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Abstract

Background

Children with coarctation of the aorta (CoA) can have a hyperdynamic and remodeled left ventricle (LV) from increased afterload. Literature from an experimental model suggests the putative 20 mm Hg blood pressure gradient (BPG) treatment guideline frequently implemented in CoA studies may permit irreversible vascular changes. LV remodeling from pressure overload has been studied, but data are limited following correction and using a clinically representative BPG.

Materials and methods

Rabbits underwent CoA at 10 weeks to induce a 20 mm Hg BPG using permanent or dissolvable suturethereby replicating untreated and corrected CoA, respectively. Cardiac function was evaluated at 32 weeks by magnetic resonance imaging using a spoiled cine GRE sequence (TR/TE/FA 8/2.9/20), 14 × 14-cm FOV, and 3-mm slice thickness. Images (20 frames/cycle) were acquired in 6-8 short axis views from the apex to the mitral valve annulus. LV volume, ejection fraction (EF), and mass were quantified.

Results

LV mass was elevated for CoA (5.2 ± 0.55 g) *versus* control (3.6 ± 0.16 g) and corrected (4.0 ± 0.44 g) rabbits, resulting in increased LV mass/volume ratio for CoA rabbits. A trend toward increased EF and stroke volume was observed but did not reach significance. Elevated EF by volumetric analysis in CoA rabbits was supported by concomitant increases in total aortic flow by phase-contrast magnetic resonance imaging.

Conclusions

The indices quantified trended toward a persistent hyperdynamic LV despite correction, but differences were not statistically significant *versus* control rabbits. These findings suggest the current putative 20 mm Hg BPG for treatment may be reasonable from the LV's perspective.

Keywords

Congenital heart disease, Cardiac function, Animal model

Introduction

Coarctation of the aorta (CoA) is a congenital cardiovascular disease characterized by severe narrowing of the proximal descending thoracic aorta. Although simple surgical correction has saved the lives of thousands of neonates and infants, and aided thousands of children, many of these individuals still have a reduced average lifespan from increased CV morbidity, including hypertension and left ventricular hypertrophy.[1], [2] Many of the long-term problems observed after treatments for CoA can be explained on the basis of abnormal cardiac and vascular biomechanics.[3] For example, patients with primary or residual CoA may have a hyperdynamic and remodeled left ventricle (LV), if exposed to a prolonged increase in afterload.[4], [5]

The mechanisms mediating persistent morbidity from CoA are difficult to study in a clinical setting due to the limited number and heterogeneity of patients at any one center; therefore, we developed a rabbit model that mimics the vascular pathology observed in humans with CoA.[6] In contrast to other aortic banding animal models, this model was designed to produce a blood pressure (BP) gradient (BPG) of 20 mm Hg across the coarctation, which is the putative treatment threshold most often found in the literature. Unfortunately, myography, histology, immunohistochemistry, and microarray analysis from aortas harvested using this model have shown a 20 mm Hg BPG causes irreversible structural and functional changes.[7, 8] Although these results suggest 20 mm Hg should not be used to guide treatment from the vasculature's perspective, a controlled study of LV remodeling and plasticity resulting from the putative treatment guideline is lacking. Therefore, this rabbit model was used with magnetic resonance imaging (MRI) to quantify alterations in LV morphology and systolic functionfrom CoA and its correction to specifically test the hypothesis that a 20 mm Hg gradient will cause changes in the myocardium that can be reversed with appropriate relief of the associated obstruction.

Material and methods

Experimental protocol

After IACUC approval, male New Zealand white rabbits ~10-week old and weighing ~1.0 kg (*n* = 7/group) were randomly designated to undergo CoA of the proximal descending thoracic aorta as discussed in detail elsewhere.[6] Briefly, a 1.6-mm diameter stainless steel wire was used with silk (permanent) or Vicryl (degradable) suture as previously described to mimic untreated CoA and surgically corrected CoA, respectively.[6] This diameter wire resulted in a 20 mm Hg BPG—the putative value for intervention in patients diagnosed with CoA[9]—at the experimental end point of 32 weeks. It is worth noting that BP is similar across species.[10] Application of LaPlace's law shows that increases in BP from the coarctation act along with local vessel or LV myocardial wall dimensions, to increase vascular or myocardial tension, respectively. This serves as the stimulus for remodeling because vascular and myocardial tissues prefer specific ranges of stress.[10, 11]

