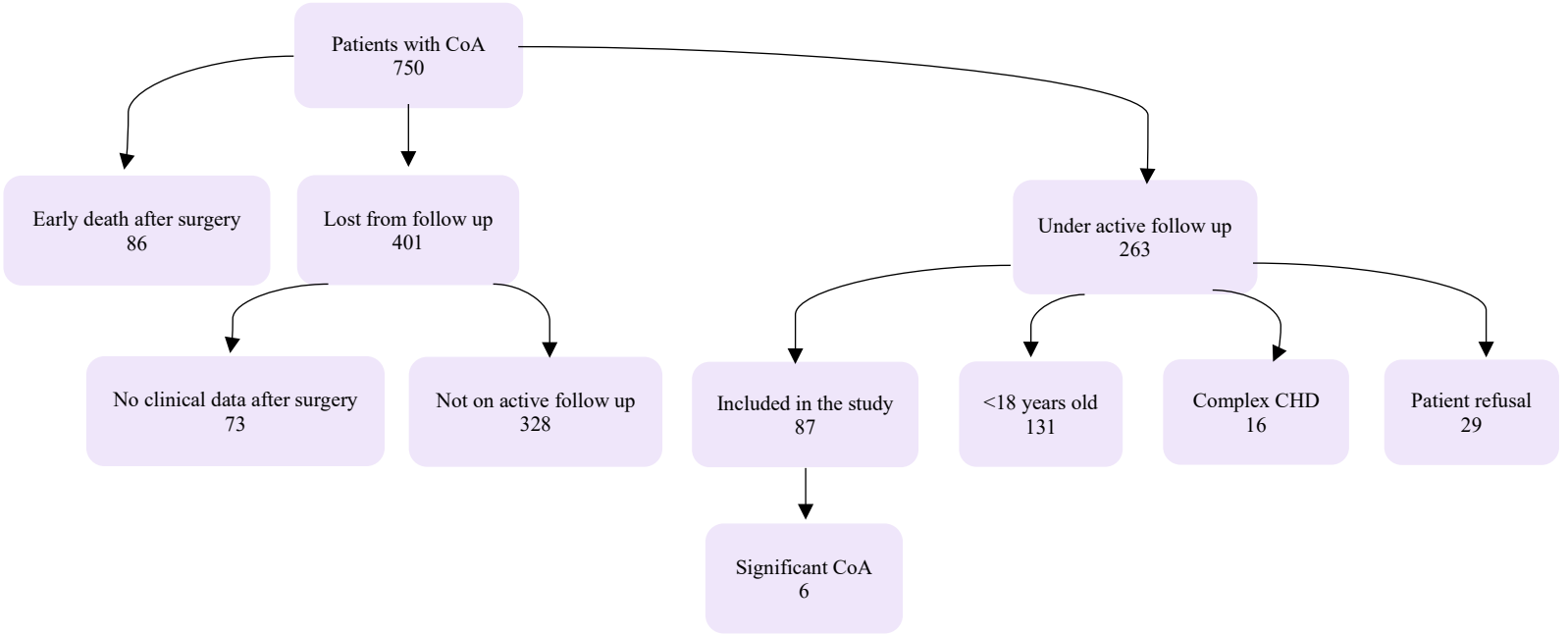

Figure 1. Patient inclusion flowchart

A total of 750 patient records were reviewed. Of these, 86 patients died in the early stages following their CoA surgical treatment. Four hundred-one patients had not attended follow-up appointments with a congenital heart disease specialist. Among them, 73 patients had no clinical data in the database other than the surgical protocol. The remaining 328 patients were alive but were either not actively attending the Adult Congenital Heart Disease (ACHD) clinic or had declined to return for follow-up visits due to the COVID-19 pandemic. There are 263 patients on the active follow-up list; half (131 patients) did not meet the age criteria, as they were under 18. Sixteen patients had complex congenital heart disease and were excluded from the study.

Additionally, 29 patients declined to participate in the trial. Eighty-seven patients met the inclusion criteria and were enrolled in the study. Six of the 87 included patients had significant CoA and met the requirements for percutaneous treatment.

The 87 patients were divided into two groups. The first group (Control group) consisted of 30 patients diagnosed with CoA but without arterial hypertension, no systolic blood pressure gradient between the upper and lower extremities, and no significant narrowing on CT scan (<30%). The remaining 57 patients were included in the second group (Mixed group) (Figure 2). A subanalysis was also performed on a subset of the Mixed group, consisting of 46 patients (Hypertensive group). This group only included patients with documented arterial hypertension, defined as office blood pressure measurements >140/90 mmHg or ambulatory blood pressure measurements >130/80 mmHg, irrespective of whether they received antihypertensive treatment.

The remaining 11 patients from the Mixed group, who demonstrated a pressure difference between arms or had residual stenosis greater than 30% on CT angiogram but did not have hypertension, were not subcategorized.

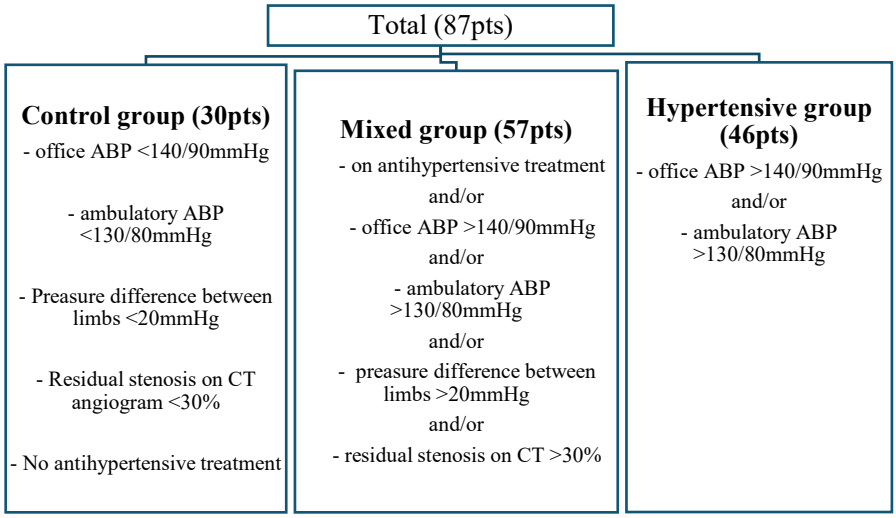

Figure 2: Criteria for the grouping of patients.

4.3 Monitoring protocol

Patients from the database who met the inclusion criteria were included in the study during the first visit. They were interviewed, and anonymized data about their health history were collected in a database specially created for the research. Demographics and medical history data (age, gender, information on comorbidities, previous surgeries or operations) and data from instrumental studies were collected (Table 1.).

Patients underwent office arterial blood pressure measurements and echocardiographic examination during their first visit. Other tests (CT scan, 24-hour blood pressure measurements, captopril renal scintigraphy scan, common carotid artery stiffness and intima-media thickness measurements, cardio-ankle vascular index, and ankle-brachial index measurements) were scheduled in 6 weeks.

Furthermore, cardiac catheterization with percutaneous stent implantation for CoA was conducted for patients who fulfilled the indications for percutaneous treatment. This subgroup of patients subsequently underwent repeat renal perfusion scans.

Table 1. Study monitoring schedule.

	Initial visit – 6 weeks	Invasive procedure	3-6 months
Consent form	X		
Inclusion/exclusion criteria	X		
Demographic data and previous surgeries	X		
Medical treatment	X		X
Office arterial blood pressure measurement	X		X
Echocardiographic Examination	X		
Blood tests	X		
IMT measurement	X		
CAVI measurement	X		
Ambulatory arterial blood pressure monitoring	X		X
Computed tomography	X		
Renal scintigraphy	X		X

4.4 Instrumental Studies

4.4.1 Office Arterial Blood Pressure Measurement

Office arterial blood pressure (ABP) measurements following the "2018 ESC and the ESH guidelines for managing arterial hypertension." (226) These measurements were performed during an initial visit with an automatic oscillometric device subject to biannual calibration. Measurements were initiated after the patient had rested quietly for a minimum of 5 minutes. The cuff was positioned alternately on the right and left brachial areas and the left thigh. Three ABP readings were taken at 1-2 minute intervals at each site. In instances of variability among these readings, the average of each side was calculated and recorded. Arterial hypertension was defined as an office systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥90 mmHg on the right arm or the patient was on antihypertensive medication.

4.4.2 Echocardiographic Examination

An echocardiographic examination was performed for all participants, lying on their left side, using the GE Vivid 4 ultrasound device (GE Healthcare, New York, USA) and a 1.0 – 5.0 MHz probe. Echocardiographic views were saved in an imaging archive. Conventional echocardiographic measurements were conducted in alignment with the recommendations for heart chamber quantification published by the American Society of

Echocardiography and the European Association of Cardiovascular Imaging in 2015. (227) All participants had a sinus rhythm during the examination. The study assessed morphometric measurements of the left ventricle (LV), systolic LV function parameters, and gradient through the CoA side. LV morphometry was evaluated in parasternal long-axis echocardiographic views.

Measured parameters included LVdd – LV diastolic diameter (cm), IVSd – Interventricular septal thickness in diastole (cm), and LVPWd – LV posterior wall thickness in diastole (cm), EDD – end-diastolic LV diameter. Global LV systolic function was evaluated by the two-dimensional Simpson's method of discs, calculating the LV ejection fraction (EF): EF (%) = LV end-diastolic volume (ml) – LV end-systolic volume (ml) / LVdd × 100. Formulas applied for calculating derived metrics:

a. LV myocardial mass (MM) (g) calculated using the formula - $MM = 1.04[(IVSd+LVPWd+EDD)^3 – EDD^3] \times 0.8 + 0.6$

b. LV mass index (LVMI) (g/m^2) calculated using the formula - LVMI = MM/body surface area.

4.4.3 Measurement of Common Carotid Artery Stiffness and Intima-Media Thickness

The common carotid artery's stiffness with distensibility and intima-media thickness (IMT) was assessed with The Art. Lab sonography system (Esaote Europe B.V., Netherlands). This advanced radiofrequency technology and ultrasound imaging with echo-tracking capabilities to noninvasively and precisely measure these parameters.

The patient is positioned supine to ensure relaxation and stability of the neck area, facilitating precise imaging of the common carotid artery. Using a 7.5 MHz linear transducer, the common carotid artery, including its bifurcation into the internal and external carotid arteries, is initially scanned in a transverse section. This step is crucial for identifying any atherosclerotic plaques that may influence the measurement of stiffness and IMT. The artery is then imaged in a longitudinal section, focusing on a segment as close as possible to the bifurcation but ensuring the segment is adequately straight and free of plaques for accurate measurement. Upon obtaining a stable and precise longitudinal image, the operator manually selects the measurement location on the arterial wall farthest from the transducer over a segment no shorter than 15 mm. The system then automatically calculates the IMT and arterial stiffness using the Quality Carotid Stiffness (QCS) abnormality threshold.

4.4.4 Measurement of Cardio-Ankle Vascular Index and Ankle-Brachial Index

The Cardio-Ankle Vascular Index (CAVI) and the Ankle-Brachial Index (ABI) measurements were performed using the Fukuda Vascular Screening System VS-1000 (Fukuda Denshi Co., Japan).

CAVI is calculated based on the velocity of the pulse wave generated by cardiac contractions as it travels down the arterial tree with the formula $CAVI = a\{(2\rho/\Delta P) \ln (sBP/dBP)PWV^2\} + b$; where:

ΔP: The difference between systolic (sBP) and diastolic (dBP) blood pressures.

ρ: Blood viscosity, which affects the resistance to blood flow.

PWV^2: The squared pulse wave velocity, indicating the speed of the pulse wave and, indirectly, arterial stiffness.

a and b: constants.

This equation is derived from the Bramwell-Hill equation and the stiffness coefficient β.

Ankle-Brachial Index (ABI) was calculated by dividing the blood pressure readings at the ankles by those at the arms. Lower values of ABI indicate reduced blood flow to the legs, suggesting the presence of arterial blockages or atherosclerosis.

Measurements for CAVI and ABI involved placing blood pressure cuffs with plethysmographic sensors on all four limbs to capture blood pressure readings and arterial waveforms. The patient had to rest in a supine position for at least 10 minutes before measurements to ensure the stability of the cardiovascular system. The calculated indices were derived from the arterial waveforms captured at the arms and ankles using an electrocardiogram and phonocardiogram.

4.4.5 Assessment of Arterial Stiffness and Central Arterial Blood Pressure

Applanation tonometry, particularly with the Sphygmocor system equipped with a high-precision piezoelectric crystal micromanometer (Millar®, Millar Instruments, USA), was used to assess arterial stiffness and central arterial blood pressure. The pulse of the radial, carotid, and femoral arteries is identified at sites where these arteries are superficial - in the wrist, neck, and groin areas. An applanation tonometry piezo crystal sensor is sequentially placed over these sites to capture the pulse waveforms. Distances on the body surface are measured between sensor placement sites. Patient demographics and measured distances are input into specialized analysis

software. To ensure accuracy, the pulse wave curves from both proximal (common carotid artery) and distal (femoral arteries) sites are recorded typically over 20 seconds for each site. The recorded data are used to calculate arterial stiffness indices such as carotid-femoral PWV, augmentation index, central arterial blood pressure, and central pulse pressure.

4.4.6 24-hour Ambulatory Blood Pressure Monitoring

24-hour ambulatory blood pressure (ABP) monitoring employed the "WatchBP O3 Ambulatory 2G" device by Microlife, Switzerland, which utilizes oscillometric tonography to measure systolic and diastolic blood pressures, heart rate (HR) and central arterial blood pressure. This device, comprising a technical and software-equipped box connected to a cuff, accurately measures systolic ABP between 60 to 299 mmHg and diastolic ABP from 30 to 200 mmHg, with a precision error margin of 1 mmHg. HR measurements range from 30 to 239 bpm.

For accurate measurements, the cuff was fitted to the patient's right arm at heart level, with cuff size selected based on the patient's arm circumference. An initial control ABP measurement was compared to an office-based oscillometric manometer reading. If discrepancies of 5 mmHg or more in systolic or diastolic ABP were observed, the cuff was adjusted and remeasured. Once correctly positioned, the box of the device was secured at the waist, and the patient proceeded with their daily routine, maintaining a diary of any significant events or changes in condition. They were instructed to pause and keep their arm still during cuff inflation.

The device was removed after 24 hours, and the gathered data was analyzed via the "WatchBP Analyzer+" software. It calculated the average daily, daytime (from 6 AM to 10 PM), and nighttime (from 10 PM to 6 AM) ABP and HR. It also determined the minimum and maximum ABP and HR, the day-to-night ABP ratio, ABP variability, and systolic and diastolic dip.

Arterial hypertension was defined as an ambulatory overall systolic blood pressure (SBP) of ≥130 mmHg or diastolic blood pressure (DBP) of ≥80 mmHg on the right arm or the patient was on antihypertensive medication.

4.4.7 Computer tomography scan

A CT scan was conducted using a 64-slice multidetector computer tomography (MDCT) (GE LightSpeed VCT, Milwaukee, Wisconsin, USA). The patient was positioned in a prone posture on the CT scanner table with arms above the head to optimize image acquisition. Intravenous contrast

(Ultravist 370 mg I/mL) was administered via the cubital vein. The contrast volume was adjusted according to the patient's body size, typically ranging from 50 to 100 mL for adults. ECG-gated CT imaging was employed to reduce motion artifacts, and thin slices (0.5–1 mm) were used to ensure high-resolution imaging. The imaging field of view extended from the aortic arch to the aorta at the diaphragm level to comprehensively evaluate the aorta and its branches.

CT scans were evaluated utilizing the OsiriX MD platform (version 13.0, Pixmeo SARL, Bernex, Switzerland). Aortic measurements were obtained from three-dimensional (3D) reconstructions using oblique angulations orthogonal to the vessel's longitudinal axis. The aortic perimeter was subsequently used to calculate the mean diameter based on the formula: mean diameter = perimeter ÷ π where π is approximately 3.14 (Figure 3.A-C). Aortic dimensions were measured at specific anatomical landmarks: the midpoint of the ascending aorta (mid-AAo, corresponding to the right pulmonary artery), the midpoint of the aortic arch (mid-Arch, located between the common carotid artery and the left subclavian artery or at the apex of the aortic arch), the isthmus, the midpoint of the descending aorta (mid-DAo, in line with the right pulmonary artery), and the aorta at the level of the diaphragm (diaph-Ao). A triangle was drawn between the apex of the arch and the midpoints of the ascending and descending aorta. The arch angle was defined as the vertex angle of the resultant triangle, and the arch width was the basal length of this triangle. The perpendicular distance from the basal length to the apex of the arch determined the arch height. The extent of residual stenosis was computed as the diameter ratio at the isthmus to the diameter of the diaphragmatic aorta (Figure 3. D).

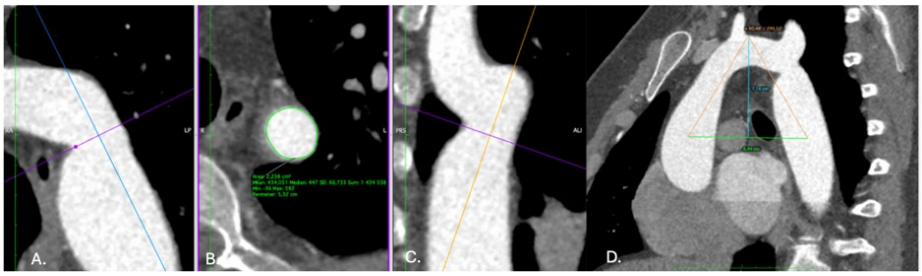

Figure 3. CT scan measurements. A and C - oblique angulations orthogonal to the vessel's longitudinal axis for mean diameter calculations (B). D – aortic arch height, width, and angulation measurements.

Qualitative evaluation of aortic arch shape categorized patients into three groups based on the aortic arch height-to-width (H/W) ratio: Crenel-type arch morphology included individuals with a H/W ratio of less than 0.65, Romanesque arch morphology comprised those with a ratio between 0.65 and 0.85. Gothic-type arch morphology was reserved for those exceeding a H/W ratio of 0.85. (160)

The CT scan did not extend to the renal arteries. However, no evidence in the literature suggests an association between coarctation of the aorta (CoA) and renal artery stenosis (RAS). Consequently, the anatomy of the renal arteries, including their length, width, or the number of accessory vessels, was not evaluated.

4.4.8 Percutaneous treatment

Patients with significant CoA underwent percutaneous treatment. Clinically significant CoA criteria:

- A systolic pressure gradient between the upper and lower limbs of >20mmHg or an echographically measured average systolic gradient of >20mmHg.
- A systolic pressure gradient between the upper and lower limbs of >10mmHg or an echographically measured average systolic gradient of >10mmHg in patients with reduced left ventricular systolic function.
- A systolic pressure gradient between the upper and lower limbs of >10mmHg or an echographically measured average systolic gradient of >10mmHg in patients with significant collateral circulation.
- The aortic diameter ratio between the CoA and the aorta at the diaphragm is <0.5 on the CT scan.

Percutaneous stenting procedures were carried out by a single operator (SC) with patients placed under general anesthesia. In all cases, femoral access was utilized. Angiography of the CoA was performed in both lateral and left anterior-oblique positions to confirm and pinpoint the location of the coarctation lesion. This was achieved using a marked pigtail catheter proximal to the lesion. Throughout this procedure, several metrics were documented, encompassing the diameters of the ascending aorta, aortic arch, coarctation site, and descending aorta, in addition to the length of the implicated segment and the extent of stenosis. The pressure gradient across the lesion was measured using a pigtail catheter pullback technique.

For patients with low blood pressure (sABP below 140 mmHg), intravenous norepinephrine infusion was administered for a minimum of 15 minutes to elevate systolic pressure to a level exceeding 140 mmHg. Only

patients with an invasively measured peak gradient across the lesion exceeding 20 mmHg and/or exhibiting a ≥50% diameter difference between the isthmus and the descending aorta at the diaphragm level underwent percutaneous stent placement. The stents were long enough (longest 45mm) to cover the coarctation site and the aortic isthmus. A balloon-expandable stent was employed and mounted on a balloon with a diameter matching that of the transverse aortic arch or the aortic diameter at the diaphragm level.

In this series of cases, pre-dilation of the lesion was not performed. The balloon was inflated until the desired diameter was achieved, ensuring good visual apposition of the stent, with a maximum pressure of 14 atmospheres. Additional dilatation during the procedure was only considered if a significant residual constriction of the stent, associated with a peak systolic gradient exceeding 10 mm, remained after the initial stent deployment. After dilatation and stent placement, a completion angiogram was performed by injecting contrast through a pigtail catheter positioned in the aortic arch. This was done to assess the outcome of the dilatation, confirm stent placement, and detect any potential complications. Subsequently, a new pressure gradient across the lesion was measured to evaluate the procedure's effectiveness. All patients after stent implantation were prescribed aspirin 0.1g OD.

4.4.9 Renal scintigraphy

All patients in the study underwent ACE inhibitor renography. (228) Only patients receiving percutaneous treatment for CoA during the study performed repeated ACE inhibitor renography scans 3-6 months later. This procedure involved the use of a radiopharmaceutical 99mTc-MAG3, which was administered via a venous line.

A one-day protocol was employed, which included the following steps:

1. A baseline fixed dose of 90 MBq 99mTc-MAG3 was given.
2. Following the baseline acquisition, an ACE inhibitor (captopril) at 50 mg was administered orally 3 hours later.
3. A second acquisition was performed 30 minutes after oral administration of the ACE inhibitor, using approximately 225 MBq of 99mTc-MAG3.

To ensure optimal results, all patients were instructed to arrive well-hydrated and were advised to drink 0.5 liter of water just before coming for the procedure. Additionally, patients were asked to empty their bladder immediately before the study. All patients were instructed to discontinue their

antihypertensive medications (ACE inhibitor and diuretics) three days before the scan.

The dynamic renograms were acquired with patients lying supine using a dual-headed Infinia Hawkeye gamma camera (GE Healthcare, USA) equipped with low-energy, high-resolution parallel hole collimators and a matrix size of 128x128 pixels. The imaging field covered both the kidneys and the bladder regions. The dynamic acquisition involved capturing images at 2 seconds per frame for the first minute and 60 seconds per frame for the following 29 minutes.

In the renal scintigraphy analysis, time-activity curves were produced by positioning a Region of Interest (ROI) over each kidney, around the background area of each kidney, and delineating the aorta (Figure 4). The assessment of renal perfusion involved quantitative analysis of the initial bolus of a radiopharmaceutical as it passed through the abdominal aorta and entered the renal arteries.

Renal function was assessed by analyzing the time-activity curve data and measuring the relative uptake of the radiopharmaceutical. Measurements for each kidney for uptake and perfusion (including uptake, T_{max}, $T_{max}/T½$ ratio, 30min/T_{max} ratio, and 20min/3min ratio) were calculated prior to and after administering the ACE inhibitor.

Specific interpretive criteria for reduced renal perfusion by Tc-99m MAG_3 scintigrams are as follows (9):

- Unilateral parenchymal retention after ACE inhibition for Tc- 99m MAG_3 scintigraphy represents a high probability (>90%) of RVH.
- Parenchymal retention is demonstrated as a change in the 30-minute/T_{max} uptake ratio of 0.15 or greater, a significantly prolonged transit time, or a change in the scintigraphic grade.
- Parenchymal retention is also determined as T_{max} prolongation of at least 2 minutes or 40% after administration of ACE inhibitors.
- A greater than 10% change in the relative Tc- 99m MAG3 uptake after ACE inhibition represents a high probability of RVH.

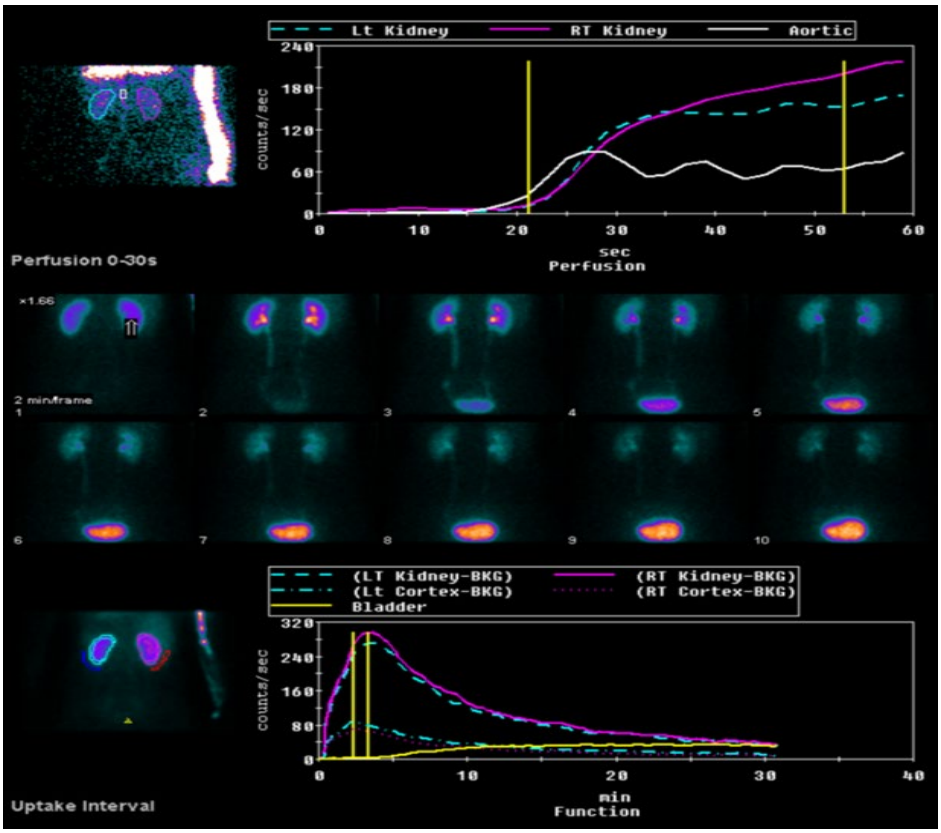

Figure 4. Renal scintigraphy scan with radioisotope Tc- 99m MAG_3 perfusion curves.

5. RESULTS

5.1 Results of the Groups Regarding Arterial Hypertension

The median age of the patients in this study was 28.7 years (interquartile range: 22.9–37.6 years). A slightly higher proportion of males comprised 55.2% (48 out of 87) of the study population. Seven patients had native CoA, while the remaining patients had undergone surgical (primarily end-to-end anastomosis, 69 patients or 86.3%) or percutaneous treatment (4 patients or 5.1%). The median age at the time of the first operation was 6.37 years (interquartile range: 1.2–11.79 years), and the median time since the last surgery was 8.7 years (interquartile range: 4.16–15.88 years).

