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The Effect of Intermittent Umbilical Cord Occlusion on Elastin Composition in the Ovine Fetus

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Abstract

This study aimed to determine the effect of varying degrees of intermittent umbilical cord occlusion (UCO) on arterial elastin composition. Over 4 days, chronically catheterized late gestation fetal sheep received 5 total UCO per day lasting 1 min/h (mild group: n = 6), 2 min/h (moderate group: n = 4), 3 min/h (severe group; n = 6); or no occlusion (control group: n = 7). Each group was evaluated for elastin content of the carotid and superior mesenteric artery (SMA), the arterial pressure response to UCO, and plasma cortisol concentration. Elastin content of the carotid artery was significantly increased by severe UCO (9.5 μg/mg versus 6.4 μg/mg; $P < .05$) and insignificantly increased in mild and moderate groups, whereas UCO had no effect on elastin content of the SMA. This dose- and site-dependent response of the vasculature appears attributable to the hemodynamic changes that accompany UCO.

Keywords

acute hypoxia, fetus, elastin, arterial

Introduction

A nuchal cord occurs when the umbilical cord becomes wrapped around the fetal neck and is detected in 25% of human pregnancies at the time of birth.[1,2] In late gestation, episodes of acute fetal hypoxemia apparent by abnormal heart rate patterns have been linked to the presence of a nuchal cord and are thought to arise from intermittent umbilical cord compression and consequent reductions in umbilical blood flow.[2] These recurrent intrauterine insults have the potential to alter fetal development in relation to the frequency and severity of insult. The cardiovascular system may be particularly susceptible to programming effects since the circulatory response to acute hypoxemia involves mediators of its development, yet vascular changes in response to umbilical cord occlusion (UCO) remain unexplored.

Essential to growth and development of the arterial system is a temporal and spatial adaptation of the vasculature to maturational changes in the physical forces it sustains.[3,4] This process involves geometric and compositional remodeling of the arterial wall, achieved by synthesis and deposition of structural proteins into the extracellular matrix by vascular smooth muscle cells.[3,5] The elastin protein is a primary constituent of the matrix which endows the vascular wall with the ability to expand and recoil and is therefore a major determinant of its viscoelastic property.[6,7] Unlike other arterial wall constituents, elastin is not appreciably synthesized in postnatal life once developmental remodeling is complete.[8-10]

In mammals, the majority of elastin deposition occurs in late gestation, wherein hemodynamic forces become highly influential, and it is during this time when symptomatic nuchal cord is likely to manifest.[3] The fetal circulatory response to UCO involves a transient rise in arterial blood pressure accompanied by a redistribution of cardiac output in favor of vital organs such as the brain.[11-13] Since elastin deposition is stimulated by blood flow in late gestation, the hemodynamic response to intermittent hypoxia may give rise to an increase in elastin content in the carotid artery which is the major supplier of blood to the brain.[9,14] Other possible mediators of perturbations in vascular development are hormones and growth factors involved in the response to acute hypoxia, including angiotensin II, TGF-β, and cortisol which is a potent stimulus for matrix protein deposition in late gestation.[4,15-17]

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The present study used the chronically catheterized ovine fetus to determine elastin content of the carotid artery and superior mesenteric artery (SMA) in relation to severity of intermittent UCO as well as characterize the corresponding fetal response in terms of arterial blood pressure and circulating cortisol concentration. While the duration and severity of UCO varies widely in the human situation, we studied varying degrees of acute hypoxia likely to result in fetal survival and previously shown to produce changes in brain development.[18,19] With regard to arterial development, we chose to centre on the extracellular matrix protein elastin given that once deposited during the brief window of early development, highly resilient mature elastin proteins do not undergo turnover and thus will endure the lifetime of an individual.[8-10] Furthermore, the abundance of elastin in large conduit arteries imparts characteristics of distensibility and elastic recoil that promote cardiovascular homeostasis by dampening the pressure oscillations produced by cardiac ejection.[7] Thus, an alteration in deposition of elastin during development may have long-term consequences for cardiovascular health.

