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The Machine and the Therapy Concept

R.N. Greenwood

Lister Renal Unit, Stevenage, UK

Abstract

Maintenance haemodialysis became established in mainstream clinical practice in the 1960s. For pragmatic reasons, diffusive dialysis was the technique which underpinned its success. Over the next 15 years it was shown that short- and medium-term survival depended only on a critical level of urea clearance being achieved. Uncomplicated technology with negligible capacity for middle molecule removal could deliver this and the case for developing more sophisticated machines able to broaden the spectrum of solute removal was unconvincing. Dialysis-related amyloidosis which was recognised in the mid-1980s as a devastating complication in long survivors disturbed this complacency. The journey to develop machines which could deliver broad-spectrum solute removal while exposing patients only to ultrapure fluids and biocompatible materials is described elsewhere in this text. The Lister Renal Unit was established in 1988. A fruitful collaboration between the multidisciplinary clinical team and engineering colleagues in the R&D Department of Fresenius contributed to a steady and in-depth understanding of the effect of superimposing convection on diffusive dialysis. From the outset only high-flux dialysis using ultrapure fluids was employed. Haemodiafiltration (HDF) was introduced in 1993. This paper summarises our observations regarding the relative contributions of natural renal function and convective blood purification to long-term outcomes. We have recently reported a 19-year experience which has allowed us to more clearly define the rationale for HDF in modern clinical practice. HDF is an engineering triumph which is likely to universally supersede diffusive dialysis. The challenge for clinicians moving forward is to learn in which treatment schedules this technology can best be deployed to improve the health prospects of patients with kidney failure.

Diffusive Dialysis in the 1960s and 1970s

In developing apparatus for maintenance blood purification, reproducing the function of the human kidney, which is a dominantly convective process, was

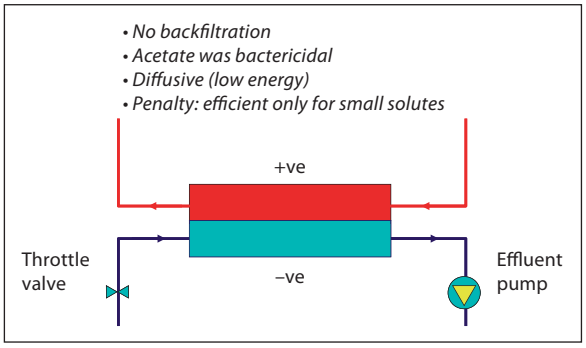

Fig. 1. Dialysis machine design in the 1970s.

probably seriously considered. Glomerular filtration rate (GFR) is approximately 100 ml/min which totals 150 litres/day of which approximately 147 litres are reabsorbed by active metabolic tubular function – a high-energy process requiring a renal blood flow rate of approximately 1.2 litres/min, a quarter of cardiac output, being taken by the kidneys. To mimic such a process in the 1960s would have been thwarted by several factors. First, there was no suitable membrane with the appropriate hydraulic permeability, the cost of replacing filtered fluid with sterile replacement fluid would have been prohibitively expensive and, much more daunting, the huge blood flow necessary to achieve this level of filtration in intermittent therapy could not be accessed from the circulation. The inevitable outcome was a diffusive system. It was fortuitous that a relatively inexpensive cellulosic membrane was available with good diffusive properties and a convenient level of hydraulic permeability which allowed a manageable amount of ultrafiltration to take place during a 6–10 h session while employing only modest transmembrane pressures. The basic laws of physics dictate that such low energy expenditure in a diffusive system would come with a cost – the inability to move large molecules from blood no matter how porous the membrane. Diffusive dialysis could only be a weak imitation of the depurative quality of natural renal function.

It is worth considering the features which enabled the simple design of early dialysis machines to be safe in clinical practice (fig. 1). Approximately 1 m^2 of cellulosic membrane was used in a flat-plate configuration. Blood was pushed in a thin film between two membrane sheets and dialysis fluid was pulled across the other side of these 'flat plates' by an effluent pump in countercurrent flow. Across the whole 1 m^2 membrane area there was positive pressure between blood and dialysate ensuring no prospect of dialysate entering the bloodstream. Acetate, which was used as an easily metabolised substitute for bicarbonate, was bactericidal. These features combined to ensure that the risks from infection from impure dialysis fluids were largely restricted to the processes of

reassembling the Kiil dialyzer and the re-use procedures which were in common usage at the time.