The cohort of 87 patients with coarctation of the aorta (CoA) was divided into two groups: the Control group (n = 30) and the Mixed group (n = 57), as described in the methodology section. Within the Mixed group, a subgroup identified as the Hypertensive group (n = 46) comprised patients who remained hypertensive, either with or without antihypertensive treatment. Table 2 presents the clinical characteristics used to categorize the patients into groups.

Table 2. Clinical characteristics to categorize patients into groups.

	Control group, N=30 Median (Q1; Q3)	**Mixed group, N=57 Median (Q1; Q3)**	**Hypertensive group, N=46 Median (Q1; Q3)**	**P-value**
Office SBP, mmHg	**128 (120; 128)*,****	**144 (140; 150)***	**144 (139; 153)****	***,****<0.001**
Office DBP, mmHg	**79 (71; 79)***	**82 (76; 90)***	81 (76; 88)	***0.028**
Ambulatory Overall SBP, mmHg	**116 (110; 118)*,****	**126 (119; 134)***	**130 (120; 134) ****	***,****<0.001**
Ambulatory Overall DBP, mmHg	71 (67; 74)	73.5 (68; 76)	73 (67; 76)	0.496
Office SBP difference RA-LL, mmHg	**-13 (-22; -4)*,****	**2 (-25; 20)***	**5 (-21; 20.5) ****	***,****0.004**
Residual stenosis on CTA, %	**14 (1; 20.2)*,****	**20.5 (9.3; 30.1)***	**20.7 (8.5; 30.4) ****	***,****0.018**
Antihypertensive treatment, N (%)	**0*,****	**45 (79.9%)***	**45 (97.8%) ****	**<0.001**

SBP – systolic blood pressure; DBP – diastolic blood pressure; RA – right arm; LL – lower limb; CTA – computer tomography angiogram. * - statistical significance between Control and Mixed groups; ** - statistical significance between Control and Hypertensive groups

Office and ambulatory blood pressure measurements and clinical characteristics highlight statistically significant differences among the three groups. The Hypertensive group shows the highest median systolic and diastolic blood pressure values with substantial differences from the Control group. Additionally, there are notable differences in residual stenosis percentages, aligning with the clinical profiles of each group.

A significant disparity in gender distribution was observed between the groups, with the highest proportion of males (80.6%) in the Hypertensive group. There were no significant differences between the groups concerning the median current age of the patients or their age at the time of the first surgery. The body mass index (BMI) was within normal ranges across all groups, with no significant differences. Notably, all seven patients with native CoA were in the Mixed group, of whom 6 had inadequate antihypertensive (AH) treatment. Most patients in all groups had undergone surgical end-to-end anastomosis, with no statistically significant difference (Table 3.).

Table 3. Baseline clinical characteristics.

	Control group, N=30 Median (Q1;Q3)	**Mixed group, N=57 Median (Q1;Q3)**	**Hypertensive group, N=46 Median (Q1;Q3)**	**P-value**
Male, n (%)	**9 (30%)*·****	**39 (68.4%)***	**29 (80.6%)****	***·****<0.001**
Age, years	28.8 (23.5; 35.1)	28.7 (22.9; 37.6)	28.4 (22.8; 36.8)	0.872
Age at first operation, years	5.77 (0.76; 12.75)	6.56 (1.7; 10.68)	5.81 (1.63; 12.14)	0.995
Time from last surgery, years	8.92 (4.16; 14.95)	8.7 (4.98; 16.13)	8.93 (3.66; 17.19)	0.483
Native CoA, n (%)	**0*·****	**7 (12.3%)***	**6 (13%)****	***·****0.065**
BMI	23.9 (21.1; 26)	24.2 (21.9; 27.5)	24.4 (22.3; 27.5)	0.195
Operation type				
End to end anastomosis, n (%)	27 (90%)	42 (84%)	33 (82.5%)	0.463
Goretex	1 (3.3%)	-	-	
Homotransplant	-	2 (4%)	1 (2.5%)	
Pericardial patch	2 (6.7%)	1 (2%)	1 (2.5%)	
Subclavian patch	-	1 (2%)	1 (2.5%)	
Stent	-	4 (8%)	4 (10%)	

BSI – body mass index. * - statistical significance between Control and Mixed groups; ** - statistical significance between Control and Hypertensive groups

The CT angiogram findings revealed a significantly greater median aortic arch width in the Hypertensive group, accompanied by a larger arch angle and a smaller height-to-width (H/W) ratio (Table 4). This reduced H/W ratio, primarily due to the increased width, suggests a less favorable geometric configuration in hypertensive patients. Precisely, this pattern aligns more with

a "Crenel" type morphology, characteristic of the Hypertensive group, than the "Gothic" morphology observed in the Control group. Despite these differences in aortic dimensions, the aortic arch height did not exhibit any statistically significant variation between the groups. This suggests that while width and angular changes are prominent in hypertensive patients, the overall vertical height of the arch remains comparable across both groups.

Table 4. CT angiography measurements.

	Control group, N=30 Median (Q1;Q3)	**Mixed group, N=57 Median (Q1;Q3)**	**Hypertensive group, N=46 Median (Q1;Q3)**	**P-value**
Ao arch hight, mm	46.5 (41; 53.4)	45.7 (40.6; 52.3)	46.5 (41.1; 52.4)	0.920
Ao arch width, mm	**59.4 (56.4; 61.6) *·*** **	**63.1 (58.9; 73.9)***	**62.9 (58.9; 75.5)****	***·****0.011**
Ao arch H/W ratio	**0.8 (0.7; 0.9)***	**0.7 (0.6; 0.8)***	**0.7 (0.6; 0.8) ****	***·****0.048**
Ao arch angle, degree	**66 (56.5; 71.1)***	**69 (64.7; 76.4)***	68.8 (64.2; 76)	***0.014**
Residual stenosis, %	**14 (1; 20.2)*·****	**20.5 (9.3; 30.1)***	**20.7 (8.5; 30.4)****	***·****0.018**

Ao arch H/W ratio – aortic arch height and width ratio. * - statistical significance between Control and Mixed groups; ** - statistical significance between Control and Hypertensive groups.

The median systolic and diastolic office blood pressure showed statistically significant median differences between the groups in both the right and left arms, with no significant differences observed in the lower limbs. However, this reflects a higher median systolic pressure gradient between the right arm and the lower limb (Table 5). Notably, there was a significant median gradient difference between the right and left arms, with the highest values observed in the Hypertensive group. The median ambulatory 24-hour systolic blood pressure was significantly higher in the Hypertensive group, while the diastolic blood pressure did not show a statistically significant difference. The groups also had no significant differences in systolic and diastolic dipping.

Table 5. Blood pressure measurements.

	Control group, N=30 Median (Q1;Q3)	**Mixed group, N=57 Median (Q1;Q3)**	**Hypertensive group, N=46 Median (Q1;Q3)**	**P-value**
Office blood pressure measurements				
Systolic BP RA, mmHg	**128 (120; 128)*,****	**144 (140; 150)***	**144 (139; 153)****	***,****<0.001**
Diastolic BP RA, mmHg	**79 (71; 79)***	**82 (76; 90)***	81 (76; 88)	***0.028**
Systolic BP LA, mmHg	**119 (115; 128) *,****	**138.5 (121; 145)***	**137 (121; 145)****	***,****<0.001**
Diastolic BP LA, mmHg	**78 (73; 84) *,****	**84.5 (77; 91)***	**84 (77; 90)****	***,****0.010**
Systolic BP LL, mmHg	143 (127; 148)	150 (125; 162)	142.5 (124; 160)	0.126
Diastolic BP LL, mmHg	74 (65; 84)	79 (70; 87)	79 (69.5; 86)	0.115
Systolic BP difference RA-LA, mmHg	**3 (-3; 11)****	9 (0; 19)	**10 (0; 20)****	****0.034**
Systolic BP difference RA-LL, mmHg	**-13 (-22; -4) *,****	**2 (-25; 20)***	**5 (-21; 20.5)****	***,****0.004**
Systolic BP difference LA-LL, mmHg	-15.5 (-30; -4)	-7 (-24; 5)	-6 (-24; 5)	0.112
24-hour blood pressure measurements				
Overall systolic BP, mmHg	**116 (110; 118) *,****	**126 (119; 134)***	**130 (120; 134)****	***,****<0.001**
Overall diastolic BP, mmHg	71 (67; 74)	73.5 (68; 76)	73 (67; 76)	0.496
Systolic Dip, %	9.5 (5.3; 13.9)	10.8 (7.3; 15.3)	14.1 (6.8; 16)	0.272
Diastolic Dip, %	12.1 (8.7; 19.1)	17 (10.2; 19.7)	15.6 (10.2; 20.0)	0.387

BP- blood pressure; LA – left arm; LL – lower limb; RA – right arm. * - statistical significance between Control and Mixed groups; ** - statistical significance between Control and Hypertensive groups.

Based on transthoracic echocardiography, left ventricular mass did not show significant differences between the groups. However, a notable difference was observed in diastolic function, as the E/e' ratio was significantly higher in the Hypertensive group. In terms of aortic valve morphology, a tricuspid aortic valve was more prevalent in the Control group (53.3%), whereas the incidence was lower in the Mixed (31.6%) and Hypertensive (30.4%) groups. Across all groups, there was a predominance of left coronary cusp and right coronary cusp fusion. A notably higher noninvasive gradient at the level of CoA was measured for the Hypertensive group (Table 6).

Table 6. Instrumental studies' results.

	Control group, N=30 Median (Q1;Q3)	**Mixed group, N=57 Median (Q1;Q3)**	**Hypertensive group, N=46 Median (Q1;Q3)**	**P-value**
Echocardiogram				
LV mass index, g/m2	85.5 (75.25; 93.45)	84.9 (74.25; 104.5)	89.9 (77.73; 102.75)	0.703
LV EF, %	55 (55; 60)	55 (55; 60)	57.5 (55; 60)	0.314
E/e'mean	**7.2 (6.4; 8.1)*·****	**7.7 (6.3; 9.3)***	**7.9 (6.5; 9.5)****	***·****0.037**
Tricuspid Ao valve	16 (53.3%)	18 (31.6%)	14 (30.4%)	0.183
Bicuspid Ao valve				0.873
LCC+RCC fusion	14 (46.7%)	32 (56.1%)	26 (56.5%)	
NCC+RCC fusion	-	3 (5.3%)	2 (4.3%)	
NCC+LCC fusion	-	2 (3.5%)	2 (4.3%)	
Mechanic prosthesis	-	2 (3.5%)	2 (4.3%)	
Gradient CoA, mmHg	**16 (12; 19)*·****	**22 (16.5; 33)***	**22 (17; 33)****	***·****0.014**
Laboratory tests				
Creatinin	**57.2 (51; 68)*·****	**76 (69.4; 85)***	**75.5 (67.7; 83)****	***·****0.004**
Urea	3.6 (2.9; 4.1)	4.8 (3.8; 5.8)	4.8 (3.8; 5.8)	0.102
Potasium	4.4 (4.2; 4.5)	4.3 (4.1; 4.6)	4.3 (4.1; 4.6)	0.826
Uric acid	**244.4 (228.8; 245)*·****	**362.8 (276; 403)***	**360 (276; 403)****	***·****0.046**
TSH	1.5 (1.1; 2.6)	1.7 (0.9; 2.2)	1.4 (0.9; 2.0)	0.382
Cholesterol	4.8 (4.4; 5.4)	4.5 (4; 5.4)	4.6 (4; 5.5)	0.872
LDL cholesterol	2.7 (2.4; 3.4)	2.9 (2.1; 3.3)	2.9 (2.1; 3.5)	0.587
HDL cholesterol	1.7 (1.4; 1.7)	1.5 (1.2; 2.1)	1.4 (1.2; 2.1)	0.291
TG	0.8 (0.7; 1.1)	1 (0.8; 1.5)	1 (0.8; 1.5)	0.057
Stiffness				
PWV	6.1 (5.7; 7)	6.2 (5.7; 7)	6.3 (5.6; 7.2)	0.595
Right CAVI	5.9 (5.3; 6.4)	5.6 (5.1; 6.2)	5.7 (5.0; 6.2)	0.154
Left CAVI	5.9 (5.4; 6.3)	5.7 (5; 6.2)	5.6 (5.0; 6.2)	0.101
Augmentation index	3 (0; 6)	3 (1; 7)	3 (-1; 8.5)	0.178
RCCA IM thickness	**586.5 (543; 671)*·****	**645 (586; 732)***	**664 (601; 735)****	***·****0.005**
LCCA IM thickness	637.5 (530; 747)	618.5 (550; 710)	639 (570; 739)	0.755
RCCA distensibility	**625.5 (494; 793)*·****	**725.5 (544; 854)***	**759 (616; 854)****	***·****0.047**
LCCA distensibility	614.5 (495; 832.5)	742 (556; 865)	756 (573; 946.5)	0.100
RCCA stiffness	2.7 (2.3; 3.4)	2.8 (2.2; 3.6)	2.8 (2.2; 3.3)	0.873
LCCA stiffness	2.5 (2.1; 3.1)	2.5 (2.2; 3.3)	2.5 (2.1; 3)	0.967

Ao – aorta; CoA – coarctation of the aorta; CT scan – computed tomography scan; CoA/diaph-Ao - coarctation of the aorta ratio with aorta at the diaphragmatic level; CoA/mid-Arch – coarctation of the aorta ratio with aortic arch diameter; BP- blood pressure; CAVI – Cardio-Ankle Vascular Index; HDL – high dencity lipoprotein; LA – left arm; LCC – left coronary cusp; LCCA – left common carotid artery; LDL – low density lipoprotein; LL – lower limb; LV – left ventricle; LV EF – left ventricle ejection fraction; NCC – noncoronary cusp; PWV - pulse wave velocity; RA – right arm; RCC – right coronary cusp; RCCA – right common carotid artery; TG – triglycerides; TSH – thyroid stimulating hormone.

While pulse wave velocity and the cardio-ankle vascular index did not differ significantly, the Hypertensive group demonstrated a thicker intima-media layer in the right common carotid (RCCA) but not in the left. This thickening in the RCCA was associated with a statistically significant increase in the distensibility. Despite this localized change in arterial distensibility, arterial stiffness remained comparable between groups on both sides of the carotid arteries.

Antihypertensive treatment in the Mixed group is shown in Figure 5.

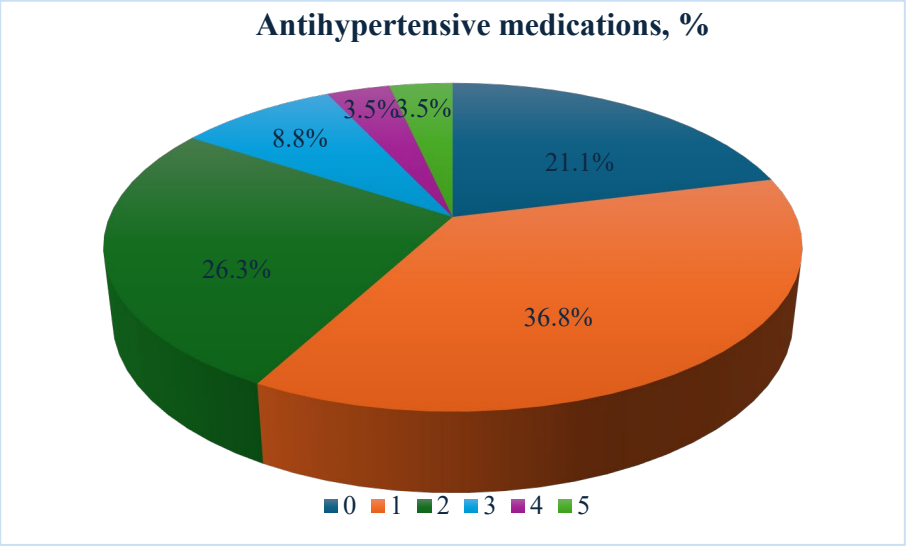

Figure 5. Antihypertensive treatment in the Mixed group.

In the Mixed group, most patients (57.9%) required either no antihypertensive treatment or were managed with only one medication. However, 42.1% of the patients (34 out of 57) were on more than two antihypertensive medications. Most patients were treated with beta-blockers or ACEI, or calcium channel blockers (CCB). A greater proportion of patients in the Hypertensive subgroup were on these medications, with a statistically significant difference observed between the groups (Figure 6).

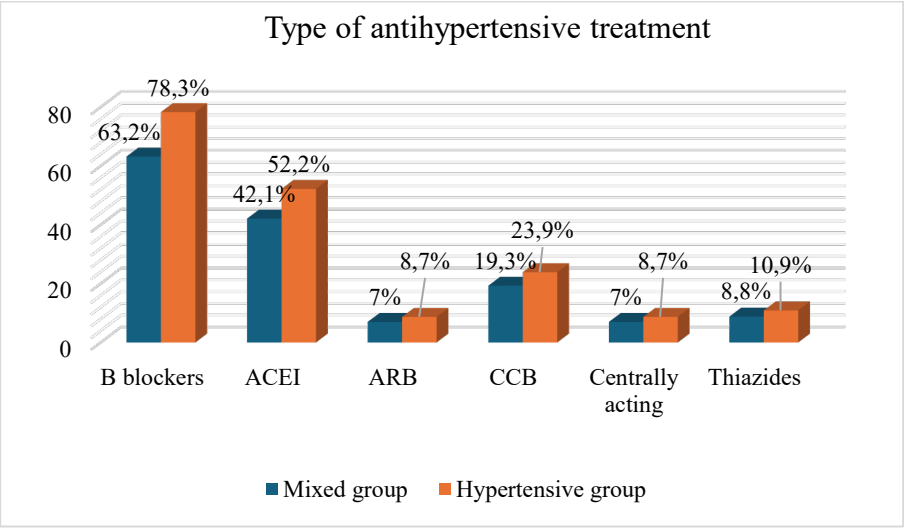

Figure 6. Antihypertensive medication distribution in Mixed and Hypertensive groups. ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; BB – beta-blockers; CCB – calcium channel blocker

Renal scintigraphy measurements before ACEI did not reveal significant differences in renal uptake percentages or times to maximum counts (T_{max}) between the groups for both kidneys (Table 7).

Table 7. Renal perfusion measurements.

	Control group, N=30 Median (Q1;Q3)	Mixed group, N=57 Median (Q1;Q3)	Hypertensive group, N=46 Median (Q1;Q3)	P-value
Uptake, %				
Left kidney	53.7 (50.1; 55.6)	53 (49; 57.9)	51.6 (48.4; 58)	0.597
Right kidney	46.3 (44.4; 49.9)	47 (42.1; 51.1)	48.4 (42; 51.8)	0.679
T_{max}, min				
Left kidney	2.9 (2.3; 3.2)	3 (2.7; 3.7)	3 (2.8; 3.6)	0.264
Right kidney	3.3 (2.7; 3.9)	3.4 (2.9; 4)	3.4 (3; 3.9)	0.514
T_{max}/T½ ratio				
Left kidney	4.8 (4; 6.3)	5.6 (4.5; 7)	5.5 (4.8; 6.8)	0.070
Right kidney	6.3 (4.3; 8)	7.1 (5.5; 10)	7 (5.5; 9.3)	0.118
30min/T_{max} ratio				
Left kidney	**0.1 (0.1; 0.1)*,****	**0.1 (0.1; 0.2)***	**0.1 (0.1; 0.2)****	***,****0.032**
Right kidney	**0.1 (01; 0.2)*,****	**0.2 (0.1; 0.2)***	**0.2 (0.1; 0.2)****	***,****0.035**
20min/3min ratio				
Left kidney	**0.1 (0.1; 0.2)*,****	**0.2 (0.1; 0.2)***	**0.2 (0.1; 0.2)****	***,****0.035**
Right kidney	**0.2 (0.1; 0.2)*,****	**0.2 (0.1; 0.3)***	**0.2 (0.1; 0.3)****	***,****0.043**
Uptake after ACEI, %				
Left kidney	53.8 (50.8; 60.4)	52.1 (49.8; 56.2)	51.7 (49.6; 56.9)	0.190
Right kidney	46.2 (39.6; 49.2)	47.6 (43.8; 50.3)	47.9 (43.1; 50.4)	0.225
T_{max} after ACEI, min				
Left kidney	**2.8 (2.7; 3.6)*,****	**3.2 (2.7; 3.9)***	**3.1 (2.7; 3.9)****	***,****0.042**
Right kidney	**3 (2.7; 3.7)*,****	**3.6 (3.2; 5.2)***	**3.6 (3.3; 5.2)****	***,****0.017**
T_{max}/ T½ after ACEI				
Left kidney	4.8 (4.3; 6.3)	5 (4; 7)	5.3 (4; 7)	0.483
Right kidney	5.8 (4.8; 7.8)	6 (5.3; 7.8)	6.3 (5.3; 9.3)	0.265
30min/T_{max} ratio after ACEI				
Left kidney	0.1 (0.1; 0.2)	0.2 (0.1; 0.2)	0.1 (0.1; 0.2)	0.068
Right kidney	0.2 (0.1; 0.2)	0.2 (0.1; 0.3)	0.2 (0.1; 0.3)	0.111
20min/3min ratio after ACEI				
Left kidney	**0.1 (0.1; 0.2)*,****	**0.2 (0.1; 0.2)***	**0.2 (0.1; 0.2)****	***,****0.029**
Right kidney	**0.2 (0.1; 0.2)***	**0.2 (0.2; 0.3)***	0.2 (0.2; 0.4)	***0.033**

T_{max} - time to maximum counts, T½ - time to half-peak counts, 30 min/T_{max} - ratio of renal counts at 30 minutes to maximum counts, 20 min/3 min - ratio of counts at 20 minutes to 3-minute counts. * - statistical significance between Control and Mixed groups; ** - statistical significance between Control and Hypertensive groups

The analysis of kidney function across the groups reveals renal performance, particularly concerning their response to ACEI administration. While the median uptake for both kidneys was relatively similar across all groups, suggesting preserved renal absorption and processing capabilities, more nuanced findings emerged in assessing renal function parameters.

The Mixed and Hypertensive groups exhibited slightly longer T_{max} values than the Control group, though these differences did not reach statistical significance. This mild delay in reaching peak renal activity may indicate a subtle reduction in kidney responsiveness, particularly in individuals with hypertension. However, the lack of statistical significance suggests that these measurable differences may have little clinical relevance.

More pronounced differences were noted in the 30min/T_{max} and 20min/3min ratios, with significantly higher values observed in the Medical and Hypertensive groups. These elevated ratios suggest impaired renal clearance in these groups, reflecting early signs of reduced kidney function. Specifically, the prolonged clearance times after ACEI administration indicate that the kidneys in the Mixed and Hypertensive groups are slower in processing and excreting substances, which may point to early-stage renal dysfunction.

Significant differences in T_{max} were particularly evident in the right kidney, where the Mixed and Hypertensive groups showed longer T_{max} values than the Control group. This suggests that ACEI administration slows down the time to peak kidney function in these groups, reflecting slower perfusion. In contrast, significant differences in the 30min/T_{max} and 20min/3min ratios were observed for the left kidney, indicating impaired clearance after ACEI administration in the Mixed and Hypertensive groups.

As assessed by comparing pre-ACEI and post-ACEI measurements, changes in renal function metrics did not reach statistical significance in either group (Table 8). This suggests that renal function remains relatively stable for the measured parameters unaffected by the hypertensive status or medical interventions.

Table 8. Renal perfusion change pre-ACEI and post-ACEI.

	Control group, N=30 Median (Q1;Q3)	**Mixed group, N=57 Median (Q1;Q3)**	**Hypertensive group, N=36 Median (Q1;Q3)**	**P-value**
Δ Uptake change %				
Left kidney	2.5 (-0.9; 9.2)	0.7 (-3.2; 3.7)	0.9 (-3.3; 4.3)	0.121
Right kidney	-2.3 (-10.1; 1.1)	-0.8 (-3.9; 4.5)	-1.2 (-5.5; 3.6)	0.072
Δ T_{max} %				
Left kidney	1.3 (-12.8; 31.6)	2.4 (-10.8; 35.5)	2.5 (-10.4; 35.5)	0.195
Right kidney	4.7 (-25.9; 25.7)	9.5 (-2.2; 48.6)	8.9 (-1.8; 57.9)	0.203
Δ T_{max}/T½ ratio %				
Left kidney	0 (-22.7; 28.6)	-4 (-27.6; 30.8)	0 (-23.8; 40)	0.419
Right kidney	2.8 (-31.6; 30)	-12.9 (-36; 29.4)	-10.7 (-22.2; 30)	0.764
Δ 30min/T_{max} ratio %				
Left kidney	0 (-16.7; 45.5)	3.6 (-11.8; 37.5)	0 (-10; 35.3)	0.594
Right kidney	9.1 (-9.5; 54.5)	7.4 (-16.7; 36.4)	7.7 (-11.8; 36.4)	0.340
Δ 20min/3min ratio %				
Left kidney	0 (-18.2; 37.5)	0 (-16.7 (38.9)	0.(-12.5; 38.9)	0.604
Right kidney	0 (-18.8; 42.9)	0 (-19; 33.3)	0 (-14.9; 23.8)	0.424

Δ - the difference between pre and post-ACEI; T_{max} = time to maximum counts, T½ = time to half-peak counts, 30 min/T_{max} = ratio of renal counts at 30 minutes to maximum counts, 20 min/3 min = ratio of counts at 20 minutes to 3-minute counts.

A logistic regression analysis was conducted with arterial hypertension as the dependent variable, evaluating various epidemiologic and clinical parameters (Table 9). The analysis identified several significant predictors for arterial hypertension.

Table 9. Univariable logistic regresion for arterial hypertension.

	Odds ratio (95% PI)	P-value
Age	1.010 (0.970-1.052)	0.628
Age at first operation	1.000 (1.000-1.000)	0.792
BMI	1.037 (0.949-1.135)	0.420
Male sex	**3.928 (1.605-9.610)**	**0.003**
Ao arch high	0.979 (0.930-1.030)	0.404
Ao arch width	**1.065 (1.011-1.121)**	**0.018**
Ao arch H/W ratio <0.65	**5.833 (1.655-20.559)**	**0.023**
Ao arch angle	**1.090 (1.031-1.154)**	**0.003**
CoA/AoD ratio	0.230 (0.029-1.844)	0.167
CoA/ T2 ratio	0.486 (0.090-2.628)	0.402
Residual stenosis on CT angiogram	1.019 (0.987-1.052)	0.255
Growth index	0.126 (0.003-5.968)	0.293
Gradient CoA (echo)	**1.050 (1.006-1.096)**	**0.025**
PWV	1.108 (0.713-1.723)	0.649
Right CAVI	0.735 (0.411-1.316)	0.301
Left CAVI	0.811 (0.455-1.444)	0.476
Creatinin	**1.073 (1.014-1.136)**	**0.014**
eGFR	0.994 (0.986-1.002)	0.155
Δ T_{max}, left kidney	1.119 (0.903-1.388)	0.304
Δ T_{max}, right kidney	1.004 (0.817-1.235)	0.967
Δ 30min/T_{max} ratio, left kidney	0.081 (<0.001-27.595)	0.398
Δ 30min/T_{max} ratio, right kidney	0.202 (0.007-6.039)	0.356
Δ 20min/3min ratio, left kidney	0.785 (0.020-31.229)	0.898
Δ 20min/3min ratio, right kidney	0.529 (0.067-4.158)	0.545

Ao – aorta; BMI – body mass index; CoA – coarctation of the aorta; AoD – aorta at the diaphragm level; T2 – aortic arch between carotic arteries; PWV - pulse wave velocity; CAVI - Cardio-Ankle Vascular Index; Δ - the difference between pre and post-ACEI; T_{max} – time to maximum count; 30 min/T_{max} – ratio of renal counts at 30 minutes to maximum counts; 20 min/3 min – ratio of counts at 20 minutes to 3-minute counts.

