Entropy of Uremia and Dialysis Technology

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Key Words

Thermodynamics · Entropy · Bioentropy · Hemodialysis ·
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kidney disease · Uremia

Abstract

The second law of thermodynamics applies with local exceptions to patient history and therapy interventions. Living things preserve their low level of entropy throughout time because they receive energy from their surroundings in the form of food. They gain their order at the expense of disordering the nutrients they consume. Death is the thermodynamically favored state: it represents a large increase in entropy as molecular structure yields to chaos. The kidney is an organ dissipating large amounts of energy to maintain the level of entropy of the organism as low as possible. Diseases, and in particular uremia, represent conditions of rapid increase in entropy. Therapeutic strategies are oriented towards a reduction in entropy or at least a decrease in the speed of entropy increase. Uremia is a process accelerating the trend towards randomness and disorder (increase in entropy). Dialysis is a factor external to the patient that tends to reduce the level of entropy caused by kidney disease. Since entropy can only increase in closed systems, energy and work must be spent to limit the entropy of uremia. This energy should be adapted to the system (patient) and be specifically oriented and personalized. This includes a multi-dimensional effort to achieve an adequate dialysis that goes

beyond small molecular weight solute clearance. It includes a biological plan for recovery of homeostasis and a strategy towards long-term rehabilitation of the patient. Such objectives can be achieved with a combination of technology and innovation to answer specific questions that are still present after 60 years of dialysis history. This change in the individual bioentropy may represent a local exception to natural trends as the patient could be considered an isolated universe responding to the classic laws of thermodynamics.

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Introduction

It is now approximately 60 years from the birth of clinical dialysis. It has been a long and complex pathway taking a dream into reality – 60 years of achievements but also six decades of challenges. Going back to the past, it might be of interest to remember the nature and the time-frame of such challenges. At the beginning the challenge was to design and develop a system capable of cleansing uremic blood. After the pioneering experiences in the first half of the 20th century, Nils Alwall and Wilhelm (Pim) Kolff developed new machines utilizing dialysis as a blood-cleansing modality. The subsequent war in Korea expanded the experience matured at the Brigham and Women's Hospital of Boston and the first challenge, feasibility, was resolved. Cleansing blood was possible and this treatment could allow survival of patients with end-

stage renal disease. In the 1960s, the real challenge was well described by a presentation of Belding Scribner in one of the EDTA annual meetings: *'Dialysis for chronic renal failure is no longer experimental; the results speak for themselves. The real challenge now is to provide dialysis to all patients who need it.'* In those years the availability of artificial kidney machines was limited and the access to the new therapy was reserved for those who met specific criteria of admission. A commission was instituted in many hospitals to decide *'who had to live and who had to die'*. Thanks to the expansion of the industry of the field and new technological advances, by the end of the 1960s, dialysis was made available to a vast population of uremic patients resolving at least in part the second challenge: the expansion of dialytic therapy. In the 1970s, dialysis machines became more reliable thanks to well-designed blood pumps, accurate dialysis fluid modules and the creation of disposable hemodialyzers. These new advances made it possible to perform safer and more reliable dialysis treatments. Nurses became confident with the new equipment and dialysis treatment time could be reduced from 12 to 4 h/session. At this point the challenge of reliability was resolved and dialysis was ready to enter the era of automation and electronics. The 1980s were basically dominated by the results of the National Cooperative Dialysis Study and its conclusion that adequate dialysis doses were needed to improve clinical outcomes. To achieve these tasks, high-efficiency dialysis techniques were required [1]. On one side this was a breakthrough with the introduction of Kt/V as a magic number to target dialysis prescription [1, 2]. On the other side this led to indiscriminate reduction of dialysis treatment time in the rush for 'rapid dialysis'. Unfortunately, the inappropriate application of new schedules presented many drawbacks resulting in uncontrolled patient overhydration, intradialytic hemodynamic instability, underdialysis and ultimately increased morbidity and mortality. Eventually, the utilization of high blood flows, high surface areas and synthetic biocompatible high-flux membranes resulted in increased delivery of the average treatment dose (high efficiency) and quality of dialysis (extended spectrum of solutes removed (high efficacy)) [3]. In the meantime, a more careful prescription of treatment time helped to further improve treatment quality. By the mid-1980s, a substantial number of patients who had been treated with chronic hemodialysis for a decade or more existed. In this subgroup of patients, the sequels of long-term treatment with chronic hemodialysis began to be recognized as in the case of the syndrome of hemodialysis-related amyloidosis. This disorder underlined the multifactorial na-

ture of hemodialysis adequacy including utilization of biocompatible high-flux membranes, pure or ultrapure dialysate, and personalized treatment and technique prescription. The challenges of biocompatibility, efficiency and efficacy were resolved describing the spectrum of criteria for the adequacy of dialysis therapy [4]. The most important technological advance in this era has definitely been the ultrafiltration control system that was applied to all dialysis machines [5].

