Studies in Computational Intelligence 405

Ahmad Taher Azar (Ed.)

# Modeling and Control of Dialysis Systems

## Volume 2: Biofeedback Systems and Soft Computing Techniques of Dialysis


Springer

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# Dedication

I dedicate this book to my wife, her endless prayers through days and nights keep lighting me the way and without her patience, understanding and support the completion of this work would not have been possible. To my dearest, beautiful and extraordinary daughters Hla and Nadine to whose love will always be an inspiration for me. I wish to dedicate this book also, to my mother. She taught me to persevere and prepared me to face challenges with faith and humility. She is a constant source of inspiration to my life. I always feel her presence used to urge me to strive to achieve my goals in life. Also, to my sisters for their endless love, patience, trust and sacrifices for me.

# Preface

The primary purpose of the book is to facilitate education in the increasingly important areas of dialysis. It is written as a textbook for a course at the graduate or upper-division undergraduate level for biomedical engineering students. The biomedical engineering is the inter marriage of engineering and medicine. The need to effectively utilize high technology equipment and systems in the dialysis field necessitates the expertise of clinical engineers, hospital physicians and computer scientists. Hardly any patient today would pass through a hospital or even a family physician's chamber without the use of this technology.

Although there is enough material in the text for nephrologists, nurses, technicians and other members of the health care team resolve the myriad of problems confronting the patients undergoing dialysis. The text is also suitable for self study and for short, intensive courses of continuing education. The authors include a senior consultant nephrologist with considerable expertise in all aspects of dialysis. Advanced topics and future challenges are addressed as well, with the researchers in the field in mind. The introductory material, application oriented techniques, and case studies should be particularly useful to practicing professionals.

While several books are available today that address the principles of dialysis, none, unfortunately, provides the practicing knowledge engineer, system analyst, and biomedical researchers with specific, practical information about various modeling and control techniques in the field of dialysis and their applications. The book discusses novel ideas and provides a new insight into the studied topics. The book on this subject will constitute an important contribution in the field of hemodialysis and peritoneal dialysis.

The book is unique for its diversity in contents, clarity and precision of presentation and the overall completeness of its chapters. Each chapter in the book openes with a chapter outline, chapter objectives, key terms list and chapter abstract. Each chapter ends with a conclusion and bibliographic references related to the text. The book is basically broken into two volumes with five parts. The first volume includes the first part of the book from chapters 1–14 which covers overview of dialysis treatment and urea kinetic modeling techniques. There are three treatment modalities

available for patients with chronic renal failure: hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (RT). Although these treatment modalities have proved to be life sustaining, patients with end-stage renal disease (ESRD) continues to grow in the worldwide. The incident population of patients with ESRD is increasing at approximately 6% each year. Kidney transplantation is considered the treatment of choice for many people with severe chronic kidney disease because quality of life and survival are often better than in people who use dialysis. Despite assiduous efforts to utilize renal transplantation as a viable option for potential recipients with ESRD, the donor organ shortage has been one of the major barriers to kidney transplantation. Patients who are not candidates for kidney transplantation or who must wait for a kidney can usually be treated with either hemodialysis or peritoneal dialysis. Dialysis prescription must ensure that an adequate amount of dialysis is delivered to the patient. Numerous studies have shown a correlation between the delivered dose of hemodialysis and patient morbidity and mortality. Therefore, the delivered dose should be measured and monitored routinely to ensure that the patient receives an adequate amount of dialysis. Urea Kinetic Modeling (UKM) is beneficial because it assists clinicians in individualizing dialysis prescriptions and provides the hemodialysis care team with guidance about which specific parameters of the prescription to modify to achieve the target hemodialysis dose. The presentation of these chapters requires only a basic knowledge of linear algebra, differential equations and probability theory.

The second volume of the book includes the remaining parts (from part 2 to part 5). The second part of the book from chapters 15–19 describes online dialysis monitoring devices and continuous therapy. In the past few years, several devices have been developed in the field of dialysis. These devices obviate the need for blood sampling, minimize random measurement errors, and allow a whole range of parameters to be calculated which are likely to be of future clinical value. These new devices also may be coupled on-line to a central database so that measured and calculated values can be recorded without manual intervention, allowing almost instant information of clinical value to the patient.

The third part of the book from Chapters 20–25 covers biofeedback Systems and soft computing Techniques of dialysis. Biofeedback represents the first step towards a ‘physiological’ HD system incorporating adaptive and logic controls in order to achieve pre-set treatment targets and to ensure delivery of the prescribed dialysis dose. Soft computing approaches in decision making have become increasingly popular in many disciplines. Soft computing concerns the use of theories of fuzzy logic, neural networks, and evolutionary computing to solve real-world problems that cannot be

satisfactorily solved using conventional crisp computing techniques. A novel applications of soft computing techniques are discussed in this part of the book. While sufficient theory of each technique is presented, it is offered in a simplified manner for the benefit of the students.

The fourth part of the book from Chapters 26–30 covers the overview of peritoneal dialysis and its modeling techniques.

Finally, the fifth part of the book has two chapters to cove the future challenges and general guidelines of dialysis.

It is hoped that the book will be a very good compendium for almost all readers — from students of undergraduate to postgraduate level and also for researchers, professionals, etc. — who wish to enrich their knowledge on dialysis systems' principles and applications with a single book in the best manner.

**Solved Examples, Applications, and Implementation Case Studies**

A vast array of illustrative examples, implementation case studies for a variety of applications, end-of-chapter questions and problems are used throughout the text. There are over 1000 questions in this textbook. The basic goals of these case studies, examples and questions are as follows:

- To help illustrate the theory.
- To encourage good problem-solving skills.
- To show how to apply the techniques.
- To help illustrate design procedures in a concrete way.
- To show what practical issues are encountered in the development and implementation of dialysis systems.

**To the Student**

The best way to learn new material is by reading, thinking, and doing. This text is designed to help you along the way by providing an overview and objectives for each section, numerous worked- out examples, exercises and self-test questions. Read each section of the text carefully and think about what you have read. Sometimes you may need to read the section more than once. Work through each example problem step by step before you try the related problem that goes with the example. After the end of each chapter, answer the essay questions and multiple choice questions. The abundance of these questions is very useful for you to check your progress and understanding as they require more systematic and in-depth thinking. If you are able to solve the chapter questions for a given objective, you have mastered that objective.

## For Instructors

### A. Instructor Solutions Manual

Fully worked-out solutions to end-of chapter questions and problems. So you can check your work.

### B. Possible Course Structures

The material in this textbook has been designed for a one-semester, two-semester, or three-quarter sequence depending on the needs and interests of the instructor. The material in the book is suitable for a number of courses at the undergraduate and graduate levels. Some possibilities are given below.

- Dialysis principles (senior undergraduate or introductory graduate-level course): Chapters 1, 2, 3, 4, 5, 7, 9, 26, 27, 30, 31 and 32.
- Modeling techniques of dialysis (senior undergraduate or graduate-level course): Chapters 6, 8, 10, 11, 12, 13, 14, 19, 25, 28 and 29.
- Online dialysis monitoring and continuous therapy (senior undergraduate or introductory graduate-level course): Chapters 15, 16, 17, 18, 19, 25.
- Biofeedback Systems and Soft computing applications in dialysis (senior undergraduate or graduate-level course): Chapters 20, 21, 22, 23, 24, and 25.
- Principles of peritoneal dialysis and its modeling techniques (senior undergraduate or graduate-level course): Chapters 26, 27, 28, 29, and 30.

## Feedback on the Book

We are deeply indebted to the many instructors and students who have offered positive feedback and suggestions for improvement. We are delighted whenever we receive email from instructors and students who use the book, even when they are pointing out an error we failed to catch in the review process. We are also open to your suggestions on how to improve the content, the pedagogy, and the presentation in this text by emailing me at ahmad_t_azar@yahoo.com. We are privileged to have the opportunity to impact the educational experience of the many thousands of future engineers who will turn the pages of this text.

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My sincere thanks to all contributing authors of this book not only because of their expertise in the science of medicine, but because they are physicians who are able to translate and apply their scientific knowledge in a practical way to allow for a systematic and evidence based plan of therapy and treatment in the best interests of patients.

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**Part III: Biofeedback Systems and Soft Computing Techniques of Dialysis**

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# Part II

# Online Dialysis Monitoring and Continuous Therapy

Chapter (15)

# On-Line Hemodialysis Monitoring: New Tools for Improving Safety, Tolerance and Efficacy

Bernard Canaud, Alexandre Granger, Leila Chenine-Khoualef, Laure Patrier, Marion Morena, and Hélène Leray-Moragués

**CHAPTER OUTLINES**

- Introduction
- Safety Monitoring Devices
- Efficacy Monitoring Devices
- Hemodynamic Monitoring Devices
- Quality Control System Devices
- Conclusion

**CHAPTER OBJECTIVES**

- Recognize the complexity of treating chronic kidney disease patients by renal re-placement therapy.
- Understand the broadness concept of dialysis adequacy.
- Underline the important role of online monitoring devices for guiding, ensuring safety and efficacy of treatment.
- Use online monitoring tools to quantify and optimize dialysis efficacy delivery.
- Assess the internal milieu monitoring of hemodialysis patient with non-invasive online monitoring devices.
- Underline the beneficial role of online monitoring coupled to feedback control (biofeedback system) to improve dialysis tolerance and quality of life.
- Implement online monitoring tools in a quality assurance system able to reduce hemodialysis patient morbidity and mortality.

**KEY TERMS**

- Hemodialysis
- Hemodialysis adequacy
- Chronic kidney disease outcome
- Online monitoring
- Efficacy
- Dialysis adequacy
- Quality control process
- Quality assurance

**ABSTRACT**

Hemodialysis adequacy is a complex concept that encompasses largely the dialysis dose appraisal based on monthly blood-based urea Kt/V measurement. Renal replacement therapies should provide an efficient way to clear adequately larger molecular weight solutes, to restore normal salt,

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electrolytes and fluid balance, to correct salt-dependent hypertension, to improve hemodynamic stability and to reduce bio-incompatibility of the hemodialysis system. Targeting such ambitious objective is obviously under the clinical supervision and judgment of nephrologists and care givers. Monitoring and achievement of these targets as a part of a continuous quality improvement process is necessary to attain dialysis adequacy goals. This review aims to provide an overview of available online hemodialysis technologies, their current applications in clinic, and the potential for future developments in improving care of chronic kidney disease patients. In order to facilitate understanding of readers we choose to classify online monitoring devices based on their clinical action.

## 15.1 INTRODUCTION

Hemodialysis adequacy is a generic term currently used to appraise the fact that dialysis dose based on urea Kt/V has been delivered to chronic kidney patient (CKD) in compliance with the best clinical practices (NKF-K/DOQI 2001; Hakim et al. 1992). This oversimplification of the dialysis adequacy concept has blunted complexity of uremic spectrum abnormalities, and has led to excessive dialysis mortality over the last two decades (Barth 1989; Greene et al. 2005; Locatelli 2003). Indirectly this observation proves that dialysis adequacy concept encompasses largely the intermittent correction of urea concentrations and must account for more profound and specific corrections of the internal milieu in CKD patients. In other words, blood purification systems should provide an efficient way to clear adequately larger molecular weight solutes and toxins in addition to urea, to restore normal salt, electrolytes and fluid balance, to correct salt-dependent hypertension, to improve hemodynamic stability and to reduce bioincompatibility of the hemodialysis system.

Targeting such ambitious objective may not be solved solely by the dialysis monitor and obviously clinical judgment and intervention of nephrologists and care givers are required (Lameire et al. 2009). Treatment schedule prescription (individual session efficacy, time duration and number of sessions per week) should be tailored and continuously adjusted over time to patient metabolic needs. Monitoring of the achievement of these targets is indeed necessary to attain dialysis adequacy goal. Monitoring of CKD dialysis patient should be integrated in the broad perspective of a continuous quality improvement process. Selected parameters of vital importance should be used as quality control indicators and treatment prescription should be consequently adjusted to achieve targeted values. It is not the purpose of this chapter to revisit either dialysis parameters or

optimal target range required to optimize outcomes of CKD dialysis patients. We refer the interested reader to specific dedicated manuscripts and guidelines (Tattersall et al. 2007). It is interest noting that in many cases such online monitoring devices are already available, allowing the clinician instantaneous and continuous access to relevant data (Locatelli et al. 2005). As example, several techniques provide measurement of continuous blood pressure and heart rate (Bos et al. 2000), urea reduction and a surrogate ionic dialysance (Mercadal et al. 1998), sodium removal and/or mass transfer (Locatelli et al. 1995), blood volume monitor (Ronco and Bellomo 1997), and blood temperature monitoring (Pérgola et al. 2004) during hemodialysis. Four categories of online devices designed for continuous monitoring are presently available: 1. Safety monitor devices; 2. Efficacy monitor devices; 3. Hemodynamic monitor devices; 4. Quality control monitor devices.

## 15.2 SAFETY MONITORING DEVICES

Since 1980s mandatory safety measures of dialysis machines have been imposed to manufacturers that are subjected to various international standards (IEC standards, International Electronical Commission; AAMI, American Association of Medical Instrumentation). The basic concept of these standards is the "first failure safety" strategy meaning that the dialysis machine must not expose the patient to a hazard when a first failure occurs in the monitor. Simultaneously, the dialysis monitor is transferred into a "safe state" that corresponds to a configuration in which a safety hazard for the patient may be excluded. Based on these requested safety measures, the user is now assured that dialysis monitors comply with the basic standards. In addition, performances and safety features of hemodialysis material need to be checked and validated by independent certified laboratories and notified bodies according to country specific regulation (e.g., LNE/GMed France; TÜV Germany; AAMI & FDA, USA) before being released on the market. As an example, in Europe all hemodialysis material including hemodialysis monitors and water treatment system is submitted to CE labeling process before any clinical use. All this complex process is intent to prevent both user and patient from any technical hazards.

The modern engineered technology of hemodialysis machines that include redundant alarms, self-test modes, and fail-safe systems has significantly minimized the hazards of extracorporeal renal replacement therapies. No report involving a patient's death could be found in the MAUDE (Manufacturer and User Facility Device Experience database) database of FDA for 2004 as result of a machine fault. On the other side, this false

safety given by new dialysis monitors has desensitized users from dangers and reduced their awareness to risks. Hemodialysis monitors are now engineered to reduce the risks for patients and for example, the alarm limits are set by the machine not by the user and cannot be switched off. In addition modern electronics allowed the automation of tests and adjustments, which were originally performed by users.

The sensors featuring modern hemodialysis monitors may be able to detect major hazards of the procedure. External blood losses or air embolism most likely occurring after disconnection of the blood circuit or dislodgement of cannulas may be detected by a sudden blood pressure drop in the extracorporeal blood circuit (venous or arterial segment). Most machines also have a venous clamp that closes automatically in case of a "blood side" alarm. Although the machine will generate an alarm and stop blood flow in case of disconnection of the blood tubing the time lag for detection of pressure drop is sufficient to expose patient to hemorrhage or air embolism. Mechanical hemolysis that may occur in the extracorporeal blood circuit resulting from high shear stress (obstruction in blood circuit from kinked or twisted lines) is detected by colorimetric sensor present in the dialysate circuit. Ultrafiltration and dialysate concentration profiles (sodium modeling) are controlled by very sensitive fluid balancing system and conductivity monitors. In addition, new technology provides very sensitive dialysate temperature sensors that may prevent any temperature derangements. Modern machines comprise additional monitors that protect against errors or wrong use of concentrate solutions. Electric shock hazard or low current pathway occurring from the dialysis machine to the patient is now virtually completely prevented by electric safety system.

Today's, it is largely proved that most hazards in hemodialysis are not caused by machine malfunction but are rather related to user errors which include incorrect setting, negligence or bypass of alarm limits. Safety monitors in hemodialysis machines cannot prevent adverse events but they are designed to detect the deviation from a controlled value (and provide audible and/or optical alarms) and to switch off operational function into a "safe state" for patient.

## 15.3 EFFICACY MONITORING DEVICES

Continuous monitoring of dialysis efficacy (e.g., urea and sodium mass transfer) has clearly shown the importance of inter-patient and intra-patient variability (McIntyre et al. 2003a; Kloppenburg et al. 1999). It is of interest noting, that variation is most likely to overestimate rather than underestimate the dialysis efficacy (Brimble et al. 2002). In addition, most

clinically relevant parameters used for CKD dialysis patient surveillance follow similar patterns over time. In these conditions, the use of punctually non-representative set of data may lead to inappropriate adjustment of dialysis therapy, either by justifying delivery of insufficient dialysis dose, or by reducing inappropriately treatment time and/or dialyzer surface and performance. Continuous monitoring using on online dialysis monitoring will allow very precise adjustments of the dialysis prescription based on repeated measurements made on every dialysis session and using trend analysis (see Fig. 15.1). This approach is now clearly challenging the current best clinical practices that are recommending adjusting the dialysis therapy based on a single urea Kt/V monthly measurement. Continuous intradialytic measurement using online monitoring devices will provide also new tools for guiding dialysis prescription and customizing dose target. In addition, online monitoring devices will provide educative and/or training tools for nurses and patient that will contribute in improving the delivered care to CKD patients.

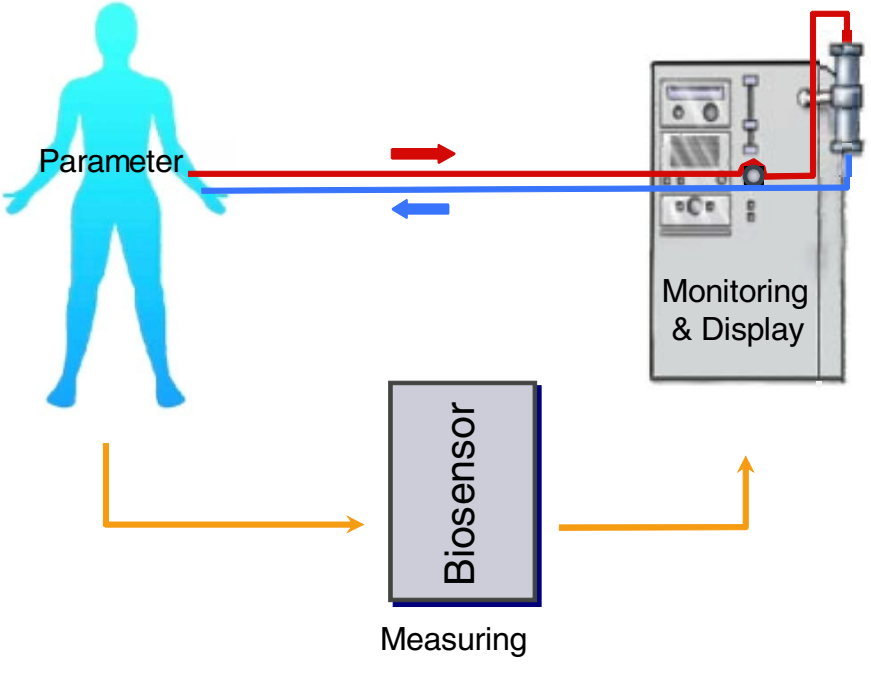


**Fig. 15.1** Biosensor (or captor) providing online monitoring of a biological parameter (e.g. Kt/V).

### 15.3.1 Urea Monitoring Devices

Urea monitoring devices have been the first to be developed and used in clinic. Historically, one important target in hemodialysis therapy is assessed by urea removal per session. Conventionally, this is expressed either by the blood urea reduction ratio (percentage reduction of urea per session) or the Kt/V (body urea clearance normalized to body water). Several blood-based methods have been proposed over the time to help clinician. In routine clinical practice, all these methods rely on measurement of blood urea reduction and require blood sampling before and after dialysis. The complexity of urea kinetic modeling (UKM) both due to the intracorporeal mass transfer resistance, that results in apparent sequestration of urea in the remote compartment ("compartmentalization effect"), and to periodical volume changes induced by weight gain and loss (ultrafiltration), it is now well recognized (Canaud et al. 2000). This is why the use of simple formulae based on percent reduction of urea and single pool Kt/V are overestimating the efficacy of dialysis delivered to patient (Daugirdas and Schneditz 1995). To overcome the difficulty of urea kinetic modeling using computerized system it has been proposed to use simplified bed-side formulae offering comparable results but more easily handled by clinicians (Garred et al. 1995; Garred 1995). It is not our intent to develop rationale and validation of these simplified formulae but we refer the interested reader to the most valuable manuscripts for more information (Depner and Daugirdas 1996; Covic et al. 1998).

#### 15.3.1.1 Online Monitoring of Urea Removal

Online measurement of urea removal using several effluent dialysate approaches obviates this need. All these approaches referring to direct dialysate quantification (DDQ) shared in common the direct measurement of urea removal in waste dialysate (or ultrafiltrate). They are widely accepted and currently represent the reference method for assessing the exact urea (or any other solute) mass removed during dialysis. Usually, they require the total collection of waste dialysate (typically 180l/session) and are not applicable in clinical routine assessment. As a more convenient alternative, the Partial Dialysate Collection (PDC) of spent dialysate has been proposed (Garred et al. 1989; Argilés et al. 1997). In this approach, a calibrated pump (or mechanically driven syringe) removes a proportion (usually 1/1000 to 1/10000) of spent dialysate during the session allowing

subsequently biochemical analysis and calculation of total urea mass removed based on aliquoted small volume of dialysate (Garred et al. 1989).

#### 15.3.1.2 Real Time Monitoring of Urea in Spent Dialysate (or Ultrafiltration)

A more refined method obviating this dialysate collection (total or partial) is clearly to monitor urea in spent dialysate directly by online measurement as presented on Figs. 15.2 and 15.3. Several methods have been proposed and implemented in urea monitoring (UM) devices. Most of them use an enzymatic urease based method, in which the breakdown products of urea (ammonium, pH) are detected either by an ion-specific electrode (Canaud et al. 1998b) or by a conductivity sensor (Canaud et al. 1997). Several UM devices have been developed and evaluated in clinical trials either in acute or chronic conditions with quite good accuracy results (Jurkiewicz et al. 1996; Lee et al. 1997). Online UM devices available today: Urea Monitor (Hospal-Gambro, Lyon, France) (Calzavara et al. 1998); Biostat1000 urea monitor (Baxter Healthcare, Deerfield, Illinois) (Depner et al. 1996; Canaud et al. 1998a; Hernandez-Herrera et al. 2001); Biotrack (Biocare Corp., Hsindu, Taiwan) (Lim et al. 1999); Urea monitoring system (UMS) (Bellco, Mirandola, Italy) (Navino et al. 1998). The most recent achievement in this field was based on the combined use of enzyme coated incorporated in microchip and ion sensitive field transistor effect (Micromedia-Hemodia, Labége, France). The biosensor accurately measures urea concentration in the effluent dialysate and transmits continuously data by WiFi connection to a remote computerized system (Micromedia). Due to the extra cost generated by the use of disposable material (urease) most of these UM devices are not anymore used in clinic for routine monitoring. An interesting approach that measures the concentration of urea and potentially other biologically relevant molecules in spent dialysate has been proposed using spectroscopic analysis of single-wavelength ultraviolet absorbance (Fridolin et al. 2002; Uhlin et al. 2003). Dialysate based urea measurements provide tool for evaluating the slope of urea decline, a surrogate of plasma urea reduction and K/V ratio, and the amount of urea removed by integrating the used dialysate flow. Based on this tool, it is possible to calculate the nitrogen appearance rate providing then a protein nutritional assessment (Luman et al. 2009). Now, the most widely used measure of dialysis adequacy is based on blood-based Kt/V, an index that has been subject to extensive studies establishing its relationship to mortality below a threshold value (Gotch and Sargent 1985;

Eknoyan et al. 2002). Both methods, however, have shown a high degree of correlation with blood-based Kt/V and should theoretically provide the same predictive value for outcome in CKD patients. Now, there are no large studies proving that these new online UM tools giving continuous monitoring of hemodialysis patients have any superior benefits in reducing mortality.

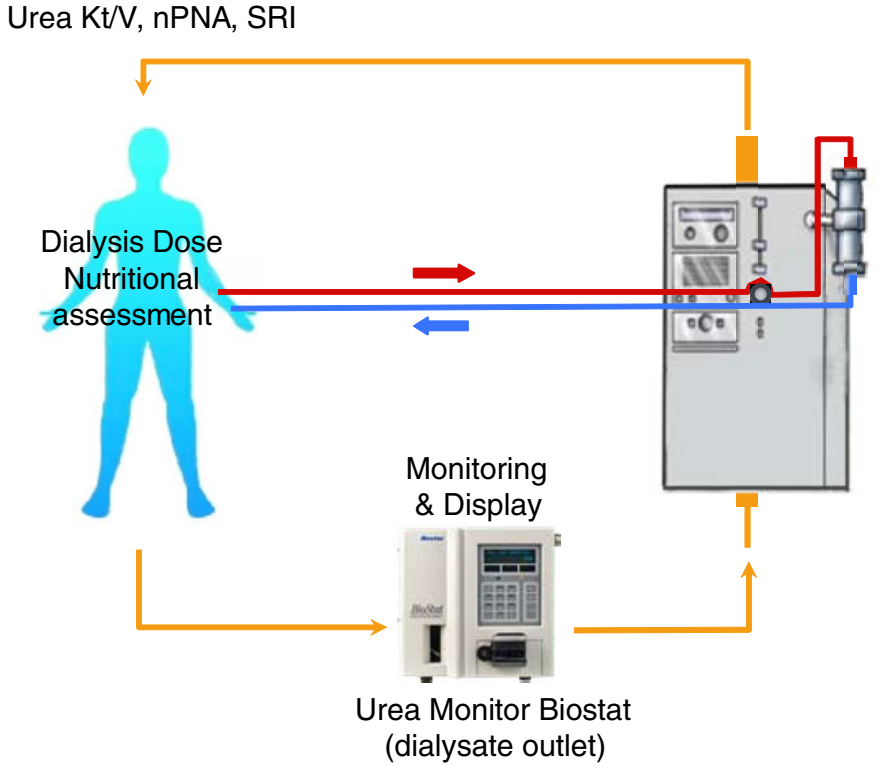


**Fig. 15.2** Urea monitoring device based on direct urea determination in the outlet dialysate (urease).

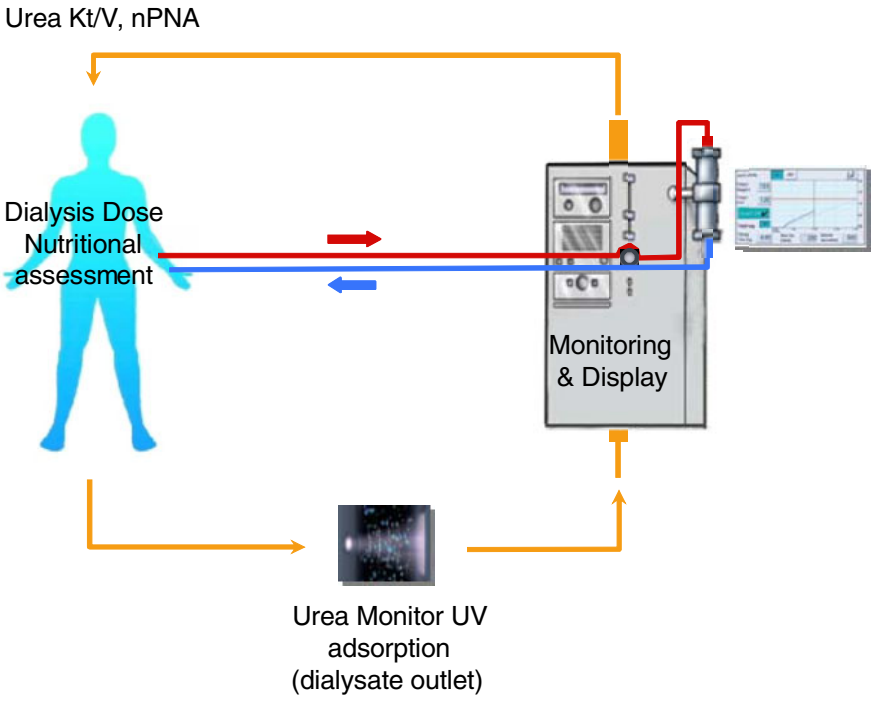


**Fig. 15.3** Urea monitoring device based on UV adsorption on the outlet dialysate.

### 15.3.2 Ionic Dialysance Monitoring

The second method currently used in clinic to monitor dialysis efficacy delivery is based on ionic dialysance measurements. In this case, the dialysance of electrolytes corrected for ultrafiltration and recirculation are measured at repeated intervals (usually every 30 minutes) throughout the dialysis session. Interestingly, it has been strongly established in several studies that ionic dialysance was very closely correlated to urea clearance and could be used as a reproducible surrogate for dialysis quantification in chronic or acute setting (Del Vecchio et al. 1998; Ridel et al. 2007). Two main ionic dialysis monitoring devices have been developed and implemented in conventional dialysis machines: Diascan (Hospal, Lyon, France) and the Online Clearance Monitor (Fresenius, Bad Homburg, Germany) are both based on the same principle (Di Filippo et al. 1998; Goldau R et al. 2002; Racki et al. 2005) and presented on Fig. 15.4. Briefly, two conductivity meters are required, monitoring inlet and outlet dialysate conductivity separately, or one meter alternatively operating at dialysate inlet and

outlet. The changes in effluent dialysate conductivity in response to predefined changes (increase and/or decrease conductivity) of fresh inlet dialysate conductivity allow ionic dialysance conductivity to be calculated by the dialysis machine. Because conductivity is related to ion concentration in which sodium concentration is largely predominant, it is possible to substitute one to the other in further calculations. Considering that the membrane transfer characteristics of sodium and urea are similar, the ionic dialysance reflects closely the clearance of urea. Finally, this measured ionic dialysance (K) can then be expressed as Kt/V index provided a V value (usually V is estimated from Watson formula) is entered into the dialysis monitor by the clinician. Measurement of ionic Kt/V implemented in several hemodialysis and online hemodiafiltration machines (Gross et al. 2007) has been validated in clinical studies and tend to correlate closely with urea-based measurements either from blood or dialysate but tending to underestimate urea clearance by 5 to 7% (Al Saran et al. 2010; Di Filippo et al. 2005). Technology based on ionic dialysance measures embarked on dialysis machine offers a convenient and cheap tool for continuous measurement of dialysis efficacy. Several studies using this method as quality control monitoring have emphasized over time the substantial degree of intrapatient variability in delivered solute removal (Katopodis and Hoenich 2002).