Within 1 week of CoA induction using the current model, rabbits develop a pronounced vascular stenosis, accompanying elevated BP in the upper body half, and the subsequent stimulus for myocardial remodeling when silk suture is used to create the CoA. Rabbits undergoing creation of the CoA with degradable suture (Vicryl) also develop an initial stenosis similar to CoA rabbits. However, degradation of Vicryl suture restores aortic diameter close to normal but with modest residual narrowing mimicking the aortic morphology often observed after surgical resection with end-to-end anastomosis in humans. Nonexperimental rabbits were also used here as a control group (Fig. 1).

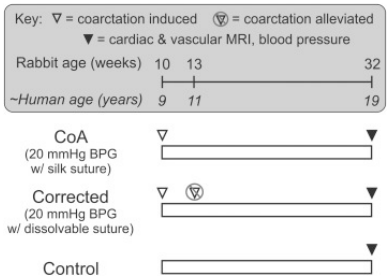

Fig. 1. Experimental protocol. Male New Zealand white rabbits aging ~10 weeks and weighing ~1.0 kg (*n* = 7/group) undergo CoA of the proximal descending thoracic aorta using a 1.6 diameter wire with silk (control group) or Vicryl(corrected group) suture to mimic untreated CoA and surgically corrected CoA, respectively. Nonexperimental rabbits were also designated for a control group. Inducing CoA with dissolvable Vicryl suture provides the stimulus of altered hemodynamics from CoA for ~5 weeks before restoring blood pressure to

normal for >4 months (i.e., ~6 human years) before the end of the experimental duration (32 weeks) when MRI and intravascular blood pressure measurements are performed.

Confirming correction of CoA by ultrasound

According to the manufacturer, Vicryl suture is completely absorbed after ~9 weeks with an initial strength of ~15 lbf and a known strength retention curve based on the number of days since suture use. An analysis using this retention curve, with knowledge of rabbit aortic diameters and integrating the distribution of tractions within this region,[12] indicates that the force exerted on the suture used to create the coarctation exceeds the strength indicated by the manufacturer after ~21 days. We sought to confirm these calculations empirically. Ultrasound studies were therefore performed by a trained sonographer to track evolution of the BPG and confirm absorption of dissolvable Vicryl sutures used in creating CoA for the corrected group of rabbits (n = 3). Rabbits were placed in a dedicated veterinary anesthesia Plexiglas-sealed induction container, and a gas mixture of isoflurane 2% mixed with 100% oxygen was passed through the chamber. Once anesthetized, rabbits were carefully removed from the chamber and the gas mixture of isoflurane/oxygen continued to be delivered via nose cone. Transthoracic ultrasound of the descending thoracic aorta was performed with an 11-MHz M12L linear array transducer interfaced to a Vivid 7 ultrasound system (GE Healthcare, Waukesha, WI). Closed chest imaging took place after the chest was carefully shaved to remove hair allowing for a gel interface between the skin and the ultrasound transducer. Long axis 2-D, color Doppler and pulsed spectral Doppler images were obtained from the area above, through, and below the coarctation region. The degree of angle correction was recorded for each animal, and this angle was repeated for all subsequent exams. Rabbits were imaged weekly until BPG equilibrated for a given rabbit. Each examination took less than 10 minutes, and rabbits were monitored continuously until ambulatory and sternal after each ultrasound examination.

Peak velocity (V) was also measured using electronic calipers available on the ultrasound system. Three cardiac cycles were measured and the average used for reporting. Peak instantaneous BPG was estimated using the modified Bernoulli equation ($4 \times V^2$). Peak instantaneous BPG values by ultrasound were only used in the present study to determine when absorption of the dissolvable Vicryl sutures used in creating CoA for the corrected group of rabbits had occurred, since BPG by catheterization obtained as discussed below in the measurement of blood pressure section represents the gold standard and preferred method, when available.[13], [14] Weekly ultrasound imaging revealed that the BPG remains elevated in corrected rabbits for 34 ± 2 days after surgical induction of the coarctation (range: 32-37 days; Fig. 2). Importantly, this information suggests that our approach of inducing CoA with dissolvable Vicryl suture provides the stimulus of altered hemodynamics from CoA for 5 weeks, before restoring BP to normal for >4 months (i.e., ~6 human years) prior to the experimental end point of 32 weeks of age used in this study.

