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EDITORIAL COMMENT

Asynchronous Shortening of Telomere Length and Cardiovascular Outcomes*

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At each end of a chromosome, telomeres with repetitive sequences of TTAGGG protect the integrity of the genome. In humans, telomere length shortening occurs at a rate of 20 to 40 base pairs per year. When telomere lengths are shortened to a critical threshold, cells will start to enter a replicative senescence process, including imbalanced cellular homeostasis, decreased function, cell cycle arrest, proliferation inhibition, and apoptosis. Human telomere lengths exhibit broad interindividual variations, which are influenced by genetic and environmental factors (1). At birth, there is synchrony, with good correlation in telomere lengths between various tissues and blood cells (2). Theoretically, muscles or heart with low replication activities will have a different rate of telomere length shortening compared with blood cells or skin with high replication activities. As we age, tissues are subjected to various pathophysiological insults, which may further change the telomere length shortening rate of different tissues. In the last several years, a growing academic interest in the systemic analysis of the asynchrony shortening of telomere lengths among different tissues has gained momentum.

Peripheral leukocyte telomere length has been the most commonly used in clinical studies. It is not easy to obtain different tissues in patients for telomere length analysis and follow-up studies clinically. Using leukocyte telomere length analysis, several cross-sectional studies observed an association between shorter leukocyte telomere length and the occurrence of coronary artery diseases (3,4). Prospective cohort studies also reported an association between decreased leukocyte telomere length with all-cause mortality after myocardial infarction (5). Single nucleotide polymorphisms of telomere-shortening alleles found in a meta-analysis of 37,684 patients with coronary artery diseases were associated with increased risks of coronary artery diseases and telomere dysfunction (6). Moreover, several risk factors for cardiovascular diseases, such as smoking, diabetes mellitus, obesity, and inflammation, are correlated with short leukocyte telomere length. In patients with heart failure, short leukocyte telomere lengths are also associated with heart failure severity, clinical outcomes, and diastolic dysfunction (7).

Although there is solid evidence that shorter leukocyte telomere lengths have adverse cardiovascular impacts, the causal or consequential relationship between leukocyte telomere length and cardiovascular diseases remains controversial. Currently, clinical studies of telomere lengths have several limitations. First, correlations of the telomere lengths in different tissues to cardiovascular diseases are currently unknown. In dogs and pigs, telomere lengths in normal somatic tissues exhibit a wide heterogeneity (8,9). Data from previous human studies showed that there is a strong correlation in telomere lengths across leukocytes, skeletal muscle, skin, and subcutaneous fat. The rates of telomere shortening are similar in these 4 tissues (10). Therefore, most of the clinical studies use leukocyte telomere lengths based on the assumption that these

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telomere lengths are representative of other tissues or organs. Second, because of the low leukocyte telomere attrition rate, most of the studies determine the telomere length changes over time by comparing patients in different age groups. This cross-sectional study design oversimplifies the complex dynamics of telomere lengths and the wide variation of telomere lengths between individuals. Therefore, the strengths of leukocyte telomere length to be offered as a solid cardiovascular biomarker remain to be determined.

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In this issue of *JACC: Basic to Translational Science*, Yin et al. (11) describe the telomere length gap between cardiac atrial tissue and leukocytes as serving as a better biomarker than leukocyte length alone for post-cardiovascular surgery events and intensive care unit (ICU) stays. The study showed that right atrial appendage telomere lengths from 163 patients with ages ranging from 30 to 89 years had no statistically significant attrition. In contrast, leukocyte and skeletal muscle telomere lengths had age-dependent attrition rates at 28 and 29 base pairs per year, respectively. Based on the findings that the right atrial appendage telomere length remained stable over decades, it was used as an innately referenced assessment of leukocyte telomere shortening in clinical patients. For each SD increment in the right atrial leukocyte telomere length difference, the risk of postoperative complication increased by 106%, and the risk of remaining in the ICU increased by 31%. Leukocyte or skeletal muscle telomere lengths alone did not confer a detectable hazard in these patients.

