

# Collateral Circulation and Secondary Hypertension Response in Adult Yucatan Minipigs after Experimental Aortic Coarctation

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## Abstract

Coarctation of the thoracic aorta was produced in 9 adult Yucatan mini pigs. A gradually aortic constriction was accomplished by placing a "C" shaped expandable occluder around the thoracic aorta. The aortic constriction was standardized by measuring the blood pressure above the coarctation with 165-170mm Hg mean arterial pressure as the target. The gradual occlusion of the aorta was performed over a period of 15 days. The pigs were studied for 4 (n=3) and 8 (n=5) weeks of cranial hypertension and then euthanized. Three animals served as controls. There were no deaths associated with placement of the occluder or constriction of the aorta and neither rear limb weakness nor neurologic dysfunction were noted. Aortic angiography demonstrated a severe grade of stenosis and extensive collateral circulation in the 8-week study pigs. This study showed that gradual coarctation of the thoracic aorta in adults and mature minipigs produces chronic and cranial hypertension and is associated with development of an extensive collateral circulation after 8 weeks of the study. The purpose of this work is to reveal the collateral growth and vascular patterns developed around the coarctation. To our knowledge, this collateral circulation response has not previously shown under these conditions and proves that adult porcine individuals can adjust their vasculature to stenotic arterial condition showing dramatical vascular changes in a relatively short period of time.

**Keywords:** Aortic coarctation; Minipig, Hypertension; Collateral circulation; Angiography

## Introduction

Coarctation of the aorta is a common cardiovascular malformation accounting for 5% to 8% of patients with congenital heart disease [1]. One out of every few thousand babies are born with a constricted aorta at a point beyond the arterial branches to the head and arms, but proximal to the kidney. This condition is known by coarctation of the aorta [2]. Elevation of the blood pressure, as well as the unusual distribution of this elevation, produces a unique physiological disturbance. The arterial pressure in the upper part of the body (cranial to the occlusion [prestenotic aorta]) usually averages from 20 to 55 per cent higher than in the lower part of the body or caudal to the occlusion (poststenotic aorta) [2,3]. With coarctation, much of the blood flow to the lower body is carried by collateral blood vessels in the body wall [3]. These vessels form to help compensate for the abnormally high vascular resistance between the upper aorta and the lower aorta. The various mechanisms involved in the pathogenesis of this type of hypertension, although important in the understanding the physiologic alterations in aortic coarctation, are unclear [2,4]. The mechanism of the upper body or prestenotic hypertension in coarctation can, in part, be explained by mechanical factors, the role played by the kidneys (one kidney Goldblatt model) and vascular wall remodeling of the arterial network [5]. Although, there is much to be gained from furthering our understanding of the causes and effects of hypertension on the cardiovascular system. Different classes of animal models of hypertension have been described in the literature. Most of them are developed in rats and present easy management and a modest cost. However, the rat can tolerate 100% of acute aortic coarctation without clinical signs and its vascular response to hypertension and collateral circulation development differ notably when it is compared with human being and large animal vasculature. In contrast, the porcine vasculature is perhaps the closest to the

human [6], and although experimental aortic coarctation has been produced in pigs before, it has been based in acute hypertension studies under anesthesia or the animals were partially coarctated when they were very young.

In the present study, we evaluate the development of chronic hypertension and collateral circulation in conscious and adult pigs during gradual and controlled aortic coarctation. The aim of our study is to reveal the extensive collateral growth occurred around the coarctation and show the increases in both lumen size and number of anastomoses between cranial and caudal intercostals arteries close to the occluder site at 8 weeks of occlusion. These neoformed vascular channels showed vascular patterns consistent with angiogenesis and arteriogenesis on both sides of the occlusion and reveals the collateral circulation as a long-term adaptation to the ischemic flow.

