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The Evolution of Biocompatibility: From Microinflammation to Microvesiscles

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1. Introduction

Haemodialysis (HD) is a life-saving treatment for patients with chronic kidney disease (CKD) stage 5. CKD persists as a chronic worldwide epidemic and HD is the more frequently (70%) adopted treatment modality. Exponential growth trend continues on a global scale. The HD population becomes every year increasingly older (average age: 75 yrs) and sicker due to the associated co-morbidities such as cardiovascular disease (heart failure, coronary heart disease, and peripheral vascular disease), diabetes, hypertension, and peripheral vascular disease. Most of the complications associated with HD involve the cardiovascular system (Go et al., 2004; Culleton et al., 1999, Goodkin et al., 2003, Foley 2004; Barret, 2002). The evolution in the history of HD technology has greatly helped to make the HD procedure a safe and more biocompatible extracorporeal therapy. However, it must be admitted that despite significant improvements in HD technology and in the management of patients due to a better understanding of uremia toxicity, improvements in dialysis technology, better correction of anaemia and metabolic abnormalities, implementation of best practice guidelines, no significant improvement has been achieved in patient survival over the last decade (Rayner et al., 2004). The extracorporeal circuit offers a large surface of contact of the blood with foreign materials, namely the dialysis membrane, the tubings and the large volumes of the dialysate. The concept of biocompatibility has greatly evolved in the last two decades. Initially, numerous studies focused on the blood-dialyzer membrane interaction, leading to the activation of plasma systems (complement, coagulation, fibrinolysis). These studies helped in the understanding of some unknown effects occurring in the early stages of the HD session leading to pulmonary sequestration of leukocytes (mainly neutrophils) that explained the profound neutropenia associated with the cuproammonium membranes. The availability of reliable testing of complement-activated

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products (C3a and C5a and their desarginated products) guided the development of less neutropenia-inducing membranes and ultimately to the final development of fully synthetic membranes which have very low if at all capacity to induce complement activation. At that time, coagulation was an important reason for frequent interruptions and delays in the HD sessions. Due to the complex interplay known to occur between the activation of the complement and coagulation systems, it became of great interest to try to reduce the propensity for intravascular coagulation. The development of high-flux membranes and growing awareness of the benefits of convective and convective/diffusive under several contexts (intradialytic cardiovascular stability, better control or the uremic status and fluid control) gave impetus to a large number of enlightening studies on another mechanism of HD bio**IN**compatibility. The contamination by bacterial products, particularly with the widespread use of bicarbonate-based dialysates opened a new era in the field of biocompatibility. The formulation of the "interleukin hypothesis" was *a posteriori* not only the basis for further studies on the monocyte stimulation during HD, but also provided a link between biocompatibility and chronic inflammation. Basically, the evolution of biocompatibility has led us to consider two sides of the same coin: on one side, the biological responses at the blood-membrane interface; on the other hand, the consequences derived from the contact on the membrane performances (e.g. hydraulic permeability and sieving coefficients).

In this review, we will summarize the most important steps in the evolution from the concept of the blood-dialyzer membrane interaction to that of the whole HD system compatibility. In face of very recent developments of cell-to-cell communication and signal transduction, we will also discuss the new hypothesis for a role of microvesicles (MVs) in cell activation, as well as in tissue and vascular repair. We will not deal with other important aspects of biocompatibility such as the oxidant stress, the relevant role of additives in dialyzer manufacturing, and of leachables and the effects of different sterilization modes.

2. Blood-membrane interaction: the role of complement, coagulation, kinin-kallikrein systems and soluble mediators

2.1 Activation of the complement alternative pathway

Early studies on biocompatibility focused on acute hypersensitivity-like reactions which in some cases were fatal. Various mechanisms were elucidated. Activation of complement was shown by Craddock *et al* in 1977 (Craddock et al, 1977). Hydroxyl radicals, present on the surface of cellulosic membranes, bind with the C3b in the blood and activate the alternative pathway leading to the release of potent anaphylatoxins, C3a and C5a. Both C3a and C5a and their relative desarginated products induce prompt activation and aggregation of polymorphonuclear neutrophils (PMNs) and leukopenia. This is a very rapid process reaching a nadir from 15 to 30 min after initiation of dialysis. Aggregates of PMNs are sequestered particularly in the lung capillaries. Although the extent of the anaphylatoxin generation and of the neutropenia is also patient-dependent, these studies failed to find a relationship with chronic clinical trade-offs despite the hypothesis that recurrent pulmonary sequestration could induce pulmonary fibrosis. Reduction of the hydroxyl groups on the membrane surface or new synthetic polymers reduced the activation of the alternative pathway of the complement cascade. Temperature could also reduce complement activation (*Maggiore Q, personal communication, 1988*). Testing