Male sex was associated with significantly higher odds of arterial hypertension, with male patients having approximately 3.9 times the odds compared to females (P = 0.003). For each millimeter increase in aortic arch width, the odds of developing arterial hypertension increased by 6.5%, and this association was statistically significant (P = 0.018).

A smaller aortic height-to-width (H/W) ratio, indicative of a "Crenel" arch morphology, was significantly associated with a higher risk of hypertension. The odds ratio of developing hypertension in patients with a

lower H/W ratio was a critical factor (OR 5.833), indicating a protective effect (P = 0.0023). An increase in the aortic arch angle was also associated with a higher risk of hypertension. For every degree increase in the arch angle, the odds of hypertension rose by 9% (P = 0.003).

The echocardiographically measured gradient across the CoA was positively associated with arterial hypertension, with each mmHg increase in the gradient being linked to a 5% rise in hypertension risk (P = 0.025) (Figure 5).

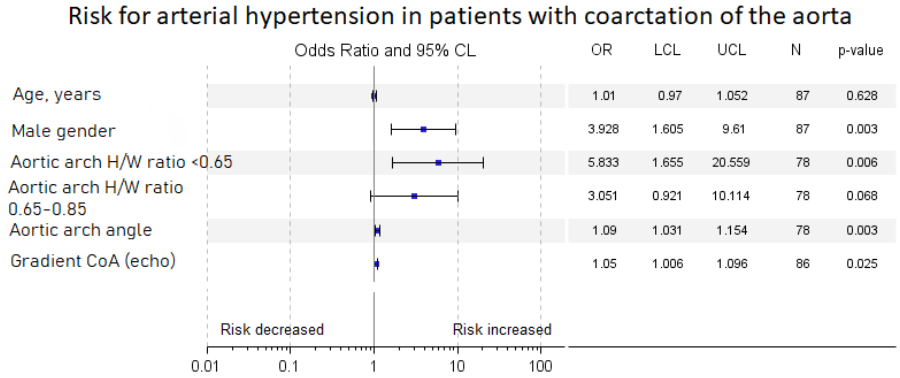

Figure 5. Univariable logistic regression for predictors of arterial hypertension.

As indicated by the large and significant odds ratio, males are at significantly higher risk of developing arterial hypertension than females. Moreover, aortic arch morphology (e.g., width, H/W ratio, and angle) also plays a crucial role in the odds of hypertension. Specifically, smaller H/W ratios and broader and more angled aortic arches significantly increase hypertension risk. In this model, factors like age, BMI, and kidney parameters (like T_{max} ratios) do not considerably affect hypertension risk.

A multivariable logistic regression model was conducted to evaluate the combined effect of various independent variables on the odds of AH (Table 10).

Table 10. Multivariable logistic regression model for arterial hypertension.

	Odds ratio (95% PI)	**P-value**
Male	3.820 (1.320-11.053)	0.013
Ao arch H/W ratio > 0.85 (Gothic arch)		n.s.s.
Ao arch angle	1.095 (1.023-1.171)	0.009
Gradient CoA (echo)	1.061 (1.009-1.115)	0.020

In this model, male sex, Ao arch angle, and CoA gradient measured by echocardiography emerged as statistically significant predictors of hypertension. Conversely, an aortic arch H/W ratio >0.85 did not significantly affect AH risk. Male patients demonstrated a nearly fourfold increased likelihood of developing hypertension compared to female patients. An increased Ao arch angle was associated with a significantly higher risk of AH, suggesting that this anatomical variation may contribute to elevated BP. Additionally, a higher CoA gradient, as measured by echocardiography, was significantly linked to an increased risk of AH, indicating that the severity of CoA plays a role in the pathogenesis of hypertension. The model demonstrates good discriminatory power with an area under the ROC curve (AUC) of 0.8016, indicating its potential utility in clinical settings for identifying individuals at higher risk of developing arterial hypertension (Figure 6).

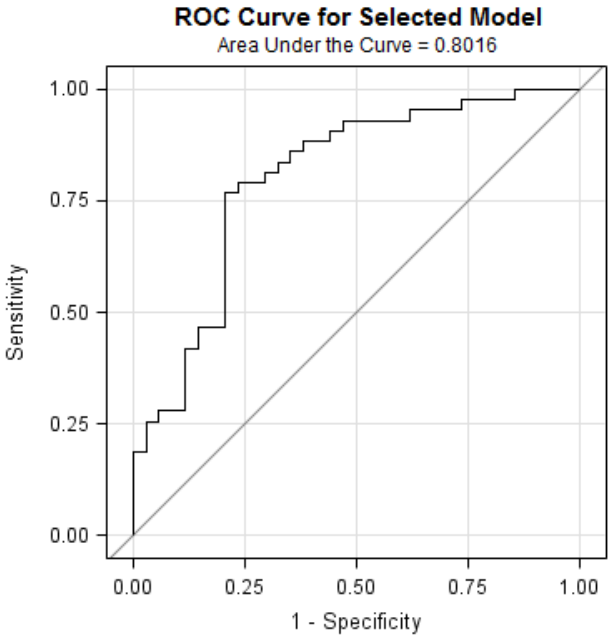

Figure 6. ROC curve for multivariable logistic regression model for arterial hypertension.

5.2 Results of the Groups Regarding Aortic Arch Morphology

This section presents the results of the second part of our study, where we analyze the morphology of the aortic arch and its correlation with renal perfusion (Table 11).

Table 11. Aortic arch morphology and renal perfusion correlation.

	Ao arch hight	Ao arch width	Ao arch H/W ratio	Ao arch angle	CoA/AoD ratio	Residual stenosis	Growth index
Before ACEI							
T_{max} LK	0.162	0.18962	0.005	-0.04251	0.004	0.06	-0.071
p-value	0.185	0.1214	0.961	0.7327	0.973	0.625	0.564
T_{max} RK	0.076	0.30867	-0.17	0.16705	0.003	0.053	-0.033
p-value	0.532	0.0099	0.1615	0.1733	0.974	0.662	0.784
T_{max}/T½ ratio LK	0.06	0.4122	-0.276	0.26581	0.051	-0.09	0.042
p-value	0.622	0.0005	0.022	0.0297	0.676	0.460	0.72
T_{max}/T½ ratio RK	0.046	0.26312	-0.187	0.1985	-0.046	0.093	-0.028
p-value	0.703	0.0289	0.12	0.1046	0.703	0.445	0.813
30min/T_{max} ratio LK	0.055	0.3453	-0.263	0.24393	-0.081	0.085	-0.169
p-value	0.654	0.0039	0.029	0.0467	0.51	0.488	0.166
30min/T_{max} ratio RK	0.005	0.18609	-0.177	0.21627	-0.071	0.084	-0.119
p-value	0.965	0.1258	0.145	0.0765	0.56	0.489	0.326
After ACEI							
T_{max} LK	-0.019	0.28883	-0.242	0.12301	0.002	0.018	0.118
p-value	0.876	0.0169	0.04	0.3213	0.985	0.883	0.334
T_{max} RK	-0.136	0.27537	-0.33	0.22101	-0.151	0.09	-0.02
p-value	0.265	0.022	0.005	0.0701	0.215	0.46	0.86
T_{max}/T½ ratio LK	0.101	0.13618	-0.109	-0.02934	-0.012	0.062	-0.08
p-value	0.412	0.2682	0.374	0.8137	0.918	0.614	0.477
T_{max}/T½ ratio RK	-0.013	0.15696	-0.208	0.09349	-0.09	0.0937	-0.03
p-value	0.915	0.1977	0.085	0.4483	0.459	0.4437	0.757
30min/T_{max} ratio LK	0.169	0.21032	-0.069	0.12545	-0.144	0.21078	-0.024
p-value	0.166	0.0852	0.575	0.3118	0.240	0.0845	0.845
30min/T_{max} ratio RK	0.034	0.16452	-0.127	0.14249	-0.256	0.296	-0.067
p-value	0.77	0.1767	0.295	0.2464	0.033	0.013	0.583

Ao – aorta; H/W ratio – aortic arch height and width ratio; LK – left kidney; RK – right kidney; T_{max} - time to maximum counts, T½ - time to half-peak counts, 30 min/T_{max} – the ratio of renal counts at 30 minutes to maximum count; block in green – statistically strong correlation; block in blue – correlation not reaching statistical significance.

The length of the Ao arch shows statistically significant positive correlations with T_{max} both before and after ACEI administration in both kidneys. Additionally, it positively correlates with the T_{max}/T½ ratio before ACEI, suggesting a potential association between aortic arch length and renal function parameters. A statistically significant negative correlation exists between the height-to-width (H/W) ratio, the T_{max}/T½ ratio, and the 30min/T_{max} ratio in the left kidney before ACEI administration but not in the right kidney. However, both kidneys showed a positive correlation with T_{max} after ACEI administration.

After this initial analysis, we methodically categorized patients into three groups based on the aortic arch height-to-width (H/W) ratio (Figure 7): Group 1 included individuals with a H/W ratio of less than 0.65, Group 2 comprised those with a ratio between 0.65 and 0.85, and Group 3 was reserved for those exceeding a H/W ratio of 0.85. Patients in Group 1 exhibit a Crenel-type arch morphology, while those in Group 3 display a Gothic-type arch morphology. Group 2 patients retain Romanesque arch morphology (Table 12).

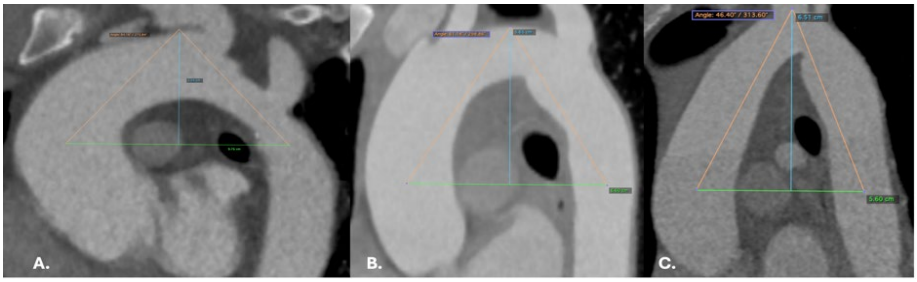

Figure 7. A. Crenel-type arch morphology (H/W ratio <0.65). B. Romanesque arch morphology (H/W ratio 0.65 – 0.85). C. Gothic-type arch morphology (H/W ratio >0.85).

Within the research cohort, the distribution of participants was as follows: Group 1 comprised 35.09% of the cohort with 28 individuals, Group 2 constituted 38.5% with 30 individuals, and Group 3 made up 25.6% with 20 individuals. Morphological variations within the aortic arch dimensions, precisely height, width, and angle when patients were stratified in Table 9. Conversely, no substantial differences were discerned in parameters such as residual stenosis and the growth index across the groups, indicating that these factors are potentially influenced by determinants other than the H/W ratio.

Table 12. Morphological variation in CT angiography.

	Group 1 (H/W <0,65) Median (Q1-Q3)	**Group 2 (H/W 0,65-0,85) Median (Q1-Q3)**	**Group 3 (H/W >0,85) Median (Q1-Q3)**	**P-value**
CT scan measurements				
Ao arch hight, mm	**39.9 (36.4; 43.25)*** **	**47.05 (42.5; 52.4)*** **	**53.6 (51.05; 57.75)*** **	***<0.001**
Ao arch width, mm	**69.7 (60.4; 84.05)*** **	**62.45 (60.4; 67.9)*** **	**56.85 (53.8; 58.9) *** **	***<0.001**
Ao arch H/W ratio	**0.58 (0.51; 0.61)*** **	**0.73 (0.7; 0.79)*** **	**0.94 (0.9; 0.98) *** **	***<0.001**
Ao arch angle, degree	**76.61 (73.14; 83.74) *** **	**67.22 (64.95; 69.5) *** **	**57.11 (54.64; 59.24) *** **	***<0.001**
Residual stenosis, %	20.76 (5.83; 26.55)	17.32 (9.33; 26.14)	15.36 (7.89; 23.85)	0.730

Ao – aorta; H/W ratio – height-to-width ratio. *** - statistical significance between all groups

Analysis of age differences at the time of study enrollment and during the initial CoA repair revealed no statistically significant differences between the groups (Table 13). Group 1 exhibited a higher proportion of male participants and a larger median body surface area (BSA). Additionally, the Crenel-type group had a significantly higher prevalence of AH compared to the other groups. The predominant surgical technique employed in all groups was end-to-end anastomosis, indicating consistency in the surgical approach among study participants. There were no significant differences in the use of antihypertensive treatments, with most patients receiving beta-blockers and ACEIs across the groups.

Table 13. Baseline clinical characteristics.

	Group 1 (H/W <0,65) n=28 Median (Q1-Q3)	**Group 2 (H/W 0,65-0,85) n=30 Median (Q1-Q3)**	**Group 3 (H/W >0,85) n=20 Median (Q1-Q3)**	**P-value**
Patients	28 (35.1%)	30 (38.5)	20 (25.6)	
Male, n (%)	19 (67.9)	17 (56.7)	7 (35)	0.067
Age, years	29.2 (23.4; 38.6)	28.6 (23.6; 36)	30.5 (22.5; 38.4)	0.951
Age at first operation, days	6.07 (0.48; 9.65)	7.69 (1.7; 14.12)	4.71 (1.77; 10.89)	0.577
Native, n (%)	2 (7.1)	3 (10)	2 (10)	0.705
Arterial hypertension	**20 (71.43%)*** **	**17 (56.6%)*** **	**5 (25%)*** **	****<0.005**
BSA	**2.01 (1.91; 2.23) *** **	**1.88 (1.75; 2.04) *** **	**1.76 (1.61; 1.89) *** **	****<0.001**
Operation type				
E-E anastomosis, n (%)	24 (92.3)	20 (74.1)	17 (94.4)	0.422
Goretex	1 (3.8)	-	-	
Homotransplant	1 (3.8)	1 (3.7)	-	
Pericardial patch	-	1 (3.7)	1 (5.6)	
Subclavian patch	-	1 (3.7)	-	
Stent	-	4 (14.8)	-	
Medications				
BB	12 (42.9)	17 (56.7)	6 (30.0)	0.177
ACEI	9 (32.1)	10 (33.3)	5 (25.0)	0.862
ARB	3 (10.7)	1 (3.3)	-	0.363
CCB	5 (17.9)	5 (16.7)	1 (5.0)	0.461
Thiazides	3 (10.7)	1 (3.3)	1 (5.0)	0.525
CAA	3 (10.7)	1 (3.3)	-	0.363
Aspirin	-	1 (3.3)	-	1.000
NOAK	2 (7.1)	1 (3.3)	-	0.619
Statins	4 (14.3)	2 (6.7)	-	0.187

BSA – body surface area; CAA- central alfa antagonist; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; BB – beta-blockers; CCB – calcium channel blocker; E-E – end-to-end anastomosis; NOAK – novel oral anticoagulant; *** - statistical significance between all groups.

During the 24-hour ambulatory blood pressure monitoring, no significant differences were observed regarding hypertension prevalence across the stratified groups (Table 14). The left ventricular mass index (LVMi) was elevated in Group 1, with an average value of 89.3 g/m². This contrasts with the LVMi values in Group 2 and Group 3, which were 86 g/m² and 80.5 g/m².

Pulse wave velocity (PWV) showed typical values with no significant variation among the groups, nor did the Cardio-Ankle Vascular Index (CAVI) measurements on either side. Similarly, the distensibility and stiffness parameters of the carotid arteries were consistent across all groups, indicating no statistically significant differences.

Table 14. Instrumental studies' results.

	Group 1 (H/W <0,65) Median (Q1-Q3)	**Group 2 (H/W 0,65-0,85) Median (Q1-Q3)**	**Group 3 (H/W >0,85) Median (Q1-Q3)**	**P-value**
Non-invasive blood pressure measurements				
Systolic BP RA, mmHg	**144 (137; 154.5) *****	**140 (134; 144) *****	**129.5 (118.5; 139.5) *****	*****<0.05**
Diastolic BP RA, mmHg	83.5 (76.5; 91)	80 (74; 86)	79 (73; 84.5)	0.125
Systolic BP LA, mmHg	140 (123; 145)	126.5 (119; 140)	126 (116; 144)	0.158
Diastolic BP LA, mmHg	83 (76.5; 90)	81.5 (72; 85.5)	80 (73; 87)	0.463
Systolic BP LL, mmHg	151 (130; 160)	145.5 (135; 160)	132 (120.5; 147.5)	0.128
Diastolic BP LL, mmHg	82 (74; 86)	73.5 (62; 82)	76 (70.5; 85)	0.202
Systolic BP difference RA-LA, mmHg	6 (0; 16.5)	11 (0; 20)	3 (-9; 9)	0.115
Systolic BP difference RA-LL, mmHg	-5 (-22; 12)	-13.5 (-24; 6)	-3.5 (-22; 12.5)	0.574
Systolic BP difference LA-LL, mmHg	-9.5 (-29; 4)	-14 (-31; -5)	-7.5 (-21; 11.5)	0.340
24 hour blood pressure measurements				
Overall systolic BP, mmHg	124 (114.5; 128.5)	119 (115; 134)	120 (111; 131)	0.938
Overall diastolic BP, mmHg	74 (68.5; 75.5)	74 (69; 78)	65.5 (63; 75)	0.144
Systolic Dip, %	10.3 (8.95; 18)	9.9 (3.7; 15)	12.45 (5.15; 16.9)	0.594
Diastolic Dip, %	18.95 (11.45; 20.6)	10.5 (7.3; 19.2)	13.65 (12.15; 19)	0.264
Echocardiogram				
LV mass index, g/m2	89.3 (83; 106)	86 (75.5; 102)	80.5 (65.85; 92.6)	0.083
LV EF, %	55 (55; 60)	55 (55; 60)	55 (55; 60)	0.719
E/e'mean	7.4 (6.54; 9.33)	7.87 (6.37; 8.83)	7.3 (5.86; 8.15)	0.601
Bicuspid Ao valve				
LCC+RCC	14 (50.0)	18 (60.0)	12 (60.0)	0.184
NCC+RCC	-	2 (6.7)	1 (5.0)	
NCC+LCC	-	-	2 (10.0)	
Mechanic prosthesis	2 (7.1)	-	-	

	Group 1 (H/W <0,65) Median (Q1-Q3)	Group 2 (H/W 0,65-0,85) Median (Q1-Q3)	Group 3 (H/W >0,85) Median (Q1-Q3)	P-value
Gradient CoA, mmHg	20 (14; 30.5)	20.5 (15; 28)	22 (12; 33)	0.927
Non-invasive blood pressure measurements				
Creatinin	**80.15 (78.08; 91.32) ***	68.7 (60; 75)	**66 (57.2; 77.13) ***	***<0.005**
Urea	5.3 (4; 6.14)	4.56 (3.8; 5.5)	3.5 (3.03; 3.95)	0.102
Potasium	4.2 (4.1; 4.72)	4.4 (4.1; 4.5)	4.4 (4.2; 4.6)	0.666
Uric acid	374 (365.64; 589)	256 (244.37; 360)	284.62 (252.4; 348.12)	0.208
TSH	1.98 (1.67; 2.23)	1.52 (1.1; 1.52)	1.11 (0.88; 2.62)	0.839
Cholesterol	4.5 (3.96; 5.25)	4.82 (4.19; 5.28)	4.55 (4.19; 6.12)	0.801
MTL	2.85 (2.07; 2.95)	3.17 (2.38; 3.68)	2.62 (2.33; 3.34)	0.725
DTL	1.49 (1.17; 1.96)	1.42 (1.27; 1.71)	1.59 (1.43; 2.14)	0.538
TG	1.02 (0.8; 1.49)	0.94 (0.81; 1.46)	1.03 (0.55; 1.16)	0.844
Stiffness				
PWV (pulse wave velocity)	6.1 (5.9; 7.2)	6.2 (5.5; 7)	6.2 (5.9; 6.9)	0.715
Right CAVI	5.65 (5; 6.2)	5.7 (5.3; 6.3)	5.6 (5.25; 6.25)	0.960
Left CAVI	5.7 (5.1; 6.2)	5.9 (5.1; 6.2)	5.5 (5.2; 6.45)	0.982
RCCA distensibility	714 (502; 843)	718 (567; 878)	658 (443; 773)	0.327
LCCA distensibility	728 (536; 865)	745 (556; 983)	618 (559; 790)	0.759
RCCA stiffness	2.96 (2.23; 3.71)	2.64 (2.33; 3.49)	2.86 (2.16; 3.46)	0.706
LCCA stiffness	2.62 (2.15; 3.61)	2.56 (2.07; 3.08)	2.47 (2.17; 2.92)	0.529

Ao – aorta; CoA – coarctation of the aorta; CT scan – computed tomography scan; CoA/diaph-Ao - coarctation of the aorta ratio with aorta at the diaphragmatic level; CoA/mid-Arch – coarctation of the aorta ratio with aortic arch diameter; BP- blood pressure; CAVI – Cardio-Ankle Vascular Index; HDL – high dencity lipoprotein; LA – left arm; LCC – left coronary cusp; LCCA – left common carotid artery; LDL – low-density lipoprotein; LL – lower limb; LV – left ventricle; LV EF – left ventricle ejection fraction; NCC – noncoronary cusp; PWV - pulse wave velocity; RA – right arm; RCC – right coronary cusp; RCCA – right common carotid artery; TG – triglycerides; TSH – thyroid stimulating hormone. * - statistical significance between Group 1 and Group 3; *** - statistical significance between all groups.

Renal perfusion assessments, as detailed in Table 15, conducted across the three groups post-captopril administration did not reveal any statistically significant disparities. Specifically, the median alteration in T_{max} for the left kidney exhibited a trend toward elongation pre-ACEI in patients with a narrow aortic arch (Gothic arch). Post-ACEI, these alterations shifted towards the Crenel-type aortic arch. This trend is reflected in the statistically significant difference in T_{max} change within the left kidney across the groups. Group 1 showed a mean T_{max} change of 0.27, Group 2 had a mean of 0.02, and Group 3 had a mean of -0.41 (p=0.044).

Table 15. Baseline measurements of renal perfusion.

	Group 1 (H/W <0,65) Median (Q1-Q3)	**Group 2 (H/W 0,65-0,85) Median (Q1-Q3)**	**Group 3 (H/W >0,85) Median (Q1-Q3)**	**P-value**
Uptake, %				
Left kidney	53.04 (47.77; 56.53)	54.13 (49.16; 57.87)	51.5 (49.72; 54.48)	0.532
Right kidney	46.96 (43.47; 52.23)	45.87 (42.13; 50.84)	48.5 (45.52; 50.28)	0.465
T_{max}, min				
Left kidney	2.91 (2.39; 3.8)	3.01 (2.75; 3.6)	3.21 (2.71; 3.98)	0.688
Right kidney	3.48 (2.79; 4.02)	3.38 (3; 3.98)	3.21 (2.78; 3.76)	0.618
T_{max}/T½ ratio				
Left kidney	6.5 (4.5; 7.25)	5.38 (4.25; 6.5)	5 (4.5; 5.75)	0.140
Right kidney	7.25 (6; 10.75)	6.5 (4.75; 9)	6.25 (5.5; 9.5)	0.394
30min/T_{max} ratio				
Left kidney	0.14 (0.11; 0.19)	0.12 (0.1; 0.14)	0.12 (0.09; 0.13)	0.088
Right kidney	0.2 (0.14; 0.24)	0.14 (0.12; 0.21)	0.14 (0.13; 0.18)	0.198
20min/3min ratio				
Left kidney	0.16 (0.12; 0.2)	0.14 (0.12; 0.18)	0.16 (0.12; 0.2)	0.735
Right kidney	0.21 (0.14; 0.28)	0.16 (0.13; 0.23)	0.18 (0.15; 0.27)	0.580
Uptake after ACEI, %				
Left kidney	52.37 (50; 58.74)	54.59 (50.69; 57.94)	52.21 (48.75; 54)	0.297
Right kidney	46.81 (41.26; 50)	45.41 (42.06; 49.31)	47.79 (46; 51.25)	0.274
T_{max} after ACEI, min				
Left kidney	3.46 (2.73; 3.97)	3.14 (2.76; 3.97)	2.83 (2.71; 3.36)	0.229
Right kidney	3.64 (3.21; 5.47)	3.59 (3.08; 4.75)	3.3 (2.72; 3.5)	0.076
T_{max}/ T½ after ACEI				
Left kidney	5.25 (4; 7)	5.13 (4; 7)	4.75 (4.25; 5.75)	0.724
Right kidney	6.25 (5.5; 9.5)	6 (4.75; 8.25)	5.5 (5; 6.5)	0.339
30min/Tmax ratio after ACEI				
Left kidney	0.14 (0.12; 0.21)	0.13 (0.1; 0.16)	0.13 (0.11; 0.18)	0.663
Right kidney	0.17 (0.14; 0.26)	0.15 (0.12; 0.27)	0.18 (0.12; 0.23)	0.557
20min/3min ratio after ACEI				
Left kidney	0.15 (0.12; 0.24)	0.16 (0.11; 0.21)	0.17 (0.12; 0.19)	0.920
Right kidney	0.18 (0.16; 0.3)	0.16 (0.13; 0.3)	0.18 (0.13; 0.24)	0.449

T_{max} = time to maximum counts, T½ = time to half-peak counts, 30 min/T_{max} = ratio of renal counts at 30 minutes to maximum counts, 20 min/3 min = ratio of counts at 20 minutes to 3-minute counts.

Although there was a visible difference in the right kidney, it did not attain statistical significance: Group 1 had a mean T_{max} change of 0.61, Group

2 had a mean of 0.21, and Group 3 had a mean of 0.11 (p=0.239). The left kidney in Group 1 exhibited the highest mean change in renal uptake, although this did not reach statistical significance (p=0.453). The median alteration in T_{max} remained statistically significant across all groups for the left kidney, but not fot the right (Table 16).

Table 16. Renal perfusion change pre-ACEI and post-ACEI.

