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Dialysis membranes in convective treatments

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Introduction

Haemodialysis is basically divided into two categories: low-flux dialysis and high-flux dialysis. Low-flux dialysis includes the standard haemodialysis technique in which dialysers with low hydraulic permeability are utilized. Blood and dialysate flow rates are at 250 and 500 ml/min, respectively and the average duration is 4 h. When the dialyser surface area is increased, and flow rates of blood and dialysate are increased up to 400 and 800 ml/min, respectively, the treatment is defined as high efficiency haemodialysis [1]. In this treatment the clearance of small molecules is remarkably increased and the treatment time generally can be shortened, but the clearance for middle to large molecules is still very low due to the permeability characteristics of the membrane.

Classic cellulosic membranes such as cuprophan are typically low-flux membranes i.e. permeability to water is in the range of 5–6 ml/h/mmHg/m^2, they are strongly hydrophilic and remarkably thin to permit an optimal utilization in diffusive treatments such as haemodialysis.

On the other hand, classic high-flux synthetic membranes originally were fully hydrophobic, strongly asymmetric and with a thick wall. They were employed principally in convective therapies such as haemofiltration due to their high hydraulic permeability, i.e. 30–40 ml/h/mmHg/m^2, and their high sieving coefficients [2].

Only recently has it been possible to design synthetic membranes with reduced wall thickness and a mixed hydrophobic–hydrophilic structure. This has permitted their use in new techniques such as high-flux haemodialysis and haemodiafiltration in which diffusion and convection are conveniently combined [3].

When high-flux membranes are utilized, three different approaches can be chosen: (i) haemofiltration is a fully convective treatment in which large amounts of ultrafiltrate are produced and replaced by a sterile substitution fluid. No dialysis fluid is present. This technique offers the advantage of excellent clearances for large molecules. The treatment, however, has only been applied in Europe because of the need for large quantities of substitution fluid in commercially prepared bags. (ii) Haemodiafiltration is a form of therapy in which diffusion and convection are conveniently combined. Dialysate is circulated countercurrent to blood but the amount of ultrafiltration exceeds the programmed patient weight loss and therefore the final fluid balance is achieved by the infusion in the venous line of appropriate amounts of substitution fluid [4–6]. Due to the high costs related to replacement solutions, new approaches have been proposed in Europe for performing haemofiltration and haemodiafiltration [7]. Part of the fresh dialysate is diverted from its line to the dialyser, it is filtered and it finally is used as a replacement solution. These on-line treatments have the advantage of reduced costs, unlimited production of substitution fluid and no need for tons of commercially produced fluid in bags. On the other hand, the microbiological and chemical purity of the on-line prepared fluid may represent a concern since no on-line controls can be made. (iii) High-flux dialysis is a technique in which highly permeable dialysers are utilized in conjunction with an accurate ultrafiltration control of the dialysis machine. Because of the nature of the hollow fibre dialyser, the correct water balance is achieved thanks to an internal filtration in the proximal part and a backfiltration in the distal part of the filter [8]. As a consequence, some of the advantages of removing larger molecules are maintained because of the internal convection, while the need for replacement solution is avoided by a significant amount of backfiltration of fresh dialysate. In this way, some of the advantages of haemodiafiltration are maintained with a simpler and easier layout of the technique [8]. Again, the dialysate purity is a key issue in this treatment where bacterial products could be back-transported into the blood together with the reverse flux of water. This may affect the entire concept of biocompatibility of the system. Concerning this aspect, great efforts have been made in improving the quality of the biomaterials used for dialysis membranes and

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at the same time of the water treatment systems [9]. Cellulosic membranes have been modified progressively to approach the performances of haemocompatibility displayed by the classic synthetic biocompatible membranes. Special filters and sorbents have been utilized in the preparation of water for haemodialysis, while high quality materials have been employed in adequate delivery circuits with appropriate piping layout [9]. This has represented an important step in the improvement of the water quality which somehow has been a neglected aspect for a long time.

