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Letters

Cancer Risk in Patients With Congenital Heart Disease Exposed to Radiation From Cardiac Procedures

Medical x-ray examinations, including computed tomography and cardiac catheterization, are frequently used for both diagnosis and treatment of congenital heart disease (CHD). At present, there is an ongoing discussion about the role of radiation exposure at early ages from these examinations and the risk for cancer in CHD patients,[1] especially in cases receiving repeated multiple procedures involving ionizing radiation.[2]

Molecular epidemiology may detect preclinical biological changes that precede and predict the subsequent development of cancer. Changes in leukocyte telomere length (LTL) and mitochondrial DNA copy number (mtDNAcn) in the blood are considered important biological mechanisms contributing to tumorigenesis.[3] Additionally, microRNAs (miRNAs) dysregulation may be central to the cellular response to radiation exposure, acting as oncogenes or tumor suppressor genes and controlling various aspects of cancer biology (eg, the DNA damage repair mechanisms, apoptosis, and cell growth).[4] We, therefore, explored the relationship between radiation exposure from cardiac procedures and biomarkers of cancer risk in peripheral blood, including LTL, mtDNAcn, and a panel of circulating cancer-associated miRNAs (miR-18, miR-21, miR-155, and miR-221) by using reverse-transcription quantitative polymerase chain reaction.

What is the clinical question being addressed?
Does exposure to low-dose ionizing radiation during cardiac procedures in patients with congenital heart disease increase the risk of cancer risk later in life?

What is the main finding?
Life-saving cardiac procedures involving x-ray exposure are associated with elevated early biomarkers of cancer risk.

We enrolled 93 patients with CHD (62 males; age 12.7 ± 11.5 years) and 131 healthy and nonsmoker subjects (69 males; age 15.9 ± 12.6 years) without a self-reported history of medical radiation exposure as control subjects. Exclusion criteria included a history of cancer or genetic disease. The Institutional Ethical Committee approved this study (Study Protocol n. 605-112019). In total, 203 cardiac catheterization procedures (median 2 [IQR: 1-3]) and 43 other high-dose medical imaging procedures (computed tomography and nuclear scintigraphy) were performed in CHD patients. The median age at first exposure was 1 year (IQR: 0.2-5.7 years). Forty-six patients (49.5%) had an age <1 year at their first procedure, with 20 patients (21.5%) undergoing catheterization within a few hours or days after birth. For data analysis, we dichotomized into 2 levels (1 to 2 and ≥3 procedures) the number of procedures with radiation exposure. Patients with ≥3 procedures had both shorter LTL ($P = 0.01$) and lower mtDNAcn ($P = 0.02$) when compared with controls (**Figure 1**). The expression of miR-155 was also increased in patients with ≥3 procedures compared with the healthy control subjects ($P = 0.03$). Multiple regression analysis identified the number of procedures with radiation exposure as the only determinant of miR-155 expression (standardized regression coefficient $\beta = 0.279$; $P = 0.02$).

Our study shows a significant association between pediatric radiation exposure from cardiac procedures and alterations of early markers of genetic instability and carcinogenesis, as well as the dysregulation of miR-155, a well-known oncogenic miRNA.

Telomere shortening, by favoring genome instability through chromosome end fusion and dicentric formation, promotes tumorigenesis.[3] Alterations in mitochondrial DNA content might damage mitochondrial functions, triggering cancer development and progression.[3]

Both short telomere and mtDNAcn variations in peripheral blood have been reported as potential biomarkers of risk or prognosis of various cancers.[3]

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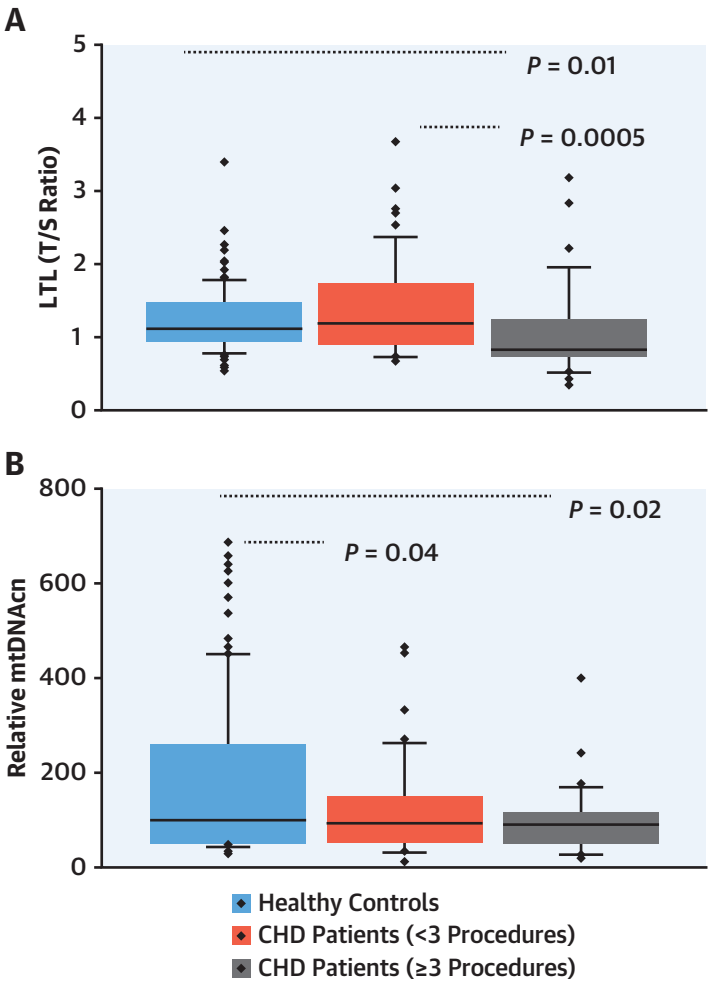
FIGURE 1 LTL and mtDNAcn



Box-and-whiskers plot of leukocyte telomere length (LTL) **(A)** and mitochondrial DNA copy number (mtDNAcn) **(B)** in congenital heart disease (CHD) patients and healthy control subjects according to the number of catheterization procedures. Box-and-whisker plots display interquartile range, median values, and maximum and minimum values. Multiple comparison tests between groups were conducted after adjustment for age and sex. T/S ratio = telomere/single copy gene-ratio.

In addition, miR-155 is an oncogenic miRNA that promotes tumor growth, angiogenesis, and inhibition of apoptosis.[5] Importantly, miR-155 is overexpressed in cells from patients with acute myeloid leukemia and several types of solid tumors in highly radiosensitive organs, such as lung, breast, and colon.[5]

Despite some limitations such the lack of individualized dose estimates for all radiation exposures, our findings support the notion that repeated cardiac procedures involving ionizing radiation exposure affect DNA structure and cellular function, which may prematurely accelerate the molecular processes driving oncogenesis.

Further longitudinal studies are certainly needed to validate the role of biomarkers for improving cancer surveillance in this vulnerable patient population.

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