complement activation (C3a or C5a plasma levels) by highly sensitive ELISA tests has become a standard requirement for the evaluation of biocompatibility ever since along with the precise characterization of the polymer structure (Krieter et al, 2008). It also became clear that synthetic polymers had a very low neutropenia-inducing effect. In some cases such as the polyacrylonitrile membrane, this was also due to the capacity of the membrane to adsorb C3b and the anaphylytoxins thus masking in fact complement activation (Pascual et al 1993) (**Figure 1**).
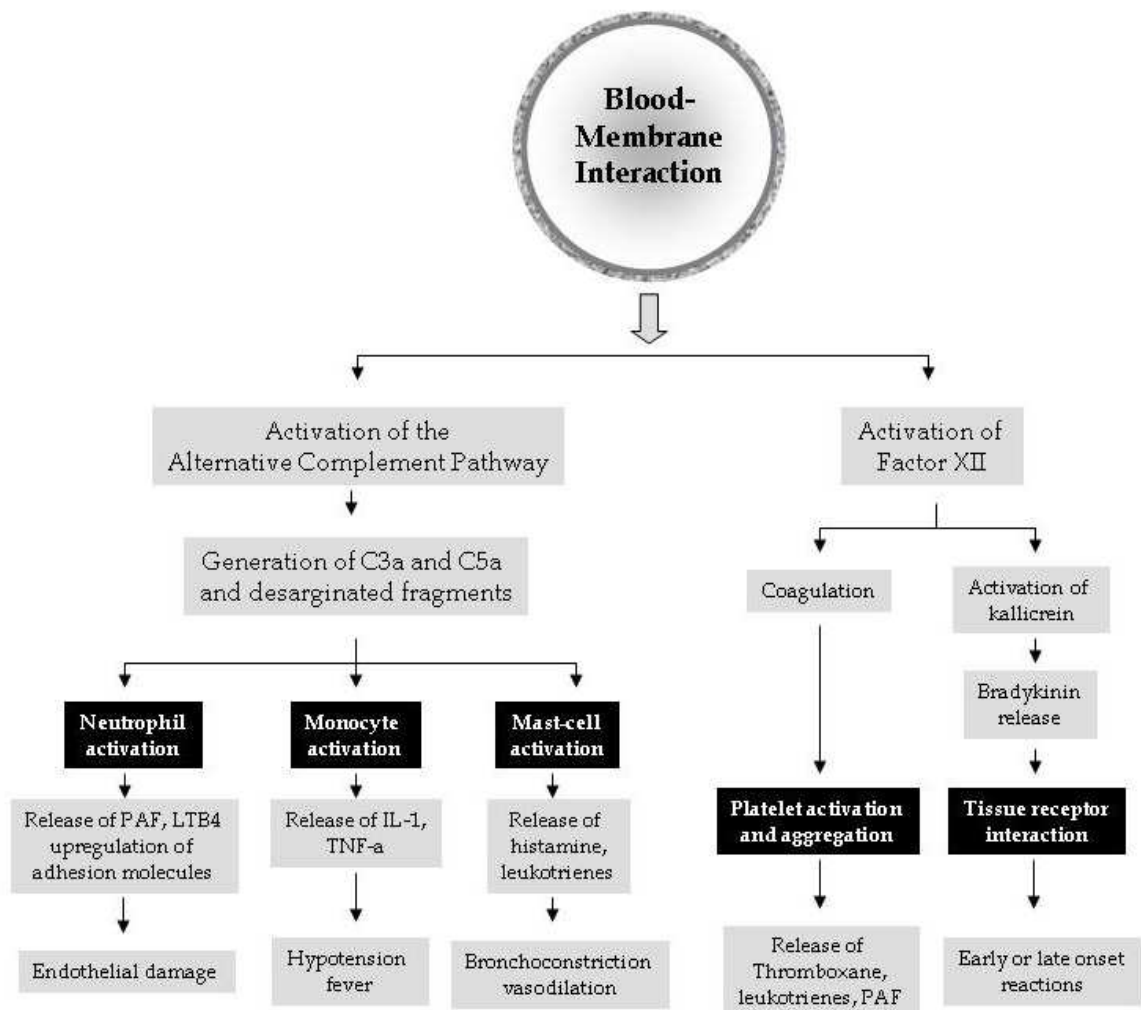

Fig. 1. Pathways involved in blood-membrane interactions. LTB4 denotes leukotriene B4, PAF, platelet-activating factor, IL-1, interleukin-1, TNF-α, tumor necrosis factor.

2.2 Activation of the coagulation system

Numerous acquired hemostatic abnormalities have been identified in chronic renal failure. HD adds to these disturbances as it repetitively implies turbulent blood flow, high shear stress, and contact of blood to artificial surfaces. Anticoagulation in HD is targeted to prevent activation of coagulation during the procedure. Most anticoagulant agents inhibit the plasmatic coagulation cascade. Still commonly used is unfractionated heparin, followed by low-molecular-weight heparin preparations with distinct advantages. Immune-mediated heparin-induced thrombocytopenia constitutes a potentially life-threatening complication of

heparin therapy requiring immediate switch to nonheparin alternative anticoagulants. Danaparoid, lepirudin, and argatroban are currently being used for alternative anticoagulation, all of which possess both advantages and limitations. Recently citrate has been proposed as anticoagulant in maintenance HD (Wright et al, 2010). In the past, empirical strategies reducing or avoiding heparin were applied for patients at bleeding risk, whereas nowadays regional citrate anticoagulation is increasingly used to prevent bleeding by allowing procedures without any systemic anticoagulation. Avoidance of clotting within the whole hemodialyzer circuit is not granted. Specific knowledge of the mechanisms of coagulation, the targets of the anticoagulants in use, and their respective characteristics constitutes the basis for individualized anticoagulation aimed at achieving full patency of the circuit throughout the procedure. Patency of the circuit is an important prerequisite for optimal HD quality. Intrinsic coagulation Hageman factor XII as well as other coagulation factors are also activated (Fischer, 2007). However, the activation of the coagulation is a very complex phenomenon that may be enhanced by different independent factors other than the membrane surface *per se* such as: the dynamics at the dialyzer heads, defects in the hollow fibre cutting of the polyurethane, any condition that predisposes for blood to be stagnant. The activation of coagulation by a membrane in a dialyzer is difficult to assess given the above-mentioned factors and the host's response to the anticoagulation regime put in place (**Figure 1**).

2.3 Activation of the kinin-kallikrein system

Surface activation of Factor XII induces the kinin-kallikrein that ensues in the generation of bradykinin (**Figure 2**).

Bradykinin is physiologically under the tight control of very potent kinases that are able to promptly lyse the molecule and inactivate its potent vasodilator activity. In certain conditions, however, the lytic effect of this kinase is deficient. This occurs in patients under therapy with angiotensin converting enzyme enzyme (ACE) inhibitors. However, there are patients who experience hypersensitivity-like phenomena, that can be reconducted to bradykinin generation, even in the absence of concomitant therapy with ACE inhibitors. The explanation of this phenomenon came from pioneering studies on angio-edema, a rare but potentially fatal condition (Adam et al., 2002). These reactions are mainly associated to defects in the enzymatic activity of the aminopeptidase P (**Figure 2**). Bradykinin acts through two types of tissue receptors: R1 are mostly located in the skin and respiratory tissues (lungs and bronchi), while R2 are mostly found in the gastrointestinal tract. The overproduction of bradykinin may lead to two different clinical presentations: the first is mainly characterized by a rapid developing skin flushing, hypotension, and dyspnoea. These reactions may be mild but very severe, fatal episodes of shock have been described. In the second instance, these reactions, which were for some time unexplained, occur after 1 h-2 hr of HD treatment, may but may be not associated with the use of ACE inhibitors. The patient has severe diarrhoea which requires immediate interruption of the extracorporeal treatment. This manifestation may unpredictably recur and disappears upon disconnection. Bradykinin-induced reaction, may in principle occur following the contact with any foreign surface. Their potential, unpredictable severity should call for immediate action even in patients with mild forms. The commonest causes have been the use of strongly negative surfaces such as AN-69 membranes (Tielemans et al., 1990), or adsorbents used in LDL

