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Fetal Growth Restriction and Hypertension in the Offspring: Mechanistic Links and Therapeutic Directions

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Hypertension, the leading cause of death among all cardiovascular disease (CVD) risk factors, affects >1.1 billion adults worldwide.^{1,2} Fetal growth restriction (FGR), generally defined as fetal growth <10th percentile for gestational age and sex, is associated with increased risk of perinatal death and increases the risk of CVD, the leading cause of mortality worldwide.^{3–6} The annual incidence of FGR varies between 5% and 15%, depending on country, thus making FGR-associated CVD a major public health concern.⁷

Systematic reviews and meta-analyses have confirmed the inverse association between lower birth weight (BW) and higher blood pressure (BP) in later life, across age groups and independent of body mass index.^{8,9} BP tracking develops quite early in life. A longitudinal study in 1797 infants noted that BP tracking became stronger with age to 4 years.^{10,11} Although experimental data strongly support the notion that FGR specifically programs hypertension, clinical studies remain equivocal.^{12,13} Furthermore, the underlying mechanisms are incompletely understood. Understanding these mechanisms will inform therapeutic approaches toward preventing or treating hypertension and attenuating CVD. Mechanistic links between FGR and hypertension include accelerated vascular aging,

programming of the renin-angiotensin system (RAS), maladaptive heart/kidney structure and physiology, sympathetic nervous system hyperactivity, and epigenetics.

Several studies noted the inverse association between BW and large artery stiffness across age groups (neonates through to ~30-year-old adults).^{14–19} Disrupted arterial elastin synthesis and deposition leads to stiffer vessels. The rate of elastin synthesis falls sharply after birth, leading to a low elastin reserve in affected individuals.²⁰ The RAS, through its various metabolites, closely regulates arterial vasculature, and heart and kidney functions. FGR in human pregnancies and animal experiments of undernutrition have also been associated with decreased numbers of nephrons.^{21,22} Other possible contributors to the prenatal programming of hypertension include superimposed hyperfiltration with activated intrarenal RAS and the sympathetic nervous system.²³ Last, the timing, severity, and duration of decreased substrate supply also impacts cardiovascular adaptations associated with FGR.²⁴

This review summarizes each of these mechanisms with a focus on prevention and therapeutic strategies across the entire life course to mitigate hypertension and CVD.

Early Vascular Aging

Effects initiated in utero (abnormal fetoplacental blood flow) and amplified after birth (infancy to old age) owing to decreased arterial compliance, have an etiologic role in primary hypertension.²⁵ The stiffened arteries may affect cardiac structure and function proximally, and high pulsatile stress may accelerate microvascular organ disease distally. Meta-analyses place arterial stiffness as an independent risk marker for future CVD risk (including hypertension) after adjusting conventional risk factors.^{26,27} Longitudinal appraisal of temporal relationships between arterial stiffness and incident hypertension suggests the precursor role for arterial properties.²⁸

Interlinking FGR, Arterial Remodeling, and Endothelial Dysfunction

Alterations in the extracellular matrix of major arteries are influenced by their elastin content.^{20,29} Multiple pathways mediate vascular pathology (Figure 1; available at www.jpeds.com). Replacement of elastin with collagen, which is 100 times stiffer, occurs in FGR and permanently alters arterial compliance.^{20,30} With normal aging, the proportion of elastin is decreased and collagen is increased, making infants with FGR a classic cohort for studying early vascular ageing. Superimposed on “normal arterial aging,” this manifests in increased large artery stiffness and clinically as high BP.

Cord blood samples from FGR deliveries indicate activated RAS, especially increased angiotensin, contributing to increased fetoplacental vascular resistance.³¹ Pregnancies complicated by FGR with Doppler alterations are associated with higher placental angiotensin-converting enzyme (ACE) activity compared with those with normal fetal growth or low BW without Doppler abnormalities.^{24,32} RAS activation contributes to age-related arterial remodeling, whereas chronic ACE inhibition (beginning at an early age) delays the progression, making it a monitoring/therapeutic target that requires more investigation.³³ Decreased endothelial-derived nitric oxide bioavailability is also linked to

vascular pathologies and lower BW infants show early, persistent signs of endothelial dysfunction.^{34,35}

