Measurement of carotid wall thickness is a research tool that has been used to risk-stratify adults with cardiovascular disease, but its clinical role is debatable according to the current American Heart Association guidelines. However, an increased aortic wall thickness has been described in individuals born small for gestational age (SGA) in early childhood, implying that they may be at risk for later cardiovascular events and more latterly increased intima-media thickness (IMT) reported in smaller vessels in these children. These findings are in support of the developmental origins hypothesis, linking an adverse intrauterine environment to the development of later disease.

See Article by Olander et al

The article by Olander et al in this issue of Circulation: Cardiovascular Imaging has used higher frequency ultrasound than previously described (between 35 and 55 Hz) to image the vascular walls of neonates and reached different conclusions, finding no evidence of increased IMT or intima-media adventitial thickness (IMAT) in babies born SGA. This raises the question whether IMT or IMAT has been reliably characterized in small babies using lower frequency ultrasound, particularly as an abnormal finding may have resulted in increased surveillance in childhood or perhaps the offer of early preventative treatment. In this article, the authors have imaged the carotid, brachial, and femoral arteries and reported vessel diameters, IMT, and IMAT in 3 groups of babies below 1 week of age: appropriate, small, and large for gestational age. They calculated carotid wall stress and examined the association of measurements with sex, gestational age, and a variety of ratios combining somatic and vessel parameters. They describe an association between lumen diameters and carotid wall stress and body size and a weaker association of these with gestational age and male sex. In spite of the high prevalence of maternal disease in the SGA and large for gestational age cohorts, there were no significant differences in IMT or IMAT between the groups, and the presence of maternal disease did not improve the statistical model.

The results of this study are in conflict with others and merit further investigation. These authors have used ultrasound imaging ≤55 Hz with axial resolution of 0.05 mm, which is much higher than in previous studies. Interestingly, despite the strength of this newer technique, the brachial vessel wall layers still could not be differentiated in almost a quarter of the SGA cohort, thus, reducing the power of the study to describe potential group differences.

The composition of the SGA group remains poorly described in many studies, with poor differentiation of the different types of fetal growth restriction. The distinction between infants who have not achieved their growth potential and have shown abnormal Doppler waveforms—usually reduced, absent, or reversed flow in the descending aorta during fetal life intrauterine growth restriction (IUGR)—and those destined to be small with normal Doppler flow profiles (SGA) is vital because the vascular influences during fetal life are different. Not only do IUGR fetuses experience direct abnormalities of vascular impedance, altering their flow patterns for sustained periods, but they are also often exposed to potential transgenerational influences. Pregnancy complications, such as low birth weight, preterm delivery, and pre-eclampsia, are associated with a 7-fold increased risk of the mother requiring hospitalization or dying from ischemic heart disease within the subsequent 2 decades.

There is valuable information on the pathophysiology of growth-restricted individuals studied longitudinally during fetal life, with some cohorts followed into adulthood. These fetal studies used wall tracking devices, with an impressive ability to track wall motion to 7.8 μm and permit the study of fetal vascular behavior. The technical performance of the equipment is important because the group of most interest, the IUGR fetuses, are often the most difficult to image using ultrasound because of their small size and frequent oligohydramnios. Wall tracking studies have described the normal gestational changes in aortic and venous vessel wall pulsations and verified the component parts of the arterial waveform in instrumented animal studies. Subsequent clinical studies have compared measurements in fetuses exposed to high afterload because of placental pathology and maternal smoking to normal pregnancies, and these observations provide information on the stressors operating within the cardiovascular system before birth that may alter the normal maturation patterns of the vessel walls in the second half of pregnancy.

The fetal arterial tree is predominantly formed of collagen, with elastin deposited exponentially during the latter half of pregnancy and into infancy. Abnormality of fetal growth may affect this process, thus, potentially increasing arterial stiffness later in life. The pathophysiology of IUGR affects organ growth and the size of the vascular beds, and reduced arterial branching has been described in the retina of adults born IUGR. A reduction in renal growth is associated with alterations in the fetal renin–angiotensin system activation,

© 2016 American Heart Association, Inc.
resulting in elevated levels of angiotensin, a powerful modulator of cardiovascular structure and function.\textsuperscript{13}

The increased distal impedance in the IUGR fetus results in abnormally fast wave reflections that reset baroreceptor function, thus, altering the balance of the sympathetic–parasympathetic system, and may be one explanation for the increased risk of acute life-threatening events and provides the substrate for life-long cardiovascular risk in these individuals.\textsuperscript{14}

Interesting parallels may be drawn between these older studies and the findings by Olander et al\textsuperscript{4} today. They describe a relationship between carotid wall stress and lumen diameters to body size, but no differences between groups. Remodeling of the vascular walls occurs to maintain stable shear stress, and one would not necessarily expect pathological differences in wall stress between the groups to be evident in early life.\textsuperscript{15}

The importance of the earlier fetal wall tracking studies is that they examined the cardioplacental circulation and could measure chronic fetal responses noninvasively in pathological settings. This relationship alters after delivery to a cardiopulmonary one, and thus, the dynamic stressors of the system that may help to explain later cardiovascular findings are removed. In IUGR, the descending aorta and inferior vena cava show reduced relative pulse amplitude, reflecting increased systemic impedance and increased venous pressure, respectively.\textsuperscript{3,8,9}