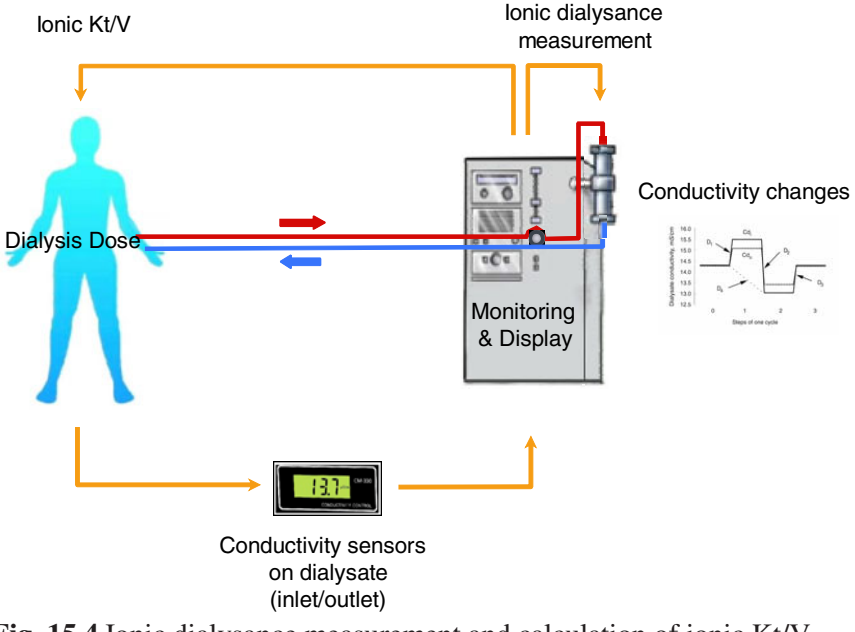


**Fig. 15.4** Ionic dialysance measurement and calculation of ionic Kt/V

### 15.3.3 Sodium Removal Monitoring

Assessment of sodium and water mass transfer data during hemodialysis are of great potential interest for guiding the extracellular and fluid volume balance of anuric CKD patients. Adequate removal of the interdialytic sodium gain is of crucial importance for adequate dialysis, correction of extracellular volume and control of arterial pressure. Measurement of sodium flux and extrapolated sodium mass removal allows individual tailoring of dietary advice and dialysate sodium profiling. Until recently, such sodium quantification was not possible in routine clinical practice. Now, based on modern technology that relies on highly accurate conductivity meters, sodium flux can be precisely assessed by comparing sodium concentration in fresh inlet and spent outlet dialysate.

Online analysis facilitates study of sodium flux in routine clinical practice. This approach has been validated in several studies. As an example, Moret et coworkers validated the conductivity monitoring, by comparing sodium removal in waste dialysate with an ionometric method to the online measurement and found a high degree of correlation (Moret et al. 2002). This study showed that ionic mass balance measured by conductivity monitoring allowing quantification of sodium mass transfer is an accurate and useful technique. Significant variation in sodium removal between individuals may be observed in a dialysis population reflecting large dietary salt intake habits. On the other side, much small variation within individual stable CKD patients may be noted when using fixed sodium dialysate concentration. Sodium mass removal is mainly achieved through the convective clearance (weight loss by ultrafiltration) to achieve dry weight. Now, serial reductions of dialysate sodium concentration led to an increase of the diffusive component of sodium loss by increasing dialysate/patient sodium gradient. As has been shown in some studies, reduction in dialysate sodium concentration may also contribute to reduce interdialytic weight gains (reducing thirst) and improved blood pressure control. Measurement of sodium flux and mass balance has a strong clinical relevance. The relationship between interdialytic weight gain, blood pressure level and dialysate sodium concentration can be optimally exploited as soon as sodium mass removal is measured by using online conductivity monitoring. Recently, the concept of sodium monitoring with individual tailoring has been expanded to achieve isonatremic dialysis session. In this quite sophisticated approach, sodium mass removal is tailored to personal individual needs while dialysate sodium concentration is targeting predialysis the plasma sodium concentration of the patient (Mercadal et al. 2008). Based on sodium monitoring and biofeedback system, excessive sodium removal

is then avoided, removal of interdialytic dietary sodium gain match precisely sodium intake while patient blood sodium concentration remains relatively stable. A schematic diagram presenting the principle of sodium biofeedback system is presented on Fig. 15.5. This customized individual approach of sodium balance control appears particularly appealing in uncompliant patients with large interdialytic volume and osmolality changes since it reduces postdialysis thirst phenomenon (Dominic et al. 1996).

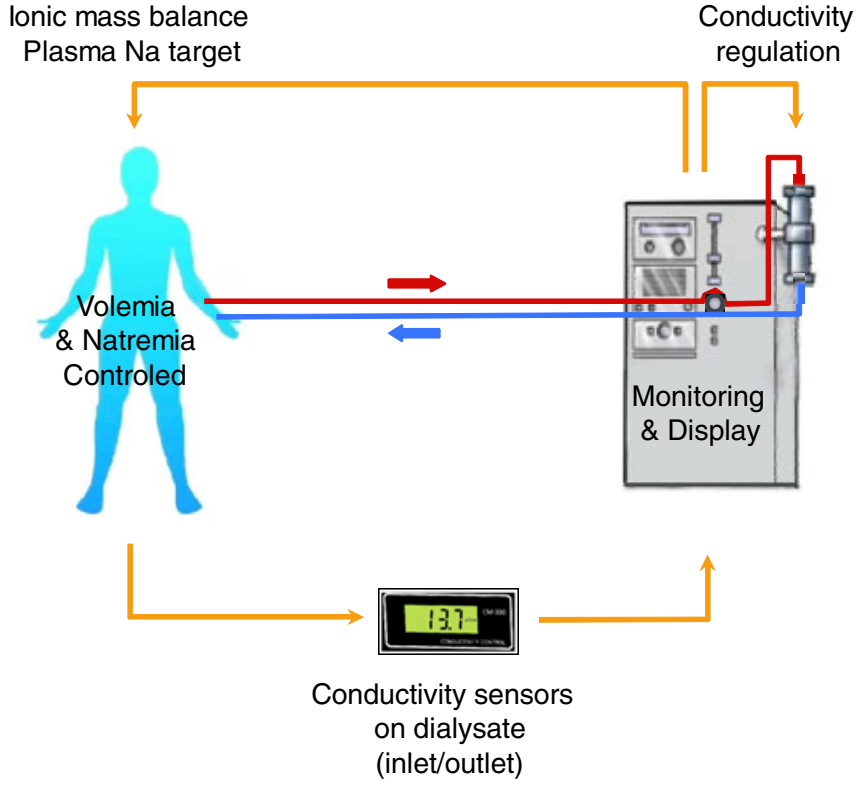


**Fig. 15.5** Biofeedback system regulating volemia and natremia based on dialysate electrolytic concentration changes

### 15.3.4 Vascular Access Monitoring Devices

Performances of vascular accesses need to be monitored to detect early dysfunction, to prevent failure and to permit correction before dialysis efficacy is altered. This is clearly stated and strongly supported by best clinical practices on vascular access (Tordoir et al. 2007). Several strategies are

proposed to monitor function of vascular access including clinical examination, bed side functional tests (blood flow, pressure, Kt/V, blood based tests, recirculation calculated from glucose infusion] or imaging techniques (Ultrasound Doppler, Contrasted fistulography or venography). It is not our intent to revisit the optimal way of managing vascular access in hemodialysis patient. Now, one may be aware that monitoring of vascular access performances may be easily performed by non-invasive online devices either embarked on dialysis machine or standalone monitors attached to blood tubing lines. Ultrasound (US) based method (HD01-03 monitor from Transonic Systems, Inc., Ithaca, NY) is widely recognized as the reference method (Krivitski 1995). Based on two external ultrasound sensors clipped on blood lines, and provided blood dilution is created by saline injection in the venous line, the US monitor has the capability of measuring the effective blood flow, the vascular flow and the access recirculation with high accuracy (Sands et al. 1996; Krivitski and Schneditz 2004). By reversing the arterial and venous lines and using the same sensors the HDD monitor will assess the cardiac output (Válek et al. 2010). Online monitoring of vascular access performances may be partly achieved by captive tools of hemodialysis machines (Bosc et al. 1998). Blood temperature monitoring (BTM) system may be used to assess the recirculation based on a thermodilution method (Schneditz et al. 1999). Recirculation measured by the thermodilution method includes the cardiopulmonary component and overestimates the value obtained by ultrasound technique up to 15% (Wang et al. 2000; Kuhn et al. 2006). Online ionic dialysance or urea clearance measurement (Ureascan) may be used alternatively to calculate recirculation and blood access flow by reversing the blood line (Mercadal et al. 2002; Lindsay et al. 2006). Values obtained by these non-invasive methods appear to be reproducible and in relatively good agreement with the ultrasound technique (Lindsay et al. 2010). However, use of these tools should remain cautious, and duplex ultrasound examination with trend analysis tend to have better predictive value (Dossabhoy et al. 2005).

## 15.4 HEMODYNAMIC MONITORING DEVICES

Preventing occurrence of hypotensive episodes and improving cardiovascular stability are important targets for improving outcomes of CKD dialysis patients. Today, these objectives should be considered as integral components of optimal dialysis therapy, since they are negatively affecting the quality of life and contributing probably to precipitate cardiovascular events in CKD patients (Tislér et al. 2003; Shoji et al. 2004). Hemodynamic monitoring devices and feedback-controlled systems ensuring real time prevention and/or correction of intradialytic hypotension are highly desirable to

improve hemodynamic stability in the context of high cardiovascular risk patients (Davenport 2009). Schematically, hemodynamic monitoring devices belong to two categories: some are passive sensors designed to measure specific patient's vital parameter; while others engineered systems are active devices using sensors with regulatory capacities via feedback controlled loop and best known as biofeedback system.

### 15.4.1 Blood Pressure Monitoring (BPM)

Blood pressure monitoring (BPM) system is currently one of the most commonly used devices to evaluate the hemodynamic tolerance of dialysis session and to judge clinical tolerance to ultrafiltration rate. Nowadays, most BPM devices are integrated in the dialysis machines or alternatively they may be provided as standalone device (Dinamap, Critikon, Tampa, USA). BPM devices record periodically systemic blood pressure and pulse rate on the patient's arm. These devices have substantially reduced care load of nursing staff and improved monitoring of dialysis patient by providing trend analysis of blood pressure over time. Now, it is important noting that peripheral blood pressure measurement may have some limitations due to vascular rigidity of brachial artery in some patients (diabetic, elderly, calcified artery), and that may reduce clinical predictive value of blood pressure monitoring. This observation has led some clinicians to propose more sensitive alternative of blood pressure and hemodynamic monitoring based on pulse pressure analysis of peripheral artery based on sphygomanometry (Mambelli et al. 2007).

### 15.4.2 Blood Volume Monitoring (BVM)

Blood Volume Monitoring (BVM) system is now widely used in hemodialysis to prevent Intradialytic hypotension. Online BVM is recording the relative blood volume change occurring during hemodialysis that reflects the unbalance between ultrafiltration and refilling rates of the vascular compartment. Intradialytic hypotension occurs when blood volume reduction is not adequately compensated by cardiovascular response (increase in vascular resistance, heart rate and/or stroke index) (Daugirdas 1991; Mitra et al. 2002). Several systems for monitoring BVM are available using different principles of measurements. The majority of these BVM devices are based on an optical measurement of hemoglobin concentration or hematocrit (Leypoldt et al. 1995; McMahon et al. 1996) while few of them are using an ultrasonographic measurement of plasma protein concentration (Johner et al. 1998). Such devices may be embarked on the dialysis

machine as technical options or may stand alone as mobile device, but usually they do not require disposable material and they do not generate extra-cost. The non-invasive character and the simplicity to use make them quite appealing and useful for clinicians. Blood volume monitoring devices may have some intrinsic technical limitations in determining absolute values (such as hematocrit, hemoglobin or total protein) but in practice, all have been proved highly correlated with relative blood volume reduction. BVM use is of help in clinical setting in achieving dry weight by avoiding hypotension and searching for the critical point that may predict the onset of crash hypotension (Barth et al. 2003). From clinical standpoint, it is known that hypotension may occur at different levels of blood volume reduction in different patients and there are also large variations within patients between dialysis sessions (Woods 2001; Basile et al. 2001b). This observation applies to individuals (Krepel et al. 2000), to groups of patients (Andrulli et al. 2002) and may be subject to time variation according to dialysis and clinical conditions (Tonelli et al. 2002). BVM devices are useful in clinic but are not definitively the ideal tool for defining dry weight (Rodriguez et al., 2005). More recently, studies of BVM monitoring have attempted to determine individual critical blood volume change by using complex mathematical modeling and fuzzy logic systems (Mancini et al. 2007). Such an approach appears to be interesting however its reliability and its predictive value preclude its routine use in clinical practice (Schmidt et al. 2001).

### 15.4.3 Biofeedback System

Biofeedback system is a further refinement of the patient management in which blood volume monitoring device is coupled to a fuzzy logic system that gives the dialysis monitor the capacity of automatically adjusting ultrafiltration rate and dialysate conductivity to maintain the blood volume trace within predefined limits (Azar 2008; Gabrielli et al. 2009). A schematic representatio is presented on Fig. 15.6. Such biofeedback systems, already available on certain dialysis machines Hemocontrol (Hospal, Lyon, France), have proved significantly reducing the frequency of hypotensive episodes experienced by hypotension prone patients (Santoro et al. 1998; Basile et al. 2001a; Ronco et al. 2000; Schmidt et al. 2001) as well as the frequency of dialysis related symptoms (nausea, cramps, fatigue, etc..) (Wolkotte et al. 2002; Santoro et al. 2002; McIntyre et al. 2003b).

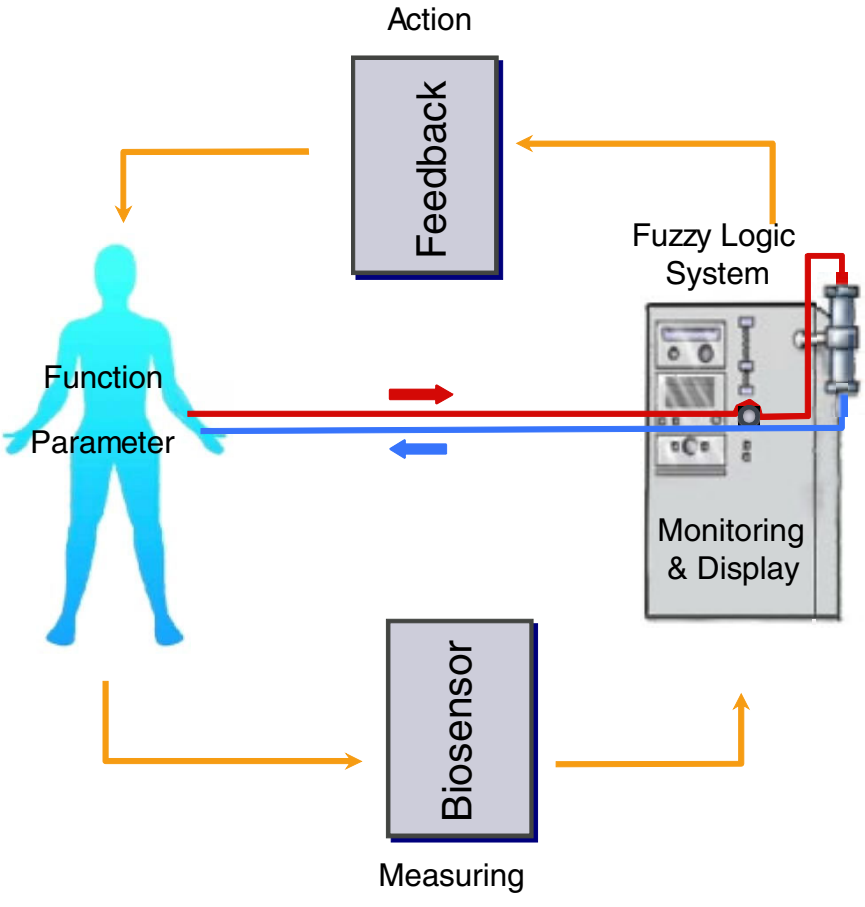


**Fig. 15.6** Biofeedback system: biosensor (or captor) providing online measurement and feedback corrective action based on fuzzy logic system

### 15.4.4 Blood Temperature Monitoring (BTM)

Blood temperature monitoring (BTM) system is now proposed on certain dialysis machines (Fresenius Medical Care, Bad Homburg, Germany). The concept has been developed as a new input component of a biofeedback control system. Online BTM device is mainly use to reduce intradialytic hypotension as presented on Fig. 15.7. The impaired cardiovascular response implicated in the pathogenesis of dialysis-induced hypotension is partly related to changes in extracorporeal blood temperature (Santoro et al. 2003). This phenomenon appears to be driven by a core temperature gain with its compensatory thermal mechanism that induces vasodilatation and tachycardia. The removal of heat by the dialysis machine via the

extracorporeal circuit and the activation of autoregulatory mechanisms (vasoconstriction, venoconstriction) attempting to preserve core temperature are then responsible for the beneficial hemodynamic effects of cooling dialysate (Maggiore et al. 2002). On short notice, it is easily foreseen that biofeedback system will couple blood volume reduction to blood temperature monitoring. Based on this system, temperature changes will be used to compensate for hypovolemia by inducing dialytic caloric losses resulting in a vasoconstriction action (Schneditz et al. 2003). BTM has other clinical applications that include total recirculation measurement based on thermodilution technique (Bonforte et al. 1995) and thermal energy balance assessment of the dialysis patient (Horácek et al. 2007).

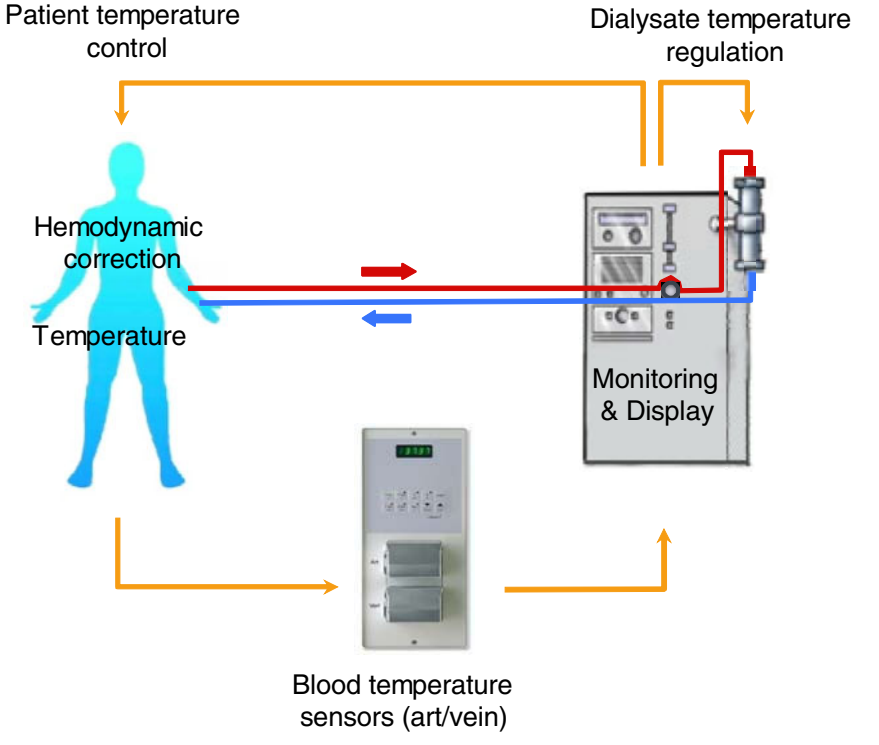


**Fig. 15.7** Blood temperature monitoring ensuring thermal balance measurement, hemodynamic stability and recirculation based on thermodilution

### 15.4.5 Online Hydraulic Permeability Monitoring

Online hydraulic permeability monitoring of the hemodialyzer membrane has been proposed for evaluating the blood protein boundary effects

(Waniewski 2006) and optimizing performances of high convective flux methods (hemodiafiltration). By means of a hemodialysis monitor equipped with four pressure transducers measuring the transmembrane pressure (TMP) and a computerized data acquisition analyzing continuously ultrafiltration rates it was then possible to evaluate changes of the coefficient of ultrafiltration (Vaussenat et al. 1997). A typical example of KUF fall during high flux postdilutional HDF obtained from on-line monitoring is given on Fig. 15.8. Interestingly, it has been shown that continuous intravenous infusion of hypertonic glucose was able to reduce the decay of KUF and to preserve the membrane hydraulic permeability (Vaussenat et al. 2000). Nowadays, hydraulic permeability monitoring (KUF and QUF) is used to develop the mixed hemodiafiltration, a treatment modality that optimize ultrafiltration rate and convective dose by combining post and predilution while maintaining TMP in a safe range of 200 to 300 mmHg (Pedrini and De Cristofaro 2003; Pedrini et al. 2006).

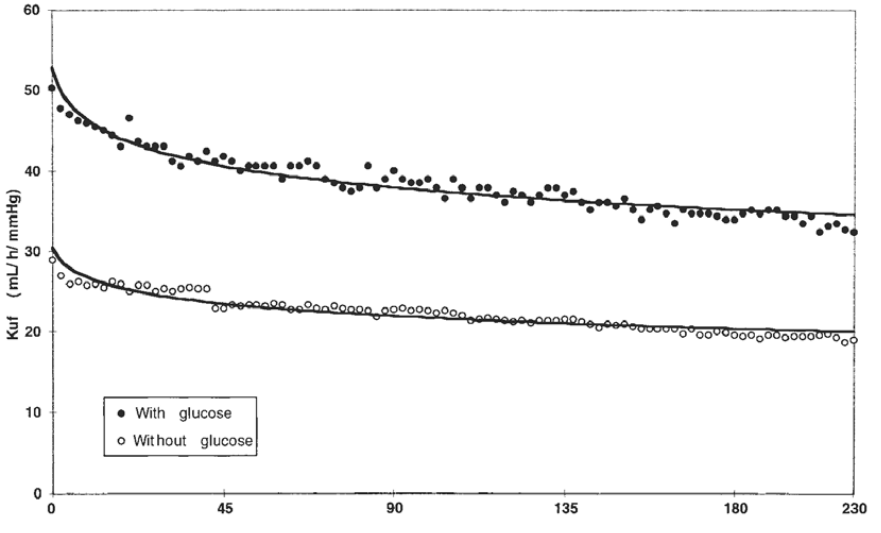


**Fig. 15.8** Typical trace of $K_{uf}$ decline during postdilutional hemodiafiltration with or without glucose infusion

### 15.4.6 Online Hemoglobin Monitoring

Online hemoglobin monitoring may be achieved by means of Blood Sensor Device (BSD). Blood volume monitoring systems that measure an absolute value of hemoglobin (or hematocrit) may be used for this

purpose. Blood sensor devices exist as integrated component of the hemodialysis machine or as external standalone mobile monitor. Several hemodialysis machines (Hemoscan from Hospal, Lyon, France (Paolini et al. 1995) and Blood Volume Monitor (BVM from Fresenius, Bad Homburg, Germany) are equipped with a blood volume monitoring system and provide in real time this information. Alternatively, standalone BSD devices (CritLine, HemaMetrics, Kaysville, USA) may be installed extemporaneously during dialysis on the arterial blood line or used offline but onsite (HemoCue AB, Ängelholm, Sweden) (Montagnac et al. 2007). In addition, HemaMetrics has developed a specific anemia management software called Crit-Line Anemia Manager (CLAM) based on hemoglobin measurement made at the beginning of each dialysis. BSD needs however to be calibrated to the local laboratory and serious caution must be considered when reading real time hemoglobin concentrations since these devices are not certified to provide blood composition picture. Once the blood sensor device of the dialysis machine has been calibrated, the correlation between estimated hemoglobin versus measured hemoglobin by an automated counter appears now to be acceptable (Chesterton et al. 2005). Clearly such BSD devices provide easy onsite non-invasive monitoring of hemoglobin, at every single dialysis session if necessary. Such monitoring provides the possibility of real time anemia management with continuous bedside hemoglobin concentrations monitoring and timely personalized erythropoietic stimulating agent adjustments.

## 15.5 QUALITY CONTROL SYSTEM DEVICES

Quality assurance (QA) process is essential in hemodialysis program for ensuring dialysis delivery dose and ultimately improving chronic kidney disease patient's outcomes. Optimal dialysis concept that was recently introduced appears to be more adapted to evaluate dialysis treatment adequacy in CKD dialysis patients (Desai et al. 2008). Optimal dialysis is an aggregate of subjective and objective criterions serving to express treatment efficacy and impacting morbidity and mortality of dialysis patient. Current methodology used by clinicians to assess dialysis efficacy relies on a targeting approach based on several vital indicators allowing fixed range of values according to evidence-based medicine (Canaud 2004; Stoffel et al. 2004). Based on this approach, it is possible to provide the individual patient with the best personal treatment options but also to ensure the same treatment quality to all patients of the dialysis unit. Continuous quality improvement (CQI) process requires a real time analysis of achieved targets in order to correct them if needed either at the individual or at the group level (Sehgal et al. 2002). Online monitoring of dialysis efficacy performed by

the monitor by means of its different devices (e.g., ionic dialysance, urea dialysis quantification, recirculation, sodium mass balance, hemoglobin concentrations, blood pressure, etc.) represents an ideal tool for continuous quality control at the individual level. Computerized system provides complementary useful tool that facilitate quality control of large dialysis population through network, data managing system and artificial intelligence (Akl et al. 2001). Based on predefined subset of analyses and graphic representation, the user (physician, nurse, patient) may have access to real time monitoring and trend analysis of individual patient or global dialysis population (Marcelli et al. 2002). Teledialysis monitoring represents a new and quite appealing adjunctive tool for facilitating and improving dialysis quality achievement in remote dialysis facilities (home dialysis program, self or limited care units, etc…) or in case of shortage of physicians (Rumpsfeld et al. 2005; Hartvigsen et al. 2007) as summarized on Fig. 15.9.