Vascular Measures as Predictors of Long-term Cardiovascular Health

The advent of high-resolution B-mode ultrasound imaging has led to cardiac intima media thickness (cIMT) being widely used as a measure of subclinical atherosclerosis in pediatric research. Children with familial hypercholesterolemia have an increased cIMT.^{36,37} In adults, cIMT predicts myocardial infarction, stroke or death, and has been used as an end point in clinical trials assessing the impact of antihypertensive medications on cardiovascular risk.^{38–41} In adults, arterial stiffness has a strong predictive value for CVD events beyond that of classical risk factors such as pulse pressure.⁴² Such use of cIMT in pediatric populations is recent. A double-blind, placebo-controlled randomized controlled trial (RCT) recruited 214 children with familial hypercholesterolemia (age range, 8–18 years). After 2 years of pravastatin therapy, the mean cIMT was decreased, whereas placebo therapy increased cIMT.⁴³ Recent studies in neonates have found aortic intima media thickness (aIMT) equally useful, with increased aIMT, stiffness, and increased BP in infants with FGR early in the postnatal period.^{14–16,44} Relevant cardiac and vascular ultrasound features that are useful for understanding this maladaptation have been summarized elsewhere.⁴⁵ At 32 weeks of gestation, growth-restricted fetuses have higher maximum aIMT and there is a correlation between fetal assessments and those 18 months after birth.⁴⁶ Systolic BP was significantly higher in the FGR subjects, correlating with both prenatal and postnatal aIMT values.⁴⁶ This differential trajectory, identified before birth, predisposes to later hypertension and CVD risk. Arterial assessments in FGR cohorts aged 8–13 years and young adults also noted increased stiffness, impedance, and higher central pulse pressure.^{47,48}

Pulse wave velocity (PWV) measures arterial stiffness and is a measure of transit time and distance between the carotid and femoral arteries. A faster aortic PWV is related to the disruption in deposition of elastin and compounded by its replacement with stiffer collagen. In 707 young adults (~30 years of age), BW inversely correlated with PWV and pulse pressure, making PWV a plausible link between BW and elevated systolic BP.¹⁹ Carotid-femoral PWV is a good surrogate CVD end point and is recognized for its excellent predictive value for CVD complications by the European Society of Cardiology guidelines.^{19,41} The Baltimore Longitudinal Study of Ageing as well as a 2014 analysis of 27 longitudinal studies noted the importance of PWV predictive value.^{26,28} Whether PWV can be used to identify individuals that were born FGR, and thus, be a target for preventive strategies to delay the progression of subclinical arterial stiffening and the onset of hypertension should be studied prospectively.

Vascular Stiffness as a Therapeutic Target

Preventive strategies to decrease the burden of adult CVD are more likely to be beneficial when implemented in early life, rather than in adulthood (after subclinical disease is established or after the onset of overt disease). In a RCT, the inverse association of BW with cIMT was present in control children (~8 years), but abrogated in those receiving a docosahexaenoic acid-rich supplement from 6 months to 5 years of age.⁴⁹ Dietary

consumption of eicosapentaenoic acid and docosahexaenoic acid has specific vascular benefits in children and adolescents who were born FGR (eg, lower BP, lower cIMT, and aIMT).⁵⁰ Furthermore, breastfeeding and postnatal nutrition improved FGR-induced cardiovascular remodeling (reduced heart sphericity and cIMT).⁵¹ RAS blockade has a significant impact on arterial structure and function independent of BP control.^{52–55} ACE inhibitors reset the balance between vasoconstriction/proliferation and vasodilatation/antiproliferation.^{56,57} In rodents, ACE inhibitors (but not β -blockers) caused regression of the media-to-lumen ratio.⁵⁸ Clinical human studies confirmed these findings, indicating that structural arterial wall remodeling (rather than increased BP alone) underlies arterial stiffening, and RAS inhibitors may slow down vascular ageing.^{59–61} In infants with severe bronchopulmonary dysplasia associated hypertension ACE inhibition decreased the aIMT and increased pulsatility.⁶² The influence of prematurity and FGR on arterial structure and function may be intertwined. Comparing preterm born adolescent females (~16 years of age) with controls, BP was significantly higher in the former, whereas carotid stiffness and PWV were comparable with controls.⁶³ In contrast, brachioradial artery stiffness and BP was significantly higher amongst preterm FGR born children but not those born preterm or term appropriate for gestation.⁶⁴

RAS Maladaptation: Increased Angiotensin II and Decreased Angiotensin-(1–7)

Increased activation of the RAS and the vasoconstricting, proliferative, inflammatory, and fibrotic actions of angiotensin II on the vasculature may have an important role to play.

