# From haemodialysis to haemodiafiltration – a step closer to a physiological kidney

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## INTRODUCTION

Haemodialysis was made possible by the combined efforts of its ingenious pioneers and one of them was Dr Wilem Kolff. He started haemodialysis in Netherlands during the difficult times in the Second World War under German occupation. His made his dialysis machines from metal cans and even scrap metal from German planes shot down in air conflict. His first 15 kidney failure patients lived only a few days but one patient (a traitor of his own country) recovered from acute renal failure and lived for 7 more years. There was great development after the Second World War and the treatment could be extended to chronic renal failure patients.

Modern haemodialysis is a very remarkable form of medical treatment in which the function of a major organ can be taken over by artificial means over a long period of time. Many chronic renal failure patients with no residual renal function can be maintained on chronic haemodialysis for decades while waiting for a cadaveric kidney transplant. Over the past decades, the cost of haemodialysis increased very little compared with general inflation, thus making it more affordable.

For the past years, the author had been advocating satellite haemodialysis which is both cost effective and can provide support for those patients who failed peritoneal dialysis. (1). The view appeared to have resonance because in satellite centres are now springing up. Just in 2013-2014 alone, there were 4 satellite centres coming into service. This confirms that haemodialysis is a safe and cost-effective mode of renal replacement therapy.

## LIMITATION OF HAEMODIALYSIS

Despite its success, there are several drawbacks in haemodialysis.

1. The patients were usually anaemic due to the decreased renal production of erythropoietin. There were bone and mineral metabolic disorders due to phosphate retention and the absence of active vitamin D. Haemodialysis can only (partially) replace the excretory function of the native kidneys, it could not replace their endocrine functions. This problem was alleviated by the availability of active form of vitamin D (calcitriol) and erythropoiesis stimulating agents like human recombinant erythropoietins.

2. Acute complications like hypotension, nausea and vomiting were during haemodialysis were common in early dialysis. These are now less common with modern dialysis machines which can control fluid removal directly and using bicarbonate as a base buffer (the 'bicarbonate dialysis'). Still, haemodialysis still impose some stress on the cardiovascular system and this may prove to be too much for frail patients.

3. For patient on long-term dialysis, complications like carpal tunnel syndrome. The patients will develop painful joints and muscle weakness. The cause is due to the development of amyloidosis as a result of the accumulation of beta 2 microglobulin in patients on long term haemodialysis. It was called dialysis related amyloidosis (DRA). This was

because while the urea and creatinine in the blood are relatively small molecules, other toxins like beta2 macroglobulin are much larger molecules (the 'middle molecules') and could not be readily removed by diffusion in the dialysis process. It is believed adequate removal of the middle molecules is the key to the prevention of chronic dialysis complications.

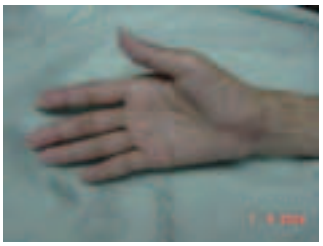

Figure 1: Carpal tunnel syndrome due to DRA, note the operation scar for the nerve release operation

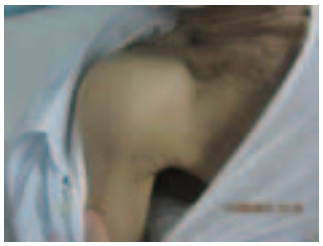

Figure 2: Shoulder swelling due to dialysis related amyloidosis, note that associated muscle wasting

In natural kidneys, substances were removal by filtration under pressure, a process known as ultrafiltration. Blood enter the glomeruli by the afferent arteriole and leave by the efferent arteriole. Since the efferent (exit) arterioles are smaller in calibre compared with the afferent arterioles, there was a filtration pressure forcing the plasma water move down the renal tubules as glomerular filtrate. Substances like water, sodium, glucose, potassium, bicarbonate, phosphate, urea and those 'middle molecules' etc are carried along with the glomerular filtrate. The normal flow rate of the plasma water across the glomeruli is 125 ml/minute or 180 litres per day. Substances like glucose were also reabsorbed but the toxins were not reabsorbed and were passed out in the urine. Since only 2 litres of urine was produced every day, it can be inferred that 99% of the fluid is reabsorbed by the renal tubules. It is noteworthy that toxins of all molecule sizes are filtered at the same rate, unlike the dialysis in which the small molecules are removed much quicker than the middle molecules.