Coming across a kidney machine first in 1978, the author observed a surprisingly unsophisticated system which looked messy and poorly engineered. From the medical point of view, it was perplexing how such a system of diffusion could reverse the symptoms of uraemia and return patients to good health (except for profound anaemia) while only small molecules were being removed from uraemic plasma.

However, clinical experience did not fit this dubious theoretical construct. The first randomised controlled trial in dialysis – the National Cooperative Dialysis Study (NCDS, 1980) – showed that a critical level of urea clearance was all that was needed for complication-free survival. The effect was noticeable by 3 months. Although the pioneering work which had been taking place in the USA [1] and in Germany at the University Hospital in Giessen [2] a few years earlier was inspiring, the overwhelming opinion of the nephrology community, was that the problems of dialysis were mostly solved and there was no need to pursue more complex technical solutions, particularly any involving expensive replacement solutions. In any case, continuous ambulatory peritoneal dialysis (CAPD) appeard as an additional bridge to transplant rather than maintenance HD. Energies became more focused on how to accommodate an expanding dialysis population in cash-strapped healthcare systems rather than on the dialysis technique itself.

Design Changes

Attending the EDTA meeting in Prague in 1980 the author observed the introduction of volumetric control of dialysis fluid with some concern. By that time there had been very significant advances in the design of dialyzers now being produced in capillary form with exciting new membranes, in particular polysulfone and polyamide. While volumetric control for ultrafiltration was necessary when using membranes with high permeability, it was clear that some of the advantages of the traditional circuit (above) would be lost. The rigid movement of dialysis fluid would almost inevitably result in infusion of dialysate into blood, which looked risky in terms of endotoxin transfer. Again, clinical experience did not fit with this theoretical construct. It appeared that 'backfiltration' did not have any clinical sequelae in an era when microbiological standards for dialysis fluid were lax. With the benefit of hindsight, this could have been explained by the excellent absorptive barriers of these membranes to microbiological transfer.

In retrospect, rigid volumetric control of dialysis fluid provided an ideal platform for the manipulation of dialysis fluid flow – the engineering starting point for the modern haemodiafiltration (HDF) machine.

The Emerging Case for Added Convection – 'Diafiltration'

For clinicians working in the UK NHS in the early 1980s, the challenges centred around more resources to create dialysis spaces, the liberalisation of acceptance of patients onto dialysis, vascular access problems, the continuing poor results of transplantation and the perpetual battle against profound anaemia. Little attention seemed to be focussed on the dialysis technique itself. All this changed in 1985 with the recognition of dialysis-related amyloidosis. Patients had been complaining for some time about symptoms of carpal tunnel syndrome and 'frozen shoulders'. First referred to as dialysis arthropathy, it was re-named more specifically as dialysis-related amyloidosis after biopsies of synovial tissue revealed deposition of long chain proteins which seemed to be preferentially deposited in joints. A short time later the building block of this particular amyloid was identified as β_2-microglobulin (β2M) which was found on the surface of most nucleated cells in the body. With a molecular weight of 11,500 there was no prospect of significant removal by diffusive dialysis.

There was more to it than this. Shaldon with a small group of enthusiasts in Europe put forward the 'interleukin hypothesis', which suggested that intimate exposure of blood to bacterial endotoxin across 'incompatible' membranes made dialysis a pro-inflammatory process which prompted the release of cytokines from circulating monocytes. It was repetitive inflammation which encouraged the deposition of β2M in joints, aided by high circulated levels. Those involved in dialysis had a new challenge. Firstly, much more attention would have to be paid to the purity of dialysis fluid. Also more attention would have to be paid to the biocompatibility of dialysis membranes. Finally, there was a direct clinical reason rather than a theoretical one to pursue the convective removal of middle molecules.

Engineers in the dialysis industry had a good starting point. At their disposal was a proven system for volumetric control of dialysis fluid and new membranes such as polysulfone, which not only had excellent diffusive and convective properties, but were also effective barriers to transfer of microbiological contaminants from dialysis fluid into blood. However, the intelligent use of these materials to develop machines that could provide broad-spectrum solute removal within the strict confines of healthcare budgets was a huge challenge. What took place over the next few years is articulated elsewhere in this book.

