We strongly encourage the formation and use of large databases of detailed prenatal and postnatal data for the benefit of patients with congenital heart defects throughout the world.

Niels B. Matthiesen, MD, PhD
Perinatal Epidemiology Research Unit
Department of Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus

Department of Pediatrics and Adolescent Medicine
Randers Regional Hospital
Randers

John R. Østergaard, MD, DMSc
Center for Rare Diseases
Department of Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus

Vibeke E. Hjortdal, MD, PhD, DMSc
Department of Cardiothoracic and Vascular Surgery
Aarhus University Hospital
Aarhus

Department of Cardiothoracic Surgery
Rigshospitalet, Copenhagen

Tine B. Henriksen, MD, PhD
Perinatal Epidemiology Research Unit
Department of Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus, Denmark

https://doi.org/10.1016/j.jpeds.2020.11.057

References

1. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics 2015;135:816-25.
2. Gaynor JW, Parry S, Moldenhauer JS, Simmons RA, Rychik J, Ittenbach RF, et al. The impact of the maternal-foetal environment on outcomes of surgery for congenital heart disease in neonates. Eur J Cardiothorac Surg 2018;54:348-53.
3. Hansen T, Henriksen TB, Bach CC, Matthiesen NB. Congenital heart defects and measures of prenatal brain growth: a systematic review. Pediatr Neurol 2017;72:7-18.e11.
4. Petit CJ, Rome JJ, Wernovsky G, Mason SE, Shera DM, Nicolson SC, et al. Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy. Circulation 2009;119:709-16.
5. Lynch JM, Buckley EM, Schwab PJ, McCarthy AL, Winters ME, Busch DR, et al. Time to surgery and preoperative cerebral hemodynamics predict postoperative white matter injury in neonates with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2014;148:2181-8.
6. Costello JM, Pasquali SK, Jacobs JP, He X, Hill KD, Cooper DS, et al. Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Circulation 2014;129:2511-7.
7. Jonas RA, Wypij D, Roth SJ, Bellinger DC, Visconti KJ, du Plessis AJ, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. J Thorac Cardiovasc Surg 2003;126:1765-74.
8. Ekelund CK, Kopp TI, Tabor A, Petersen OB. The Danish Fetal Medicine database. Clin Epidemiol 2016;8:479-83.
9. Bliddal M, Broe A, Pottegard A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. Eur J Epidemiol 2018;33:27-36.
10. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563-91.
11. Petersen JP, Mølholm B, Cueto H, Pryds OA, Trautner S, Zachariassen G, et al. [Neonatal survival and health in Denmark]. Ugeskr Laeger 2020;182:14A.
12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7 Suppl):30-3.
13. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39(7 Suppl):38-41.
14. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541-9.

Fetal growth restriction, nutrition, and the renin-angiotensin system

To the Editor:

We read with interest the recent comprehensive review by Sehgal et al on the mechanism of fetal growth restriction (FGR)-associated hypertension, focusing on prevention and therapeutic strategies across the life course to mitigate hypertension and cardiovascular disease.[1]

Early nutrition is important. Although the prenatally activated intrarenal renin-angiotensin system (RAS) strongly contributes to FGR-associated hypertension, the review clearly showed that dealing appropriately with postnatal nutrition and nutrition in infancy can ameliorate FGR-associated hypertension. This is most important as a countermeasure for postnatal rapid weight gain (catch-up growth that occurs in small for gestational age infants because of FGR), which leads to increased insulin resistance.[2-4] Breastfeeding slows weight gain because the low protein content of breast milk (compared with infant formula) reduces circulating levels of insulin and insulin-like growth factor-I, which accelerate growth.[5] Insulin resistance also upregulates the RAS; therefore, suppressing rapid weight gain in infancy may have a favorable effect of not activating the RAS as a cause of hypertension.[6,7]

Sehgal et al also mentioned that maladaptive changes of the intrarenal RAS (increased angiotensin II and decreased angiotensin-[1-7]), independent of the systemic RAS, play an important role in the pathophysiology of FGR-induced hypertension and renal injury.[1,8]

In general, because of enhanced sodium intake systemic RAS activity is suppressed. We believe that sodium intake

and intrarenal RAS activity are related to regulating blood pressure in infants with FGR. Sodium intake has been recently reported to remain elevated in pediatric population[9]; therefore, in providing dietary guidance or intervention for children born with a risk of FGR-associated hypertension, the relationship of amount of salt in the diet and the intrarenal RAS should be considered.