## Materials and Methods

### Animal model

Animal care in this study conformed to the guidelines of the University Laboratory Animal Care Committee of Texas A&M University. Coarctation of the aorta was induced in 9 mature (8-12-month-old) male Yucatan minipigs (Panapinto Micro Minipigs®; Masonville, CO, USA) (nos 1-9), weighing between 25 and 41kg. The pigs, which were kept in separate cages, were allowed to become acclimatized to the experimental environment for a minimum of 15 days before any intervention. All the animals were fed daily with 1lb of LabDiet® Mini-pig HF Grower Granulated (PMI Nutrition International, Inc, St Louis, MO, USA), divided into three feeds. Pigs were restrained in a sling and then mask induced with isoflurane and intratracheal intubation was performed for maintenance of anesthesia and for ventilation support during the surgery. The approach to the caudal thoracic aorta was made through the eighth intercostal space from a left lateral thoracotomy. The vascular occluder was placed around the aorta over a previous Gortex banding and the ends were sutured together with non-absorbable material. The tubing of the occluder was passed through the chest wall to the dorso-caudal area of the neck, where a titanium subcutaneous vascular access port (VAP) (TI-VAP; Access Technologies, Skokie, IL, USA) had been placed.

### Occlusion and blood pressure monitoring

Aortic occlusion was started one week after surgery. Blood pressures above the coarctation were measured using two different invasive methods: a carotid vascular catheter attached to a vascular access port (VAP) inserted in 3 animals and a PROPAQ 106 Vital Signs Monitor (Protocol Systems Inc. Beaverton, OR, USA). In 6 pigs, a telemetric method (Data Sciences Inc., MN, USA, model TA111PA-D70) was used to record blood pressure and the telemetry unit catheter was tunneled subcutaneously to the internal thoracic artery and positioned in the vessel distal to its origin at the aorta. Before occlusion was started, a baseline blood pressure was recorded from each animal. Then, variable amounts (0.3-0.5ml) of 50% dextrose were added to the occluder port. This operation was repeated every other day until target pressure was

reached. Thereafter, blood pressure averages were taken every day for the telemetry animals and twice a week for the carotid VAP group. Target day was considered day 1 of the hypertension study and data was registered during 8 weeks.

### Renin activity

Plasma renin activity (PRA) was determined from plasma samples taken from normotensive (control) minipigs weekly, and from hypertensive minipigs every other day for the first 2 weeks, then once weekly. PRA was measured on 1.0ml aliquots of EDTA-treated plasma using the GammaCoat Plasma Renin Activity RIA Kit, supplied by DiaSorin, Inc., Stillwater, MN. In this assay, an ACE inhibitor (phenylmethylsulfonyl fluoride) is added to plasma and the rate of angiotensin I synthesized over time by renin is measured using a competitive RIA with <sup>125</sup>I-labeled angiotensin I and anti-angiotensin I antibody coated test tubes. In-house tests of assay precision have shown within run and between run coefficients of variation of less than 10% and angiotensin I recovery of approximately 100% at physiologic levels of activity. The antibody coated test tube method has a minimal sensitivity to angiotensin I levels down to 18.0pg/tube which, based on preliminary experiments, is well below the level of sensitivity necessary to assess PRA in swine plasma.

### Angiographic studies

After placement of the vascular occluder, control aortic angiograms were performed before the occlusion was initiated. The aortic angiograms (lateral and dorso-ventral) were made using a fluoroscope with a programmed phototimer (RTP9211G-PG, 1990, Toshiba Medical Systems, Inc, Tustin, CA, USA). A 7 F catheter was placed in the left carotid and 20ml of contrast was injected in each projection with a multiple injector (Medrad Mark V Plus, manufactured by Medrad UK, Ltd). After 8 weeks of hypertension, a second aortic angiogram was performed in 5 animals of the study to reveal and evaluate the presence and size of collateral arteries. Euthanasia was delayed for two days later to allow the contrast agent to be cleared. A complete necropsy was performed.

### Control study

Three pigs served as controls for blood pressure measurements, renin activity and collateral circulation development. In these pigs, blood pressure was measured by inserting a carotid (VAP) in one pig and telemetry units in the other two animals. Blood samples were taken through a vascular access port. None of these animals underwent a thoracotomy for placement of an aortic occluder.

