The Role of Biological Age in Cardiovascular Disease

Eugeniusz Hrycek, MD & Wojciech Wójakowski, MD
Third Division of Cardiology, Medical University of Silesia, Katowice, Poland

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ABSTRACT

Age is an important prognostic factor in both primary and secondary prevention of coronary heart disease. The progress in molecular biology resulted in the introduction of the notion of biological age which facilitates the objective estimation of the organism’s regenerative potential. The purpose of this paper is to review the effects of several aspects of biological age on the development and progression of coronary heart disease. The term biological age is defined and its markers are characterised. The influence of risk factors for coronary heart disease and heart failure on biological age is also discussed. Special emphasis is placed on the clinical aspects of cellular senescence in cardiovascular system.

Age is an important prognostic factor in both primary and secondary prevention of coronary heart disease. Age considerations are inherent in several tools used for risk quantification including the Score, Grace or Framingham Risk Scores. Investigations into molecular mechanisms of regeneration resulted in the introduction of the notion of biological age, which is a determinant of the regenerative potential of an organism. Defining the biological age consists of the determination of a number of biological age markers including telomeres – complexes of nucleic acids and chromatin - stabilising proteins. Cellular senescence induces proportional telomere shortening, a characteristic that helps define the biological age. Other molecular markers that reveal the biological age are cell cycle regulator proteins (p53, p16, p27) and senescence-associated beta-galactosidase (SA-β-gal). Figure 1 illustrates the relationships between the biological age markers.

Biological ageing diminishes the regenerative capacity of the cardiovascular system. A number of cells have been identified that appear to be responsible for the regeneration of cardiovascular system components including endothelial progenitor cells (EPC), cardiac progenitor cells (CPC) and smooth muscle progenitor cells (SMPC). Recent research seems to confirm the role of biological age in cardiovascular system regeneration. Kajstura et al. have demonstrated that, from 20 to 100 years of age, the pool of cardiomyocytes is replaced 15 times in women and 11 times in men. Paradoxically, cardiomyocyte turnover increases with the biological age of the heart, which probably represents a compensatory mechanism for lower regenerative potential of the cells. Figure 2 presents the role of particular components engaged in cardiovascular system regeneration.

THE EFFECT OF SOME SELECTED RISK FACTORS FOR CARDIOVASCULAR DISEASE ON BIOLOGICAL AGE

Diabetes mellitus and oxidative stress

Diabetes mellitus affects the prognosis in the primary and secondary prevention of cardiovascular disease. Risk quantification scores consider diabetes as a coronary heart disease risk equivalent. Salpea et al. demonstrated that type 2 diabetes was associated with shorter leukocyte telomere length (LTL)². It was also observed that diabetes accelerated LTL shortening in patients with a history of myocardial infarction³. Moreover, an association was shown between the impaired function of circulating endothelial progenitor cells (EPCs), impaired neovascularisation process and the activation of the p53 signalling pathway⁴. From a molecular perspective, diabetes generates high levels of oxidative stress resulting in cell damage and accelerated ageing.

SHC is a adaptor protein that exists in three isoforms, i.e., p46Shc, p52Shc, and p66Shc. The p66Shc adaptor protein has potential implications for cellular senescence resulting from the induction of mitochondrial oxygenation-reduction processes in response to oxidative stress. Reactive oxygen species (ROS) cause damage to nuclear and cytoplasmic structures ultimately resulting in impaired function and apoptosis⁵,⁶. Thus, potentially dysfunctional cells exposed to oxidative stress are eliminated. ROS formation associated with SHC expression is paradoxically involved in the process.

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Senescence cells reveal lower migration and differentiation ability. They are characterized by shorter telomeres, lower telomerase activity and increased expression of cell cycle regulators (p27, p16, p53). These regulators habit the division of potentially insufficient cell. Moreover, the release of senescence-associated beta-galactosidase in the senescence cells is present.

**Abbreviations:** P16 = p16 protein, P27 = p27 protein, P53 = p53 protein
Therefore the p66Shc gene seems to be of important significance in the pathophysiology of ageing and the development of cardiovascular disease. p66Shc knockout mice display decreased susceptibility to atherosclerotic plaque formation, more efficient endothelium-dependent relaxation, and higher resistance to reperfusion injury associated with oxidative stress. Inactivation of the p66Shc gene also protects against age-dependent endothelial dysfunction. Deletion of the p66shc gene in experimental animals with insulin-dependent diabetes mellitus prevents cardiac progenitor cells from telomeric shortening and limits the accumulation of senescence-associated proteins p53 and p16INK4. These findings seem to suggest that negative adaptations in the function of cardiac progenitor cells resulting from diabetes-enhanced oxidative stress are among the underlying causes of diabetic cardiomyopathy. Another report indicates a fundamental role of p66Shc in angiotensin II-mediated myocardial remodelling.