Materials and Methods

All surgical and experimental procedures followed the guide to the care and use of experimental animals approved by the Canadian Council on Animal Care Regulations and The University of Western Ontario Animal Ethics board. Umbilical cord occlusion is an established model of acute hypoxia in the ovine fetus.[12,20,21] Surgical preparation and experimental manipulations were performed as previously described.[12,13]

Surgical Procedure

Pregnant mixed Western ewes between 113 and 117 days of gestation (term = 147 days) were chronically instrumented using sterile technique under general anesthesia (1 g thiopental sodium in solution, intravenously (IV) for induction; Abbott Laboratories Ltd, Montreal, Canada; followed by 1% to 1.5% halothane in O_2 for maintenance). Prior to surgery, an analgesic was given intramuscularly to the ewe (0.2 g ketoprofen, Merial Canada Inc, Quebec, Canada). A midline incision was made in the lower abdominal wall, and the uterus was palpated to determine the fetal number and position. The upper body of the fetus and the proximal portion of the umbilical cord were exteriorized through an incision in the uterine wall. Polyvinyl catheters (Scientific Commodities, Lake Havasu city, Arizona) were placed in the right and left fetal brachiocephalic arteries (0.72:1.22 mm) for measurement of blood pressure and sampling, the right fetal brachiocephalic vein (0.72:1.22 mm) for administration of antibiotics and transfusion of maternal blood, and the right maternal femoral vein (1.68:2.39 mm) for administration of antibiotics, sampling and euthanasia. In experimental animals an inflatable silicone occluder cuff (OCHD16; In Vivo Metric, Healdsburg, California) was positioned around the umbilical cord and secured to the abdominal skin, and the volume required for complete inflation was determined (4 - 6 cc). Once the fetus was returned to the uterus, a catheter was placed in the amniotic fluid cavity for the measurement of amniotic pressure. Antibiotics were administered intra-operatively to the mother, (0.2 g trimethoprim and 1.2 g sulfadorine (IV), Schering Canada Inc, Pointe-Claire, Quebec, Canada) fetus (IV) and amniotic cavity (1 million IU penicillin G sodium, Pharmaceutical Partners of Canada, Richmond Hill, Ontario, Canada). The uterus and abdominal wall incisions were sutured in layers and catheters exteriorized through the maternal flank and secured to the back of the ewe in a plastic pouch.

Ewes were allowed a 3- to 4-day postoperative period prior to experimentation, during which the antibiotic regime was administered. Arterial blood was sampled for evaluation of maternal and fetal conditions and catheters were flushed with heparinized saline to maintain patency.

Experimental Protocol

Following recovery, fetuses were studied over a 4-day period. Umbilical cord occlusion was achieved by completely inflating the cuff with sterile saline using the predetermined volume. Over a 5-hour period, the mild group received a single 1-minute occlusion every hour (n = 6), the moderate group a single 2-minute occlusion every hour (n = 4), the severe group a single 3-minute occlusion every hour (n = 6) and the control group received no occlusion (n = 7). For each experimental day, the 5-hour occlusion series was preceded by a 2-hour baseline and followed by a 2-hour recovery period. On days 1 and 4, fetal blood samples were taken during baseline and recovery for measurement of cortisol, blood gases, lactate, and pH. Additionally, fetal blood gases, lactate, and pH were measured 5 minutes before the occlusion, at the end of the occlusion, and 5 minutes after the occlusion, for the first and last occlusion of each day.

Measurement of blood gases, blood pressure, and heart rate. Blood was analyzed for blood gases, oxygen saturation, lactate, and pH using a blood gas analyzer (ABL-725, Radiometer, Copenhagen, Denmark) and corrected for fetal temperature (T = 39.5°C). Plasma aliquots from samples drawn at baseline, post-UCO (first and last UCO), and recovery were stored at −80= °C for later cortisol analysis. Fetal arterial blood pressure, adjusted for amniotic fluid pressure, was continuously monitored with pressure transducers (Cobe, Arvada, Colorado) and recorded on a data acquisition system (Powerlab model ML 795, ADI Instruments, Colorado Springs, Colorado). Fetal heart rate (FHR) was derived from the arterial blood pressure waveform. The control group was subjected to the same blood sampling and cardiovascular monitoring regime as the experimental group.

