Cardiovascular Remodeling in the Small for Gestational Age Infant

– Implications and Future Directions –

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Small for gestational age (SGA) is defined as birth weight less than the 10th percentile for gestational age.¹ One of the causes of SGA is placental insufficiency, wherein oxygen and nutrition deprivation result in adaptive cardiovascular changes in the fetus.^{2,3} Fetal adaptations to the suboptimal uterine environment include development of a more globular ventricular shape and increased transverse diameter, shortened sarcomere length and increased aortic intima-media thickness.^{4,5} These adaptations may serve to redistribute cardiac output and maintain oxygen and nutrient delivery to vital tissue beds including the brain and heart. Such adaptations may alter cardiovascular development and markedly change cardiac structure and function. This may result in short and

longer-term cardiovascular complications.^{6–9} However, the nature and extent of cardiovascular morbidity, particularly as function of the severity of SGA, remain poorly understood.

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The study by Akazawa et al¹⁰ in this issue of the Journal advances our collective knowledge on the link between SGA status and cardiac function during infancy. The primary objective of the study was to compare cardiovascular structure and function among infants with various degrees of SGA severity and appropriate for gestational age (AGA) matched controls. In the study, 38 infants with mild forms (birth weight 10th to

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3rd percentile; $n=20$) and severe (birth weight <3rd percentile; $n=18$) of SGA were compared with 30 AGA (birth weight between 10th and 90th percentile) controls. Extensive echocardiographic analysis, including myocardial deformation imaging (MDI), was utilized. MDI is a novel technique for assessment of myocardial performance. It assesses strain, defined as the change in length of the myocardium relative to its resting length (expressed as a percentage). In contrast with traditional echocardiography, MDI directly measures myocardial function, does not require geometric assumptions, and provides quantitative data to guide clinical care.¹¹ In adult populations, MDI has uncovered myocardial dysfunction earlier in the disease process than conventional echocardiography.¹² Although normative data on MDI in healthy infants have been well characterized, studies using MDI techniques in infants with pathologic conditions remain limited.¹³

We applaud the authors for their application of MDI imaging among a high-risk subgroup of infants – specifically SGA infants. One of the primary findings in the present study was that, although most conventional and tissue Doppler imaging parameters were similar among infants with mild SGA and control infants, MDI allowed differentiation not only between mild SGA and controls infants, but also between infants with severe and mild forms of SGA. Thus, MDI may be superior to conventional echocardiography in the detection of myocardial dysfunction. At the very least, it complements conventional echocardiographic assessments in providing a more comprehensive assessment of myocardial performance. However, a number of barriers exist prior to widespread adoption of MDI as part of routine cardiovascular assessment. Consistent with previous studies,¹⁴ MDI was not possible for all patients recruited because of technical issues, including inadequate resolution in speckle-tracking analysis.

Limitations of the present study are appropriately acknowledged by the authors, including the single-center study design, cross-sectional nature of the study and possible selection bias because of the nonconsecutive selection of neonates. Although intrauterine growth restriction indicates the presence of a pathophysiologic process occurring in utero that limits fetal growth,¹ an infant born SGA has not necessarily suffered from growth restriction and may be constitutionally normally small. Therefore, even among SGA subgroups, the likelihood for marked heterogeneity in phenotypic expression is recognized.

We congratulate Akazawa and colleagues for their important contribution highlighting the short-term cardiovascular consequences of SGA status across a range of echocardiographic and physiologic parameters (Figure). However, a fundamental question remains – what do we do with the knowledge that SGA infants show early evidence of cardiovascular remodeling and dysfunction? Although early detection of changes in cardiovascular structure and function among infants with SGA is an important first step, evidence-based applications of these findings on management and longer-term outcomes are needed to determine the clinical significance of these findings. Based on previous studies in SGA infants, future studies should comprehensively assess cardiovascular health across a range of echocardiographic and clinical (lipid panels, markers of systemic inflammation: pro-B-type natriuretic peptide) parameters. Provided evidence of increased risk in adulthood,¹⁵ trending cardiac performance in SGA infants throughout adolescence and into adulthood may have merit. Closer monitoring may help to develop individualized, evidence-based

management and surveillance protocols for this at-risk subgroup of infants. Long-term studies, including more robust cardiovascular follow-up, for these at-risk infants are needed. Although our understanding of the link between suboptimal uterine environments and adverse adult outcomes has grown, additional data on the mechanistic underpinnings and value of therapeutic interventions during this time period remain poorly understood. Given that 5–10% of pregnancies result in infants who are SGA and that heart disease remains the number 1 killer of adults, the need to develop evidence-based surveillance and treatment protocols can have vast implications for our patients.

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