apheresis (Owen et al., 1994) or in Hemodiafiltration (HDF) with regeneration of the ultrafiltrate (Tetta C, Wratten ML, unpublished observation, 2001). The appearance of signs and symptoms of a hypersensitivity-related event can be dramatic in the practice of HD. The complexity of the causal factors and the underlying mechanisms are often difficult to unveil (Arenas et al., 2006). The majority of reported cases have been due to ethylene oxide (ETO) (Poothullil et al., 1975), triggered by both immunoglobulin E (IgE) and non-IgE factors (Johansson et al., 2001). However, a considerable number of publications have focused on other HD substances and materials such as heparins, different dialyser membranes, iron, erythropoietin, polyacrylonitrile AN69® high flux membranes, latex, antiseptic or formaldehyde (Ebo et al, 2006). Many different underlying mechanisms have been postulated. Hypersensitivity reactions have been estimated to occur in ~4/100000 dialysis treatments. A postal survey of all HD centres in the UK suggested that 1/20 to 1/50 patients may be susceptible to anaphylactoid reaction to a new hemodialyser at some time in between, while the risk of reaction occurring with any single HD session is~1/1000 to 1/5000. Although it is likely that many reactions are unrecognized or unreported, the scale of the problem is larger than many nephrologists have suspected (Nicholls et al., 1987).
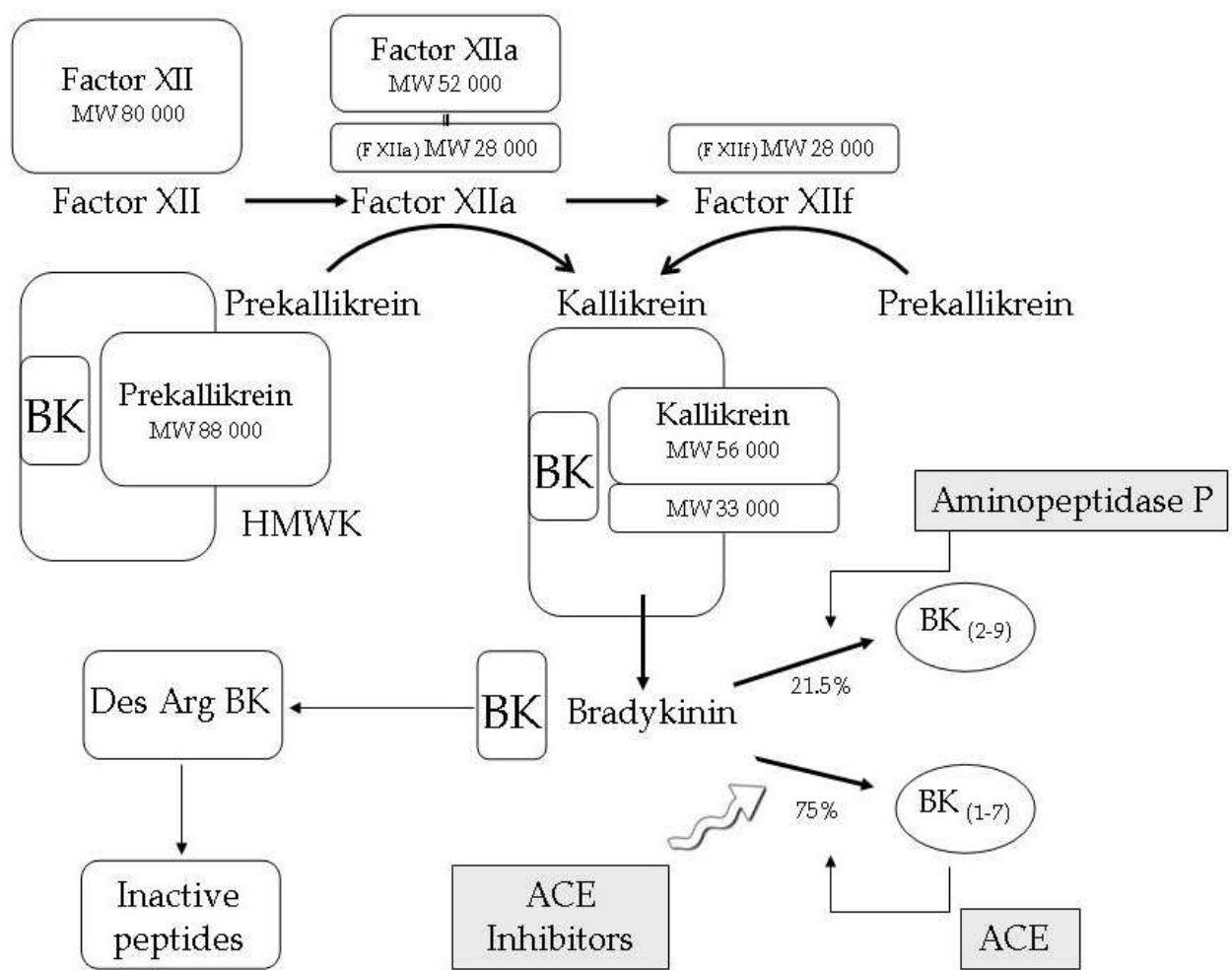

Fig. 2. Activation of the kinin-kallikrein system and generation of bradykinin (BK)

2.3.1 Soluble mediators

Many soluble mediators are produced and released following the blood-membrane interaction. Products of the phospholipase A2 such as platelet-activating factor (PAF) and leukotrienes are released by the direct interaction of PMNs and platelets with complement-activating membranes. Although in the presence of blood, the mechanisms of production of PAF and leukotrienes can not be readily differentiated from the activation, as they follow the same kinetics, we could show that for PAF for example, its production and release could be observed in complement-independent conditions such as in the absence of plasma by purified cells incubated with flat HD membranes (Tetta et al., 1996). A large number of studies have also suggested the occurrence in the plasma of lytic enzymes normally present in the vacuoles of inflammatory cells such as elastases, and metalloenzymes. The release of these lytic enzymes is caused by a phenomenon named by cell physiologists as "frustrated phagocytosis".

3. The effect of blood on dialyzer performances

When blood enters the HD system *via* the arterial line, a complex interplay of factors alters membrane performances *e.g.* clearances, ultrafiltration rates and sieving coefficients. These factors are patient- and system- dependent.

3.1 Patient-dependent factors

3.1.1 Albumin: Relevant amount of albumin fragments are detectable in the serum of patients undergoing HD. Uremia appears to facilitate the fragmentation of albumin and/or the retention of albumin fragments in blood (Donadio et al., 2009). Depending on their molecular weight, albumin fragments may be either lost in the dialysate or remain trapped in the wall of the hollow fibre. More in general, plasma proteins may cause a phenomenon names as "protein fouling".