On the fourth day of study ewes, fetuses were sacrificed with an overdose of barbiturate after the 2-h recovery period (30 mg pentobarbital sodium, Fatal-Plus; Vortech Pharmaceuticals, Dearborn, Michigan); the fetus was delivered immediately by

cesarean section and weighed. Approximately 2 cm of the carotid artery was taken above the aortic arch and the superior mesenteric was excised between its origin and the first pancreatic branch. Vessels were stripped of connective tissue, fast frozen in liquid nitrogen, and stored at −80°C for later analysis.

Biochemical analysis: Thawed samples were diced and weighed.

Measurement of elastin composition. Extraction and quantification of elastin was performed as previously described.[22-24] After the tissues were weighed they were treated with 0.25 mol/L oxalic acid and then placed into a boiling water bath for 60 minutes for extraction of insoluble elastin. After centrifugation (3000 rpm for 10 minutes), the liquid was retained and the extraction procedure repeated for the remaining residue. It was confirmed that 2 heat extractions resulted in complete solubilization of elastin. Elastin was recovered from the liquid extract and precipitated using fastin dye reagent: 5,10,15,20-tetraphenyl-21,23-pophrine sulfonate, and quantified according to the manufacturer's instructions for the Fastin elastin assay (Biocolor, Belfast, Ireland). Absorbance of standards (0, 12.5, 25, 50, and 70 μg/μL) and samples were read on a microplate reader (Multiskan Ascent, Thermo labsystems, Fischer Scientific, Ottawa, Canada) using a 509 nm blue green filter. The amount of elastin present was determined from the standard curve and expressed as μg per mg tissue. The intra-assay and inter-assay coefficients of variation for the Fastin elastin assay were 5.9% and 9.9%, respectively.

Measurement of circulating cortisol. Cortisol plasma concentration was measured using an enzyme-linked immunosorbent (ELISA) assay (ALPCO Diagnostics, Salem, New Hampshire); the intra-assay and inter-assay coefficients of variation for the cortisol ELISA were 5.6% and 7.1%, respectively.

Data Analysis and Statistical Procedures

Analyses of the raw blood pressure signal and heart rate data were performed using powerlab software (Powerlab, ADI Instruments, Colorado Springs, Colorado). During the baseline and recovery periods on days 1 and 4, 20 minutes averages of fetal mean arterial blood pressure (MAP), systolic pressure (SysP), pulse pressure (PP), and FHR were calculated for each fetus. Within-group comparisons of baseline and recovery values across the 4 experimental days were made by a one-way ANOVA for repeated measures. For each UCO on days 1 and 4, 30-second averages of MAP and PP data and 10-second averages of FHR data were calculated over 2 minutes prior to the onset of occlusion and over the course of the response, for the determination of the maximum change (Δ) in MAP and the duration of the rise in MAP. Also, 10-minute averages of MAP, PP, and SysP, from the onset of UCO, were measured and used to calculate the mean pre- to post-UCO change in these variables. Differences between groups in elastin content of the carotid and superior mesenteric arteries were assessed using a one-way ANOVA. Cortisol concentrations were analyzed using repeated measures, and group means were calculated. A post hoc Bonferroni test was performed with findings of significant difference. Results are presented as ± SEM.

Results

Gestational age and birth weight were similar across groups. Experimental groups comprised 7 control, 6 mild, 4 moderate, and 6 severe animals. There were no significant differences in fetal oxygenation and MAP at baseline on day 1 between the 4 groups ([control PaO_2: 23.6 ± 0.9 mm Hg; MAP: 37.6 ± 4.5 mm Hg), (mild PaO_2: 23.3 ± 0.9 mm Hg; MAP: 39.7 ± 3.7 mm Hg), (moderate PaO_2: 22.1 ± 0.4 mm Hg; MAP: 42.5 ± 2.5 mm Hg), (severe PaO_2: 22.0 ± 1.2 mm Hg; MAP: 40.0 ± 3.4 mm Hg]). There was no change in baseline MAP over the 4-day experiment. As well, baseline cortisol levels were similar among groups on day 1 and within groups across the study ([day 1: control: 2.4 ± 0.3 μg/dL; mild: 3.4 ± 0.1 μg/dL; moderate: 3.1 ± 0.9 μg/dL; severe: 2.5 ± 0.6 μg/dL), (day 4: control: 5.4 ± 2.6 μg/dL; mild: 6.8 ± 4.0 μg/dL; moderate: 7.0 ± 3.3 μg/dL; severe: 3.2 ± 0.6 μg/dL)].