Yin et al. (11) are to be congratulated for providing valuable data defining the telomere attrition rates in human skeletal muscle, leukocytes, and right atrial appendage. Lack of age-associated telomere length shortening in the right atrial appendage provides a new insight into human telomere length physiology. Nonetheless, some limitations of this research should be acknowledged. First, the characteristics of the study patients must be considered before generalizing these results. Right atrial appendages were from patients with coronary artery diseases, valvular heart diseases, and ascending aorta diseases. The extent of right-side heart failure, tricuspid regurgitation, and right atrial fibrosis must be confirmed and analyzed with telomere length data. In humans, there is a cardiomyocyte-specific telomere shortening in left ventricular samples from patients with heart failure compared with samples from healthy individuals (12). The shortened telomeres are specific only to cardiomyocytes within diseased hearts and are associated with DNA damage. Consistent with the findings from Yin et al. (11), the left ventricular telomere length exhibits no age-dependent changes. Second, clinical studies using human myocardial tissues have inherent high background noise. The intraoperative myocardial samples are usually larger (30 to 50 mg) than endomyocardial biopsy samples (5 mg). The right ventricular changes after pulmonary hypertension, tricuspid regurgitation, or atrial fibrillation further complicate the sampling differences. To use right atrial telomere length as a reference standard for telomere shortening, the biopsy site will need to be assessed. Third, this trial was a proof-of-concept study, and short-term in-hospital complications and lengths of ICU stay were used as primary endpoints. Although the telomere length is used as a marker for biological aging, the telomere length shortening is affected by sepsis (13), inflammation (14), viral infection (15), and stress (16). These factors may directly affect both the telomere length shortening and the short-term in-hospital complications with prolonged ICU stays. Therefore, as Yin et al. pointed out, future studies must determine whether the cardiac leukocyte telomere length differences or the shorter leukocyte telomeres are more clinically relevant risk factors.

Although our chronological aging occurs at a constant rate, the biological aging process develops at a more complicated pace. Yin et al. (11) have provided important new insights with regard to different rates of telomere shortening among tissues. Previous human studies have suggested that genetic determination of the telomere length is tissue independent (10,17), and telomeres shorten at equivalent rates in multiple tissues. These studies are limited by the difficulties in obtaining multiple human tissue samples and relatively small study subject numbers. The study statistical power is further affected by the slow telomere attrition rate, which would require a relatively high subject number and long study duration. Theoretically, multiple tissues can have similar biological aging processes at baseline. However, as aging processes occur, there would be some parts of the system exhibiting accelerated biological aging and becoming the critical point of system failure. Having a good reference telomere length, such as the right atrial appendage, would be critical for delineating the process of biological aging in the future.

Future applications of this cardiac-referenced leukocyte telomere length could be incorporated with single-cell telomere length measurement (18). Global single-cell or single-molecule telomere

analysis with the Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 genome editing system to covalently tag the telomeric repeats can track individual telomere length in the context of whole genomic DNA (19). Current telomere length measurements use a large population of different cells, which usually represent the average telomere length and mask the heterogeneity of telomere dynamics in single cells. In murine hearts, telomerase activities are heterogeneous among cells with markers for cardiomyocyte, endothelial cells, and putative cardiac stem cells (20). These small populations of cells with low-level telomerase activities arise from subpopulations of different cell types and maintain the cardiac telomere homeostasis (21). In human hearts, cardiomyocytes have telomere attrition different from other cell types. The cell type-specific telomere attritions study using single-cell telomere length measurement and analysis will broaden our views of telomere biology in cardiovascular diseases in the future.

In summary, current evidence for the leukocyte telomere length and cardiovascular diseases is solid but remains too limited and ill-defined to be translated into clinical usage. Targeting telomere length or telomerase activity may be a potential therapeutic option for cardiovascular diseases, and it is therefore pertinent to have an accurate telomere length measurement for evaluating the therapeutic goal and outcomes.

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