Smoking should be emphasised among free-radical generators; the result is oxidative stress. High levels of oxidised-LDL effectively mediate the ageing process, and have been shown to inhibit telomerase activity in endothelial progenitor cells.

Hypertension

The effect of hypertension on biological age has been documented both in human and animal models. It was demonstrated that leukocyte telomere shortening was associated with a higher risk of developing hypertension and, consequently, coronary heart disease. It was also reported that elevated blood pressure increased p16INK4A expression in rat left ventricular cardiomyocytes and cardiac arteries. The level of hypertension-induced p16INK4A protein expression correlated with the severity of left ventricle fibrosis. The role of the renin-angiotensin system in biological senescence has also been investigated. Kunieda et al. demonstrated that angiotensin II induced premature senescence of vascular smooth muscle cells.

The process is probably mediated by angiotensin II receptor type 1 (AT1) and the cytoprotective angiotensin II receptor type 2 (AT2) mediated antisenesence signalling. Vasan et al. demonstrated an inversely proportional correlation between renin-to-aldoosterone ratio and LTL. Interestingly, increased plasma endothelin-1 levels associated with telomerase deficiency in mice resulted in hypertension.

Gender, physical activity, smoking and lipid disturbances

Due to the fact that women show longer telomeres compared to men, a novel endothelium-associated protective estrogen effect on telomeres has been postulated resulting from de novo synthesis of telomeric DNA, enhanced telomerase activity through human telomerase reverse transcriptase (hTERT) phosphorylation and the production of nitric oxide.

Epidemiological evidence has confirmed that physical activity is associated with reduced risk of cardiovascular disease. Exercise also turns out to act as a telomere protecting factor which was confirmed by the analysis of telomere biology of circulating leukocytes in human and animal models. Most probably Long- and short-term physical effort up-regulates telomere-stabilising proteins and prevents cardiomyocyte apoptosis.

BIOLGICAL AGE AND SECONDARY PREVENTION OF CORONARY HEART DISEASE

So far we have defined biological age, characterised its standard markers, and discussed the effects of some selected risk factors for coronary heart disease on biological age.

Another patient group comprises individuals involved in the programme of secondary preventive therapies for coronary heart disease. Telomere shortening seems to be a primary abnormality in the pathogenesis of coronary heart disease. Reduced LTL is also predictive of increased risk of mortality in patients with stable coronary artery disease. A prospective study of Farzaneh et al. revealed that LTL in patients with stable coronary heart disease may undergo dynamic changes, i.e., may increase, decrease or remain unchanged in patients with stable coronary heart disease. Advanced biological age is also related to the function of vascular endothelium. Satoh et al. demonstrated EPC telomere erosion in CAD, and protective effect of intensive lipid-lowering therapy on endothelial progenitor cell telomeres. Telomere shortening of autopsised coronary endothelial cells of CAD patients was also confirmed.

Table 2 presents the role of biological age in the pathogenesis of myocardial infarction, the risk of which is increased in patients with telomere shortening.

Heart failure (HF) is the end-stage of a variety of cardiovascular entities. Enhanced cardiomyocyte apoptosis has been implicated as a pathogenic mechanism underlying the development of HF; the process is associated with fibrosis. Table 1 shows selected research reports confirming the role of biological age advancement in HF. Protein p53 seems to act as a key mediator of HF development. Interestingly, it has been hypothesised that telomere shortening might contribute to higher susceptibility to anaemia in HF patients. An association has also been suggested between biological age and HF severity.

LTL has been show to correlate with the results of echocardiographic examinations. LTL was positively associated with left ventricular mass and wall thickness. Thus, LTL might facilitate the prognosis of left ventricular hypertrophy.

An inverse association of LTL with common carotid artery intima-media thickness and more extensive coronary artery calcification (CAC) has also been found.

SUMMARY

To summarise, in the future biological age may become an important therapy target and therapy determinant. Although there are a multitude of risk factors for coronary heart disease, biological age represents their common molecular denominator.
### Table 1: Selected research reports confirming the role of biological age advancement in Heart Failure.

