Vascular Pharmacology 93–95 (2017) 14–19

Contents lists available at ScienceDirect

Vascular Pharmacology

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

Review

Platelet oxidative stress as a novel target of cardiovascular risk in frail older people

Francisco Fuentes[a], Iván Palomo[b,**], Eduardo Fuentes[b,c,*]

[a] Becario Obstetricia y Ginecología Universidad Católica del Maule, Talca, Chile
[b] Platelet Research Center, Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Interdisciplinary Excellence Research Program on Healthy Aging (PIEI-ES), Universidad de Talca, Talca, Chile
[c] Núcleo Científico Multidisciplinario, Universidad de Talca, Talca, Chile

ARTICLE INFO

Keywords:
Platelet
Frailty, cardiovascular diseases
Oxidative stress

ABSTRACT

The average lifespan of humans and the percentage of people entering the 65 and older age group are growing rapidly. Within this age group, cardiovascular diseases (CVD) increase steeply and are the most common cause of death. During aging, experimental and clinical studies support the pivotal role played by reactive oxidant species in the mechanism of platelet activation. Frailty has been implicated as a causative and prognostic factor in patients with CVD. Oxidative stress is increased in frail older people, and may lead to accelerated aging and higher incidence of oxidative diseases such as CVD. The present article aims to highlight the relative contribution of platelet oxidative stress as a key target of frailty in elderly people with CVD.

1. Introduction

The average lifespan of humans and the percentage of people entering the 65 and older age group are growing rapidly [1]. Within this age group, cardiovascular diseases (CVD) increase steeply and are the most common cause of death [2]. Aging poses the largest risk factor for CVD. Thus the incidence of thrombosis increases sharply with age: it is very rare in young individuals (< 1 per 10,000 per year) but increases to ~ 1% per year in the elderly, which indicates that aging is one of the strongest and most prevalent risk factor for thrombosis [3]. Platelets play a central role in thrombus initiation and propagation [4].

Platelets have a dynamic functional repertoire that mediates haemostatic function and inflammatory responses [5]. However, many of these functions are altered in older adults, promoting a pro-thrombotic and pro-inflammatory milieu and contributing to an increased risk of CVD [6–9]. During aging, experimental and clinical studies support the pivotal role played by reactive oxidant species (ROS) in the mechanism of platelet activation [10–12]. ROS formation is functionally relevant for platelet activation [13].

Frailty is a common clinical syndrome in older adults that carries an increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality [14]. There is a growing interest in the relevance of this syndrome in CVD. Frailty has been implicated as a causative and prognostic factor in patients with CVD [15]. Oxidative stress is increased in frail older people, and may lead to accelerated aging and a higher incidence of oxidative diseases such as CVD [16]. The present article aims to highlight the relative contribution of platelet oxidative stress as a key target of frailty in elderly people with CVD.

2. Cardiovascular diseases in elderly people

The CVD (i.e., acute myocardial infarction, cerebrovascular disease and peripheral arterial thrombosis) are the leading causes of death in the world, accounting for 17.3 million deaths per year, a number that is expected to grow to > 23.6 million by 2030 [17–19]. The majority of CVD are caused by risk factors, such as high blood pressure, cholesterol, overweight/obesity, tobacco use, lack of physical activity and diabetes [20,21].

Population aging is progressing rapidly. Between 2000 and 2050, the proportion of the world's population over 65 years is expected to double from 11% to 22% [22–24]. Older populations in developed countries have shown a decrease in the prevalence of disabilities and an increase in chronic diseases over the past decades, such as CVD [1,25–29]. Distribution of the risk factors for CVD is quite high in the adult population, especially in the over 65 age group, which can result in serious health problems and increased rates of chronic diseases, especially CVD [30]. CVD is present in ~ 60% of older people [31,32]. Even, the incidence and prevalence of CVD increase steeply with

* Correspondence to: E. Fuentes, Platelet Research Laboratory, Universidad de Talca, Talca, Chile.
** Corresponding author.
E-mail addresses: ipalomo@utalca.cl (I. Palomo), edfuentes@utalca.cl (E. Fuentes).

http://dx.doi.org/10.1016/j.vph.2017.07.003
Received 7 March 2017; Received in revised form 18 May 2017; Accepted 10 July 2017
Available online 11 July 2017

advancing age, a tendency dependent on the age-related changes in vascular and haemostatic systems [3,33–36]. Cardiovascular risk factors and existing cardiovascular disease have been linked to increased risk of the frailty syndrome in older people [37,38].

3. Frailty syndrome in elderly people

Frailty is one of the geriatric syndromes considered highly prevalent in old age and has an important relationship with mortality and morbidity [39,40]. The frailty syndrome is defined as being an increase in the individual's vulnerability to stressors caused by a gradual and progressive abnormal functioning of multiple organ systems, along with a notable dysregulation of the neuroendocrine and immune systems, thereby endangering homeostasis [41,42]. The frailty index approach readily identifies frail people at risk of death, presumably because of its use of multiple health deficits in multidimensional domains [43]. Thus frailty is defined as three or more of the following: sarcopenia (low appendicular skeletal mass adjusted for height and body fat), weakness (grip strength), self-reported exhaustion, low activity level, and slow walking speed. Prefrail men met one or two criteria; robust men had none [40].