Fetal arterial oxygen pressure (PaO_2), oxygen saturation (O_2 sat), and carbon dioxide pressure ($PaCO_2$) changed in a graded fashion across mild, moderate, and severe groups (Table 1). Fetal arterial oxygenation and pH returned to preocclusion levels by 5 minutes of postocclusion in all experimental groups. An immediate deceleration in FHR accompanied UCO of each degree, with a return to baseline within 3 minutes (Figure 1). Mild, moderate, and severe occlusions produced a transient rise in MAP, Sys P, and PP. The max Δ in MAP and the mean Δ in MAP associated with cord occlusion in each group are shown in Table 2. The mean level of MAP over the 10-minute period following the onset of UCO, as well as the duration of the rise in MAP post-UCO, is also shown in Table 2. The mean Δ in SysP stimulated by UCO increased in magnitude across groups (mild: 12.3 ± 1.0 mm Hg; moderate: 17.6 ± 1.1 mm Hg; severe: 20.0 ± 1.5 mm Hg, $P < .01$). Although PP increased in response to UCO, the mean Δ in PP did not differ between groups (mild: 5.2 ± 0.3 mm Hg; moderate 4.9 ± 0.7 mm Hg; severe: 6.2 ± 0.8 mm Hg).

A trend toward increasing elastin content of the carotid artery with increasing severity of fetal hypoxemia was apparent, the difference was only significant for the severe group ($P < .05$) (Table 2, Figure 2). In contrast, elastin content of the SMA did not differ between the 3 UCO groups and the control group (Figure 2).

There was no consistent cortisol response to mild UCO on day 1 or 4.

However, repeated measures analysis revealed post-UCO plasma cortisol concentration to be consistently elevated in all fetuses made moderately or severely hypoxic on days 1 and 4 ($P < 0.05$). The percentage change in cortisol concentration associated with UCO on day 1 for the moderate group was 69.4% ± 8.9% and for the severe group 95.2% ± 17.6%; and

Table 1. Blood Gases, Lactate, and pH Values Pre- and End-UCO[a]

	PaO_2 (mm Hg)		O_2 sat (%)		CaO_2 (mm Hg)		Lact (mmol/L)		pH	
	Pre-UCO	End-UCO	Pre-UCO	End-UCO	Pre-UCO	End-UCO	Pre-UCO	End-UCO	Pre-UCO	End-UCO
Mild (n = 6)	23.6 ± 0.5	9.8 ± 0.9[b,c]	63.4 ± 1.8	12.8 ± 3.3[b,c]	48 ± 0.6	53.7 ± 1.1[b,c]	1.1 ± 0.1	1.0 ± 0.1[c]	7.36 ± 0.2	7.32 ± 0.0[b,c]
Moderate (n = 4)	22.2 ± 0.7	7.3 ± 0.8[b,c]	57.6 ± 1.9	7.4 ± 1.6[b,c]	49 ± 0.7	62.1 ± 1.4[b,c]	1.4 ± 0.2	1.9 ± 0.3[b,c]	7.35 ± 0.1	7.26 ± 0.1[b,c]
Severe (n = 7)	23.0 ± 0.7	4.7 ± 1.1[b,c]	66.5 ± 1.1	2.8 ± 2.0[b,c]	47.9 ± 0.5	68.0 ± 2.3[b,c]	1.1 ± 0.2	2.2 ± 0.1[b,c]	7.37 ± 0.0	7.23 ± 0.0[b,c]

[a] Fetal arterial blood samples were drawn and analyzed for blood gases, lactate (lact) and pH; 5 minutes before (pre) and at the end of (end) umbilical cord occlusion (UCO). Hypoxia in response to UCO occurred in a graded fashion across mild, moderate, and severe UCO groups.

