Journal of Molecular and Cellular Cardiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Age-associated pro-inflammatory remodeling and functional phenotype in the heart and large arteries

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ARTICLE INFO

Article history:
Received 27 October 2014
Received in revised form 20 January 2015
Accepted 2 February 2015
Available online xxxx

Keywords:
Aging
Proinflammation
Cardiovascular remodeling
Ventricular–arterial coupling

ABSTRACT

The aging population is increasing dramatically. Aging-associated stress simultaneously drives proinflammatory remodeling, involving angiotensin II and other factors, in both the heart and large arteries. The structural remodeling and functional changes that occur with aging include cardiac and vascular wall stiffening, systolic hypertension and suboptimal ventricular–arterial coupling, features that are often clinically silent and thus termed a silent syndrome. These age-related effects are the result of responses initiated by cardiovascular proinflammatory cells. Local proinflammatory signals are coupled between the heart and arteries due to common mechanical and humoral messengers within a closed circulating system. Thus, targeting proinflammatory signaling molecules would be a promising approach to improve age-associated suboptimal ventricular–arterial coupling, a major predisposing factor for the pathogenesis of clinical cardiovascular events such as heart failure.

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http://dx.doi.org/10.1016/j.yjmcc.2015.02.004
0022-2828/Published by Elsevier Ltd.

1. Introduction

The world population is aging. Aging is a major risk factor for cardiovascular diseases such as hypertension, atherosclerosis and heart failure, due mainly to the increase in allostatic load and subsequent pro-inflammatory processes within the cardiovascular system [1,2]. Allostatic load represents the consequence of cumulative exposure to physiologic, socioeconomic and psychological stressors across the life span, resulting in heightened neuroendocrine and neural responses, including increase in sympathetic nerve activity, which ultimately have detrimental effects [1,2]. Augmented angiotensin II (Ang II) signaling appears to be especially important and interestingly, blockade of Ang II signaling alleviates allostatic load and ameliorates inflammatory stress and the incidence of cardiovascular disease in animal models [3,4].

The steep rise in the incidence of hypertension, atherosclerosis, and chronic heart failure with advancing age is related at least in part to a continuum of adverse structural remodeling and functional changes in the cardiovascular system [4]. These include an increase in stiffening of the heart and vessels, reduced coronary and peripheral blood flow reserve, blood pressure lability, endothelial dysfunction, cardiac hypertrophy, and suboptimal mechanical coupling between the left ventricle and the arterial system (ventricular–arterial coupling) [5–8]. These functional and structural changes are the result of a cellular and extracellular pro-inflammatory phenotypic shift in both the heart and large arteries [4,9], which lowers the threshold for pathologic stimuli and increases the propensity for cardiovascular disease (Fig. 1) [4,7,8]. Thus, targeting age-associated pro-inflammatory signaling may be an evidence-based approach to tackle the epidemic of cardiovascular disease in the elderly.

2. The cardiovascular functional phenotype with advancing age

Adverse remodeling with aging contributes to a constellation of the related signs of a cardiovascular silent syndrome which occurs in the aging population, including increased systolic blood pressure (SBP), increased pulse wave velocity (PWV), endothelial dysfunction, and cardiac diastolic dysfunction [4]. Cross-sectional measures of SBP show a continuous rise until the eighth or ninth decade, whereas diastolic blood pressure (DBP) increases until the fifth decade, after which it plateaus or decreases [10]. Consequently, pulse pressure continually increases while mean arterial pressure initially increases and ultimately levels off with advancing age [10]. The increase in SBP with increasing age is accompanied by an increase in longitudinal PWV [10,11]. Carotid-femoral PWV has emerged as a "gold-standard" for the non-invasive measurement of large arterial stiffness. With aging, the left ventricular (LV) wall becomes stiffened with a decrease in compliance; these changes result in significant diastolic LV dysfunction comprising a prolongation of isovolumic relaxation time, and increase in LV end-diastolic pressure and an enlargement of the left atrium but generally no decline in systolic function as assessed by ejection fraction (EF) [5–9,12,13].

As well as the stiffening of the heart and the arterial system, the mechanical coupling between the left ventricle and the systemic circulation typically becomes impaired [5–8,13]. Ventricular–arterial

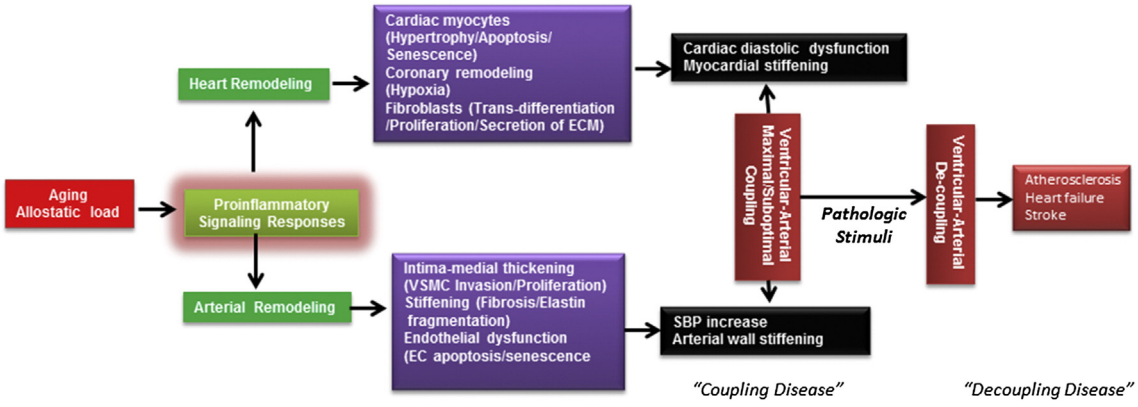

Fig. 1. Impact of proinflammatory signaling on heart and arterial phenotype and ventricular–arterial coupling with advancing age. Aging increases allostatic load, including Ang II signaling, leading to proinflammation. With aging, adverse remodeling develops in both the heart and large arteries, which is the underlying mechanism of abnormal arterial–ventricular coupling. A mismatched or suboptimal arterial–ventricular mechanical coupling, sometimes known as "coupling disease", is manifested by increases in SBP and left ventricular diastolic dysfunction. Suboptimal arterial–ventricular coupling increases the susceptibility to complications such as heart failure, atherosclerosis and stroke (sometimes termed "de-coupling diseases"), in response to pathologic stimuli such as ischemia.

Please cite this article as: Wang M, Shah AM, Age-associated pro-inflammatory remodeling and functional phenotype in the heart and large arteries, J Mol Cell Cardiol (2015), http://dx.doi.org/10.1016/j.yjmcc.2015.02.004