Clinical importance of biocompatibility and its effect on haemodialysis treatment

Karel Opatrný Jr

Department of Medicine I, Charles University Medical School, Pilsen, Czech Republic

Keywords: biocompatibility; bradykinin; complement; ethylene oxide; perfluorohydrocarbon; thrombogenicity

Introduction

Inadequate biocompatibility of current dialysis systems results, upon contact of blood with the artificial surface, in a variety of interactions including coagulation, thromboocyte, leukocyte and complement activation, production of cytokines, β-2 microglobulin, bradykinin and free oxygen radicals, and other events. These reactions may cause injury to the patient. A substantial role in biocompatibility is played by the dialysis membrane, representing >90% of the area with which blood is in contact within the extracorporeal circuit. However, biocompatibility should be seen in a broader context, not only regarding the dialysis membrane and the materials it is made from. The reactions occurring as blood flows through the extracorporeal circuit depend on the type of the dialyser/filter that the membrane is placed in, on the procedure that the dialyser/filter is used for, and which type of patient is being treated [1,2].

Biocompatibility has long been considered as one of the main issues in dialysis treatment. However, there have been claims recently that either biocompatibility involves only a host of clinically irrelevant laboratory findings, or that the biocompatibility issue has essentially been solved. The present paper, including references to some concepts regarding thrombogenicity, complement activation, ethylene oxide, bradykinin and perfluorohydrocarbon components, suggests that the issue of biocompatibility has affected and continues to affect the way in which dialysis is performed, and that the issue of bio(in)compatibility warrants further attention.

Thrombogenicity

Partial elimination of thrombogenicity, i.e. an ability of the system or material to induce or promote thrombus formation, through the use of hirudin and, particularly, heparin, made it possible to start testing dialysis in animal experiments and to start using it in human medicine.

The endeavour to reduce thrombogenicity led to the development of new membranes. Efforts were made to modify the membrane surface by, for example, the binding of heparin, antiplatelet drugs, fibrinolytics or other agents. Thrombogenicity prompted the introduction of numerous antithrombotics into dialysis treatment and the development of many techniques and protocols related to their administration. Thrombogenicity provided an impetus to an improvement of the rheological properties of dialysers and the extracorporeal circuit as such, and to elimination of blood–air contact, and other measures.

Despite all attempts, thrombogenicity has remained an unsolved problem. Membranes and antithrombotics employed in clinical practice activate haemostasis. Even clinically uncomplicated haemodialysis has been shown to be associated with a significant increase in the plasma levels of the thrombin–antithrombin III complex, a sensitive marker of coagulation system activation. The increase may be as high as in thrombotic states, such as, for example, disseminated intravascular coagulation (DIC) [3].

The need for better thrombogenicity elimination results from the following facts: routine systemic administration of antithrombotic agents carries the risk of bleeding, which is already increased in patients with uraemic bleeding disorders. Thrombi on the dialysis membrane reduce the procedure’s efficacy.
increase the volume of residual blood in the dialyser and make renal anaemia even more severe. Consumption of coagulation factors and thrombocytes on the dialysis membrane may induce DIC-like impaired haemostasis. The early and frequent development of atherosclerosis and its thrombotic complications in long-term haemodialysis patients cannot be explained by mere accumulation of traditional risk factors. A role for repeat return of activated thrombocytes and coagulation factors from the extracorporeal circuit to the patient’s circulation cannot be excluded. If the implantable kidney remains an alternative to current blood purification methods, its thrombogenicity must be overcome by techniques different from those employed to date.

**Complement activation**

The finding by Craddock *et al.* [4] that complement activation in the initial phase of dialysis by the alternative pathway and involving a cellulose membrane causes transient leukopenia and hypoxaemia had a major impact. Complement activation was found to be related to anaphylactoid reactions, hypotension, pyrogenic reactions, amyloid formation, impaired immunity, catabolism and other complications.