[b] Pre-versus end-UCO differences are all significant at $P < .01$ for all groups, except for lactate values for the mild group.

[c] End-UCO values between the groups are all significant at $P < .01$.

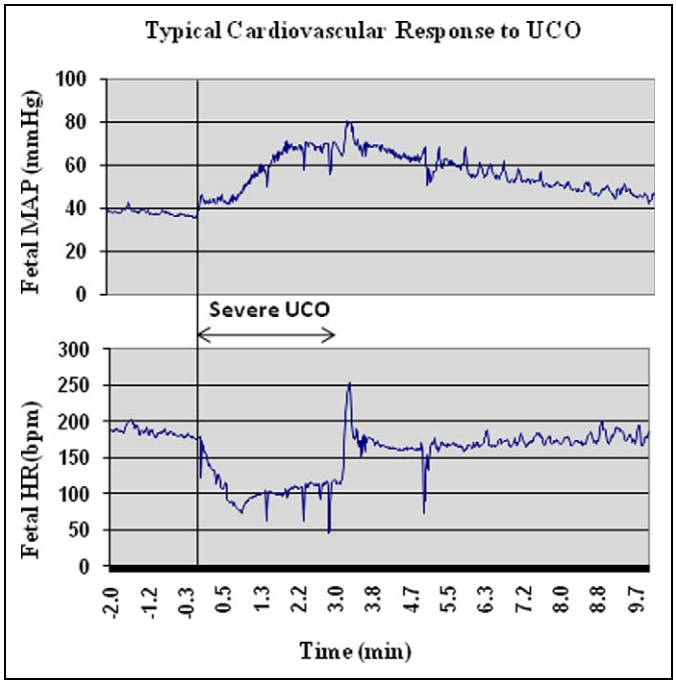

Figure 1. The typical response to umbilical cord occlusion (UCO) of each degree was characterized by a transient fall in fetal heart rate and fetal mean arterial blood pressure. Shown is the blood pressure and heart rate response to severe UCO. The 3-minute UCO was initiated at time 0 minutes (as indicated by the horizontal line). Blood pressure was measured from the brachiocephalic artery and heart rate was derived from the arterial blood pressure waveform.

day 4 for the moderate group was 76.8% ± 38.6% and for the severe group 112.1% ± 32.7%.

Discussion

The present study is the first to examine the effect of acute intermittent hypoxia on fetal arterial remodeling. Three degrees of acute, reversible hypoxemia without cumulative acidosis due to varied duration of UCO were produced repeatedly over 4 days in the late gestation ovine fetus. Fetuses exposed to intermittent hypoxia exhibited increased elastin content of the carotid artery in relation to the control group, with the most pronounced change observed in the severe UCO group. In contrast, no change in elastin content of the superior mesenteric artery was found. A transient rise in fetal blood pressure accompanied hypoxemia of each degree, and was increased in magnitude across mild, moderate and severe groups. We surmise that this circulatory adjustment to UCO accounts for the differential response in protein accumulation between the carotid and the superior mesenteric artery.

Compliance of central conduit arteries, which is largely a function of the abundant elastin protein, is an important and independent determinant of cardiovascular health because it determines pulsatile load of the system.[7] Since there is no appreciable synthesis of elastin after development, the content of elastin is largely determined in fetal life. Degradation and fragmentation of elastin over age in postnatal life due to repeated bouts of cyclic stretch have been implicated in the progression of hypertension and cardiovascular disease.[25,26] Therefore, the increase in elastin concentration of the fetal carotid artery in response to acute intermittent hypoxia may protect against the development of cardiovascular disease in postnatal life; thus the present study provides evidence for potentially beneficial programming in response to an acute prenatal insult.

