Advance in Membrane Technology

Claudio Ronco, MD

Speaker 1:	00:00	And I will introduce the first speaker, which is well known from everyone in the room here. Professor Claudio Ronco from the St. Bortolo Hospital in Vicenza, is going to speak about advance in membrane technology and we will leave all the questions at the end.
Speaker 2:	00:48	ladies and gentlemen, I have been asked to cover the aspects that are related to technology, which is a pretty boring topic, but you can find everything in this book that we have recently published. In fact, the creation of this book has been a lot of discussion, has been sometime depression. In some cases Dr Kellogg wanted to kill me. But then at the end we organized everything to have him very happy and very relaxed. Nothing that cannot be cured with a nice Amarone . So let me tell you this is a totally different speech from what you're probably used because I'm going to tell you what is the problem, the solutes and how we have technology to remove them. You know, in uremia you have small molecules. In inflammation, we start to have cytokines, and in sepsis we have even in the toxic in LPS and this is a profile of a retention molecule in a patient assessed by proteomics that shows clearly somethings.
Speaker 3:	02:08	First of all we need to take care of urea kinetics small molecules. Second, there is a role for middle molecular weight toxins. Third large molecules are also important and here you see there is a wide spectrum of molecules that need to be removed. In sepsis, we're specifically interested in the inflammatory markers. Now these inflammatory markers are in a spectrum molecular weight that does not allow us to use only one treatment to remove them. So we need different processes. One is separation by barrier, typical is dialysis, right? The other is by a solid agent which is using adsorption. So I'm going to talk about the diffusion, convection and adsorption in combination. And first of all the fusion as you may recall, is a kind of a mechanism when you can remove a small molecule due in response to a concentration gradient, but also the thickness of the membrane is important.
Speaker 3:	03:19	But the concentration gradient is also respondent to a diffusion coefficient of small solids. As you can see here, free diffusion coefficient tend to decrease with the increase of molecular weight of the solute. Now you expect given by the diffusion coefficient a certain clearance, but sometimes you don't get

that clearance because of electrical charges, because of protein binding because of other things or you may have higher clearance because of high ultrafiltration rate and a specific statical or configuration. Convection is a different story. With convection you use ultrafiltration to bring with it solutes across the membrane and the ratio between the concentration in the ultrafiltered and the plasma gives you the sieving coefficient. Ultrafiltration is given in response to a transmembrane impression, which is basically hydraulic and oncotic And as you can see here, the relationship between ultrafiltration and transmembrane impression gives you the permeability coefficient of the membrane. So basically when we use dialysis we are using diffusion base techniques, when we use hemofiltration, we're using convection based technique, but there is another issue which is important, which is the type of the solute. Here you see two different solutes which have a very different molecular weight, but as you can see they look like very similar. Why? Because what is important is the statistical configuration and there is a kind of the importance of the molecular radius rather than the molecular weight. The other thing is interaction with the solvent water has different electrical charges and as you can see the water molecules interact to create a special network molecules. Now let's take for example phosphate. Phosphate can be monophasic biphasic, triphasic and having these different forms of phosphate interact in a different way with a water molecules. So for example, the triphasic phosphate as an hydration shell that makes this molecule very big and that's why it's so complicated to remove it.

Speaker 3: 05:56 Now membranes can be classified by composition and structure or by performance characteristic like low fluks high fluks or by typical surface modification. Initially we had the cellulosic membrane, very, very thin membrane hydrophilic but with very poor permeability for middle to high molecular weight solutes. Then we use the hemofiltration membranes with like polysulfones with typical characteristic of being hydrophobic. And finally today we have what we call a thin and highly permeable membrane. In fact, if you consider a thin low flux membrane, you see thin low flux membrane is good for the fusion but doesn't get this bigger solutes through the thick high flux membrane, however, may allow you to transport by convection but it is too thick to work in the fusion. So that's why you need the combination of these characteristics.

Speaker 3: 07:11 And today we have new spinning technologies that allow us to result into a better structure of membranes. For example, if you look at the structure of pores in the past, these pores were

extremely.heterogeneous while in the nanocontrolled membranes. Now they have a very nice characterized structure. What is important is the surface of the membrane at the blood membrane interface and the density of the polymer at that level characterize the permeability of the different membranes. Not only that, it characterize the surface which is a roughness and hydrophilic hydrophobic micro domains. In this case for example, you see some hydrophilic micro domains that are indicated. Why is it important to have some relationship with water? Because if you wet the membrane, you will interact with the membrane and the solvent and look at the slide. If you have a continuous fluid phase, then you can diffuse through the membrane.