Mechanisms

There are 2 primary pathways within the RAS; the first consists of ACE-angiotensin II-angiotensin II type 1 receptor. Renin converts angiotensinogen into angiotensin I, which ACE then converts into angiotensin II, which acts at the angiotensin II type 1 receptor to increase BP via vasoconstriction, kidney salt, and water retention (via stimulating aldosterone release), and augmenting sympathetic nervous system tone.^{65,66} The counter-regulatory ACE2-angiotensin-(1–7)-Mas receptor pathway protects against angiotensin II-mediated increased BP.⁶⁷ ACE2 converts angiotensin II into angiotensin-(1–7), which acts at the Mas receptor to promote vasodilation, increased kidney salt and water excretion, and increased parasympathetic tone.^{65,68–70} RAS is also immunomodulatory: angiotensin II promotes oxidative stress leading to inflammation and ultimately fibrosis, whereas angiotensin-(1–7) promotes nitric oxide production and mitigates angiotensin II-mediated inflammation.⁷¹ ACE and ACE2 also inactivate angiotensin-(1–7) and angiotensin I by converting them into less bioactive peptides.^{72,73} Thus, the balance between these RAS pathways is an important mediator in the pathogenesis of organ injury, as loss of angiotensin-(1–7) and/or increased angiotensin II can promote organ injury and hypertension development.⁷⁴

Maternal/placental RAS dysregulation causing increased ACE-angiotensin II pathway expression and activity can contribute to placental insufficiency and resultant FGR, as well as mediate FGR-induced programmed hypertension in the offspring.⁷⁵ The same holds true

for ACE2-angiotensin-(1–7) pathway suppression as an important contributor to FGR-induced hypertension.⁶⁷ FGR likely impairs beneficial cardiovascular and renal effects mediated via the angiotensin II type 2 receptor in offspring.⁷⁶ Betamethasone-exposed sheep fetuses demonstrated higher BP, higher circulating ACE activity, lower ACE2 activity, and lower renal angiotensin-(1–7) levels associated with increased oxidative stress.⁷⁷ Prenatal glucocorticoid-induced models of FGR in sheep consistently demonstrate that RAS programming in the brain and kidneys contribute to development of hypertension and can precede overt disease.^{78–81}

Prediction of Later Disease

In humans, clinical evidence is lacking regarding the short- and long-term effects of FGR on offspring RAS expression, in part owing to the lack of a widely accepted research and clinical definition of FGR. Being born small for gestational age (BW <10th percentile for gestational age and sex) is a commonly used surrogate measure of FGR.^{5,82,83} Recent evidence supports the notion that perinatal RAS programming persists across the life span. Among children born term, low BW was associated with increased circulating ACE activity and angiotensin II compared with those born appropriate for gestational age; both circulating ACE activity and angiotensin II also positively correlated with BP.⁸⁴ Compared with term deliveries, adolescents who were born preterm with very low BW had lower plasma angiotensin-(1–7) relative to angiotensin II concentrations, lower estimated glomerular filtration rate and increased proportion of high BP. High BP persisted into young adulthood; obesity and female sex magnified these programming effects.^{85–89}

Therapeutic Targets

Further investigations are required to establish these causal mechanisms and to develop preventative and therapeutic strategies aimed at blocking or reversing abnormal RAS programming to shift the balance away from angiotensin II and back toward angiotensin-(1–7). RAS blockade with ACE inhibitors to block angiotensin II production, and angiotensin II receptor blockers to block angiotensin II's actions via its receptor are mainstays in treating hypertension. Clinical trials are needed to investigate if increasing angiotensin-(1–7), in addition to decreasing angiotensin II, could reverse or attenuate these programmed alterations over the life span to prevent hypertension and CVD or to reverse subclinical disease. Novel therapeutics, such as angiotensin-(1–7) itself or orally available analogues as well as ACE2, could be administered in the neonatal or early childhood period to upregulate angiotensin-(1–7) at the expense of angiotensin II, especially during periods of active injury.^{90–92} For example, angiotensin-(1–7) attenuated vasoconstriction and induce renal vasodilation in adults.^{93,94} However, to date no trials have attempted to reverse programmed RAS alterations to prevent or attenuate disease.

