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Coronary Intimal Thickening: Once Again

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In a letter to the Editor, Briana and Malamitsi-Puchner[1] commented our recently published paper in which we showed that intimal thickening already begins in fetal life and progresses through childhood and adolescence.[2] Our work is in line with studies by Barker about the fetal origins of adult disease which led to "The Barker Hypothesis", indicating that the pathogenesis of cardiovascular (CV) disease begins in utero.[3]

Briana and Malamitsi-Puchner[1] recently evaluated cord blood serum for potentially prognostic biomarkers for CV disease in large-for-gestational-age compared to appropriate-for-gestational-age neonates. Among other biomarkers, the authors[1] studied serum cardiotrophin-1, a cardiomyocyte-produced chemokine that plays a fundamental role in fetal heart development and whose expression is increased by hypoxia, mechanical stress, and pro-inflammatory cytokines such as interleukin-1B. The authors[1] also studied serum levels of cardiac myocyte sarcomeral protein titin involved in sensing and responding to myocardial stress. As a result, Briana and Malamitsi-Puchner[1] propose that cord blood serum concentrations of both cardiotrophin-1 and titin could represent prognostic biomarkers for future CV disease.[4]

In addition, another study by Milei et al[5] analyzed autopsy heart samples from 22 fetal sudden intrauterine death and 36 sudden infant death victims, all between the 32nd week of gestation and 1 year of age. In 28 of 58 cases, the mothers were smokers. Coronary lesions were detected in 10 of 12 fetuses and in 15 of 16 infants whose mothers smoked, while only 5 cases (2 of 10 fetuses and 3 of 20 infants) of arterial lesions were found in cases of nonsmoking mothers ($P < 0.001$). These results suggest an increase in arterial lesions in fetuses and infants of smoking mothers.[5]

We also studied intimal thickening in congenital heart defects (CoHD) because these alterations or their repair process lead to a higher risk for adult CV disease. We examined the coronary arteries of a total of 98 autopsies from patients with CoHD ranging between 4 days and 17 years (mean age: 2.4 years), among whom 32% were surgically repaired. We determined that 84% of surgically repaired patients with CoHD presented at least 1 coronary artery with intimal hyperplasia, in contrast with 47.3% in nonsurgical patients ($P < 0.001$). In addition, 68% of coronary arteries from surgically repaired patients presented intimal hyperplasia in >1 artery, compared to 25% in the patients with CoHD without surgery ($P < 0.001$). Hence, these results suggest a higher rate of coronary intimal hyperplasia in surgically repaired patients with CoHD as compared to nonrepaired ones.[6] This high incidence was correlated with intimal decrease in estrogen receptor α (ERα) expression, an increment in transforming growth factor β1 (TGF-β1) expression and in apolipoprotein B (apoB) deposition, which allowed us to conclude that a decrease in ERα and augmented expression of TGF-β1 expression may contribute to the development of atherosclerotic coronary artery disease in patients with CoHD.[6,7] A case report illustrating our findings described an aneurysm in the left main coronary artery of a 2-year-old patient. This aneurysm presented intimal hyperplasia and strong apoB deposition.[8]

As mentioned in the Briana and Malamitsi-Puchner letter,[1] it is important to search for early biomarkers of CV disease at an early age in order to implement preventive strategies. In this regard, we suggest that special attention should be given to children of smoking mothers and to patients with CoHD, particularly if they underwent reparative surgery.

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