With the advent of short, highly efficient dialysis techniques, clinical tolerance became the first priority in dialysis. The first approach was 'treatment personalization': each patient began to be considered a single entity requiring a specific treatment prescription and a personalized schedule. The deeper understanding that the patient may change throughout the dialysis treatment introduced the concept of 'treatment profiling'. Sodium concentration in dialysate and ultrafiltration rates could be 'profiled' throughout the session in the attempt to timely prevent intradialytic physiological changes induced in the patient. Unfortunately, in spite of the introduction of computer-based algorithms for the first time in dialysis, the profiles were 'blind' and the approach showed important limitations. However the concept was interesting and it found the solution in the application of on-line sensors, and a biofeedback loop designed to modify prescription parameters on the basis of online signals suggesting instantaneous patient's requirements [6]. This resulted in a significant reduction of dialytic hypotension solving at least in part the challenge of tolerance. Among the last achievements, the extended application of on-line hemodiafiltration and the use of ultrapure dialysate certainly represented important steps forward in the attempt to achieve not only an efficient therapy but also improved long-term outcomes [7].

Dialysis in the new millennium is struggling to find its role between a commodity and a high-tech therapy. Healthcare plans are getting tighter with reimbursement and part of the money usually spent for technological advances is now allocated to important pharmacological therapies for anemia correction and phosphate control. The high cardiovascular morbidity and mortality requires a plan for a 'cardioprotective' hemodialysis with improved metabolic control and lower inflammatory stimuli. The use of ultrapure dialysate and techniques to assess optimal hydration status will certainly help in these tasks. New challenges are also represented by the expansion of dialysis to emerging countries with less financial resources. From the technological point of view, development of sorbent-based therapies and machine miniatur-

ization may represent important new areas of investigation together with development of wearable technologies. In this effort, nanotechnology and information technology combined may result in significant advances.

There is high pressure to send as many patients as possible at home to perform renal replacement therapy outside the hospitals. This has resulted in a series of investigations on the feasibility of home dialysis with current techniques and the possible evolution towards wearable devices. Between the 1960s and 1990s, several attempts were made to develop a wearable artificial kidney (WAK) [8–10]. These attempts failed because the technology for making a truly wearable kidney was not available. These early devices used either ultrafiltration only or ultrafiltration with filtrate regeneration by charcoal, and did not remove urea because total dialysate regeneration was too heavy and bulky. These techniques were combined with intermittent hemodialysis. It was quite obvious that these developments would not lead to an industrial product. For this reason, many questions were not even raised. However, more recently the concept of the WAK has been resurrected [11–13] thanks to new projects. This has triggered renewed attempts around the world to develop WAKs. Today, WAKs are technologically feasible, and although a proof-of-principle prototype of the hemodialysis WAK was successfully tested for up to 8 h in the clinic [12, 14], several basic questions remain to be answered: What safe and reliable method for blood access will be used? What are the risks related to the wearability of the system and how will they be mitigated? Can the WAK be disconnected by the patient, and, if yes, how? How will the WAK be carried: a belt, a jacket or a bag? How will the patient sleep with the WAK? How long can the system be operated without recharging the batteries, reloading the sorbents or replacing the extracorporeal system? How would the patient be trained for regular maintenance and emergencies? In addition, technical questions related to electromagnetic interference and the use of new technical devices, e.g. novel blood pumps and dialysate/filtrate regeneration devices, have to be clarified. Without answering these questions, one cannot expect to get reliable answers from patients when they are asked whether they would use a WAK. The answers to these questions should take into account the perception of patients about the risks and problems related to home hemodialysis. Patient-perceived barriers are primarily fears of self-cannulation, a catastrophic event and it being a burden on the family. Other problems related to home hemodialysis, like the cost of suitably adapting the home, should be considered [15–17].