### Statistical methods

The results of the systolic, diastolic and mean blood pressure were expressed as mean±SD. Deviation from normal distribution was evaluated by Kolmogorov-Smirnov statistic test. The follow-up data was divided in four different moments of the research experience to compare blood pressures between hypertensive pigs: Surgery day, 1<sup>st</sup> target day (Mean Arterial Blood Pressure ≥150mmHg), after 4 weeks of hypertension (n=3) and after 8 weeks of hypertension (n=5). Comparison of the evolution of these

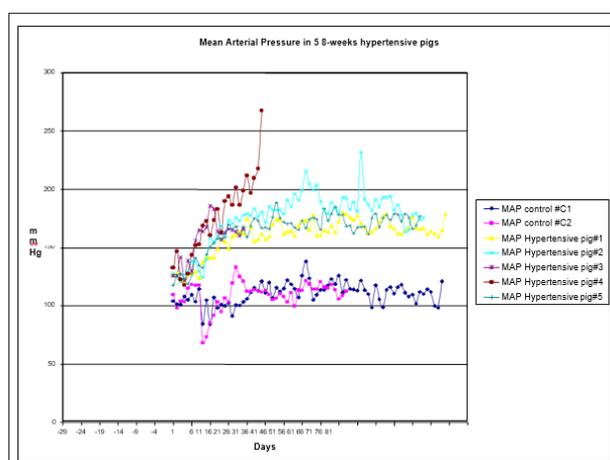
different measurements between hypertensive animals was made by paired Student's t test to analyze the differences between the mean values in paired samples. Comparisons of the mean values between hypertensive animals and control animals in the same chronological moments were used by unpaired Student's t test for independent samples. Statistical significance was taken as a p value < 0.05. Data analysis was performed using the SPSS Statistical Package (version 10.0 for Windows).

## Results

### Hypertension study and plasma renin activity

Coarctation of the middle thoracic aorta was successfully performed on 9 animals of the study, all of whom developed hypertension (Figure 1). The mean blood pressure was maintained at greater than 165mmHg during the 4 and 8-week study period. Target blood pressure in all pigs was reached between 17-39 days from the initial occlusion. Arterial blood pressures and the

heart rate were easily recorded throughout the study and the pigs showed no signs of ischemic paralysis during the development of hypertension. Blood pressure could be analyzed by the Student's t test for paired samples between the mean values of hypertensive pigs. Four moments of the experience were taken into consideration: Surgery day, 1<sup>st</sup> target day, after 4 weeks of hypertension and after 8 weeks hypertension. The mean values of mean arterial blood pressure (MAP) in paired samples are summarized in Table 1. Systolic and diastolic blood pressures evolution followed a similar pattern to MAP. Surgery day mean values of blood pressures, n=8, 146±12/109±11mmHg were significantly lower to 1<sup>st</sup> target day mean values, n=8 (174±17/126±14)mmHg, also to 4 weeks mean values, n=8 174±17/126±14 mmHg and to 8 weeks mean values, n=5 200±30/160±13mmHg, p<0.05. Mean values from 1<sup>st</sup> target day were significantly lower comparing with 4 (n=8) and 8 (n=5) weeks of hypertension, p<0.05. Finally, there were no significant differences between 4 (n=5) and 8 (n=5) weeks of hypertension, p>0.05.



**Figure 1:** Mean arterial blood pressures in five 8-weeks hypertensive pigs compared with two control pigs' study (dashed lines).

**Table 1:** Evolution of map in hypertensive pigs along the experience.

	n	Mean	SD	p*
Surgery day	8	126,52	7,34	
Day 0(1 <sup>st</sup> target day)	8	148,46	7,41	<0,001
Surgery day	8	126,52	7,34	
4-week hypertension	8	179,36	13,46	<0,001
Surgery day	5	125,40	5,42	
8-week hypertension	5	178,43	20,38	0,003
Day 0(1 <sup>st</sup> target day)	8	148,46	7,41	
4-week hypertension	8	179,36	13,46	0,001
Day 0(1 <sup>st</sup> target day)	5	147,42	6,47	
8-week hypertension	5	178,43	20,38	0,029
4-week hypertension	5	179,81	17,08	
8-week hypertension	5	178,43	20,38	0,880

Comparison of the mean values between hypertensive pigs and controls were taken into consideration by unpaired Student's t test for independent samples. This test showed that there were significant differences in the mean values of surgery day, 1<sup>st</sup> target

day, and 4 weeks of hypertension between the hypertensive animals and the controls at the same chronological references, p< 0.05 (Table 2). Mean values of the controls at surgery day were n=3 122±12/94±11mmHg, at 1<sup>st</sup> target day were n=3

