EDITORIAL

Failing Hypertensive Heart: a Question of Altered Telomere Biology?

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Hypertensive heart disease is defined by the presence of left ventricular (LV) hypertrophy in hypertensive patients not presenting other causes of LV growth (such as aortic stenosis, hypertrophic cardiomyopathy, or cardiac amyloidosis). Despite improvements in the treatment and control of arterial hypertension, recent decades have seen increases in the prevalence of hypertensive heart disease and the associated risk of heart failure (HF) with either preserved or HF with reduced ejection fraction (HFrEF), even in the absence of ischemic heart disease.[1] It is therefore important to determine the molecular mechanisms underlying the myocardial alterations that facilitate the transition from initially compensatory LV hypertrophy to maladaptive LV hypertrophy and HF. Alterations observed in the failing hypertensive myocardium include increased cardiomyocyte death, especially by apoptosis, which can reduce contractile mass and thus affect contractility and systolic function,[2] as well as facilitating wall thinning, LV dilation, and further systolic dysfunction.[3]

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In this issue of *Hypertension*, Brandt et al[4] provide novel experimental and clinical evidence linking hypertensive HFrEF to the shortening of cardiomyocyte telomeres. Telomeres are specialized chromatin structures at the ends of eukaryotic chromosomes that preserve genome stability and integrity. These DNA segments contain multiple noncoding double-stranded repeats of a G-rich tandem sequence and end in a short 3' single-stranded overhang. Telomere length is principally maintained by 2 independent mechanisms: an enzyme-dependent mechanism involving de novo synthesis of telomere DNA, catalyzed by telomerase RNA component and telomerase reverse transcriptase, and a telomerase-independent mechanism involving homologous-recombination–mediated DNA replication. Telomerase activity is regulated by the shelterin multiprotein complex, which also protects telomeres against attrition. In most tissues, one of the major factors determining telomere ablation is aging. Moreover, in vitro studies, animal studies, and human longitudinal studies have shown that telomere damage and shortening are induced by several stress factors, including oxidative stress.[5] Cells with critically short telomeres undergo chromosomal end-to-end fusions, cell cycle arrest, cellular senescence, and apoptosis.[6]

Telomere damage and shortening may play important roles in the occurrence and development of cardiovascular disorders, including hypertension and associated target organ damage.[7] Late generation telomerase RNA component-knockout mice with critically short telomeres exhibit elevated cardiomyocyte apoptosis, LV dilation, wall thinning, and systolic dysfunction.[8] Moreover, a mouse model of hypertrophic HF induced by severe mechanical overload revealed a series of cardiac alterations, including shortened telomeres, activation of DNA damage Chk2 (checkpoint kinase), diminished expression of the shelterin subunit telomere repeat binding factor 2, increased cardiomyocyte apoptosis, and systolic dysfunction, alterations that were prevented by ectopically expressing telomerase reverse transcriptase.[9] Likewise, endomyocardial biopsies from patients with HF with LV hypertrophy and LV dilation reveal short telomeres and elevated cardiomyocyte senescence and apoptosis.[9,10] The pathophysiology of hypertension is thought to involve a critical action of oxidative stress, resulting from increased generation of reactive oxygen species by

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nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXes).[11] In particular, hypertension-associated oxidative stress has been proposed to accelerate telomere attrition and promote the progression of LV hypertrophy to HF.[12]

Using an in vivo mouse model of hypertensive HFrEF driven by excess neurohormonal activation (induced by angiotensin II infusion, high-salt diet, and unilateral nephrectomy), Brandt et al[4] found that cardiomyocyte telomere shortening is characteristic of advanced hypertensive HFrEF (Figure). Based on a thorough characterization of their mouse model and in vitro experiments with angiotensin II-treated H9C2 cardiomyocytes and adult mouse cardiomyocytes, the authors propose that neurohormone-dependent cardiomyocyte telomere shortening is largely driven by increased expression of the NADPH oxidase gp91phox/NOX2 (Figure [A]). This effect is mediated through myocardial loss of the telomere-specific antioxidant PRDX1 (peroxiredoxin 1), increased expression of Hdac6 (histone deacetylase 6, the enzyme that deacetylates PRDX1), and increased reactive oxygen species and oxidative DNA damage. Supporting this conclusion, the effects of angiotensin II on cardiomyocytes were fully or partially abrogated upon genetic deletion or pharmacological inhibition of gp91phox/NOX2 or pretreatment of cells with an Hdac6 inhibitor (Figure [A]). Since HFrEF is prevalent in both sexes and the authors exclusively studied male mice, future studies should include female mice. Further research should also examine whether the newly described molecular mechanisms linking HFrEF to telomere length have any impact on cardiomyocyte regeneration and survival through effects on cell senescence or death. It will also be of interest to examine if neurohormonal activation promotes the accumulation of cardiomyocytes with critically short telomeres (<3 kb), which might trigger cell senescence and death independently of average telomere length[13] and can be quantified with the same high-throughput-quantitative-fluorescence in-situ hybridization method the authors used to measure mean telomere length.