The membrane structure

Membrane structure and geometry may strongly affect the results one can achieve in convective therapies. Membranes can be divided into different categories according to chemical composition, structure, porosity and other parameters (Table 1). Some of these membranes are reported in Table 2. The parameters controlling membrane permeability and performance are summarized in Table 3. The different composition and process of manufacturing can result in final membranes with different membrane porosity, interaction with water and solute sieving coefficients. The performance is affected substantially by the number of pores, their size and distribution. As can be seen in Figure 1, different pore distribution curves may result in specific curves of observed sieving coefficients during convective therapies.

Table 1. Membranes for renal replacement therapy

Chemical composition	Cellulosic	Synthetic
Structure	Homogeneous	Asymmetrical
Porosity	Hydrogel	Microporous
Interaction with water	Hydrophilic	Hydrophobic
Thickness	Small	Large
Biocompatibility	Low	High
Electrical charges	Mixed	Negative
Hydraulic permeability	Low flux	High flux

The manufacturing process including the speed of membrane formation and the different equilibrium reached between the polymer, the solvent and the non-solvent may affect the final structure of the membrane [10]. Under different conditions, the geometrical structure of the membrane can become finely microporous or fingertype (Figure 2). In both cases, the inner skin layer of the membrane is the real sieving barrier for solutes while the rest of the membrane structure is offering mechanical resistance and structural support. A typical example of a polyamide membrane is reported in Figure 3. Depending on the process of membrane formation, a second, external skin layer can be present and this may further affect convective performances of the membrane. One important characteristic of the membrane is its interaction with water. Original high-flux membranes were almost completely hydrophobic and this caused some unwanted effects in terms of protein interaction and diffusivity. Modern synthetic membranes have been modified to achieve a higher degree of interaction with water and more hydrophilic characteristics. This was achieved by addition of PVP to the polymeric paste. After sterilization,

Table 2.

Classical	Modified	Synthetic modified
Cellulosic membranes		
Cuprophan (Akzo)	Diaphan CA 2.5 (Akzo)	Hemophan (Akzo)
RC (Asahi)	CA (Toyobo, Althin)	SMC (Akzo)
RC (Tejin)	CTA (Toyobo, Althin)	PEG (Asahi)
RC (Terumo)		PAN-RC (Asahi)
SCE (Tehin, Althin)		Excebrane (Terumo)
Synthetic membranes		
Hydrophilic native	Hydrophilic modified mixture	Hydrophilic/hydrophobic
EVAL C (Kuraray)	DIAPES (Membrana)	SPAN (Membrana)
EVAL D (Kuraray)	PA (Gambro)	PAN-DX (Asahi)
	PS (Toray)	PAN (AN 69 Hospal)
	PS (Minntech)	PMMA (Toray)
	PEPA (Nikkiso)	PC (Gambro)

Table 3. Parameters controlling membrane permeability and performance

	Choice of polymer	Composition of the polymeric paste	Process conditions	Stabilizing additives	Drying and sterilization	Modifications of the surface
Polymer structure	x					
H_2O interaction	x			x		x
Symmetry		x	x			
Thickness	x			x	x	
Pore size and distribution		x	x	x	x	

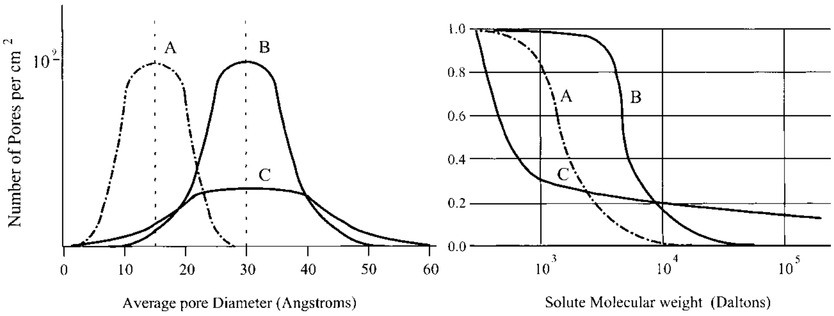


Fig. 1. Characterization of three different membranes by pore distribution and sieving. The left diagram shows the number of pores in relation to the average pore size. The right diagram shows the sieving profile of the membranes. Membrane A has a large number of pores with a restricted range of pore sizes. Membrane B has a large number of pores with a restricted range of pore sizes, but with larger average pore size than membrane A. Membrane C has a small number of pores distributed over a wide range of sizes.