110±32/86±14 mmHg and at 4 weeks of hypertension were n=3 132±11/99±15mmHg. Hypertension was reversed in a pig of the study, the pre-occlusion average arterial pressures of 143±16/111±6 (127±7)mmHg increased to 175±9/158±10 (164±8) after target pressure were reached until day 20 of the study when arterial blood pressure decreased to 125±23/107±26 (114±24)mmHg. Additional pressure on the occluder was not successful in increasing the pressure, and the occlusion was completely removed on day 21 of the study. The pressure increased slightly after removal of

the aortic occlusion (171mmHg on day 25) and then decreased to lower than normal values before stabilized. The mean PRA from normotensive controls was 0.48±0.25±g/ml/hr over a 30-day period. In hypertensive minipigs, the PRA increased 5-fold or more within 5 days of the first occlusion of the aorta. Within 30 days of reaching target blood pressure of 150mmHg or more the PRA had returned to pre-occlusion levels, regardless of whether or not further inflation of the occluder and further constriction of the aorta occurred.

**Table 2:** MAP study: Comparisons between hypertensive and control group.

	Hypertensive			Controls			p*
	n	Mean	SD	n	Mean	SD	
Surgery day	8	126,52	7,34	3	102,15	16,18	0,006
Day 0(1 <sup>st</sup> target day)	8	148,46	7,41	3	95,58	20,15	0,039
4-week hypertension	8	179,36	13,46	3	118,92	3,47	<0,001
8-week hypertension	5	178,43	20,38	1	108,90	NA	NA

\*Student's t test between the mean values for independent samples.

### Angiographic study

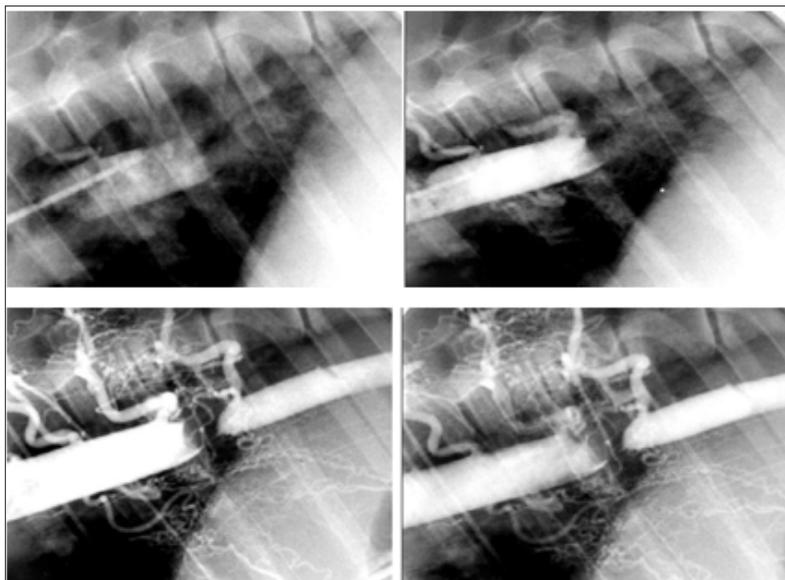
A clear and well-developed collateral circulation was observed in all the animals of the angiographic study after 8 weeks of reported hypertension (n=5), as was the effectiveness of the occluder to produce a complete obstruction of the thoracic aorta in an adult model (Figure 2) and (Figure 3). This extensive collateral circulation involved the intercostal arteries and their anastomoses cranial and caudal to the occlusion showing the characteristic corkscrew shape because of their circuitous course. These plexuses of curly arteries spanned through the intercostals muscles and the muscular collateral arteries network between the proximal aorta and distal aorta were clearly identified in the angiograms and were always compared with the control images (Figure 4) as normal references. The intercostal arteries were more tortuous and appeared to have an increased lumen and length compared with controls. Some other

images revealed the presence of hypertrophied intercostal arches coming from the internal thoracic artery and anastomosing with dorsal intercostal arteries supplying blood flow to the caudal part of the aorta. A different process of collateralization could also be shown on the angiograms, where it appeared that the vasa vasorum of the aorta cranial to the occluder arose directly from the lumen of the aorta and bypassed the occlusion downstream from the lesion. In addition, we have observed small vascular channels running along the aorta wall, the pleura and mediastinum area towards the diaphragm and caudally to the occlusion of the aorta (Figure 2) and (Figure 3). At necropsy, the animals showed a significant enlargement of the dorsal intercostal arteries cranial and caudally to the occluder compared with the controls. There were also important changes observed in the adventitia vessels of the aorta wall of the hypertensive pigs which appeared more noticeable and pronounced.