Speaker 3: 08:20

But if you have a discontinuous fluid phase, typical of hydrophobic membrane, then you cannot diffuse. Another aspects which is important for membrane is the combination of pore density and pore size, pore density affects the membrane permeability coefficient and the ultrafltration coefficient. While the pore size distribution characterize the sieving coefficient. So today we have a different type of sieving curves for different membranes, meet flux , high flux, and even for high cut-off membrane. Let me show how we do this. First of all, if you want to increase pore density, you will have a better membrane for diffusion. And in fact at the given blood flow, you see two different membranes the one on the right has much more pores and therefore works much better in diffusion But if you want to remove larger solids, you have to move the spectrum of pores on the right side.

Speaker 3: 09:24

And this is what happened with high flux trying to control however the distribution of pores. Can this be controlled? Well, when you try to do an high cut-off membrane, you cannot really stop at the real cut-off of the membrane. So you end up well beyond. The distribution is such that you lose allbumin and that's a problem. And in fact, in recent hight cut -off membrances has been clearly demonstrated that you can lose some albumin. Again, these curves makes the characterization of different memories and, we can ask our selves what is the membrane that we need? If we want to, for example, remove mediators of inflammation, well maybe we need the smart membrane. Smart membrane is a membrane in which you can control very well the dimension of the pores. But you can have larger pores as large as possible. And this is what we call membranes with the high retention onset. You see the difference between the two curves? The red line shows a membrane with a very high retention onset. It has the same cut off point where the sieving coefficient is 0.1, but it has a very

different retention onset point on top of it. So what I demonstrated to you is that different sieving coefficients, even though you may end up with the same cut off, may be very different for different membranes with different distribution. That's why when you evaluate a membrane, you have to evaluate a membrane from a multidimensional point of view, not just the cut off nor just the ultrafiltration flux. How are these members mounted in dialyzers where all the fibers, flat sheet membranes. The important thing is that we, we should consider that these dialyzers require a special characteristic and operation. For example, if you have a clean membrane inside the dialyzer, then sieving coefficient, will be exactly what has been analyzed at the beginning and clearance will be ultrafiltration time-saving coefficient, but that's where pre-dilution or post dilution can make a difference in cleaning up the membrane. And when you use studies, for example, to evaluate the flow distribution inside dialyzer, you have to consider that if the blood is well distributed, the blood flow velocity is important because it keeps the viscosity of blood very low. But if the blood is uneven distributed, then in that case you may have stagnation and you end up with decrease in ultrafiltration rate over time and decrease in sieving coefficient for solutes over time.

Speaker 3: 12:38 Now membranes can be an active component because it can adsorb different things and here we come with the possibility in the future to design smart membranes that can filter and adsorb in combination. Part of this can be done through surface modification and some of these modification can be done by coating and by coating. You can improve by a compatibility permeability and have a non fouling effect.

Speaker 3: 13:10 What I want to show you is that we recently have membranes in which adsorption has become an important issue, but you can also coat membrane like in this case the N 69 EST with heparin or adsorbed on the surface and therefore changing completely the shape of the behavior of the membrane. The moving to another dimension which is bio property. Well talking about bio properties, we recently have explored the possibility of studying the use of membrane heparin coated with vitamin E in a kind of antioxidant therapy. The strategy is that by coating the membrane with vitamin E, not only you can adsorb oxident stress species, but you can also adsorb them in the point where they are generated. So you can really do what we call antioxidants CRRT. And we have proven actually this in a treatment where you can see that the level of, different, oxidant species, are much, much lower at 24 hours compared to the standard filter.

