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Age-independent telomere shortening and ion-channel defects in SCD

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In the Review article by Fyhrquist *et al.* (The roles of senescence and telomere shortening in cardiovascular disease. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2013.30),[1] the authors extensively appraise the role in cardiovascular diseases of telomere length homeostasis in response to senescence, oxidative stress, and various other factors. The measurement of leukocyte telomere length to determine telomere size might be an important biomarker to predict cardiac disease outcomes. We agree with most of the conclusions of the authors in this Review and wish to add a new dimension by proposing a possible mechanism by which chronic oxidative stress in the cardiac microenvironment, as a result of ion-channel defects, might cause telomere shortening, which supports the hypothesis of arrhythmia-induced cardiac dysfunction.[2]

We previously reported the direct correlation between telomere length attrition and sudden cardiac death (SCD) using the processes of leukocyte-telomere-length measurement and comparative genomic hybridization. This analysis revealed defects in key ion-channel genes that had a strong correlation with telomere attrition when compared with age-matched controls.[2] Fyhrquist and colleagues reviewed some work on the role of the mitochondria in cardiovascular disease, but ion channels—which have a crucial role in maintaining cellular homeostasis, particularly in the heart—were not discussed.

Fyhrquist *et al.* proposed that the hypothesis of telomere dysfunction might converge with that of mitochondrial dysfunction. They highlighted reports of the presence of increased numbers of senescent cardiomyocytes that express p16, p21, and p53, and which have short telomeres, in the ageing heart.[3] In our study, the mean age of individuals who experienced SCD was 24.7 years (range 12–33 years), and they were compared with controls with a mean age of 23 years (range 21–28 years).[2] Severe telomere shortening and ion-channel defects were present in both the cardiomyocytes and peripheral blood lymphocytes of individuals who experienced SCD when compared with age-matched and sex-matched controls.[2] This phenomenon was observed independently of age.[2] Post-mortem examinations did not reveal signs of atherosclerotic plaques or cardiomyopathy, which ruled out age-related cardiac dysfunction and degeneration. Therefore, given that in this population, age-induced telomere shortening is well controlled for, the SCD cohort can be used as a model to study telomere attrition.

The association between SCD and arrhythmias is well established.[4,5] In our study of SCD, we reported deletion of *KCNA4* and amplification of *RYR2* genes, which actively regulate potassium-channel homeostasis.[2] These copy number changes in ion-channel genes correlate with telomere regulatory defects in regions such as 3q26 and 18q11.2.[2,6–8] We have also reported that mouse cells that lack telomerase reverse transcriptase are hypersensitive to oxidative stress, and that these mice display rapid upregulation of inflammatory cytokines and increased mortality compared with wild-type mice.[9,10] We speculate that ion-channel defects and electrical abnormalities of the heart might accelerate telomere shortening by increasing chronic oxidative stress and, thus, cause SCD.

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Competing interests
The authors declare no competing interests.

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