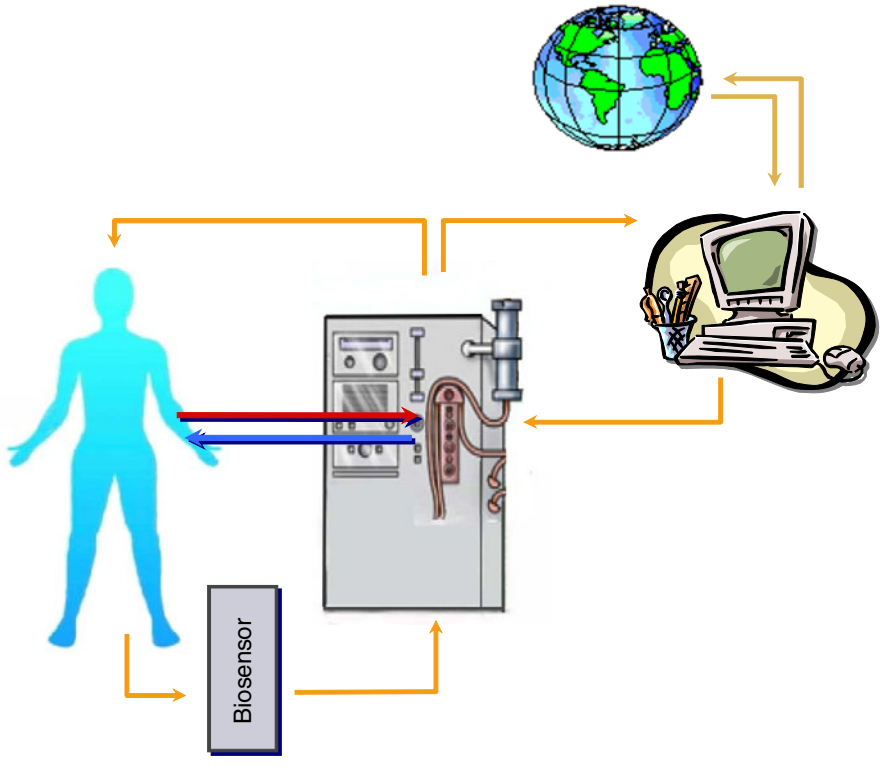


**Fig. 15.9** Teledialysis monitoring on remote computerized data management systems

## 15.6 CONCLUSIONS

Over the last few decades, it is fascinating to realize how impressive innovations have been introduced in the field of hemodialysis technology. Technological advance has been clearly beneficial to hemodialysis chronic kidney disease patient: on one side, it has enhanced performance and safety of the extracorporeal renal replacement therapy; on the other side, it has contributed to improve the hemodialysis cardiovascular tolerance and the quality of life of patients; and lastly, it has introduced a new dimension in the extracorporeal treatment based on online monitoring of crucial parameters of hemodialysis patients opening then new avenues for biofeedback and quality control systems. Most of online "tools" describe in this chapter are under current clinical evaluation and should not be considered as "toys" since scientific evidences are lacking. Indeed, translation of these technical progresses into clinical outcomes improvements will take time. Now, the implementation of these new online monitoring devices on hemodialysis machines will never substitute physician clinical judgment but certainly will facilitate and improve the management of chronic kidney disease patient (Spiegel et al. 2010).

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## ESSAY QUESTIONS

1. What criterion is used to assess the dialysis dose in hemodialysis patient?
2. List the main categories of online devices designed for continuous monitoring.
3. What does "first failure safety" strategy mean?
4. What does mean dialysis adequacy in hemodialysis patient?
5. What are the main hazards and/or life threatening complications that a dialysis patient is faced to during a hemodialysis session?
6. How the hemodialysis monitor technical configuration is designed to prevent risk associated hemodialysis sessions?
7. How urea monitoring devices work during hemodialysis session? What sort of information these urea monitoring tools provide to the clinician?
8. How the ionic dialysance compare to urea clearance during hemodialysis session? What is the clinical relevance and the interest of using ionic dialysance monitoring during hemodialysis?
9. Why monitoring vascular access and extracorporeal blood flow is important during hemodialysis? What sort of informations are providing the current online access monitoring devices?
10. How cardiovascular tolerance is evaluated during hemodialysis session? On which base the ultrafiltration is determined in a hemodialysis patient? How ultrafiltration rate affects the blood pressure control of dialysis patient?
11. Why blood volume monitoring of dialysis patient is interesting during dialysis session? How the blood volume change is assessed during hemodialysis session?
12. What is the role of biofeedback control system in hemodialysis? What is the present application of these tools and for what purpose?

## MULTIPLE CHOICE QUESTIONS

### Choose the best answer

1. Validated dialysis adequacy targets include…
   A. Kt/V > 1.4
   B. Pre-dialysis blood pressure < 140/90 mmHg
   C. Inorganic phosphate < 1.5mmol/l
   D. $B_2$-Microglobulin < 20 mg/l

E. Albumin > 38g/l
F. A, B, C and E
G. B, C, D and E
H. A, B, C and D
I. A, C, D and E

2. Dialysis dose as expressed by urea Kt/V means…
A. Dialyzer urea clearance
B. Fractional urea body clearance
C. Equivalence of renal function
D. Dialysis adequacy
E. Vascular access performance

3. Life threatening complications of hemodialysis session include…
A. Hemorrhage
B. Infection
C. Air embolism
D. Hemolysis
E. Pulmonary edema
F. B, C and D
G. A, C and D
H. B, C, and E
I. A, B and C

4. Urea monitoring devices are useful for…
A. Measuring urea kinetic in dialysate
B. Evaluating dialysis efficiency
C. Performing quality control of dialysis patient without blood sampling
D. Assessing nutritional status and protein intake
E. A, B, and C
F. A, C, and D
G. A, B, and D
H. B, C, and D

5. Urea sensors are based on…
A. Enzymatic urease
B. Ion specific electrode (pH, ammonium)
C. Conductivity sensor
D. UV absorbance
E. Colorimetric change

F. A, B, and C
G. B, C, and D
H. A, C and D
I. A, B, and D

6. Ionic dialysance monitoring is a method that…
A. Checks the ionic composition of the dialysate
B. Evaluates the dialysis dose
C. Facilitates sodium dietary counseling
D. Is superimposable to urea clearance
E. Offers a convenient tool for quality control
F. B, D, and E
G. A, B, and C
H. B, C, and D
I. A, C and D

7. Sodium modeling in dialysis has some beneficial effects on…
A. Dietary sodium restriction
B. Hemodynamic tolerance of session
C. Customizing sodium profile
D. Preventing hypotensive episodes
E. Preventing loss of residual renal function
F. C, D, and E
G. B, C, and D
H. A, B, and C
I. A, C and D

8. Biofeedback controlled systems are used…
A. To enhance dialysis dose delivery
B. To improve hemodynamic tolerance of session
C. To reduce sodium and fluid overload
D. To reduce treatment time
E. To reduce the use of antihypertensive drugs
F. A, B
G. B, C
H. C, D
I. D, E

9. Vascular access performances measurement are based on…
A. Effective access flow
B. Venous pressure changes over time
C. Recirculation

D. Dialysis dose delivery
E. Arterial pressure changes
F. B, C, and D
G. A, C, and E
H. A, B, and C
I. A, C and D

10. Online monitoring of vascular access performances use tools…
A. Hematocrit based methods
B. Pressure changes methods
C. Blood temperature method
D. Ultrasound based methods
E. Ionic dialysance methods
F. B, C, and E
G. A, B, and E
H. B, C, and D
I. C, D and E

11. Blood pressure monitoring is useful to…
A. Follow blood pressure changes over dialysis time
B. Evaluate hemodynamic tolerance
C. Prevent cardiac insult
D. Guide blood pressure and extracellular fluid volume control
E. Prevent cardiac arrhythmia
F. A, B, and D
G. A, B, and C
H. B, C, and E
I. B, C, and D

12. Blood volume monitoring uses biosensors…
A. Pressure based
B. Hematocrit based
C. Hemoglobin based
D. Protocrit based
E. B, C, and D
F. A, B, and C
G. A, C, and D
H. A, B, and D

13. Blood volume reduction during dialysis reflects…
A. Hemodynamic instability
B. Inadequacy of cardiovascular adaptation

C. Temperature changes in dialysis
D. Ultrafiltration rate applied
E. Imbalance between ultrafiltration and refilling rates
F. A, B
G. B, C
H. C, D
I. D, E

14. Biofeedback controlled machines are associated with…

A. Reduced incidence of hypotensive episodes
B. Improved quality of life
C. Improved cardiovascular stability and rapid recovery after dialysis
D. Reduced consumption of water and salt
E. Better outcomes of patients
F. A, B
G. A, C
H. B, D
I. D, E

15. Blood temperature monitoring…

A. Improves quality of life of dialysis patients
B. Reduces the incidence of hypotensive episodes
C. Enhances performances of dialysis session
D. Facilitates blood access flow
E. Reduces mortality of dialysis patients

16. Feedback controlled thermal balance in dialysis is associated with…

A. Improvement of hemodynamic tolerance
B. Reduced Intradialytic morbidity
C. Enhanced dialysis dose delivery
D. Better outcomes of dialysis patients
E. Reduced infection episodes
F. A, B
G. B, C
H. C, D
I. D, E

17. Online blood sensor device may be used…

A. To monitor hemoglobin concentration changes
B. To assess blood volume changes induced by the ultrafiltration

C. To optimize anemia management and erythropoietin use
D. To assess dry weight and refilling capacity
E. To improve hemodynamic tolerance
F. A, B, C and D
G. B, C, D and E
H. A, B, C and E
I. A, C, D and E

18. Online hemodiafiltration technique is associated…

A. Improvement of hemodynamic stability
B. Higher clearances for large molecular weight solutes
C. Reserved to expert center and for research purposes
D. Improvement of dialysis patient outcomes
E. Requirement of ultrapure water and dialysis fluid
F. A, B, C and D
G. B, C, D and E
H. A, B, C and E
I. A, B, D and E

19. Online monitoring devices provide tools for…

A. Better dialysis efficacy
B. Continuous control of dialysis dose delivery
C. Assessment of intrapatient variability
D. Training and self-control tools for nurses
E. Improving dialysis tolerance and quality of life of patient
F. A, B, C and D
G. B, C, D and E
H. A, B, C and E
I. A, B, D and E

20. Quality assurance process in dialysis facilities rely on…

A. Online monitoring tools
B. Physicians and nurses expertise
C. Validated protocols and achievement of targeted dialysis adequacy parameters
D. Teledialysis monitoring
E. Computerized data management
F. A, B, C and D
G. B, C, D and E
H. A, B, C and E
I. A, B, D and E

Chapter (16)

# Ionic Dialysance and Conductivity Modeling

Francesco Locatelli, Celestina Manzoni, Giuseppe Pontoriero, Andrea Cavalli, Salvatore Di Filippo, and Ahmad Taher Azar

**CHAPTER OUTLINES**

- Introduction
- History of conductivity clearance
- Conductivity measurement methodology
- Assessment of hemodialysis adequacy by ionic dialysance
- Calculation of access flow from ionic dialysance measurements
- Conductivity Kinetic Modeling
- Conclusion and final remarks

**CHAPTER OBJECTIVES**

- To understand the concept of ionic dialysance
- To know the main possible uses of ionic dialysance in achieving sodium balance and delivered dialysis dose quantification

**KEY TERMS**

- Conductivity
- Ionic dialysance
- Urea clearance
- Mass balance error
- Dialysis adequacy
- Access flow rate
- Access recirculation
- Sodium balance
- Single pool sodium kinetic model
- Cardiovascular stability

## ABSTRACT

In the 1993 two papers showed that instantaneous ionic dialysance can be measured without the need for blood or dialysate sampling and at no extra cost, simply by using two conductivity probes placed at the dialyzer inlet and outlet or a single probe alternately activated at the inlet and outlet. Given the very close correlation between the conductivity of dialysate and its sodium content it has been suggested that ionic dialysance can be considered equivalent to effective sodium dialysance. When ionic dialysance value is known it is possible to indirectly derive the plasma

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water conductivity value and thus the sodium concentration. The possibility to estimate sodium dialysance and plasma water sodium concentration without the need for blood samples and laboratory determination makes it very easy to apply the sodium kinetic model changing it in a conductivity kinetic model. Moreover, because of the similar molecular weight of sodium chloride and urea it has been suggested that ionic dialysance can also be considered equivalent to effective urea clearance. Thus, it should be possible to use ionic dialysance instead of urea clearance for the routine monitoring of delivered dialysis dose. Therefore, ionic dialysance seems a very promising and easy tool to improve dialytic treatment.

## 16.1 INTRODUCTION

Given the very close correlation between the conductivity of dialysate (an electrolyte solution) and its sodium content it has been suggested that ionic dialysance can be considered equivalent to effective sodium dialysance and because of the similar molecular weight of sodium chloride and urea, it can also be considered equivalent to effective urea clearance.

When ionic dialysance value is known it is possible to indirectly derive the plasma water conductivity value and thus the sodium concentration. The possibility to estimate sodium dialysance and plasma water sodium concentration without the need for blood samples and laboratory determination makes it very easy to apply the sodium kinetic model changing it in a conductivity kinetic model. In order to optimize hemodialytic treatment an inexpensive method allowing matching intradialytic hydro-sodium removal with interdialytic load is of paramount importance. The validity of the conductivity kinetic model and the possibility to use it instead of sodium kinetic modeling to routinely estimate sodium balance was clinically tested and the conductivity kinetic model resulted very accurate in matching hydro-sodium removal with interdialytic load. This plays as pivotal a role in preventing or at least reducing intradialytic

hypotension and other adverse effects of sodium depletion as in preventing or at least containing the overhydration which can favour or destabilize hypertension, induce left ventricular hypertrophy or even cause acute pulmonary edema.

It has been suggested that ionic dialysance may be considered equivalent to effective urea clearance. Thus, it should be possible to use ionic dialysance instead of urea clearance for the routine monitoring of delivered dialysis dose. Unfortunately, attempts to determine the in vivo relationship between ionic dialysance and urea clearance have led to discordant findings. Such different findings can be at least partially explained by the fact that ionic dialysance values may vary widely depending on the different methods used to modify inlet dialysate conductivity during their measurements. Recently it has been shown that the mean value of repeated ionic dialysance determinations obtained using a single-step inlet dialysate conductivity profile underestimates urea clearance corrected for access recirculation but provides a clinically adequate estimate of urea clearance corrected for total recirculation.

This is obviously important to quantify delivered dialysis dose which is related to morbidity and mortality of dialysis patients. If the urea distribution volume is known, that is total body water volume; ionic dialysance determination makes it possible to determine the Kt/V, which is the index usually used to quantify the delivered dialysis dose. Even if the simple Kt is assumed as index of delivered dialysis dose, by following the Kt through the dialysis session makes it possible to promptly know any reduction in ionic dialysance that can mean a reduction in delivered dialysis dose and that can prompt the search for the possible causes: reduction of effective blood flow, partial dialyzer clotting, access recirculation. Therefore, ionic dialysance seems undoubtedly a very promising and easy tool to improve dialytic treatment.

## 16.2 HISTORY OF CONDUCTIVITY CLEARANCE

### 16.2.1 Concept of Clearance

The correct estimate of urea clearance requires the determination of the amount of urea leaving the blood as well as that appearing in the dialysate. Usually urea clearance at blood side is estimated starting from the "in vitro" value, the calculation of the dialyzer mass transfer area coefficient (KoA) and then urea clearance recalculation for different blood and dialysate flows (Sargent and Gotch 1989). In vivo urea clearance from the blood side ($K_b$) is usually determined according to:

$$K_b = \frac{Q_B\left(C_{Bi} - C_{Bo}\right)}{C_{Bi}} + \left[\frac{Q_f \times C_{Bo}}{C_{Bi}}\right] \tag{16.1}$$

Where $Q_B$ is the whole blood flow rate (ml/min), $Q_f$ is the ultrafiltration rate (mL/min) and C is plasma water urea concentration (mg/dl) at the inlet ($C_{Bi}$) and outlet ($C_{Bo}$) ports of the dialyzer.

In vivo whole blood flow rates are influenced by negative pre-pump pressure, especially at high blood flow rates. According to Depner et al. (1990) the "effective whole blood flow" rate ($Q_{Be}$) can be estimated from the nominal $Q_B$ ($Q_{Bn}$) using the following formulas (Depner et al. 1990; Daugirdas and Depner 1994):

**For $Q_{Bn} < 200$ ml/min**

$$Q_{Be} = Q_{Bn} \tag{16.2}$$

**For $Q_{Bn} > 200$ ml/min**

$$Q_{Be} = Q_{Bn} \times \left[1 - \left(\frac{\left(Q_{Bn} - 200\right)}{2000}\right)\right] \tag{16.3}$$

According to these formulas, at $Q_{Bn}$ values of 300 and 400 ml/min, $Q_{Be}$ values of respectively 285 and 360 ml/min can be predicted. The "effective flow" of urea is represented by the "blood water flow" ($Q_e$), which is

always lower than $Q_{Be}$ and can be estimated by taking into account hematocrit (Ht), the intracellular distribution of urea (Fr) and the volume fraction of hydrated proteins ($\alpha$) according to the following equation (Sargent and Gotch 1989)

$$Q_e = Q_{Be} \times \left( \frac{F_p - Ht}{100 \times (F_P - F_r)} \right) \tag{16.4}$$

$F_p$ can be calculated as $F_p = 1-\alpha$, where $\alpha$ is considered to be 0.0107 times the concentration of total plasma proteins in g/dl (Colton et al. 1970). The equilibrium distribution coefficient for the ratio of erythrocyte to plasma concentrations ($F_r$) can be assumed to be 0.86 (Colton et al. 1970). On the basis of these data, and assuming a hematocrit value of 30% and a physiological total protein concentration, the "blood water flow" can be estimated as being about 90% of the $Q_{Be}$ and nearly 80% of $Q_{Bn}$. Finally, "in-vivo urea clearances" values are always lower than their in vitro counterparts because of cardiopulmonary recirculation (Schneditz et al. 1992) and (when present) access recirculation. Urea clearance corrected for total recirculation (access plus cardiopulmonary), is calculated from the product of the diffusive value ($K_b$) and the $C_{Bi}/C_s$ ratio, where $C_s$ is the plasma water urea concentration in the inlet blood sample obtained after reducing the pump speed to 50 ml/min for 2 minutes (Schneditz et al. 1992). If systemic blood would be accessible the blood-side clearance corrected for recirculation could be written directly as the effective blood side urea clearance (KeUB) (Kuhlmann et al. 2001):

$$\text{KeUB} = \frac{Q_s C_s - C_{Bo}\,(Q_s - Q_f)}{C_s - C_{Di}} = \frac{Q_s C_s - C_{Bo}\,(Q_s - Q_f)}{C_s} \tag{16.5}$$

Where $Q_s$ is the systemic blood flow rate. Equation (16.5) is the extracted mass flow divided by the gradient. With no urea in the dialysate inlet, $C_{Di}$ is zero and the right term is equivalent. Assuming the fraction of recirculation, R, is known, the concentration of the arterial blood at the filter inlet would mix with the venous outlet blood according to:

$$C_{Bi} = (1 - R) \times C_s + (R \times C_{Bo}) \tag{16.6}$$

$$\Rightarrow C_s = \frac{C_{Bi} - RC_{Bo}}{1 - R} \tag{16.7}$$

The systemic blood flow is decreased by the recirculated fraction and can be calculated as follows:

$$Q_s = [1 - R] \times Q_e \tag{16.8}$$

By substituting Eq. (16.7) and Eq. (16.8) into Eq. (16.5), the effective blood side urea clearance corrected for recirculation can be calculated (Kuhlmann et al. 2001):

$$\begin{aligned} \text{KeUB} &= \frac{(1-R)\,Q_e \left[\dfrac{C_{Bi} - RC_{Bo}}{1-R}\right] - C_{Bo}\left[((1-R)\,Q_e) - Q_f\right]}{\dfrac{C_{Bi} - RC_{Bo}}{1-R}} \\ &= \frac{(1-R)\left[Q_e C_{Bi} - C_{Bo}(Q_e - Q_f)\right]}{C_{Bi} - RC_{Bo}} \end{aligned} \tag{16.9}$$

### Example 16.1

Calculate the effective blood side urea clearance corrected for recirculation for a dialysis patient if the whole blood flow rate is 250 ml/min, ultrafiltration rate is 20.84 ml/min, plasma water urea concentrations at the inlet and outlet ports of the dialyzer are 129 mg/dL and 27 mg/dL, respectively and the access recirculation is 3.78%.

### Solution

Since the nominal blood flow $Q_{Bn}$ > 200 ml/min, the "effective whole blood flow" rate ($Q_{Be}$) can be estimated according to Depner formula as follows:

$$Q_{Be} = Q_{Bn} \times \left[1 - \left(\frac{(Q_{Bn} - 200)}{2000}\right)\right] = 250 \times \left[1 - \left(\frac{(250 - 200)}{2000}\right)\right]$$

$$= 243.8 \text{ ml/min}$$

The effective "blood water flow" ($Q_e$) = 0.9 × $Q_{Be}$ = 219.4 ml/min

The effective blood side urea clearance corrected for recirculation can be calculated according to Eq. (16.9) as follows:

$$\text{KeUB} = \frac{(1-R)\left[Q_e C_{Bi} - C_{Bo}(Q_e - Q_f)\right]}{C_{Bi} - RC_{Bo}} = 172.5 \text{ ml/min}$$

In vivo urea clearance determination at dialysate side ($K_d$) is calculated according to:

$$K_d = \frac{Q_{Do}\left(C_{Do} - C_{Di}\right)}{C_{Bi}} \tag{16.10}$$

Where $Q_{Do}$ is the outlet dialysate flow rate (mL/min) and is calculated as: $Q_{Di} + Q_f$, $C_{Di}$ is the dialysate concentration at the dialyzer inlet (mg/dL) and $C_{Do}$ is the dialysate concentration at the dialyzer outlet (mg/dL). Obviously also the $K_d$ values must be corrected for recirculation as follows (Kuhlmann et al. 2001):

$$\text{KeUD} = (1 - R)\frac{C_{Do}(Q_{Di} + Q_f)}{C_{Bi} - RC_{Bo}} \tag{16.11}$$

Where $C_{Do}$ is the urea concentration at the dialysate outlet of the dialyzer. Equations (16.9) and (16.11) can be utilized to control if the mass balance across the filter is correct. This helps to identify erroneous laboratory measurements. The mass balance error (MBE %) relates the difference in mass flux that has been found by a corresponding blood side and dialysate side measurement to the mean mass flux of both measurements (Di Filippo et al. 2001).

$$\text{MBE}\,(\%) = \frac{\text{Dialysate side urea quantity-Blood side urea quantity}}{\left(\text{Dialysate side urea quantity+Blood side urea quantity}\right)/2}$$

$$\text{MBE}\,(\%) = 2 \times \left[\frac{(Q_{Di} + Q_f)\,C_{Do} - \left(Q_{ei}\,C_{Bi} - Q_{eo}\,C_{Bo}\right)}{(Q_{Di} + Q_f)\,C_{Do} + \left(Q_{ei}\,C_{Bi} - Q_{eo}\,C_{Bo}\right)}\right] \tag{16.12}$$

Where $Q_{ei}$ and $Q_{eo}$ are the effective water blood flow rates at the dialyser inlet and outlet, respectively, $Q_{Di}$ is the inlet dialysate flow rate (ml/min). $Q_{eo}$ can be calculated as $Q_{ei} - Q_f$. Only if the error in the mass balance between the two fluxes (that of urea leaving the blood and that of urea appearing in the dialysate) is less than 5% the clearance value can be assumed to be technically correct.

### Example 16.2

Using the same data in Example 16.1, Calculate the effective dialysate side urea clearance corrected for recirculation for a dialysis patient if the

dialysate flow rate is 500 ml/min and the outlet dialysate urea concentration is 50 mg/dL.

### Solution

The effective blood side urea clearance corrected for recirculation can be calculated according to Eq. (16.11) as follows:

$$\text{KeUD} = (1-\text{R})\frac{C_{Do}(Q_D + Q_f)}{C_{Bi} - RC_{Bo}} = (1-0.0378)\times\frac{45\times(500+20.84)}{129-(0.0378\times 27)}$$

$$= 176.2 \text{ ml/min}$$

### Example 16.3

Using the same data in Examples 16.1 and 16.2, calculate the mass balance error (MBE %).

### Solution

The mass balance error (MBE %) can be calculated according to Eq. (16.12) as follows:

$$\text{MBE}(\%) = 2\times\left[\frac{(Q_{Di}+Q_f)\,C_{Do} - (Q_{ei}\,C_{Bi} - Q_{eo}\,C_{Bo})}{(Q_{Di}+Q_f)\,C_{Do} + (Q_{ei}\,C_{Bi} - Q_{eo}\,C_{Bo})}\right]$$

$Q_{eo} = Q_{ei} - Q_f = 219.4 - 20.84 = 198.6$ ml/min

$$\text{MBE}(\%) = 2\times\left[\frac{45\times(500+20.84) - (219.4\times 129 - 198.6\times 27)}{45\times(500+20.84) - (219.4\times 129 - 198.6\times 27)}\right]$$

$$= 0.0214\times 100 = 2.14\%$$

Since MBE is less than 5%, then the mass balance across the filter is correct.

### 16.2.2 Concept of Dialysance

More complex than urea clearance is the determination of sodium dialysance ($D_{Na}$):

$$D_{Na} = \frac{J_{Na}}{\Delta C} \tag{16.13}$$

Where $J_{Na}$ is sodium flux and $\Delta C$ is the diffusive gradient.

At constant values of dialysate and blood water fluxes ($Q_{Di}=Q_{Do}$; $Q_{ei}=Q_{eo}$) sodium flux ($J_{Na}$) is calculated as follows:

**At the dialysate side:**

$$J_{Na} = Q_{Di} \times (C_{Nai} - C_{Nao}) \tag{16.14}$$

**At blood side:**

$$J_{Na} = Q_{ei} \times (C_{Nai} - C_{Nao}) \tag{16.15}$$

Where $Q_{Di}$ is the inlet dialysate flow rate (mL/min) and the sodium concentrations $C_{Na}$ (mEq/L) refer to total sodium. The diffusive gradient ($\Delta C$) is calculated as:

$$\Delta C = \left[ Na^{+}_{pwi} \times \alpha - Na^{+}_{D_i} \right] \tag{16.16}$$

Where $Na^{+}_{pwi}$ and $Na^{+}_{Di}$ are ionized sodium concentrations. While all the ionized sodium in the dialysate is diffusible, in the plasma water because the Donnan effect of proteins, at a physiological protein concentration, the diffusible fraction is around 95% of ionized sodium concentration. Thus,

$$D_{Na} = \frac{Q_{Di} \times (C_{Nai} - C_{Nao})}{\left[ Na^{+}_{pwi} \times 0.95 - Na^{+}_{D_i} \right]} \tag{16.17}$$

Also in this case sodium dialysance must be corrected for recirculation; this means that $Na^{+}_{pwi}$ must be determined also after $Q_B$ reduced to 50 ml/min per 2 min ($Na^{+}_{pws}$). Thus,

$$\text{Effective Sodium Dialysance} = \left[ \frac{Q_{Di} \times (C_{Nai} - C_{Nao})}{(Na^{+}_{p_{wi}} - Na^{+}_{D_i})} \right] \times \frac{Na^{+}_{p_{wi}}}{Na^{+}_{p_{ws}}} \tag{16.18}$$

Sodium concentrations are currently measured by means of flame photometry and indirect ionometry that give the same results and by direct ionometry with different results. Flame photometry determines total sodium concentrations but when the solute is the plasma this method invariably underestimates the real total sodium concentration (pseudohyponatremia) and the result has to be corrected. Direct ionometry measures ionized sodium concentrations. When the solute is the plasma, in the case of a photometrically measured sodium concentration (NaT) of 140mEq/l, the corrected plasma water sodium concentration (NaP) at a physiological protein

concentration is usually 9mEq/l higher than NaT. The NaT is usually corrected for the plasma water fraction by means of the equation proposed by Waugh (Waugh 1969) by using the measured total plasma protein concentration ($T_P$) in grams per deciliter:

$$NaP = NaT \times \left[ \frac{100}{(99.1 - 73 \times T_P)} \right] \tag{16.19}$$

The determined ionized concentration ( $Na_P^+$ ) is 2mEq/l higher than NaT and about 6 mEq/L lower than NaP. The ultrafiltrate sodium concentration measured by flame photometry and indirect ionometry once again refers to total sodium concentration (NaUF) but, because ultrafiltrate is protein-free, there is no need for correction. Ultrafiltrate sodium is partially complexed with ultrafiltrable anions and, as in plasma water, the ionized sodium can be measured by direct ionometry; the concentration is usually 5-6 mEq/l lower than that of total sodium. Similarly, total dialysate sodium concentration (NaD) is measured by flame photometry and indirect ionometry; ionized sodium concentration ( $Na_D^+$ ) by direct ionometry; as the amount of complexed sodium in the usual dialysate is about 4mEq/l, $Na_D^+$ is about 4mEq/l less than NaD (see Fig. 16.1).