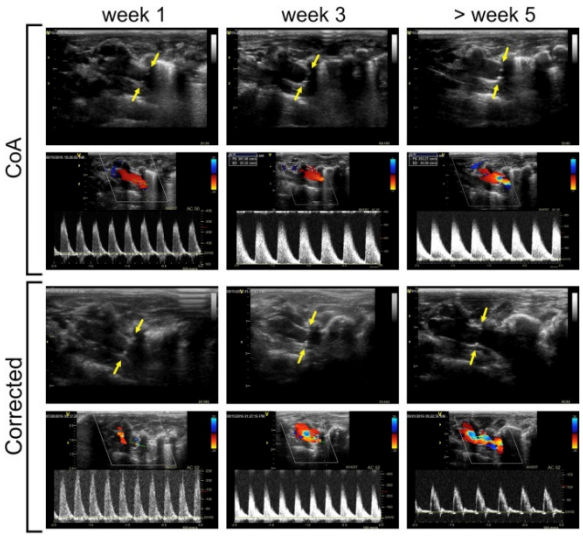

Fig. 2. Ultrasound studies were performed weekly to track evolution of the BPG and confirm absorption of dissolvable Vicryl sutures used in creating the coarctation for the corrected group of rabbits. This is illustrated in the figure. CoA rabbits (top two rows) have persistent narrowing and elevated blood flow through the coarctation region for the full experimental duration. Conversely, the BPG remains elevated in corrected rabbits (bottom two rows) only for 34 ± 2 days (~5 weeks) after surgical induction of the coarctation. The two images on the lower right show how diameter in the coarctation region is largely restored after 5 weeks, resulting in a decrease in blood flow and velocity through the coarctation region. (Color version of figure is available online.)

Magnetic resonance imaging

Rabbits were anesthetized using ketamine (22 mg/kg) and xylazine (2.5 mg/kg) to undergo cardiovascular MRI using a 3T GE Signa Excite scanner (GE Healthcare, Waukesha, WI) in the supine, head first position using a quadrature knee coil. Monitoring equipment used to ensure an adequate level of anesthesia included an external pulse oximeter (Nonin Medical Inc, Plymouth, MN) and core temperature sensor approved for use in the MR environment. Cardiac triggering was obtained using a peripheral pulse oximeter attached to the right ear that also provided heart rate (HR). Animals were allowed to breath freely during the entire imaging session.

Time-resolved 2D anatomic and through-plane phase contrast-MRI (PC-MRI) was performed orthogonal to the ascending aorta (AscAo) just distal to the aortic valve to calculate cardiac output and total aortic flow. Velocity encoding was optimized to maximize the dynamic range when calculating blood flow velocity at this location (Table 1). Average rabbit HRs ranged from ~100 to 200 beats per minute. Twenty 2D velocity-encoded magnitude and phase images were acquired per cardiac cycle resulting in a temporal resolution between 15 and 30 ms. Other imaging parameters included 12 × 12-cm field of view, a 256 × 224 acquisition matrix, TR of 8.5 ms, TE of 1.7 ms, flip angle of 20°, and a slice thickness of 3 mm. Time-resolved volumetric blood flow was determined from this PC-MRI data as previously described.[15] Total flow was determined by integrating the area under each AscAo blood flow waveform. The time points of maximum blood flow were aligned for measurements made from rabbits in each group, and the waveforms were then ensemble averaged to generate representative plots.

Table 1. Imaging parameters.