	Group 1 (H/W <0,65) Median (Q1-Q3)	**Group 2 (H/W 0,65-0,85) Median (Q1-Q3)**	**Group 3 (H/W >0,85) Median (Q1-Q3)**	**P-value**
Δ Uptake				
Left kidney	1.2 (0.09; 3.42)	0.45 (-1.42; 2.28)	0.31 (-2.57; 2.12)	0.453
Right kidney	-1.2 (-4.68; -0.09)	-0.45 (-2.28; 1.42)	-1.09 (-2.5; 2.57)	0.489
Δ T_{max}				
Left kidney	**0.27 (-0.05; 1.11) *****	**0.02 (-0.29; 0.75) *****	**-0.41 (-1.18; 0.36) *****	*****<0.05**
Right kidney	0.61 (-0.02; 2.03)	0.21 (-0.25; 1.54)	0.11 (-1.18; 0.36)	0.239
Δ T_{max}/T½ ratio				
Left kidney	-0.25 (-2; 1)	0.25 (-1.25; 2)	-0.25 (-1.5; 1)	0.593
Right kidney	-1 (-3; 1.5)	-0.25 (-1.75; 1.25)	-1.25 (-3.25; 0.25)	0.375
Δ 30min/T_{max} ratio				
Left kidney	0 (-0.02; 0.06)	0.01 (-0.01; 0.05)	0.02 (-0.02; 0.05)	0.991
Right kidney	0.01 (-0.04; 0.08)	0.02 (-0.02; 0.06)	0 (-0.03; 0.03)	0.680
Δ 20min/3min ratio				
Left kidney	0 (-0.03; 0.06)	-0.01 (-0.01; 0.06)	-0.02 (-0.03; 0)	0.202
Right kidney	0 (-0.06; 0.08)	0 (-0.04; 0.03)	-0.03 (-0.07; -0.01)	0.089

Δ - the difference between pre and post-ACEI; T_{max} = time to maximum counts, T½ = time to half-peak counts, 30 min/T_{max} = ratio of renal counts at 30 minutes to maximum counts, 20 min/3 min = ratio of counts at 20 minutes to 3-minute counts. *** - statistical significance between all groups.

While the T_{max}/T½ ratio change and the 30min/T_{max} ratio change for both kidneys did not show statistically significant differences across the groups, a negative mean change was observed in the 20min/3min ratio change for the left kidney in Group 3, which did not approach statistical significance (p=0.089). This finding may suggest a potential alteration in early renal function or perfusion.

5.3 Determinants of renal perfusion alterations

The linear regression model for the difference of pre-ACEI and post-ACEI of time to maximum counts (ΔT_{max}), in which higher values show a higher risk of renovascular hypertension, demonstrates that age significantly impacts ΔT_{max} decretion in the right kidney prior-ACEI and post-ACEI, potentially indicating age-related renal function incline (Table 17). Although there is a trend for females to have a lower ΔT_{max} in the left kidney, this finding was not statistically significant. However, females exhibit a significantly

lower ΔT_{max} in the right kidney compared to males, suggesting gender-related differences in right renal function.

Table 17. Linear regression model for variables influencing ΔT_{max} (time to maximum counts difference pre-ACEI and post-ACEI).

	Δ T_{max} LK		**Δ T_{max} RK**	
Dependant variable	**Coefficient**	**P-value**	**Coefficient**	**P-value**
Age	-0.025	0.304	**-0.054**	**0.021**
Age at first operation	-0.015	0.741	-0.058	0.190
Female gender	-0.933	0.089	**-1.318**	**0.012**
Ao arch H/W ratio	**-3.952**	**0.018**	-1.746	0.282
Aortic arch H/W ratio <0.65	**1.913**	**0.010**	1.014	0.166
Aortic arch H/W ratio 0.65 – 0.85	**1.691**	**0.022**	0.813	0.258
Aortic arch angle	**0.058**	**0.048**	0.018	0.541
Residual stenosis	-0.021	0.284	0.003	0.890
Overall systolic BP	0.016	0.691	-0.002	0.947
Systolic BP difference RA-LL	0.010	0.460	**0.024**	**0.044**
RCCA IM thickness	-0.001	0.800	0.001	0.676
RCCA distensibility	0.001	0.273	**0.003**	**0.002**
RCCA stiffness	-0.062	0.812	-0.038	0.850
LCCA IM thickness	-0.001	0.612	-0.002	0.299
LCCA distensibility	0.001	0.463	**0.003**	**0.002**
LCCA stiffness	-0.275	0.356	-0.042	0.859
PWV	-0.030	0.908	-0.120	0.647
R-CAVI	-0.317	0.340	-0.046	0.896
L-CAVI	-0.620	0.061	-0.522	0.131
eGFR	-0.006	0.173	-0.002	0.546

A higher aortic arch H/W ratio is associated with a significant reduction in ΔT_{max} in the left kidney, indicating an effect on renal hemodynamics. Still, it does not significantly affect the right kidney. Conversely, a H/W ratio of less than 0.65 is significantly associated with increased ΔT_{max} in the left kidney, suggesting a favorable impact of specific aortic arch morphologies on left kidney perfusion without a significant effect on the right kidney. Similarly, a H/W ratio between 0.65 and 0.85 significantly increases the ΔT_{max} in the left kidney. A wider Ao arch angle is linked to a slight but significant increase in ΔT_{max} in the left kidney, likely reflecting altered hemodynamics due to aortic structure changes. This relationship does not extend to the right kidney.

A more significant systolic BP difference between the right arm and left leg is significantly associated with increased ΔT_{max} in the right kidney, suggesting affected right renal function. Furthermore, greater right common carotid artery (RCCA) distensibility is significantly related to an increase in ΔT_{max} in the right kidney, indicating a vascular connection between RCCA

properties and right renal hemodynamics. This association was also observed with the distensibility of the left common carotid artery (LCCA).

In the linear regression model for Δ 30min/T_{max} ratio (Table 18), none of the variables tested— including age, gender, Ao arch H/W ratio, Ao arch angle, residual stenosis, systolic BP, and carotid artery metrics (RCCA and LCCA)— demonstrated a significant impact on Δ 30min/T_{max} ratio in either the left or right kidneys. However, RCCA intima-media (IM) thickness showed borderline significance for the right kidney, suggesting a potential influence on right renal function. These findings indicate no strong associations between the tested variables and changes in Δ 30min/T_{max} ratio in either kidney within this cohort.

Table 18. Linear regression model for variables influencing Δ30min/T_{max} ratio (difference pre-ACEI and post-ACEI)

	Δ 30min/T_{max} ratio LK		**Δ 30min/T_{max} ratio RK**	
Dependant variable	**Coefficient**	**P-value**	**Coefficient**	**P-value**
Age	-0.000	0.930	0.000	0.971
Age at first operation	-0.002	0.295	-0.001	0.805
Female gender	-0.030	0.121	-0.030	0.398
Ao arch H/W ratio	0.015	0.804	-0.129	0.229
Aortic arch H/W ratio <0.65	0.001	0.981	0.069	0.153
Aortic arch H/W ratio 0.65 – 0.85	0.012	0.641	0.052	0.269
Aortic arch angle	-0.000	0.823	0.002	0.399
Residual stenosis	0.000	0.548	0.001	0.242
Overall systolic BP	-0.002	0.439	-0.001	0.293
Systolic BP difference RA-LL	0.001	0.309	0.001	0.247
RCCA IM thickness	0.000	0.127	0.000	0.083
RCCA distensibility	0.000	0.168	0.000	0.214
RCCA stiffness	-0.009	0.291	-0.006	0.680
LCCA IM thickness	0.000	0.201	0.000	0.336
LCCA distensibility	0.000	0.925	0.000	0.644
LCCA stiffness	0.001	0.940	-0.009	0.549
eGRF	-0.000	0.337	0.000	0.929

The analysis of variables influencing the 20min/3min ratio difference prior-ACEI and post-ACEI did not reveal any significant associations (Table 19). Age showed a borderline effect on Δ20min/3min ratio in the left kidney, suggesting that older individuals may experience a slight reduction, although this result is not definitively significant. Conversely, age did not considerably impact the Δ20min/3min ratio in the right kidney. Female gender was significantly associated with a lower Δ 20min/3min ratio in the left kidney than males. In contrast, although there was a trend toward a lower Δ20min/3min ratio in the right kidney among females, this effect did not reach statistical significance.

A higher aortic arch height-to-width (H/W) ratio is significantly associated with a reduction in Δ 20min/3min ratio in the right kidney. Conversely, a lower H/W ratio (< 0.65) is significantly associated with an increase in Δ 20min/3min ratio in the right kidney, suggesting that this specific ratio may benefit right kidney function. No significant effect of the H/W ratio is observed for the left kidney.

Table 19. Linear regression model for variables influencing Δ30min/T_{max} ratio (difference pre-ACEI and post-ACEI)

	Δ 20min/3min ratio LK		**Δ 20min/3min ratio RK**	
Dependant variable	**Coefficient**	**P-value**	**Coefficient**	**P-value**
Age	-0.002	0.084	-0.002	0.401
Age at first operation	-0.003	0.282	-0.000	0.953
Female gender	**-0.074**	**0.012**	-0.089	0.103
Ao arch H/W ratio	-0.066	0.470	**-0.336**	**0.042**
Aortic arch H/W ratio <0.65	0.046	0.265	**0.153**	**0.041**
Aortic arch H/W ratio 0.65 – 0.85	0.054	0.187	0.097	0.185
Aortic arch angle	0.000	0.931	0.004	0.216
Residual stenosis	-0.001	0.531	0.001	0.444
Overall systolic BP	-0.001	0.585	-0.000	0.900
Systolic BP difference RA-LL	0.001	0.100	0.001	0.259
RCCA IM thickness	0.000	0.868	0.000	0.397
RCCA distensibility	0.000	0.114	0.000	0.169
RCCA stiffness	-0.008	0.550	0.003	0.872
LCCA IM thickness	-0.000	0.851	-0.000	0.950
LCCA distensibility	0.000	0.457	0.000	0.248
LCCA stiffness	-0.002	0.918	-0.015	0.549
PWV	0.017	0.251	0.030	0.268
R-CAVI	0.007	0.717	0.041	0.252
L-CAVI	-0.014	0.482	-0.004	0.910
eGFR	-0.000	0.428	0.000	0.595

5.4 Results of renal flow changes in significant CoA

This part of the study describes clinically significant CoA patient group subanalysis.

Six patients were enrolled in this group (Table 20). The mean age at the time of inclusion was 36.7±24.05 years, and 4 out of the six patients (66.67%) were male. Among these patients, three presented with native CoA, while the remaining three had previously undergone different types of repair: one with a homotransplant followed by stent implantation, one with end-to-end anastomosis, and one after percutaneous stent implantation. All participants underwent invasive gradient measurements and percutaneous stent placement. Renal perfusion scans were repeated between 3 and 6 months after the procedure.

Table 20. Clinical and procedural data of patients with clinically significant CoA.

Patient	Sex	Age (years)	BMI	Primary diagnosis	Age at repair (days)	Mode of primary repair	Repeat repairs	AH medication	Stenosis	Invasive gradient	Stent	Residual gradient	Complication	AH 6 months post procedure
1	M	69	27.78	CoA	-	-	-	BB, ACEI, CCB	78.34%	43mmHg	8zig CCP 20X28	0mmHg	-	BB, ACEI, CCB,
2	M	30	24.82	CoA	4409	Homotransplant	Stent	BB	35.46%	20mmHg	8zig CCP 20X45	9mmHg	Ao rupture	BB, ACEI
3	F	69	25.81	CoA	-	-	-	BB, ACEI, Th, AB, statin	40.9%	14mmHg	8zig CCP 20X34	0mmHg	-	BB, ARB, statins
4	F	26	22.04	CoA, BAV	-	-	-	BB, ACEI	30.6%	23mmHg	8zig CCP 18X28	0mmHg	-	-
5	M	18	21.93	CoA, BAV	13	E-E anastomosis	-	BB, ACEI	21.1%	20mmHg	8zig CP 25X45 8zig CCP 25X45	1mmHg	-	BB, ARB
6	M	18	18.52	CoA	3515	Stent	-	BB, ACEI	50%	0	8zig CP 16X52	0mmHg	-	BB, ACEI

BMI – body mass index; CAA – centrally acting alfa agonist; CoA – coarctation of the aorta; BAV – bicuspid aortic valve; BB – beta-blockers, ACEI - Angiotensin-converting-enzyme inhibitors; CCB – calcium channel blockers; Th – thiazides; statin – statins; CCP - covered Cheatham-Platinum stent; CP - Cheatham-Platinum stent; E-E anastomosis – end to end anastomosis; M-male; F-female. AH – antihypertensive.

The mean overall systolic BP on 24-hour ambulatory blood pressure monitoring was 129.67±17.62 mmHg, while the mean diastolic BP was 68.67±10.21 mmHg. The mean systolic and diastolic dips were 13.73±10.4% and 10.47±9.42%, respectively. The mean systolic BP difference between the right arm and the lower leg in-office BP measurements was 23±21.06 mmHg. An echocardiographic evaluation revealed a mean LV mass index of 86.3±14.45 g/m², a mean LV ejection fraction of 58.33±2.58%, and a mean gradient at the level of the CoA of 26.78±11.14 mmHg. The CT angiogram showed the aortic arch with a mean height of 60.22±14.13 mm and a width of 78.58±37.81 mm, with an arch angle of 63.61±13.95 degrees. The mean stenosis of the CoA was 37.63±21.59%.

All patients received antihypertensive treatment, with a minimum of one medication and a maximum of four medicines used for blood pressure control. For hypertension management, all six patients were on beta-blockers. Additionally, five patients (83.3%) were also prescribed ACEI. Patients requiring three or more medications had combinations that included ARB, CCB, thiazide diuretics, or centrally-acting antihypertensive drugs. Only one patient was on statin therapy.

The renal perfusion scans, conducted as an essential measure before invasive investigation, did not reveal significant differences in pre- and post-ACEI (Table 21).

Table 21. Renal perfusion scan before intervention.

	Pre-ACEI	Post-ACEI	ΔPre-Post ACEI	P-value
Uptake, %				
Left kidney	52.56 (5.399)	54.83 (3.877)	2.27 (4.864)	0.704
Right kidney	47.44 (5.399)	45.17 (3.877)	-2.27 (4.864)	0.625
T_{max}, min				
Left kidney	3.79 (0.728)	3.2 (0.626)	-0.59 (1.188)	0.786
Right kidney	4.08 (0.834)	3.91 (1.082)	-0.17 (1.461)	0.291
T_{max}/T½ ratio				
Left kidney	6.92 (2.733)	6.75 (2.743)	-0.17 (1.842)	0.745
Right kidney	8.21 (2.956)	7.83 (5.012)	-0.38 (3.711)	0.546
30min/T_{max} ratio				
Left kidney	0.17 (0.102)	0.21 (0.103)	0.04 (0.098)	0.625
Right kidney	0.19 (0.092)	0.24 (0.128)	0.05 (0.109)	0.920
20min/3min ratio				
Left kidney	0.26 (0.164)	0.23 (0.118)	-0.03 (0.12)	0.914
Right kidney	0.27 (0.135)	0.28 (0.171)	0.01 (0.166)	0.880

Δ - the difference between pre and post-ACEI; T_{max} = time to maximum counts, T½ = time to half-peak counts, 30 min/T_{max} = ratio of renal counts at 30 minutes to maximum counts, 20 min/3 min = ratio of counts at 20 minutes to 3-minute counts.

A notable proportion of patients (4 out of 6, 66.67%) required intravenous norepinephrine infusion for at least 15 minutes to elevate their

systolic blood pressure above 140 mmHg during invasive pressure gradient measurement. The mean invasive gradient was 19.67±14.542, highlighting the increased hemodynamic challenge necessitating intervention. All patients subsequently underwent percutaneous stent placement. Technical success (appropriate stent placement and residual pressure gradient <10 mmHg) was achieved in all patients. Only one patient (patient 2) had a significant complication – aortic wall rupture with extravasation and bleeding to mediastinum due to stent post-dilation with a high-pressure balloon (Atlas Gold 20X40mm, 10ATM). A covered stent CCP 8ZIG 45 with BiB 20X45mm was implanted to cover arterial wall damage. The patient remained with a residual gradient of 9mmHg and was discharged seven days post-procedure.

Subsequent repeat renal scintigraphy was conducted 3-6 months after the procedure. After comparing the pre-and post-stent implantation measurements, no statistically significant changes in renal perfusion scan were observed (Table 22).

Table 22. Renal perfusion change pre-ACEI and post-ACEI.

	Pre-stent implantation, Mean (SD)	**Post-stent implantation, Mean (SD)**	**P-value**
Δ Uptake			
Left kidney	2.01(3.023)	2.27 (4.864)	1.0000
Right kidney	-3.71(6.129)	-2.27 (4.864)	0.6875
Δ T_{max}			
Left kidney	0.26 (0.837)	-0.59 (1.188)	0.3125
Right kidney	0.39 (1.286)	-0.17 (1.461)	0.8438
Δ T_{max}/T½ ratio			
Left kidney	-0.71 (1.134)	-0.17 (1.842)	0.4063
Right kidney	0.79 (2.985)	-0.38 (3.711)	0.4063
Δ 30min/T_{max} ratio			
Left kidney	-0.01 (0.043)	0.04 (0.098)	0.4375
Right kidney	0 (0.047)	0.05 (0.109)	0.3125
Δ 20min/3min ratio			
Left kidney	0 (0.035)	-0.03 (0.12)	0.8438
Right kidney	0.01 (0.029)	0.01 (0.166)	0.8750

Δ - the difference between pre and post-ACEI; T_{max} = time to maximum counts, T½ = time to half-peak counts, 30 min/T_{max} = ratio of renal counts at 30 minutes to maximum counts, 20 min/3 min = ratio of counts at 20 minutes to 3-minute counts.

Figure 8. describes individual renal perfusion changes in each patient before and after stent implantation.

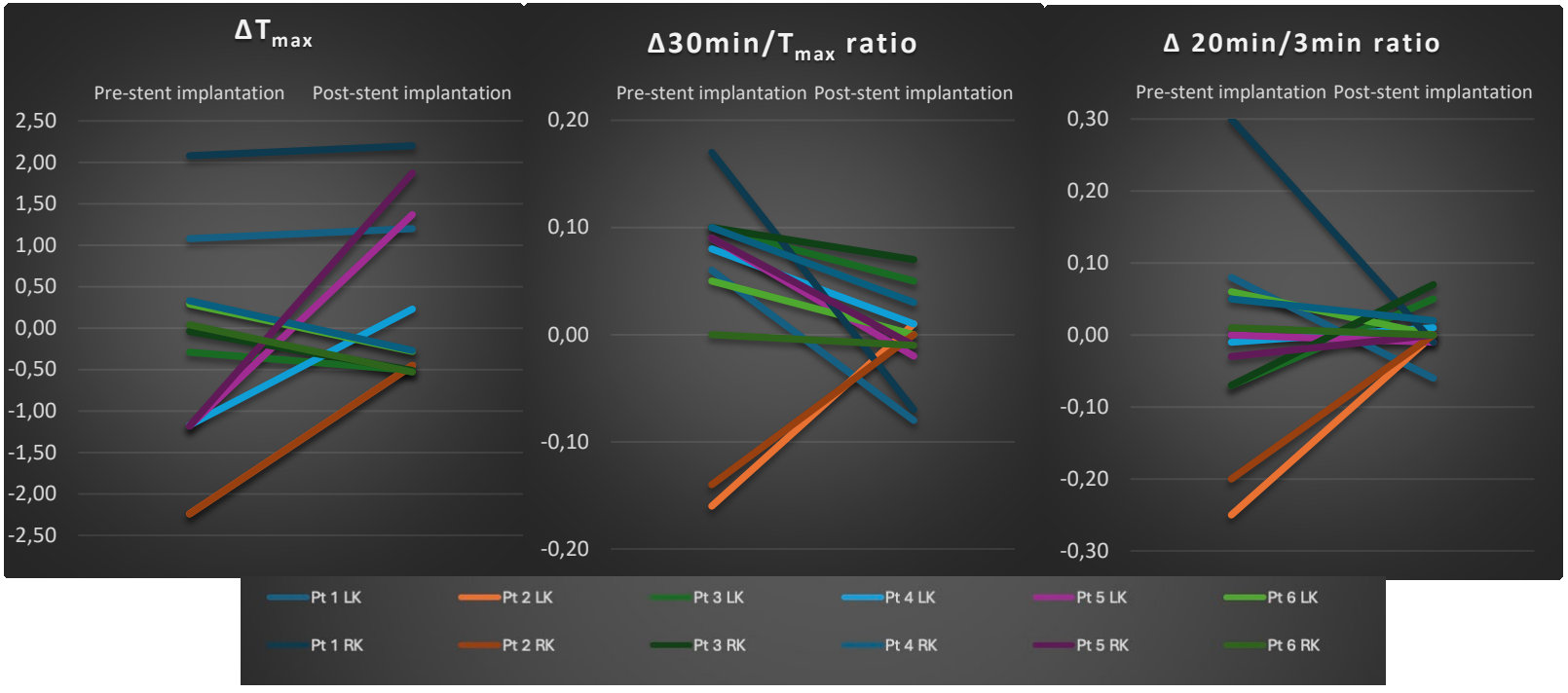

Figure 8. Individual renal perfusion changes in each patient before and after stent implantation. Pt – patient; LK – left kidney; RK – right kidney.

Despite some prolongation in T_{max} and observed increases in the 30min/T_{max} and 20min/3min ratios in certain patients, most demonstrated modest improvements in renal perfusion and function post-stent implantation. The elevated ratios in some patients may indicate dehydration, resulting in reduced renal clearance and impaired perfusion. Considering the limited sample size, these results should be interpreted cautiously, as individual patient factors or potential measurement errors may influence the observed variability.

Only one patient (patient 4) completely stopped her antihypertensive treatment after stent implantation due to normalized blood pressure. The rest of the patients had no significant change in their medications.

6. DISCUSSION

To the investigator's knowledge, this is the first study to assess CoA and renal perfusion. As detailed below, the primary findings were obtained in a patient cohort with CoA.

1. Male sex was associated with a 3.9-fold increased risk of developing arterial hypertension compared to females.
2. A Crenel-type aortic arch was identified as a significant risk factor for arterial hypertension, with an odds ratio of 5.833 compared to a Gothic-type aortic arch.
3. The probability of developing arterial hypertension increased by 6.5% for each millimeter increase in aortic arch width.
4. A wider aortic arch angle was associated with a higher risk of arterial hypertension, with each unit increase in the angle correlating to a 9% increase in risk.
5. An elevated echocardiographic gradient across the CoA was positively associated with arterial hypertension, with each mmHg increase leading to a 5% increase in risk.
6. CoA patients with arterial hypertension exhibited increased intima-media thickness and enhanced distensibility in the right common carotid artery. No similar changes were observed in the left common carotid artery.
7. Hypertensive patients demonstrated slower renal perfusion (prolonged T_{max}) and impaired clearance (elevated 30min/T_{max} and 20min/3min ratios, pre- and post-ACEI) in both kidneys.
8. Age significantly affected ΔT_{max} in the right kidney, with older patients demonstrating a reduced T_{max} difference pre- and post-ACEI, suggesting potential age-related improvement in renal function.
9. Females exhibited a significantly lower ΔT_{max} in the right kidney than males, indicating better right renal function in females.
10. Aortic arch types wider than Gothic-type (Crenel-type and Romanesque) were associated with reduced perfusion in the left kidney and reduced clearance in the right kidney.
11. CoA patients with a more significant systolic blood pressure difference between the right arm and left leg and increased distensibility in the right common carotid artery were at higher risk for parenchymal retention in the right kidney.
12. Female gender was associated with better renal clearance in the left kidney, as indicated by a lower Δ20min/3min ratio.

13. Due to the small sample size, we could not assess the impact of stent implantation and gradient reduction on renal perfusion improvement in patients with significant CoA.

6.1. Patient population

Historically, coarctation of the aorta without treatment was associated with a severe prognosis; archival data from the 1930s to the 1960s demonstrate that approximately 25% of individuals affected by this condition did not survive beyond their 20th birthday. Our database has been compiling data on the coarctation of the aorta post-surgical patients since early 1964. Nevertheless, 78.6% (590 of 750) of these patients either died early or were lost to follow-up. This elevated mortality rate may be attributed to the nascent stage of surgical techniques and healthcare systems at the time. Patients were classified as lost to follow-up if they had not attended a scheduled appointment with a congenital cardiologist for a period exceeding five years, a situation that the level of patient education may influence.

The majority of participants in this study were young adults, with a median age of 28. Of these, 91% had undergone surgical intervention, whereas only seven individuals had had native untreated coarctation of the aorta remaining. Patients with complex congenital heart disease were excluded from our study. It is hypothesized that the reduced incidence of late hypertension in complex CoA cases may be due to diminished stimulation of the baroreceptor reflex in the pre-stenotic area, likely resulting from decreased systemic blood flow and pressure before intervention—a scenario not typically present in cases of simple CoA. (158,159) This distinction is evident when comparing complex and simple CoA repair groups, with the former showing an arterial hypertension odds ratio (OR) of 4.01 and a 95% confidence interval (CI) ranging from 1.30 to 12.41. (103)

6.2. Risk factors for arterial hypertension in CoA patients.

In our study, only 34.48% of patients (30 out of 87) achieved optimal long-term outcomes, characterized by the absence of hypertension, less than moderate restenosis in CT angiography, and no significant pressure difference between limbs. A substantial proportion, 46 patients (52.87%), experienced poor control of their hypertension despite the use of antihypertensive medications.

Long-term observational studies have shown that arterial hypertension persists in approximately 41% of patients, even 24 years after their initial CoA repair. Males are more commonly affected by CoA, with incidence ratios

varying from 1.27:1 to 1.74:1 compared to females. (46) In our cohort, hypertension, as determined by office or 24-hour ambulatory blood pressure measurements, was observed in 52.87% of patients, with a male predominance at a ratio of 3.9:1. This prevalence of AH is notably higher than the 23% previously reported in the literature, suggesting that the burden of hypertension may be more significant in our cohort than generally observed in earlier studies. (147) This disparity may be related to updated diagnostic criteria or demographic differences. Additionally, males with CoA are more likely to present with more frequent and severe aortic arch anomalies, such as the crenel-type aortic arch, which is associated with an increased risk of hypertension, as observed in our cohort.