3.1.2 Plasma viscosity which is related (but not exclusively) to albumin, fibrinogen and lipids.

3.1.3 Free hemoglobin: *In vitro* data have shown that blood circulation produces an increase of up to 280% in free hemoglobin levels and an increase of 320% in electronegative LDL (LDL(-) subfraction, a highly atherogenic form of oxidized LDL. The significant correlation between LDL(-) and free hemoglobin levels shows the oxidative activity of free hemoglobin (Ziouzenkova et al., 1999) (**Figure 3**).

3.1.4 System-dependent factors

3.1.4.1   Several factors are here involved such as the **vascular access flow rate**, and **the pump rate** and the response of the dialyzer depending on the membrane resistance and geometry. As seen from a kinetic perspective, the blood flow, and pressures are on-off events which are reflected in a "push-pull" effect on the dialyzer hollow fibre. Although these effects are still not completely known, they seem to be relevant on the shear rates, the erythrocyte orientation, leading in the worst conditions to predispose to their agglutination and clogging of the hollow fibre. Calculating clearances, ultrafiltration rates and sieving coefficient using aqueous solution can lead to an overestimate of 30%and is therefore hardly informative of the dialyzer behaviour in vivo. Finally, it was shown that sieving coefficients may change over the time of treatment rendering the calculation of clearances on the basis of the quantization of urea on the ultrafiltrate may also lead to an overestimation of the dialyzer performances (Claure-Del Granado et al., 2010).
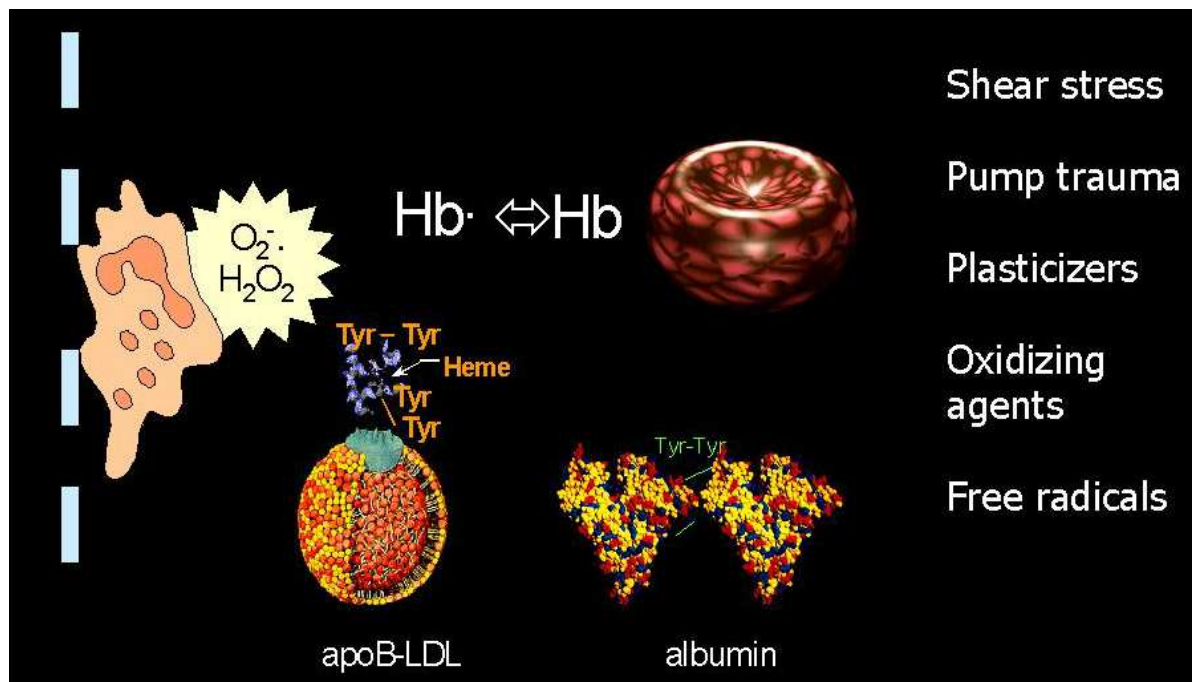
Fig. 3. Microhemolysis is the release of small quantities of hemoglobin (micro- or nanomolar) from erythrocytes. The tyrosine of a hemoglobin molecule can undergo a transition to a reactive free radical. This can react with other protein tyrosine residues to form a dityrosine molecule. Microhemolysis occurs during the HD procedure in which the erythrocytes are slightly damaged and tend to „leak" very small quantities of hemoglobin. This is a very common phenomena in HD and should not be confused with gross hemolysis.

4. The evolution of treatment biocompatibility

4.1 From system biocompatibility to systemic chronic inflammation

The concept that inflammation underlines many diseases once considered to be linked to degenerative processes has revolutionized the approach to the research into the pathogenesis and new therapeutics alike. In the field of cardiovascular disease, the process of endothelial dysfunction, vascular damage and atherosclerosis is now seen as a continuum (Libby et al., 2002). Cardiovascular disease is among the leading cause of morbidity and mortality in CKD patients on maintenance HD (US Renal Data System, 1997; Parfey & Foley, 1999). Even before reaching the state of chronic kidney disease Stage 5, patients with chronic renal failure present signs of chronic inflammation. Once patients are on HD, the risk of cardiovascular death is approximately 30 times higher than in the general population, and still remains 10 to 20 times higher after stratification for age, gender, and presence of diabetes. Traditional risk factors seem inadequate to explain the remarkable prevalence of cardiovascular disease observed in the uremic population (Foley et al 1998).

4.1.1.1 Systemic Chronic Inflammation

Inflammatory mechanisms play a relevant role in the development and progression of atherosclerosis (Ross, 1999) and heart failure (Vasan et al., 2003). Epidemiological studies in the general population have shown that even minor elevations of C-reactive protein (CRP), an acute phase reactant that markedly increases during an inflammatory response (Ridker PM, et al., 1997) predict the development of coronary heart disease and cardiac failure