Moreover, examination of the component parts of the arterial waveform are altered when there is increased placental resistance. In normal pregnancies, the placenta becomes a low-impedance organ, and animal studies have confirmed that the increase in maximal incremental velocity and late decremental velocity components of the arterial waveform reflects improved ventriculovascular coupling (as the fetal myocardium matures) and allows the gestational increase in cardiac output, respectively.\textsuperscript{11} However, the magnitude of gestational change is reduced in IUGR, implying that increased systemic impedance reduces cardiac performance.\textsuperscript{3} These observations are a plausible explanation for the differences described in young adults born with IUGR, but absent in those with normal growth. The morphological influence of fetal flow on vessel growth has been well described in young adults born at term and studied prenatally. The 18-year-olds born with IUGR had smaller lower limb conduit vessels compared with controls born appropriately grown.\textsuperscript{10} Although there were no differences in arterial stiffness, assessed by pulse wave velocity, or endothelial-dependent or -independent measures of vascular function at age 18 years of age, in these cohorts, an increased resting heart rate was recorded in the IUGR group, suggesting altered parasympathetic cardiovascular control.

Early effects of growth restriction on vascular stiffness and blood pressure have proved difficult to verify. No studies have reported elevated blood pressure in childhood in a large cohort of growth-restricted fetuses using robust techniques. Epidemiological studies into the developmental origins of adult disease have described higher systolic and diastolic blood pressure and reduced arterial compliance in association with poor fetal growth and social deprivation in adults,\textsuperscript{16,17} but blood pressure tracks along growth centiles, and no study has yet described movement from the lowest to highest centiles.

The normal postnatal increase in blood pressure was described in a longitudinal study of term healthy newborns studied at 4 days (after closure of the arterial duct) and throughout early childhood.\textsuperscript{18} The authors-recorded blood pressure was higher by 6 mm Hg in awake neonates and rose within the first 6 weeks after delivery and was relatively stable thereafter. The equipment most frequently used to measure blood pressure works on the oscillometric principles, measuring vessel wall pulsation on the cuff. In 1992, Thoresen and Cowan\textsuperscript{19} published an assessment of the performance of this equipment describing 95% confidence interval for 1 measurement of ±7.2 mm Hg; for 3 measurements of ±4.1 mm Hg, and for 10 consecutive measurements of ±2.3 mm Hg. However, blood pressure measurement remains difficult in infants, and the estimated limits were high in Olander’s study at 6 to 7 mm Hg, despite using the recommended mean of 3 measurements. Important confounders in measuring blood pressure include the presence of a patent arterial duct. This lowers diastolic pressure and consequently increases pulse pressure. Factors influencing its patency include gestational age at birth and at time of study. Gestational age at delivery in Olander’s paper was 3 weeks less in the 11 IUGR compared with the 28 SGA infants in the pooled SGA cohort; however, the SGA cohort was older at time of study than the appropriate for gestational age or late for gestational age cohort, permitting a higher proportion of these ducts to close. The results seem to confirm this because patent arterial duct was seen in 21% of the SGA cohort compared with 30% of the appropriate for gestational age and 42% of the late for gestational age, and this may have contributed to the increased diastolic blood pressure measured in the SGA cohort overall. Therefore, an alternative interpretation of the blood pressure data may be that the SGA cohort had a normal diastolic blood pressure compared with the lower values measured in the appropriate for gestational age and late for gestational age groups, where there was a higher proportion with patent arterial duct.

A further difficulty with the interpretation of somatic and cardiac output data is the manipulation of the raw measurements to account for differences in body size. Most measures, such as body surface area or flow in mL/kg/min, are crude and prone to error, mainly because of mathematical squaring of diameter measurements. Moreover, body weight is usually composed of differing proportions of lean or fatty tissue in cohorts investigating fetal growth restriction. It would, therefore, be advantageous to assess body composition using other techniques, such as magnetic resonance imaging, to allow more granular interpretation of the results.\textsuperscript{20} Olander et al\textsuperscript{4} report that body surface area was an independent predictor of IMT and IMAT, but the body composition of the individual groups remains unknown, and it is difficult to infer a pathophysiological process.

What May Assist the Design of Future Prospective Studies?
Serial fetal measurements form the bedrock in characterizing the study cohorts appropriately at birth. New techniques, such as high-frequency ultrasound and magnetic resonance imaging, will permit better pre- and postnatal imaging and tissue characterization. Studies require sufficient power to be able to provide robust conclusions about fetal programming responses to the adverse intrauterine environment and
possible transgenerational effects. There are sufficient fetal and neonatal studies now to allow appropriate power calculations to be made. Finally, resting measurements may not discriminate between IUGR and normal cohorts studied in early life. In IUGR fetuses, there is a response to an adverse cardiopla-cental circulation, and perhaps, an appropriate physiological challenge may be required to demonstrate group differences postnatally.

Disclosures
None.

References

Kry Womos: Editorials cardiovascular disease fetal development fetal programming ultrasound vascular imaging
A Womb With a View
Helena M. Gardiner

Circ Cardiovasc Imaging. 2016;9:
doi: 10.1161/CIRCIMAGING.116.005437
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/9/e005437

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/