The deleterious effects of complement activation led to the development of procedures reducing or preventing its effects on patients. Cellulose membranes were modified to contain fewer hydroxyl groups. They were succeeded by cellulose acetate membranes, membranes with hydroxyl groups replaced by diethylaminoethyl groups, synthetically modified cellulose or vitamin E-bound membranes. Synthetic membranes made of polysulfone, polyanime, polycarbonate, etc., inducing less complement activation, or adsorbing potentially harmful activation products so they would not enter the patient’s bloodstream, such as the AN69 polycrylonitrile membrane, found wider use.

Of the numerous studies addressing the clinical importance of complement activation during haemodialysis, I will mention two regarding mortality.

Himmelfarb and co-workers analysed 153 patients with acute renal failure (ARF) undergoing dialysis, using either membranes from regenerated cellulose associated with potent complement activation, or membranes from polymethylmethacrylate or polysulfone, which are weak complement activators. The survival was significantly better in the patients dialysed with membranes with low complement activation [5]. The importance of more biocompatible membranes (as regards complement) in the treatment of ARF is also supported by the latest meta-analysis of published prospective studies [6].

An analysis of >4000 long-term dialysis patients has shown that both overall mortality and mortality from infectious causes were significantly lower with synthetic or substituted cellulose membranes associated with lower complement activation compared with regenerated cellulose membranes, featuring higher complement activation [7].

There were also studies not supporting the concept of a deleterious effect of complement activation. Besides, for a correct interpretation of the above two studies, it should be remembered that an association between patient outcome and a dialysis membrane does not necessarily imply causality. While well designed, the studies are not devoid of methodological flaws. In Bloembergen *et al.*’s study, membranes with lower complement activation were also high flux. The outcome may have been influenced both by higher biocompatibility and by flux rates. The results of the recently published HEMO Study did not demonstrate a difference between low- and high-flux membranes in the mortality of chronic haemodialysis patients [8], a fact indirectly supporting the importance of biocompatibility in Bloembergen’s study. In addition, higher membrane flux rates are not only a confounder. High-flux membranes allow C5a and C3a complement components and factor D to enter the dialysate [9]. The amount of C5a, C3a and factor D entering the patient’s bloodstream is decreased; hence, high-flux membranes may improve biocompatibility.

Although some questions remain unanswered, complement activation due to bioincompatibility has had a major effect on dialysis treatment. Industrialized nations saw a dramatic drop in the use of membranes made from regenerated unsubstituted cellulose, which were replaced by membranes with lower complement activation.

**Hypersensitivity reactions (HSRs)**

*Ethylene oxide (ETO) and HSR*

While rare, HSRs are a feared complication of haemodialysis considering their potential for a serious and eventually fatal course. In the 1980s, their incidence was 3.3/1000 patients/year with capillary, and 0.3/1000 patient/year with plate dialysers. This substantial difference was due to ETO used for dialyser sterilization, which remained in the potting material of capillary dialysers. ETO forms conjugates with serum albumin (ETO–HSA) which act like antigens. In the 1980s, when ETO was widely used for dialyser sterilization, two-thirds to three-quarters of HSR patients had antibodies against the ETO–HSA complex.

Understanding the role of ETO in HSR had multiple effects on haemodialysis. Manufacturers learned that the amount of residual ETO in dialysers depends on the materials and on the sterilization technique used, e.g. the temperature. The kinetics of ETO release from dialysers during storage were established. Clinicians became aware of the importance of dialyser rinsing immediately before haemodialysis to remove ETO [10]. There was a significant
shift in the numbers of dialysers sterilized with ETO to alternative techniques, mainly to steam sterilization.

**Bradykinin and HSR**

In the early 1990s, HSRs occurred more often in patients treated with angiotensin-converting enzyme inhibitors (ACEIs) receiving dialysis with an AN69 polyacrylonitrile membrane. Some authors speculated that bradykinin might be responsible for these reactions.