Engineering and Clinic Collaboration

In 1988 a new kidney service was established with an estimated catchment population of about 1.1 million people centred in Stevenage, which is 35 miles north of London. While at Barts Hospital in London there had been some contact with the R&D team at Fresenius in Bad Homburg, but shortly before the opening

of the Lister Renal Unit (LRU) a meeting took place with Hans Polaschegg to discuss a possible cooperation between clinicians and engineers in the development of new ideas. Although the precedent had long been set for cooperation between clinicians and pharmaceutical companies, this was forward thinking from a technology company. From the outset, the LRU would have a commitment to biomedical engineering developments and the arrangement provided a valuable opportunity for R&D engineers led by Hans Polaschegg and assisted by Thomas Roy to have access to the clinical environment. At one point there were more engineers and computer people employed in the LRU than nurses. The former included Colin Aldridge and a young Paul Chamney. Matthias Kramer was a regular collaborator.

From the outset, high-flux membranes, chiefly polysulfone, were used in all patients. Experience with online HDF dated from about 1992. Much investment was made in bacteriological surveillance of dialysis water and substitution fluid. Rigorous test schedules were developed.

At that time there was acute awareness of the emergence of clinical standards for dialysis which came chiefly from the USA in response to the poor outcomes in HD. In order to protect patients from the risks associated with reducing dialysis times which was taking place in the USA and then across Europe, the LRU enthusiastically embraced urea kinetic modelling as a means to ensure that adequate doses of dialysis were delivered either by high-flux dialysis or HDF. Dr. James Tattersall was a founder member of the LRU. His pioneering work in kinetic modelling, which furthered the understanding of the impact of natural kidney function on health and survival of patients on CAPD and HD, was highly valued. In the mid-1990s my close colleague, Dr. Ken Farrington, assumed a leadership role in the clinical research programme. In the last few years, researchers at the LRU have reported a 19-year experience with high-flux dialysis and HDF. HDF has become the preferred modality for all patients, our ability to deliver this for all being constrained only by the finances available. HDF is favoured for patients who have lost natural kidney function and who tend to have a high muscle mass. The next few paragraphs summarise the main clinical findings over nearly two decades of observation.

Natural Residual Renal Function and HDF

The classical form of urea kinetic modelling as described by Frank Gotch and John Sargent recognises the contributions of both dialysis and residual renal function (RRF) to overall dialysis dose. One of our first observations was that the initiation of dialysis has no effect whatsoever on the decline in natural kidney function, be it in CAPD patients or in high-flux dialysis/HDF [3]. This was in contrast to many prior studies which had suggested that HD, unlike CAPD,

leads to rapid decline in RRF. We concluded that, just as RRF is an important determinant of the health and indeed the survival of patients on peritoneal dialysis, the same is also likely to apply to patients on HD.

A study comparing the use of high-flux polysulfone membranes with low-flux polysulfone and cellulosic membranes concluded that it was flux, not biocompatibility, which determined β2M levels. It became apparent in the mid-1990s that amyloidosis had virtually disappeard and no longer seemed to be an long-term outcome after 10 years on dialysis. It is likely that the accumulation of β2M itself was not the cause of amyloidosis, which vindicated somewhat Shaldon's views about the inflammatory nature of dialysis related to water quality. The disappearance of dialysis amyloid was probably driven chiefly by adherence to standards which had been set for the microbiological purity of dialysis fluids.

C-reactive protein (CRP) is a routine laboratory test which found a place into routine clinical practice in the mid-1990s as a very useful marker of systemic inflammation. We observed CRP levels in our dialysis patients over a number of years and although there were many 'spikes' recorded in many patients, the vast majority of these could be explained by discrete clinical events and did not seem to relate to the dialytic process itself. Essentially, patients on high-flux dialysis and HDF did not experience inflammation, at least as identified by routine temperature and CRP estimations. As has been pointed out by Thomas Roy, it was necessary to overcome some of the fears that had been perpetuated about the potential for inflammation using on-line technology. It is the author's view that this fear has now been firmly put to rest. This is a tribute to the innovation of sequential filtration and the refinement of pre-dialysis tests for filter integrity in ensuring purity of dialysis fluid and HDF replacement fluid.

The contribution of RRF to overall 'renal replacement' in dialysis patients is illustrated in figure 2. At the LRU, mean GFR at dialysis initiation is 8.7 ml/min as measured by creatinine clearance. On average, RRF continues to make a useful contribution for up to 5 years. At dialysis initiation, GFR equates to about 87 litres/week convection. A patient on HDF would experience about 60 litres/week of added convection over the basic diffusive process – a similar order of magnitude.