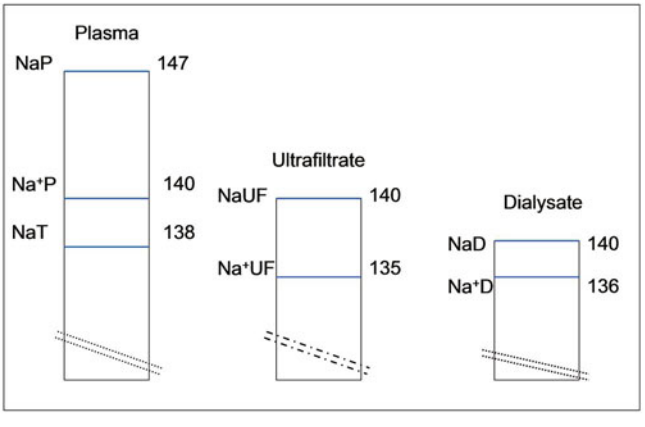


**Fig. 16.1** Relationship between total plasma sodium concentration (NaT), Plasma Water Sodium Concentration (NaP) and Ionized Sodium Concentration (Na+P) in blood; between Total (NaUF) and Ionized Sodium ( $Na_{UF}^+$ ) in the Ultrafiltrate; between Total (NaD) and Ionized Sodium ( $Na_D^+$ ) in Dialysate.

In order to choose the correct dialysate sodium concentration, it is first necessary to know the blood sodium concentration available for diffusion. The blood-dialysate concentration gradient for sodium diffusion flux across the dialyzer is a function of the sodium activity. It has been shown that the ionized sodium concentration in the ultrafiltrate is less than that in plasma water as a result of the Donnan effect: as plasma proteins cannot cross the dialysis membrane and are charged negatively, some cations must be retained in the blood in order to maintain electroneutrality. The ionized sodium concentration in the ultrafiltrate should be considered as the blood concentration capable of crossing the membrane, and therefore the concentration available for diffusion. It means that the inlet blood sodium concentration measured by direct potentiometry should be corrected by a factor of 0.96 (corresponding to the ratio between the ionized sodium concentration in the ultrafiltrate and the ionized sodium concentration in the plasma water) to obtain the concentration of dialysate sodium by direct potentiometry at which diffusion flux is zero. In the dialysate (which is protein-free), the ionized sodium concentration directly measured by ionometry should be considered as the concentration available for diffusion. In the dialysate, at constant concentration of other ions, there is a direct and linear correlation between the sodium concentration and the conductivity value of the solution (at least for conductivity values from 12 to 16 mS/cm).

## 16.3 CONDUCTIVITY MEASUREMENT METHODOLOGY

Since the early 1990s the concepts of conductivity measurements have been reported. The conductivity methodology named as the effective ionic dialysance method. In the 1993, nearly at the same time, two papers were published showing that instantaneous ionic dialysance can be measured without the need for any blood or dialysate sampling, and at no extra cost, simply by using two conductivity probes placed at the dialyzer inlet and outlet or a single probe alternately activated at the inlet and outlet (Polaschegg 1993; Petitclerc et al. 1993). This allows repeated measurements of ionic dialysance that can be used to obtain the mean value for the dialytic session as a whole (Lindsay and Sternby 2005) (see Fig. 16.2).

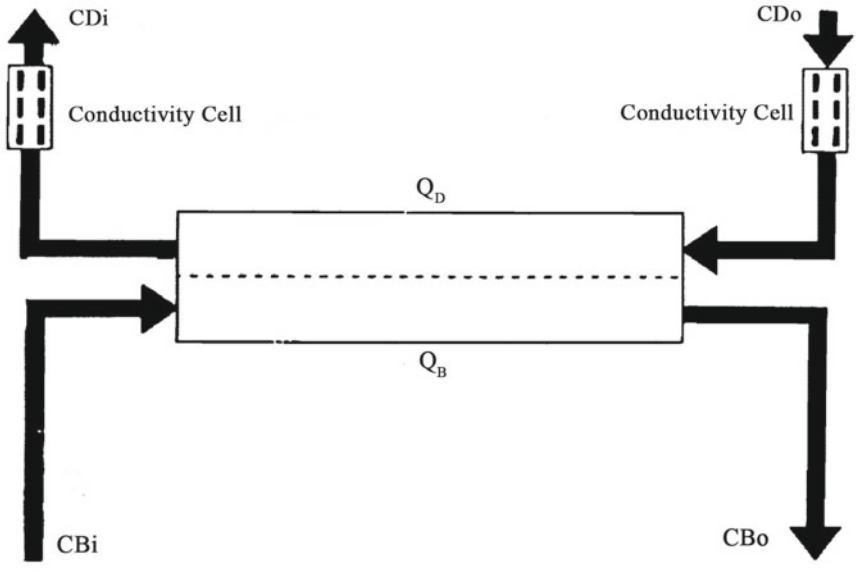


**Fig. 16.2** Setup for dialysance measurement. $C_{Bi}$ ($C_{Bo}$): blood inlet (outlet) concentration. $C_{Di}$ ($C_{Do}$): dialysate inlet (outlet) concentration. $Q_B$ ($Q_D$) blood (dialysate) flow. [Adapted from Lindsay RM, Sternby J (2005) Future directions in dialysis quantification. Semin Dial.; 14(4):300-7, with permission]

As stated at the beginning of the chapter, given the very close correlation between the conductivity of an electrolyte solution and its sodium content, it has been suggested that ionic dialysance can be considered equivalent to effective sodium dialysance, and because of the similar molecular weight of sodium chloride and urea, it can also be considered equivalent to effective urea clearance (see Table 16.1). Thus, it should be possible to use ionic dialysance instead of urea clearance for the routine monitoring of delivered dialysis dose. Ionic dialysance can be defined as the ratio between the ionic flux (easily derivable from dialysate flow rate and inlet and outlet dialysate conductivity) and the corresponding diffusive gradient between patient and dialysate.

**Table 16.1** Ionic dialysance versus urea clearance. [Adapted from Mercadal L, Ridel C, Petitclerc T (2005) Ionic dialysance: principle and review of its clinical relevance for quantification of hemodialysis efficiency, Hemodial Int.; 9(2):111-9, with permission].

| First Author, Year (System) | Measurement Protocol Of K And D |
|---|---|
| Petitclerc et al (1993) (Hospal) | Direct measurements of K with dialysate and arterial blood samplings, 4 measures/session vs. 10 measures of dialysance/session. |
| Gotch et al (1995) (Fresenius) | Direct measurements of K with dialysate, arterial and venous blood samplings. K, mean of the measurements from the dialysate and blood side. |
| Mercadal et al (1998) (Hospal) | Direct measurement of K from blood (n=16) and dialysate side (n=88) paired with D measurement. |
| Locatelli et al (1999) (Hospal) | Six anuric patients, 3 measurements of D and K at each dialysis session with variable blood flow from 200 to 400 mL/min. Direct measurement of K from blood and dialysate side. Arterial urea concentration calculated from blood sampling with blood pump running (UpwA) and with reduced blood flow at 100 mL/min (UpwS): effective clearance ($_eK$) = UK*UpwA/UpwS. |
| Lindsay et al (2001) (Hospal) | 192 paired measurements of D and K obtained from 48 dialysis sessions of eight patients. Transonic for recirculation measurement and effective blood flow for K calculated from blood side. K calculated from blood and dialysate side: 175 measurements with mass balance error < 5%. |
| Di Filippo et al (2001) (Fresenius) | K direct measurements from blood and dialysate side, 145 values with mass balance error < 5% and correction for total recirculation |
| Goldau et al (2002) (Fresenius) | Direct measurement of K blood-side, n=162 Fresenius system modified for using pulse step |
| Mercadal et al (2002) (Hospal) | K direct measurements from dialysate side (n=50) paired with D on patients dialyzed on venous central catheters. |

Unfortunately, it is impossible to determine patient conductivity directly in routine practice. The mathematical model elaborated by Polaschegg (1993) and Petitclerc et al (1993) overcomes this problem by calculating ionic dialysance as the ratio between two differences: 1) the difference between two ionic fluxes (obtained by changing the baseline inlet dialysate conductivity for a few minutes) and 2) the difference between the corresponding diffusive gradients. Since the basic assumption of the model is that patient conductivity does not change during the short time needed to make the measurements (because of the low entity of sodium fluxes and the high value of the sodium distribution volume), the two values of patient conductivity cancel each other out, and the difference between the diffusive gradients is reduced to the difference between the two values of inlet dialysate conductivity.

According to Polaschegg (1993):

$$D = -Q_D \times \left[ 1 - \frac{(C_{do2} - C_{do1})}{(C_{di2} - C_{di1})} \right] \tag{16.20}$$

The only difference according to Petitclerc et al (1993) is in that $Q_D$ is including ultrafiltration value ($Q_f$):

$$D = -Q_f \times \left[ 1 - \frac{(C_{do2} - C_{do1})}{(C_{di2} - C_{di1})} \right] \tag{16.21}$$

Furthermore the obtained value takes into account the access recirculation when it is present. This method only requires that dialysis monitor be equipped with one more conductivity probe placed at the outlet port of the dialyzer so to made possible to measure inlet and outlet dialysate conductivity ($C_{do1}$, $C_{do2}$) at two different inlet values ($C_{di1}$, $C_{di2}$).

Afterwards, the main problem in using the new technology was in that there was no consensus concerning the relationship between ionic dialysance and urea clearance. Using a Fresenius Medical Care module and high-flux polysulfone dialyzers, it has been found that the ratio between ionic dialysance and urea clearance corrected for access recirculation was $1.00 \pm 0.007$ (Gotch et al. 1995), but Manzoni et al (1996), who used the Hospal-France Biofeedback Module and acetate cellulose dialyzers, found that the values of ionic dialysance were clearly lower than those of urea clearance (a ratio of $0.89 \pm 0.04$). Some in vitro results suggested that the correlation between ionic dialysance and urea clearance may also depend

on the type of dialyzer (Ebben et al. 1996). According to these authors, when using an uncharged membrane (polysulphone) urea clearance is equal to ionic dialysance while when using a negatively charged membrane (cellulose acetate) urea clerance results higher than ionic dialysance. These results however were not confirmed by further studies.

Further different results have been reported by Mercadal et al (1998). Using an Integra Hospal Dasco module and charged membranes, they found that the ratio between ionic dialysance and urea clearance was 0.98 $\pm$ 0.05 for clearance values of less than 185 ml/min and 0.90 $\pm$ 0.05 for clearance values of more than 185 ml/min; when uncharged membranes were used, the ratio at clearances of less than 185 ml/min significantly decreased to 0.95 $\pm$ 0.06, but was similar to the mean charged membrane value in the other case (0.90 $\pm$ 0.03). Altogether, these results give a ratio always less than 1.

The real relationship between urea clearance and ionic dialysance was therefore still unknown. The mathematical model extensively described (Polaschegg 1993; Petitclerc et al. 1993) makes it possible to calculate ionic dialysance by measuring the difference between two ionic fluxes and two dialysate inlet conductivities on the assumption that patient conductivity at the inlet port of dialyzer does not change during the short time needed for the measurements, an assumption based on the rationale that such a small amount of sodium transfer has no significant effect on plasma water sodium concentration because of the high sodium distribution volume. However, as differences in the entity and direction (increase or decrease) of the change in inlet dialysate conductivity can affect ionic flux through different changes in inlet plasma water conductivity caused by cardiopulmonary recirculation, it is likely that the different modalities used in applying the method could lead to different values of effective ionic dialysance.

To verify, in a large number of patients and by means of serial in vivo measurements, whether the value of ionic dialysance is affected by the method of determination as a consequence of the effect of cardiopulmonary recirculation on inlet plasma water conductivity when inlet dialysate conductivity is changed, thirty-three patients were studied during 186 dialysis sessions (Di Filippo et al. 2001). All of the treatments were given using a modified Fresenius Medical Care 4008 B machine equipped with meters to measure inlet and outlet dialysate conductivity ($C_{di}$ and $C_{do}$). The machine varied $C_{di}$ twice or three times per session according to the following pattern: (see Fig. 16.3)

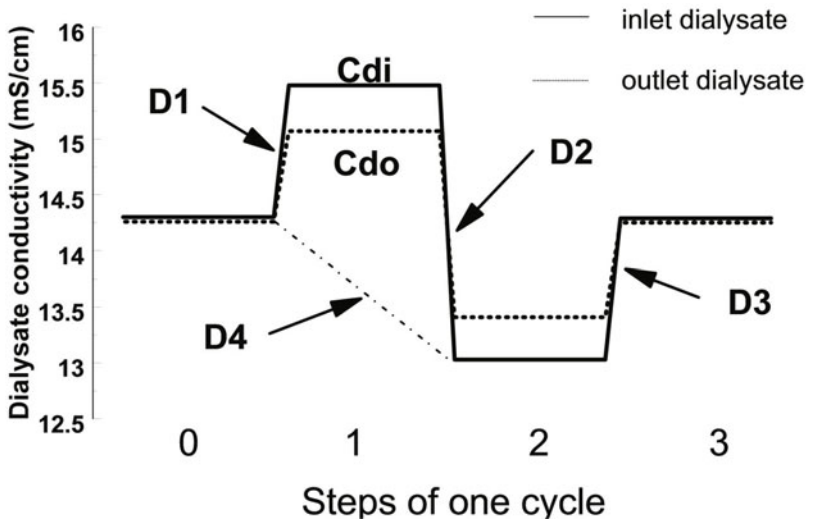


**Fig. 16.3** Pattern of variation of inlet (solid line) and outlet (dashed line) dialysate conductivities. Starting at baseline conductivity (Step 0), the inlet dialysate conductivity ($C_{di}$) increased by 8% (Step1). After the target value was reached, $C_{di}$ decreased to 8% below baseline (Step 2). When $C_{di}$ reached the new target, it was returned to the starting value (Step 3). D1 through D4 are the four steps of dialysance obtained for each cycle. [Adapted from Di Filippo S, Manzoni C, Andrulli S (2001) How to determine ionic di alysance for the online assessment of delivered dialysis dose. Kid ney Int ; 59(2):774-782, with permission]

Starting from baseline conductivity (step 0), $C_{di}$ was increased by 8% (step 1). After $C_{di}$ had reached the target value, which took 8 to 10 minutes because of feedback regulations, it was lowered to 8% below the baseline value (step 2). After 8 to 10 minutes, when it had reached the new target, it was returned to its starting value (step 3). All of the measurements were made at the prescribed ultrafiltration rate. During the same dialysis session and immediately after the completion of each cycle of dialysate conductivity changes, blood and dialysate samples were collected in order to determine urea clearance at both the blood side ($K_b$) and dialysate side ($K_d$) according to Eq. (16.1) and Eq. (16.10) by replacing $Q_B$ in Eq. (16.1) with $Q_{ei}$.

After collecting the blood and dialysate samples for urea clearance determinations, access recirculation was measured by means of a thermal dilution technique (BTM; Fresenius Medical Care, Bad Homburg, Germany http://www.fmc-ag.com/) using temperature sensors. Using the $C_{di}$ and $C_{do}$

values obtained at each step, ionic dialysance (D) was calculated according to Polaschegg (1993):

$$D = Q_{Do} \times \left[ \frac{\Delta C_{di} - \Delta C_{do}}{\Delta C_{di}} \right] = \left[ Q_{Di} + Q_f \right] \times \left[ \frac{\Delta C_{di} - \Delta C_{do}}{\Delta C_{di}} \right] \quad (16.22)$$

Where ΔCd is the difference between dialysate conductivity (mS/cm) at the two steps considered; i and o stand for inlet and outlet values. Equation (16.22) can be written in another form as follows:

$$ID = \left( Q_{Di} + Q_f \right) \times \left[ 1 - \frac{C_{do1} - C_{do0}}{C_{di1} - C_{di0}} \right] \quad (16.23)$$

Where $Q_{Di}$ is dialysate flow at the inlet port of the dialyzer in ml/min; $Q_f$ is ultrafiltration rate in ml/min; $C_{di1}$ is inlet dialysate conductivity during step 1 in mS/cm; $C_{do1}$ is outlet dialysate conductivity during step 1, in mS/cm; $C_{di0}$ is inlet dialysate conductivity during step 0, in mS/cm; $C_{do0}$ is outlet dialysate conductivity during step 0, in mS/cm.

Four values of dialysance were obtained for each cycle: D1 from steps 0 to 1, D2 from steps 1 to 2, D3 from steps 2 to 3, and D4 from steps 0 to 2 (see Fig. 16.3). The mean values resulted: D1=171±21 ml/min; D2=181±21 ml/min; D3=189±23ml/min; D4=190±23ml/min. The results show that ionic dialysance strictly depends on the method of determination. The fact that D1 (steps 0 to 1) was lower than D2 (steps 1 to 2) and D2 was almost always lower than D3 (steps 2 to 3) and D4 (steps 0 to 2) suggests that the ratio between the ionic flux ($\Delta C_{di}$-$\Delta C_{do}$) and the diffusive gradient ($\Delta C_{di}$) was not constant.

It was hypothesized that the change in inlet dialysate conductivity can modify ionic flux as a result of the effect of cardiopulmonary recirculation on inlet plasma water conductivity ($C_{pwi}$). Increased $C_{do1}$ caused by increased values of $C_{di1}$ (step 0 to 1 in the study) will cause an increase in $C_{pwi1}$ and this will decrease the conductivity gradient within the dialyzer, decrease the values of ionic flux and lead to lower values of D. Baseline inlet plasma water conductivity ($C_{pwi0}$) was estimated according to the following equation, using the mean of the four dialysance values (Di Filippo et al. 2001):

$$C_{pwi0}\left(\text{mS/cm}\right) = C_{di0} - \left[ \frac{Q_{Do0} \times \left( C_{di0} - C_{do0} \right)}{D_m} \right] \quad (16.24)$$

Where $D_m$ is the mean of the four ionic dialysance values D1, D2, D3 and D4; 0 stands for step 0 (baseline).

Starting from $C_{pwi0}$, the outlet $C_{pwo1}$ and inlet $C_{pwi1}$ plasma water conductivity values at step 1 were calculated according to the following equations, taking into account the effect of cardiopulmonary recirculation ($R_{cp}$) (Di Filippo et al. 2001):

$$C_{pwo1}\left(\text{mS/cm}\right)=\frac{\left[Q_{ei}\times C_{pwi0}\right]+\left[Q_{Do}\times\left(C_{di1}-C_{do1}\right)\right]}{Q_{eo}} \qquad (16.25)$$

Where $$Q_{eo}=Q_{ei}-Q_f$$

$$C_{pwi1}=\frac{\left[Q_{ei}\times R_{cp}\times C_{pwo1}\right]+\left[Q_{ei}\times\left(1-R_{cp}\right)\times C_{pwi0}\right]}{Q_{ei}} \qquad (16.26)$$

Starting from $C_{pwi1}$, the same equations were used to calculate $C_{pwo2}$ and $C_{pwi2}$. The inlet plasma water conductivity at step 3 ($C_{pwi3}$) was assumed to be equivalent to $C_{pwi0}$. The thermal dilution technique (BTM)-determined total recirculation ($R_t$) value of less than 10% was assumed to correspond to cardiopulmonary recirculation ($R_{cp}$) (Schneditz et al. 1992). A BTM value of more than 10% suggested the presence of vascular access recirculation. The $R_{cp}$ can be calculated according to (Schneditz et al. 1992):

When $R_t < 10\%$

$$R_{cp}=R_t \qquad (16.27)$$

When $R_t > 10\%$

$$R_{cp}=\frac{C_s-C_A}{C_s-C_V} \qquad (16.28)$$

Where $C_S$ is the systemic urea concentration (mg/dL); $C_A$ is the arterial urea concentration (mg/dL) and $C_V$ is the venous urea concentration (mg/dL). Systemic urea concentration $C_S$ can be calculated as (Schneditz et al. 1992; Depner et al. 1999):

$$C_S=\frac{C_A}{F_{cp}} \qquad (16.29)$$

Where $F_{cp}$ is the adjustment factor for cardiopulmonary recirculation and is calculated as follows (Schneditz et al. 1992; Depner et al. 1999):

$$F_{cp} = \frac{1}{\left[1 + \frac{D_m}{3000 \times BS - 800}\right]} \tag{16.30}$$

Where BS is the body surface ($m^2$) and is calculated according to Dubois and Dubois (1989):

$$\begin{aligned} BSA\ (m^2) = 0.007184 \times \text{post-HD body weight}^{0.425}\ (Kg) \\ \times \text{height}^{0.725}\ (cm) \end{aligned} \tag{16.31}$$

The study results show that the conventional diffusive gradient (the difference between inlet dialysate conductivity values) was always higher than the actual diffusive gradient (which takes into account the variation in inlet plasma water conductivity values) in steps 0 to 1 and 1 to 2. Consequently, for mathematical reasons, conventional dialysance values are lower than actual values. As expected, the four ionic dialysance values, recalculated using the diffusive gradients corrected for cardiopulmonary recirculation, were similar in the four steps. As far as the relationship between ionic dialysance and urea clearance is concerned, because there is no reason for supposing modifications in inlet plasma water urea concentration as a result of changes in inlet dialysate conductivity, it seems likely that the discrepancy between ionic dialysance and urea clearance is due to the fact that the conductivity and urea concentration gradient within the dialyzer are not proportional during the different steps. In this study, the values of D3 and D4 were similar to those of urea clearance and therefore in line with those of Gotch et al (1995). These results may mean that the method used by these Authors led to a condition in which inlet plasma water conductivity was kept constant. On the other hand, the D1 and D2 values were lower than effective urea clearance and in line with the results obtained from Manzoni et al (1996) study in which the Hospal Module consistently increased inlet dialysate conductivity to determine dialysance values.

### Example 16.4

For the same patient data in Examples 16.1 and 16.2, the outlet measured dialysate conductivity values are 14.26 mS/cm and 15.06 mS/cm when the inlet dialysate conductivity values are 14.3 mS/cm and 15.5 mS/cm, respectively. Calculate:

a) Ionic dialysance

b) Difference between ID and effective blood and dialysate urea clearances corrected for recirculation calculated in Examples 16.1 and 16.2.

### Solution

a) $$D = [500 + 20.84] \times \left[ \frac{(15.5 - 14.3) - (15.06 - 14.26)}{(15.48 - 14.3)} \right] = 173.6 \text{ ml/min}$$

b) Since access recirculation $R_t = 3.78\% < 10\%$, then

$$R_{cp} = R_t$$

This means that the effective blood clearance is corrected for cardiopulmonary recirculation. The difference between ID and KeUB is 173.6-172.5= 1.11 mL/min, and the ID/KeUB ratio is 1.01.

The difference between ID and KeUD is 173.6-176.2= −2.6 mL/min, and the ID/KeUD ratio is 0.985.

An important study has been subsequently performed to better investigate the mechanisms determining the ratio of conductivity clearance to urea clearance (Gotch et al. 2004). A previously unrecognized technical cause of a low ratio between conductivity clearance and effective urea clearance was elucidated resulting from recirculation through the dialyzer of an acute change in systemic blood conductivity/Na ($\Delta C_s Na$ or $\Delta C_{ns}$) induced during the measurement. Recirculation of the acute $\Delta C_s Na$ or $\Delta C_{ns}$ through the dialyzer ($R_s$) results in decreased Na diffusion gradient during measurement and error in calculated clearance. The on-line clearance monitor (OLC) used for these studies was developed by Fresenius Medical Care, North America, and was incorporated into the Fresenius 2008 H dialysate delivery system and comprises (see Fig. 16.4) (Gotch et al. 2004):

1) Conductivity meters and thermistors deployed in both the dialyzer inlet and outlet dialysate flow paths to monitor conductivity and temperature in the two streams ($C_{ndi}$, $C_{ndo}$)

2) A modified dialysate-proportioning hydroblock, which can provide conductivity-controlled abrupt, sequential increase and decrease in pumping rate of acid concentrate to increase and decrease dialysate inlet Na concentration rapidly

3) Software to control the acid concentrate pump, monitor $C_{ndi}$, $C_{ndo}$, inlet and outlet dialysate flow rates ($Q_{Di}$, $Q_{Do}$) and $Q_f$ and to provide automated calculation of the effective conductivity clearance ($K_{ecn}$).

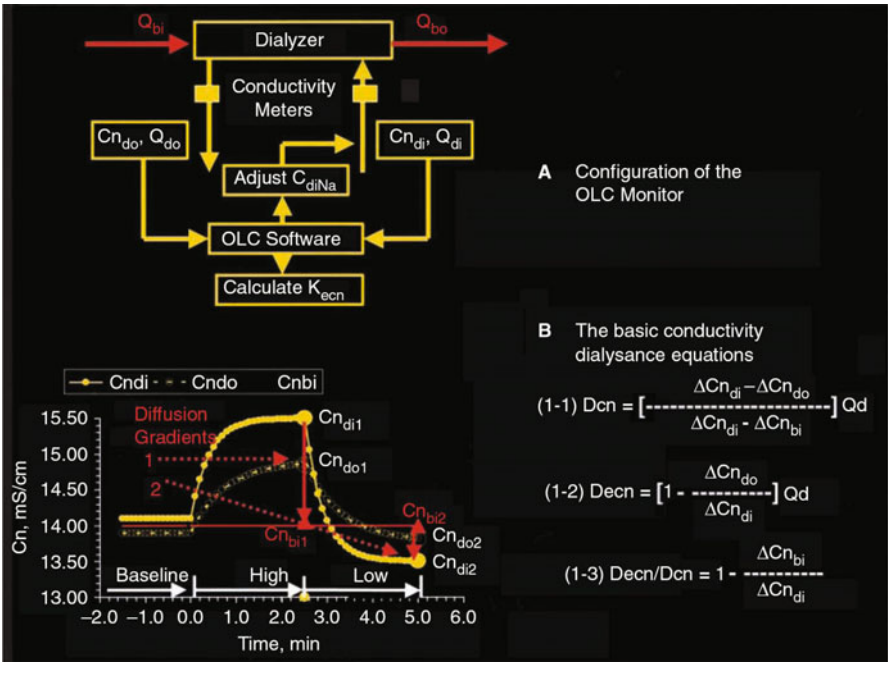


**Fig. 16.4** (A) A schematic depiction of the on-line clearance monitor. (B) Typical dialysate inlet and outlet conductivity profiles and a stable blood inlet profile. The three basic conductivity dialysance equations are shown. [Adapted from Gotch FA, Panlilio FM, Buyaki RA (2004) Mechanisms determining the ratio of conductivity clearance to urea clearance. Kidney Int ; 66 (Suppl 89): S3-S24, with permission].