To test the potential clinical value of their observations in cell and animal models, Brandt et al[4] examined endomyocardial biopsies from patients with HFrEF of nonischemic origin enrolled in the My Biopsy-HF study of the response to guideline-directed medical therapy. They found that baseline telomere length was shorter in patients with persistent HFrEF (n=10) than in patients showing partially or fully recovered LV systolic

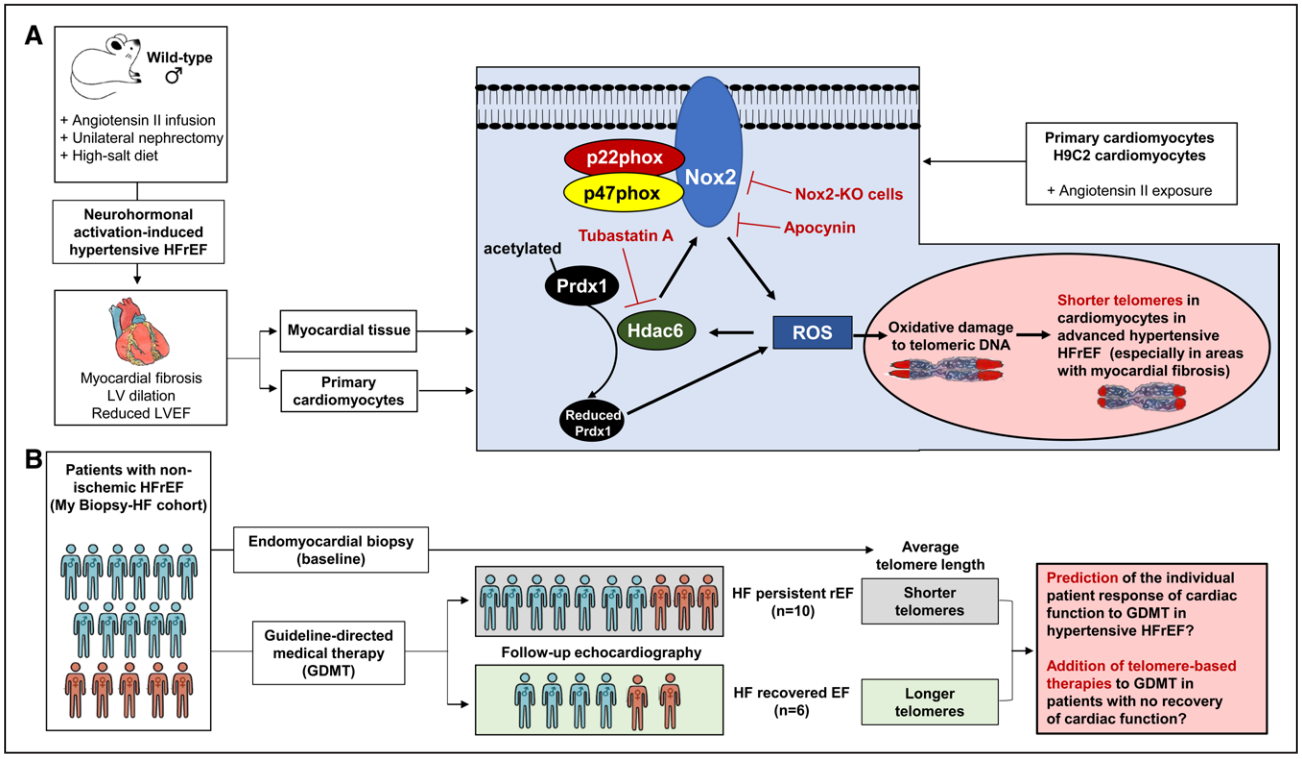

Figure. Working model based on the results presented by Brandt et al.[4]
A, Cellular and mouse models of neurohormonal activation suggest that cardiomyocyte telomere shortening is a characteristic of advanced hypertensive heart failure with reduced ejection fraction (HFrEF). Telomere ablation in this setting occurs through a mechanism involving activation of the NADPH oxidase gp91phox/NOX2, causing myocardial loss of antioxidant PRDX1 (peroxiredoxin 1), due at least in part to its deacetylation via Hdac6 (histone deacetylase 6) activation. These alterations increase reactive oxygen species (ROS) and oxidative nucleic acid damage, including to telomere DNA. Angiotensin II-dependent alterations are prevented or diminished by genetic disruption of gp91phox/NOX2 and by pharmacological inhibition of gp91phox/NOX2 and Hdac6. **B**, Analysis of an all-comer population of patients with nonischemic HFrEF undergoing guideline-directed medical therapy revealed that telomere length in endomyocardial biopsies predicts the degree of recovery of cardiac function at echocardiographic follow-up (shorter telomeres detected in HF patients with persistent LV dysfunction).

function at follow-up (n=6), suggesting that telomere length in myocardial tissue predicts the degree of cardiac function recovery in HFrEF patients (Figure [B]). Study limitations include the small cohort size, the failure to specify the number of hypertensive patients in each group, and the omission of the time of follow-up. Moreover, endomyocardial biopsies is contraindicated in many hypertensive heart disease patients and thus alternative methods are required. One possible parameter is leucocyte telomere length, which is reported to be lower in hypertensive patients than in age-matched normotensive individuals.[14] The length of telomeres in leukocytes was also found to be lower in patients with HFrEF than in an age- and sex-balanced control group, correlating with the severity of disease and independent of the ischemic or nonischemic cause of HF.[15] Specific studies are warranted to determine if leukocyte telomere length could be used to stratify the HFrEF risk of hypertensive heart disease patients, thus helping to identify patients who, in addition to conventional therapy, might benefit from antioxidant or antideacetylation measures. Leukocyte telomere length might also be used to predict cardiac function recovery in hypertensive HFrEF patients receiving medication.

Brandt and colleagues are to be congratulated for revealing previously unrecognized molecular pathways potentially involved in the interplay between telomere biology and hypertensive heart disease that hint at routes toward future telomere-based personalized prevention or HF therapy. Future mechanistic experimental studies and larger human cohort studies are certainly warranted to test these intriguing possibilities.

ARTICLE INFORMATION

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