After 60 years of hemodialysis we are facing successful achievements but also new challenges that were not even imaginable at the beginning. For those who think that nothing changed in the field, I would like to remind the typical dialysis room of 20 years ago where more than half of the patients were vomiting, having headache or lying on the bed with raised legs. Today, in spite of the significant ageing of the dialysis population and the significant increment of comorbid conditions, the dialysis room is quiet and patients are frequently annoyed by a medical round interrupting their book reading, e-mail handling or movie watching on satellite TV. A recommendation for young nephrologists should be made following Hans D. Polaschegg's recommendation to not think that everything has been done in dialysis. Many challenges have been solved but many others are just around the corner. Young nephrologists should look at the past to build their future and the future of our patients. Technology can help but one must control and apply technology in the right way, using it as a complementary aid to medicine and not as a substitute for good clinical care. In these messages, a clear call to action emerges to undertake a holistic approach to the dialysis patient. A multidisciplinary approach is needed where renal physicians interact with other medical disciplines but also with other fields using the acronym GRIN to describe the most interesting science areas of the future, namely Genetics, Robotics, Information Technology, and Nanotechnology. With this integrated approach, new avenues can be explored including microfluidics, nanomedicine, miniaturization and biophysics. In this view, we can describe uremia and dialysis technology using the parallel of thermodynamics in biology and the example of entropy.

Biology and Thermodynamics

The second law of thermodynamics explains the phenomenon of irreversibility and the increasing entropic trend of nature. An individual can be physically described as a carbon-based living unit that responds to the unifying principles of physics, chemistry and biology: the second law of thermodynamics. As the philosopher P.W. Bridgman said, there have been nearly as many formulations of the second law as there have been discussions of it but nevertheless the German scientist Rudolf Clausius laid the foundation for the second law of thermodynamics in 1850 by examining the relation between heat transfer and work [18]. His formulation of the second law is known as the Clausius statement: 'Heat can never pass

from a colder to a warmer body without some other change, connected therewith, occurring at the same time.' This means that no process is possible whose sole result is the transfer of heat from a body of lower temperature to a body of higher temperature or, heat cannot spontaneously flow from cold regions to hot regions without external work being performed on the system. An important and revealing idealized special case is to consider applying the second law to the scenario of an isolated system (in our case the patient), made up of two parts: a subsystem of interest, and the subsystem's surroundings. The individual is a universe in itself and the surrounding subsystem is the environment where he lives. The second law of thermodynamics expresses the tendency for entropy to increase in isolated systems. Similar to man-made machines, living structures are subjected to entropy generation, becoming 'worn' and 'damaged' from use [19]. Entropy is a term coined in 1865 ($\epsilon\nu\tau\rho\omicron\pi\eta$ = turning toward) describing the level of disorder of a system (entropy increases in isolated systems) or the amount of thermal energy not available to do work. In general it can be considered a measure of a tendency of a process to proceed in a particular direction (randomness and disorder) and has a dimension described by the ratio energy/temperature. Even though thermodynamics does not describe processes as a function of time, the second law defines a unique direction of time as the direction in which total entropy increases, and it makes no distinction between living and non-living things. Living organisms are characterized by a high degree of molecular structure and assembly organized in cells, tissues and organs. According to the second law of thermodynamics, the total entropy of a system must increase steadily. Living organisms follow this rule but some exceptions may occur if an intervention is made external to the biological system. Thus the decrease in entropy that accompanies growth of living systems must always be accompanied by an increase in entropy in the surrounding physical environment. The individual preserves a low level of entropy throughout time (demonstrated by growth and organ function) by consuming nutrients that are progressively disordered and increase their level of entropy. Nutrients produce heat and there is a continuous and delicate balance between energy consumption and slowing down the increase in entropy. While in the first part of life this energy balance facilitates growth and organization, the process of ageing can be considered a progressive increase of molecular and biological chaos reaching with death the thermodynamically favored state. Thus the level of entropy during life is well described by a U-shaped curve

Fig. 1. According to the second law of thermodynamics, spontaneous chemical and biological reactions are always accompanied by a decrease in free energy. The free energy lost appears either as heat (enthalpy) or is used to increase entropy. Entropy has a peculiar behavior during life span: it tends to decrease in the growing individual at the expense of an increase in entropy in the surrounding system, while it progressively increases with ageing yielding a maximum level of entropy and chaos when death occurs. In any moment of life, critical illness as in the case of cancer may induce a sudden increase in entropy in the organism with possible fatal consequences.

with a trend towards decrease (or better slower increase) in the development phase and a faster increase towards the end of life. Individuals maintain an equilibrium in which life is sustained by a delicate equilibrium until sudden events as acute illness disrupt such equilibrium. In this moment, a dramatic increase in what we may define as 'bioentropy' occurs and a consequent acceleration towards death is observed (fig. 1).