(Liuzzo et al 1994, Lagrand et al., 1999, Badht et al, 2002). C-reactive protein may directly promote the development of atherosclerosis, through complement activation, tissue damage and activation of endothelial cells. Recent studies performed in CKD patients have shown that CRP is a strong predictor of cardiovascular death (Stenvinkel, 2001, Kaysen, 2005). The link between CRP and cardiovascular risk was initially thought to be indirect, reflecting circulating CRP only to the extent of the acute phase reaction in response to nonspecific stimuli such as confounding risk factors, atherosclerosis, vascular injury, ischemia and necrosis. **(Figure 4).**
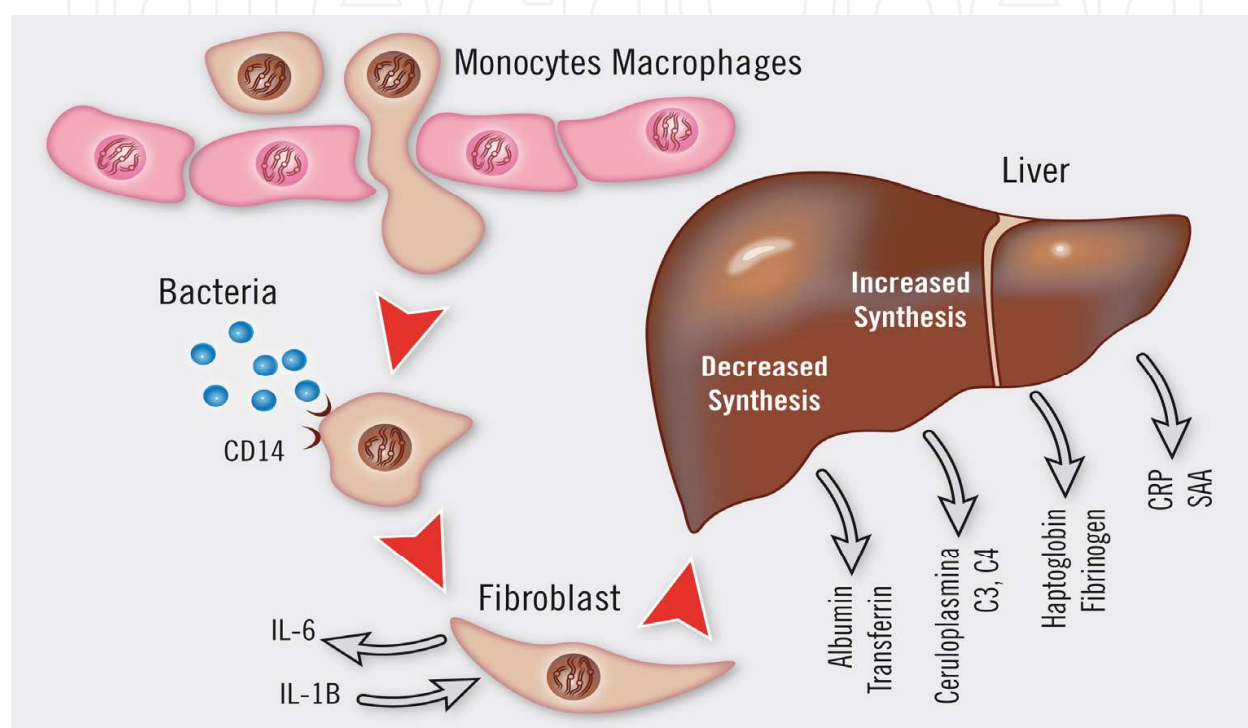

Fig. 4. Acute phase response is a defence response which occurs as a consequence of an inflammatory stimulus occurring in the blood or at tissue level. The enhanced production of interleukin-6 (IL-6), the most potent inducer of this reaction at the level of the liver, triggers the synthesis of newly synthesized proteins, e.g., C-reactive protein (which plasma levels may increase up to 50-to 100-fold the normal levels) as well as to the shut-down of the translation of genes coding for proteins, e.g., albumin.

Stenvinkel et al (1999) first convincingly showed that the malnutrition-inflammation complex syndrome described as MIA syndrome is associated with the highest mortality rates in ESRD. Their results were confirmed and extended (Panichi et al. 2008). As reviewed by Stenvinkel & Barany (2002), there is consensus on a link between CKD and inflammation. A number of studies have highlighted the association between increased inflammatory indexes and a reduced response to Erythropoietin-stimulating agents (ESAs), in particular, high CRP levels were found in HD patients requiring higher ESAs doses (Singh et al., 2007; Bradbury et al. 2009). However, the association between ESAs resistance and increased CRP levels (Barany et al. 1997; Gunnell et al. 1999) is unclear. Plasma IL-6 rather than CRP seem to better predict outcomes in CKD patients (Panichi et al., 2004). Various possible explanations may underline the advantage of IL-6 over CRP as a predictor of ESAs resistance. One possibility is that IL-6, being located upstream in the cascade of events

which lead to the synthesis of many acute-phase reactants, is a better marker for the inflammatory burden affecting the development of CVD (Panichi et al., 2011). A frequently asked question is what is the contribution of HD bioincompatibility to the chronic inflammatory state. In this context, the evolution of HD technology has moved the focus from membrane bioincompatibility only to a more complex and integrated view of the HD system. The possibility that HD may be shift to a "cardioprotective" therapy is inherent to new technologies in machines, water treatment, dialysis fluids and blood tubings.