Purpose	Blood flow	Cardiac function
Sequence	2D fastcard PC	Fastcard spoiled GRE
TR/TE/flip angle	8.5 ms/1.7 ms/20°	7.5 ms/2.7 ms/20°
Slice thickness	3.0 mm	3.0 mm
Acquisition matrix	256 × 224	256 × 256 (6-8 slices to cover the LV)

Field of view	12 × 12 cm	14 × 14 cm
VENC	120 cm/sec	N/A
Cardiac frames	20	20

Morphologic and functional changes in the LV due to CoA and its correction were quantified using a prospectively gated cine-spoiled GRE (i.e., cine SPGR) sequence. Using standard cine imaging techniques, 6-8 contiguous short axis planes were imaged, covering the LV from the apex to base of the heart.[16] During the cardiac cycle, 20 images were acquired at each slice location, which again yielded a temporal resolution of 15 to 30 ms. Short axis cine imaging used a field of view of 14 × 14 cm, a 256 × 256 acquisition matrix, TR of 7.5 ms, TE of 2.7 ms, flip angle of 20°, and a slice thickness of 3 mm.

Cardiac function data were analyzed by standard methods with planimetry of the epicardium and endocardium at peak systole and end diastole for each short axis slice using QMass (Medis Corp, Leiden, The Netherlands). The papillary muscles were excluded from the ventricular lumen and included with myocardial mass calculations. This allowed determination of LV mass, end-systolic and end-diastolic LV volumes, LV stroke volume, and LV ejection fraction. LV thickness was also quantified along the anteroseptal and inferolateral wall locations to determine whether remodeling was concentric, as would be expected for remodeling due to increased afterload.

Measurement of blood pressure

After detailed offline analysis of MRI data, rabbits were again anesthetized for measurement of BP prior to tissue harvest. Proximal and distal BP waveforms were measured simultaneously with the same model transducer (Harvard Apparatus, Holliston, MA) from which waveforms were digitally recorded at 720 Hz using a computer interfaced with an analog-to-digital converter. Transducers were attached to 5 inch noncompliant fluid-filled catheters. The proximal fluid-filled catheter was inserted into the common carotid artery and advanced retrograde into the aortic arch. The distal fluid-filled catheter was inserted into the femoral artery and advanced retrograde into the aortoiliac bifurcation. Rabbits were euthanized after BP measurement by an intravenous overdose of pentobarbital sodium(100 mg/kg).

Statistical analysis

All data shown are presented as mean ± standard error of the mean. Statistical evaluations were performed using one-way analysis of variance, followed by Tukey post hoc analysis. A *P*-value < 0.05 was considered statistically significant.

Results

The current model of CoA revealed a statistically significant increase in systolic and mean BP while under isoflurane when measured proximal to the coarctation for CoA as compared to both control and corrected rabbits (Table 2). Importantly, a mean BPG of 20 ± 2 mm Hg ($P < 0.05$) was measured across the coarctation region compared to control (3 ± 2 mm Hg; Fig. 3A), and this BPG was restored to control levels in corrected rabbits (3 ± 1 mm Hg) at the end of the experimental protocol. When assessed by catheter at the time of peak systole, the peak BPG was 31 ± 3 mm Hg ($P < 0.05$) across the CoA, which was significantly greater than that observed for control (11 ± 3 mm Hg; Fig. 3A) or corrected rabbits (17 ± 2 mm Hg; Fig. 3B).

Table 2. Hemodynamic and cardiac function indices (n = 7/group; mean ± standard error of the mean).

Index	Control	CoA	Corrected
Blood pressure (mm Hg)			
Systolic	67 ± 2.9	99 ± 6.8*†	69 ± 3.3

Mean	60 ± 3.4	87 ± 8.1*†	61 ± 3.9
Diastolic	56 ± 3.7	74 ± 9.8	54 ± 3.8
Heart rate (bpm)	163 ± 12	147 ± 9	150 ± 13
LV ejection fraction (%)	60.6 ± 1.82	66.4 ± 2.36	65.0 ± 2.98
LV stroke volume (mL)	1.87 ± 0.20	1.99 ± 0.21	1.93 ± 0.10
LV mass/volume ratio (g/mL)	1.24 ± 0.15	1.81 ± 0.26*	1.35 ± 0.15

∗CoA rabbits significantly different from control rabbits ($P < 0.05$).
†CoA rabbits significantly different from correct rabbits ($P < 0.05$).