PVP becomes part of the membrane and extraction of the single compounds becomes almost impossible.

Another important characteristic of a membrane is the zeta potential. Theoretically, it can be defined as the electrical differential potential between the surface of the membrane and the fluid flowing on the surface. This factor may contribute to explain some unclear blood–membrane interactions or solute permeability characteristics. Electrical charges and membrane composition strongly affect the behaviour of the membrane in terms of haemocompatibility. This, however, is not the topic of interest in this review and therefore biocompatibility issues are not discussed in detail.

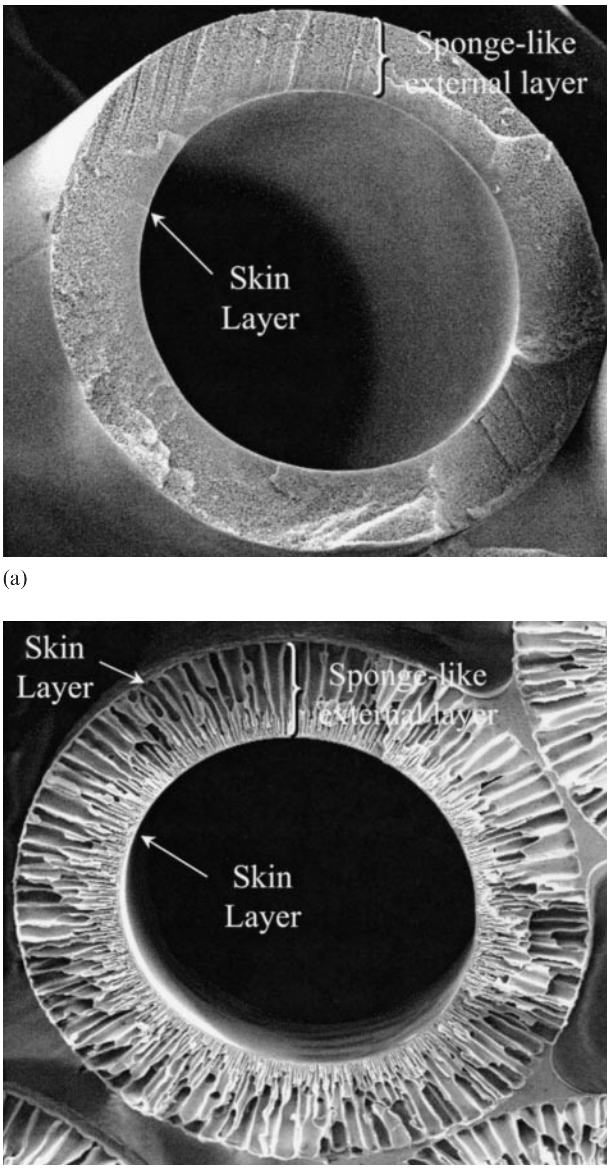
Membrane function in convection

Some of the above-mentioned characteristics of high-flux membranes tend to affect the permeability characteristics observed in the clinical setting, although the operational characteristics of the treatment are often the most important variable. In particular, hydraulic permeability and sieving properties of membranes are strongly determined by blood flow conditions and blood composition. Membranes interact with proteins, and at low blood flows the protein deposition at the blood–membrane interface tends to be greater. This is due mainly to a lower gradient of velocity between blood and the fibre wall. This lower shear effect will lead to thicker boundary layers of proteins and greater concentration polarization which in turn result in lower hydraulic permeability and lower observed sieving coefficients. Wall shear rates are also affected by blood viscosity, haematocrit and plasma protein concentration. When blood viscosity is higher, there is a lower flow velocity in the peripheral fibres of a haemodialyser. All these problems are enhanced when high filtration fractions are obtained in hollow fibre haemodialysers. High filtration fractions result from increased filtration rates at a given plasma flow. This is the case when low blood flows are present in the system and convective therapies are prescribed with excessive ultrafiltration rates. This unphysiological condition is deleterious for the hollow fibre which becomes progressively clogged and displays a reduction in permeability and sieving coefficients. For all these reasons, convective therapies should be performed only when blood flows are sufficiently high or in the case of large amounts of pre-dilution.

