CONFLICTS OF INTEREST

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João GAMA MARQUES✉[1,2], Elias BARRETO[1], Francisco MONIZ PEREIRA[1,3], Isabel FERNANDES[1], Rui DURVAL[1,3], António BENTO[1,4]

1. Hospital Júlio de Matos. Centro Hospitalar Psiquiátrico de Lisboa. Lisboa. Portugal.
2. Clínica Universitária de Psiquiatria e Psicologia Médica. Faculdade de Medicina. Universidade de Lisboa. Lisboa. Portugal.
3. Departamento de Psicologia. Universidade Autónoma de Lisboa. Lisboa. Portugal.
4. Universidade Lusófona de Humanidades e Tecnologias. Lisboa. Portugal.

Autor correspondente: João Gama Marques. joaogamamarques@gmail.com

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Cardiometabolic Risk in Childhood: Could Bilirubin Act as a Circadian Clock-Related Mediator Via Autonomic Dysfunction?

Risco Cardiometabólico na Infância: Pode a Bilirrubina Atuar como Mediador Associado ao Relógio Circadiano Via Disfunção Autonómica?

Keywords: Autonomic Nervous System; Bilirubin; Child; Circadian Rhythm; Hypertension

Palavras-chave: Bilirrubina; Criança; Hipertensão; Ritmo Circadiano; Sistema Nervoso Autónomo

The interesting paper from Yu and colleagues on the association of neonatal serum bilirubin and childhood hypertension recently published in Plos One,[1] flagged up a plausible role of bilirubin as a mediator of hypertension in later life. This is a highly important topic since hypertension, a main cause of cardiometabolic associated morbidity and mortality, may affect 2% to 4% of children. Bilirubin is a toxic end-product of heme catabolism in the body, commonly seen in newborns and causing jaundice. It is detoxified mainly in the liver by means of several steps involving circadian regulated enzymatic processes.[2] A balanced autonomic output to the liver is crucial for maintenance of the circadian rhythmicity that ensures the normal function of liver metabolic enzymes and glucose level.[3] Bilirubin production is known to oscillate in a circadian fashion. Several studies showed that free bilirubin is negatively associated with hypertension and other cardiometabolic risk factors, although with controversial issues remaining to be clarified. A non-dipping hypertensive profile was also linked with nocturnal lower bilirubin levels compared to those having a dipper hypertensive profile, consolidating the circadian signature on hyperbilirubinemia associated hypertension. Furthermore, bilirubin seems to increase after light therapy not only as a result of activation of photoreceptors but also impacted by circadian clock regulatory mechanisms.[4] Nonetheless, in their retrospective study, the authors of the aforementioned paper found that neonatal serum bilirubin levels were positively associated with childhood blood pressure/hypertension in preterm infants. This suggests that neurotoxicity of bilirubin and its plausible impact on autonomic pathways via sympathetic nerve fibers may be involved in the neonatal pathophysiological mechanisms leading to hypertension. Interestingly, in a prospective study in full-term newborn infants it was found that severe unconjugated hyperbilirubinemia may cause cardiac autonomic dysfunction, with parasympathetic predominance.[5] These findings can also raise the important question of whether newborn babies with kernicterus are predisposed to developing hypertension or cardiovascular morbidity. Despite the contradictory observations, the relationship of hyperbilirubinemia and autonomic function and their circadian variations is particularly important in preterm babies due to the immature nature of the brain-blood barrier and consequent higher risk of toxicity and encephalopathy leading to autonomic related cardiovascular and metabolic signs.

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Miguel MEIRA E CRUZ✉[1,2], Isabel ROCHA[2], Oliviero BRUNI[3]
1. Sleep Unit. Centro Cardiovascular. Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
2. Cardiovascular Autonomic Function Lab. Centro Cardiovascular. Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
3. Department of Developmental and Social Psychology. Universitat Sapienza. Rome. Italy.
Autor correspondente: Miguel Meira e Cruz. mcruz@medicina.ulisboa.pt
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