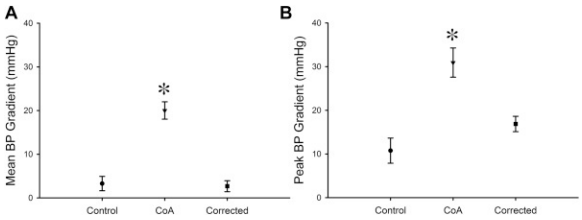

Fig. 3. Mean (A, left) and peak (B, right) blood pressure gradients across the coarctation region as measured with fluid-filled catheters at the conclusion of the experiment (i.e., 32 weeks of age). Data = means ± standard error of the mean. *CoA rabbits significantly different from control rabbits ($P < 0.05$).

There were several time points during which cardiac output as assessed by PC-MRI was statistically different in CoA and/or corrected *versus* control rabbits (Fig. 4A). Total flow was increased in CoA relative to control and corrected rabbits (Fig. 4B).

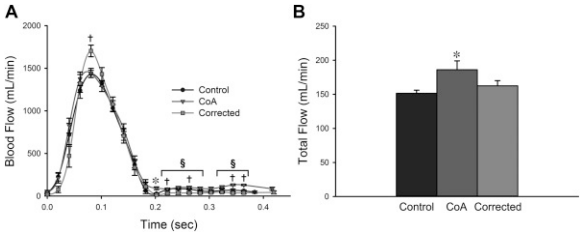

Fig. 4. Cardiac output from the collection of rabbits in each experimental group, as assessed by PC-MRI in the ascending aorta (A). The time points of maximum blood flow were aligned for measurements made from rabbits in each group, and the waveforms were then ensemble averaged to generate the representative plots shown. Total flow is also shown (B) and was determined by integrating the area under each AscAo blood flow waveform. Data = means ± standard error of the mean. *CoA rabbits significantly different from control rabbits ($P < 0.05$); †corrected rabbits significantly different from control rabbits ($P < 0.05$); and §CoA rabbits significantly different from correct rabbits ($P < 0.05$).

There were no differences in HR between experimental groups (Table 2). There was a trend toward increasing stroke volume and ejection fraction for CoA and corrected *versus* control rabbits, but this difference did not reach significance. Representative LV morphologic images from rabbits in each group are shown in Figure 5. There was a significant increase in LV mass for CoA *versus* control and corrected rabbits. Local thickness was increased along the anteroseptal and inferolateral locations of the LV wall in CoA rabbits (Table 3), but no differences in thickness were noted between values at these locations within groups. LV mass/volume ratios increased significantly for CoA rabbits, consistent with this compensated state of the LV (Table 2).

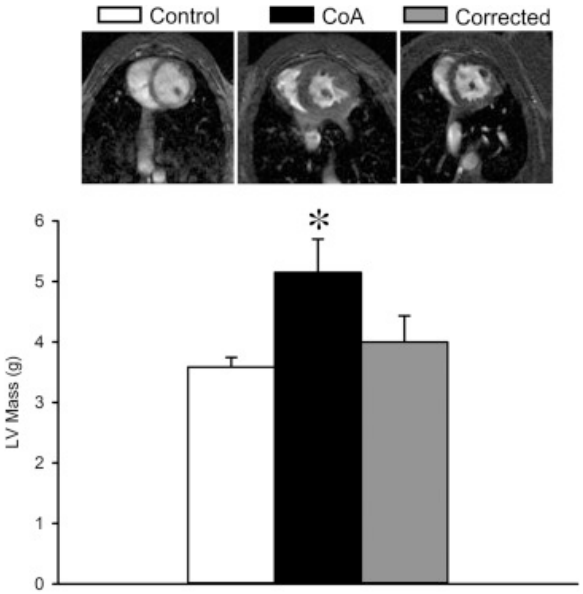

Fig. 5. Representative magnetic resonance images obtained at the center of hearts from rabbits in each experimental group (top), and LV mass measurements from the collection of rabbits (*n* = 7) in each group (bottom). The images selected for presentation in each group (top) represent those with an LV mass near the mean for the group (bottom). Data = means ± standard error of the mean. *CoA rabbits significantly different from control rabbits ($P < 0.05$).