Substrate Delivery and Fetal Heart Maladaptation

Fetal acute hypoxia leads to increased circulating noradrenaline, peripheral vasoconstriction and hypertension in the fetus, resulting in redistribution of blood flow are key adaptations to chronic hypoxemia.^{95,96}

Mechanisms

Although FGR sheep with chronic hypoxemia have no change in blood flow to the brain, heart, and adrenals (Figure 2; available at www.jpeds.com), they do have a decrease in oxygen and glucose delivery to the heart.^{97–99} This decreased substrate delivery to the heart is associated with a delay in cardiomyocyte maturation and a lesser number of fetal cardiomyocytes in the fetus that is sustained into adolescence.^{100–103} In addition, the mature cardiomyocytes that contribute to heart growth by hypertrophy are relatively larger in the FGR heart compared with the normally grown fetus.¹⁰⁰ This factor is mediated by changes in signaling pathways that promote cardiac hypertrophy, such as angiotensin II, insulin-like growth factor 1 and 2 receptor, and noradrenalin.^{104,105}

Prediction of Later Disease

The timing, severity, and duration of reduced substrate supply leading to FGR negatively influences the developing fetus's cardiovascular development and physiology.²⁴ FGR directly affects the heart by way of altered myofiber architecture, reduction in cardiac sarcomeric proteins, increased glycogen and collagen deposition, and interstitial fibrosis.^{106,107} These effects are complemented by increased myocardial workload in the face of elevated placental resistance. FGR-induced fetal hypertension also contributes to cardiac hypertrophy. Human placental histopathology has recently noted vascular changes in FGR placentae.¹⁰⁸ In utero cardiac remodeling has been noted by multiple investigators previously.^{109–111} Whether these early cardiovascular changes predict later-onset hypertension is as yet unknown.

Therapeutic Targets

Alterations in cardiac morphology are accompanied by subclinical cardiac dysfunction that can be demonstrated by fetal echocardiography.^{109–111} Several pathways have been identified as targets of intervention to improve heart health in the growth-restricted fetus, but must be tested in preclinical models to determine optimal timing and targets. In sheep models of chronic hypoxemia and FGR, fetal mean arterial BP is maintained but femoral artery blood flow is decreased compared with the normally grown fetus owing to greater dependence on the RAS and sympathetic tone.^{24,112–115} Infusion of an ACE inhibitor after approximately 135 days of gestation resulted in a greater hypotensive response in chronically hypoxemic FGR sheep fetuses when compared with normoxemic fetuses.¹¹³ High habitual fish intake (n-3 poly unsaturated fatty acid content) has shown to increase BW, possibly owing to the ratio of biologically active prostacyclins to thromboxanes, reducing blood viscosity, and thereby facilitating placental blood flow.^{116–118} In an RCT of 533 pregnant women, supplementation of 2.7 g/day of n-3 poly unsaturated fatty acid affected maternal thromboxane and prostacyclin production and pregnancies in the n-3 poly unsaturated fatty acid group weighed 107 g more (95% CI, 1–214).^{119,120} Although promising, the data are not yet sufficient to support a dietary supplementation recommendation. Oxidant injury is one of the proposed mechanisms. A double-blind, placebo-controlled RCT in FGR pregnancies is currently underway to assess the impact of maternal antenatal melatonin supplementation on early childhood neurodevelopmental

(ACTRN12617001515381). Whether melatonin has the potential to alter the cardiometabolic milieu remains to be seen.