## HAEMOFILTRATION

Haemodialysis removes toxins by diffusion. The blood and dialysate are separated by a semi-permeable membrane and the toxin diffuse from the blood to the dialysate and drained away. It is an efficient method of toxin removal but only for small molecules. Since the removal of the middle molecules is deemed important in the prevention of chronic dialysis complications, efforts were made to increase its removal. One way was to increase the dialysis time or the dialysis frequency, but this would pose significant financial and logistic problems.

Another way was to improve the rate of removal of the middle molecules. One way is to increase the surface area of the semi-permeable membrane to allow for more molecular channels. The large surface area, combined with the longer dialysis time, constitutes the 'square meter-hour' concept in the early dialysis days, ie you can increase the surface area or the dialysis time. The problem is that early dialysis membrane was made of cellulose derived membrane and the pores were relatively small.

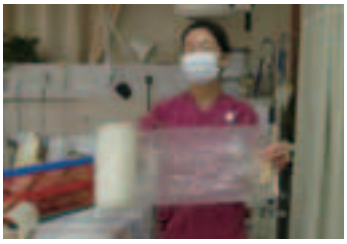

Figure 3: Early dialyser membrane with small pores

The diffusion movement of middle molecules was restricted. With the improvement in polymer (plastic) technology, synthetic membranes were available in which membrane pores could be made bigger, allowing the middle molecule to pass through. Instead of flat membranes, they were made in the form of hollow capillary fibres which can stand a high pressure due to the cylindrical configuration.

Figure 4: An early hollow fibres dialyser with synthetic membrane

Even with the availability of a 'large pore' membrane, it was found that the rate of removal was not much increased. This is because according to the law of diffusion, the rate of diffusion of a substance is inversely proportional to the square root of its molecular weight. Hence a large molecule would diffuse more slowly than smaller molecules.



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For this reason, efforts were made to mimic the natural kidney by modification of the conventional blood and dialysate circuit. A negative pressure was applied on the dialysate side to draw plasma water from the blood compartment to the dialysate compartment, taking the toxins with it. This is known as haemofiltration. Toxins in the plasma water are removed at the same rate independent of their molecular weight by the 'solvent drag'.

Nephrologists had long experience with ultra-filtration when they applied a negative pressure to a standard dialyser to remove water from the blood of a fluid overloaded patient, a process known as 'dry dialysis'. However, it was not until the availability of haemofilters with highly porous membrane that blood can be filtered at a sufficient rate. Haemofiltration was successfully used to treat acute renal failure patients with unstable conditions because the stress on the body was less. They need to continue for a few days until the native kidneys recovered or the conditions improved so that convention dialysis can be performed. Such process is called Continuous Renal Replacement therapy CRRT and it was described elsewhere (2).

Riding on the success of the CRRT, there were attempts to apply haemofiltration to stable patients. The aim is for better middle molecule removal and better cardiovascular stability. It was postulated that if 20 litres of plasma water were filtered three times a week, sufficient middle molecules could be removed to prevent the development of dialysis related amyloidosis and other complications.

It is obviously not possible for a patient to lose 20 litres of water and hence fluid replacement is necessary. The replacement fluid would need to contain electrolytes and buffer bases. It would need to be sterile. The fluid came in 4.5 litre bags. With the introduction of microprocessors, one can instruct the machine how much fluid to be removed and replaced. For a patient with 4 litres of excess fluid, one can remove 20 litres of fluid (together with the toxins, including the middle molecules) and replace with 16 litres of replacement fluid.