Our data demonstrated that patients with wide aortic arches (Crenel-type) had an odds ratio of 5.833 for developing arterial hypertension compared to those with narrow arches (Gothic-type). This finding may be attributed to more significant hemodynamic disturbances in Crenel-type arches, characterized by pronounced tortuosity and undulating, "crenelated" segments. The increased tortuosity in these arches likely contributes to turbulent blood flow, heightened vascular resistance, and increased strain on the arterial walls. Furthermore, the irregular morphology of the Crenel arch may negatively impact the elasticity and compliance of the aorta, reducing its capacity to accommodate changes in blood flow during the cardiac cycle. In contrast, the Gothic-type arch, with its more triangular or steep configuration, may facilitate more direct and streamlined blood flow, thereby reducing vascular resistance compared to the Crenel-type arch. In our patient cohort, we did not observe evidence of increased vascular stiffening, as both pulse wave velocity (PWV) and cardio-ankle vascular index (CAVI) values were within normal ranges across all groups. This may be attributable to the relatively young age of our study population.

CoA frequently results in alterations in aortic geometry, including changes in the aortic arch angle. In some cases, the aortic arch becomes more tortuous, with a widened angle as a compensatory mechanism for the narrowed segment of the aorta. A wider aortic arch can significantly affect hemodynamics, potentially increasing turbulence and resistance to blood flow. Our study reflects these changes, demonstrating that the risk of developing hypertension increases by 6.5% for each rise in millimeter in aortic arch width.

Furthermore, we identified an even stronger correlation between the aortic arch angle and hypertension, where each unit increase in the arch angle is associated with a 9% rise in the odds of developing arterial hypertension. These findings suggest that both the width and angle of the aortic arch may

serve as predictive markers for the development of hypertension in CoA patients. Monitoring these parameters could provide valuable insight into the risk of hypertension and guide clinical management strategies aimed at mitigating this risk.

In patients with CoA, the narrowing of the aorta creates a pressure gradient, with elevated pressures in the vessels proximal to the coarctation and reduced pressures distally. A wider aortic arch may amplify this pressure gradient, contributing to more severe hypertension proximal to the coarctation site. Moreover, a wider arch could indicate a heightened risk of persistent hypertension, even after successful CoA repair. Specific surgical techniques that result in a wider aortic arch postoperatively may increase the risk of hypertension. This highlights the need for careful surgical planning, especially in pediatric patients, where aortic arch development is still active and can have long-term consequences. Refining surgical techniques to prevent excessive widening of the aortic arch may reduce the likelihood of future hypertension.

For patients with wider aortic arches, aggressive management of modifiable risk factors for hypertension is crucial. This could include lifestyle modifications, dietary interventions, and early initiation of antihypertensive therapy. Early and proactive management may be essential in preventing the long-term cardiovascular complications associated with hypertension in this population.

Ongoing echocardiographic monitoring is essential to assess for residual gradients or re-coarctation after repair. A rising gradient may indicate that the coarctation site is narrowing again, necessitating further intervention. Our data suggests that for every one mmHg increase in the pressure gradient across the coarctation in echocardiogram, there is a 5% increase in the risk of developing hypertension. Patients with higher gradients across the coarctation site are at greater risk and should be closely monitored for signs of arterial hypertension.

In patients with CoA, persistent elevation of blood pressure, particularly in the upper body, triggers adaptive changes in the arterial system to withstand the increased pressure. In particular, the right common carotid artery is exposed to higher systemic pressures, contributing to the increased intima-media thickness (IMT) observed in our study. This thickening of the arterial wall represents a physiological response to increased shear stress and pressure, reinforcing the artery at the expense of flexibility.

Our study found that only the right common carotid artery exhibited increased IMT and distensibility, while the left did not show similar changes. This may be attributable to asymmetric hemodynamic forces in CoA patients, where blood flow dynamics and pressures are unequal between the two sides

of the body. The right common carotid artery arises from the brachiocephalic trunk, the first major branch of the aortic arch, and is more directly exposed to the elevated pressures of blood exiting the heart. In contrast, the left common carotid artery originates directly from the aortic arch and, due to the CoA, may experience different pressure dynamics. This difference could explain the lack of significant vascular remodeling in the left carotid artery.

The increased distensibility observed in the right common carotid artery is somewhat unexpected, as hypertension typically leads to arterial stiffening. However, this finding suggests a compensatory response, wherein the right carotid artery maintains or enhances its ability to expand and contract despite the increased IMT. One possible explanation is that the artery adapts to the increased pulsatile flow and pressure by becoming more compliant, potentially buffering the effects of hypertension on the vascular system. However, this enhanced distensibility may not be beneficial in the long term, as it could predispose the artery to dilation and increase the risk of vascular complications such as aneurysms.

It could also be associated with the relatively young age of our patient population, which may not yet exhibit signs of early vascular aging. Younger arteries may have a greater adaptive capacity to withstand higher pressures without developing the stiffening typically associated with hypertension.

In our study, exercise tests were not administered to all patients because existing data suggest no significant differences in blood pressure responses during physical exertion between individuals who have undergone CoA correction and control groups. (194) However, exercise-induced hypertension might serve as an early indicator for the development of chronic hypertension in adults who have undergone CoA repair.

6.3 Renal perfusion changes in patients with aortic coarctation

Our study on renal perfusion scans in hypertensive patients following the administration of ACEI has unveiled significant alterations in renal function. The key findings, including a prolonged time to maximum activity (T_{max}) and elevated 20-minute to 3-minute (20min/3min) ratios in both kidneys, collectively point towards impaired renal perfusion and reduced filtration efficiency, commonly observed in hypertension. These findings are crucial in understanding the early indicators of renal dysfunction in hypertensive patients with CoA.

The T_{max} represents the time required for the kidneys to reach peak activity after administering a tracer during the perfusion scan. In hypertensive patients, a prolonged T_{max} reflects delayed renal perfusion, indicating that the

kidneys take longer to process and filter blood. This delay is likely indicative of underlying microvascular dysfunction, a common characteristic of hypertensive individuals. The prolonged T_{max} may serve as an early indicator of subclinical renal damage in patients with CoA, even before the emergence of overt clinical symptoms of renal impairment.

The 20min/3min ratio evaluates renal clearance dynamics by assessing how efficiently the kidneys can clear the tracer substance over time. Elevated ratios in hypertensive patients suggest slower renal clearance following ACEI administration, which points to impaired kidney function. This finding indicates that the kidneys are less efficient in filtration and excretion, likely due to reduced renal perfusion pressure. The elevated ratios suggest that hypertensive patients may already be experiencing early-stage renal dysfunction, even in the absence of overt kidney disease symptoms. Over time, hypertension may further exacerbate this clearance impairment, potentially leading to more significant renal damage.

Hypertensive patients often exhibit subclinical changes in renal function that precede overt kidney damage, and these findings may serve as early markers for identifying individuals at increased risk of developing more severe renal impairment.

Our data indicate that age significantly influences the ΔT_{max} in the right kidney, with older patients with CoA demonstrating a reduced difference in T_{max} before and after ACEI administration. This suggests a complex interplay between age-related vascular changes and renal perfusion dynamics. As individuals age, the kidneys undergo several structural and functional alterations, including a reduced glomerular filtration rate (GFR), decreased renal blood flow, and increased vascular stiffness. The smaller ΔT_{max} observed in older CoA patients implies that their kidneys exhibit a less pronounced response in T_{max} activity following ACEI administration, potentially indicating a greater resistance to ACEI-induced hemodynamic changes.

One explanation for this finding could be that age-related vascular changes, such as reduced arterial elasticity and slower blood flow, result in a more stable or less variable response to ACEI. In patients with long-standing CoA, the kidneys may have adapted to a chronic state of reduced perfusion, rendering them less responsive to the vasodilatory effects of ACEI. Consequently, the reduced ΔT_{max} may reflect a more stabilized renal hemodynamic environment, where fluctuations less influence the kidneys in systemic blood pressure.

In contrast, younger hypertensive patients with CoA may display a more significant change in T_{max} following ACEI administration, as their kidneys are still compensating for elevated blood pressure through

hyperfiltration. The larger ΔT_{max} in younger patients suggests that their kidneys are more sensitive to the vasodilatory and antihypertensive effects of ACEIs as they actively manage elevated pressures. In older patients, however, the smaller ΔT_{max} may indicate that their kidneys are no longer in a state of hyperfiltration, potentially signifying a stabilization or improvement in renal perfusion efficiency over time.

The reduced ΔT_{max} in older CoA patients may also imply that the efficacy of ACEIs in enhancing renal perfusion diminishes with age. As age-related vascular rigidity and reduced responsiveness to vasodilators become more pronounced, the capacity for ACEIs to improve renal perfusion may be decreased in older individuals with CoA.

While the reduced ΔT_{max} in older CoA patients may suggest a potential age-related stabilization or improvement in renal function, further research is required to elucidate the underlying mechanisms fully. Future studies should explore how age-related vascular and renal physiology changes impact the response to ACEIs and whether these findings are authentic across more extensive and diverse patient populations.

The lower ΔT_{max} in the right kidney and lower Δ20min/3min ratio in the left kidney observed in females with CoA in our study suggest that women may have more efficient renal perfusion than males. Gender differences in renal physiology are well-documented, with hormonal factors playing a significant role.(229) Estrogen, for example, exerts vasodilatory effects that help protect blood vessels and maintain renal perfusion. It is known to have renoprotective properties by promoting renal blood flow and preserving kidney function, particularly in premenopausal women. In contrast, males may experience higher renal vascular resistance due to the pro-hypertensive effects of testosterone, contributing to slower renal perfusion and excretion, as indicated by the higher ΔT_{max} and Δ20min/3min ratio observed in males. Our study also showed that males with CoA are at greater risk of developing hypertension at an earlier age, which may further exacerbate these renal perfusion differences.

However, it is essential to consider that the protective effects of estrogen in females may diminish with age, particularly after menopause, when estrogen levels decline. This underscores the importance of considering age in the context of gender differences in renal physiology. Postmenopausal women become more susceptible to hypertension and its associated renal complications, potentially reducing the observed renal protection seen in younger or premenopausal women. Thus, the more efficient renal perfusion in females with CoA may be most pronounced in younger or premenopausal populations.

Our study revealed apparent differences between left and right kidney parameters, which is consistent with findings reported by Leew et al.(230) Their analysis of renal blood flow asymmetry in patients with moderate to severe hypertension demonstrated that such asymmetry can be observed in up to 51% of hypertensive patients with angiographically confirmed patent renal arteries. Interestingly, patients with and without asymmetry did not differ significantly in age, body mass index, blood pressure, creatinine clearance, renal volume, or renin-angiotensin system activity. This suggests that substantial differences in renal blood flow between the left and right kidneys can occur independently of these common clinical factors. The study indicates that renal blood flow asymmetry may result from structural or functional differences or a combination. Asymmetric alterations at the interlobar and arcuate arteries level could contribute to these discrepancies. Moreover, asymmetry appears to be a consistent characteristic in certain patients, which may affect the accuracy of diagnostic tests reliant on renal blood flow measurements.

6.4 Coarctation of the aorta gradient and its reduction influence on renal perfusion.

The primary goal of stent implantation in patients with CoA is to reduce the pressure gradient between the upper and lower body. This is typically accomplished by expanding the narrowed aortic segment, allowing for more balanced blood flow and preventing cardiovascular complications such as left ventricular hypertrophy and systemic hypertension. However, as shown in our study, renal perfusion may not significantly improve post-stent implantation despite the successful reduction in the pressure gradient.

The lack of significant improvement in renal perfusion suggests that CoA patients may require long-term renal monitoring and management, even after the aortic narrowing has been corrected. This finding highlights the complexity of CoA-related renal impairment, where restoring aortic blood flow does not necessarily lead to an immediate or complete resolution of renal perfusion issues.

There has yet to be a consensus on defining the severity of CoA across various studies. Recurrent coarctation (ReCoA) is commonly defined as an invasive systolic pressure gradient across the CoA site of ≥ 20 mmHg (118–120) or when the aortic diameter ratio between the narrowest point of the CoA and the aorta at the diaphragm is less than 50%. (124,125) In our study, these criteria were fulfilled by 6.89% of the patients (6 out of 87), all of whom underwent percutaneous stent implantation. Conversely, other research has

not definitively linked residual narrowing of the aorta with arterial hypertension. (4,42–44) Consequently, there remains ambiguity in deciding whether to treat medically managed hypertension in CoA patients when invasive intervention criteria are not met, highlighting a gray area in clinical decision-making.

The data regarding the impact of pressure gradient release on hypertension outcomes remains controversial. Some studies suggest that incomplete relief of stenosis may contribute to the development of hypertension, indicating that inadequate intervention at the stenotic site could precipitate elevated blood pressure. (176,177) However, other researchers have not established a clear correlation between the prevalence of hypertension and the presence or absence of re-stenosis, suggesting variability in individual responses or potential influence of other vascular or systemic factors. (151,180)

Our study findings indicate that irrespective of the severity of residual stenosis, there was no significant reduction in renal perfusion among patients with CoA. This observation suggests that the degree of anatomical narrowing may not directly correlate with renal blood flow impairment in these patients. This outcome highlights the complexity of CoA's impact on renal physiology and suggests that other factors might influence renal perfusion beyond the anatomical characteristics of the aortic narrowing. However, a negative renal scintigraphy test result does not conclusively eliminate the possibility of some level of blood pressure amelioration following revascularization.

One previous study demonstrated no significant correlation between absolute or percentage changes in pressure gradients after stenting for CoA and reductions in systolic blood pressure at follow-up assessments. (179) This finding aligns with our data, where only one out of six patients discontinued antihypertensive medication post-stent implantation. The remaining patients either mildly reduced their medication dosage or maintained their pre-procedure treatment regimen.

This observation suggests that the mechanical relief of CoA by stenting, although effective at alleviating the structural bottleneck in the aorta, does not necessarily translate into immediate or significant improvements in blood pressure management. This could imply that long-standing vascular changes or adaptive physiological responses in these patients may not be fully reversible with stenting alone. It underscores the need for continued management of hypertension in CoA patients post-intervention, including ongoing medication therapy and regular monitoring of blood pressure.

It is essential to acknowledge that current guidelines for managing coarctation of the aorta were developed during an era predominantly

characterized by surgical interventions, which entailed significant risks associated with thoracic surgery, ambiguous effects on minor gradients, and the frequent use of prosthetic materials. Given the recent advancements and the prevalent adoption of catheter-based techniques, re-evaluating the risk-benefit ratio may warrant modifications to existing recommendations. There may be justification for considering re-intervention at lower systolic arm-leg blood pressure gradients than currently recommended. Nonetheless, it is crucial to clearly articulate the rationale for any intervention and the specific clinical challenges being addressed. Our findings indicate that despite gradient relief at the isthmus level, there was no observed change in renal perfusion. The lack of statistically significant changes in renal perfusion parameters before and after stent implantation in patients with clinically significant CoA can be attributed to the limited sample size.

Nevertheless, the observed trends indicate potential benefits of percutaneous treatment. A minor change in perfusion time (T_{max}) was noted before and after ACEI administration post-stent implantation, compared to the changes observed before stenting. These findings suggest that correcting CoA by reducing the gradient might improve renal perfusion, potentially mitigating long-term renal impairment risk.

The potential modulation of baroreceptor responses, which could serve as a therapeutic target for regulating arterial blood pressure, was beyond the scope of our study. Consequently, additional research is needed to validate potential changes in clinical practice guidelines based on these insights.

7. LIMITATIONS

The limitations of our study are essential for the proper interpretation of the results. Firstly, as a single-center, non-randomized trial, the generalizability of the findings to broader patient populations may be limited. Secondly, the small sample size restricted our ability to detect statistically significant differences in key outcomes, such as the effect of stent implantation on renal perfusion. A small sample size reduces the statistical power of the study, increasing the likelihood of Type II errors, where actual differences or effects may go undetected.

Additionally, some tests were conducted outside of the planned time frame due to disruptions caused by the COVID-19 pandemic. This also affected patient inclusion, as some individuals were unable or unwilling to attend follow-up visits, further limiting the study's scope.

This study did not include a control group of healthy individuals without coarctation or hypertension. Such a control group would have been challenging to obtain, as renal scintigraphy involves radioactive isotopes, specifically 99mTc-MAG3. From a bioethical perspective, it would be unacceptable to subject healthy individuals to this procedure solely for research purposes. Instead, we compared our findings with reference values from the literature, commonly used to assess normal renal perfusion in other pathologies. Additionally, we excluded patients younger than 18 years of age, as they represent a vulnerable population in clinical studies, and the use of 99mTc-MAG3 poses a radiation risk that is particularly concerning for pediatric patients.

The renal perfusion scan was conducted following the hospital’s methodology. However, there was no unified protocol for patient self-preparation for the scintigraphy, such as discontinuing medications or ensuring adequate saline volume during the scan. This inconsistency could be addressed by implementing a standardized patient checklist before the scan. Developing a comprehensive patient preparation protocol, including specific medication management and hydration guidelines, could enhance the accuracy and reliability of renal perfusion scans. By standardizing these preparatory steps, we can minimize variability and improve the diagnostic utility of the scans. Additionally, a second scan was performed 30 minutes after oral administration of the ACE inhibitor. It is possible that extending this interval to 60 minutes could allow more time for the ACEI to exert its full effect, potentially providing more accurate insights into the ACEI’s impact on renal perfusion.

This study was relatively short, limiting the ability to observe long-term trends in renal perfusion changes. Implementing a long-term follow-up protocol would provide more comprehensive data on the individual progression of renal perfusion changes over time. A more extended observation period could help identify patterns and correlations that are not apparent in a short-term study. This would enhance our understanding of how renal perfusion changes evolve, potentially leading to more effective interventions for hypertensive patients.

These factors must be considered when interpreting the study's conclusions. A larger, multicenter, randomized controlled trial would be necessary to overcome these limitations. Such a study would not only enhance the statistical power but also improve the representativeness and external validity of the findings, allowing for more definitive conclusions regarding the effects observed in our study. This approach would provide a more robust basis for clinical decision-making and guideline development.

8. CONCLUSIONS

1. Patients with coarctation of the aorta who have arterial hypertension demonstrate a delay in renal perfusion and renal clearance compared to those without hypertension.
2. Compared to other types of aortic arch, the Crenel-type (wide) aortic arch is characterized by renal parenchymal retention and reduced clearance function.
3. The presence of arterial hypertension in patients with coarctation of the aorta is associated with male gender, older age, broader aortic arch, and remaining echocardiographic gradient at the coarctation site.
4. Increased intima-media thickness and enhanced arterial distensibility in patients with coarctation of the aorta are correlated with an elevated risk of renal parenchymal retention.

9. RECOMMENDATIONS FOR CLINICAL PRACTICE

1. In patients with coarctation of the aorta and arterial hypertension, regular assessment of renal function should be incorporated into routine follow-up to detect early signs of renal impairment.
2. Patients with Crenel-type arches should be closely monitored by kidney imaging and functional assessments as they may have a higher risk of renal complications.
3. Given the association between hypertension and male gender, older age, wider aortic arch, and higher echocardiographic gradient, targeted hypertension management strategies should be employed, including earlier intervention and closer monitoring in these high-risk subgroups.

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11. SUMMARY

Aortos koarktacija (AoKo) yra viena dažniausių įgimtų širdies ydų, užimanti penktąją vietą pagal dažnumą. (1–5) Ši būklė pasižymi aortos susiaurėjimu, kuris sukelia kraujospūdžio padidėjimą viršutinėse galūnėse ir viršutinėje kūno dalyje, tuo pačiu sumažindamas kraujo tekėjimą į distaliau nuo susiaurėjimo esančias sritis.

Pagrindinis rizikos veiksnys šiems pacientams, ypač tiems, kuriems nebuvo atliktas chirurginis gydymas, yra nuolatinė arterinė hipertenzija viršutinėje kūno dalyje. (7) Hipertenzijos etiologija pacientams su AoKo yra laibai daugialypė. Ji apima likutinį susiaurėjimą, netipišką aortos lanko geometriją, endotelio disfunkciją, pakitusį arterijų lygiųjų raumenų reaktyvumą, aortos sienelės pakitimus, lemiančius padidėjusį arterijų standumą, ir sumažėjusį baroreceptorių jautrumą, kuris sukelia padidėjusį simpatinės nervų sistemos aktyvumą. (8–12)

Tarp mechanizmų, susijusių su AoKo ir hipertenzijos išlikimu po korekcijos, yra renino-angiotenzino-aldosterono sistemos aktyvacija, reiškinys taip pat stebimas renovaskulinės ligos atvejais. Inkstų scintigrafija su kaptopriliu yra diagnostinis testas, galintis nustatyti renovaskulines sąlygas ir prognozuoti gydymo atsaką. (13,14) Tyrimai parodė, kad inkstų scintigrafija turi aukštą jautrumą (87% iki 96%) ir specifiškumą (85% iki 95%) diagnozuojant inkstų arterijos stenozę ir renovaskulinę hipertenziją. (13,16) Kai kurie tyrimai rodo, kad teigiamas inkstų scintigrafijos rezultatas gali numatyti renovaskulinės hipertenzijos pagerėjimą po inkstų arterijos revaskuliarizacijos. (16,17)

Ankstyva diagnostika ir savalaikis chirurginis arba intervencinis gydymas tampa labai svarbūs, siekiant išvengti arterinės hipertenzijos išsivystymo. (18) Nepaisant sėkmingų ankstyvų intervencijų, išlieka didelė širdies ir kraujagyslių patologijų vystymosi rizika susijusi su sistemine arterine hipertenzija (AH) išliekančia maždaug 41% pacientų net ir praėjus 24 metams po pradinio chirurginio gydymo. (20) Dažniausias fenotipas pacientams su AoKo yra izoliuota sistolinė hipertenzija. (21)

Inkstų scintigrafija paprastai nėra naudojama kaip standartinis diagnostinis įrankis vertinant pacientus su AoKo, įtariamus dėl liekamosios hipertenzijos.

Tyrimo hipotezė:

Pacientai, sergantys negydyta natūralia aortos koarktacija arba tie, kuriems buvo atlikta chirurginė korekcija ir kurie turi arterinę hipertenziją, pasižymi sumažėjusia inkstų perfuzija, palyginti su pacientais, sergančiais natūralia ar chirurgiškai koreguota aortos koarktacija, bet neturinčiais arterinės hipertenzijos.

Tyrimo tikslas:

Pagrindinis šio tyrimo tikslas yra pirmą kartą žmonėms ištirti inkstų perfuzijos būklę pacientams, sergantiems negydyta natyvia arba koreguota aortos koarktacija, atsižvelgiant į hipertenzijos buvimą. Antrinis tikslas yra išnagrinėti ryšį tarp aortos lanko anatominių ypatybių, hipertenzijos ir inkstų kraujotakos.

Tyrimo uždaviniai:

1. Įvertinti arterinės hipertenzijos ryšį su inkstų perfuzija pacientams, sergantiems negydyta natūralia arba anksčiau koreguota aortos koarktacija.
2. Ištirti ryšį tarp aortos lanko tipo ir inkstų perfuzijos pacientams, sergantiems aortos koarktacijja.
3. Nustatyti veiksnius susijusius su hipertenzijos išsivystymu pacientams, sergantiems aortos koarktacija.
4. Įvertinti miego arterijų kraujagyslių remodeliacijos įtaką inkstų perfuzijai pacientams, sergantiems aortos koarktacija.
5. Išanalizuoti perkateterinių intervencijų dėl aortos koarktacijos poveikį inkstų kraujotakai.

Ginamieji teiginiai:

1. Arterinė hipertenzija pacientams, sergantiems aortos koarktacija, yra susijusi su inkstų perfuzijos sumažėjimu.
2. Aortos lanko morfologija susijusi su inkstų perfuzijos pokyčiais.
3. Arterinės hipertenzijos rizika pacientams, sergantiems aortos koarktacija, tiesiogiai susijusi su stenozės sunkumu.
4. Padidėjęs miego arterijų standumas pacientams, sergantiems aortos koarktacija, neigiamai įtakoja inkstų perfuziją.
5. Slėgio gradiento sumažėjimas po perkateterinių intervencijų pacientams, sergantiems kliniškai reikšminga aortos koarktacija, lemia inkstų perfuzijos pagerėjimą.

Inovatyvumas ir tyrimo naujumai

Nepaisant sėkmingų chirurginių ar intervencinių aortos koarktacijos korekcijų, pacientams ir vėliau gali išlikti rizika vėlyvoms komplikacijoms, tokioms kaip arterinė hipertenzija. Dabartinės klinikinės gairės daugiausia dėmesio skiria slėgio skirtumui tarp viršutinių ir apatinių galūnių mažinimui. Tačiau trūksta tyrimų apie gyvybiškai svarbių organų, ypač žemiau aortos susiaurėjimo, perfuzijos sutrikimus ir jų poveikį arterinės hipertenzijos valdymui. Šiame tyrime tiriami įvairūs veiksniai, kurie turi įtakos inkstų perfuzijai šioje pacientų grupėje. Mūsų žiniomis, tai pirmasis tyrimas, nagrinėjantis inkstų perfuziją pacientams, sergantiems aortos koarktacija. Įrodyta, kad inkstų scintigrafija pasižymi aukštu diagnostiniu tikslumu

nustatant kliniškai reikšmingą inkstų arterijos stenozę ir renovaskulinę hipertenziją. Tikimasi šio tyrimo rezultatais suteikti reikšmingų įžvalgų, siekiant priimti sprendimus dėl aortos koarktacijos korekcijos ir gydymo bei potencialiai gerinant pacientų gydymo rezultatus. Pacientai, kurių inkstų perfuzija sumažėjusi, gali gauti naudos iš ankstyvesnės intervencijos, o tie, kurių inkstų kraujotaka nepažeista, galėtų būti gydomi su aukštesniu chirurginio ar perkateterinio gydymo slenksčiu.

Tyrimo metodika

Šis prospektyvinis tyrimas buvo atliktas Vilniaus universiteto ligoninėje Santaros klinikose (VUL SK). Leidimą atlikti biomedicininį tyrimą suteikė Vilniaus regiono biomedicininių tyrimų etikos komitetas (Nr. 2019/5-1113-61). Šiame perspektyviniame tyrime buvo įtraukti suaugusieji, kuriems diagnozuota natūrali arba po korekcijos atlikta aortos koarktacija. Prieš įtraukiant į tyrimą, iš pacientų buvo gautas informuotas ir pasirašytas sutikimas dalyvauti.

Doktorantas Sigitas Čėsna parengė tyrimo įtraukimo ir stebėjimo protokolą. Doktorantas taip pat atrinko pacientus tyrimui, atliko invazines procedūras ir stebėjo pacientus.