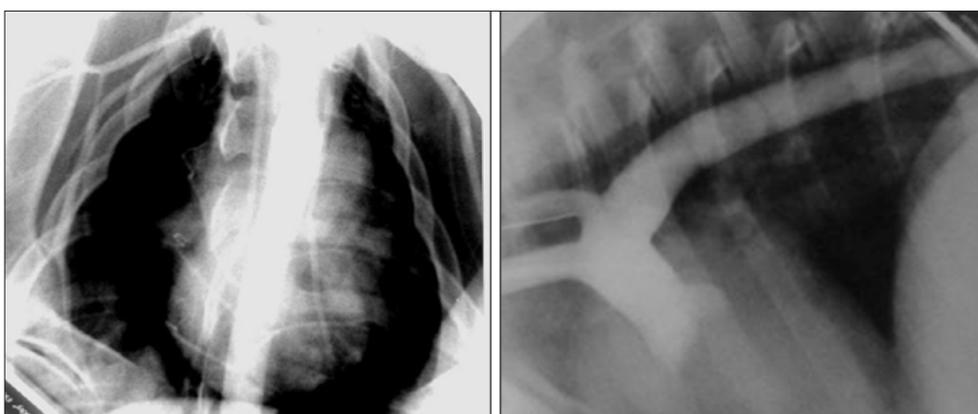


**Figure 2:** Aortic angiograms that show extensive collateral circulation where intercostal arteries are clearly involved and their anastomosis through muscular collateral arteries network are also appreciated. Notice the extremely severe grade of aortic stenosis.

CR: Cranial; R: Right



**Figure 3:** Fluoroscopic angiographic study in lateral projection shows sequential angiograms images. Notice the delay of the contrast re-entrance after coarctation site and the severe grade of aortic stenosis. CR: Cranial



**Figure 4:** Angiograms control. Lateral and dorso-ventral projection respectively.

CR: Cranial; R: Right

## Discussion

### Hypertension in aortic coarctation

All 9 animals under aortic coarctation showed a significant cranial hypertension during 4 or 8 weeks when compared with the control group. All hypertensive animals developed a rise in the systolic, mean, and diastolic blood pressures above the constriction which resembles the hypertension occurring in humans with coarctation of the aorta [1,7]. There was also a pronounced increase in the diastolic phase of the blood pressure, next to the mean blood pressure. The presence of diastolic hypertension can be interpreted as evidence of a generalized increase in vascular tone [1,7]. The important changes affecting the arterial blood pressures values were showed a long the first 28 days (4 weeks) of the study. In this period of time body suffers a great adaptation to the severe aortic stenosis and reaches a level of hypertension next to the maximum that an organism can tolerate before a fatal vascular accident could happen.

The PRA levels in hypertensive pigs increased 5-fold over normotensive- control levels within 5 days fo the first occlusion of the aorta. Within 30 days of reaching target blood pressure of  $\geq 150$ mmHg of the hypertensive pigs, the PRA levels returned to pre-occlusion values. Thus, the PRA course in this study was consistent with an aortic coarctation induced model of hypertension in rat [8]. In our opinion, the activity of the renin-angiotensin system could be the main factor in the early development of hypertension. However, other factors must also be involved to explain the chronic and sustained hypertension seen in these animals. In suprarenal aortic constriction, augmented aortic impedance and shear stress might share with the humoral and neural systems a physiopathological role in the increase of arterial pressure [9].