The author performed one of the earliest haemofiltration procedures in Hong Kong using a Gambro haemofiltration machine. The blood from the patient was taken to a haemofilter, a negative pressure was used to draw the water from the blood compartment and was drained to container connected to a weighing scale. The clinician had to input the total ultrafiltrate volume and the volume to be removed. The haemofiltration machine would then weight the ultrafiltrate removed and control the replacement pump to return the replacement fluid. The machine would stop after the prescribed ultrafiltration volume has reached.

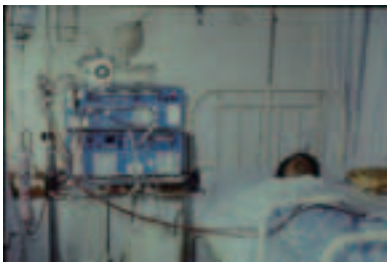

Figure 5 and 6: Hemofiltration in progress

The system worked. The main problem was the high cost of the 'haemofilter' and the replacement fluid. In haemodialysis treatment, one dialysis would need 150 litres of dialysate but it was prepared by diluting dialysate concentrated with 'treated water', only about 5 litres of concentrate is needed for each dialysis and it was not expensive. For a typical haemofiltration, 20 litres of replacement fluid was needed and it was expensive. For a large dialysis centre with multiple patients performing haemofiltration, storage of the replacement fluid would pose a storage space problem.

Compared with haemodialysis, it was reported that patients tolerate the treatment with less symptoms like hypotension or muscle cramps during the treatment. Due to the relatively high capital and recurrent cost, it was not widely practiced and hence the there was limited data on long term effect with this mode of treatment.

## ON-LINE HAEMOFILTRATION

Since the chief obstacle for the wide spread use of haemofiltration is the need for large volume of replacement fluid, attempts were made to produce the fluid from a suitable concentrate (the 'concentrate'). That idea was borrowed from haemodialysis methodology. In haemodialysis, the haemodialysis machine would dilute one part of dialysate concentrate with 34 part of water

to make the dialysate. Similarly, the haemofiltration machine would dilute the concentrate with water to produce the replacement fluid, thus saving the storage space, the cost and nursing time. However, such water needs to be of very high sterility. In haemodialysis, the blood and dialysate are separated by the dialysis membrane. Even if there are bacterial contamination in the dialysate, the bacteria cannot go into the blood because of they are too large to pass through the dialyser membrane. However, in haemofiltration, the replacement fluid goes directly into the patient's circulation and any bacteria or endotoxin would go the blood stream directly.

Figure 7: The reverse osmosis module and the pump

Modern haemodialysis centres have a 'water treatment plant' which can produce highly purified water. Inside the plant, the raw water (tap water) would need to undergo filtration, water softening, activated charcoal filtration (to remove chlorines or chloramines in the water) and then to a 'reverse osmosis' machine.

The later process involved pumping the water under high pressure against a synthetic membrane. The bacteria, pyrogens, trace metals etc are effectively rejected and only high quality water pass through. The water was then disturbed to the haemodialysis or haemofiltration machines by specially designed stainless steel pipes which can be regularly sterilized with high temperature, thus ensuring sterility while avoiding the dangers of chemical sterilization.

Figure 8: The stainless steel piping to carry the purified water to dialysis machines

The product water has to undergo periodic water testing to ensure of the sterility. The standard is much higher than those for haemodialysis. In addition to testing bacterial counts, there was test for the endotoxin as well because endotoxin can by itself cause fever and inflammation and can even diffuse across the dialysis membrane. The test usually employed is the limulus amebocyte lysate test. Limulus amebocyte is the blood cells (amebocyte) of the horseshoe crab (limulus). It is known that the blood of a horseshoe crab would gel when it is in contact with Gram negative bacteria. The limulus blood cells were extracted, put in pure water for them to burst to get a 'lysate' and the resulting substance will gel in contact with endotoxin. This formed a reliable way of detecting endotoxin and test kits are now commercially available for clinical use.