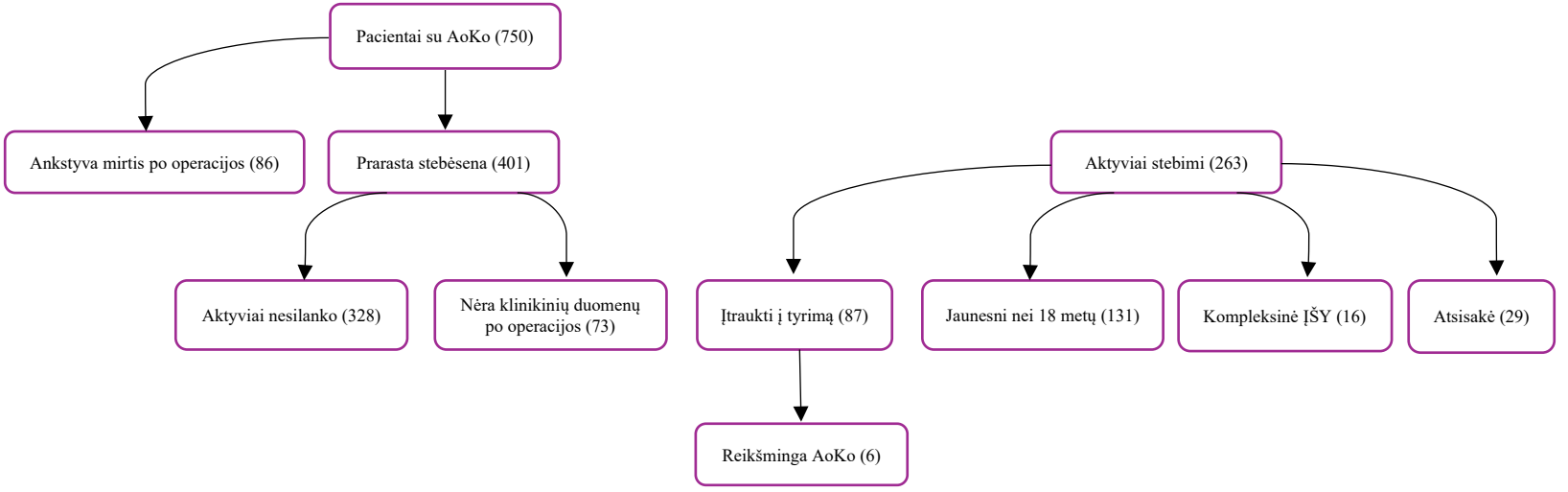
Įtraukimo kriterijai:

- Suaugę pacientai (> 18 metų)
- Pacientai su natyvine arba po chirurginio ar perkateterinio aortos koarktacijos gydymo.

Neįtraukomo kriterijai:

- Pacientai, sergantys sudėtingomis įgimtomis ligomis, susijusiomis su kairiosios širdies pažeidimais (pvz., ženkli likutinė aortos vožtuvo stenozė ar nesandarumas, mitralinio vožtuvo liga ar Shone sindromas)
- Nėščios pacientės arba planuojančios nėštumą tyrimo metu.

Potencialūs kandidatai įtraukimui į mūsų tyrimą buvo atrinkti iš mūsų suaugusiųjų įgimtų širdies ligų (ACHD) klinikos pacientų duomenų bazės (1 pav.). Šioje duomenų bazėje registruojami pacientai nuo 1964 metų. Pradiniam atrankos etapui buvo peržiūrėti asmenys, kurie anksčiau mūsų įstaigoje buvo chirurgiškai arba intervenciniu būdu gydyti dėl aortos koarktacijos, arba pacientai, turintys natūralią aortos koarktaciją.



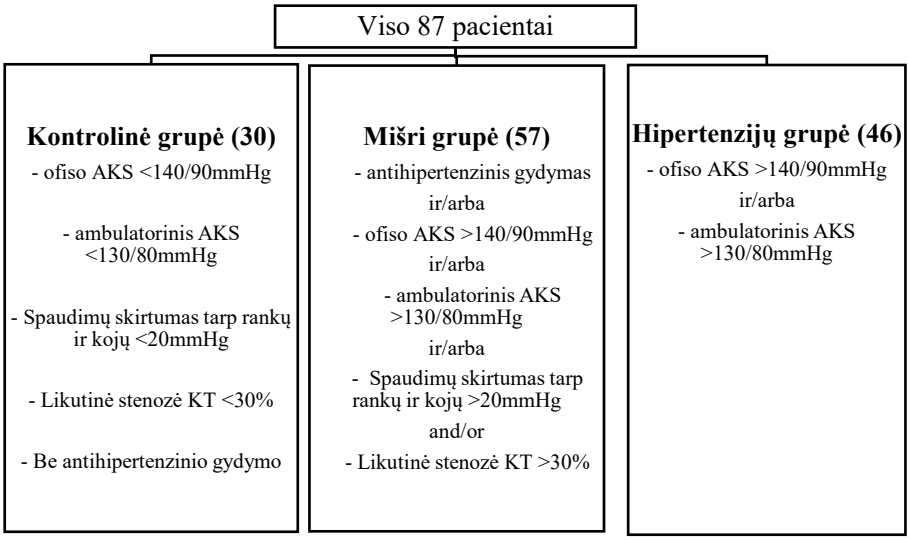
1 pav. Pacientų įtraukimo schema.

Iš viso buvo peržiūrėti 750 pacientai. Iš jų 86 pacientai mirė ankstyvuoju laikotarpiu po chirurginio aortos koarktacijos gydymo. 401 pacientas neatvyko į tolesnius apsilankymus pas įgimtų širdies ligų specialistą. Tarp jų 73 pacientai neturėjo jokių klinikinių duomenų duomenų bazėje, išskyrus chirurginį protokolą. Likę 328 pacientai buvo gyvi, tačiau jie arba aktyviai nesilank Suaugusiųjų įgimtų širdies ligų (ACHD) klinikoje, arba atsisakė atvykti į pakartotines konsultacijas dėl COVID-19 pandemijos.

Aktyviame stebėjimo sąraše buvo 263 pacientai, iš kurių pusė (131 pacientas) neatitiko amžiaus kriterijų, nes jiems buvo mažiau nei 18 metų. Šešiolika pacientų turėjo sudėtingas įgimtas širdies ligas ir nebuvo įtraukti į tyrimą. Be to, 29 pacientai atsisakė dalyvauti tyrime. Įtraukimo kriterijus atitiko 87 pacientai ir jie buvo įtraukti į tyrimą. Iš šių 87 pacientų šeši turėjo ženklią aortos koarktaciją ir atitiko perkateterinio gydymo reikalavimus.

87 pacientai buvo suskirstyti į grupes. Pirmąją grupę (Kontrolinė grupė) sudarė 30 pacientų, kuriems buvo diagnozuota aortos koarktacija, tačiau jie neturėjo arterinės hipertenzijos, jų sistolinis kraujospūdis tarp viršutinių ir apatinių galūnių nesiskyrė, o kompiuterinės tomografijos (KT) tyrime nebuvo reikšmingo susiaurėjimo (AoKo <30%). Likę 57 pacientai buvo įtraukti į antrąją grupę (Mišri grupė) (2 pav.). Taip pat buvo atlikta subanalizė Mišrios grupės daliai, kurią sudarė 46 pacientai (Hipertenzinė grupė). Šioje grupėje buvo tik tie pacientai, kuriems buvo užfiksuota arterinė hipertenzija, apibrėžta kaip ofiso kraujospūdis >140/90 mmHg arba ambulatorinis kraujospūdis o>130/80 mmHg, nepriklausomai nuo to, ar pacientai vartojo antihipertenzinius vaistus.

Likę 11 pacientų iš Mišrios grupės, kurie turėjo spaudimo skirtumą tarp rankų ir kojų arba turėjo daugiau nei 30% likutinę stenozę KT angiografijoje, tačiau neturėjo hipertenzijos, nebuvo atskirai suskirstyti į pogrupius.



2 pav. Pacientų suskirstymas į grupes.

Stebėjimo protokolas

Įtrauktų pacientų dalyvavimas tyrime truko 3-6mėn., per kuriuos buvo atlikti tyrimai (1 lentelė).

Lentelė 1. Tyrimo stebėjimo grafikas.

	Pradinis vizitas – 6 sav.	Širdies kateterizacija	3-6 mėn.
Sutikimo forma	X		
Įtraukimo/neįtraukimo kriterijai	X		
Epidemiologiniai duomenys ir ankščiau buvusios operacijos	X		
Medikamentinis gydymas	X		X
Spaudimo matavimas kabinete	X		X
Ultragarsinis širdies tyrimas	X		
Laboratoriniai kraujo tyrimai	X		
Intimos-medijos storio matavimas	X		
CAVI indekso matavimas	X		
24val. AKS matavimas	X		X
KT angiografija	X		
Inkstų scintigrafija	X		X

Arterinė hipertenzija buvo apibrėžiama kaip vidutinis dienos sistolinis kraujospūdis (SKS) ≥130 mmHg arba diastolinis kraujospūdis (DKS) ≥80 mmHg, matuojant naudojant ambulatorinį arterinio kraujospūdžio stebėjimą (aAKS), arba >140/90mmHg matuojant gydytojo kabinete.

Ženkli aortos koarktacija buvo apibrėžiama pagal kompiuterinės tomografijos (KT) angiografiją, kuomet buvo nustatomas ≥50% diametrų skirtumas tarp siauriausios vietos isthmus srityje ir nusileidžiančios aortos diafragmos lygyje.

Pacientams, kurie atitiko neinvazinius kriterijus perkateteriniam koarktacijos gydymui, buvo atliekama širdies kateterizacija. Ši procedūra apėmė angiografiją ir spaudimų matavimą ties ta vieta, kur buvo atliktas ankstesnis aortos koarktacijos chirurginis ar perkateterinis gydymas ar nustatyta siauriausia vieta KT angiografijos metu. Pacientams, kurių tiesiogiai matuoti maksimalūs gradientai per koarktacijos vietą viršijo 20 mmHg ir/arba kurių skersmens skirtumas tarp isthmus ir nusileidžiančios aortos diafragmos lygyje buvo ≥50%, buvo atliekama perkateterinis stento implantavimas. Šiam pacientų pogrupiui vėliau buvo atliekami pakartotiniai inkstų perfuzijos tyrimai.

Instrumentiniai tyrimai:

- AKS matavimas gydytojo kabinete.
- Ultragarsinis širdies tyrimas.
- Bendros Miego Arterijos Standumo ir Intima-Media Storio Matavimas.
- Širdies-Kulkšnies Kraujagyslių Indekso ir Kulkšnies-Žasto Indekso Matavimas.
- Arterijų Standumo ir Centrinio Arterinio Kraujospūdžio Vertinimas.
- 24val. AKS matavimas.
- Kompiuterinės tomografijos angiografija.
- Perkateterinis gydymas.
- Inkstų Scintigrafija. Tc-99m MAG3 ir I-131 OIH scintigramos vertinimo kriterijai (9):
  - Ženklus vienpusis parenchimos kaupimas po AKFI skyrimo.
  - Didesnis nei 0,15 prieš ir po AKFI 20 minučių/T_{max} santykio pokytis nurodo reikšmingai prailgėjusią perfuziją.
  - T_{max} padidėjimas bent 2 minutėmis arba 40% po AKFI nuorodo uždelstą kontrasto išskyrimą į inkstų geldelę.
  - Didesnis nei 10% pokytis santykiniame Tc-99m MAG3 kaupime po AKFI nurodo didelę renovaskulinės hipertenzijos tikimybę.

REZULTATAI

1 dalis. Pacientai sergantys aortos koarktacija ir turintys arterinę hipertenziją

Visų tyrime dalyvavusių pacientų vidutinis amžius buvo 28,7 metų (tarpkvartilinis intervalas: 22,9–37,6 metai). Šiek tiek didesnė dalis tyrimo dalyvių buvo vyrai – 55,2% (48 iš 87). Septyni pacientai turėjo natyvinę aortos koarktaciją (AoKo), o likusiems pacientams buvo atlikta chirurginė korekcija (daugiausia anastomozė galas su galu, 69 pacientams arba 86,3%) arba perkateterinis gydymas (4 pacientams arba 5,1%). Vidutinis amžius pirmosios operacijos metu buvo 6,37 metų (tarpkvartilinis intervalas: 1,2–11,79 metai), o nuo paskutinės operacijos buvo praėję vidutiniškai 8,7 metų (tarpkvartilinis intervalas: 4,16–15,88 metai).

87 pacientų, sergančių AoKo, kohorta buvo padalinta į dvi grupes: Kontrolinę grupę (n = 30) ir Mišrią grupę (n = 57), kaip aprašyta metodologijos skyriuje. Mišrioje grupėje buvo identifikuota Hipertenzinė pogrupė (n = 46), kurią sudarė pacientai, kuriems išliko hipertenzija, nepaisant to, ar jie vartojo antihipertenzinius vaistus, ar ne. 2 lentelėje pateikiamos klinikinės charakteristikos, naudotos pacientams į grupes suskirstyti.

Lentelė 2. Klinikinės charakteristikos pacientų skirstymui į grupes.

	Kontrolinė grupė, N=30 Mediana (Q1; Q3)	**Mišri grupė, N=57 Mediana (Q1; Q3)**	**Hipertenzijos grupė, N=46 Mediana (Q1; Q3)**	**P reikšmė**
Ofiso sAKS, mmHg	**128 (120; 128)*·****	**144 (140; 150)***	**144 (139; 153)****	***·****<0,001**
Ofiso dAKS, mmHg	**79 (71; 79)***	**82 (76; 90)***	81 (76; 88)	***0,028**
Ambulatorinis paros sAKS, mmHg	**116 (110; 118)*·****	**126 (119; 134)***	**130 (120; 134) ****	***·****<0,001**
Ambulatorinis paros dAKS, mmHg	71 (67; 74)	73.5 (68; 76)	73 (67; 76)	0,496
sAKS skirtumas DR-K, mmHg	**-13 (-22; -4)*·****	**2 (-25; 20)***	**5 (-21; 20,5) ****	***·****0,004**
AoKo stenozė KT angiografijoje, %	**14 (1; 20,2)*·****	**20.5 (9,3; 30,1)***	**20.7 (8,5; 30,4) ****	***·****0,018**
Antihipertenzinis gydymas, N (%)	**0*·****	**45 (79,9%)***	**45 (97,8%) ****	**<0,001**

sAKS – sistolinis arterinis kraujo spaudimas; dAKS – diastolinis arterinis kraujo spaudimas; DR – dešinė ranka; K – koja; KT – kompiuterinės tomografijos angiografija; * - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Mišrios grupių; ** - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Hipertenzijos grupių.

Ofiso ir ambulatoriniai kraujospūdžio matavimai bei klinikinės charakteristikos parodė statistiškai reikšmingus skirtumus tarp trijų grupių. Hipertenzinėje grupėje užfiksuotos didžiausios sistolinio ir diastolinio kraujospūdžio medianos, kurios reikšmingai skiriasi nuo Kontrolinės grupės.

Be to, pastebėti reikšmingi likutinės stenozės procentų skirtumai, atitinkamai kiekvienoje grupėje.

Tarp grupių buvo pastebėtas reikšmingas lyčių pasiskirstymo skirtumas, didžiausia vyrų dalis (80,6%) buvo Hipertenzinėje grupėje. Kalbant apie dabartinį pacientų amžių ar jų amžių pirmosios operacijos metu, reikšmingų skirtumų tarp grupių nebuvo. Kūno masės indeksas (KMI) visose grupėse buvo normos ribose, be reikšmingų skirtumų. Svarbu paminėti, kad visi septyni pacientai, sergantys natyvine aortos koarktacija, buvo Mišrioje grupėje, iš kurių 6 pacientai turėjo nepakankamą antihipertenzinį gydymą. Daugumai pacientų visose grupėse buvo atlikta chirurginė anastomozė galas su galu, tačiau statistiškai reikšmingų skirtumų nebuvo (3 lentelė).

Lentelė 3. Pagrindinės klinikinės charakteristikos.

	Kontrolinė grupė, N=30 Mediana (Q1; Q3)	**Mišri grupė, N=57 Mediana (Q1; Q3)**	**Hipertenzijos grupė, N=46 Mediana (Q1; Q3)**	**P reikšmė**
Vyriška lytis, n (%)	**9 (30%)*,****	**39 (68,4%)***	**29 (80,6%)****	***,****<0,001**
Amžius, m	28,8 (23,5; 35,1)	28.7 (22,9; 37,6)	28,4 (22,8; 36,8)	0,872
Amžius pirmos operacijos metu, m	5,77 (0,76; 12,75)	6.56 (1,7; 10,68)	5,81 (1,63; 12,14)	0,995
Laikas nuo paskutinės operacijos, m	8,92 (4,16; 14,95)	8.7 (4,98; 16,13)	8,93 (3,66; 17,19)	0,483
Natyvinė AoKo, n (%)	**0*,****	**7 (12.3%)***	**6 (13%)****	***,****0,065**
KMI	23,9 (21,1; 26)	24.2 (21,9; 27,5)	24,4 (22,3; 27,5)	0,195
Operacijos tipas				
Anastomozė gals su galu (%)	27 (90%)	42 (84%)	33 (82,5%)	0,463
Goretex	1 (3,3%)	-	-	
Homotransplantatas	-	2 (4%)	1 (2,5%)	
Perikardo lopas	2 (6,7%)	1 (2%)	1 (2,5%)	
Poraktikaulinis lopas	-	1 (2%)	1 (2,5%)	
Stentas	-	4 (8%)	4 (10%)	

KMI – kūno masės indeksas. * - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Mišrios grupių; ** - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Hipertenzijos grupių.

KT angiografijos rezultatai parodė, kad Hipertenzinėje grupėje buvo reikšmingai didesnis vidutinis aortos lanko plotis, kartu su didesniu lanko kampu ir mažesniu aukščio ir pločio santykiu (A/P) (4 lentelė). Šis sumažėjęs A/P santykis, daugiausia dėl padidėjusio pločio, rodo mažiau palankią aortos lanko konfigūraciją pacientams sergantiems hipertenzija. Tiksliau sakant, ši konfigūracija labiau atitinka Crenel-tipo morfologiją, būdingą Hipertenzinei grupei, nei Gotikinį lanką labiau būdingą Kontrolinėje grupėje. Nepaisant šių aortos matmenų skirtumų, aortos lanko aukštis tarp grupių statistiškai reikšmingai nesiskyrė. Tai leidžia manyti, kad nors hipertenzija sergantiems

pacientams ryškūs pločio ir kampo pokyčiai, bendras lanko vertikalus aukštis išlieka panašus abiejose grupėse.

Lentelė 4. Kompiuterinės tomografijos duomenys.

	Kontrolinė grupė, N=30 Mediana (Q1; Q3)	**Mišri grupė, N=57 Mediana (Q1; Q3)**	**Hipertenzijos grupė, N=46 Mediana (Q1; Q3)**	**P reikšmė**
Ao lanko aukštis, mm	46,5 (41; 53,4)	45,7 (40,6; 52,3)	46,5 (41,1; 52,4)	0.920
Ao lanko plotis, mm	**59,4 (56,4; 61,6)*,****	**63,1 (58,9; 73,9)***	**62.9 (58,9; 75,5)****	***,****0,011**
Ao lanko A/P santykis	**0,8 (0,7; 0,9)***	**0.7 (0,6; 0,8)***	**0,7 (0,6; 0,8) ****	***,****0,048**
Ao lanko kampas, laipsniais	**66 (56,5; 71,1)***	**69 (64,7; 76,4)***	68,8 (64,2; 76)	***0,014**
Liekamoji AoKo stenozė, %	**14 (1; 20,2)*,****	**20,5 (9,3; 30,1)***	**20,7 (8,5; 30,4)****	***,****0,018**

A/P - ilgio ir pločio santykis. * - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Mišrios grupių; ** - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Hipertenzijos grupių.

Nors pulsinės bangos greitis ir kulkšnies indeksas statistiškai reikšmingai nesiskyrė, Hipertenzinėje grupėje buvo pastebėtas storesnis dešinės bendrosios miego arterijos intimos-medijos sluoksnis, tačiau kairėje pusėje nenustatytas toks skirtumas. Šis sustorėjimas dešinėje buvo susijęs su statistiškai reikšmingu išsitempimo padidėjimu. Nepaisant šio lokalizuoto arterijų išsitempimo pokyčio, arterijų standumas abiejose miego arterijose išliko panašus tarp grupių.

Mišrioje grupėje daugumai pacientų (57,9%) nereikėjo antihipertenzinio gydymo arba buvo gydomi tik vienu vaistu. Tačiau 42,1% pacientų (34 iš 57) vartojo daugiau nei du antihipertenzinius vaistus. Dauguma pacientų buvo gydomi beta adrenoblokatoriais, AKF inhibitoriais arba kalcio kanalų blokatoriais. Didesnė dalis pacientų Hipertenzinėje pogrupėje vartojo šiuos vaistus, ir tarp grupių buvo pastebėtas statistiškai reikšmingas skirtumas.

Inkstų scintigrafijos matavimai prieš AKF inhibitorių skyrimą neparodė reikšmingų skirtumų tarp grupių inkstų kaupime ar laike iki maksimumo (T_{max}) abiejuose inkstuose (5 lentelė).

Lentelė 5. Pradiniai inkstų perfuzijos matavimai.

	Kontrolinė grupė, N=30 Mediana (Q1; Q3)	**Mišri grupė, N=57 Mediana (Q1; Q3)**	**Hipertenzijos grupė, N=46 Mediana (Q1; Q3)**	**P reikšmė**
Kaupimas, %				
Kairysis inkstas	53,7 (50,1; 55,6)	53 (49; 57.9)	51.6 (48,4; 58)	0,597
Dešinysis inkstas	46,3 (44.4; 49.9)	47 (42,1; 51,1)	48,4 (42; 51,8)	0,679
T_{max}, min				
Kairysis inkstas	2,9 (2,3; 3,2)	3 (2,7; 3,7)	3 (2,8; 3,6)	0,264
Dešinysis inkstas	3,3 (2,7; 3,9)	3,4 (2,9; 4)	3,4 (3; 3,9)	0,514
T_{max}/T½ santykis				
Kairysis inkstas	4,8 (4; 6,3)	5,6 (4,5; 7)	5,5 (4,8; 6,8)	0,070
Dešinysis inkstas	6,3 (4,3; 8)	7.1 (5,5; 10)	7 (5,5; 9,3)	0,118
30min/T_{max} santykis				
Kairysis inkstas	**0,1 (0,1; 0,1)*,****	**0,1 (0,1; 0,2)***	**0,1 (0,1; 0.2)****	***,****0,032**
Dešinysis inkstas	**0,1 (0,1; 0,2)*,****	**0,2 (0,1; 0,2)***	**0,2 (0,1; 0,2)****	***,****0,035**
20min/3min santykis				
Kairysis inkstas	**0,1 (0,1; 0,2)*,****	**0,2 (0,1; 0,2)***	**0,2 (0,1; 0,2)****	***,****0,035**
Dešinysis inkstas	**0,2 (0,1; 0,2)*,****	**0.2 (0,1; 0,3)***	**0,2 (0,1; 0,3)****	***,****0,043**
Kaupimas po AKFI, %				
Kairysis inkstas	53,8 (50,8; 60,4)	52,1 (49,8; 56,2)	51,7 (49,6; 56,9)	0.190
Dešinysis inkstas	46,2 (39,6; 49,2)	47,6 (43,8; 50,3)	47.9 (43,1; 50,4)	0,225
T_{max} po AKFI, min				
Kairysis inkstas	**2,8 (2,7; 3,6)*,****	**3,2 (2,7; 3,9)***	**3,1 (2,7; 3,9)****	***,****0,042**
Dešinysis inkstas	**3 (2,7; 3,7)*,****	**3,6 (3,2; 5,2)***	**3,6 (3,3; 5,2)****	***,****0,017**
T_{max}/ T½ santykis po AKFI				
Kairysis inkstas	4,8 (4,3; 6,3)	5 (4; 7)	5,3 (4; 7)	0,483
Dešinysis inkstas	5,8 (4,8; 7,8)	6 (5,3; 7,8)	6,3 (5,3; 9,3)	0,265
30min/T_{max} santykis po AKFI				
Kairysis inkstas	0,1 (0,1; 0,2)	0,2 (0,1; 0,2)	0,1 (0,1; 0,2)	0.068
Dešinysis inkstas	0,2 (0,1; 0,2)	0,2 (0,1; 0,3)	0,2 (0,1; 0,3)	0,111
20min/3min santykis po AKFI				
Kairysis inkstas	**0,1 (0,1; 0,2)*,****	**0,2 (0,1; 0,2)***	**0,2 (0,1; 0,2)****	***,****0,029**
Dešinysis inkstas	**0,2 (0,1; 0,2)***	**0,2 (0,2; 0,3)***	0,2 (0,2; 0,4)	***0,033**

T_{max} - laikas iki maksimalios skaičiavimų reikšmės, T½ - laikas iki pusinio piko skaičiavimų reikšmės, 30 min/T_{max} - inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų, 20 min/3 min = skaičiavimų santykis po 20 minučių iki skaičiavimų po 3 minučių; * - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Mišrios grupių; ** - statistiškai reikšmingi skirtumai tarp Kontrolinės ir Hipertenzijos grupių.

Abiejų inkstų vidutinis kaupimas buvo gana panašus visose grupėse, tai rodo išsaugotą inkstų absorbcijos funkciją. Tačiau vertinant inkstų funkcijos parametrus išryškėjo ženklesni pakitimai. Mišrioje ir Hipertenzinėje grupėse T_{max} vertės buvo šiek tiek ilgesnės nei Kontrolinėje grupėje, nors šie skirtumai nebuvo statistiškai reikšmingi. Šis nedidelis vėlavimas iki didžiausio inkstų aktyvumo gali reikšti lengvą inkstų reakcijos sumažėjimą, ypač hipertenzija sergantiems asmenims. Tačiau statistinio reikšmingumo nebuvimas rodo, kad šie matuojami skirtumai gali neturėti didelės klinikinės reikšmės.

Ryškesni skirtumai buvo pastebėti 30min/T_{max} ir 20min/3min santykių rodikliai, kai Mišrioje ir Hipertenzinėje grupėse buvo pastebėtos reikšmingai aukštesnės vertės. Šie padidėję santykių rodikliai rodo sutrikusį inkstų klirensą šiose grupėse, kas atspindi ankstyvus sumažėjusios inkstų funkcijos požymius. Ypač ilgesnis klirenso laikas po AKF inhibitorių vartojimo rodo, kad Mišrios ir Hipertenzinės grupės pacientų inkstai lėčiau apdoroja ir pašalina medžiagas, kas gali reikšti ankstyvą inkstų funkcijos sutrikimą.

Lentelė 6. Inkstų perfuzijos pokyčiai prieš ir po AKFI.