Kidney Maladaptation and Influence of the Autonomic Nervous System

Kidneys undergo maladaptation in response to uteroplacental insufficiency and FGR with reduction in nephron numbers and hyperfiltration injury through the remaining nephrons. Delivery of high-pressure waveform, undampened by stiff major arteries, affects glomerular filtration. FGR has been shown to be associated with persistent aortic wall thickening and higher microalbuminuria during infancy.⁴⁶

Mechanisms

Nephron number correlates positively with BW, and decreased in nephron numbers may increase the risk of hypertension.^{121,122} Maternal protein restriction reduced numbers of glomeruli, increased glomerular size, reduced glomerular filtration rate, and higher BP.²¹ In sheep, prenatal glucocorticoid administration increased offspring BP, a decreased number of nephrons, and reduced glomerular filtration rate related to alterations to the renal RAS and sodium handling, in a sex-specific manner.^{81,123–125} Glucocorticoid exposure from gestational days 15 to 19 in the rat programmed higher BP associated with a decreased number of nephrons in male offspring, whereas early exposure from gestational days 13 to 14 programmed higher BP that was not associated with a change in nephron number.¹²⁶ A decreased glomerular filtration rate was associated with decreased numbers of nephrons in male rats exposed to glucocorticoids but not maternal protein restriction.^{21,127} Once again, the timing and the type of insult seems critical. The relative contribution of the sympathetic and/or the parasympathetic nervous system to increased hypertension or CVD risk originating in early life remains unclear. Furthermore, a significant increase in heart rate in response to stress is associated with increased sympathetic and decreased parasympathetic nervous system activity in low BW women but not men, suggesting that discrepancies in sex-specific outcomes may be due to age or puberty status.¹²⁸ Increased sympathetic nervous system activity is a mediator of increased heart rate in response to stress in low BW children and adolescents.¹²⁹

Prediction of Later Disease and Therapeutic Targets

The role of the kidney in the developmental origins of hypertension extends beyond the contribution of nephron endowment. BP is regulated by activation of the RAS and sympathetic nervous systems. The reliance on either of these systems differs in growth-restricted FGR fetuses compared with normally grown fetuses. Many regulatory systems contribute to sodium and fluid balance and vascular and nervous system tone in the long-term BP control, including the RAS, and are therefore potential targets for therapeutic interventions.^{67,86,130,131} The promising potential of ACE inhibition has already been indicated elsewhere in this article. Prenatal exposure to maternal high salt intake programs sympathetic activation and increased BP response to stress in female but not male littermates, indicating that sex alters the developmental origins of sympathetic nervous system activation in a manner that is insult-specific.¹³² Infusion of an α -adrenergic antagonist, phentolamine, resulted in a greater fall in fetal BP in the FGR vs control fetuses

that was related to the degree of hypoxemia.¹¹² An inverse relationship between the magnitude of the fetal hypotensive response to α -adrenergic blockade and arterial PO₂ suggested increased reliance on sympathetic tone to regulate BP in FGR. Chronic maintenance of BP through α -adrenoceptor activation in fetal life has long-term consequences for cardiovascular health. Renal denervation abolishes placental insufficiency- or perinatal dexamethasone-exposed programmed hypertension, implicating a role for the renal nerves.¹³³⁻¹³⁵ A summary of therapeutic constructs is presented in Figure 3 (available at www.jpeds.com).

Collectively, these studies indicate a critical role for the sympathetic nervous system in the etiology of increased BP in offspring exposed to FGR and other perinatal risk factors. Despite differences in the type of developmental insult, common mechanistic pathways contribute to the developmental origins of hypertension. Further investigation into the mechanisms involved in sympathetic activation and hypertension in individuals with FGR may lead to therapeutics and pharmacological targets to diminish CVD risk in this population.

Epigenetics: Generational Maladaptations

The role of epigenetic mechanisms in the developmental origins of cardiorenal disease is not yet clearly understood. Epigenetics implies inherited changes that do not alter the underlying DNA sequence, but ensure minute regulation of gene expression that may influence disease susceptibility in later life. Alcohol exposure during pregnancy is an example that alters the methylation patterns of several imprinted genes.¹³⁶ Programming is initiated very early via epigenetic phenomena that occur preconception, periconception, or during gestation.^{105,137,138} Dietary protein restriction of pregnant rats induces, and folic acid supplementation prevents, epigenetic gene expression modification in offspring.¹³⁹ FGR rats have changes in lung expression of specific microRNA that increase RAS molecules.¹⁴⁰ Epigenetic processes can have a graded effect (as opposed to all-or-none), similar to the graded association between BW and chronic disease.¹⁴¹ In a study done on maternal low-protein rats, Bogdarina et al noted that alteration of DNA methylation of one or more RAS component genes might result in the development of hypertension. angiotensin AT1b receptor gene expression is highly dependent on promoter methylation; upregulation by the first week of life resulted in increased receptor protein expression.¹⁴²