Although elevated mean arterial pressure (MAP) has traditionally been considered to be an important indicator or initiator of cardiovascular risk in hypertension, mounting evidence suggests that increased pulse pressure is as or more important

Safar & Boudier [10]. Of particular note, data from surgically created aortic coarctations in animals reveal striking evolutions of wall geometry, structure, and properties that appear to be driven primarily by increased pulse pressure, not MAP [11]. It also appears that the associated arterial adaptations progress at different rates and to different extents both temporally (first at basal rates, then rapidly, then back to nearly normal values) and spatially (from proximal to distal sites) [12]. Although additional experimental data will be needed to understand better these spatio-temporal adaptations, computational fluid–solid-growth models (FSG) [13] offer considerable promise both in the design and interpretation of such experiments and in implicating possible biomechanical mechanisms [14]. Further investigations may allow us to discern which vascular growing factors participate cranially and caudally to the stenosis where flow and pressure are vastly different.

### Collateral circulation

The angiographic studies revealed a severe aortic stenosis and an extensive development of collateral circulation affecting the intercostals arteries, intercostals muscles arteries, and internal thoracic. These collateral vessels appeared abnormal and showed evident tortuosity. The angiograms performed showed a clear vascular situation of a total aortic occlusion in some of the animals of the study. Under this situation, the aortic flow had to be diverted through narrower vessels and used the intercostals arteries and intercostals muscle arteries as the first collateral vessels to be involved. These images also demonstrate the profound influence of aortic impedance and wall shear stress cranial to the occluder. The flow in these collateral vessels was conducted from the high-pressure area and high shear stress zone located just before the occluder placement to the low pressure along the thoracic aorta caudal to the occluder. The vascular net is capable of sensing changes within its surroundings, integrating these signals by intercellular communication, and changing itself through the local production of mediators that influence structure as well as function. Thus, the vascular adjustment suffered by the animals of the study and the emergence of molecular and vascular biology in hypertension research has redefined our understanding of the role of the vasculature as a vital organ in the pathogenesis of hypertension [15]. There is no doubt that mechanical conditions to explain development of hypertension are present in our aortic coarctation model although the pathways mediating the response of endothelial cells to hemodynamic stimuli are still unknown [16]. On the other hand, in any adult organism a deficit in the blood flow gives rise to two different mechanisms: angiogenesis and arteriogenesis [17]. In our opinion, these mechanisms are both present in our study based on the observations of the angiogram's images. These vascular processes are basically different and take place in two distinct types of vessels: capillaries and collateral arteries, respectively. We believe that hypoxia is one of the triggers for the neovascularization from the preexisting vasa vasorum of the aorta, in addition to the inflammatory factors that occur due to the presence of the occluder against the aortic wall. The important role of the vasa vasorum has been described previously where the hypertrophied collateral circulation can be associated to hypertrophied vasa vasorum.

This process has been attributed to the revascularization of an occluded internal carotid artery in atherothrombotic occlusion and in experimental hypercholesterolemia of coronary arteries [18,19]. Arteriogenesis process is defined as the *in-situ* growth of muscular collateral arteries (arterioles that interconnect two feeding arteries) in response to a physiological stimulus caused by the occlusion of an artery [17,20]. The significant collateral circulation that were present in the animals of our study involved the intercostals arteries and intercostals muscle arteries which showed an increase of lumen and length of these vessels comparing their angiographic images with the control references. There is no doubt that angiogenesis is mainly caused by hypoxia [21]. While this mechanism remains undisputed for angiogenesis, it is most probably not applicable for arteriogenesis because arteriogenesis proceeds in an environment that is not ischemic or is much less ischemic than tissue where the angiogenesis occurs [22,23]. This fact was also reflected in the angiograms where the muscle neofomed arteries were more evident at the cranial area, in front of the occluder.

In conclusion, this study shows that gradual coarctation of the aorta in adults and mature minipigs produces cranial hypertension and an extensive collateral circulation. The collateral vessels, demonstrated by angiography and at necropsy after 8 weeks of the study, can reduce the often-fatal consequences of the large vessel occlusion. Our angiographic studies show vascular processes consistent with arteriogenesis and angiogenesis phenomena bypassing the site of occlusion. We believe that this vascular model based in aortic coarctation in adults minipigs can contribute to a better understanding of the vascular changes and angiogenesis and arteriogenesis processes under this clinical condition. Further investigations will contribute to understand the biomechanical mechanisms implicated in the collateral circulation formation.

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