	Kontrolinė grupė, N=30 Mediana (Q1; Q3)	**Mišri grupė, N=57 Mediana (Q1; Q3)**	**Hipertenzijos grupė, N=46 Mediana (Q1; Q3)**	**P reikšmė**
Δ Kaupimas				
Kairysis inkstas	2,5 (-0,9; 9,2)	0,7 (-3,2; 3,7)	0,9 (-3,3; 4,3)	0,121
Dešinysis inkstas	-2,3 (-10,1; 1,1)	-0,8 (-3,9; 4,5)	-1,2 (-5,5; 3,6)	0,072
Δ T_{max}				
Kairysis inkstas	1,3 (-12,8; 31,6)	2,4 (-10,8; 35,5)	2,5 (-10,4; 35,5)	0,195
Dešinysis inkstas	4,7 (-25,9; 25,7)	9,5 (-2,2; 48,6)	8,9 (-1,8; 57,9)	0,203
Δ T_{max}/T½ santykis				
Kairysis inkstas	0 (-22,7; 28,6)	-4 (-27,6; 30,8)	0 (-23,8; 40)	0,419
Dešinysis inkstas	2.8 (-31,6; 30)	-12,9 (-36; 29,4)	-10,7 (-22,2; 30)	0.764
Δ 30min/T_{max} santykis				
Kairysis inkstas	0 (-16,7; 45,5)	3,6 (-11,8; 37,5)	0 (-10; 35,3)	0,594
Dešinysis inkstas	9,1 (-9,5; 54,5)	7,4 (-16,7; 36,4)	7,7 (-11,8; 36,4)	0,340
Δ 20min/3min santykis				
Kairysis inkstas	0 (-18,2; 37,5)	0 (-16,7 (38,9)	0.(-12,5; 38,9)	0,604
Dešinysis inkstas	0 (-18,8; 42,9)	0 (-19; 33,3)	0 (-14,9; 23,8)	0,424

Δ - pokytis prieš ir po AKFI; T_{max} - laikas iki maksimalios skaičiavimų reikšmės, T½ - laikas iki pusinio piko skaičiavimų reikšmės, 30 min/T_{max} - inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų, 20 min/3 min - skaičiavimų santykis po 20 minučių iki skaičiavimų po 3 minučių.

Reikšmingi T_{max} skirtumai ženklesni dešiniajame inkste, kur Mišrioje ir Hipertenzinėje grupėse T_{max} vertės buvo ilgesnės nei Kontrolinėje grupėje. Tai rodo, kad AKF inhibitorių vartojimas lėtina laiką iki aukščiausio inkstų veiklos aktyvumo lygio šiose grupėse, atspindėdamas lėtesnę perfuziją. Priešingai, reikšmingi skirtumai 30min/T_{max} ir 20min/3min santykių rodikliuose buvo pastebėti kairiajame inkste, rodantys pablogėjusį klirensą po AKF inhibitorių vartojimo Mišrioje ir Hipertenzinėje grupėse.

Lyginant prieš AKF inhibitorių ir po jų vartojimo atliktus matavimus, inkstų funkcijos rodiklių pokyčiai nė vienoje grupėje nepasiekė statistinio reikšmingumo (6 lentelė). Tai rodo, kad inkstų funkcija, vertinant pagal išmatuotus parametrus, išlieka santykinai stabili, nepriklausomai nuo hipertenzijos būklės.

Logistinė regresinė analizė buvo atlikta su arterine hipertenzija kaip priklausomu kintamuoju, siekiant įvertinti įvairius epidemiologinius ir klinikinius parametrus (7 lentelė). Analizė atskleidė keletą reikšmingų arterinės hipertenzijos prognostinių veiksnių.

Lentelė 7. Vienmatė logistinė regresija dėl arterinės hipertenzijos.

	Šansų santykis (95% PI)	P reikšmė
Amžius	1,010 (0,970-1,052)	0,628
Amžius pirmos operacijos metu	1,000 (1,000-1,000)	0,792
KMI	1,037 (0,949-1,135)	0,420
Vyriška lytis	**3,928 (1,605-9,610)**	**0,003**
Ao lanko aukštis	0,979 (0,930-1,030)	0,404
Ao lanko plotis	**1,065 (1,011-1,121)**	**0,018**
Ao lanko A/P santykis <0.65	**5,833 (1,655-20,559)**	**0,023**
Ao lanko kampas	**1,090 (1,031-1,154)**	**0,003**
AoKo/AoD santykis	0,230 (0,029-1,844)	0,167
AoKo/ T2 santykis	0,486 (0,090-2,628)	0,402
AoKo stenozė KT angiografijoje	1,019 (0,987-1,052)	0,255
Gradientas AoKo (echo)	**1,050 (1,006-1,096)**	**0,025**
PBG	1,108 (0,713-1,723)	0,649
Dešinė CAVI	0,735 (0,411-1,316)	0,301
Kairė CAVI	0,811 (0,455-1,444)	0,476
Kreatininas	**1,073 (1,014-1,136)**	**0,014**
eGFR	0,994 (0,986-1,002)	0,155
Δ T_{max}, kairysis inkstas	1,119 (0,903-1,388)	0,304
Δ T_{max}, dešinysis inkstas	1,004 (0,817-1,235)	0,967
Δ 30min/T_{max} santykis, kairysis inkstas	0,081 (<0,001-27,595)	0,398
Δ 30min/T_{max} santykis, dešinysis inkstas	0,202 (0,007-6,039)	0,356
Δ 20min/3min santykis, kairysis inkstas	0,785 (0,020-31,229)	0,898
Δ 20min/3min santykis, dešinysis inkstas	0,529 (0,067-4,158)	0,545

Ao – aorta; A/P santykis – aortos aukščio ir pločio santykis; KMI – kūno masės indeksas; AoKo – aortos koarktacija; AoD – aorta ties diafragmos lygiu; T2 – aortos lankas tarp miego arterijų; PBG – pulsinės bangos greitis; CAVI – kardiokulkšnies kraujagyslių indeksas; Δ – skirtumas tarp matavimų prieš ir po AKF inhibitorių vartojimo; T_{max} - laikas iki maksimalios skaičiavimų reikšmės, T½ - laikas iki pusinio piko skaičiavimų reikšmės, 30 min/T_{max} - inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų, 20 min/3 min - skaičiavimų santykis po 20 minučių iki skaičiavimų po 3 minučių.

Vyriška lytis buvo susijusi su reikšmingai didesne arterinės hipertenzijos tikimybe, vyrams turint maždaug 3,9 karto didesnę tikimybę, palyginti su moterimis (P = 0,003). Aortos lanko pločio padidėjimas vienu milimetru arterinės hipertenzijos išsivystymo tikimybę didina 6,5%, ir ši sąsaja buvo statistiškai reikšminga (P = 0,018).

Mažesnis aortos aukščio ir pločio (A/P) santykis, rodantis Crenel-tipo lanko morfologiją, buvo reikšmingai susijęs su didesne hipertenzijos rizika. Mažesnio A/P santykio pacientų hipertenzijos išsivystymo šansų santykis buvo svarbus veiksnys (OR 5,833) (P = 0,0023). Taip pat padidėjęs aortos lanko kampas buvo susijęs su didesne hipertenzijos rizika. Aortos lanko kampo padidėjimas vienu laipsniu hipertenzijos tikimybę padidina 9% (P = 0,003).

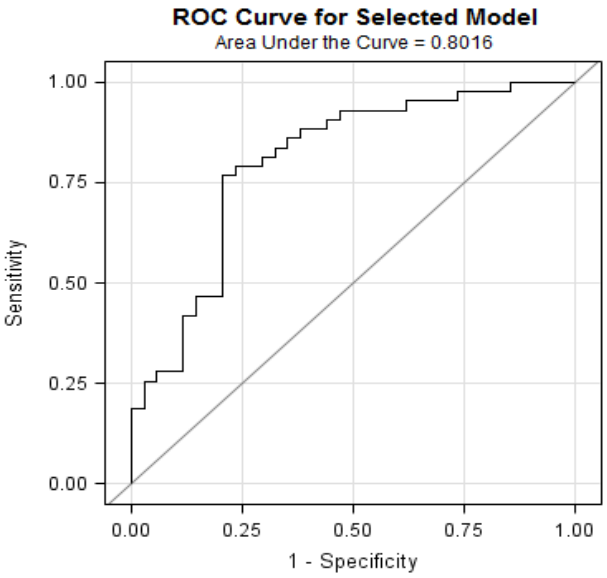
Echokardiografiškai išmatuotas gradientas per AoKo buvo teigiamai susijęs su arterine hipertenzija – kiekvienam mmHg gradiento padidėjimui hipertenzijos rizika išaugo 5% (P = 0,025) (5 pav.).

Buvo sukurtas daugiamatės logistinės regresijos modelis, siekiant įvertinti įvairių nepriklausomų kintamųjų bendrą poveikį arterinės hipertenzijos tikimybei (8 lentelė).

Lentelė 8. Daugiamatės logistinės regresijos modelis arterinei hipertenzijai.

	Šansų santykis (95% PI)	P reikšmė
Vyriška lytis	3,820 (1,320-11,053)	0,013
Ao lanko A/P santykis> 0.85 (Gotikinis lankas)		n.s.s.
Ao lanko kampas	1,095 (1,023-1,171)	0,009
Gradientas AoKo (echo)	1,061 (1,009-1,115)	0,020

Šiame modelyje vyriška lytis, aortos lanko kampas ir echokardiografiškai išmatuotas AoKo gradientas buvo statistiškai reikšmingi hipertenzijos prognostiniai faktoriai. Priešingai, aortos lanko A/P santykis >0,85 neturėjo reikšmingo poveikio AH rizikai. Vyrai turėjo beveik keturis kartus didesnę tikimybę susirgti hipertenzija, palyginti su moterimis. Platesnis aortos lanko kampas buvo susijęs su reikšmingai didesne AH rizika, tai reiškia, kad šis anatominis variantas gali prisidėti prie padidėjusio kraujospūdžio. Be to, didesnis AoKo gradientas, matuojamas echokardiografijos metu, buvo reikšmingai susijęs su didesne AH rizika. Modelis pasižymi gera galia, kurio kreivės po ROC plotas (AUC) siekia 0,8016, tai rodo jo galimą naudingumą klinikinėje praktikoje nustatant asmenis, kuriems yra didesnė arterinės hipertenzijos išsivystymo rizika (6 pav.).



3 pav. ROC kreivė daugiamatei logistinės regresijos modeliui dėl arterinės hipertenzijos.

2 dalis. Grupių rezultatai, susiję su aortos lanko morfologija

Šioje dalyje analizuojama aortos lanko morfologija ir jos sąsaja su inkstų perfuzija (9 lentelė).

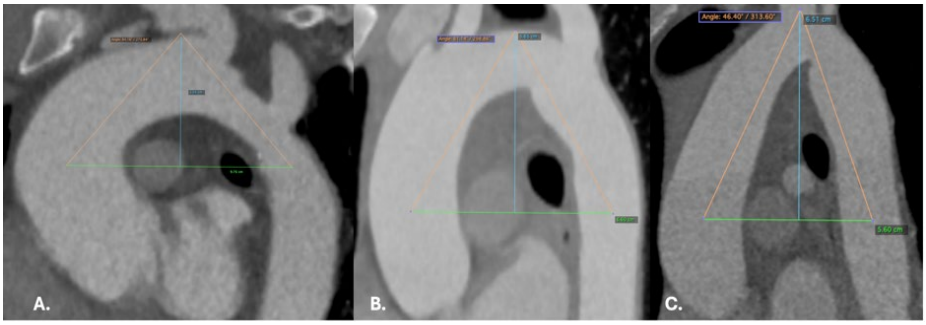
Lentelė 9. Aortos lanko parametrų ir inkstų scintigrafijos koreliacijų lentelė.

	Ao lanko aukštis	Ao lanko plotis	Ao lanko A/P santykis	Ao lanko kampas	AoKo/AoD santykis	AoKo stenozė
Prieš AKFI						
T_{max} KI	0,162	0,18962	0,005	-0,04251	0,004	0,06
P reikšmė	0,185	0,1214	0,961	0,7327	0,973	0,625
T_{max} DI	0,076	0,30867	-0,17	0,16705	0,003	0,053
P reikšmė	0,532	0,0099	0,1615	0,1733	0,974	0,662
T_{max}/T½ santykis KI	0,06	0,4122	-0,276	0,26581	0,051	-0,09
P reikšmė	0,622	0,0005	0,022	0,0297	0,676	0,460
T_{max}/T½ santykis DI	0,046	0,26312	-0,187	0,1985	-0,046	0,093
P reikšmė	0,703	0,0289	0,12	0,1046	0,703	0,445
30min/T_{max} santykis KI	0,055	0,3453	-0,263	0,24393	-0,081	0,085
P reikšmė	0,654	0,0039	0,029	0,0467	0,51	0,488
30min/T_{max} santykis DI	0,005	0,18609	-0,177	0,21627	-0,071	0,084
P reikšmė	0,965	0,1258	0,145	0,0765	0,56	0,489
Po AKFI,						
T_{max} KI	-0,019	0,28883	-0,242	0,12301	0,002	0,018
P reikšmė	0,876	0,0169	0.04	0,3213	0,985	0,883
T_{max} DI	-0,136	0,27537	-0,33	0,22101	-0,151	0,09
P reikšmė	0,265	0,022	0,005	0,0701	0,215	0,46
T_{max}/T½ santykis KI	0,101	0,13618	-0,109	-0,02934	-0,012	0,062
P reikšmė	0,412	0,2682	0,374	0,8137	0,918	0,614
T_{max}/T½ santykis DI	-0,013	0,15696	-0,208	0,09349	-0,09	0,0937
P reikšmė	0,915	0,1977	0,085	0,4483	0,459	0,4437
30min/T_{max} santykis KI	0,169	0,21032	-0,069	0,12545	-0,144	0,2107
P reikšmė	0,166	0,0852	0,575	0,3118	0,240	0,0845
30min/T_{max} santykis DI	0,034	0,16452	-0,127	0,14249	-0,256	0,296
P reikšmė	0,77	0,1767	0,295	0,2464	0,033	0,013

T_{max} - laikas iki maksimalios skaičiavimų reikšmės, T½ - laikas iki pusinio piko skaičiavimų reikšmės, 30 min/T_{max} - inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų.

Aortos lanko ilgis rodo statistiškai reikšmingas teigiamas koreliacijas su T_{max} tiek prieš, tiek po AKF inhibitorių vartojimo abiejuose inkstuose. Be to, jis teigiamai koreliuoja su $T_{max}/T½$ santykiu prieš AKF inhibitorių vartojimą, kas rodo galimą ryšį tarp aortos lanko ilgio ir inkstų funkcijos parametrų. Statistiškai reikšminga neigiama koreliacija pastebima tarp aukščio ir pločio santykio (A/P), $T_{max}/T½$ santykio ir 30min/T_{max} santykio kairiajame inkste prieš AKF inhibitorių vartojimą, tačiau dešiniajame inkste šios koreliacijos nėra. Vis dėlto abiejuose inkstuose buvo teigiama koreliacija su T_{max} po AKF inhibitorių vartojimo.

Po pradinės analizės pacientai metodiškai suskirstyti į tris grupes pagal aortos lanko aukščio ir pločio (A/P) santykį (4 pav.): 1 grupė apima pacientus, kurių A/P santykis yra mažesnis nei 0,65; 2 grupę sudaro tie, kurių santykis yra tarp 0,65 ir 0,85; o 3 grupė buvo sudaryta iš pacientų, kurių A/P santykis viršija 0,85. 1 grupės pacientams būdinga „Crenel“ tipo (plataus) lanko morfologija, o 3 grupės pacientai atitinka Gotikinį aortos lanko morfologiją. 2 grupės pacientai turi normalios formos lanką (10 lentelė).



4 pav. Aortos lanko morfologijos skirstymas. A. Crenel tipo lanko morfologija (A/P santykis <0,65). B. Normalaus tipo aortos lanko morfologija (A/P santykis 0,65 – 0,85). C. „Gotikinis aortos lankas (A/P santykis >0,85).

1 grupę sudarė 35,09% visų pacientų (28 pacientai), 2 grupę – 38,5% (30 pacientų), o 3 grupę – 25,6% (20 pacientų). Morfologiniai aortos lanko matmenų pokyčiai, tokie kaip aukštis, plotis ir kampas, buvo analizuojami pagal pacientų suskirstymą 9 lentelėje. Tokiuose parametruose kaip likutinė stenozė ir augimo indeksas tarp grupių reikšmingų skirtumų nepastebėta.

Lentelė 10. Morfologiniai pokyčiai KT angiografijoje.

	Grupė 1 (A/P <0,65) Mediana (Q1-Q3)	**Grupė 2 (A/P 0,65-0,85) Mediana (Q1-Q3)**	**Grupė 3 (A/P >0,85) Mediana (Q1-Q3)**	**P reikšmė**
KT angiografija				
Ao lanko aukštis, mm	**39,9 (36,4; 43,25)*** **	**47,05 (42,5; 52,4)*** **	**53,6 (51,05; 57,75)*** **	***<0,001**
Ao lanko plotis, mm	**69,7 (60,4; 84,05)*** **	**62,45 (60,4; 67,9)*** **	**56,85 (53,8; 58,9) *** **	***<0,001**
Ao lanko aukščio ir pločio santykis (A/P)	**0,58 (0,51; 0,61)*** **	**0,73 (0,7; 0,79)*** **	**0,94 (0,9; 0,98) *** **	***<0,001**
Ao lanko kampas, laipsniai	**76,61 (73,14; 83,74) *** **	**67,22 (64,95; 69,5) *** **	**57,11 (54,64; 59,24) *** **	***<0,001**
Liekamoji AoKo stenozė, %	20,76 (5,83; 26,55)	17,32 (9,33; 26,14)	15,36 (7,89; 23,85)	0,730

Ao – aorta; H/W santykis – aukščio ir pločio santykis. *** - statistiškai reikšmingi skirtumai tarp visų grupių.

Statistiškai daugiau vyrų buvo pirmojoje grupėje, taip pat šioje grupėje nustatyta didesnė vidutinė kūno paviršiaus ploto (BSA) vertė. Be to, plataus aortos lanko grupėje hipertenzija (AH) buvo žymiai dažnesnė nei kitose grupėse. Statistiškai reikšmingų amžiaus skirtumų tarp grupių nenustatyta (11 lentelė).

Lentelė 11. Bazinės charakteristikos.

	Grupė 1 (A/P <0,65) Mediana (Q1-Q3)	**Grupė 2 (A/P 0,65-0,85) Mediana (Q1-Q3)**	**Grupė 3 (A/P >0,85) Mediana (Q1-Q3)**	**P reikšmė**
Pacientai	28 (35.1%)	30 (38.5)	20 (25.6)	
Vyriška lytis, N (%)	19 (67.9)	17 (56.7)	7 (35)	0.067
Amžius, m	29.2 (23.4; 38.6)	28.6 (23.6; 36)	30.5 (22.5; 38.4)	0.951
Amžius operacijos metu, m	6.07 (0.48; 9.65)	7.69 (1.7; 14.12)	4.71 (1.77; 10.89)	0.577
Natyvinė AoKo, N (%)	2 (7.1)	3 (10)	2 (10)	0.705
Arterinė hipertenzija	**20 (71.43%)*** **	**17 (56.6%)*** **	**5 (25%)*** **	***<0.005**
KPP	**2.01 (1.91; 2.23) *** **	**1.88 (1.75; 2.04) *** **	**1.76 (1.61; 1.89) *** **	***<0.001**

KPP – kūno paviršiaus plotas.

Inkstų perfuzijos vertinimai, išsamiai aprašyti 12 lentelėje, atlikti visose trijose grupėse po kaptoprilio skyrimo, neatskleidė statistiškai reikšmingų skirtumų. Kairiojo inksto T_{max} medianų pokyčiuose stebėta ilgėjimo tendencija prieš AKFI vartojimą pacientams su siauru aortos lanku (Gotikinio tipo lankas).

Lentelė 12. Inkstų perfuzijos rezultatai pacientams su skirtinga aortos lanko morfologija.

	Grupė 1 (A/P <0,65) Mediana (Q1-Q3)	**Grupė 2 (A/P 0,65-0,85) Mediana (Q1-Q3)**	**Grupė 3 (A/P >0,85) Mediana (Q1-Q3)**	**P reikšmė**
Kaupimas, %				
Kairysis inkstas	53,04 (47,77; 56,53)	54,13 (49,16; 57,87)	51,5 (49,72; 54,48)	0,532
Dešinysis inkstas	46,96 (43,47; 52,23)	45,87 (42,13; 50,84)	48,5 (45,52; 50,28)	0,465

	Grupė 1 (A/P <0,65) Mediana (Q1-Q3)	Grupė 2 (A/P 0,65-0,85) Mediana (Q1-Q3)	Grupė 3 (A/P >0,85) Mediana (Q1-Q3)	P reikšmė
T_{max}, min				
Kairysis inkstas	2,91 (2,39; 3,8)	3,01 (2,75; 3,6)	3,21 (2,71; 3,98)	0,688
Dešinysis inkstas	3,48 (2,79; 4,02)	3,38 (3; 3,98)	3,21 (2,78; 3,76)	0,618
T_{max}/T½ santykis				
Kairysis inkstas	6,5 (4,5; 7,25)	5,38 (4,25; 6,5)	5 (4,5; 5,75)	0,140
Dešinysis inkstas	7,25 (6; 10,75)	6,5 (4,75; 9)	6,25 (5,5; 9,5)	0,394
30min/T_{max} santykis				
Kairysis inkstas	0,14 (0,11; 0,19)	0,12 (0,1; 0,14)	0,12 (0,09; 0,13)	0,088
Dešinysis inkstas	0,2 (0,14; 0,24)	0,14 (0,12; 0,21)	0,14 (0,13; 0,18)	0,198
20min/3min santykis				
Kairysis inkstas	0,16 (0,12; 0,2)	0,14 (0,12; 0,18)	0,16 (0,12; 0,2)	0,735
Dešinysis inkstas	0,21 (0,14; 0,28)	0,16 (0,13; 0,23)	0,18 (0,15; 0,27)	0,580
Kaupimas po AKFI, %				
Kairysis inkstas	52,37 (50; 58,74)	54,59 (50,69; 57,94)	52,21 (48,75; 54)	0,297
Dešinysis inkstas	46,81 (41,26; 50)	45,41 (42,06; 49,31)	47,79 (46; 51,25)	0,274
T_{max} po AKFI, min				
Kairysis inkstas	3,46 (2,73; 3,97)	3,14 (2,76; 3,97)	2,83 (2,71; 3,36)	0,229
Dešinysis inkstas	3,64 (3,21; 5,47)	3,59 (3,08; 4,75)	3.3 (2,72; 3,5)	0,076
T_{max}/ T½ po AKFI				
Kairysis inkstas	5,25 (4; 7)	5,13 (4; 7)	4,75 (4,25; 5,75)	0,724
Dešinysis inkstas	6,25 (5,5; 9,5)	6 (4,75; 8,25)	5.,5 (5; 6,5)	0,339
30min/T_{max} santykis po AKFI				
Kairysis inkstas	0,14 (0,12; 0,21)	0,13 (0,1; 0,16)	0,13 (0,11; 0,18)	0.663
Dešinysis inkstas	0.,17 (0,14; 0,26)	0,15 (0,12; 0,27)	0,18 (0,12; 0,23)	0,557
20min/3min santykis po AKFI				
Kairysis inkstas	0,15 (0,12; 0,24)	0,16 (0,11; 0,21)	0,17 (0,12; 0,19)	0,920
Dešinysis inkstas	0,18 (0,16; 0,3)	0,16 (0,13; 0,3)	0,18 (0,13; 0,24)	0,449

T_{max} = laikas iki maksimalios skaičiavimų reikšmės, T½ = laikas iki pusinio piko skaičiavimų reikšmės, 30 min/max = inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų, 20 min/3 min = skaičiavimų santykis po 20 minučių iki skaičiavimų po 3 minučių.

Po AKFI šie pokyčiai išryškėjo platesnio tipo aortos lanko grupėje. Ši tendencija atsispindi statistiškai reikšmingame T_{max} medianos pokytyje kairiajame inkste tarp grupių. T_{max} pokyčio mediana 1 grupėje buvo 0,27, 0,02 antroje grupėje, o 3 grupės pokyčio mediana buvo -0,41 (p=0,044) (13 lentelė).

Lentelė 13. Inkstų perfuzijos pokyčiai prieš ir po AKFI pacientams su skirtinga aortos lanko morfologija.

	Grupė 1 (A/P <0,65) Mediana (Q1-Q3)	Grupė 2 (A/P 0,65-0,85) Mediana (Q1-Q3)	Grupė 3 (A/P >0,85) Mediana (Q1-Q3)	P reikšmė
Δ Kaupimas				
Kairysis inkstas	1,2 (0,09; 3,42)	0,45 (-1,42; 2,28)	0,31 (-2,57; 2,12)	0.453
Dešinysis inkstas	-1,2 (-4,68; -0,09)	-0,45 (-2,28; 1,42)	-1,09 (-2,5; 2,57)	0,489
Δ T_{max}				
Kairysis inkstas	**0.27 (-0.05; 1.11) *****	**0.02 (-0.29; 0.75) *****	**-0.41 (-1.18; 0.36) *****	*****<0.05**
Dešinysis inkstas	0,61 (-0,02; 2,03)	0,21 (-0,25; 1,54)	0,11 (-1,18; 0,36)	0,239

	Grupė 1 (A/P <0,65) Mediana (Q1-Q3)	Grupė 2 (A/P 0,65-0,85) Mediana (Q1-Q3)	Grupė 3 (A/P >0,85) Mediana (Q1-Q3)	P reikšmė
Δ T_{max}/T½ santykis				
Kairysis inkstas	-0,25 (-2; 1)	0,25 (-1,25; 2)	-0,25 (-1,5; 1)	0,593
Dešinysis inkstas	-1 (-3; 1,5)	-0,25 (-1,75; 1,25)	-1,25 (-3,25; 0,25)	0,375
Δ 30min/T_{max} santykis				
Kairysis inkstas	0 (-0,02; 0,06)	0,01 (-0,01; 0,05)	0,02 (-0,02; 0,05)	0.991
Dešinysis inkstas	0,01 (-0,04; 0,08)	0,02 (-0,02; 0,06)	0 (-0,03; 0,03)	0,680
Δ 20min/3min santykis				
Kairysis inkstas	0 (-0,03; 0,06)	-0,01 (-0,01; 0,06)	-0,02 (-0,03; 0)	0,202
Dešinysis inkstas	0 (-0,06; 0,08)	0 (-0,04; 0,03)	-0,03 (-0,07; -0,01)	0,089

Δ - pokytis prieš ir po AKFI; T_{max} = laikas iki maksimalios skaičiavimų reikšmės, T½ = laikas iki pusinio piko skaičiavimų reikšmės, 30 min/max = inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų, 30 min/3 min = skaičiavimų santykis po 30 minučių iki skaičiavimų po 3 minučių; *** - statistiškai reikšmingas skirtumas tarp visų grupių.