Figure 9: The limulus

Figure 10: The ultra-filter at the back of the machine

As a further safe guard, the treated water was passed through very fine filters ('ultrafilter') situated at the back of the machine and the product water was very pure (the 'ultrapure water').

Inside the machine, the product water was diluted with bicarbonate powder (to provide the buffer base) and a suitable concentrate (to provide the electrolytes). The dilution was monitored continuously by measuring the conductivity caused by the electrolytes.

With the online HF, we had an 'artificial kidney' which can mimic the natural kidneys in the way that sit remove waste by filtration instead of by diffusion.

## HAEMODIAFILTRATION (HDF)

One drawback of the HF is that although the middle molecule removal is enhanced, the amount of small molecules removed is less than conventional dialysis because only 20 litres of plasma water was filtered. On the other hand, haemodialysis is an efficient way for removing small molecules. It is possible to include a dialysate circuit inside the haemofilter so that there are combined dialysis and haemofiltration to remove

both the small and middle molecules at the same time. This is called haemodiafiltration (haemodialysis + haemofiltration) or HDF.

Indeed of buying dedicated HF machines, modern haemodialysis machines can have the hydraulic path programmed to perform HDF. They can monitor the fluid removal very accurately and they had a fluid replacement pump in addition to the usual blood pump. The replacement fluid produced by the online process can be used both as a dialysate and replacement solution. The path for the dialysate/replacement solution was controlled by a microprocessor with the instruction programmed by the user.

Since HDF came of age, manufacturers in the haemodialysis industry started to offer 'high flux dialysers'. They are dialysers made of synthetic membranes with large pores for easier fluid removal. It was found that they can be used in HDF instead of the expensive haemofilters. HDF was initially much more expensive because of the hardware and the haemofilters. With the coming of more modern dialysis machines and the availability of the high flux dialysers to replace haemofilters, the cost is much reduced and now the price differential is not large.

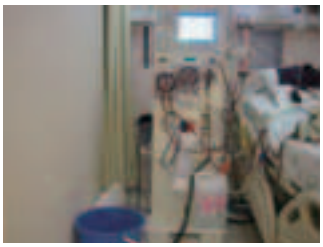

Figure 11 and Figure 12: The HDF in progress. Note the expensive haemofilter was used before the availability of high flux dialysers

The membrane used in the haemofilter or the high flux dialyser has a porous structure like a sponge. As the plasma water pass through the membrane during HDF, some of the endotoxins and interleukins in the filtrate can be adsorbed by the membrane. There are some reports of its benefits in sepsis patients but further studies are needed.

## HIGH FLUX DIALYSIS WITH ULTRAPURE DIALYSATE

Though the cost of HDF is coming down, it is still more expensive than convention dialysis and not all centres have the modern dialysis machines which can perform HDF. Nephrologists were looking into ways to achieve higher middle molecule removing without the complexity of the HDF and one method is to use 'high flux' dialysers with conventional haemodialysis machines.

'High flux dialysers' had been in the market for over ten years. Its membrane had large pores for better removal of water and toxins. One of the main drawback was that since the membrane was so 'porous', a large amount of water passed into the dialysate when the blood entered the dialyser, and to compensate for the excessive water lost, some water had to move back into the dialyser at the exit end of the dialyser. This was known as 'back-filtration' and the whole process was controlled by the dialysis machine. Since water moves from the dialysate back to the blood in the back-filtration, some of the endotoxins in the dialysate (due to water impurity) might enter the blood stream and the back-filtration was considered a disadvantage of the high flux dialysers.