Entropy and Kidney Function

In the early phases of life, the evolution of structured nephron mass and kidney function characterizes a period of minimal individual entropy with high consumption of externally provided energy. Kidneys are designed to maintain homeostasis which can be defined as the exact opposite of internal chaos. Thus we may say that kidney function is one of the main mechanisms in the body to limit entropy. Kidney disease, either acute or chronic, may have a tremendous impact on this equilibrium inducing a sudden increase in individual entropy. Ironically, uremia is characterized by a decrease in appetite and

Fig. 2. The natural course of entropy is disrupted by the effects of kidney disease and uremia. The sudden increase in entropy and the trend towards biological chaos is mitigated by dialysis technology recovering at least in part the original curve of individual entropy. This is achieved at the expense of consumption of resources in the environment surrounding the kidney patient.

nutritional intake, further aggravating the disruption of homeostasis and the progression towards a logical thermodynamic state of maximal chaos: death. In such circumstances, medical interventions such as dialysis are designed to slow down the increase in bioentropy and to reconstitute a nearly normal thermodynamically sustainable curve of energy consumption and life (fig. 2).

Bioentropy, Kidney Disease and Dialysis Technology

Hemodialysis intended as renal replacement therapy is a barrier against entropy increase. Of course once again, consumption of resources and energy sources external to the patient are required to make the increase in entropy reversible. In order to be effective however, dialysis must be a true renal replacement correcting all possible abnormalities induced by acute or chronic kidney disease. While in acute kidney injury however the potential for tissue and organ regeneration is significant, in end-stage kidney disease, recovery of renal function is impossible and progressive deterioration of metabolic processes are becoming manifest in all areas where the therapy result is inadequate.

For this reason a major effort should be made to render hemodialysis a complete treatment, well beyond some limited measures of efficiency such as small molecular

Fig. 3. Radar graph depicting several vectors that quantitatively describe the many low entropy conditions achieved in healthy status with a normal GFR. Functions are close to 100% in all explored areas.

weight solute clearance and Kt/V . The radar graph in figure 3 shows the multidimensional domain of healthy status in the presence of normal GFR. Figure 4 describes how several parameters may be dramatically affected by the onset of uremic symptoms or simply by a decrease of GFR. There is of course a correlation between the abnormality of the graph and the severity of kidney disease. In figure 5 we report a nearly optimal result achievable with an adequate renal replacement therapy when most abnormalities are corrected even though the level of correction is still limited compared to the normal kidney. Figure 6 describes the characteristic results generally achievable with the three possible treatments of uremia such as hemodialysis, peritoneal dialysis and kidney transplant. It is evident that every technique has advantages and disadvantages and a rounded shape of the graph is almost impossible to achieve. Taking hemodialysis as an example, technology may contribute to modify the achievements of each different modality enhancing specific advantages (fig. 7). We analyzed however only some of the factors required to make a renal replacement therapy effective and completely adequate. They are listed in figure 8 where not only the entropy of the individual is considered with the required corrections of the several factors leading to internal chaos, but also the interactions with the environment external to the patient, to make the treatment sustainable and widely accessible.

Fig. 4. Radar graph identifying the numerous functions disrupted by kidney disease and the uremic state, with a reduction in organ performance and healthy status consequent to specific increase in local entropy at cellular, tissue and organ level. In some cases, such as acid base balance, the specific function may be operating at a level lower than 20% of the original capacity.

Fig. 5. Objectives and achievable corrections with an adequate renal replacement therapy. Many of the targets are identified at a level higher than 60% of the original homeostatic capacity.

Fig. 6. Characteristics of different renal replacement treatments in terms of performance for selected operational and clinical targets.

Fig. 7. Characteristics of different types of hemodialysis in terms of performance for selected operational and clinical targets.

Fig. 8. Requirements for a holistic approach to renal replacement therapy.

Conclusions

An important consideration concerns the holistic approach to the problem of uremia and the remaining challenges still to be solved. These are basically of two types: short- and long-term challenges. At short term, the physician must carefully observe the patient to establish if specific derangements are present. We described this with an index called MDt/P as opposed to Kt/V (Clearance $\times$ Time/Volume). While Kt/V is basically a fractional measure of clearance of small molecules, MDt/P stands for Medical doctor $\times$ Time/Patient and describes the time spent at the bedside by the physician. This time will be crucial to identify immediate problems and necessary interventions such as correction of electrolytes and acid base, correction of anemia and hyposideremia, correction of calcium and phosphate disorders, adjustment of medications and finally establishment of the correct dry

weight. The long-term problems such as skeletal, muscular, gastrointestinal and cardiovascular disorders induced by chronic uremia and inadequacy of dialysis therapy should be tackled with new techniques, new devices and innovation in general. We know what dialysis has done so far. Results are incredible but several clinical needs remain unanswered. The challenge of the coming future will be to evaluate the level of entropy in our patients on dialysis and use innovation and technology to maintain this entropy as low as possible. That will result not only in a longer life for our patients but also in a better life. In this evaluation the entropy of the patient and the surrounding environment should also be considered to make the progress of dialysis therapy affordable and sustainable though optimization of available resources.

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Disclosure Statement

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