4.1.1.2 The Interleukin Hypothesis

Originally introduced as an elegant concept in 1986 (Bingel et al., 1986), the "interleukin hypothesis" was first coined to indicate the production of interleukin-1, the endogenous pyrogen as produced by the result of complement-activated mononuclear cells. Indeed, the interleukin hypothesis explained much more than was initially predictable. Several studies have ever since reported an increased cytokine production secondary to blood interaction with contaminated dialysate. Interleukin-1 (IL-1), tumor necrosis factor-a (TNF-a) and mainly IL-6 are the 3 proinflammatory cytokines that are involved in the pathogenetic aspects of HD-related disease (as reviewed by Lonnemann, 2004, Panichi et al., 2000 (**Figure 5**).
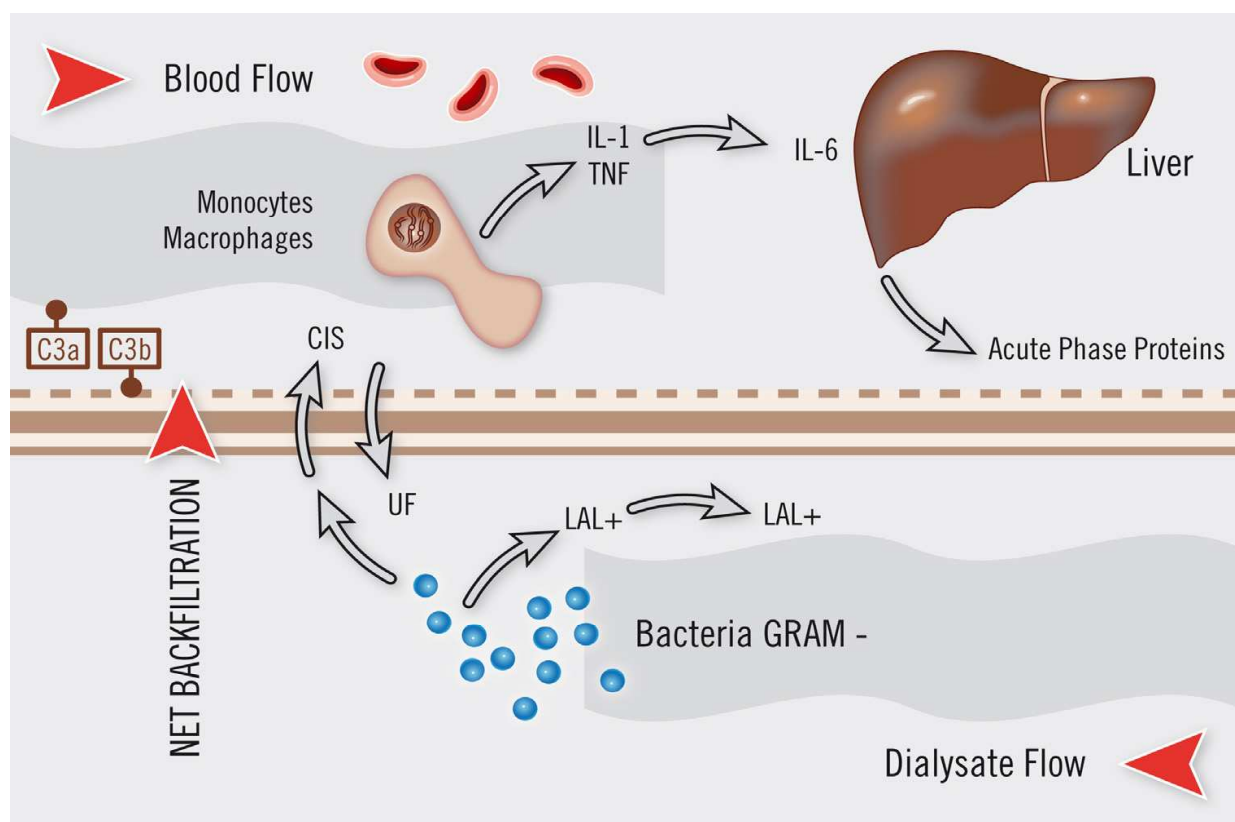

Fig. 5. Here are schematically depicted the mechanisms related to the backdiffusion/backfiltration of bacteria-derived contaminants from the dialysate into the blood. Their interaction with circulating monocytes/macrophages leads to the activation of innate immunity and to the attendant triggering of proinflammatory cytokines (interleukin-1 (IL-1), tumor necrosis factor-α. Abbreviations: CIS, cytokine-inducing substances; LAL, *Limulus amoebocyte* lysate, UF, ultrafiltrate.

The proposed mechanisms include blood interaction with endotoxins from the contaminated dialysate through HD membranes. A large number of studies have greatly contributed to increasing our knowledge in the mechanisms of endotoxin transfer across the membrane In fact, when using high permeability membranes, backfiltration and backdiffusion occur and have ebeen extensively described (Fiore & Ronco, 2007, Ronco, 2007). Thus, the transmembrane passage of endotoxins or other cytokine stimulating substances (CIS) occurs during HD (Schindler et al., 2004, Tetta et al., 2006). The reduction of backfiltration of standard dialysate may reduce the plasma concentration of IL-1ra, a sensitive indicator of inflammation in HD patients (*Dinarello personal communication, 2004*), and IL-1 (Panichi et al., 1998). Studies on large groups of patients have shown that high-volume exchange HDF, a treatment in which dialysate backfiltration is minimal, if any, is associated with significantly lower CRP plasma values (Panichi et. 1998). Comparing in a double cross-over study patients treated with high-flux and on line HDF using ultrapure dialysate and infusate, it was shown that a significant reduction of pro-inflammatory CD14+/CD16+ mononuclear subset (Carracedo et al., 2006) occurs in on line HDF. These studies emphasize that the convective component has an additional anti-inflammatory effects (Ramirez et al., 2007).

The new technology of pyrogen-adsorbing, non-complement activating, high-permeability synthetic membrane and dedicated machines (Tetta et al., 2011), as well as the awareness of the deleterious effects derived from contamination of dialysis fluids has reduced the clinical impact to a periodic microinflammatory stimulus. Undoubtedly, the availability of monitors for on-line HDF and its increased popularity have spurred more restrictive measures on safety issues and monitoring. Water quality is a mandatory issue. The safety of online HDF has been shown repeatedly in several monocenter (Canaud et al., 1998, Pizzarelli et al., 1998 and multicenter studies (Canaud et al., 2001,Vaslaki et al., 2000).

Nowadays, the philosophy of ''ultrapure dialysate''is in common practice (Kessler et al., 2002). The clinical, consolidated experience on line HDF warrants well-defined procedures and leaves no space for ''experiments'' in what is now routine (Canaud et al, 2011). The ''hemocompatibility network'' should eventually prevent the periodic microinflammation induction through the implementation of rigid protocols of disinfection and maintenance of water-treatment systems and HD monitors (Cappelli et al., 2006; Kessler et al. 2002).

5. Microvesicles: their nature, release and pathophysiological relevance

A chronic inflammatory state has been widely documented since the early stages of CKD and becomes more pronounced in those with CKD stage V undergoing HD. Oxidant stress (Wratten et al., 2000, Morena et al. 2011), endothelial dysfunction (Recio-Mayoral et al., 2011), high circulating cytokine-producing monocyte subpopulation (Ramirez et al., 2006), reduced number and/or impaired function of endothelial progenitor cells (Krenning et al., 2009), are today considered as hallmarks of vascular damage and defective repair. Uremia also causes telomere shortening and premature cellular senescence of immunocompetent cells (Jimenez et al, 2005). In recent years, increasing attention has been drawn by the awareness of the pathophysiologic role of small, circular membrane fragments named as Microvesiscles (MVs) (Ratajczak et al., 2006) (**Figure 6**).
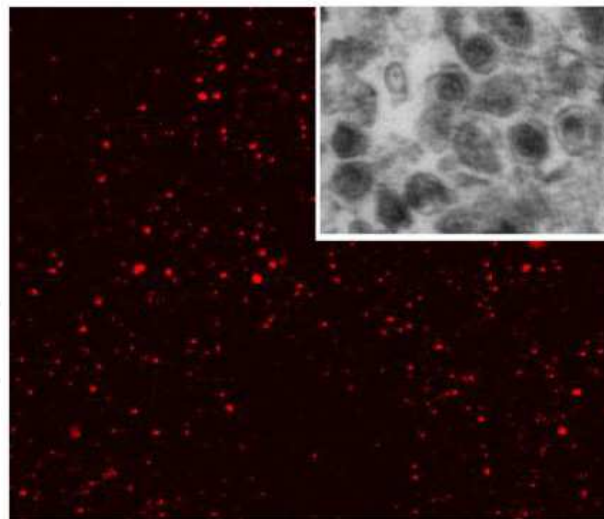
Representative micrograph showing purified MV labelled with the fluorescent dye PKH26 observed by confocal microscope (original magnification X630). The inset shows the transmission electronmicroscope appearence of purified MV (original magnification X25,000).