3 dalis. Inkstų perfuzijos pokyčius lemiantys veiksniai

Tiesinės regresijos modelis, skirtas nustatyti skirtumą tarp laiko iki maksimalaus kaupimo prieš AKF inhibitorių vartojimą ir po jo (ΔT_{max}), kur didesnės vertės rodo didesnę renovaskulinės hipertenzijos riziką, rodo, kad amžius reikšmingai veikia ΔT_{max} sumažėjimą dešiniajame inkste prieš ir po AKF inhibitorių vartojimo, potencialiai nurodydamas su amžiumi susijusį inkstų funkcijos sumažėjimą (14 lentelė). Nors yra tendencija, kad moterų ΔT_{max} kairiajame inkste yra mažesnis, šis rezultatas nebuvo statistiškai reikšmingas. Tačiau moterys rodo reikšmingai mažesnį ΔT_{max} dešiniajame inkste, palyginti su vyrais, kas leidžia manyti, kad egzistuoja lyčių skirtumai dešiniojo inksto funkcijoje.

Lentelė 14. Tiesinės regresijos modelis kintamiesiems, įtakojantiems ΔT_{max} (prieš AKF inhibitorių vartojimą ir po jo).

	Δ T_{max} KI		**Δ T_{max} DI**	
Priklausomas kintamasis	**Koeficientas**	**P reikšmė**	**Koeficientas**	**P reikšmė**
Amžius	-0,025	0,304	**-0,054**	**0,021**
Amžius operacijos metu	-0,015	0,741	-0,058	0,190
Moteriška lytis	-0,933	0,089	**-1,318**	**0,012**
Ao lanko A/P santykis	**-3,952**	**0,018**	-1,746	0,282
Ao lanko A/P santykis <0.65	**1,913**	**0,010**	1,014	0,166
Ao lanko A/P santykis 0.65 – 0.85	**1,691**	**0,022**	0,813	0,258
Ao lanko kampas	**0,058**	**0,048**	0,018	0,541
AoKo stenozė	-0,021	0,284	0,003	0,890
Vidutinis paros sAKS	0,016	0,691	-0,002	0,947
sAKS skirtumas tarp DR-K	0,010	0,460	**0,024**	**0,044**
DBMA IM storis	-0,001	0,800	0,001	0,676
DBMA elastiškumas	0,001	0,273	**0,003**	**0,002**
DBMA standumas	-0,062	0,812	-0,038	0,850
KBMA IM storis	-0,001	0,612	-0,002	0,299

	Δ T_{max} KI		Δ T_{max} DI	
Priklausomas kintamasis	**Koeficientas**	**P reikšmė**	**Koeficientas**	**P reikšmė**
KBMA elastiškumas	0,001	0,463	**0,003**	**0,002**
KBMA standumas	-0,275	0,356	-0,042	0,859
PBG	-0,030	0,908	-0,120	0,647
D-CAVI	-0,317	0,340	-0,046	0,896
K-CAVI	-0,620	0,061	-0,522	0,131
eGFR	-0,006	0,173	-0,002	0,546

A/P – aortos lanko aukščio ir ilgio santykis; DBMA – dešinė bendroji miego arterija; KBMA – kairė bendroji miego arterija; IM – intima-media storis; PBG – pulsinės bangos greitis; D-CAVI – dešinės pusės kardiokulkšnies kraujagyslių indeksas; K-CAVI – kairės pusės kardiokulkšnies kraujagyslių indeksas

Didesnis aortos lanko A/P santykis yra susijęs su reikšmingu ΔT_{max} sumažėjimu kairiajame inkste, rodant poveikį inkstų hemodinamikai, tačiau reikšmingos įtakos dešiniajam inkstui jis neturi. Priešingai, A/P santykis, mažesnis nei 0,65, yra reikšmingai susijęs su padidėjusiu ΔT_{max} kairiajame inkste, kas rodo palankų tam tikrų aortos lanko morfologijų poveikį kairiojo inksto perfuzijai, neturintį reikšmingos įtakos dešiniajam inkstui. Panašiai, A/P santykis tarp 0,65 ir 0,85 reikšmingai padidina ΔT_{max} kairiajame inkste. Platesnis aortos lanko kampas yra susijęs su nedideliu, bet reikšmingu ΔT_{max} padidėjimu kairiajame inkste. Šis ryšys dešiniajame inkste nepastebėtas.

Didesnis sistolinio kraujospūdžio skirtumas tarp dešinės rankos ir kojos yra reikšmingai susijęs su padidėjusiu ΔT_{max} dešiniajame inkste, rodant paveiktą dešiniojo inksto funkciją. Be to, didesnis dešinės bendrosios miego arterijos (DBMA) elastiškumas yra reikšmingai susijęs su ΔT_{max} padidėjimu dešiniajame inkste, nurodant kraujagyslių ryšį tarp DBMA savybių ir dešiniojo inksto hemodinamikos. Šis ryšys taip pat pastebėtas su kairės bendrosios miego arterijos elastiškumu.

Tiesinėje regresijos analizėje $\Delta 30min/T_{max}$ santykiui (15 lentelė) nė vienas iš tirtų kintamųjų – įskaitant amžių, lytį, aortos lanko A/P santykį, aortos lanko kampą, AoKo stenozę, sistolinį kraujospūdį ir miego arterijos rodiklius (DBMA ir KBMA) – neturėjo reikšmingos įtakos $\Delta 30min/T_{max}$ santykiui nei kairiajame, nei dešiniajame inkstuose. Vis dėlto DBMA intimos-medijos (IM) storis parodė ribinį reikšmingumą dešiniajam inkstui, rodant galimą poveikį dešiniojo inksto funkcijai. Šie rezultatai rodo, kad tirtų kintamųjų ir $\Delta 30min/T_{max}$ santykio pokyčių abiejuose inkstuose šioje kohortoje stiprios sąsajos nenustatyta.

Lentelė 15. Tiesinės regresijos modelis kintamiesiems, įtakojantiems Δ30min/T_{max} (prieš AKF inhibitorių vartojimą ir po jo).

	Δ 30min/T_{max} santykis KI		**Δ 30min/T_{max} santykis DI**	
Priklausomas kintamasis	**Koeficientas**	**P reikšmė**	**Koeficientas**	**P reikšmė**
Amžius	-0,000	0,930	0,000	0,971
Amžius operacijos metu	-0,002	0,295	-0,001	0,805
Moteriška lytis	-0,030	0,121	-0,030	0,398
Ao lanko A/P santykis	0,015	0,804	-0,129	0,229
Ao lanko A/P santykis <0.65	0,001	0,981	0,069	0,153
Ao lanko A/P santykis 0.65 – 0.85	0,012	0,641	0,052	0,269
Ao lanko kampas	-0,000	0,823	0,002	0,399
AoKo stenozė	0,000	0,548	0,001	0,242
Vidutinis paros sAKS	-0,002	0,439	-0,001	0,293
sAKS skirtumas tarp DR-K	0,001	0,309	0,001	0,247
DBMA IM storis	0,000	0,127	0,000	0,083
DBMA elastiškumas	0,000	0,168	0,000	0,214
DBMA standumas	-0,009	0,291	-0,006	0,680
KBMA IM storis	0,000	0,201	0,000	0,336
KBMA elastiškumas	0,000	0,925	0,000	0,644
KBMA standumas	0,001	0,940	-0,009	0,549
PBG	-0,000	0,337	0,000	0,929

A/P – aortos lanko aukščio ir ilgio santykis; DI – dešinysis inkstas; KI – kairysis inkstas; DBMA – dešinė bendroji miego arterija; KBMA – kairė bendroji miego arterija; IM – intima-media storis; PBG – pulsinės bangos greitis; D-CAVI – dešinės pusės kardiokulkšnies kraujagyslių indeksas; K-CAVI – kairės pusės kardiokulkšnies kraujagyslių indeksas

Analizuojant kintamuosius, įtakojančius Δ20min/3min santykio skirtumą prieš ir po AKF inhibitorių vartojimo, reikšmingų sąsajų nenustatyta (16 lentelė). Amžius parodė ribinį poveikį Δ20min/3min santykiui kairiajame inkste, kas leidžia manyti, kad vyresniems asmenims gali pasireikšti nedidelis šio santykio sumažėjimas, nors šis rezultatas nėra statistiškai reikšmingas. Priešingai, amžius reikšmingai neįtakojo Δ20min/3min santykio dešiniajame inkste. Moters lytis buvo reikšmingai susijusi su mažesniu Δ20min/3min santykiu kairiajame inkste, lyginant su vyrais. Tuo tarpu dešiniajame inkste pastebėta tendencija, kad moterų Δ20min/3min santykis buvo mažesnis, tačiau šis poveikis nepasiekė statistinio reikšmingumo.

Didelis aortos lanko A/P santykis buvo reikšmingai susijęs su sumažėjusiu Δ20min/3min santykiu dešiniajame inkste. Priešingai, mažas A/P santykis (<0,65) buvo reikšmingai susijęs su padidėjusiu Δ20min/3min santykiu dešiniajame inkste, kas leidžia manyti, kad šis santykis gali būti naudingas dešiniojo inksto funkcijai. Kairiajam inkstui A/P santykio reikšmingo poveikio nepastebėta.

Lentelė 16. Tiesinės regresijos modelis kintamiesiems, įtakojantiems Δ20min/3min (prieš AKF inhibitorių vartojimą ir po jo).

	Δ 20min/3min santykis KI		**Δ 20min/3min santykis KD**	
Priklausomas kintamasis	**Koeficientas**	**P reikšmė**	**Koeficientas**	**P reikšmė**
Amžius	-0,002	0,084	-0,002	0,401
Amžius operacijos metu	-0,003	0,282	-0,000	0,953
Moteriška lytis	**-0,074**	**0,012**	-0,089	0,103
Ao lanko A/P santykis	-0,066	0,470	**-0,336**	**0,042**
Ao lanko A/P santykis <0.65	0,046	0,265	**0,153**	**0,041**
Ao lanko A/P santykis 0.65 – 0.85	0,054	0,187	0,097	0,185
Ao lanko kampas	0,000	0,931	0,004	0,216
AoKo stenozė	-0,001	0,531	0,001	0,444
Vidutinis paros sAKS	-0,001	0,585	-0,000	0,900
sAKS skirtumas tarp DR-K	0,001	0,100	0,001	0,259
DBMA IM storis	0,000	0,868	0,000	0,397
DBMA elastiškumas	0,000	0,114	0,000	0,169
DBMA standumas	-0,008	0,550	0,003	0,872
KBMA IM storis	-0,000	0,851	-0,000	0,950
KBMA elastiškumas	0,000	0,457	0,000	0,248
KBMA standumas	-0,002	0,918	-0,015	0,549
PBG	0,017	0,251	0,030	0,268
D-CAVI	0,007	0,717	0,041	0,252
L-CAVI	-0,014	0,482	-0,004	0,910
eGFR	-0,000	0,428	0,000	0,595

A/P – aortos lanko aukščio ir ilgio santykis; DI – dešinysis inkstas; KI – kairysis inkstas; DBMA – dešinė bendroji miego arterija; KBMA – kairė bendroji miego arterija; IM – intima-media storis; PBG – pulsinės bangos greitis; D-CAVI – dešinės pusės kardiokulkšnies kraujagyslių indeksas; K-CAVI – kairės pusės kardiokulkšnies kraujagyslių indeksas.

4 dalis. Kliniškai reikšmingos AoKo pacientų grupės inkstų perfuzijos analizė.

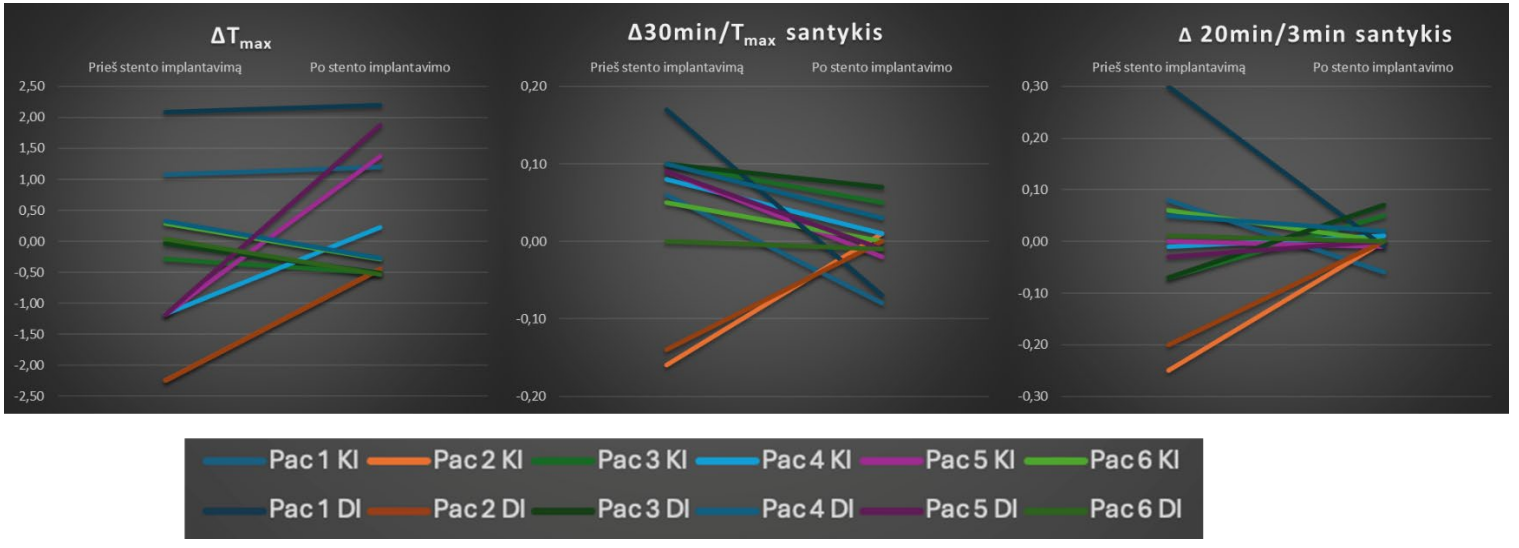
Šioje tyrimo dalyje aprašoma kliniškai reikšmingos AoKo pacientų grupės subanalizė. Į šią grupę buvo įtraukti šeši pacientai. Vidutinis amžius įtraukimo metu buvo 36,7 ± 24,05 metų, o 4 iš šešių pacientų (66,67%) buvo vyrai. Tarp šių pacientų trims buvo diagnozuota natyvinė AoKo, o likusiems trims buvo atliktos skirtingos procedūros: vienam buvo atliktas korekcija panaudojant homotransplantatą, po kurios buvo atlikta stento implantacija, kitam atlikta anastomozė galas su galu, o dar trečiam pacientui atlikta perkateterinė stento implantacija. Visiems dalyviams buvo atlikti invaziniai gradiento matavimai ir perkateterinė stento implantacija. Inkstų perfuzijos skenavimas buvo pakartotas per 3–6 mėnesius po procedūros. Palyginus prieš ir po stento implantavimo matavimus, statistiškai reikšmingų pokyčių inkstų perfuzijoje nestebėta (17 lentelė).

Lentelė 17. Pacientų inkstų perfuzijos pokyčių palyginimas prieš ir po stentavimo.

	Prieš stentavimą, Vidurkis (SD)	Po stentavimo, Vidurkis (SD)	P reikšmė
Δ Kaupimas			
Kairysis inkstas	2,01(3,023)	2,27 (4,864)	1,0000
Dešinysis inkstas	-3,71(6,129)	-2,27 (4,864)	0,6875
Δ T_{max}			
Kairysis inkstas	0,26 (0,837)	-0,59 (1,188)	0,3125
Dešinysis inkstas	0,39 (1,286)	-0,17 (1,461)	0,8438
Δ T_{max}/T½ santykis			
Kairysis inkstas	-0,71 (1,134)	-0,17 (1,842)	0,4063
Dešinysis inkstas	0,79 (2,985)	-0,38 (3,711)	0,4063
Δ 30min/T_{max} santykis			
Kairysis inkstas	-0,01 (0,043)	0,04 (0,098)	0,4375
Dešinysis inkstas	0 (0,047)	0,05 (0,109)	0,3125
Δ 20min/3min santykis			
Kairysis inkstas	0 (0,035)	-0,03 (0,12	0,8438
Dešinysis inkstas	0,01 (0,029)	0,01 (0,166)	0,8750

Δ - pokytis prieš ir po AKFI; T_{max} = laikas iki maksimalios skaičiavimų reikšmės, T½ = laikas iki pusinio piko skaičiavimų reikšmės, 30 min/max = inkstų skaičiavimų santykis po 30 minučių iki maksimalių skaičiavimų, 30 min/3 min = skaičiavimų santykis po 30 minučių iki skaičiavimų po 3 minučių.

5 pav. aprašo individualius inkstų perfuzijos pokyčius kiekvienam pacientui prieš ir po stento implantacijos. Nepaisant kai kuriems pacientams stebėto T_{max} prailgėjimo ir padidėjusių 30min/T_{max} bei 20min/3min santykių, dauguma pacientų parodė nežymius inkstų perfuzijos ir funkcijos pagerėjimus po stento implantacijos. Padidėję santykiai kai kuriems pacientams gali rodyti dehidrataciją, dėl kurios sumažėja inkstų klirensas ir sutrinka perfuzija. Atsižvelgiant į ribotą imties dydį, šiuos rezultatus reikia interpretuoti atsargiai, nes stebimą variabilumą gali įtakoti individualūs paciento veiksniai ar galimos matavimo klaidos.



5 pav. Individualūs inkstų perfuzijos pokyčiai kiekvienam pacientui prieš ir po stento implantacijos. Pac – pacientas; KI – kairysis inkstas; DI – dešinysis inkstas.

Tik viena pacientė po stento implantavimo visiškai nutraukė antihipertenzinį gydymą dėl normalizuoto kraujospūdžio. Likusiems pacientams reikšmingų pokyčių gydyme nepastebėta.

Pagrindiniai radiniai

Tyrėjo žiniomis, tai yra pirmasis tyrimas, vertinantis aortos koarktaciją (CoA) ir inkstų perfuziją. Žemiau pateikiamos pagrindinės išvados, gautos tiriant pacientų kohortą su CoA:

1. Vyriška lytis buvo susijusi su 3,9 karto didesne arterinės hipertenzijos rizika, palyginus su moteriška lytimi.
2. Crenel tipo aortos (platus) lankas nustatytas kaip reikšmingas arterinės hipertenzijos rizikos veiksnys, kurio šansų santykis buvo 5,833, lyginant su Gotikiniu aortos lanku.
3. Arterinės hipertenzijos tikimybė didėja 6,5% su kiekvienu milimetru didėjant aortos lanko pločiui.
4. Platesnis aortos lanko kampas buvo susijęs su didesne arterinės hipertenzijos rizika, kai kiekvienas kampo padidėjimo laipsnis buvo susijęs su 9% rizikos padidėjimu.
5. Padidėjęs echokardiografinis gradientas per AoKo buvo teigiamai susijęs su arterine hipertenzija –gradiento padidėjimas vienu mmHg buvo susijęs su 5% rizikos padidėjimu.
6. AoKo pacientams, sergantiems arterine hipertenzija, buvo pastebėtas padidėjęs intimos-medijos storis ir pagerėjęs elastiškumas dešinėje bendrojoje miego arterijoje. Panašių pokyčių kairėje bendrojoje miego arterijoje nebuvo pastebėta.
7. Hipertenzija sergantiems pacientams buvo nustatyta lėtesnė inkstų perfuzija (prailgėjęs T_{max}) ir pablogėjęs klirensas (padidėję 30min/T_{max} ir 20min/3min santykiai prieš ir po AKF inhibitoriaus skyrimo).
8. Amžius reikšmingai įtakoja ΔT_{max} dešiniajame inkste – vyresni pacientai parodė sumažėjusį T_{max} skirtumą prieš ir po AKF inhibitorių, kas gali rodyti su amžiumi susijusį inkstų funkcijos pagerėjimą.
9. Moterims buvo nustatyta reikšmingai mažesnė ΔT_{max} reikšmė dešiniajame inkste, rodanti geresnę dešiniojo inksto funkciją, palyginti su vyrais.
10. Platesni aortos lanko tipai nei Gotikinis aortos lankas buvo susiję su sumažėjusia kairiojo inksto perfuzija ir sumažėjusiu dešiniojo inksto klirensu.
11. AoKo pacientai, turintys didesnį sistolinio kraujospūdžio skirtumą tarp dešinės rankos ir kojos bei padidėjusį dešinės bendrosios miego arterijos elastiškumą, buvo didesnės parenchiminio pažeidimo dešiniame inkste rizikos grupėje.

12. Moterų lytis buvo susijusi su geresniu inkstų klirensu kairiajame inkste, kaip rodo mažesnis Δ20min/3min santykis.
13. Dėl nedidelės imties nebuvo įmanoma įvertinti stento implantacijos ir gradiento sumažinimo poveikio inkstų perfuzijos pagerėjimui pacientams, sergantiems kliniškai riekšminga AoKo.

Išvados:

1. Pacientams, sergantiems aortos koarktacija ir arterine hipertenzija, nustatomas uždelstas inkstų perfuzijos ir inkstų klirenso laikas, palyginti su pacientais be hipertenzijos.
2. Platus aortos lankas pasižymi inkstų parenchimos susilaikymu ir sumažėjusia klirenso funkcija, palyginti su kitų tipų aortos lankais.
3. Arterinė hipertenzija pacientams, sergantiems aortos koarktacija, yra susijęs su vyriška lytimi, vyresniu amžiumi, platesniu aortos lanku ir likusiu echokardiografiniu gradientu koarktacijos vietoje.
4. Padidėjęs miego arterijų intimos ir medijos storis bei elastiškumas pacientams, sergantiems aortos koarktacija, yra susijęs su padidėjusia inkstų parenchimos susilaikymo rizika.

12. REKOMENDACIJOS KLINIKINEI PRAKTIKAI

1. Pacientams, sergantiems aortos koarktacija ir arterine hipertenzija, reguliarus inkstų funkcijos vertinimas turėtų būti įtrauktas į įprastinį stebėjimą, siekiant nustatyti ankstyvus inkstų pažeidimo požymius.
2. Pacientai, turintys platų aortos lanką, turėtų būti atidžiai stebimi atliekant inkstų vaizdinius ir funkcinius tyrimus, nes jiems gali būti didesnė inkstų komplikacijų rizika.
3. Atsižvelgiant į hipertenzijos ryšį su vyriška lytimi, vyresniu amžiumi, platesniu aortos lanku ir didesniu echokardiografiniu gradientu, turėtų būti taikomos tikslinės hipertenzijos valdymo strategijos, įskaitant ankstesnę intervenciją ir atidesnį stebėjimą šiose didelės rizikos grupėse.

13. LIST OF PUBLICATIONS

The main findings of the doctoral dissertation were published in the following articles:

Bambul Heck P, Fayed M, Hager A, **Cesna S**, Georgiev S, Tanase D, Horer J, Ewert P, Eicken A. Sequential dilation strategy in stent therapy of the aortic coarctation: A single centre experience. Int J Cardiol. 2021 Feb 3;S0167-5273(21)00120-0.

Cesna, S.; Bielinis, A.; Zvirblis, T.; Miglinas, M.; Tarutis, V. Influence of Aortic Arch Morphology on Renal Perfusion in Patients with Coarctation of the Aorta: An Exploratory Study. *Medicina* 2024, *60*, 886. https://doi.org/10.3390/medicina60060886

Other articles:

1. **Cesna S**, Eicken A. Percutaneous techniques for treatment of tricuspid valve dysfunction in congenital heart disease - an emerging therapy. Expert Rev Cardiovasc Ther. 2021 Sep;19(9):817-824. doi: 10.1080/14779072.2021.1865154. Epub 2020 Dec 28. PMID: 33336614.
2. Buono A, Medda M, **Cesna S**, Davidavicius G, Casilli F, Bande M, Pellicano M, Tespili M, Ielasi A. Snaring the Transcatheter Heart Valve Delivery System During Aortic Valve Replacement: When and Why. Cardiovasc Revasc Med. 2021 Jul;28S:81-84. doi: 10.1016/j.carrev.2021.02.018. Epub 2021 Feb 16. PMID: 33674218.
3. Bajoras V, Diečkus L, Wong I, Laurinavičienė A, Davidavičius G, **Čėsna S**. Transcatheter aortic valve implantation in patients with anomalous coronary artery. Catheter Cardiovasc Interv. 2023 Jan 14. doi: 10.1002/ccd.30540. Epub ahead of print. PMID: 36640415.
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5. Palevičiūtė E, Čelutkienė J, Šimbelytė T, Gumbienė L, Jurevičienė E, Zakarkaitė D, **Čėsna S**, Eichstaedt CA, Benjamin N, Grünig E. Safety and effectiveness of standardized exercise training in patients with pulmonary hypertension associated with heart failure with preserved ejection fraction (TRAIN-HFpEF-PH): study protocol for a randomized controlled multicenter trial. Trials. 2023 Apr 19;24(1):281. doi: 10.1186/ s13063-023-07297-x. PMID: 37072812; PMCID: PMC10114476.

6. Ivanauskiene T, **Cesna S**, Grigoniene E, Gumbiene L, Daubaraite A, Ivanauskaite K, Glaveckaite S. Balloon Pulmonary Angioplasty for Inoperable Chronic Thromboembolic Pulmonary Hypertension: Insights from a Pilot Low-Volume Centre Study and a Comparative Analysis with Other Centres. Medicina (Kaunas). 2024 Mar 11;60(3):461. doi: 10.3390/medicina60030461. PMID: 38541187; PMCID: PMC10972510.

Theses and presentations of the main findings of the doctoral dissertation:

1. Cesna S, Bielinis A, Miglinas M, Tarutis V. Renal perfusion changes in aortic coarctation patients: REPACO trial. AEPC2024, Porto, Portugal
2. Cesna S. Three Minute Thesis competition, 2nd place, Vilnius University, Vilnius, Lithuania
3. Cesna S, Bielinis A, Cerlinskaite-Bajore K, Tarutis V. Renal perfusion changes after aortic coarctation stenting. AEPC 2023, Dublin, Ireland.
4. Cesna S, Bielinis A, Cerlinskaite-Bajore K, Tarutis V. Severity of aortic coarctation impact to renal perfusion. AEPC 2023, Dublin, Ireland.
5. Cesna S., Zikaite P, Simonavicius P, Tarutis V. Treatment difficulties in young adults with residual arterial hypertension after early aortic coarctation repair. EUROGUCH 2019, Zagreb, Croatia

Other presentations:

Cesna S. Coarctation of the aorta: clinical cases. Heart beats for education. #2Coarctation. Association of European pediatric cardiology. 21/12/2022

14. BRIEF INFORMATION ABOUT THE AUTHOR

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- 2011 Fellow for congenital heart disease interventions at Deutschen Herzzentrum München (6 months), Munich, Germany
- 2012 – 2013 Fellow for adult congenital heart disease at University College Hospital (UCLH) Heart Hospital, London, United Kingdom
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