<table>
<thead>
<tr>
<th>I. p.</th>
<th>Author</th>
<th>Year</th>
<th>Study group</th>
<th>Cell population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Leri A et al.</td>
<td>1998</td>
<td>Dogs affected by pacing-induced heart failure</td>
<td>cardiomyocytes</td>
<td>Increased expression of p53 in experimental HF35.</td>
</tr>
<tr>
<td>2</td>
<td>Kajstura et al.</td>
<td>2003</td>
<td>19 patients with idiopathic dilated cardiomyopathy</td>
<td>cardiomyocyte</td>
<td>Shortening of telomeres in cardiomyocytes obtained from patients suffering from idiopathic dilated cardiomyopathy36.</td>
</tr>
<tr>
<td>3</td>
<td>Hidemasa Oh et al.</td>
<td>2003</td>
<td>HF patients (qualified for heart transplantation)</td>
<td>cardiomyocyte</td>
<td>Shortening of telomeres and decreased expression of TRF2 in apoptotic cardiomyocytes37.</td>
</tr>
<tr>
<td>4</td>
<td>Leri et al.</td>
<td>2003</td>
<td>telomerase knockout mouse</td>
<td>cardiomyocyte</td>
<td>Relation between HF and p53 expression38.</td>
</tr>
<tr>
<td>5</td>
<td>Urbanek K. et al.</td>
<td>2005</td>
<td>HF patients</td>
<td>CSC</td>
<td>Shortening of telomeres in CSCs mobilized during ischemic HF39.</td>
</tr>
<tr>
<td>6</td>
<td>Newcastle 85+ study</td>
<td>2006</td>
<td>89 patients (85-year old)</td>
<td>PBMCs</td>
<td>Relation between Ejection Fraction and telomere length40.</td>
</tr>
<tr>
<td>7</td>
<td>van der Harst P et al.</td>
<td>2007</td>
<td>620 HF patients</td>
<td>leukocyte</td>
<td>Shortening of LTL in chronic heart failure patients41.</td>
</tr>
<tr>
<td>8</td>
<td>Wong et al.</td>
<td>2009</td>
<td>866 HF patients</td>
<td>leukocyte</td>
<td>Relation between kidney dysfunction and LTL shortening in chronic heart failure patients42.</td>
</tr>
<tr>
<td>9</td>
<td>Das B et al.</td>
<td>2010</td>
<td>Transgenic mice</td>
<td>cardiomyocyte</td>
<td>Key role of p53 protein in cardiac hypertrophy during HF43.</td>
</tr>
<tr>
<td>10</td>
<td>Wong et al.</td>
<td>2010</td>
<td>875 HF patients</td>
<td>leukocyte</td>
<td>LTL as independent risk factor of anaemia development during chronic heart failure44.</td>
</tr>
</tbody>
</table>

### Table 2: The role of biological age in the pathogenesis of myocardial infarction

<table>
<thead>
<tr>
<th>I. p.</th>
<th>Author</th>
<th>Year</th>
<th>Study group</th>
<th>Cell population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brouillette</td>
<td>2003</td>
<td>203 premature MI patients</td>
<td>leukocyte</td>
<td>LTL shortening as a risk factor of premature MI45.</td>
</tr>
<tr>
<td>2</td>
<td>Fitzpatrick et al.</td>
<td>2007</td>
<td>419 patients</td>
<td>leukocyte</td>
<td>Increased MI risk in patients (below 74 year old) with shortening of LTL46.</td>
</tr>
<tr>
<td>3</td>
<td>Salpea KD et al.</td>
<td>2008</td>
<td>369 subjects (18-28 year old) whose father developed MI before 55 year of life.</td>
<td>leukocyte</td>
<td>Relation between risk of MI in patients from study group with shortening of LTL47.</td>
</tr>
<tr>
<td>4</td>
<td>Spyridoulos Ip</td>
<td>2008</td>
<td>50 MI PATIENTS</td>
<td>granulocyte</td>
<td>Shortening of telomeres on the bone marrow level in patients after MI48.</td>
</tr>
<tr>
<td>5</td>
<td>Zee RY et al.</td>
<td>2009</td>
<td>14 916 healthy subjects</td>
<td>leukocyte</td>
<td>LTL shortening as a risk factor of premature MI49.</td>
</tr>
</tbody>
</table>

*BMCC*: bone marrow cells  *CHF*: chronic heart failure  *CSC*: cardiac stem cells  *DM2T*: diabetes mellitus type 2  *HF*: heart failure  *LTL*: leukocyte telomere length  *MI*: Myocardial Infarction  *p53*: p53 protein  *PBMCs*: peripheral blood mononuclear cell  *TRF2*: telomeric repeat binding factor 2
REFERENCES