RRF is powerful. We have observed that higher intradialytic ultrafiltration rates are required in patients who have a residual urea clearance (KrU) <1 ml/min [4]. Whilst this might seem intuitively obvious, it is an important observation since DOPPS data shows us that a high ultrafiltration rate carries a significant risk. Patients with KrU >2 ml/min have superior phosphate control. This is important since high serum phosphate is also associated with increased mortality risk in HD patients.

Patients with KrU <2 ml/min have a higher erythropoietin resistance index, which may reflect increased uraemic toxicity in patients who have lost their residual kidney function. Patients who have KrU >1 ml/min at 3 months

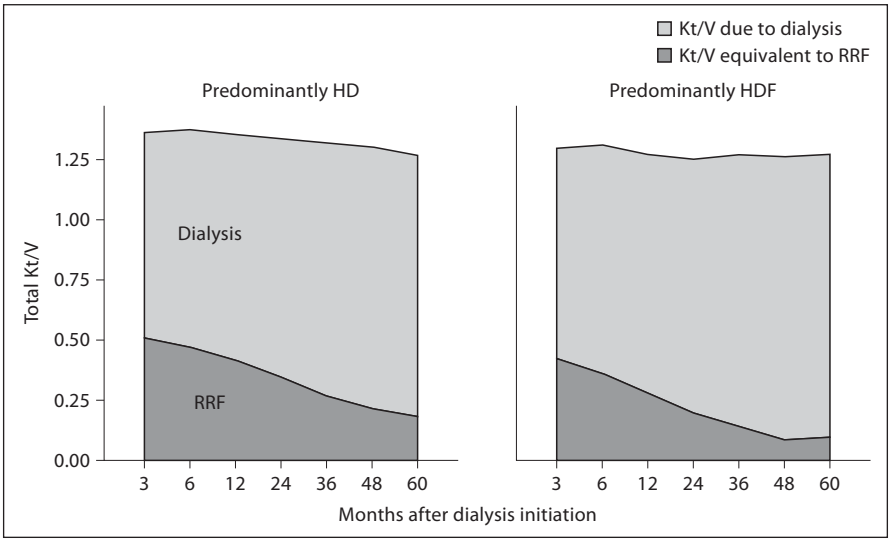

Fig. 2. Contributions of dialysis and RRF.

following dialysis initiation have an improved survival over those patients who are oliguric. The presence of RRF therefore seems to be a strong predictor of wellbeing and possibly survival in dialysis patients.

Clinical Rationale for HDF

In our patients, β2M levels increase with dialysis vintage and as natural renal function declines. These trends are observed in patients receiving high-flux dialysis or HDF. RRF is the major determinant of β2M levels. However, in patients who become oliguric, HDF has measurable superiority over high-flux dialysis in abrogating further rises in β2M levels [5]. It is justifiable to propose that HDF provides superior replacement of lost natural kidney function than high-flux dialysis.

The rationale for HDF is therefore strongest in patients who have the greatest potential for a long-term survival and in patients who have lost natural renal function. It is worth noting that patients who choose home HD are generally constituents of this group. Patients who have failed on peritoneal dialysis are often in this group as are those who are highly sensitised and experience a long wait for transplantation or those who have rejected several transplants.

HDF is clearly an evolutionary milestone in dialytic blood purification. While doctors have often agonised over evidence to justify change in practice our engineering colleagues seem to have been less constrained and moved

ahead to develop the most logical way to purify blood using currently available materials. In the case of HD, this has been cleverly executed and an improved 'broad-spectrum' blood purification therapy has been provided to users whilst remaining within the constraints of reimbursement.

The author recognises the managerial firmness of purpose of Dr. Gatti and colleagues which must have been necessary to overcome regulatory approval hurdles and to encourage R&D over such a long time-scale. As clinicians we applaud the decision made to incorporate HDF as the standard feature of operation of the Fresenius 5008 which would no longer be regarded as an optional extra. To the author's knowledge, no depletion syndromes have been identified whilst employing broad-spectrum solute removal. There seems very little justification therefore in continuing to administer diffusive HD as a routine treatment. 'HDF is common sense'.

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Dr. R.N. Greenwood
Lister Renal Unit, Coreys Mill Lane
Stevenage SG1 4AB (UK)
Tel. +44 1438 781157
E-Mail dr.greenwood.home@virgin.net