Osamu Arisaka, MD, PhD
Go Ichikawa, MD, PhD
Department of Pediatrics
Nasu Red Cross Hospital
Ohtawara

Department of Pediatrics
Dokkyo Medical University School of Medicine
Mibu

Satomi Koyama, MD, PhD
Department of Pediatrics
Dokkyo Medical University School of Medicine
Mibu

Toshimi Sairenchi, PhD
Department of Public Health
Dokkyo Medical University School of Medicine
Mibu, Tochigi-ken, Japan

https://doi.org/10.1016/j.jpeds.2020.11.044

References

1. Sehgal A, Alexander BT, Morrison JL, South AM. Fetal Growth restriction and hypertension in the offspring: mechanistic links and therapeutic directions. J Pediatr 2020;224:115-23.
2. Arisaka O, Ichikawa G, Koyama S, Sairenchi T. Childhood obesity: rapid weight gain in early childhood and subsequent cardiometabolic risk. Clin Pediatr Endocrinol 2020;29:135-42.
3. Miyamoto K, Tsuboi T, Suzumura H, Arisaka O. Relationship between aortic intima-media thickening, serum IGF-1 and low-density lipoprotein particle diameter in newborns with intrauterine growth restriction. Clin Pediatr Endocrinol 2009;18:55-64.
4. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, Casano P, de Zegher F. Abdominal fat partitioning and high-molecular-weight adiponectin in short children born small for gestational age. J Clin Endocrinol Metab 2009;94:1049-52.
5. Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, et al. European Childhood Obesity Trial Study Group. Lower protein in infant formula is associated with lower weight up to age 2 years: a randomized clinical trial. Am J Clin Nutr 2009;89:1836-45.
6. Liu Z. The renin-angiotensin system and insulin resistance. Curr Diab Rep 2007;7:34-42.
7. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Re 2013;15:59-70.
8. Yang T, Xu C. Physiology and pathophysiology of the internal renin-angiotensin system: an update. J Am Soc Nephrol 2017;28:1040-9.
9. Brouillard AM, Deych E, Canter C, Rich MW. Trends in sodium intake in children and adolescents in the US and the impact of US Department of Agriculture guidelines: NHANES 2003-2016. J Pediatr 2020;225:117-23.

Reply

To the Editor:

We were pleased to receive the comments by Arisaka et al regarding our recent review of fetal growth restriction (FGR) and programmed hypertension. We agree that rapid weight gain, development of obesity, and high sodium intake during the first year of life and throughout childhood are likely major factors that further promote hypertension development in children with FGR in an additive or even multiplicative fashion, mediated in part through renin–angiotensin system (RAS) alterations (**Figure**).[1-6] The adverse health outcomes of FGR combined with rapid postnatal growth (mismatch hypotheses) have been reported.[7,8] Therefore, preventive and therapeutic strategies centered on early-life nutrition to target the RAS may be beneficial in mitigating several perinatal programming mechanisms.

Introduction of solid foods during infancy increases salt intake. A high percentage of 12- to 24-month-old children exceed "adequate levels" of salt intake.[9] In school-age children, increased processed food consumption increases salt intake. In infants, reducing salt intake by one-half yielded a 2.5-mm Hg reduction in systolic blood pressure (BP).[9] In young adults, reduced salt intake can induce relatively rapid and sustained[10] decreased BP. In a long-term study, neonates on a low-salt diet for the first 6 months of life had 2.1-mm Hg lower systolic BP compared with controls on a normal salt diet, and at the 15-year follow-up they had 3.6-mm Hg lower systolic BP.[11] This indicates that salt intake in early life can induce sustained changes in BP, an important intervention

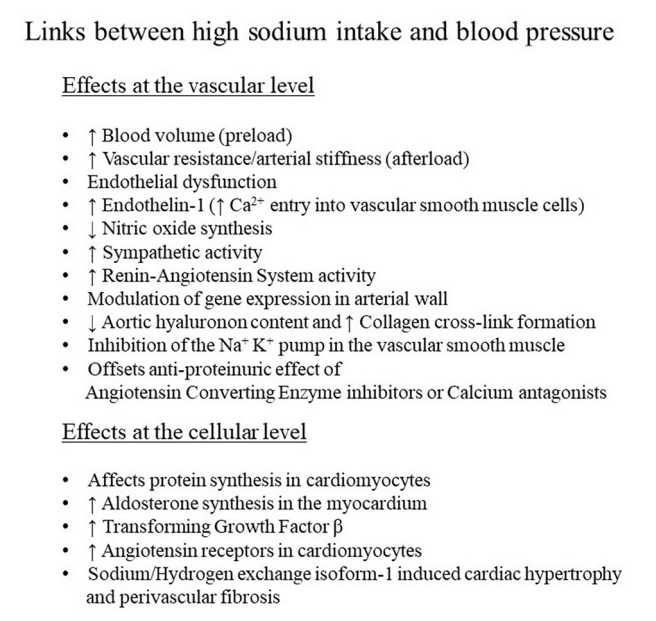

Figure. Vascular and cellular effects of salt.