The thermistors and conductivity meters had resolution to $\pm$ 0.01 degrees centigrade and $\pm$ 0.001 mS/cm, respectively (Gotch et al. 2004). The OLC software monitors the high/low $C_{ndi}$ and $C_{ndo}$ profiles at very frequent

intervals and identifies steady state as the point when dialysate conductivity becomes stable in both inlet and outlet dialysate. The time required to reach steady state is 2 to 3 minutes for each of the sequential high/low profile segments so the total test time for each measurement of $K_{ecn}$ is in the order of 4 to 6 minutes. A brief stable Na diffusion gradient between blood and dialysate must be created in order to reliably measure $K_{ecn}$. This was accomplished in the on-line clearance monitor (OLC) used for these studies by an automated abrupt increase of inlet dialysate Na ($C_{di}Na$) to 155 mEq/L, followed by an abrupt decrease to 135 mEq/L (Gotch et al. 2004). The two-step, high/low dialysate profiles result in two momentary steady-state diffusion gradients from which $K_{ecn}$ can be measured.

The clearance equations for gradient 1 and gradient 2 can be combined to calculate $K_{ecn}$ from the change from high to low dialysate inlet and outlet conductivity ($\Delta C_{ndi}$, $\Delta C_{ndo}$) and any change in $\Delta C_{nbi}$. $\Delta C_{nbi}$ is never measured and is assumed to be 0. An overview of the mechanisms resulting in decreased $K_{ecn}$ is shown in Fig. 16.5 (Gotch et al. 2004).

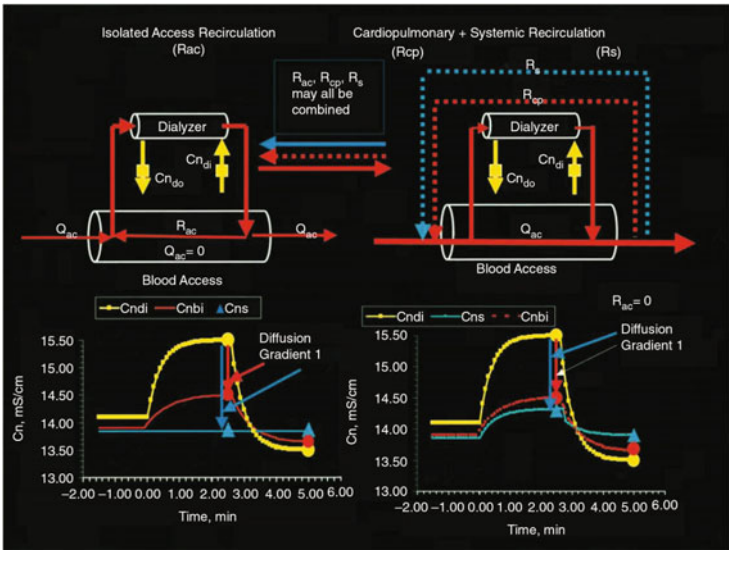


**Fig. 16.5** The left upper and lower panels depict the effect of isolated access recirculation on effective conductivity dialysance. The right panels illustrate the effects of cardiopulmonary and salt loading with systemic recirculation on effective conductivity dialysance. Note that in each instance the effect is mediated by increase and decrease in the blood inlet conductivity and reduction of the diffusion gradient. . [Adapted from Gotch FA, Panlilio FM, Buyaki RA (2004) Mechanisms determining the ratio of conductivity clearance to urea clearance. Kidney Int ; 66 (Suppl 89): S3-S24, with permission].

All mechanisms changing blood inlet conductivity reduce the diffusion gradient and result in decreased $K_{ecn}$. Access recirculation means direct recirculation of a fraction of dialyzer outflow blood to the inflow stream. $C_{nbi}$ rises and falls with $C_{ndi}$ and $C_{ndo}$ but the systemic blood conductivity ($C_{ns}$) is constant. In both the instances of cardiopulmonary recirculation ($R_{cp}$) and systemic recirculation ($R_s$) some fraction of the blood outlet stream with sequential high and low blood conductivity ($C_{nbo}$) is recirculated back to the blood inlet after mixing with the cardiopulmonary or cardiopulmonary plus systemic circulation, respectively, reducing the gradient between $C_{nbi}$ and $C_{ndi}$. These studies show the presence or absence of $R_{cp}$ and $R_s$ are determined by the duration and amount of net Na flux between blood and dialysate during the $K_{ecn}$ measurement, and hence, on the duration and shape of the dialysate conductivity profile. Modeling of $R_{ac}$, $R_{cp}$, and $R_s$ shows their effects on $K_{ecn}$ are multiplicative when more than one mechanism is operative (Gotch et al. 2004). These data show effective conductivity clearance ($K_{ecn}$) measured with a short, asymmetric, high/low dialysate conductivity profile is equal to effective urea clearance ($K_{eu}$) over wide ranges of blood access recirculation and urea clearance ($K_u$) in a large and unselected patient population.

Thus, Gotch et al found almost identity between ID and urea clearance corrected for access recirculation (Gotch et al. 2004); on the contrary, previous studies reported ID values very close to those of urea clearance corrected for total recirculation (i.e., access plus cardiopulmonary recirculation) thus significantly underestimating urea clearance corrected for only access recirculation (Mercadal et al. 1998; Lindsay et al. 2001). However, such different findings can be at least partially explained by the fact that ID values may vary widely depending on the different methods used to modify inlet dialysate conductivity during their measurement (Di Filippo et al. 2001; Gotch et al. 2004).

The aim of a new study (Di Filippo et al. 2005) was to assess whether determining ID by means of a single-step conductivity profile (in which the inlet conductivity profile is changed to a fixed value and then restored to its baseline value) affects the relationship between urea clearance and ID observed when using a two-step conductivity profile. To this end, the mean values of repeated instantaneous ID measurements throughout the dialysis session obtained using a single-step inlet conductivity profile ($_m$ID) were compared with the mean values of urea clearance corrected for access recirculation alone, total (access plus cardiopulmonary) recirculation, and the entire post-dialysis urea rebound. Eighty-two dialysis sessions were performed in 82 anuric patients on chronic thrice-weekly hemodialysis using an Integra dialysate delivery machine (Hospal, Medula, Italy) equipped with the Diascan Module (Gambro, Dasco, Italy) for the automatic determination of ID

and the Quantiscan Module (Gambro, Dasco, Italy) for the fractional collection of outlet dialysate. The Diascan module has a temperature-compensated conductivity probe activated at the dialysate outlet: a microprocessor increases or reduces the pumping rate of acid concentrate to increase or reduce the baseline inlet dialysate conductivity ($C_{di}$) by 1mS/cm for 2 minutes. Software records the values of inlet and outlet dialysate conductivity ($C_{do}$) during this phase ($C_{di1}$, $C_{do1}$; step 1) and after $C_{di}$ is moved back to the prescribed baseline value ($C_{di0}$,$C_{do0}$; step 0). ID is then calculated.

The ID measurement procedure takes about 6 minutes, and the first determination is completed 15 minutes after the start of the session; further determinations are automatically made every 30 minutes. The Quantiscan module is a peristaltic pump that works on an outlet dialysate line by continuously collecting a reduced volume sample (0.1% of total dialysate flow). The outlet dialysate flow rate ($Q_{Do}$) is separately computed using continuous signals from flow meters located within the volumetric ultrafiltration control system, and displayed on the screen of the dialysis monitor. Using this device, a difference of only 0.3 $\pm$ 2.6% has been reported between the computed and collected total dialysate volume (Ronco et al., 2000). At each session, 3 blood samples were taken to determine plasma urea ($U_p$) and total protein ($T_P$) concentrations, in order to be able to calculate urea concentration in plasma water ($U_{pw}$) using the following equation (Colton et al. 1970):

$$U_{PW}\left(\text{mg/ml}\right) = \frac{U_p}{\left(100 - 1.07 \times T_P\right)} \qquad (16.32)$$

The first blood sample was taken immediately before the start of the dialysis treatment ($U_{pw0}$), the second at the end of the session at the inlet port of the dialyzer after slowing $Q_{Bi}$ to 50 ml/min for 2 minutes ($U_{pwt2}$), and the third 30 minutes after the end of the session ($U_{pwt30}$). In 31 of the 82 patients, an "immediate" post-dialysis blood sample was also drawn at the inlet port of the dialyzer after slowing $Q_{Bi}$ to 100ml/min for approximately 10 seconds ($U_{pw10}$). The same 31 patients also had samples for the analysis of systemic plasma water sodium concentration, hematocrit (Ht), hemoglobin (Hb), and inlet dialysate sodium concentration ($Na_{di}$) drawn before the start of the dialysis session; systemic plasma water sodium concentration was also determined at the end of the session, and the mean value of the initial and final measurements ($Na_{pws}$) was used for the analysis. Plasma water and dialysate ionized sodium concentrations, and Ht and Hb were measured by means of direct ionometry (Di Filippo et al. 2005).

Whole body clearance ($K_{wb}$, i.e., dialyzer urea clearance corrected for total recirculation and post-dialysis urea rebound) was determined according

to the following equation, using the Direct Dialysate Quantification (DDQ) method described by (Depner et al. 1996).

$$K_{wb}\left(\text{ml/min}\right)=\frac{V_{Do}\times U_{Do}\times\ln\left(\frac{U_{pwt30}}{U_{pw0}}\right)}{T_d\times\left(U_{pwt30}-U_{pw0}\right)} \tag{16.33}$$

Where $V_{Do}$ is the volume of total dialysate with ultrafiltration in mL; $U_{Do}$ is the dialysate urea concentration in mg/mL; $U_{pw0}$ is the urea plasma water concentration at the start of the dialytic session in mg/mL; $U_{pwt30}$ is the urea plasma water concentration at 30 minutes after the end of the session, in mg/mL and $T_d$ is the dialysis time in min.

Whole body clearance was then used to calculate urea clearance corrected for access recirculation ($K_{eu1}$) according to:

$$K_{eu1}\left(\text{ml/min}\right)=K_{wb}\times\frac{U_{pwt30}}{U_{pw10}} \tag{16.34}$$

Where $U_{pwt10}$ is the urea plasma water concentration at the end of the session after slowing $Q_{Bi}$ to 100 mL/min for approximately 10 seconds, in mg/mL.

The urea clearance corrected for both access and cardiopulmonary recirculation ($K_{eu2}$) is calculated according to (Di Filippo et al. 2005):

$$K_{eu2}\left(\text{ml/min}\right)=\frac{K_{wb}\times U_{pwt30}}{U_{pwt2}} \tag{16.35}$$

Where $U_{pwt2}$ is the urea plasma water concentration at the end of the session after slowing $Q_{Bi}$ to 50 mL/min for two minutes, in mg/mL.

Starting from $Na_{pws}$, plasma water sodium concentrations at the inlet ($Na_{pwi}$) and outlet ($Na_{pwo}$) ports of the dialyzer during step 1 ($Na_{pwi1}$, $Na_{pwo1}$) and step 0 ($Na_{pwi0}$, $Na_{pwo0}$) were estimated according to the following equations (Di Filippo et al. 2005):

$$Na_{pwo}\left(\text{mEq/L}\right)=\left[Na_{pws}-\frac{K_{eu1}}{Q_{ei}}\left(\alpha\times Na_{pws}-Na_{Di}\right)\right] \tag{16.36}$$

and

$$Na_{pwi}\left(\text{mEq/L}\right)=\frac{\left[\left(1-R_{cp}\right)\times Q_{ei}\times Na_{pws}\right]+\left[R_{cp}\times Q_{ei}\times Na_{pwo}\right]}{Q_{ei}} \tag{16.37}$$

Where $Q_{ei}$ is calculated as follows according to Sargent and Gotch (1996):

$$Q_{ei} = Q_{bei} \times \left[ \frac{F_p - Ht}{100 \times \left( F_p - F_r \right)} \right] \tag{16.38}$$

$F_r$ and $F_b$ using the following equations (Colton et al. 1970):

$$F_r\,(g/dl) = 1 - 0.0107 \times Hb \tag{16.39}$$

$$F_p\,(g/dl) = 1 - 0.0107 \times T_P \tag{16.40}$$

After a 2-minute period (considering the Donnan factor as being equal to 0.967) using $K_{eu1}$ as dialyzer urea clearance, the cardiopulmonary recirculation ($R_{cp}$) is calculated as follows (Di Filippo et al. 2005):

$$R_{cp} = \frac{U_{pwt2} - U_{pwt10}}{U_{pwt2} - U_{pwV}} \tag{16.41}$$

Where $U_{pwV}$ is urea plasma water concentration at the outlet port of the dialyzer in mg/ml and can be calculated as follows (Di Filippo et al. 2005):

$$U_{pwV} = \frac{U_{pwt10} - K_{eu1}}{Q_{ei} \times U_{pwt10}} \tag{16.42}$$

Finally, $Na_{pwi1}$ and $Na_{pwi0}$ were used to calculate the expected ID/$K_{eu1}$ ratio according to the following equation (Di Filippo et al. 2005):

$$\frac{ID}{K_{eu1}} = 1 - \frac{\alpha \times \Delta Na_{pwi}}{\Delta Na_{Di}} \tag{16.43}$$

Where

$$\Delta Na_{pwi} = Na_{pwi1} - Na_{pwi0} \tag{16.44}$$

$$\Delta Na_{Di} = Na_{Di1} - Na_{Di0} \tag{16.45}$$

Where $Na_{pwi1}$ is the plasma water sodium concentration at the inlet port of the dialyzer during step 1 in mEq/L; $Na_{pwi0}$ is the plasma water sodium concentration at the inlet port of the dialyzer during step 0, in mEq/L; $Na_{Di1}$ is the dialysate sodium concentration at the inlet port of the dialyzer during step 1, in mEq/L; $Na_{Di0}$ is the dialysate sodium concentration at the inlet port of the dialyzer during step 0, in mEq/L.

Dialysate sodium concentration ($Na_{Di}$) during ID measurement was estimated from dialysate conductivity, being the ratio between $Na_{Di}$ and dialysate conductivity determined during "baseline" conditions. The urea clearance values obtained using the direct dialysate quantification (DDQ)

method were adopted as the reference and compared with the arithmetical mean of the ID measurements.

The difference between $_{m}ID$ and $K_{eu2}$ was -5 $\pm$ 10 ml/min (95% CI -7 to -3ml/min; P<0.001) and the ID/$K_{eu2}$ ratio was 0.98 $\pm$ 0.06, thus indicating a mean underestimate of $Ke_{u2}$ by $_{m}ID$ of only 2%. In the group of 31 patients for whom $U_{pwt10}$ values were available, the difference between $_{m}ID$ and $K_{eu1}$ was -21 $\pm$ 10 ml/min (95% CI -25 to -17 ml/min; P< 0.01) and the $_{m}ID/K_{eu1}$ ratio was 0.90 $\pm$ 0.05, thus indicating an underestimate of $K_{eu1}$ by $_{m}ID$ of 10%.

These results in 82 patients show that the $_{m}ID$ determined by the Diascan Module incorporated in the Integra dialysate delivery machine provides an adequate estimate of urea clearance corrected for total recirculation ($K_{eu2}$) as the $_{m}ID/K_{eu2}$ ratio indicates a mean underestimate of $K_{eu2}$ by $_{m}ID$ of only 2%; on the other hand, $_{m}ID$ underestimated $K_{eu1}$ by 10% and overestimated $K_{wb}$ by 11%.

The significant underestimate of $K_{eu1}$ by $_{m}ID$ is a theoretically expected result insofar as ID should be equal to $K_{eu1}$ only when the plasma water sodium concentration at the dialyzer inlet port ($Na_{pwi}$) is kept constant during ID measurement (Polaschegg 1993). On the other hand, if $Na_{pwi}$ changes during ID measurement, ID underestimates $K_{eu1}$ to a degree which is directly proportional to $\Delta Na_{pwi}$ and inversely proportional to $\Delta Na_{Di}$. This explains the considerably different results obtained by Gotch et al (2004), with their 2-step conductivity profile for the determination of ID, which indicated an ID/$K_{eu1}$ ratio approaching identity (1.01) and an ID/$K_{eu2}$ ratio of 1.06. In their study, the changes in dialysate conductivity during ID measurements (an increase to a fixed value of 155 mEq/L, followed by decrease to a fixed value of 135 mEq/L) were planned a priori in order to minimize the $\Delta Na_{pwi}/\Delta Na_{Di}$ ratio, which was actually very close to zero (0.03). In the 31 patients of the last study for whom $Na_{pwi}$ was derived during step 0 ($Na_{pwi0}$) and step 1 ($Na_{pwi1}$) from the measured values of systemic plasma water concentration, dialysate conductivity, and cardiopulmonary recirculation, it was found a mean change in $Na_{pwi}$ and $Na_{Di}$ during the ID determinations of, respectively, 0.45 mEq/L and 6.67 mEq/l, thus giving a mean $\Delta Na_{pwi}/\Delta Na_{Di}$ ratio of 0.07. On the basis of these results and the equation giving the expected ratio between ID and $K_{eu1}$ we should therefore have expected to find a mean underestimate of $K_{eu1}$ by $_{m}ID$ of 7%, which is slightly different from the actual underestimate of 10%. This discrepancy can be explained by possible inaccuracies in deriving $\Delta Na_{pwi}$ and $\Delta Na_{Di}$ (i.e. the 2 factors required to calculate the expected ratio between ID and $K_{eu1}$).

These data confirm the results of previous studies using a single-step conductivity profile for the determination of ID that found similarity between ID

and $K_{eu2}$, and an underestimate of $K_{eu1}$ by ID. (Lindsay et al., 2001) reported a mean ID/$K_{eu1}$ ratio of 0.95 and a mean ID/$K_{eu2}$ ratio of only 0.99 in 8 patients with no access recirculation and a consequent dialyzer urea clearance ($K_d$) equal to $Ke_{u1}$. Similar results were obtained by Mercadal et al (2002) who observed a mean underestimate of $K_{eu1}$ by ID of 10% when $K_{eu1}$ was more than 180 ml/min (as it was in these patients) (Mercadal et al. 1998) and identity between ID and $K_{eu1}$ in the absence of cardiopulmonary recirculation, when $Na_{pwi}$ is inevitably kept constant during ID determination (Mercadal et al. 2002). Taken together, these results clearly confirm that the ratio of ID to urea clearance greatly depends on the method used to modify inlet dialysate conductivity during the determination of ID, as has previously been pointed out in other reports (Di Filippo et al. 2001; Gotch et al. 2004).

These results show for the first time in a relatively large population of hemodialysis patients that the mean value of repeated ionic dialysance determinations obtained using a single-step inlet dialysate conductivity profile underestimates urea clearance corrected for access recirculation, but provide a clinically adequate estimate of urea clearance corrected for total recirculation. They also further underline the importance of dialysate inlet conductivity during ionic dialysance measurements in determining the relationship between ionic dialysance and urea clearance, which may explain the different results obtained in previous studies using a 2-step conductivity profile.

The availability of on-line measurements of ionic dialysance may aid the monitoring of the dialysis dose at each session because instantaneous ID can be measured simply by using 2 conductivity probes placed at the dialyzer inlet and outlet, without the need for any blood or dialysate sampling (Polaschegg 1993; Petitclerc et al. 1993). This allows repeated ID measurements that can be used to calculate the mean value for the dialysis session as a whole (several reasons can reduce the depurative efficacy so that an only one urea clearance determination can be misleading). Moreover the on-line knowledge of the actual value may allow achieving at each session the prescribed dose.

## 16.4 ASSESSMENT OF HEMODIALYSIS ADEQUACY BY IONIC DIALYSANCE

After the American National Cooperative Dialysis Study (NCDS) first demonstrated that patient morbidity and treatment failure are related to inadequate dialysis doses (Gotch and Sargent 1985), a number of reports subsequently indicated an association between dialysis doses and mortality rate (Owen et al. 1993; Hakim et al. 1994; Parker et al. 1994). Since there is often a difference, sometimes large, between the prescribed and delivered

dose, the quantification of the delivered dialysis dose is an essential element in the management of chronic hemodialysis treatment. The most useful and widely applied index to prescribe as well to assess the actually delivered dose is the Kt/V proposed by Sargent and Gotch, where K is the clearance of urea (commonly accepted as the marker solute for uremic toxicity), t is the duration of the session and V is the volume of urea distribution.

The gold standard for the determination of Kt/V is the Direct Dialysate Quantification (DDQ method), because this allows the most reliable calculation of the V value and, consequently, of K value (Garred et al. 1989; Bosticardo et al. 1994; Cheng et al. 1998). Dialysate side urea monitoring methods provide many advantages over blood side methods, both in terms of measurement ease and accuracy of results. Because the measurement is continuous or semi-continuous, it is less prone to sampling and measurement errors. Traditional blood-side methods also require an accurately known value of effective clearance, including any correction for recirculation if it exists. In order to determine these values, three additional blood samples are required. Blood-side methods are also only accurate if urea follows single pool kinetics. In contrast, dialysate side methods do not require knowledge of clearance, and can in fact accommodate sessions where the clearance rate changes over the session. This method can work under conditions of rapid dialysis where urea may follow multiple pool kinetics. All dosing assessments using blood sampling are in a way "indirect" measure of dialysis quantification. For this reason, direct measurement of urea concentrations in dialysate have been advocated as a superior approach to kinetic modeling, with the added advantage of its potential to be real time monitoring of dialysis quantification (Lindsay and Sternby 2005). However, the DDQ method requires the total or partial collection of spent dialysate, and is thus inapplicable in everyday clinical practice. Blood-side Kt/V can be determined by means of various kinetic models, the most widely used being the single-pool, variable-volume urea kinetic model (SPVV-UKM). The Kt/V determined in this way is relatively insensitive to errors in the estimate of effective urea clearance because these lead to corresponding misestimations of volume of urea distribution and so the ratio remains correct. However, the urea kinetic model requires the taking of blood samples before and after each treatment to determine BUN values (Sargent and Gotch 1980), which is why delivered dialysis is only quantified from time to time (usually monthly) and there is the obvious risk that even significant variations in the delivered dose during different sessions may go unnoticed. Furthermore, urea transfer from one body compartment to another is not instantaneous (especially when high-efficiency regimens are used) and the disequilibrium revealed by

post-dialytic urea rebound lasts for 30-60 min after the dialytic session. In order to avoid a significant underestimate of the volume of urea distribution and so a significant overestimation of the Kt/V when using the single-pool UKM, the blood sample for post-dialysis BUN analysis has to be drawn when the urea rebound is exhausted, that is, almost 30 minutes after the end of the session (Pedrini et al. 1988).

The alternative or simplified methods (Smye et al. 1994; Daugirdas and Schneditz 1995) obviated the problem of delayed post-dialysis blood sampling, but since they also require two or three blood samples, they are not suitable for routine use. The result is that delivered dialysis dose is quantitated infrequently, and given the sometimes large difference between prescribed and delivered dialysis caused by several not always easily identifiable factors, there is a risk that treatment inadequacy may go unnoticed. Therefore, the main goal is to find a reliable, easy, noninvasive, and inexpensive method of determining the dose of dialysis effectively delivered, ideally at each session. Since the urea distribution volume does not change over brief periods of time and treatment length is a known parameter, what is needed is a means of establishing effective urea clearance throughout the dialytic session.

One of the advantages of measuring Kt/V during hemodialysis is the ability to calculate the patient's urea distribution volume (V). A reliable estimate of V allows the correct assessment of protein intake from urea generation rate (Kloppenburg et al. 2001) and allows lean body mass (LBM) to be calculated according to the well-established finding that 73% of LBM is body water (Muldowney and Healy 1967). Direct dialysis quantification (DDQ) is considered the gold standard for determining V, but it is impractical for routine use because it requires equilibrated post-dialysis plasma water urea concentration (Depner et al. 1996). The single pool variable volume urea kinetic model (SPVV-UKM) is easier to use because it does not need a delayed post-dialysis blood sample (Gotch 1992); end-dialysis plasma water urea concentrations ($U_{pwt}$) are determined in blood samples drawn immediately after the end of the dialysis session, after approximately 10 seconds of reduced blood flow to 100 ml/min ($U_{pwt10"}$). However, in order to obtain results that are consistent with the DDQ method, SPVV-UKM requires a correct estimate of dialyzer urea clearance ($K_d$) throughout the dialysis session. Using "formal" SPVV-UKM, $K_d$ is calculated from a generic dialyzer transport constant (overall permeability area product, or KoA) and the prescribed blood and dialysate flows with the assumption that both these flows are constant throughout the treatment and there is no dialyzer clotting or access recirculation. However, there may be significant errors in these calculated dialyzer clearances resulting frequently in overestimation of $K_d$ and secondary overestimation of V (Depner 1996).

Ionic dialysance (ID) may accurately estimate "effective" urea clearance (Di Filippo et al. 2001; Lindsay et al. 2001; Mercadal et al. 2002) (i.e., dialyzer urea clearance corrected for total recirculation) (Gotch 1994). Because ID does not need blood and dialysate samples or laboratory tests, repeated determinations are available and allow an adequate estimate of "effective" urea clearance throughout the dialysis session. Some studies of the quantification of the normalized dialysis dose using ionic dialysance are summarized in Table 16.2 (Lindsay and Sternby 2005). Peticlerc et al (1993) showed a very good correlation between delivered Kt/V as measured by DDQ and by the conductivity method; and likewise Gotch et al (1995) using a similar technology, also reported that the effective ionic dialysance very accurately predicts effective urea clearance with a coefficient of variation of only 6.7% and thus can provide inexpensive automatic measurements of delivered Kt/V every dialysis. In slight contrast to this, Manzoni et al (1996) with a small number of patients, found some discrepancies between Kt/V values based on the effective ionic dialysance when compared with DDQ studies (Lindsay and Sternby 2005). Manzoni et al (1996) showed an undervaluation of the dialysis dose by Dt/V of 22% compared to $Kt/V_{urea}$ by direct quantification. $V_{urea}$ for Dt/V was given by the formulas of Watson et al (1980) or was taken equal to 55% of the dry weight and was 17% greater than the value calculated from direct quantification (Kloppenburg et al. 2001). Del Vecchio et al (1998) measured $V_{urea}$ with a SPVV corrected by rebound with blood sampling 30 min after the end of dialysis. Instead of taking the urea clearance given by the manufacturer in the SPVV model, a mean value of D during the session was introduced. The calculated $V_{urea}$ from SPVV was used for the calculation of Dt/V the following month for each patient (corrected by the variation of the dry weight if necessary). Dt/V was compared to $Kt/V_{urea}$ by SPVV measured with the constant of the manufacturer the month after. This study, however, brings evidence that, with evaluation of $V_{urea}$ by SPVV and D at the same time, further evaluation of Dt/V is close and almost equal to a reference measurement of $Kt/V_{urea}$ by SPVV corrected by the rebound (Mercadal et al. 2005).

Di Filippo et al (1998) published similar results (see Table 16.2) (Mercadal et al. 2005). Wuepper et al (2003) compared $Kt/V_{urea}$ by equilibrated SPVV and Dt/V with $V_{urea}$ by Watson or $V_{urea}$ measured by bioimpedance and found a slight difference of 0.15 (see Table 16.2). The most expected results for the clinicians are the comparison between Dt/V and the most widespread simplified equation for the calculation of $Kt/V_{urea}$ by Daugirdas. Studies comparing Dt/V with the Daugirdas second-generation equation corrected by the rebound (equivalent to the double-pool model) showed very close evaluation of the dialysis dose with difference inferior to 5%

(Petitclerc and Coevoet 2001; McIntyre et al. 2003), and even equal to 2.54% on the larger study (McIntyre et al. 2003). In these studies, $V_{urea}$ in the Dt/V formula was simply evaluated by Watson et al (1980). Dt/V with $V_{urea}$ by Watson slightly underestimates $Kt/V_{urea}$ Daugirdas corrected by the rebound. For Dt/V with $V_{urea}$ by Watson et al (1980) greater than 1.2, Albadawy et al (2000) found that all the $Kt/V_{urea}$ of Daugirdas were greater than 1.2 (Mercadal et al. 2005). For Dt/V between 1 and 1.2, 33 of 35 dialysis sessions had a $Kt/V_{urea}$ Daugirdas greater than 1.2 and for Dt/V inferior to 1, all the dialysis sessions had $Kt/V_{urea}$ Daugirdas less than 1. Making sure that Dt/V is greater than 1.2 would ensure that the patient receives the dialysis recommended dose (Mercadal et al. 2005).