Table 3. LV thickness quantified along the anteroseptal and inferolateral walls (*n* = 7/group; mean ± standard error of the mean).

Thickness (mm)	Control	CoA	Corrected
Anteroseptal wall	2.44 ± 0.12	4.42 ± 0.57*	3.70 ± 0.30
Inferolateral wall	2.94 ± 0.27	4.65 ± 0.43*	3.91 ± 0.26

∗ CoA rabbits significantly different from control rabbits ($P < 0.05$).

Discussion

The study of persistent morbidity in patients with CoA after correction is difficult in a clinical setting due to the limited number and heterogeneity of CoA patients. Although remodeling of the LV in response to pressure overload has been studied in numerous animal models, there is a paucity of data using a clinically representative BPG that also includes data after correction of the coarctation. We therefore conducted this MRI-based investigation with a novel animal model of CoA and correction focusing on the putative clinical treatment guideline of 20 mm Hg to better assess alterations in LV morphology and function at this level of obstruction.

The statistically significant increases in LV mass observed for the CoA rabbits in the present study was ~46% above control levels, which is similar to values seen previously during the compensation phase of LV remodeling.17, 18 The increase in total AscAo flow, as well as trends toward increases in LV ejection fraction, LV stroke volume and LV mass/volume ratio further supports the presence of LV remodeling before the transition to decompensated pressure-overload LV hypertrophy. Increased thickness from anteroseptal and inferolateral measurements between CoA *versus* control and corrected groups, but not for individual animals within groups, indicates concentric remodeling exists (as would be expected in this model of increased afterload).

Clinically, systolic BPG measured by appropriately sized cuffs is the first method used to assess patients with CoA. In this approach, clinicians measure the difference in systolic BP for a site above the narrowed site of CoA (arm BP), comparing this value with systolic BP for the descending thoracic aortabelow the narrowing (leg BP). When the results from these clinical examination suggest CoA, the next step is ultrasound (i.e., echo) imaging of

the heart with attention to the arch. Just as was conducted in the present study, the severity of CoA is most often assessed by two-dimensional echo and spectral Doppler analysis. The Doppler peak instantaneous BPG across the narrowing is then estimated by the modified Bernoulli equation. However, invasive cardiac catheterization measuring the peak-to-peak gradient across the CoA represents the gold standard in the pediatric population.[13], [14] Although Doppler-measured BPG tends to overestimate catheter-measured BPG in many cases, Doppler peak instantaneous BPG correlates reasonably well with catheter peak-to-peak BPG in patients with native or recurrent CoA that do not have collateral vessels or retrograde flow during diastole. Nevertheless, we also chose to report mean BPG in the present study because this value has importance in terms of understanding blood flow, cardiac output, aortic remodeling, and residual resistance. The peak systolic BPG reported here in corrected rabbits (17 ± 2 mm Hg) is likely due to increased flow at the peak systolic time point as measured by PC-MRI. Flow at this time may reflect the presence of some residual arch narrowing and/or stiffening limiting BP-induced dilation upstream as a result of aortic remodeling proximal to the coarctation, which has previously been reported with the current experimental model.[7], [8] Modest residual narrowing also seems to be present from Figure 2 of the present study. Differences in mean BP are responsible for blood flow from one location to another in the circulation, and we recall that flow (i.e., cardiac output) equals BP divided by resistance. The mean BPG for corrected rabbits (3 ± 1 mm Hg) was similar to control rabbits (3 ± 2 mm Hg), suggesting that with similar cardiac outputs (as reported here), total systemic resistances should also be similar and any residual narrowing is likely minimal for most of the cardiac cycle.