Fig. 6.

For long time MVs were considered to be inert cellular debris. The frequently observed vesicles by electron microscopy in the interstitial space of tissues or in blood were considered as the consequence of cell damage or the result of dynamic plasma membrane turnover (Siekevitz et al., 1972). As the vesicle population detectable both *in vitro* and *in vivo* is a mixed population of exosomes and shedding vesicles, we will refer to them collectively as MVs. Released MVs may remain in the extracellular space in proximity of the place of origin or may enter into the biological fluids reaching distant sites. This may explain the presence of MVs in plasma, urine, milk and cerebrospinal fluid. The bulk of MVs present in the circulation is derived from platelets (George, 1982), and in less extent from other blood cells and endothelial cells (Martinez et al., 2005). The MVs derived from platelets are also designed as microparticles while those derived from polymorphonuclear leukocytes are also named ectosomes (Hess et al., 1999). Finally, MVs released during morphogenesis of multicellular organisms are indicated as argosomes (Greco et al., 2001). Besides normal cells, also tumor cells may release MVs and in patients suffering for neoplastic diseases tumor-derived MVs may be detected within the biological fluids (Kim et al, 2003, Iero et al., 2008). Therefore, MVs are an assorted population, differing in cellular origin, number, size and antigenic composition (Diamant et al., 2004) shed by various cell types in physiological and pathological conditions. The release of MVs may be constitutive or consequent to cell activation by soluble agonists, by physical or chemical stress such as the oxidative stress and hypoxia, and by shear stress (Ratajczak et al., 2006). Exosomes have an endosome origin and are a rather homogenous population with a size ranging from 30 to 120nm (7). They are stored as intraluminal vesicles within multivesicular bodies of the late-endosome and are released when these multivesicular bodies fuse with the cell membrane. Our knowledge on

the mechanism of assembly and sorting of the exosomes is only partial, due to the fact that a common sorting signal for all cell types has not so far been identified (Johnstone et al., 2006). Shedding vesicles are usually larger than exosomes with size ranging from 100nm to 1μm. Formation of shedding vesicles takes place from the budding of small cytoplasmic protrusions followed by their detachment from the cell surface. This process is dependent on calcium influx, calpain and cytoskeleton reorganization.

5.1 MV biological activities

It is now recognized that MVs are an integral part of the intercellular microenvironment and may act as regulators of cell-to-cell communication. This concept is based on the observation that MVs released from a given cell type may interact through specific receptor-ligands with other cells leading to target cell stimulation directly or by transferring surface receptors (Janowska-Wieczorek et al., 2001, Morel et al., 2004). This interaction may either be limited to a receptor-mediated binding to the surface of target cells forming a platform for assembly of multimolecular complexes or leading to cell signaling, either be followed by internalization as result of direct fusion or endocytic uptake by target cells (Cocucci et al., 2008). Once internalized, MVs can fuse their membranes with those of endosomes, thus leading to a horizontal transfer of their content in the cytosol of target cells. Alternatively, they may remain segregated within endosomes and be transferred to lysosomes or dismissed by the cells following the fusion with the plasmamembrane, thus leading to a process of transcytosis. It was proposed that MV-mediated cell-to-cell communication emerged very early during evolution as a template for the development of further more refined mechanisms of cell communication (Ratajczak et al., 2006). MVs may influence the behavior of target cells in multiple ways.

5.1.1 MVs may act as signaling complexes by direct stimulation of target cells (Ratajczak et al., 2006, Cocucci et al., 2008). MVs derived from platelets, for instance, play an important role in coagulation as their phosphatidylserine-enriched membranes provide a surface for assembly of clotting factors (Zwaal et al., 2004). After activation, platelets shed MVs coated with tissue factor which may interact with macrophages, neutrophils and other platelets by ligation with molecules expressed on the surface of these cells such as P-selectin (Polgar et al., 2005). On the other hand, MVs released from neutrophils express activated Mac-1 able to induce platelet activation (Andrews & Berndt, 2004). Moreover, platelet-derived MVs, besides coagulation, trigger various cell responses as they activate endothelial cells (Barry et al., 1997), polymorphonuclear neutrophils (Miyhamoto et al., 1988) and monocytes (Barry et al., 1999). .

5.1.2 MVs may act by transferring receptors between cells. The transferring of receptors between cells is supported by the observation that bystander B cells rapidly acquire antigen receptors from activated B cells by a membrane transfer (Quah et al., 2008).

5.1.3 MVs may deliver proteins within the target cells. An example of this mechanism is the recently reported MV-mediated transfer of a cell death message via encapsulated caspase-1 (Sarkar et al., 2009). It has been found that endotoxin stimulated monocytes induce the cell death of vascular smooth muscle cells by releasing MVs containing caspase-1. This trans-cellular apoptosis induction pathway depends on the function of the delivered caspase-1 within the target cells. It has been also suggested that MVs may contribute to dissemination of certain infective agents, such as HIV or prions (Facler & Peterlin, 2000, Fevrier et al., 2004).

5.1.4 MVs may mediate a horizontal transfer of genetic information. The occurrence of epigenetic changes has been frequently reported in co-culture conditions. An explanation of this phenomenon is the transfer of genetic information between cells. We demonstrated that MVs derived from human endothelial progenitors (EPC) can also act as a vehicle for mRNA transport among cells (Deregibus et al., 2007). MVs generated from EPC were incorporated in normal endothelial cells by interaction with α4- and β1-integrins expressed on their surface and activated an angiogenic program. Besides mRNA, MVs may transfer microRNAs (miRNA) to target cells (Yuan et al., 2009). Since miRNAs are naturally occurring regulators of protein translation, this observation opens the possibility that stem cells can alter the expression of genes in neighbouring cells by transferring microRNAs contained in MVs. We recently characterized miRNA shuttled by MVs released by human adult mesenchymal stem cells (MSCs) (Collino et al., 2010). Hierarchical clustering and similarity analysis of microRNAs showed that microRNA compartmentalization and secretion by MVs are both highly regulated processes.

5.2 Microvesicles in CKD

The biologic role of MVs and their implication in pathophysiology depends on the several factors namely the cell of origin, their phenotype, the genetic material (mRNA and microRNA) and the target cells. In CKD, several studies have accrued evidence that MVs or MPs could participate to the vascular damage and the evolution of the atherosclerotic lesion.