Because V is directly proportional to urea clearance and inversely proportional to the magnitude of drop in plasma water urea concentration in UKM, by using ID as input parameter to SPVV-UKM, correct V values can be expected when end-dialysis plasma water urea concentrations are determined in blood samples taken at the end of the session with the blood pump speed reduced to 50 ml/min for 2 minutes ($U_{pwt2'}$) (Schneditz et al. 1992). Underestimation of V secondary to the use of ID, always lower than $K_d$, will be compensated by overestimation of V secondary to the use of $U_{pwt2'}$, which is always higher than $U_{pwt10}$.

A large study (Di Filippo et al. 2004) was performed to determine whether the V values determined by means of SPVV-UKM, ID, and $U_{pwt2'}$ ($V_{ID}$) are similar to those determined by the "gold standard" DDQ method ($V_{DDQ}$). Theoretically, with UKM, whole body clearance ($K_{wb}$) and equilibrated post-dialysis plasma water urea concentration should be used to obtain V values consistent with $V_{DDQ}$ values. In the UKM, V is directly correlated with urea clearance, which means that the use of $K_d$ higher than $K_{wb}$ will lead to a systematic overestimation of V; on the other hand, V is inversely correlated with the magnitude of drop in plasma water urea concentration ($U_{pw0}$-$U_{pwt30}$); this means that sampling 10 seconds after the end of the dialysis session will lead to a systematic underestimation of V because $U_{pwt10}$ is always lower than $U_{pwt30}$. On the basis of these relationships, it can be expected that correct V values will be obtained if the overestimation of $K_{wb}$ using $K_d$ is counterbalanced by the overestimation of ($U_{pw0}$-$U_{pwt30}$) using $U_{pw10}$.

In the "formal" SPVV-UKM, $K_d$ is calculated from blood and dialysate flow rates using the dialyzer mass transfer area coefficient (KoA). However, there may be significant errors in these calculated dialyzer clearances, resulting often in overestimation of $K_d$ and secondary overestimation of urea distribution volume.

**Table 16.2** Quantification of the normalized dialysis dose using ionic dialysance. [Adapted from Mercadal L, Ridel C, Petitclerc T (2005) Ionic dialysance: principle and review of its clinical relevance for quantification of hemodialysis efficiency, Hemodial Int.; 9(2):111-9, with permission].

| Reference (System) | Measurement Protocol Of $Kt/V_{urea}$ | Measurement Protocol Of V | Comparison K vs. D | Comparison $Kt/V_{urea}$ Vs. Dt/V |
|---|---|---|---|---|
| Petitclerc et al (1995) (Hospal) | DDQ, n=12 sessions; dialysate collection and blood samplings at the start and immediately after dialysis. | V = 55% of dry weight for both Dt/V and $Kt/V_{urea}$ | Correlation $K_{DDQ}$ and D, r = 0.94; CI of the difference, 95%; –8 mL/min ± 4 mL/min. | $Dt/V = 0.11+0.89 \times Kt/V_{DDQ}$, r = 0.94. |
| Di Filippo et al (1996) (Hospal) | $Kt/V_{dp}$ with delayed blood samplings 30 min after or immediate blood samplings and the Daugirdas or Smye equation , n = 4 | $V = Dt/(Kt/V_{urea}\ dp)$; D, mean of the measurements of the whole session. | Not evaluated | ${}_{dp}Kt/V_{urea}$ = 1.09±0.17, $Kt/V_{Smye}$ = 1.12±0.19, $Kt/V_{Daugirdas}$ = 1.13±0.17, Dt/V = 1.11±0.17. |
| Manzoni et al (1996) (Hospal) | Direct quantification with partial dialysate collection and delayed blood sampling 30 min after dialysis; mean D, mean of all the measurements of D during a session | V = 55% of the dry weight: 32.7±4.6 L; $V_{Watson}$ 32.9±2.0 L; $V_{urea}$ by DDQ, 28.2±2.4 L; mean difference, 4.7± 3.3 L between Watson and DDQ (17%). | D = 155±22 mL/min vs. $K_{DDQ}$ = 175±21 mL/min, D/K = 0.89±0.03; results of nine dialysis sessions. | 23 dialysis sessions, Dt/V with V=55%; 22% inferior to $Kt/V_{DDQ}$, Dt/V with $V_{urea}$ Watson = 23% inferior to $Kt/V_{DDQ}$. |

**Table 16.2** (Continued)

| | | | | |
|---|---|---|---|---|
| Di Filippo et al 1998 (Hospal) | $Kt/V_{urea}$ by SPVV equilibrated three point blood samplings start of dialysis, 70 min of dialysis with blood pump running, end of dialysis, end +30 min, and next session $Kt/V_{urea}$ by Smye and $Kt/V_{urea}$ by Daugirdas | V calculated with SPVV using D instead of K manufacturer at Month 0 $V_{urea}$ of Month 0 used for the calculation of Dt/V at Month 1. | Not evaluated | Dt/V = 1.14±0.16, $Kt/V_{eqSPVV}$ = 1.14±0.17; mean difference with Dt/V, 0.00±0.07; 95% CI of the imprecision, 0.14; variation of D during dialysis session = 3.6%; $Kt/V_{Smye}$ = 1.10±0.18; mean difference Smye vs. $SPVV_{eq}$ = –0.03±0.06; $Kt/V_{Daugirdas}$ = 1.13±0.17; mean difference with $Kt/V_{SPVVeq}$ = –0.01±0.06. |
| Del Vecchio et al (1998) (Hospal) | $Kt/V_{urea}$ by SPVV; blood samplings at start of dialysis, +30 min, and at the start of the next session. | $V_{urea}$ from SPVV with D instead of K manufacturer, $V_{urea}$ =29±5.9L or 50.1±9.3% of body weight. | Not evaluated | Comparison 1 month after initial evaluation of $V_{urea}$ corrected with variation of the dry weight; n=18; Dt/V=1.18±0.15 vs. $_{eq}Kt/V$ = 1.18 ± 0.16; mean difference, 0.00±0.07; 95% CI of the imprecision, 0.14 ($Kt/V_{urea}$ range, 0.9-1.4). |

**Table 16.2** (Continued)

| | | | | |
|---|---|---|---|---|
| Albadawy et al (2000) (Hospal) | $Kt/V_{urea}$ by Daugirdas. | $V_{urea}$ by Watson for Dt/V. | Not evaluated | R = 0.69; for Dt/V > 1.2, all the $Kt/V_{Daugirdas}$ are > 1.2; for Dt/V between 1 and 1.2, 33/35 sessions have $Kt/V_{Daugirdas}$ > 1.2; for Dt/V <1: no $Kt/V_{Daugirdas}$ are >1. |
| Kuhlmann et al (2001) (Fresenius) | 118 measurements of D and K (dialysate and blood side). | Not mentioned | K blood side = 152 ± 11 mL/min; K dialysate side = 152 ± 11 mL/min; D = 150±12 mL/min; correlation K blood side vs. D, r = 0.86; mean difference, –1.88 ± 3.86 %; K dialysate side vs. D, r =0.82; mean difference, 1.64± 4.68% (D undervalues K). | n = 35 $Kt/V_{urea}$ by SPVV equilibrated vs. Dt/V, r = 0.98; mean difference, 1.13 ± 3.63%; $Kt/V_{Daugirdas}$ vs. Dt/V, n = 34; r = 0.95; mean difference, 9.90 ± 6.53%; $Kt/V_{DDQ}$ vs. Dt/V, r = 0.90; mean difference, –3.82 ± 6.28 %. |

**Table 16.2** (Continued)

| | | | | |
|---|---|---|---|---|
| Petitclerc and Coevoet (2001) (Hospal) | $Kt/V_{urea}$ by Daugirdas second generation With Correction for rebound by the "rate equation" | $V_{urea}$ By Watson For Dt/V. | Not Evaluated | $Kt/V_{urea} = 0.284 + 0.814 \times Dt/V$ (n=351 Sessions; $R^2 = 0.61$). |
| McIntyre et al 2003 (Hospal) | $Kt/V_{urea}$ by Daugirdas with blood sampling 30 min after dialysis. | $V_{urea}$ by Watson for Dt/V. | Not evaluated | Kt/V = 1.13±0.02 vs. Dt/V = 1.1±0.02 (n = 316; $r^2 = 0.92$; p = 0.02). Dt/V underestimates Kt/V by 2.54 % (95 % CI, 0.85 % - 4.2 %). |
| Wuepper et al (2003) (Fresenius) | $Kt/V_{urea}$ by SPVV equilibrated three points, n = 40. | $V_{urea}$ by bioimpedance, Watson, SPVV. | Not evaluated | $Kt/V_{urea}$ by SPVV = 1.31±0.14; $Dt/V_{Watson}$ = 1.34±0.12; Bland-Altman analysis with $Kt/V_{SPVV}$ = –0.15; SD=0.1; linear regression analysis, r=0.56, slope = 0.58±0.08. $Dt/V_{bioimpedance}$ = 1.51±0.21; Bland-Altman with $Kt/V_{SPVV}$ = 0.02; SD = 0.14; linear regression analysis, r = 0.64, slope = 1.1±0.13. |
| Di Filippo et al (2004) (Hospal) | $Kt/V_{urea}$ by DDQ, $Kt/V_{urea}$ by SPVV equilibrated three points, n = 82. | $V_{urea}$ from SPVV with D instead of K manufacturer, $V_{DDQ}$ = 42.2±5.8/wt %; $V_{spvv}$ = 42.6±5.5/wt %; $V_{urea}$ Watson = 53.7 ± 6.4 /wt%. | Not evaluated | $Kt/V_{urea}$ by $_{eq}$DDQ = 1.40±0.21; Dt/V =1.54±0.23; mean difference, 0.13±0.06 (95% CI, 0.12-0.15; p < 0.001). |

Repeated determinations of ionic dialysance may constitute an accurate estimate of "effective" urea clearance during the entire dialysis session. Using ID, correct V values can be expected when end-dialysis plasma water urea concentrations are determined in the blood sample taken at the end of the session with the blood pump speed reduced to 50 ml/min for two minutes; underestimation of V secondary to the use of ID, always lower than $K_d$, will be compensated by overestimation of V secondary to the use of $U_{pwt2'}$, always higher than $U_{pwt10''}$. This study of Di Filippo et al (2004) shows that by using ID and $U_{pwt2'}$ as input parameters to SPVV-UKM it is possible to obtain urea distribution volume values that are not different from the values obtained according to the DDQ method. In this study at a mean $Kt/V_{dp}$ level of 1.4, $V_{ID}$ values resulted only 1% higher as a mean than $V_{DDQ}$ values, and the difference between $V_{ID}$ and $V_{DDQ}$ resulted significantly associated with $Kt/V_{dp}$ values. This is in agreement with comparative theoretic analysis between double-pool and single-pool model showing that the ratio between single-pool V and double-pool V is a function of administered dialysis dose, and predicting to be 0.88 at $Kt/V_{dp}$ level of 0.5, 0.97 at $Kt/V_{dp}$ level of 1.0, and 1.00 at $Kt/V_{dp}$ level of 1.3 (Gotch 1992). This has important clinical implications, particularly in those circumstances in which a low value of Kt/V is prescribed, such as in daily hemodialysis or in patients with substantial residual renal function, and equations to convert single-pool volume in double-pool volume at any level of administered dialysis dose have been suggested (Daugirdas and Smye, 1997) and validated (Daugirdas et al. 1999). The same study also shows that commonly used anthropometric equations overestimated $V_{DDQ}$ by 29% on average. This overestimation is consistent with the results from other studies (Kloppenburg et al. 2001; Schneditz et al. 1995).

Therefore, nowadays the availability of monitors allowing determining ID allows the correct determination of V and so of PCR. It has been shown that PCR values obtained according to UKM using ID as dialyzer urea clearance corrected for total recirculation were quite similar to those obtained by the DDQ method, actually considered the "gold standard method".

## 16.5 CALCULATION OF ACCESS FLOW FROM IONIC DIALYSANCE MEASUREMENT

The study of Mercadal et al (1999) allows determination of access blood flow from ionic dialysance. In this study the vascular access blood flow rate was evaluated in 30 patients treated by chronic hemodialysis. Six patients had a graft and 24 a native vein fistula. Dialysis sessions were

carried out on an Integra® dialysis monitor (Hospal Dasco SpA, Medolla, MO, Italy) equipped with the Diascan® module automatically providing each 30 minutes with the value of effective ionic dialysance from dialysate conductivity values recorded at the dialyzer outlet for the two levels of dialysate conductivity at the dialyzer inlet (Mercadal et al. 1999).

In the absence of recirculation, the ionic dialysance reflects the dialyzer urea clearance (Mercadal et al. 1998). If the recirculation ratio (R) is not null, the value (D) of ionic dialysance measured by conductivity reflects the actual urea clearance of the patient taking recirculation into account, and is called "effective dialysance" (Petitclerc et al. 1993; Mercadal et al. 1999). Effective dialysance (D) is related to dialysance $D_0$ of the dialyser, measured in the absence of recirculation according to the following equation (Petitclerc et al. 1993):

$$D = D_o \frac{1-R}{1-R\left[1-\frac{D_0-Q_f}{Q_B-Q_f}\right]} \tag{16.46}$$

After reversing blood lines for a few minutes, the value ($D_{rev}$) of ionic dialysance measured by conductivity takes the recirculation ratio ($R_{rev}$) into account. The relationship between $D_{rev}$ and $D_0$ is given by (Mercadal et al. 1999):

$$D_{rev} = D_o \frac{1-R_{rev}}{1-R_{rev}\left[1-\frac{D_0-Q_f}{Q_B-Q_f}\right]} \tag{16.47}$$

Where $R_{rev}$ is the recirculation after reversing the blood lines and can be calculated according to:

$$R_{rev} = \frac{Q_B-Q_f}{Q_A+(Q_B-Q_f)} \tag{16.48}$$

Subsituting from Eq. (16.48) into Eq. (16.47) yields (Mercadal et al. 1999):

$$D_{rev} = D_o \frac{Q_A}{Q_A-Q_f+D_o} \tag{16.49}$$

From Eq. (16.49), $Q_A$ can be calculated as (Mercadal et al. 1999):

$$Q_A = \frac{(D_o - Q_f) \times D_{rev}}{D_o - D_{rev}} \tag{16.50}$$

Assuming the absence of recirculation when blood lines are in normal position, the measured value (D) of ionic dialysance for the same values of dialyzer blood flow $Q_B$ and ultrafiltration rate $Q_f$ is equal to $D_o$. Consequently (Mercadal et al., 1999):

$$Q_A = \frac{(D - Q_f) \times D_{rev}}{D - D_{rev}} \tag{16.51}$$

Equation (16.51) shows that the access flow, $Q_A$ can be estimated from the measurement of ionic dialysance at normal position (assuming the absence of access recirculation) and at reverse position of blood lines. For $Q_f = 0$, Eq. (16.51) results in (Mercadal et al. 1999):

$$Q_A = \frac{(D \times D_{rev})}{D - D_{rev}} \tag{16.52}$$

The model of Mercadal et al (1999) assumes the absence of recirculation with blood lines in a normal position. Therefore a dialyzer blood flow rate ($Q_B$) is chosen to be lower than or equal to 250 ml/min in order to avoid access recirculation, because new techniques using nonurea based methods have given evidence of the absence of access recirculation in most patients at low $Q_B$ values (Sherman et al. 1997). This condition was verified in the study by using the ultrasound dilution method on each patient. The proposed model by Mercadal et al (1999) provides a valuable estimation of the vascular access flow and is fully noninvasive, easy to perform (no need of bolus injection and of accurate measurement of $Q_B$), and inexpensive. Consequently, this method seems suitable for monitoring access blood flow in hemodialyzed patients.

## 16.6 CONDUCTIVITY KINETIC MODELLING

### 16.6.1 Sodium Balance

Intradialytic water and sodium removal are defined as being adequate in relationship to the interdialytic intake when the water/sodium balance is zero, that is when the final dry body weight is reached and the final plasma water sodium concentration is constant. For this purpose, the required

water removal can be easily quantitated because it corresponds to the interdialytic increase in body weight. In contrast, given that it is affected by various factors, a mathematical kinetic model must be used at the start of treatment in order to predict final plasma water sodium concentration and to calculate the needed dialysate sodium concentration.

In 1980, Gotch et al proposed a single-pool sodium kinetic model based on the following assumptions: 1) Only sodium and its accompanying anions are important as effective osmotic substances in the extracellular fluid; and 2) the effective intracellular and extracellular osmolalities are equal at all times (Gotch et al. 1980). Since the effective osmotic substances do not move across the cell membrane, any change in extracellular osmolality will be followed by a transcellular fluid shift until effective osmolality again reaches transcellular equilibrium. Therefore, although sodium is distributed almost exclusively in the extracellular compartment, it is osmotically distributed in total body water, and a single pool is assumed for sodium modeling purposes.

On the basis of these assumptions, the amount of osmotically active cations present in total body water can be calculated as the product of plasma water sodium concentration multiplied by the volume of total body water, and serial changes in this product will describe serial changes in body sodium content. A measure of total body water can be reached using the urea distribution volume estimated according to the single-pool urea kinetic model. Serial changes in total body water over short periods of time are considered to be equal to change in body weight. The magnitude of interdialytic sodium intake over a dialysis treatment cycle is calculated as the difference between the product of plasma water sodium concentration multiplied by total body water volume at the beginning of dialysis and that calculated at the end of the previous session, whereas intradialytic sodium removal is calculated as the difference between the products of plasma water sodium concentration multiplied by the volume of total body water at the beginning and at the end of the same session. Sodium balance over the treatment cycle is equal to sodium load minus sodium removal.

This early analytical single-pool sodium kinetic model for evaluating sodium balance in hemodialysis was developed assuming that the ultrafilterable and diffusible plasma water sodium concentrations are the same (corresponding to plasma water sodium concentration multiplied by the Donnan factor) and using flame photometry to determine plasma and dialysate sodium concentrations. This makes it possible to calculate the dialysate sodium concentration needed to achieve the desired end-dialysis plasma water sodium concentration. The validity of this model was

evaluated in 13 hemodialysis sessions (involving 6 patients) by determining the difference between the end-dialysis plasma water sodium concentrations predicted by the model and the measured values. The results show that the end-dialysis plasma water sodium concentration predicted by the model had an imprecision of $\pm$ 2.9 mEq/L, with the imprecision of photometry accounting for 40% of the overall error and the imprecision of the estimated sodium dialysance and model error accounting for the remaining 60% (Gotch 1980). Di Filippo et al (1996) modified this single-pool sodium kinetic model by using blood and dialysate sodium concentrations determined by means of more precise direct potentiometry and assuming that 97% of the ionized plasma water sodium is diffusible. The clinical results obtained using this kinetic model to calculate the dialysate sodium concentration required to reach a pre-established target of end-dialysis plasma water sodium activity had an imprecision of less than 0.84 mEq/L, with laboratory error accounting for 58% of the overall error and imprecision in the estimate of sodium dialysance and model error accounting for the remaining 42%. Unfortunately, although they make it possible to reach the desired intradialytic sodium removal, these models are unsuitable for routine clinical application because the required initial sodium plasma water concentration and sodium dialysance in real time are cumbersome to obtain in routine dialysis.

Given the linear correlation between the sodium content and conductivity of each electrolyte solution, conductivity values can be used instead of sodium concentration values. Sodium dialysance can be easily estimated according to the basic theory developed by Polashegg (1993) if dialysate conductivity is measured at the dialyzer inlet and outlet ports at two different inlet values. After estimating ionic dialysance, plasma water sodium concentration can be easily derived as plasma water conductivity ($C_{pw}$) using the following equation (Locatelli et al. 2000):

$$C_{pw}\left(\text{mS/cm}\right) = C_{di} - \left[\frac{Q_d}{D} \times \left(C_{di} - C_{do}\right)\right] \tag{16.53}$$

Finally, since conductivity is determined by all of the ions (cations and anions) in the solution, the Donnan factor will be equal to 1. The sodium kinetic model is therefore changed to the conductivity kinetic model (Petitclerc et al. 1992), which, without the need for any blood sampling or laboratory determinations, makes it possible to predict final plasma water

conductivity ($C_{pwt}$) when inlet dialysate conductivity is known (Locatelli et al. 2000):

$$C_{pwt}\,(\text{mS/cm}) = C_{di} - \left(C_{di} - C_{pw0}\right) \times \left(\frac{V_t}{V_0}\right)^{D \times \left[\frac{1}{Q_f} - \frac{1}{Q_e}\right]} \tag{16.54}$$

Where V is water body volume (mL); 0 and t stand for the start and the end of dialysis session. $Q_f$ is the ultrafiltration rate (mL/min), and $Q_e$ is the blood water flow (mL/min). $V_0 = V_t + Q_f$ and $T_d$ is the session length in minutes.

The required inlet dialysate conductivity ($C_{di}$) to achieve a target final plasma water conductivity ($C_{pwt}$) is calculated according to the conductivity kinetic model for hemodialysis (Locatelli et al. 2000):

$$C_{di} = \frac{C_{pwt} - C_{pw0} \times \left(\frac{V_t}{V_0}\right)^{D \times \left[\frac{1}{Q_f} - \frac{1}{Q_e}\right]}}{1 - \left(\frac{V_t}{V_0}\right)^{D \times \left[\frac{1}{Q_f} - \frac{1}{Q_e}\right]}} \tag{16.55}$$

The validity of the conductivity kinetic model has been confirmed in 57 hemodialysis sessions scheduled to obtain end-dialysis plasma conductivity values of between 14.0 and 14.8 mS/cm (Locatelli et al. 1995). The dialysis monitor (Monitral S Hospal) was equipped with the specially designed Biofeedback Module (COT Hospal) connected to the dialysate line between the dialyzer and the dialysis machine. By means of a single temperature-compensated conductivity probe, which was alternately activated at the dialysate inlet and outlet, the module measures the difference between inlet and outlet dialysate conductivity values before and after a change in inlet dialysate conductivity of about 1mS/cm over a short period of about two minutes, thus determining sodium dialysance as ionic dialysance and sodium concentration as plasma water conductivity. Moreover, the module is capable of automatically controlling inlet dialysate conductivity (according to the single-pool conductivity kinetic model) in order to achieve the prescribed end-dialysis plasma water conductivity. The only data required are the patient's initial body weight, body weight loss, and treatment time. The results of this study show that the accuracy of the conductivity kinetic model is good (a mean difference between observed and

predicted values of -0.04 mS/cm), with an imprecision of less than 0.14 mS/cm, roughly equivalent to less than 1.4 mEq/L in terms of sodium concentration. The conductivity kinetic model may therefore be used instead of the sodium kinetic model, and the fact that it does not require any blood sampling or laboratory determinations makes it suitable for routine clinical application.

The importance of a method for accurately modulating sodium removal at each dialysis session lies in the fact that it could reduce intradialytic hypotension that is the most frequent intradialytic complication which is strictly related to intradialytic blood volume changes mainly depending on sodium removal. On the other hand, volume control can allow to achieve a better control of hypertension, one of the main determinants of left ventricular hypertrophy, an important cause of the high cardiovascular mortality of dialyzed patients. Of further interest are some clinical results suggesting that cardiovascular instability can be significantly reduced by individualizing dialysate conductivity in order to match interdialytic sodium loading and dialytic sodium removal (Locatelli et al. 1998).

### 16.6.2 Cardiovascular Stability

Paired filtration dialysis (PFD) is a hemodiafiltration technique in which convection and diffusion take place separately by means of a hemofilter and a hemodialyzer combined in a single unit (Ghezzi et al. 1983); it can therefore be considered to be the combination of post-dilution hemofiltration and mainly diffusive hemodialysis. A PFD single-pool sodium kinetic model has been developed by combining the equations for instantaneous sodium fluxes in hemodialysis and post-dilution hemofiltration (Di Filippo et al. 1997) with blood and dialysate sodium concentrations being determined by direct potentiometry. Moreover, ultrafilterable and diffusible plasma water sodium concentrations are not considered to be the same, but ionometric sodium is assumed to correspond to ultrafilterable fraction and 97% of this to the diffusible fraction. Clinical results have confirmed the validity of this PFD sodium single-pool kinetic model. The mean difference between the expected and measured end-PFD plasma water ionized sodium concentrations was $0.00 \pm 0.55$ mEq/L, which means that the model is very accurate, and its imprecision in predicting final plasma water sodium concentration is of less than 1.1 mEq/L and nearly equivalent to that of the hemodialysis model. On the basis of the linear relationship between ultrafiltrate conductivity and plasma water sodium concentration values, it was also developed a PFD single-pool conductivity kinetic model in which conductivity is used instead of sodium concentration. The validity of this

model as an alternative to the sodium kinetic model in optimizing sodium removal has been confirmed in clinical tests. The mean difference between the predicted and measured end-PFD ultrafiltrate conductivity was 0.01± 0.05 mS/cm with an imprecision of less than 0.1 mS/cm. The greater accuracy and precision of the PFD model than the hemodialysis model are not surprising if it is considered that plasma water conductivity is measured in the ultrafiltrate, but only estimated from ionic dialysance in the hemodialysis kinetic model. A multicenter, prospective, controlled trial involving hemodialysis patients prone to dialysis hypotension was carried out in order to test whether cardiovascular stability could be improved by using the online conductivity ultrafiltrate kinetic modeling to reduce variability in sodium balance (Locatelli et al. 1998). Forty-nine uremic patients on chronic three times weekly hemodialysis treatment, who had been affected by symptomatic hypotension during three or more dialytic sessions in the month preceding study entry, were recruited from 16 participating centers. The study had a 16-week cross-over design involving a run-in period of four weeks followed by three consecutive, four-week treatment periods (two treatments given in two sequences: ABB or BAA).

The blood and dialysate flows and the ultrafiltration rate were kept constant for all of the PFD sessions. The type of reinfusate used for each patient was always the same. The reinfusate sodium concentrations and the patient's dry body weight were left to the usual policy of the attending physician and were not changed throughout the study. During treatment A, PFD was administered using constant dialysate conductivity equal to that used during dialysis treatment before the study run-in period. During the experimental treatment (B), the dialysate conductivity (and thus dialysate sodium concentration) was calculated according to the model in order to obtain post-dialysis ultrafiltrate conductivity equal to the mean value determined in each patient during the run-in period. In this way, sodium removal should exactly match the interdialytic sodium load at each dialysis and thus possibly reduce the negative clinical effects of too much or too little sodium removal related to the variability in sodium intake from one session to another. The results of this study showed that the application of the conductivity kinetic model significantly reduced the intradialytic drop in systolic blood pressure in comparison to standard treatment (P=0.001), without any period or carryover effect. There was also a steady trend toward a reduction in the frequency of intradialytic symptoms, as well as in asymptomatic or symptomatic hypotension. This is consistent with a trend toward a better cardiovascular stability, although at different non-significant P values. There was no difference between the two treatments in terms of mean pre-dialysis and post-dialysis body weight or in the

ultrafiltrate and dialysate conductivity values. The average estimated sodium balance was therefore similar between the two treatments. In accordance with the study design, end-dialysis ultrafiltrate conductivity was the same for the two treatments. Only the variability of this value was lower during the experimental treatment and should be the key factor related to the better cardiovascular stability.

Although only future studies will allow a complete exploration of the potential clinical benefits of the more extensive use of conductivity kinetic modeling, it seems that the bulk of the results obtained thus far demonstrate its clinical relevance in handling the sodium pool. Given that ionic dialysance can be easily, inexpensively and repeatedly measured at each dialysis session without the need for blood sampling or laboratory determinations we can expect that sodium kinetic modeling will soon become a part of everyday clinical practice.

## 16.7 CONCLUSION AND FINAL REMARKS

The availability of new monitors, already spreading on a large scale, able to automatically carry out repeated determinations of ionic dialysance represents an extraordinary technological progress in hemodialysis therapy. According to the method developed by Polashegg and Petitclerc, ionic dialysance can be calculated simply by measuring inlet and outlet dialysate conductivity at two different inlet conductivity values.

The possible applications of ionic dialysance determination right now developed are related to three essential aspects of hemodialysis treatment: sodium and water removal, dialysis dose delivering and vascular access flow determination.