Haemodialysis membranes do not remove solutes by filtration or diffusion alone. Adsorption is an important mechanism that may contribute to the final amount of solute removal. In synthetic membranes, solutes are not only adsorbed on the inner surface of the membrane, but they can also be adsorbed onto the supporting external sponge layer. This external adsorption probably does not contribute to the net solute removal, since the adsorbed molecules would have been removed anyway in the filtrate. However, the sponge structure is responsible for retaining the molecules which cannot be found in the filtrate, making the calculation of sieving coefficients or direct dialysate quantification methods worthless for the accountability of solute removal. The typical case occurs with β_2-microglobulin, in which measurements of the sieving coefficient are extremely fallacious. However, adsorption appears to be an important issue for removing endotoxin and other bacterial products during fluid filtration. This mechanism, in fact, not only permits the avoidance of dangerous effects of backfiltration with contaminated solutions, but it is also used for repeated filtration of dialysate to obtain ultrapure fluid for reinfusion. Based on this concept, on-line haemofiltration and haemodiafiltration are performed today with a remarkable degree of safety and clinical tolerance. The problem is mainly that of ensuring a continuous quality control and redundant efficiency so that any accidental rupture or membrane leakage can be overcome by a subsequent stage of dialysate filtration.

The membrane and the haemodialyser design

The membrane cannot be considered as a single entity and simply as a biomaterial. It is the barrier for solute separation processes and it may perform very differently depending on the device in which it is employed. For this reason, the membrane should be seen as a



(a)

(b)

Fig. 2. Electron micrographs of cross-sections of two hollow fibre membranes. Arrows point to the skin layer. The top picture shows a microporous membrane. The lower picture shows a fingertype membrane.

component in a more complex structure which includes the blood side (or blood compartment) and the dialysate side (or compartment).

The blood compartment of an ideal haemodialyser should be characterized by the compromise between a low priming volume and a maximal blood–membrane contact surface [11]. The hollow fibre design has certainly contributed to the achievement of better results compared with the flat sheet configuration. The blood ports, considered for many years simply as arterial and venous ends of the unit, today represent sites of great importance. The arterial port must have a minimal stagnation of flow and it should guarantee a homogeneous distribution of blood flow in all the fibres of the bundle. For this purpose, different types of flow distributors have been proposed, but the most efficient is the conic structure with reduced space between the cap and the potting. No dead spaces or irregularities in the internal surface should be present. All these features should be accompanied by an accurate cutting of the fibres that prevents any collapse or accidental obstruction of the fibre internal lumen. The sterilization procedure may be critical in preserving the structure of the polyurethane utilized for the potting. In some cases, in fact, gamma-sterilized units have displayed unwanted cracking of the potting structure.

The length and the number of the fibres characterize the hydraulic resistance of the filter. In treatments utilizing high rates of convection, filtration pressure equilibrium may occur along the length of the filter. As blood moves through the filter, water is removed by filtration, and haematocrit and plasma protein tend to increase. As a consequence, the oncotic power of plasma becomes as high as the internal hydrostatic pressure, and filtration ceases. This phenomenon causes possible inconvenience in the distal part of the filter where a highly viscous blood is flowing inside the hollow fibres. Easy clotting or alteration in flow distribution may occur under such circumstances. Today, with the increased average haematocrit due to the large use of erythropoietin, all dialysers are forced to operate under conditions of highly viscous blood. As a result, the entire system may be affected and it may be likely that peripheral fibres operate with much lower flows compared with the central fibres of the bundle. This results in lower velocity gradients at the blood–membrane interface (low wall shear rates) with less than optimal operational conditions of those fibres.

To adapt the hydraulic resistance of the haemodialysers to the different operational conditions and the different treatment techniques, hollow fibres with different inner diameters have been designed. In an attempt to reduce the blood compartment resistance, the inner diameter has been increased in some filters from 200 to 250 μm [12]. These filters have been used mainly in arterio-venous circuits as well as in patients treated with continuous renal replacement therapies. In filters for babies or neonates, the inner diameter has been increased up to 500 or even 1000 μm [13]. The purpose of these approaches has been the attempt to reduce the rate of obligatory filtration at a given blood flow. In other words, because of a lower resistance, these filters permit higher blood flows to be obtained at a given arterio-venous pressure gradient (in arterio-venous circuits) and they present a lower internal pressure drop in the presence of a pumped extracorporeal circuit with a consequent lower rate of obligatory filtration. Obligatory filtration depends on the pressure generated inside the filter: at a constant venous pressure, the higher the resistance of the filter, the higher is the pressure drop in the filter and the higher will be the pressure at the inlet of the filter. As a consequence, the average pressure in the blood compartment will be higher and so will be the filtration rate at a given blood flow and venous pressure [14,15].