5.2.1 Circulating platelet-derived microparticles (PMPs) with procoagulant activity are considered a potential cause of thrombosis in uremic patients undergoing HD (Ando et al., 2002). Elevated counts of circulating PMPs have been reported in association with thrombotic disorders, such as cerebrovascular accidents (Katopodis et al., 1997), unstable angina (Katopodis et al., 1997), and acute myocardial infarction (Gawaz et al., 1996). In addition, PMPs that adhered to vascular endothelium and leukocytes activate such cells and transport their chemical mediators to those cells, potentially leading to the development of thrombosis and atherosclerosis (Mallat et al., 1999, Barry et al., 1997).

5.2.2 Endothelial MVs (EMVs) - Treatment modalities that reduce the inflammatory potential of the cells originating MVs have interestingly been correlated with a decreased number of endothelial microparticles (Carracedo et al., 2005, Ramirez et al., 2005). Circulating EMPs have recently been reported to correlate with impaired vascular function in HD patients (Faure et al., 2006). A recent study showed an increase in the percentage of CD14+CD16+ monocytes in CKD-NonD and HD patients. In PD patients, regardless of RRF, the percentage of CD14+CD16+ was similar to controls (Merino et al., 2010). It is interesting to note that HD patients displayed significantly higher apoptotic EMPs and VEGF levels than the two PD and CKD-non dialyszed groups. In contrast, there were no differences between CKD-NonD and PD groups. In CKD-non dialyszed and HD patients, the percentage of CD14+CD16+ was correlated with endothelial damage. It appears that PD, compared with HD, reduces but does not fully prevent the endothelial damage induced by uremia, in spite of presenting a microinflammatory status similar to that of the controls. The role of EMVs is still to be elucidated in the complex unbalance observed in CKD patients between circulating endothelial cells and endothelial progenitor cells.

5.2.3 MVs in treatment modalities

Preliminary studies in our laboratory have shown an interesting trend in the reduction of total MVs in a cross-over clinical study when patients shifted from high-flux HD to on-line HDF (**Figure 7**).
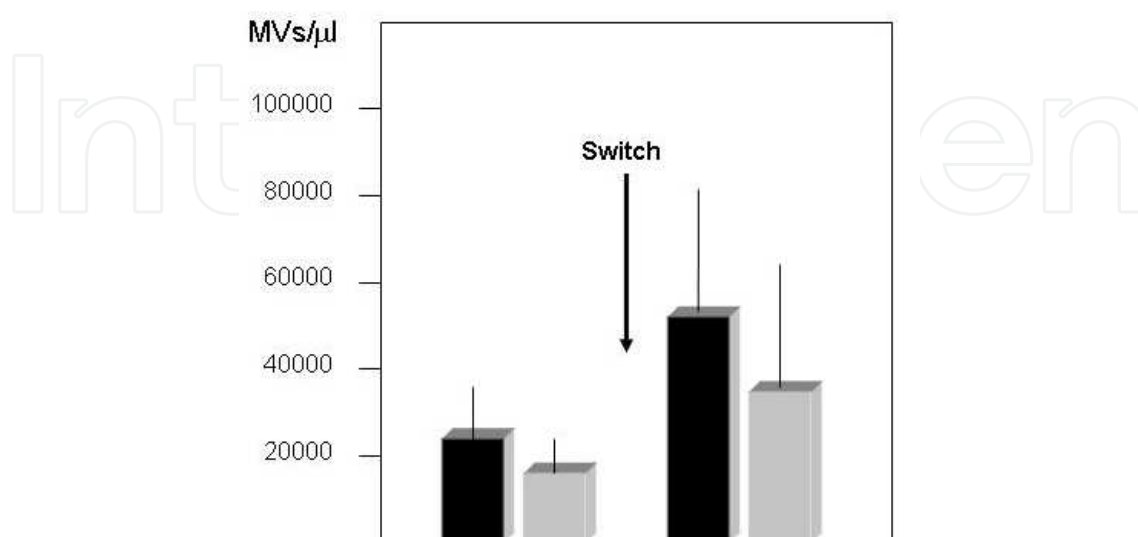

Fig. 7. Total MVs count in patients on maintenance HD. In a cross-over design, 8 patients were started on bicarbonate HD (black columns) and 8 patients on on-line HDF (grey columns). MVs were counted by cytofluorimetry. MVs were also characterized (data not shown) by the following specific markers: CD62P, CD41, CD42, CD31, for platelets; CD45, for leukocytes; CD31, CD146, CD144 for the endothelium: CD235 and CD242 (ICAM 4), for erythrocytes.

More studies are needed to better assess the relevance of these observations and to better characterize the type and biological effects of the MVs. It is still to be fully elucidated whether MVs are a consequence or a cause of disease. Increasing evidence for their pathophysiologic role in other human diseases such as sepsis and tumors (Camussi et al., 2011) is rapidly accruing. Many points require further investigation. i. The stimuli and the molecular pathways that regulate the assembly within MVs of the biological active molecules that they shuttle. ii. The stimuli that trigger their release. iii. The surface receptors that may confer selective specificity. iv. The full diagnostic potential of MVs in different pathological conditions. v. The strategy to inhibit formation or to remove from circulation potentially harmful MVs. The recognition of MVs has opened a new era and new perspectives of investigation also in biocompatibility of extracorporeal treatments.

6. Conclusions

The outlook of more biocompatible and physiological dialysis is today confronted with a older and sicker population in need of maintenance HD. The knowledge of biological mechanisms operating at the system level will be approached with the help of improved technologies hopefully able to reduce the deleterious effect of the repetitive contact with a foreign surface and to insure optimal performances for the elimination of small and middle molecule solutes. Advances in dialyzer membranes and geometries, as well as blood tubings

together with new concepts in machine technology have already shown their great potential to improve survival and cardiovascular stability.

7. Conflict of interest

Ciro Tetta and Emanuele Gatti are full-time employees of Fresenius Medical Care.

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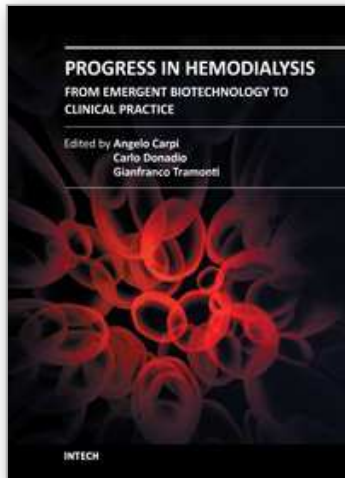
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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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