As far as sodium and water removal is concerned, considering the correlation between dialysate conductivity and its sodium content, ionic dialysance can be considered equivalent to effective sodium dialysance. When ionic dialysance value is known, it is possible to derive the plasma water conductivity value and so the patient natremia. The possibility to estimate sodium dialysance and patient natremia whithout any blood sample and laboratory determination makes very easy the application of sodium kinetic model, usually very difficult to use. By using the conductivity instead of sodium concentration some conductivity kinetic models have been developed allowing to easily calculating the dialysate conductivity needed to achieve the desired sodium removal, so allowing to individualize the prescription according to each patient characteristics and avoiding the inappropriate intradialytic sodium removal sometime consequent to the use of

standard dialysate. By achieving at the end of a dialysis session the patient dry body weight and a constant plasma conductivity value it is possible to remove an amount of water and sodium perfectly equivalent to the inter-dialytic load. The importance of that is showed by the fact that the clinical application of the conductivity kinetic model was associated with a better cardiovascular stability during the treatment. Moreover, by removing all the sodium introduced by foods, we could avoid the risk of an insufficient sodium removal determining increase in blood pressure and the risk of pulmonary edema.

As far as the dialysis efficiency monitoring is concerned, because of the similar molecular weight of sodium chloride and urea it has been suggested that ionic dialysance can be considered equivalent to effective urea clearance. Since ionic dialysance determination does not need blood or dialysate samples neither laboratory tests, it is possible to made repeated determinations during the dialysis session and thus obtain an adequate estimate of effective urea clearance actually referred to the entire session. That's very important in quantify delivered dialysis dose which is correlated with patients morbidity and mortality. Once urea distribution volume (V), corresponding to total body water volume, is known, it is immediately determinable the Kt/V, the index usually used to quantify the dialysis dose. Although only Kt is assumed as index of delivered dialysis dose, by following the DI values during the session it is possible to quickly find out any reduction in ionic dialysance value that can detect the insufficiency of delivered dialysis dose and therefore that could induce to search for the possible causes: reduction of effective blood flow or reduction of dialysate flow or partial dialyzer clotting, access recirculation.

Finally, the access flow monitoring is very important to early detect a malfunction, mainly responsible of morbidity and costs of hemodialysis treatment. Since the recirculation entity caused by the reverse position of blood lines is dependent by the access flow, recently several noninvasive techniques to estimate the access blood flow have been proposed, mainly based on the measurement of the blood dilution obtained by a saline bolus injection. Since the ionic dialysance value determined according the conductivity model takes into account the access recirculation, the access flow can be estimated from the measurement of ionic dialysance obtained at normal position and at reverse position of blood lines, The model is fully noninvasive not needing saline bolus injection and the results are equivalent to those obtained by the ultrasound method considered the most accurate.

In conclusion, the conductivity method represents nowadays the more promising technological innovation because its applications seem to be able to substantially modify hemodialysis treatment, especially allowing the monitoring and the on-line management of several essential treatment parameters thank to the elimination of the need for blood and dialysate samples and laboratory determinations that made just now impossible the routine application of sodium kinetic models and delivered dialysis dose assessment.

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## ESSAY QUESTIONS

1. What does ionic dialysance mean?
2. For which the reason it has been suggested that ionic dialysance can be considered equivalent to effective sodium dialysance?
3. Why ionic dialysance should be considered equivalent to effective urea clearance?
4. The adequacy in sodium removal in hemodialysis is obtained when sodium balance is zero that is when intradialytic removal is equivalent to interdialytic load. How can this goal be reached?
5. Which is the reason to explain the different relationship between ionic dialysance and urea clearance obtained by using different methodology and commercial systems in conductivity measurement?
6. How to measure sodium concentrations?
7. One of the advantages of measuring Kt/V during hemodialysis is the ability to calculate the patient's urea distribution volume (V). What important parameter can be estimated starting from a reliable estimate of V?
8. How can the final plasma water sodium concentration be predicted at the start of the treatment and how the needed dialysate sodium concentration can be calculated?
9. List the main advantages and disadvantages of direct dialysate quantification (DDQ) method.
10. Why, urea kinetic models are unsuitable for routine clinical application?
11. Is there any clinical evidence that on-line conductivity kinetic modeling can improve cardiovascular stability?

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. To correctly estimate the urea clearance at blood side the urea "effective flow" is represented by…
   A. whole blood flow
   B. blood water flow
   C. plasma flow

2. To determine the urea clearance at dialysate side the removed urea must be reported to…
   A. urea concentration in whole blood
   B. urea concentration in plasma
   C. urea concentration in plasma water

3. The urea clearance value can be assumed to be technically correct only if the mass balance error is less than…
   A. 20%
   B. 10%
   C. 5%

4. To calculate the sodium flux in determining sodium dialysance the sodium concentrations must be measured by…
   A. Flame photometry or indirect ionometry
   B. Direct ionometry
   C. Flame photometry or ionometry

5. The plasma water urea concentration in the inlet blood sample obtained after reducing the pump speed to 50 ml/min for two minutes is corrected for…
   A. Access recirculation
   B. Cardiopulmonary recirculation
   C. Total recirculation

6. Because the Donnan effect of proteins, at a physiological protein concentration, the diffusible fraction of ionized sodium in the plasma water is…
   A. All the ionized sodium
   B. Around the 95% of ionized sodium concentration
   C. Around the 80% of ionized sodium concentration

7. To obtain the concentration of dialysate sodium by direct potentiometry at which diffusion flux is zero, the inlet blood sodium concentration measured by direct potentiometry should be corrected by a factor of…
   A. 1.0
   B. 0.96
   C. 0.80

8. What is the space in which sodium is osmotically distributed?
   A. Intracellular compartment
   B. Extracellular compartment
   C. Total body water

9. Real total sodium concentration determined in plasma by flame photometry is invariably…
   A. Overestimated
   B. Underestimated
   C. Correct

10. For whole blood flow rate $Q_B$=300ml/min, Ht=30%; total protein concentration= 7 g/dl, the $Q_e$ (blood water flow) will be…

A. 300 ml/min
B. 285 ml/min
C. 258 ml/min

11. For a photometrically measured plasma sodium concentration of 140 mEq/l, the corrected plasma water sodium concentration at a protein concentration of 7g/dl will be…

A. 140 mEq/l
B. 142 mEq/l
C. 149 mEq/l

12. If the nominal blood flow rate ($Q_{Bn}$) is lower than 200 ml/min, then, the effective whole blood flow rate ($Q_{Be}$) is…

A. Lower than nominal blood flow rate ($Q_{Bn}$)
B. Greater than nominal blood flow rate ($Q_{Bn}$)
C. Equal to the nominal blood flow rate ($Q_{Bn}$)

13. If the inlet blood sodium concentration measured by direct potentiometry is 140 mEq/L, the concentration of dialysate sodium by direct potentiometry at which diffusion flux is zero, is…

A. 140 mEq/L
B. 135 mEq/L
C. 142 mEq/L

14. If the whole blood flow rate is 300 ml/min, the Effective whole blood flow rate ($Q_{Be}$) will be…

A. 250 ml/min
B. 350 ml/min
C. 300 ml/min
D. 285 ml/min

15. If the whole blood flow rate is 300 ml/min, ultrafiltration rate is 8.34 ml/min, plasma water urea concentration at the inlet and outlet ports of the dialyzer are 130 mg/dL and 36 mg/dL, respectively and the access recirculation is 4.09%, then the effective blood side urea clearance corrected for recirculation for will be…

A. 180.5
B. 178.2
C. 182.2
D. 170.5

16. Using the same data in question 15, if the dialysate flow rate is 500 ml/min and the outlet dialysate urea concentration is 49 mg/dL, the effective dialysate side urea clearance corrected for recirculation will be…

A. 185.9
B. 182.2
C. 195.5
D. 212.5

17. Using the same data in questions 15 and 16, the mass balance error (MBE %) will be…

A. 5.09 %
B. 2.02 %
C. 3.04 %
D. 6.06 %

18. For the same patient date in in questions 15 and 16, the outlet measured dialysate conductivity values are 14.42 mS/cm and 15.16 mS/cm when the inlet dialysate conductivity values are 14.49 mS/cm and 15.65 mS/cm, respectively, the ionic dialysance will be…

A. 185.9
B. 182.2
C. 175.6
D. 184.1

19. In UKM, Urea distribution volume is…

A. Directly proportional to urea clearance and inversely proportional to the magnitude of drop in plasma water urea concentration.
B. Inversely proportional to urea clearance and directly proportional to the magnitude of drop in plasma water urea concentration.
C. Inversely proportional to urea clearance and inversely proportional to the magnitude of drop in plasma water urea concentration.
D. Directly proportional to urea clearance and directly proportional to the magnitude of drop in plasma water urea concentration.

20. If the inlet and outlet dialysate conductivity are 14.49 mS/cm and 14.42 mS/cm, respectively, the dialysate flow rate is 500 ml/min and the measured ionic dialysance is 184.1 ml/min, then plasma water conductivity ($C_{pw}$) will be…

A. 14.25
B. 15.35
C. 14.29
D. 14.42

Chapter (17)

# Optical Monitoring of Dialysis Dose

Fredrik Uhlin and Ivo Fridolin

**CHAPTER OUTLINES**

- Background of optical dialysis dose monitoring
- Overview of optical principles in spectroscopy and biofluid optics
- Dialysis dose monitoring utilizing optical techniques
- Clinical parameters from optical dialysis dose monitoring
- Optical monitoring of uremic toxins beyond urea
- Future directions in optical monitoring of dialysis dose
- Conclusion

**CHAPTER OBJECTIVES**

- Describe the basic principles in spectroscopy and biofluid optics
- Present and compare optical methods for dialysis dose monitoring
- Describe how to calculate dialysis dose from UV absorbance measurements
- Describe how to calculate solute removal and nutrition parameters from UV-absorbance measurements
- Describe future directions in optical monitoring of dialysis dose

**KEY TERMS**

- Dialysis dose
- On-line monitoring
- Optics
- UV absorbance
- Near infrared spectroscopy (NIRS)
- Solute removal
- Nutrition assessment


## ABSTRACT

Utilizing optics in hemodialysis estimating quality parameters for dialysis dose has been developed during the last ten years. In principle, two optical techniques have made progress toward clinical use, namely the ultraviolet (UV) absorbance- and the near infrared (NIR) techniques. Both methods have shown reliable results of estimating urea in the spent dialysate resulting in the possibility to calculate urea-based quality parameters of dialysis dose in terms of Kt/V and URR. Even nutrition parameters derived from optical urea estimations has been provided to be possible using the UV absorbance method. The UV absorbance method cannot measure urea


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as a single solute; instead the high correlation between urea concentration and UV absorbance in spent dialysate is utilized when estimating urea parameters. The NIR-method can measure urea directly using signal processing of the raw NIR spectra. Predicted urea concentrations from the NIR measurement show an excellent agreement to urea concentrations measured by the standard chemical assays. The UV-method has recently been commercialized as a monitoring tool for dialysis dose in terms of the urea-based parameters, Kt/V and URR. On-going research is now focusing to monitor even other waste solutes than urea in spent dialysate. This aims to move towards a more comprehensive picture of the dialysis clearance process that is strongly linked to morbidity and survival of the dialysis patients compared with current dialysis dose calculations.

## 17.1 BACKGROUND OF OPTICAL DIALYSIS DOSE MONITORING

Optical methods in hemodialysis dose monitoring have a young history, started for approximately thirty years ago with the development of the high performance liquid chromatography (HPLC) technique, which utilizes Ultraviolet/Visible (UV/Vis) spectroscopic data for analysis (Gordon et al. 1975; Asaba et al. 1979; Schoots et al. 1985; Grof and Menyhart 1982). HPLC were utilized for molecule separation and identification of contents in plasma, urine and also spent dialysate (Brunner and Mann, 1984; Mabuchi and Nakahashi 1987, Vanholder et al. 1992, 1994). The "era of uremic toxins search" was born.

Utilizing standard laboratory photometers as a measure of solute removal during hemodialysis was introduced by Boda and coworkers (Boda et al. 1977). They demonstrated an exponential decrease of UV absorption in spent dialysate at 210 nm. With the introduction of light-fiber optics in the mid-1980s and the monochromator-detector developments in early-1990s, Near Infrared spectroscopy (NIRS) became more powerful for scientific research. Still, one had to wait until the end of the 20$^{th}$ century, when both UV- and NIRS- techniques took steps forward in development as tools applied for hemodialysis dose monitoring.

Aside dialysate based measurements, early attempts by optical disposable blood ultrafiltrate based sensors to measure urea content in blood entering the dialyzer were made (Lindsay et al. 1993), (Smirthwaite et al. 1993). The sensors drew periodic ultrafiltrate samples across permeable capillaries through which arterial line blood flows. A urea reading was then derived from an optical density measurement of the plasma sample

after mixing with the reagents. Some small clinical studies to validate the monitors were also carried out (Lindsay et al. 1993; Smirthwaite et al. 1993). Typical disadvantages were related to blood handling (e.g. sterility), need for disposables, etc. Today, the most promising and clinically appropriate optical sensors monitoring dialysis dose are measuring elimination of uremic solutes in the spent dialysate. For this reason, this chapter focuses mostly on this kind of optical systems.

## 17.2 OVERVIEW OF OPTICAL PRINCIPLES IN SPECTROSCOPY

Optical dialysis monitoring techniques utilize mostly phenomena described by the optics of biological fluids. The term biological fluids covers all kind of fluids produced by living organisms like blood, lymph, saliva, mucus, gastric juice, urine, aqueous humour, semen etc. Also spent dialysate can be classified as a biological fluid derived by filtering the compounds usually less in size than 50 000 Dalton from blood through a dialyzer membrane into the pure dialysate containing water and electrolytes.

From the viewpoint of optics, biological tissues and fluids can be divided into two large classes: (1) strongly scattering (opaque) tissues and fluids, such as skin, brain, vessel walls, eye sclera, blood, milk and lymph, and (2) weakly scattering (transparent) tissues and fluids such as cornea, crystalline lens, vitreous humour, aqueous humour of the front chamber of the eye (Tuchin 2000) and spent dialysate. For the second class, consisting of weakly scattering tissues and fluids, the Beer-Lambert law is often applicable (Regan and Parrish 1982).

In this section we will present a short description of the electromagnetic spectrum, some basic principles about photon propagation in biological fluids, Beer-Lambert law, examples how this could be utilized as a measurement and further most important components in an Ultra Violet (UV), Visible (Vis), Near Infrared (NIR) spectrophotometer.

### 17.2.1 Electromagnetic Radiation

Generally, electromagnetic (EM) radiation is classified by wavelength into radio wave, microwave, infrared, the visible region we perceive as light, ultraviolet, X-rays and gamma rays. The behaviour of EM radiation depends on its wavelength. Fig. 17.1 shows an illustration of the EM spectrum range. Infra-Red (IR) is per definition EM radiation with wavelength range between 760 nm-0.5 mm, Vis 390-770 nm and UV 100-400 nm. The

EM spectrum of UV light can be subdivided in a number of ways. The draft ISO standard on determining solar irradiances (ISO-DIS-21348; Van de Hulst 1980) describes the following ranges relevant to dialysis optical monitoring:

- Ultraviolet A, long wave (UVA) 400 nm–315 nm;
- Ultraviolet B or medium wave (UVB) 315 nm–280 nm;
- Ultraviolet C, short wave (UVC) 280 nm–100 nm.

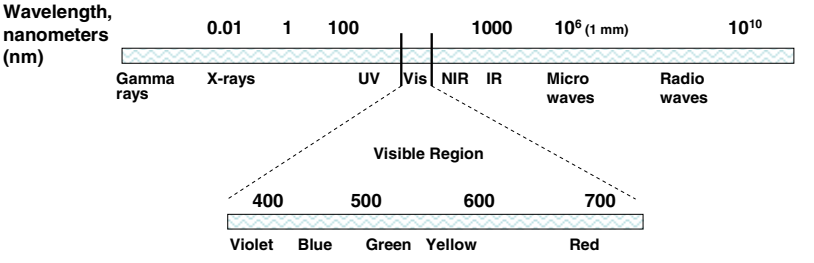



**Fig. 17.1** Illustration of the electromagnetic spectrum range

The infrared (IR) part of the electromagnetic spectrum covers the range from roughly 300 GHz (1 mm) to 400 THz (750 nm). It can be divided into three parts:

- Far-infrared, from 300 GHz (1 mm) to 30 THz (10 μm). The lower part of this range may also be called microwaves. This radiation is typically absorbed by so-called rotational modes in gas-phase molecules, by molecular motions in liquids, and by phonons in solids.
- Mid-infrared, from 30 to 120 THz (10 to 2.5 μm). Hot objects (black-body radiators) can radiate strongly in this range. It is absorbed by molecular vibrations, where the different atoms in a molecule vibrate around their equilibrium positions. This range is sometimes called the fingerprint region since the mid-infrared absorption spectrum of a compound is very specific for that compound.
- Near-infrared, from 120 to 400 THz (750 nm to 2500 nm). Physical processes that are relevant for this range are similar to those for visible light.

In the context of NIR spectroscopy, wavelength is measured in "wave numbers", which have the units $cm^{-1}$, wave number = 1 / wavelength in centimeters.

"Light" is usually defined as visible EM radiation of the entire EM spectrum where the human eye is sensitive (Sliney and Wolbarsht 1980; Judy 1995; Saleh and Teich 1991; Welch and van Gemert 1995). But the term light is often extended to adjacent wavelength ranges that the eye cannot detect (Welch and van Gemert 1995). Spectroscopy can detect a much wider region of the EM spectrum than the visible range. A common laboratory spectrophotometer can detect wavelengths from 200 nm to 2500 nm. Detailed information about the physical properties of objects e.g. gases and fluids can be obtained from this type of device.

### 17.2.2 Photon Propagation in Biological Fluids

Interaction between light/EM radiation and molecules in e.g. a biological fluid result in different phenomenon that could be utilized during measurements to identify molecules that are solved in the fluid and even possibilities to estimate the concentration. In this sub-section, some basic parts of those phenomenons will be described.

In principle, photons emerged from a source and propagating into a medium can be (see Fig. 17.2):

1) On the surface of the medium (van de Hulst 1980; Ishimaru 1991; Saleh and Teich 1991):
    - Reflected off the medium.
    - Penetrated (transmitted) into the medium.

2) Inside the medium:
    - Absorbed by the medium.
    - Scattered by the medium.
    - Internally reflected, becoming once again the subject of absorption.
    - Scattered in the medium (Welch et al. 1995).

3) Emerged from the medium:
    - Transmitted with no effect, unscattered (primary or direct) transmission (van de Hulst 1980).
    - Transmitted after attenuation (absorption and scattering) in the medium, diffuse transmission (van de Hulst 1980; Welch and van Gemert 1995).

- Reflected from the medium (backscattered after scattering in the medium), diffuse reflection (van de Hulst 1980).

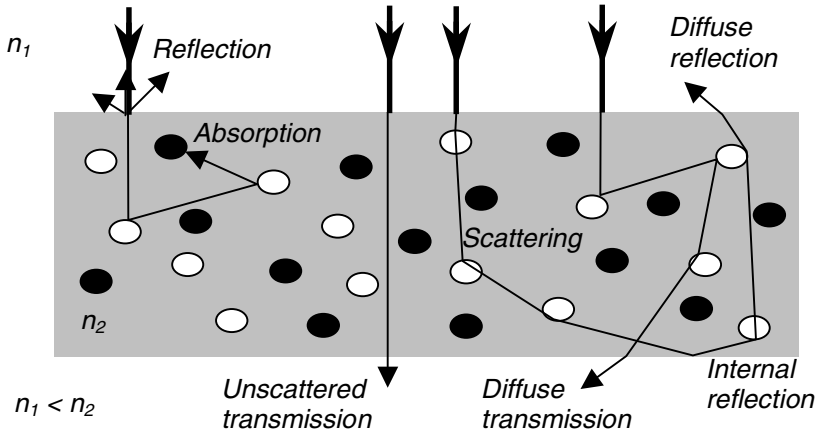



**Fig. 17.2** Schematics of photon propagation into, inside and from a medium; ●- absorber, o – scatterer, $n_1$ and $n_2$ are the refractive indices of two different media

In tenuous media, like spent dialysate, all the incident light is either absorbed, transmitted or reflected, and scattering from other regions of the medium can be ignored (Welch et al. 1995). For this reason we will consider only the parameters absorbance, transmittance and neglect scattering in the following description. This is the reason why absorption spectroscopy in the spent dialysate can be successfully applied for dialysis monitoring. For the tense medium, like blood, scattering should be taken into account.

#### 17.2.2.1 Photon Propagation into a Medium

At the boundary between two media of different refractive indices incident light is split into two – a refracted (or transmitted) and a reflected portion (Saleh and Teich 1991).

#### A. Refraction

Refraction occurs whenever a beam of light passes from one transmitting medium to another having a different refraction index (Sliney and Wolbarsht 1980; Saleh and Teich 1991). The index of refraction, n, of a

transparent medium is a direct measure of its optical density and is equal to the ratio of the speed of light in a vacuum, c, to the speed of light in the medium, v:

$$n = \frac{c}{v} \tag{17.1}$$

Refractive indexes are usually equal to or greater than 1: for air $n \approx 1$, for water $n \approx 1.33$ and for tissue, $n \approx 1.44$ (can vary from 1.33 to about 1.55) (Bolin et al. 1989; Duck 1990; Welch et al. 1995; Tuchin 2000).

**Snell's law** or the law of refraction relates the angle of incidence $\theta_1$ (angle between the incident ray and the normal) to the angle of refraction $\theta_2$ (angle between the refracted ray and the normal):

$$n_1 \sin\theta_1 = n_2 \sin\theta_2 \tag{17.2}$$

From Snell's law it can be derived that in order to minimize refraction, the angle of incidence $\theta_1$ should be as close as possible to 0 degree in which case $\sin 0° = 0$. This is the reason why collimated beams perpendicular to any kind of surfaces in the optical (focusing, filtering) systems, aimed to guide the light through, are utilised in the spectrophotometers helping to minimize loss of light from the source.

## B. Reflection at the Surface

A portion of the photons is reflected at the surface due to the difference in the index of refraction of the two media and the angle of incidence of the photons. The measure of the fraction of light that is reflected by a material is called its reflectance. Specular reflection (mirror-like) is the reflection in which incident parallel rays remain parallel after reflection and the angle of reflection equals the angle of incidence. Specular reflection occurs when the size of the surface irregularities is less than the wavelength of the incident radiation (Sliney and Wolbarsht 1980).

In the case of unpolarised light, the specular reflectance $R_s$, is given by Fresnel's formula (Welch et al. 1995).

$$R_s = \frac{1}{2}\left(\frac{\tan^2(\theta_1 - \theta_2)}{\tan^2(\theta_1 + \theta_2)} + \frac{\sin^2(\theta_1 - \theta_2)}{\sin^2(\theta_1 + \theta_2)}\right) \tag{17.3}$$

Diffuse surface reflection occurs when the surface irregularities are randomly oriented and are much greater than the wavelength of the incident

radiation (Sliney and Wolbarsht 1980). Diffuse surface reflection gives the reflected rays that are scattered in a random fashion and are not parallel (Ryer 1998). The isotropic diffuse surface reflectance follows Lambert's law stated by Lambert in 1760 (Regan and Parrish 1982) which is also known as the Cosine law of Reflection (Sliney and Wolbarsht 1980; Regan and Parrish 1982; Born and Wolf 1975; Ishimaru 1978).

$$I = \frac{P\rho\cos\theta}{\pi d^2} \tag{17.4}$$

Where I is the reflected irradiance from the surface, P is collimated beam power upon the surface, θ is the angle between the incident ray and the surface's normal, ρ is the diffuse reflection coefficient for the given wavelength and d is the distance from the diffuse reflection spot on the surface to the detector (Sliney and Wolbarsht 1980).

It is important to notice that diffuse and specular reflections at the surface are highly wavelength dependent. Many reflections are a combination of both components. One manifestation of this is a spread reflection, which has a dominant directional component that is partially diffused by surface irregularities (Ryer 1998) (see Fig. 17.3).

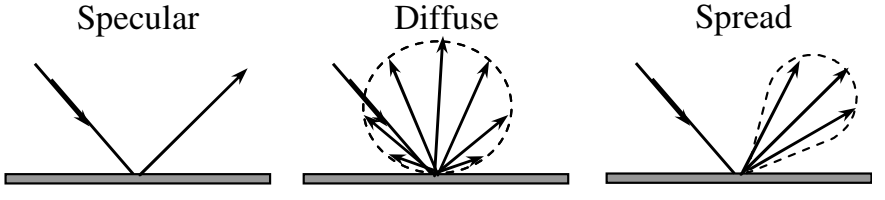



**Fig. 17.3** Specular, diffuse and spread reflection from a surface

### C. Transmission

The measure of the fraction of light that is penetrated (transmitted) into a medium is called transmission, T (Saleh and Teich 1991). For a unit of irradiance the light transmitted into a medium is (Welch et al. 1995).

$$T = 1 - R \tag{17.5}$$

where R is the reflectance.

#### 17.2.2.2 Photon Propagation Inside a Medium

Photons that propagate inside a medium can be absorbed by the molecules in the sample.

**A. Absorption**

During absorption spectroscopy an incident photon can be absorbed by a molecule and then the photon energy is converted into an excitation of that molecule's electron cloud. This type of interaction is sensitive to the internal structure of the molecule, since the laws of quantum mechanics only allow for the existence of a limited number of excited states of the electron cloud of any given chemical species. Each of these excited states has a defined energy; the absorption of the photon has to bridge the energy gap between the ground state (lowest energy state) and an allowed excited state of the electron cloud. Molecules can therefore be identified by their absorption spectrum: Their wavelength-dependent capacity for absorbing photons depends on the energy spacing of the states of their electron cloud. If the frequency of the radiation matches the vibration frequency of the molecule then radiation will be absorbed, causing a change in the amplitude of molecular vibration. Molecules which strongly absorb Vis light, appear coloured to the human eye and are therefore called, chromophores, i.e. "carriers of colour."

**B. Fluorescence**

In absorption, the signal of molecules in a sample is direct but it can be done with higher sensitivity by using an indirect approach, fluorescence detection. Then the ingoing light will give the absorbing molecules excited states of their electron cloud (higher energy). From this state the molecule can shift, “relax”, to the electronic ground state by transforming the excess energy into an outgoing emitted light having longer wavelengths than the ingoing light. Different molecules have different emitted spectrum which is utilized during the fluorescence measurements (Lakowicz 2006).

#### 17.2.2.3 Photon Propagation from a Medium

Photons can also pass through the sample and the transmitted photons can be measured.

**A. Transmittance**

A part of photons can pass the medium without interacting with it at all. Those photons are transmitted through the medium and are sources to

measure a quantity called transmittance (Saleh and Teich 1991). Transmittance in spectroscopy is defined mathematically later in this chapter.

## B. Spectrophotometer

The basic parts of a spectrophotometer are a light/radiation source, a sample holder of transparent material e.g. cuvette of glass, a monochromator or diffraction grating ("wavelengths selector"), a photo/radiation detector and finally a signal processor. Fig. 17.4 shows a UV-Vis-NIR spectrophotometer schematically including the basic components. The radiation sources are often a tungsten filament (300-2500 nm) or a halogen lamp and a deuterium lamp, which has continuous radiation intensity over the UV region (190-400 nm). Recently, light emitting diodes (LED) and Xenon Arc Lamps are introduced (Skoog et al. 2007). The detector is typically a photodiode or a charge-coupled device (CCD). Photodiodes are used with monochromators, which filter the EM so that only EM of a single wavelength reaches the detector. Diffraction gratings ("beam splitter") are used with CCDs, which collects light of different wavelengths on different pixels.