Limitations to Current Knowledge

The relatively low prevalence of FGR in most birth cohorts, the heterogeneity in definitions of FGR, and the heterogeneity of causes of FGR have limited clinical studies to date.^{4,13,82,83} Furthermore, it is crucial to accurately and consistently measure BP and define hypertension and related cardiac, kidney, and vascular outcomes to aid in comparing different clinical studies and pooling analyses. Developing reliable biomarkers to identify early or subclinical alterations in these mechanisms is vital. Inherent to this point is the reproducible measurement of components of the RAS that depend upon appropriate and rigorous blood and urine sample collection, processing, storage, and analytic methodologies.¹⁴³ An improved understanding of the epidemiology of developmental origins of disease will

aid in differentiating the risk imparted by FGR relative to other perinatal factors. This process should be the precursor to define that risk and enact therapeutic strategies to prevent or attenuate the early development of disease throughout the life span.

Moving Forward: Prevention and Therapeutics to Attenuate Maladaptation

Improving nutrition and living conditions between conception and early childhood and avoiding rapid increased in body size is key.¹⁴⁴ In effect, the concept of mitigation through nutrition starts much earlier. Increased breast milk intake improved the metabolic and cardiovascular outcomes of growth-restricted animals.¹⁴⁵ FGR was the strongest predictor of cardiovascular remodeling and BP at 4–5 years of age, breastfeeding for >6 months, and healthy fat dietary intake were associated with improved cardiac geometry and lower cIMT. Furthermore, overweight/obesity was associated with higher cIMT in FGR children compared with children born appropriate for gestational age.⁵¹ Evidently, postnatal nutrition ameliorates FGR-associated cardiovascular remodeling, identifying itself as an intervention option. A recent RCT indicates that micronutrient intervention in infancy (such as iron supplements) may modify the inverse association between BW and risk of hypertension.¹⁴⁶

Monitoring childhood body weight and BP are essential for those whose BW were toward the lower end of the normal range or <10th percentile. The 2017 American College of Cardiology/American Heart Association and the American Academy of Pediatrics Clinical Practice Guidelines for High Blood Pressure in Adults and Children recommend screening BP in patients with a significant perinatal history; however, FGR per se is not included as a perinatal risk factor.^{147,148} This high-risk population includes those whose body mass index increases across percentiles. Prevention is paramount as the BP of patients with hypertension who had lower BW may be more difficult to control, often requiring multiple antihypertensive medications.^{149,150}

Conclusions

Through the multiple mechanistic links outlined above, FGR is an important risk factor for later-onset hypertension. Better maternal periconception nutrition and health as well as management of preeclampsia, a common cause of FGR, are key toward prevention. Low-cost interventions such as breastfeeding and targeted early nutritional interventions need to be reinforced, and large-scale population-based studies are needed to assess their impact on future incidence of hypertension and CVD. Establishment of clinical normative values of arterial thickness and PWV could aid in identifying subclinical disease and identify appropriate therapeutic windows. Existing drugs (ACE inhibitors, angiotensin II receptor blockers) or novel therapies that can target the RAS to decrease angiotensin II's actions and promote angiotensin-(1–7) may be useful in preventing hypertension or CVD or treating subclinical disease. Whether ACE inhibitors, with their arterial wall-modulating properties, may be beneficial to nephron preservation in this population remains to be determined. Measures of vasculature tone/function as end points for clinical assessments and therapeutics seem plausible as biomarkers, as are RAS measurements. Physical activity (avoidance of sedentary lifestyle) and improved lean-fat ratio may be key to attenuate the development of the metabolic syndrome and hypertension. Age-appropriate interventions,

covering the life course nature of the disease (and its progression), may have a significant impact on preventing or delaying adult-onset CVD in this population.