4. Frailty and cardiovascular diseases

Frailty is considered as an early stage of poorer health in elderly people [42,44,45]. Due to the aging and increasingly complex nature of our patients, frailty has become a high-priority theme in cardiovascular medicine [46]. Evidence suggests a bidirectional connection between frailty syndrome and CVD in the elderly population [47]. Both conditions adversely affect health and decrease the quality of life of older people [46,48]. The overall prevalence of frailty in adults aged 65 years and older has been estimated at approximately 10%. However, in patients with significant CVD, the prevalence may be as high as 60% [49]. Frail patients experienced a higher estimate of the likelihood of cardiovascular death, myocardial infarction, or stroke events compared with non-frail patients [50–53]. A study carried out on 54,250 elderly patients demonstrated an increased risk of death in those with concomitant frailty and CVD with an adjusted odds ratio ranging from 1.6 to 4.0 [15]. In addition, pre-frailty, which is potentially reversible, is independently associated with a higher risk of older adults developing CVD [54]. The relationship between frailty and CVD indicates a common pathway in their pathophysiological mechanisms. This could be explained by an abnormal increase of platelet oxidative stress in elderly people.

5. Antioxidant status of elderly people

In humans, the antioxidant system includes a number of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), nonenzymatic antioxidants such as glutathione (GSH), protein -SH, ascorbic acid, and uric acid, and dietary antioxidants [55]. The excessive production of free radicals in the organism, and the imbalance between the concentrations of these and the antioxidant defenses may be related to processes such as aging [56].

The results showed that the majority of the elderly people showed a significant decrease in oxidative stress [57]. Meanwhile in frail elderly people, oxidative stress was reported to increase, while in free-living elderly this increase was not always significant [58,59]. The comparison between middle-aged and older subjects regarding oxidative stress parameters also suggests a progressive and slow decline of nonenzymatic antioxidants and an increase of the enzymatic antioxidants activities relative to age [60–62]. Thus the induction in activity of enzymatic antioxidants during human aging may be a compensatory response of the individual to increased oxidative stress [63,64]. In this way, levels of oxidative stress increase cannot entirely be attributed to a decrease in the activities of the antioxidant defense system as various factors may contribute to this process [65,66].

6. Platelet activation and pro-thrombotic risk in elderly people

Platelets are anucleate cells derived from cytoplasm of megakaryocytes, small and discoid in shape, with dimensions of approximately 1.5–3.0 μm in diameter [67]. The primary function of circulating platelets during the hemostatic process is to stop blood loss after tissue trauma [68,69]. However, the barrier between physiological hemostasis and pathological thrombosis is very narrow, and it has been increasingly recognized that CVD—a leading cause of morbidity and mortality among elderly people—is strongly influenced by platelet activation contributing to the development of acute thrombotic events [10,70–72]. In this context, the process of platelet activation, aggregation, and subsequent thrombus formation at sites of atherosclerotic plaque rupture is a dynamic process that is frequently initiated by platelet adhesion to the damaged vessel wall [5,69].

In older adults, platelet activation promotes pro-thrombotic and thus contributes to an increased risk of CVD [4]. Elderly people experience a shift of the hemostatic balance towards increased clotting and decreased fibrinolysis [73]. Thus aging may lead to changes intrinsic to the platelet that contributes to increased platelet activation and arterial thrombosis in the elderly [8]. Increased platelet activity has been correlated with an increase of platelet phospholipid content, suggesting an age-related increase in trans membrane signaling or second messenger accumulation [6]. Even, bleeding time was significantly reduced in older subjects [74].

7. Role of platelet oxidative stress and cardiovascular risk

Oxidative stress is caused by the imbalance between ROS production and antioxidant defense capability (enzymatic and nonenzymatic antioxidants) [75]. Thus oxidative stress refers to elevated intracellular levels of ROS that cause damage to lipids, proteins and DNA [76].

Upon activation, platelets produce ROS that has been widely implicated in pathogenesis of CVD [10,77]. ROS formation is functionally relevant for platelet activation. ROS including superoxide anion ($O_2.^-$), hydroxyl radicals (OH) or hydrogen peroxide (H_2O_2) act as second messengers in platelet activation via calcium mobilization, nitric oxide inactivation and through the interaction with arachidonic acid to give formation of isoprostanes, among others [78,79].

Platelets generate ROS through several intracellular sources such as NADPH oxidase, cyclooxygenases, uncoupled endothelial nitric oxide synthase (eNOS), xanthine oxidase (XO) and mitochondrial respiration [80–83]. Of the various potential sources of ROS in platelets the role of NADPH oxidase seems to be the most relevant. Activation of platelet NADPH oxidase (gp91phox) is crucial for $O_2.^-$ production [84]. The reduction of the cytosolic concentration of H_2O_2 by catalase or inhibition of NADPH oxidase by chemical inhibitors has be associated to a significant reduction of calcium mobilization, GPIIb/IIIa opening and platelet aggregation [85,86].

The $O_2.^-$ formation by hyperactive platelets during hyperhomocysteinemia or hyperglycemia may be one mechanism that contributes to prolonged thrombus formation [87–89]. On the other hand, increased lipid peroxidation correlates with platelet oxidative stress and cardiovascular complications [90,91]. The isoprostanes are a unique series of prostaglandin-like compounds formed in vivo via the non-enzymatic free radical-initiated peroxidation of arachidonic acid [92]. Elevated levels of 8-isoprostaglandin F2 alpha (8-isoPGF2α), an isoprostane of platelet lipid peroxidation, are associated with systemic and local platelet activation in CVD [93,94]. Other products of platelet lipid peroxidation are soluble CD36 (sCD36) and soluble CD40L (sCD40L), and these are increased in patients with symptomatic atherosclerotic carotid plaques and are related to plaque instability [95–97].

Elderly patients represent a growing and challenging segment of CVD. Antiplatelet therapy represents the mainstay of treatment for