Acta Biomaterialia 8 (2012) 2288–2296

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

Complement profile and activation mechanisms by different LDL apheresis systems

Anders Hovland [a,b,*], Randolf Hardersen [c], Erik Waage Nielsen [b,d], Terje Enebakk [c], Dorte Christiansen [e], Judith Krey Ludviksen [e], Tom Eirik Mollnes [e,f], Knut Tore Lappegård [a,b]

[a] Coronary Care Unit, Division of Internal Medicine, Nordland Hospital, Bodø, Norway
[b] Institute of Clinical Medicine, University of Tromsø, Norway
[c] Dialysis Unit, Division of Internal Medicine, Nordland Hospital, Bodø, Norway
[d] Department of Anesthesia, Nordland Hospital, Bodø, Norway
[e] Somatic Research Laboratory, Nordland Hospital, Bodø, Norway
[f] Institute of Medical Biology, University of Tromsø, Norway

ARTICLE INFO

Article history:
Received 24 October 2011
Received in revised form 29 January 2012
Accepted 21 February 2012
Available online 25 February 2012

Keywords:
Extracorporeal circulation
Lipid
Complement
Biocompatibility

ABSTRACT

Extracorporeal removal of low-density lipoprotein (LDL) cholesterol by means of selective LDL apheresis is indicated in otherwise uncontrolled familial hypercholesterolemia. During blood–biomaterial interaction other constituents than the LDL particles are affected, including the complement system. We set up an ex vivo model in which human whole blood was passed through an LDL apheresis system with one of three different apheresis columns: whole blood adsorption, plasma adsorption and plasma filtration. The concentrations of complement activation products revealed distinctly different patterns of activation and adsorption by the different systems. Evaluated as the final common terminal complement complex (TCC) the whole blood system was inert, in contrast to the plasma systems, which generated substantial and equal amounts of TCC. Initial classical pathway activation was revealed equally for both plasma systems as increases in the C1rs–C1inh complex and C4d. Alternative pathway activation (Bb) was most pronounced for the plasma adsorption system. Although the anaphylatoxins (C3a and C5a) were equally generated by the two plasma separation systems, they were efficiently adsorbed to the plasma adsorption column before the "outlet", whereas they were left free in the plasma in the filtration system. Consequently, during blood–biomaterial interaction in LDL apheresis the complement system is modulated in different manners depending on the device composition.

1. Introduction

Heterozygous familial hypercholesterolemia is common and, due to high levels of low-density lipoprotein (LDL) cholesterol, carries a high risk of premature atherosclerosis if not treated [1]. In most cases the disease is controlled by lipid lowering medication, but in some instances extracorporeal treatment by means of LDL apheresis is necessary [2]. This treatment is highly effective in reducing LDL cholesterol and clinical end-points [2,3]. The artificial surfaces may, however, affect other constituents of the blood in an adverse manner. Studies on blood–biomaterial interaction during extracorporeal treatment have demonstrated that complement activation may be triggered by biomaterial surfaces [4], and studies in hemodialysis have shown that hemodialysis membranes trigger the complement system [5]. The biocompatibility of dialysis membranes is also linked to clinical end-points [6]. Studies indicate that the alternative pathway (AP) of complement activation is important when foreign surfaces interact with blood [7,8]. The alternative pathway can be activated directly by the surface or amplified after initial activation by classical or lectin pathway activation [4,9], in both cases playing a pivotal role in the degree of activation beyond C3. Notably, even if the biomaterial surfaces induce complement activation, the membranes may also adsorb complement factors such as C3a and C5a [10]. Consequently, it is the net result after extracorporeal treatment that is of clinical importance. This is in accordance with the definition of biocompatibility as being "the ability of a material to perform with an appropriate host response in a specific application" [11], recently revised to "Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy" [12].

Complement activation may be of particular clinical importance for patients undergoing long-term, potentially lifelong, LDL apheresis treatment as the complement system plays a role in the development of atherosclerosis [13]. Whereas activation of the initial

* Corresponding author at: Coronary Care Unit, Division of Internal Medicine, Nordland Hospital, Bodø, Norway. Tel.: +47 75534000; fax: +47 75534742.
E-mail address: anders.w.hovland@gmail.com (A. Hovland).

1742-7061/$ - see front matter © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.actbio.2012.02.017