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Glossary

ACE	Angiotensin-converting enzyme
aIMT	Aortic intima media thickness
BW	Birth weight
BP	Blood pressure
cIMT	Carotid intima media thickness
CVD	Cardiovascular disease
FGR	Fetal growth restriction
PWV	Pulse wave velocity
RAS	Renin-angiotensin system
RCT	Randomized controlled trial

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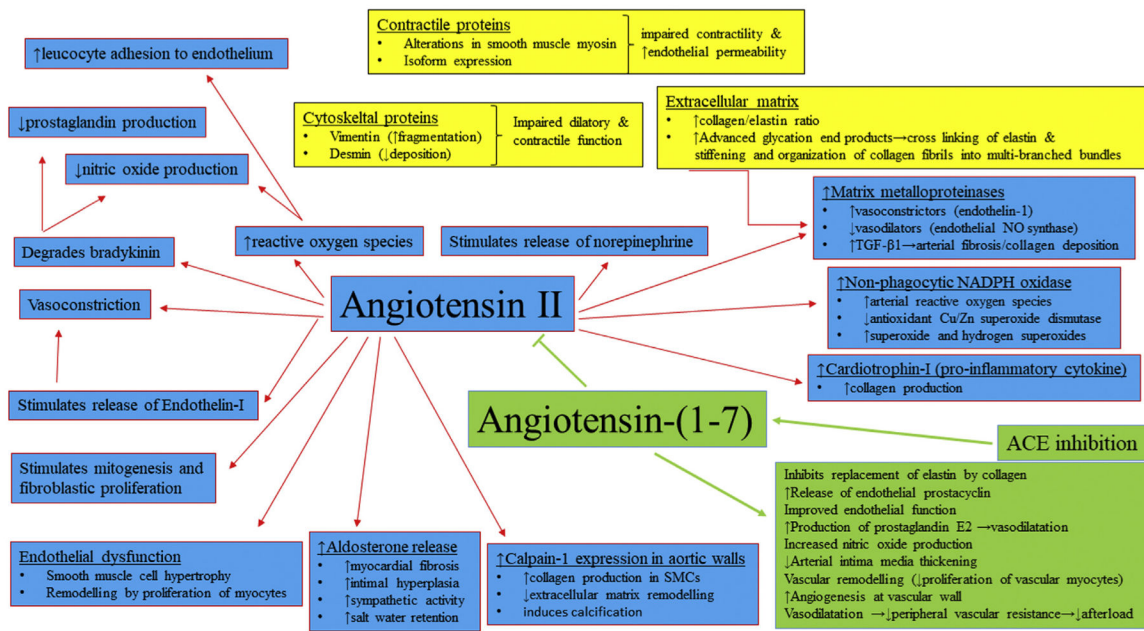


Figure 1. Mechanisms involved in increased arterial thickness and stiffness (central role of the RAS). *ACE2*, angiotensin-converting enzyme 2; *Ang-(1-7)*, angiotensin-(1-7); *AT₁R*, angiotensin II type 1 receptor; *MasR*, Mas receptor; *NO*, nitric oxide; *TGF*, transforming growth factor.