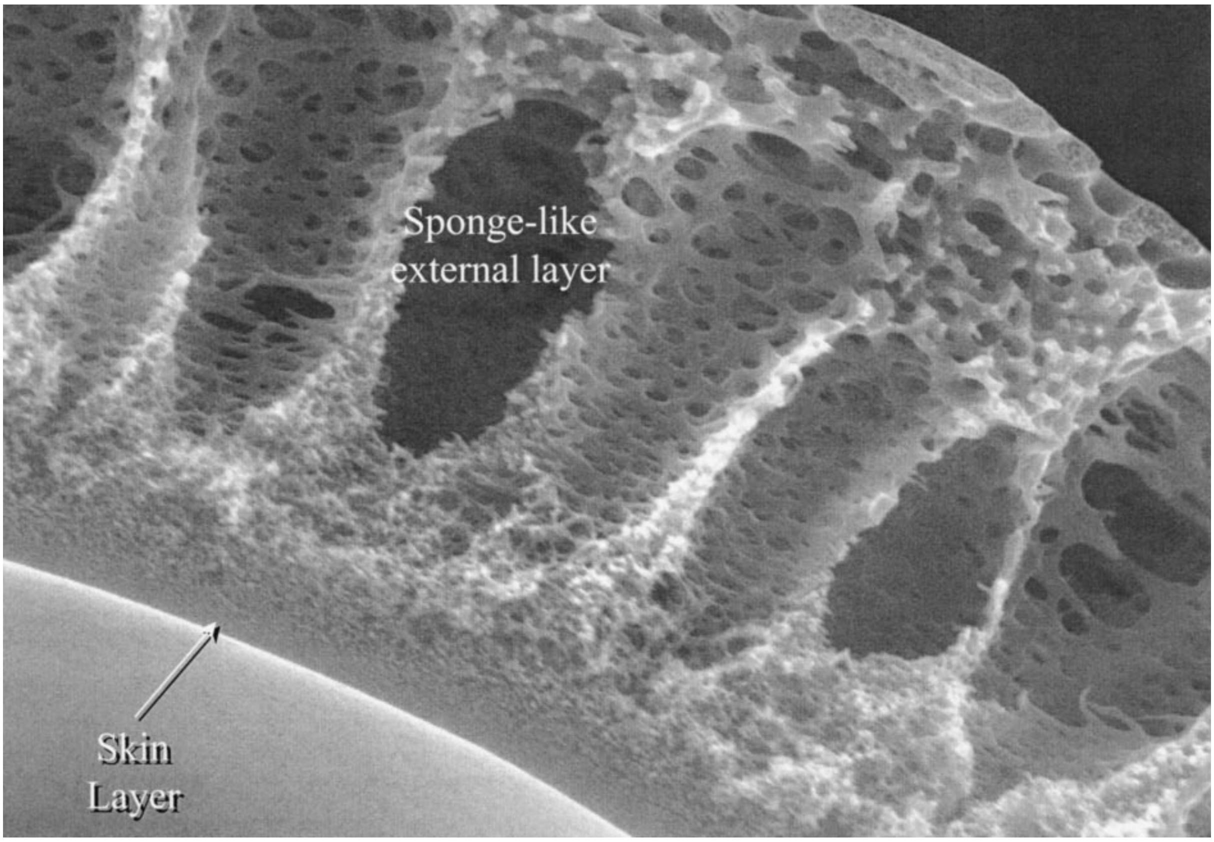


Fig. 3. Scanning electron micrograph of a polyamide membrane showing a cross-section of the sponge-like external layer and an arrow pointing to the skin layer.