Alterations in vascular development produced by repeated UCO may be mediated by the changes in hemodynamic conditions and circulating hormones that occur in response to acute hypoxia or by direct effects of oxygen tension. Fetuses exposed to intermittent hypoxia in this study exhibited increased elastin content of the carotid artery in relation to control, with the most pronounced change in the severe group. We propose that the increase in elastin content of the carotid artery resulted primarily from hypoxic-induced changes in hemodynamic regulators of protein deposition. A transient rise in fetal blood pressure accompanied hypoxemia of each degree and was increased in magnitude across mild, moderate, and severe groups. It is known that redistribution of cardiac output with preference to the brain accompanies elevated blood pressure during acute hypoxia.[11-13] Although blood flow was not measured in the present study, an increase in blood flow constituting both pressure and resistance elements and proportional to the observed increase in blood pressure is expected to occur in the carotid artery. Animals were examined in late gestation which corresponds to a time when elastin synthesis accelerates and becomes highly related to blood flow, in both human and sheep.[3] The regulatory role of blood flow in elastin deposition during development has been demonstrated in fetal sheep by correlational analysis in various vessels and by experimental manipulations in neonatal rabbits whereby increases in local blood flow stimulate increases in arterial elastin content and decreases in elastin accumulation result from reductions in blood flow, with no effect on collagen.[9,14,27,28] Only severe hypoxemia produced an average level of fetal MAP over the 10-minute period following the onset of UCO that was significantly greater than control values; and this level approaches that previously reported in newborn lambs at the time of peak elastin synthesis.[3] Therefore, a developmentally determined threshold level of blood flow stimulating an upregulation in elastin synthesis may have been achieved during severe UCO, resulting in the marked response of elastin accumulation in the carotid artery observed in this group.

Interestingly, elastin content of the SMA was found to be unchanged by UCO. Blood flow through the carotid artery versus the SMA would differ dramatically during UCO due to local changes in vascular resistance that function in redistributing cardiac output with preference to the brain; whereas blood pressure would be similar between these 2 vessels. Previous studies have reported blood flow to the digestive tract to be maintained during complete occlusion similar in degree to that used in the present study and to only decrease in more severe hypoxemia with developing acidosis.[16,29,30] It is important to note that the relation between hemodynamic forces and elastin

Table 2. Elastin Content of the Carotid Artery and Fetal Circulatory Response to UCO[a]

Group	Elastin	Mean Δ MAP	Max Δ MAP	Post mean MAP	Duration
Control (n = 7)	5.7 ± 0.4	2.1 ± 0.5	4.0 ± 1.7	41.51 ± 2.8	–
Mild (n = 6)	7.0 ± 0.7	10.0 ± 0.9[b]	21.1 ± 2.5[b]	47.6 ± 2.5	10.4 ± 2.5
Moderate (n = 4)	7.4 ± 0.7	14.8 ± 0.9[b,c]	32.4 ± 1.6[b,c]	52.0 ± 1.0	14.3 ± 0.6[c]
Severe (n = 6)	9.5 ± 1.0[d]	17.0 ± 0.7[b,e]	34.5 ± 0.6[b,e]	54.0 ± 2.4[d]	17.4 ± 1.2[e]

[a] Elastin content (μg/mg tissue); mean Δ in fetal MAP (mm Hg) was calculated from 2-minutes averages pre-UCO and 10-minutes averages from the onset of UCO; max Δ in fetal MAP was calculated from pre-UCO averages and the highest value achieved post-UCO. Control values were derived by the same calculations at time points matching UCO data. Duration of the rise in MAP was measured as the time (minute) from the onset of UCO to the return of baseline values. For differences between groups a one-way ANOVA was used.
[b] $P < .01$ versus control.
[c] $P < .05$ versus mild.
[d] $P < .05$ versus control.
[e] $P < .01$ versus moderate.