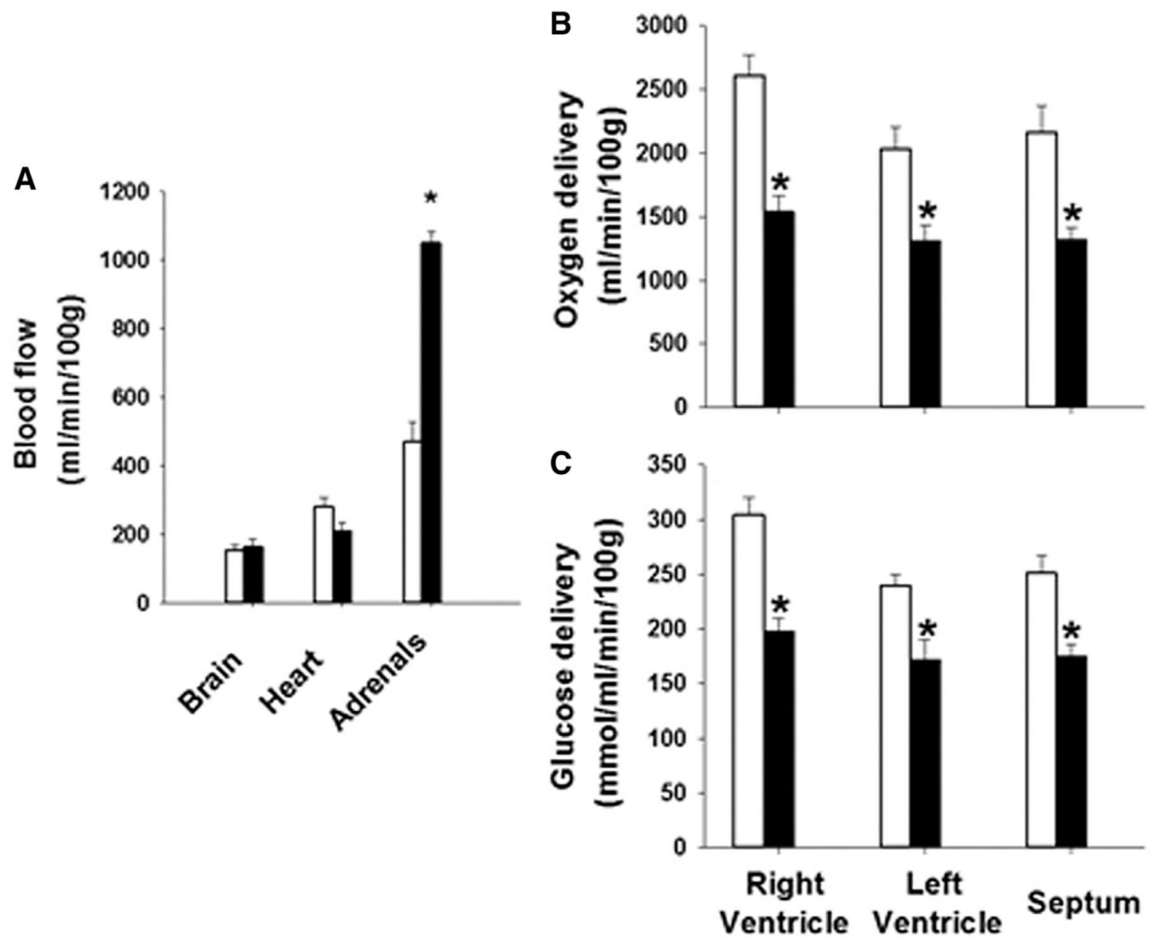


Figure 2.

There is no change in blood flow to the brain or heart but an increase in blood flow to the adrenal glands in the chronically hypoxemic intrauterine growth restriction (IUGR) (black bars) compared with the control (white bars) fetus, **A**. However, there is a decrease in oxygen and glucose delivery to the heart of the IUGR fetus compared with controls, **B** and **C**.

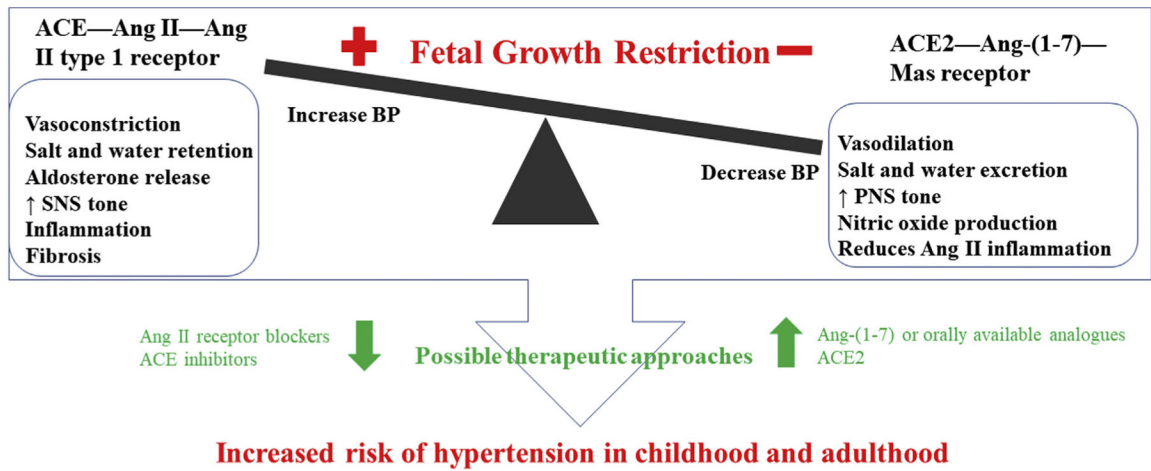


Figure 3. Summary of therapeutic constructs. *Ang*, angiotensin; *SNS*, sympathetic nervous system; *PNS*, parasympathetic nervous system.