The opposite approach has been suggested in the attempt to maintain very high wall shear rates and to increase the obligatory filtration. This has been obtained by reducing the internal diameter down to 175 µm. In these circumstances, the cross-sectional area of the filter will be reduced and the average flow velocity per fibre will increase. At the same time, the pressure drop in the blood compartment will significantly increase. With the use of dialysis machines with accurate ultrafiltration control systems, this will result in higher rates of filtration–backfiltration at a given net filtration rate. This will increase the convective component of the transport, without requiring replacement fluid reinfusion as in the case of haemodiafiltration. A similar approach has been proposed recently by placing a constriction ring around the fibre bundle in the mid segment of the dialyser, with the aim of increasing the pressure drop both in the blood and in the dialysate compartment [14].

The aim of this approach was to determine if convective transport and the rates of filtration–backfiltration in high-flux dialysis could be increased by altering the structure of the hollow fibre dialyser. Such a result could be achieved by increasing the pressure drop in both the blood and the dialysate compartments such as to increase the positive transmembrane pressure gradient in the proximal part of the filter, and the negative pressure gradient in the distal part. This can be performed by several methods including the use of two dialysers in series [16]. However, other methods have been proposed such as the use of a fixed O-ring on the dialysate side to alter the pressure profile at least in the dialysate compartment of the dialyser. This is expected to increase proximal filtration and distal backfiltration, by increasing the resistance to flow in the dialysate compartment, with improved convective removal of large solutes and no need for replacement solution. The net fluid balance is in fact maintained unchanged [14]. The clearances of urea, creatinine and phosphate are not significantly different in this modified haemodialyser, but the efficiency for larger molecules is definitely enhanced [14].

The dialysate compartment has been overlooked for many years, being considered of negligible importance in the performance of haemodialysers. A few modifications were introduced over the years such as the position of the Hansen connectors in the case (same side or opposite sides), without a real analysis of the optimal configuration. Initial studies on solute clearances at different dialysate flows demonstrated that by increasing the dialysate flow over a certain limit (600 ml/min) with standard dialysers, the clearance of small molecules could be negatively affected [17]. This effect was attributed to a channelling phenomenon that was creating a preferential flow of dialysate in the region external to the bundle with consequent stagnation in the internal region of the haemodialyser. The first attempt to reduce this phenomenon was the application of an 'overflow' ring internal to the case, to force the dialysate flow into the internal regions of the bundle. Other types of distributors were designed for this purpose, achieving an improved performance of the dialyser at higher dialysate flow rates. More recently, studies on flow distribution have pointed out the importance of the bundle design *per se* [18]. First of all, the density of the fibres inside the case affects the resistance to dialysate flow and may contribute to a variable distribution of dialysate flow within the fibres. Furthermore, the phenomenon of 'packing' of the fibres was responsible for an inhomogeneous distribution of the flow and possible stagnation in various segments of the bundle.

The final effect of stagnation may be the reduction of the gradients for diffusion. However, another condition in which the gradient for diffusion is reduced is when high convective rates are utilized in haemodiafiltration. Under such circumstances, in fact, ultrafiltrate is transported on the other side of the membrane with a solute concentration similar to that of plasma water. This will result in similar solute concentrations on both sides of the membrane, and diffusion ceases. The phenomenon is aggravated further if fresh dialysis solution is not flowing homogeneously on the dialysate side external to the fibres washing away the ultrafiltrate. In this condition, stagnation will occur and performance of the haemodialyser will be negatively affected.

To prevent this phenomenon, two major techniques have been applied [18]. The first consists of the placement of space yarns between the fibres to create a better distribution path of the dialysate solution. The second is the creation of the so-called 'Moiré structure' which consists of a waived shape of the hollow fibres that prevents the packing of the fibres and maintains the dialysate path open in the entire cross-sectional area of the bundle. Not only is a homogeneous distribution of the flow obtained with these approaches, but a significant increase in solute clearances can also be achieved.

In conclusion, the membrane structure and material certainly affect the performance of the haemodialysis process. When high convective rates are prescribed, high-flux synthetic membranes must be utilized. Their performances are strongly affected by several factors other than the original material, such as geometry of the haemodialyser and hollow fibre design. Thanks to the improved design and membrane characteristics, newer treatments such as on-line haemofiltration and haemodiafiltration can be performed easily. Higher convection rates will permit us to understand the effective benefit of convection over diffusion, without facing the limitations imposed in the past by the inadequate available technology.

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