Upon contact of blood with the AN69 membrane, bradykinin tends to be formed at higher rates as a result of the membrane's negative charge, compared with membranes made of other materials. ACEIs prevent bradykinin degradation even in renal failure patients. At the same time, bradykinin's biological effects are consistent with manifestations of HSR. Plasma bradykinin levels correlate with the incidence of HSR. The possibility of preventing reactions by administering icatibant (HOE 140), an agent blocking B2 receptors via which bradykinin acts, suggests a causality between HSR and bradykinin.

The relationships between biocompatibility, bradykinin and HSR underline the need for a comprehensive perspective of biocompatibility. Although bradykinin formation depends primarily on the membrane's negative charge, it is also significantly dependent on other factors. For example, bradykinin formation is significantly enhanced by plasma dilution and the decrease of blood pH when dialysis is initiated by a routine rinse with saline [11]. Current knowledge of bradykinin underlines the role of a patient's medication. A biologically active metabolite of bradykinin, des-arg⁹-bradykinin, which accumulates in serum aminopeptidase P deficiency, has been shown to be important for the reactions to occur.

Bradykinin overproduction related to bioincompatibility stimulated, before dialysis using an AN69, the introduction of an extracorporeal circuit rinse, with a solution with bicarbonate preventing both bradykinin formation and the HSR. Some authors have proposed to replace ACEIs with angiotensin II receptor blockers. The AN69 membrane was modified to retain its superiority regarding other biocompatibility parameters and in blood purification, while reducing bradykinin formation. Modification using polyethyleneimine, employed in the AN69ST membrane, not only reduced the negative charge and bradykinin formation, but also decreased membrane thrombogenicity [12].

**Reactions related to perfluorohydrocarbon (PF 5070)**

There were 12 dialysis-related sudden deaths among patients with chronic renal failure in three Spanish dialysis centres within 15 days in 2001. Shortly afterwards, more deaths (>50 in all) were reported from other parts of the world occurring under similar clinical circumstances, i.e. several hours into the procedure or after the end of the session. The patients experienced dyspnoea, chest pain, nausea, vomiting, hypotension, heart and circulatory arrest. Attempts at resuscitation failed. Autopsy showed the presence of gas in the right heart and in the pulmonary vascular bed. The common denominator was a treatment with Althane dialysers manufactured by Baxter International, Inc., at its plant at Ronneby, Sweden.

Although the renowned German TÜV agency, using recognized tests, declared the dialysers non-defective, the reality was different. Given the current level of knowledge, it seems that the dialysers contained perfluorohydrocarbon. This substance was used in the manufacturing process to repair capillaries with impaired integrity. Perfluorohydrocarbon subsequently was not removed from the dialysers and was not released until the start of the haemodialysis, causing pulmonary vessel obstruction and, eventually, death [13,14].

The tragic events related to the use of perfluorohydrocarbon have not been fully clarified and are subject to medical and forensic investigations. A definite lesson to be learned will not be available until the results of these investigations have been disclosed. The main question is why and how the failure in manufacture or quality control of the dialysers occurred. Clearly, more attention should be given to reviewing literary data. In recent years, perfluorohydrocarbon has been proposed, for example, to speed up thrombus dissolution, to improve visualization in echocardiography, and so on. However, a report saying that intravenous fluorocarbon may cause fatal pulmonary air embolism appeared already >25 years ago [15]. The relevant regulatory bodies should re-assess the procedures used for dialyser testing. To the clinician, this sad story should serve as a reminder that even chronic dialysis may still offer surprises and that adequate clinical, laboratory and autopsy examinations continue to be a necessity in long-term dialysis patients.

**Acknowledgements.** Supported by the Main Research Project (No. 206032, 111400002) ‘Renal Replacement Therapy by Dialysis and Transplantation’ of the Charles University Medical School in Plzeň.

**References**