Not unexpectedly, those rabbits with CoA at study conclusion were hypertensive compared with control rabbits and compared with the corrected group (Table 2). Hypertension (HTN) is a known long-term complication of CoA with implications for long-term cardiovascular health, leading to LV hypertrophy and being a “risk factor” for the development of atherosclerosis. Clinical experience notes a 10%-20% risk for residual HTN, even if the CoA was repaired in infancy.[19] It has been shown that 24-hour BP assessment may unmask the presence of HTN, which is missed with simple BP spot assessments in the clinic. Those patients with “masked HTN” have increased LV mass index and diastolic dysfunction when compared with subjects having normal BP on 24-hour assessment.[20] The similarity of LV results for corrected *versus* control rabbits represents the most interesting portions of this study, suggesting correction of a 20 mm Hg BPG may preserve cardiac function and LV dimensions. However, it is worth noting that corrected rabbits collectively had almost the same LV EF as CoA rabbits, with an LV mass similar to those in control rabbits. These differences did not reach significance with the sample size of the current investigation but may be hypothesis generating in terms of an acceptable BPG for the LV given other research from corrected CoA in a persistent hyperdynamic state.[4], [5]

Methods for ventriculoarterial coupling allow researchers to relate ventricular elastance to the vasculature using the effective arterial elastance function.[21] However, such methods are not trivial to employ clinically or experimentally and there is therefore a paucity of the data relating the impact of changes in aortic morphology to LV structure and function in the setting of CoA.[22] The current model may be important in this regard. For example, recent literature suggests the putative treatment guideline of 20 mm Hg BPG frequently implemented in CoA studies causes potentially irreversible vascular changes despite correction when assessed by myography, histology, immunohistochemistry, and gene microarray analysis.[7], [8] However, the current results from the same group of rabbits where these vascular changes were measured suggest that, from the LV's perspective, the current putative gradient for correction seems reasonable. Although it is reassuring to note there are seemingly different levels of plasticity within the cardiovascular system, this presents a potential difficulty when deciding when to intervene, as permanent cardiac changes do not appear to accompany a BPG <20 mm Hg.

The current animal model of CoA devoid of underlying genetic precursors for changes in cardiac or vascular morphology, and without concomitant anomalies that often present with CoA in humans, may have added value beyond that presented here. This model may now be employed in future research efforts of more complex

disease to allow systematic study of the effects of coarctation on the myocardium and impacted vasculature from changes in local hemodynamics. Future research efforts may also employ the current rabbit CoA model to assess the clinical course in animals when myocardial function is not optimal. Longer follow-up may also be undertaken in future studies to simulate adult pathology resulting from residual CoA. Finally, this model may be useful, as attempts are made to optimize interventional options for arch repair, such as through the development of vascular stents having properties more akin to native vessels.

The current results should be interpreted relative to several potential limitations. The vascular pathology from the current model has striking similarities to that found in humans. However, the current model induces CoA in 10-week-old juvenile rabbits, which remains in place for corrected rabbits until the equivalent of 11-12 human years of age. The age of onset used to date in the model may therefore suggest the current results could be more applicable to cases of BPG resulting from recoarctation after treatment early in life, rather than cases of native CoA. However, a recent review of ~400 coarctation patients at our center revealed that the age when surgical treatment was imposed in these patients ranged from 0 to 37 years (mean = 2.6 years). 73% of these patients were treated by age 2, and another ~22% had an average age of 12 years at the time of surgery. These age distributions in humans with CoA lend support to the use of juvenile rabbits in the present study, while also underscoring the need to repeat the current work with neonatal rabbits in future studies. The present study was also limited in follow-up to 32 weeks (i.e., human equivalent 19 years), as this research focused on disease in a pediatric-equivalent cohort. Thus, long-term consequences of a residual 20 mm Hg BPG, remaining into adult years, could not be assessed here but will be the focus of future studies as time and funding permit.

The current data suggest the increase in systolic pressure induced by the CoA results in myocardial hypertrophy, which resolves following repair of the CoA (in the corrected group). The findings of this study indicate this rabbit model can be used to elucidate the complex ventricular remodelingcapabilities of the heart under different loading conditions such as those occurring in CoA and a wide variety of congenital heart diseases.

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Authors' contributions: M.M.S. and I.F. contributed to data analysis, interpretation of results, and manuscript preparation. In addition to these areas, D.C.W., L.M.H., and J.F.L. conceived the study design and conducted the imaging studies.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

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