Thrombosis Research (2007) **119**, 679–686

THROMBOSIS RESEARCH

intl.elsevierhealth.com/journals/thre

REGULAR ARTICLE

Aspirin failure course during exercise and its connection with soluble CD40L

Wiktor Kuliczkowski [a,*], Malgorzata Kobusiak-Prokopowicz [a], Iwona Prajs [b], Bozena Karolko [a], Walentyna Mazurek [a]

[a] *Department of Cardiology, Wroclaw Medical University, Pasteur 4 Street, 50-367 Wroclaw, Poland*
[b] *Department of Hematology, Wroclaw Medical University, Pasteur 4 Street, 50-367 Wroclaw, Poland*

Received 21 November 2005; received in revised form 7 May 2006; accepted 8 May 2006
Available online 14 June 2006

KEYWORDS
Aspirin resistance;
Exercise;
sCD40L;
Ischemic heart disease

Abstract

Introduction: The aspirin failure (resistance) is a still discussed and highly studied problem. This phenomenon is observed in rest, but could be precipitated by an exercise. The aspirin resistance was also linked with the inflammatory process which is a key event for the atherosclerosis development. Platelets seem to play an important role also in that setting, probably by the CD40—CD40L axis. The aim of the study was to assess the frequency of the aspirin failure induced by the exercise and the role of sCD40L in that regard.
Materials and methods: The study included 40 patients with established coronary artery disease. The control group consisted of 10 patients without coronary artery disease matched for age. All patients and controls were on 75 mg of aspirin for at least 30 days and had treadmill testing and blood collected for measurement of sCD40L and optical platelet aggregation with ADP, collagen and arachidonic acid. Aspirin resistance was defined as a maximal aggregation with ADP and collagen exceeding 70%.
Results: There were 15 aspirin-resistant patients in the studied group (37%). There were significantly higher concentration of sCD40L (ng/ml) in aspirin-resistant patients in comparison with aspirin-sensitive ones before testing ($7{,}9 \pm 2{,}5$ vs. $5{,}1 \pm 3{,}5$, $p < 0{,}05$) and on the top of it ($8{,}1 \pm 2{,}9$ vs. $4{,}5 \pm 3{,}9$, $p < 0{,}05$). There were 3 persons who become resistant on the top of the exercise which was connected with the significant increase of sCD40L concentration in that group (from $7{,}6 \pm 1{,}9$ before exercise to $10{,}1 \pm 2{,}9$ on the top of the exercise, $p < 0{,}05$). There was also a positive correlation between the sCD40L level before and on the top of the exercise in an aspirin-resistant group ($r = 0{,}48$ for both, $p < 0{,}05$). Patients who were aspirin-

Abbreviations: ADP, adenosine diphosphate acid; PTCA, percutaneous transluminal coronary angioplasty.

* Corresponding author. Tel./fax: +48 713270961.
E-mail address: wiktor6@wp.pl (W. Kuliczkowski).

0049-3848/$ - see front matter
doi:10.1016/j.thromres.2006.05.003

resistant at rest had also significant elevation of platelet aggregation on the top of the exercise (ADP (%) from 90,5 ± 8,6 to 95,0 ± 6,5, $p<0,05$ and collagen (%) from 87,8 ± 8,7 to 92,1 ± 8,0, $p<0,05$).
Conclusions:

1. Aspirin resistance phenomenon is present in about 37% patients on 75 mg aspirin daily.
2. Aspirin-resistant patients have higher platelet aggregation during the exercise.
3. Moderate physical exercise provokes 12% increase in the aspirin resistance phenomenon occurrence.
4. Aspirin resistance is connected with higher sCD40L level at rest and exercise provoked aspirin resistance is connected with the sCD40L concentration increase.

Introduction

Activated platelets forming the clot are one of the most important players in the setting of acute coronary syndromes [1]. Platelets are also believed to play an important role in the initiation and progression of the atherosclerotic plaque growth [2]. There are possible some pharmacological modulation of their deleterious actions with clopidogrel and acetylsalicylic acid (aspirin). Aspirin was shown to reduce cardiovascular deaths by about 25% in a variety of clinical situations from acute coronary syndromes to stable ischemic heart disease [3]. Nevertheless there are still some patients who despite aspirin intake experience recurrent cardiac ischemic events. It is improbable that only one drug would be able to cope with atherosclerotic complications, but nevertheless its inefficacy on the clinical or laboratory level was proposed to be named as an "aspirin resistance" [4]. Currently, based on recent research and opinion evolution it is better to name this phenomenon as an "aspirin failure" [5]. While it is known and described for more than 20 years now it has still an obscure mechanism, although we know that patients experiencing such an condition have worse outcome in comparison with "aspirin responders" [6—8].

In the majority of studies platelets are shown to be activated during physical exercise [9,10]. Some studies of the ischemic heart disease patients indicate on the contrary the lower degree of platelet activation during exercise [11,12]. Nevertheless aspirin blocks only one pathway of platelet activation and exercise seams to overpass the antiplatelet effect of the drug, yet also in this regard there are conflicting results which depend on the method of platelet function study, the exercise protocol, the level of the exercise reached and the group of patients studied [13]. The dynamic changes of aspirin resistance phenomenon during exercise are also not well understood and described [14,13]. Presumably patients who develop aspirin resistance during exercise could be at higher risk for ischemic events like patient with aspirin resistance present already at rest. Platelet high activity, despite aspirin treatment, can have different explanations [15]. One of them could be a higher level of inflammation in "resistant" patients in comparison with responders. Situation like that would activate platelets via the production of TXA_2 by endothelial cells and white blood cells, through pathways not blocked by aspirin [16]. There could be also other inflammation-associated pathways that could activate platelets rending them less responsible to aspirin.

We know that apart form being a main actor in the circle of coagulation taking place on the ruptured atherosclerotic plaque, platelets itself can be one of the triggers of the inflammatory process. Recently there was described a new axis linking coagulation and inflammation; namely CD40/CD40L axis. CD40 which is a member of TNF-family membrane receptors was found first on lymphocytes, afterwards on almost all types of leukocytes, vascular endothelial cells and recently on platelets [17,18]. The CD40L expressed on stimulated platelets is subsequently cleaved, which generates a soluble hydrolytic fragment termed sCD40L. Essentially all of the sCD40L generated during the clotting of whole blood is derived from platelets [19]. It was shown to be higher in patients with unstable angina, myocardial infarction, hypercholesterolemia and diabetes and to be an independent risk factor for death and non fatal myocardial infarction in