Speaker 3:	14:31	The second part is relevant to adsorption. Sorbents have been used in hemoperfusion for years, but basically there is a rationale for the use which is the limited efficiency of membrane in one side. The other is that sorbents sometimes must be biocompatible and adequately designed. How do they work? They work for three different adsorption mechanism. Vander Waal forces, ionic bonds and hydrophobic bonds, but in order to adsorb, you need to have a safe and effective sorbent material, an adequately designed cartridge and optimal utilization of the available surface. This is a serious of requirements for a suitable adsorbent material that at the end comes also to the point to the possibility to regenerate or to have a very low cost to making sure that you can afford to use it. We have natural sorbents and synthetic sorbents and we have different examples like polyimide fibers, functionalize with diethylaminoethyl compounds, polycistronic fibers coated with and functionalize with polymyxin B or copolymeric particles.
Speaker 3:	15:51	These particles are very interesting because they are the base for the new sorbent cartridges and they can actually become like a three dimensional polymeric network and they may come in fibers, granules, spheres, flakes powder. The most interesting aspect about this, and I don't want to go through all the calculations, is that one gram of substance can have something like 1000 square meters of surface for adsorption, which is just fantastic. But you cannot predict, you have to do these curves that are called isotherms that allow you to measure exactly how they work. Also in the past chills, fever, aluminum load
Speaker 3:	16:44	were all limitation for the application sorbent because of biocompatibility.
Speaker 5:	16:49	We for example, had uncoated charcoal. You cannot use uncoated charcoal directly on blood because its not biocompatible. And you can immediately see from the structure of this, you can use different particles. Like hydrophobic resin that are however, coated with a specific, biocompatible coating that however make the resin
New Speaker:	17:24	biocompatible. And you can see here how clean the different surface of these beads are. They can be actually a little dirty after 24 hour use, but the problem is that this coating may limit the access of the molecule to the sorbent. So you are again back to the problem of membranes. We have started recently biocompatibility of different cartridges. These produced in Japan with this machine and we have found that they are very biocompatible. Again, biocompatibility is insured, but how

efficient can they be compared to the huge surface area that they have.

Speaker 3: 18:04 The problem is that the solute only diffuses in the very, very superficial part of the bead leaving the rest of the sorbent unused. So when we study a sorbent, we have to study the external phase. Then we start to study the interface and then we have to study the surface diffusion along the pore side. This is the structure of the bead that is well characterized by the presence of different layers of adsorption and the presence of ions and counter ions that provide also the banding of different electrolytes. The external phase is normally used by the tortuosity of the path that the bladder has to follow and we started this with contrast to analyze the design of the structure. Here you see a well-designed cartridges which is practically completely occupied by blood and also has a very stable pressure drop over time.

Speaker 3: 19:11 Not only that no change in platelet, no change in Leukocyte and very clean, cartilage at the end. It has to be strong. The particles must be strong, otherwise they may be released into the circulation. To prevent this, we have screens and retention screens that allow this to do this. Now how the distribution is govern is a complicated thing, but basically what you want to know is that you want the concentration of the solute to be practically becomes zero when the blood leaves the cartridge so that you are utilizing the maximum of the cartridge. If you have a condition where you have flow through practically, you are not utilizing at the best at the overall amount of the sorbent that you have. How do you use sorbent? Well directly in contact with blood in this case before a dialyzer or in contact with plasma after a plasma filtration in contact with the ultrafiltrate and this is in contact with the plasma.

Speaker 3: 20:22 Now I'd like to conclude saying that we have sepsis as an infection and immuno altered immuno response and then organ damage, right. If this is the case, we could try to remove endotoxin at the beginning, remove proinflammatory mediators in between and support organ when this occurs in the later stage of sepsis and high endotoxin correlates with mortality. So removing endotoxin at the beginning is a kind of a good strategy and this has been done in some studies that are still going on with the polymyxin B sorbent and the adsorption comes through ionic bonds but also hydrophobic binding forces. The other is cytokine removal by director hemoperfusion, like the cytosorb technique and so on. That is indirect contact with blood or coupled plasma filtration adsorption where the sorbent is in contact with the plasma. The results we can

achieve are very interesting. This is a case for example that we treated, with cytosorb to solve and we had an improvement had the capacity to present the antigen, specifically the HLA, DR expression on monocytes will significantly increased showing that we are probably reconstructing the equilibrium in the immuno system that was lost, but we can also use a highly adsorption membrane not only for filtration but also for adsorbing different substances.

Speaker 3: 22:05 And in fact that we have proposed that this kind of known selecting adsorption may help to cut the peaks of the pro and anti inflammatory mediators or in a mess that you may have in a cytokine storm in a septic patient. So if action, altered immune response, organ damage, endotoxin removal, cytokine removal, organ failure support, I think that this sequential approach may be logical and I gave you all the details unfortunately running like crazy on how we design membranes for this purpose, how we design the sorbent for this purpose and how much attention is placed today in bio and hemo compatibility. If you want to hear more, come to Vicenza in Italy next year. Actually this year in May and we will be happy to receive you there. Thank you very much.