Analysis of the mechanics showed that in a flux dialysis, about 7 litres of water moved out from the blood to the dialysate through ultrafiltration, and this was compensated by the back-filtration. With the wide availability of the ultrapure water and the endotoxin testing, back-filtration is no longer a danger. Thus in a high flux dialysis, it was possible to obtain a degree of haemofiltration (about 7 litres instead of 20 litres) together with haemodialysis. Thus it is possible for perform a 'moderate' HDF on a conventional haemodialysis machine using a high flux dialyser at the cost of a conventional haemodialysis. However, the degree of ultrafiltration cannot be reliably predicted.

Figure 13: High flux dialysis with moderate HDF effect

## SUMMARY

In the past three decades, great improvement has been made in renal replacement therapy. The availability of recombinant erythropoietin and active vitamin D derivatives helped to improve the symptoms and complications of renal failure.

For the past 50 years, scientists had been looking for an artificial kidney which can mimic the natural kidneys. The HDF is the closest approximation but it is expensive. Haemodialysis using high flux dialyser with ultrapure dialysate is cheaper and can achieve reasonable middle molecules clearance.

HDF is now available at an affordable price. We now have a system in which the toxin molecules were removed by filtration, very much like our native kidneys. However, haemodialysis or HDF can only replace natural kidney function intermittently (say three times a week, each time 5 hours) and at best partially. It is still very much inferior to our native kidneys. Our kidneys works 24 hours a day with removal of toxins at all molecular sizes and with endocrine function as well. They set the golden standard which human inventions can hardly match.

## DECLARATION OF INTEREST

Dr. HO Chung Ping is the director of the Integrated Dialysis Facilities (HK) Ltd and Ms. AU Yim Fong is the Centre Manager. No financial funding was received.

## FIGURES

Figure 1 and 2: Dialysis related amyloidosis
Figure 3: Early dialyser membrane with small pores
Figure 4: Hollow fibre dialyser with an early synthetic membrane
Figure 5: Machine haemofiltration. Note that there was no dialysate to the haemofilter.
Figure 6: Machine haemofiltration. Note that the ultrafiltrate was collected in the rectangular container, the replacement fluid was in 4.5 litre bags. Both were hanging below the haemofiltration machine and connected to weighing device.
Figure 7: The reverse osmosis module and the pump
Figure 8: The stainless steel piping to carry the purified water to dialysis machines
Figure 9: The limulus
Figure 10: The ultra-filter at the back of the machine
Figure 11 and Figure 12: The HDF in progress. Note the expensive haemofilter was used before the availability of high flux dialysers.
Figure 13: High flux dialysis with moderate HDF effect

## References

(1) Ho CP, Au YF, Haemodialysis as a practical mode of therapy in Hong Kong, *HKMA CME Bulletin*, February 2011
(2) Ho CP, Wong S L – Continuous Renal Replacement Therapy from Ground Zero, *HKMA CME Bulletin*, July 2015

## Q&A Self-assessment Questions:

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Answer these on page [•] or make an online submission at: www.hkmacme.org
Please indicate whether the following statements are true or false.

1. The patients develop painful joints and muscle weakness is due to the development of amyloidosis as a result of the accumulation of beta 2 microglobulin after years of haemodialysis.
2. Beta 2 macroglobulin is a middle molecules and could not be readily removed by diffusion in the dialysis process.
3. In natural kidneys, the flow rate of the plasma water across the glomeruli is 20 litres per day.
4. In haemofiltration, urea toxins in the plasma water are removed at the different rate depends of their molecular weight by the 'solvent drag' of negative pressure.
5. Haemofiltration was successfully used to treat acute renal failure patients with unstable conditions.
6. The replacement fluid goes directly into the patient's circulation needs to be of very high sterility in haemofiltration.
7. The replacement fluid produced by the online process cannot be used both as a dialysate.
8. Haemodialysis using high flux dialyser with ultrapure dialysate is cheaper and can achieve moderate middle molecules clearance.
9. The high flux dialyser has a porous structure like a sponge to absorb some of the endotoxins and interleukins in the filtrate in sepsis patients.
10. The product water for haemodiafiltration has to undergo higher standard of water testing including bacterial counts and test for endotoxin.