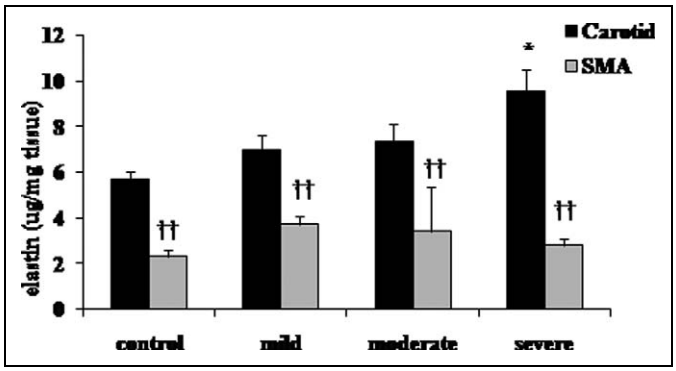

Figure 2. Elastin composition in the carotid versus superior mesenteric artery (SMA). Total soluble elastin was extracted with oxalic acid and quantified using a biochemical assay; values are expressed as μg/mg tissue and ± SEM. The control group (N = 7) received no umbilical cord occlusions (UCO); the mild hypoxic groups (N = 6) received 1 minute UCO/h; the moderate hypoxic group (N = 5) 2 minutes UCO/h and the severe hypoxic group (N = 6) received 3 minutes UCO/h. Elastin composition was higher in the severe group compared to control ($P < .05$). * Hypoxic groups vs. control $P < .05$; †† SMA vs. carotid artery $P < .01$.

accumulation has been studied primarily in large arteries, thus it is possible that a different regulatory function of mechanical stimuli pertains to remodeling of small muscular arteries such as the SMA.

In addition to locally mediated arterial remodeling, changes in circulating hormones induced by acute hypoxemia may contribute to the high elastin content observed with severe UCO. In agreement with previous work, we found circulating cortisol to rise in response to UCO.[31-33] Cortisol stimulates both elastin and collagen synthesis and is thought to mediate the precipitous rise in protein accumulation that occurs in late gestation.[3] However, plasma cortisol elevations, which would presumably have a systemic effect, do not explain the differential response of the carotid versus the SMA to acute hypoxia. Alternatively, muscular arteries may respond differently to cortisol. Nevertheless, there was no cortisol response to mild UCO; whereas elastin content was increased in mild, moderate, and severe compared to control.

Changes in oxygen tension are known to cause modifications in arterial structure and function. The oxygen-regulated response to hypoxia in vessels undergoing growth and development has been studied extensively in neonates exposed to chronic hypobaric hypoxia. The accelerated elastin accumulation which contributes substantially to morphometric changes in this model is attributed primarily to hypoxic-stimulated changes in mechanical load rather than to changes in oxygen tension.[34-36] In fact, elastin production is blunted in cultured smooth muscle cells exposed to hypoxia.[37] Additional effects of hypoxia including changes in matrix protein turnover and vasoconstriction have been shown to occur only with prolongation of hypoxia therefore transient reductions in oxygenation produced by UCO in the present study were likely inconsequential in comparison to hemodynamic influences.[38,39]

Quantitative analysis of elastin composition was undertaken as opposed to measurement of mRNA expression, since absolute and relative content of elastin determines arterial stiffness. However, the increase in elastin relative to tissue weight suggests that either elastin alone is increased or the other wall components have decreased. It is probable that the former has occurred since collagen deposition and smooth muscle cell proliferation are known to increase in response to hypoxia, cortisol and mechanical load.[4,6,26,38] Structural constituents of the arterial wall control passive mechanical properties: elastin is the primary determinant of elastic modulus at low distending pressure, while extensibility at high pressure is a function of collagen.[7] Absolute and relative increases in elastin quantity enhance arterial distensibility at physiological pressures over which mechanical load is transferred from elastin to collagen. The organization and cross-linking of ECM proteins, which may have been altered by acute hypoxia, also play a role in arterial mechanics.[23,26]

The small number of animals in the moderate group is a weakness of the study. As well, interpretation of the results in terms of factors responsible for upregulation of elastin accumulation in the carotid artery is speculative given the absence of blood flow data.

In summary, acute, reversible fetal hypoxemia due to intermittent UCO appears to accelerate developmental deposition of elastin in the carotid artery in relation to the severity of insult; whereas matrix elastin content of the SMA is not affected. Although there are several possible mediators of this synthetic response, the current data suggest hemodynamic stimuli to play the primary role.

As this study is the first to reveal perturbations in fetal arterial remodeling in response to intermittent hypoxemia, it implores a number of potential routes for future inquiries including the effect on additional structural factors such as collagen content and cross-linking, resultant modifications in vascular morphology and long-term consequences for postnatal arterial function.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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