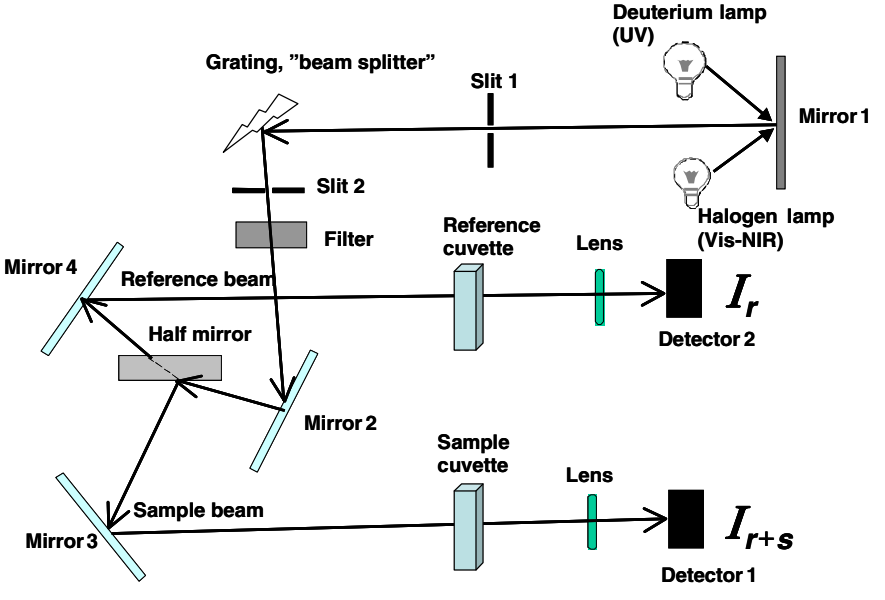



**Fig. 17.4** Schematically illustration of components in a double beam UV/Vis/NIR spectrophotometer

A spectrophotometer can be either single beam or double beam. In a single beam instrument, all of the light passes through the sample cell. The ingoing light ($I_o$) must be measured by removing the sample. In a double-beam instrument, the light is split into two beams by a half mirror before it reaches the sample (see Fig. 17.4). One beam is used as the reference; the other beam passes through the sample. Some double-beam instruments have two detectors (photodiodes), and the sample and reference beam are measured at the same time.

Samples for UV/Vis/NIR spectrophotometry are most often liquids, although the absorbance of gases and even of solids can also be measured. Samples are typically placed in a transparent cell, a cuvette. Cuvettes are often rectangular in shape, commonly with an internal width (path length, l) of 1 cm (see Fig. 17.5). The type of sample container used must allow radiation to pass over the spectral region of interest. The most widely applicable cuvettes are made of high quality fused silica or quartz glass because these are transparent throughout the UV, Vis and NIR regions. Glass and plastic cuvettes are also common, although glass and most plastics absorb in the UV, which limits their usefulness in this region (Skoog et al. 2007). A complete spectrum of the absorption at all wavelengths of interest can often be produced directly by a more sophisticated spectrophotometer. In a spectrophotometer different wavelengths can be selected as single ones or scanned over an optical wavelength range.

Instrumentation for NIR spectroscopy is partially similar to instruments. There is a source, a detector, and a dispersive element (such as a prism, or, more common, a diffraction grating) to allow the intensity at different wavelengths to be recorded. Fourier transform (FT) NIR instruments using an interferometer are also common, especially for wavelengths above ~1000 nm. Depending on the sample, the spectrum can be measured in either reflection or transmission. Common quartz halogen light bulbs are most often used as broadband sources of NIR radiation for analytical applications. LEDs are also used; they offer greater lifetime and spectral stability and reduced power requirements.

Qualitative and quantitative spectroscopic methods typically require the application of multivariate calibration algorithms and statistical methods (i.e. chemometrics) to model spectral response to chemical or physical properties of the samples used for calibration. The method relies on the spectra-structure correlations existing between a measured spectral responses caused by harmonics of the fundamental vibrations occurring at infrared frequencies. These harmonic vibrations occur at unique

frequencies depending upon the quantity of absorber (analyte), type of absorbing molecules present within the sample, and the sample thickness. Quantitative methods are possible where changes in the response of the spectrophotometer are proportional to changes in the concentration of chemical components, or in the physical characteristics (scattering/ absorptive properties) of samples undergoing analysis.

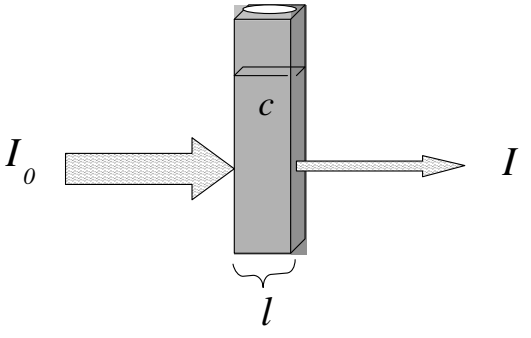



**Fig. 17.5** Cuvette with a sample containing an absorber with concentration (c). Ingoing light ($I_0$) and outgoing light (I) after absorption in the sample when passing through the cuvette with the optical path length, l.

## C. Transmittance and Absorbance

The amount of transmitted and absorbed portion of EM radiation in the medium (e.g. in a dialysate sample) can be characterised by the parameters transmittance T, and Absorbance A in the spectrophotometer. In order to utilize EM radiation for measurement of constituents in a fluid, the sample is applied in an optical cuvette (see Fig. 17.5). Through the calibration and measurement procedures one determines the amount of the ingoing light illuminating the sample symbolized by $I_0$ and the outgoing light I symbolizing the intensity of the light after passing the sample as the remaining ingoing light partly absorbed by the sample (see Fig. 17.5). Having knowledge about those parameters one can determine transmittance T, and Absorbance A as:

Transmittance:
$$T = \frac{I}{I_0} \quad \Rightarrow \quad \%\,T = \frac{I}{I_0} \cdot 100\% \tag{17.6}$$

Absorbance:
$$A = -\log T = -\log \frac{I}{I_0} = \log \frac{I_0}{I} \tag{17.7}$$

**Example 17.1**

*For the following given transmittances, determine the corresponding absorbance*

a) T = 1.00 (100 %T)
b) T = 0.10 (10 %T)
c) T = 0.001 (0.1 %T)

**Solution**

The absorbance can be calculated according to Eq. (17.7) as follows:

a) $A = -\log 1 = 0.00$
b) $A = -\log 0.1 = 1.00$
c) $A = -\log 0.001 = 3.00$

The intensity often has the units of $W/m^2$ (Tuchin 2000; Sliney and Wolbarsht 1980; Saleh 1991) but can also be expressed in W if measured as the radiant power (Mann et al. 1974).

### 17.2.3 Beer- Lambert Law

The law describing the amount of incident radiation, absorbed by a homogeneous medium placed in a collimated beam of radiation, was first developed in 1729 by a priest at Le Havre, Pierre Bouguer, and later elaborated by Johann Lambert in 1760 (Regan and Parrish 1982). They demonstrated that the proportion of radiation, absorbed by a homogeneous medium, is independent of the intensity of the radiation. In 1852 August Beer found that the transmission of radiation by a homogeneous medium is dependent only upon the number of molecules through which the radiation travels. He showed that the number of exchanges of energy was directly proportional to the number of absorbing molecules (Regan and Parrish 1982). The derivation and the mathematical expression of both Beer's laws can be found in several sources (Brown 1980; Glasser 1961; Regan and Parrish 1982). The Bouguer-Lambert law may be combined with Beer's law to describe how the fraction of the incident radiation absorbed is related to the concentration and the path length through the solution (Maass 1977; Regan and Parrish 1982; Brown 1980; Björn 1965; Bashford 1987). This law has come to bear the name Beer-Lambert law, or simply Beer's law (Mann et al. 1974).

The Beer- Lambert law states that the absorbance of light intensity is proportional to the concentration of the substance. It means that the amount of e.g. UV-light absorbed when passing through a cuvette

(manufactured by UV-transparent material such as quartz) with spent dialysate is linearly dependent on the concentration c [mol/L] of the absorbing solute, the optical pathlength in (l) [m] (depth of the cuvette) and the extinction coefficient ε [$m^{-1}$ $(mol/L)^{-1}$], even called the molar absorptivity at a certain wavelength (Glasser 1961). If $I_0$ is the intensity of the incident light and I is the intensity transmitted light through the medium, the absorbance (A), dimensionless, is:

$$A = \log_{10}\left[\frac{I_0}{I}\right] = \varepsilon \cdot c \cdot l \tag{17.8}$$

If ε is known for a substance the absorbance (A) can be calculated by multiplying the path length and the concentration of the substance. If ε is known for a substance and A is obtained from a measurement, it is possible to derive the concentration as:

$$c = \frac{A}{\varepsilon \cdot l} \tag{17.9}$$

In our case, when the spent dialysate contains several different absorbing compounds, the overall extinction coefficient is the linear sum of the contributions of each compound. However all the components are not identified and probably there is interference between different substances which make it difficult to separate and determine the concentrations of each solute. Absorbance of a solution, obtained by a double beam spectrophotometer, is given by the Lambert -Beer law as (Hahn et al. 1979; Zwart et al. 1984):

$$A = \log\frac{I_0}{I_{r+s}} - \log\frac{I_0}{I_r} = \log\frac{I_r}{I_{r+s}} \tag{17.10}$$

Where $I_0$ is the intensity of incident light from the light source $I_r$ is the intensity of transmitted light through the reference solution (e.g. pure dialysate) and $I_{r+s}$ is the summated intensity of transmitted light through the reference solution mixed with the solution (e.g. pure dialysate + waste products from the blood).

The common assumptions to utilise absorbance calculated according to the Beer-Lambert law to determine concentration are:

1) The radiation is monochromatic (Regan and Parrish 1982; Mann et al. 1974; Glasser 1961; Björn 1965).
2) The irradiating beam is parallel (collimated) across the sample (Regan and Parrish 1982; Glasser 1961).
3) The absorption of radiation for a given species is independent of that of other species (Regan and Parrish 1982; Glasser 1961).

4) Only the non-scattered and not-absorbed photons are detected from the medium (Welch and Gemert 1995)
5) The incident radiation and the concentration of the chromophores are not extremely high (Mann et al. 1974; Togawa et al. 1997).

The Beer-Lambert law for monochromatic light can be derived solving a differential equation for a solution with a finite depth containing chromophores and is given in detail in many sources (Mann et al. 1974; Regan and Parrish 1982; Sliney and Wolbarsht 1980). Analysis of a mixture is based fundamentally on the fact that the absorptions, at each wavelength, of separate components in the mixture are additive, provided that chemical or interfering physical reactions between the components do not occur (Glasser 1961), and the solute concentrations are not very high (not usually found in biological media). In this case, in a medium containing n different absorbing compounds with the concentrations of $c_1 ... c_n$ [mol/L] and the extinction coefficients of $\varepsilon_1 ... \varepsilon_n$ [$m^{-1}$ $(mol/L)^{-1}$], the overall extinction coefficient is simply the linear sum of the contributions of each compound:

$$A = \log_{10}\left[\frac{I_0}{I}\right] = \left(\varepsilon_1 c_1 + \varepsilon_2 c_2 + ... + \varepsilon_n c_n\right) l \qquad (17.11)$$

## 17.3 DIALYSIS DOSE MONITORING UTILIZING OPTICAL TECHNIQUES

Several solutes in spent dialysate identified as uremic toxins by Prof Vanholder and colleagues in the European Uraemic Toxin (EUTox) Work group have been measured utilizing UV absorbance in HPLC technique (Vanholder et al. 2008, 2004, 2003a, b). Their research has been followed with great interest for fronting the question: Could some of these identified molecules be measured with optical techniques on-line? At the present two optical techniques for dialysis dose monitoring have been investigated in several studies, UV absorbance and NIRS. Other approaches have also been investigated but more limited so far, e.g. utilizing the Vis region for measurement. In this chapter, the UV absorbance and the NIRS technique will be discussed that up to day have been developed further and have presented several promising results as potential monitoring tools for hemodialysis.

### 17.3.1 UV – Spectroscopy

The first available publication about how UV-transmittance of the spent dialysate has been measured at 254 nm, believed to be the best wavelength to monitor the efficacy of hemodialysis, was written by an Hungarian group (Gal and Grof 1980). Also, there was concluded that the hardly diffusible constituents had a higher elimination rate compared to the removal rate of small, more readily diffusible components. Many of those things have shown to be different according by the knowledge we have today. Almost two decades later, a work aiming to monitor the dialysis liquid during hemodialysis by UV absorbance, was presented by Vasilevski et al from St:Petersburg (Vasilevski and Kornilov 1999). This group discussed also UV extinction as an indicator of nucleic acid metabolism (Vasilevsky and Konoplyov 2005).

In a very short time, in 2001, independent studies from abovementioned about on-line monitoring of solutes in dialysate using UV absorbance were published (Fridolin et al. 2001; Fridolin et al. 2002), investigating possibility to monitor removal of different uremic solutes in the spent dialysate, and firstly describing how to estimate urea Kt/V by UV absorbance, as an illustrative example. The first clinical study, connecting the UV-technology with a real clinical application - with dialysis dose calculated as Kt/V using UV absorbance - was reported by Uhlin et al (2003). Apparently, since this, there was no clinical study published, where dialysis dose calculated as Kt/V or URR using UV absorbance had been presented. A fruitful and exiting collaboration between Uhlin and Fridolin et al. within the field of optical UV absorbance dialysis dose monitoring has been followed. In connection with commercialisation of the UV-technology for dialysis dose monitoring during last couple of years, new interest has arisen towards the field. Recently, some works related to spectroscopical analysis of uremic substances in dialysate are presented by the groups from Japan (Umimoto et al. 2007a, b; Umimoto et al. 2009), and from St:Petersburg (Vasilevski and Konoplev 2009). The clinical validation of a clinical prototype device (Luman et al. 2009a), and the commercially available UV absorbance dialysis dose monitor have been also presented recently (Castellarnau et al. 2010).

#### 17.3.1.1 Clinical Setting during UV Absorbance Monitoring

During the on-line clinical experiments using UV absorbance a commercial available double beam spectrophotometer was connected to the fluid outlet of the dialysis machine and ended in a tank equipped with a

scale were all spent dialysate was collected (see Fig. 17.6). Total Dialysate Collection (TDC), in the tank (see Fig. 17.6), started when the blood filled the dialyser and ended when the blood was returned to the patient (after 3-5 hours) at the end of the dialysis. After its weight was recorded and the collected spent dialysate was carefully stirred, a TDC sample ($D_{total}$) sample location 2 (see Fig. 17.6), was sent to the laboratory, and urea concentration (mmol/L) was measured. Urea concentrations in the dialysate ($D_{urea}$) later used for correlation analyses and mathematically transformations, were also determined at scheduled times during dialysis: at 5, 15, 30, 60, 90, 120, 180 and 240 min (also at 270 and 300 min, if the treatment was longer than 240 min) from samples taken from the dialysate drain tube, sample location 1 (see Fig. 17.6).

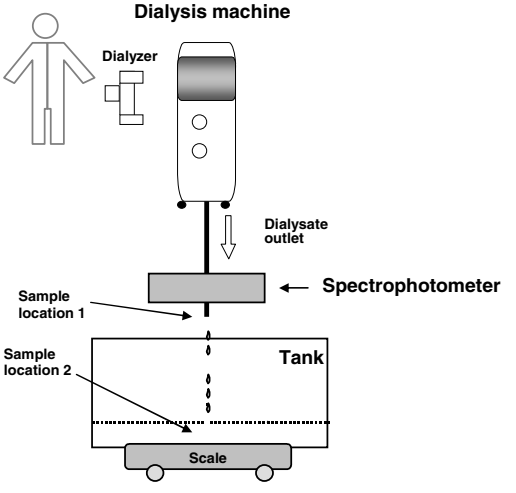



**Fig. 17.6** Schematical set up during the clinical UV absorbance experiments. Sample location 1 = Drain sample (flowing dialysate) and sample location 2 = Tank sample (accumulated dialysate)

An optical flow cuvette with a path length of 10 mm, Fig. 17.7a, was connected to the drain tube and placed at the sample holder in the spectrophotometer (see Fig. 17.7b); the reference holder was left empty during on-line measurements.

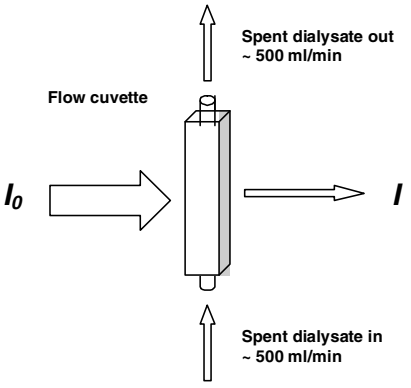



**Fig. 17.7a** The optical flow cuvette schematically.

**Fig. 17.7b** Photo of the optical flow cuvette inserted in an UV/Vis/NIR spectrophotometer where drain tube is connected. A window for the light beam is also seen on the black wall behind the cuvette.

Before start of study treatment, UV absorbance was measured on pure dialysate from the dialysis machine and applied as a zero baseline for the reference.

#### 17.3.1.2 Visualization of the Clearance Process with UV Absorbance

During the experiments, one single wavelength was selected during the entire dialysis treatment. The obtained UV absorbance curve from on-line measurements of spent dialysate, Fig. 17.8, was used to estimate urea

based clinical parameters such as the dialysis dose (Kt/V) and total removal of urea (TRU), which will be described later in this chapter. UV absorbance drops and peaks, which normally occurred at predestined intervals during the dialysis, correspond to self-test of the dialysis machine. The drops and peaks corresponds to periodical self-tests of the dialysis machine when dialysate is set in by pass mode and no fresh dialysis fluid is pumped through the dialyzer.

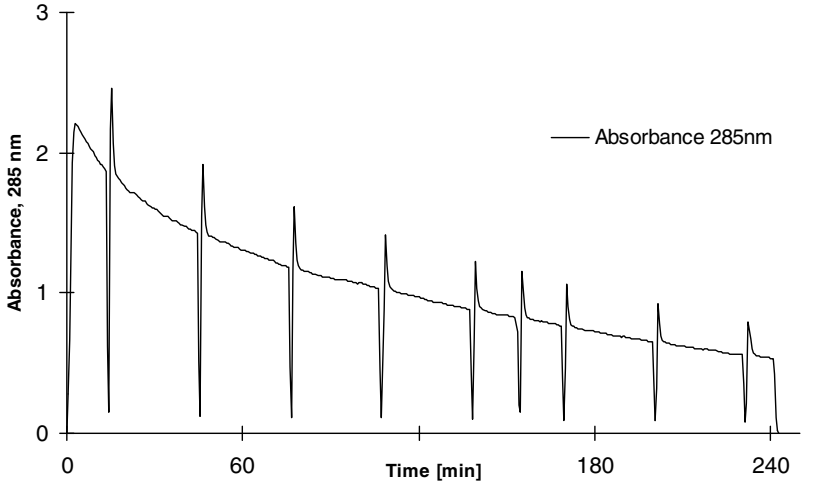
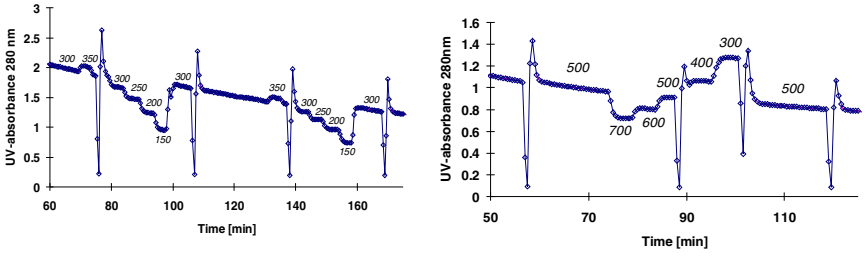



**Fig. 17.8** A typical on-line UV absorbance curve during a single hemodialysis treatment where UV absorbance, at the wavelength 285 nm, is plotted against time

When utilizing the UV absorbance technique, unique information about the solute clearance process could be visualized in real time (Uhlin et al. 2006a, 2006b). Variations in clearance due to e.g. alarm situations and problems with blood access can be noticed and effects after interventions in order to increase clearance can be evaluated. Figures 17.9a and 17.9b show the result of changes in UV absorbance when manipulating the blood- and dialysate flow respectively.




(a) (b)

**Fig. 17.9** Response to manipulations during two dialysis treatments; (a) changes in blood flow, and (b) changes in dialysate flow. The changes lasting for 5 min each. The blood- and dialysate flow rate in mL/min is presented in the figure. [Reprinted with permission from Uhlin et al. 2006a]

Figure 17.10 shows clinical situations and the effect visualized in changes in UV absorbance, the effect of interventions (adjustment of needle position) to increase the blood flow in the artery needle (Uhlin et al. 2006a).

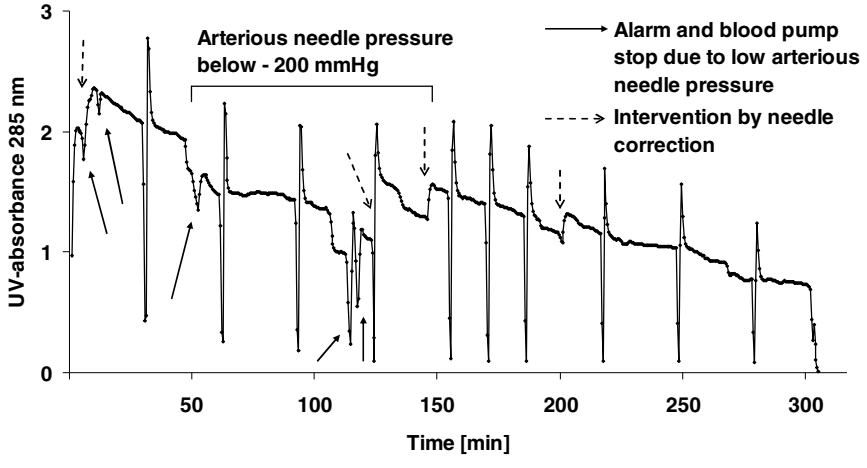



**Fig. 17.10** A problematic treatment, where the main problem was bad flow in the artery needle. The blood pump flow was set to 300 ml/min throughout the treatment

This restricted flow resulted in several interruptions and alarms and an abnormal curve shape can be visualized (compare to Fig. 17.8). This treatment had a low reduction ratio of waste solutes when blood samples pre-and post-dialyses were analyzed, compared to a non-problematic treatment of the patient.

#### 17.3.1.3 UV-Spectra of the Spent Dialysate and UV Chromophores in the Uremic Fluids

To detect the UV absorbance spectra of spent dialysate, samples were taken from the drain tube of the dialysis machine at different times during treatment (sample location 1, see Fig. 17.6). It is known that during the first 60 minutes the removal rate of water soluble solutes is highest compared to later period in the dialysis treatment resulting from so called double-pool behaviour of the solute removal during dialysis. Therefore the samples were taken more frequent in the beginning of treatments. Figure 17.11 shows an UV absorbance spectrum where samples taken at different times during a treatment are scanned over the entire UV range.

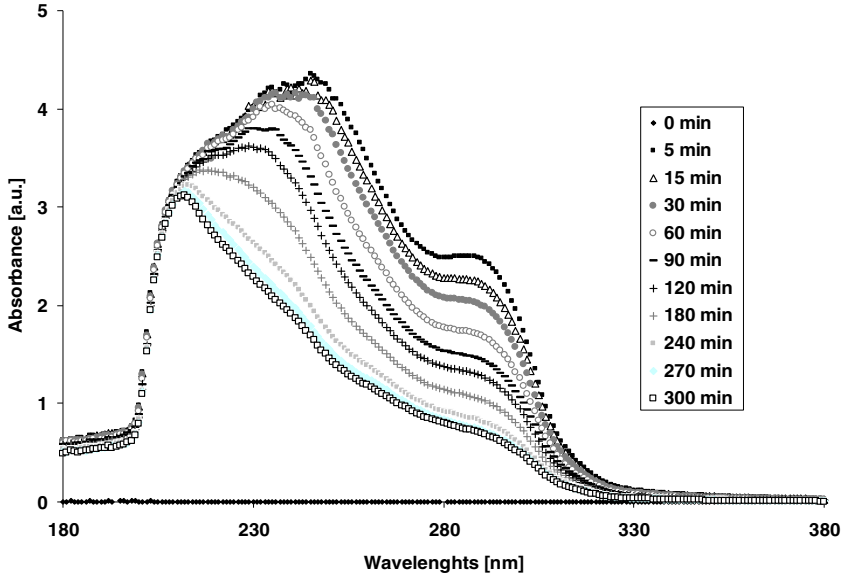



**Fig. 17.11** Scanning of collected spent dialysate taken at different times during one dialysis session over the UV range when using pure dialysate as a reference fluid

As shown the UV absorbance is highest for the samples taken early in treatment. For reference solution, pure dialysate was used taken before the start of the dialysis treatment, marked as 0 min in Fig. 17.11 (absorbance $\approx 0$). In spent dialysate the absorbance in the upper half of the UV region (260-330 nm) is easily to measure due to a suitable dynamic range of the absorbance signal. But in the lower half of the UV-range

(approx. 200- 250 nm) the absorbance value could be often too high with the optical path length of 10 mm.

A number of the higher prevalent peaks on the HPLC profiles of the uremic serum from the earlier HPLC studies indicate that there exists a group of compounds – UV chromophores – which are the main cause of the cumulative and integrated UV absorbance (Schoots et al. 1989; Vanholder et al. 1992). Recent HPLC studies investigated the uremia related UV absorbance profiles of the serum and the spent dialysate and removal of uremic retention solutes in connection with optical dialysis adequacy monitoring (Lauri et al. 2006; Lauri et al. 2010a, b). The chromatographic peaks were detected by a UV detector at wavelengths of 254 and 280 nm. Those studies indicated that the main solute responsible for the UV absorbance in the spent dialysate is a low-molecular-weight water-soluble non-protein bound compound uric acid (UA) (see Fig. 17.12). Spiking experiments and UV spectra between 200-400 nm allowed recognize predominant uremic toxins in 5 chromatographic peaks identified as creatinine (CR), uric acid (UA), hypoxanthine (HX), indoxyl sulphate (IS), and hippuric acid (HA) (Lauri et al. 2010a, b). Moreover, 2 persistent, but non-identified peaks - peak 1 (P1) and peak 2 (P2) - were detected (Lauri et al. 2010b). The relative contribution from the area of 10 main peaks to the total area of all detected peaks in percentage was about 90 % at 280 nm (Lauri et al. 2006).

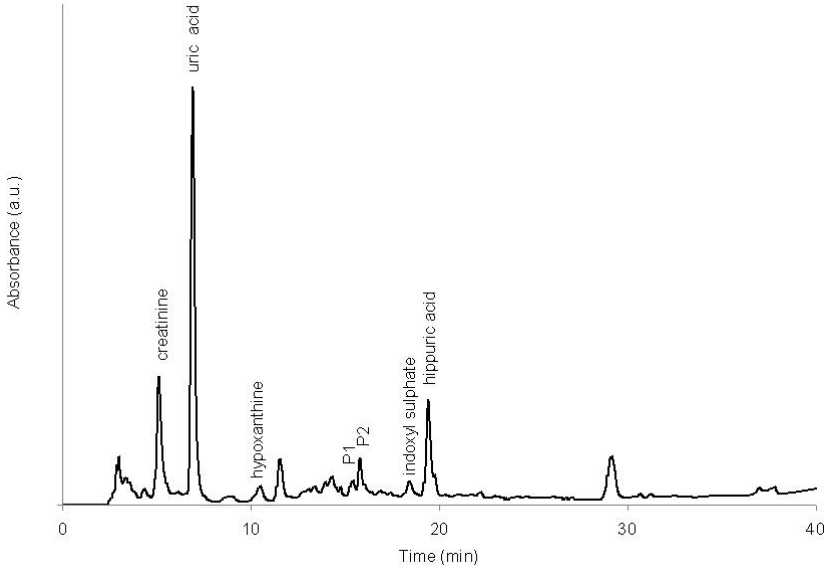



**Fig. 17.12** The representative HPLC chromatogram of the serum monitored at the wavelength of 254 nm. Identified peaks are presented.

The number of detected HPLC peaks was not significantly different for a serum filtered through the 3 kDa or 70 kDa cut off filters, and was lower for the spent dialysate, indicating that the MW of the main UV chromophores in the uremic fluids do not exceed 3 kDa (see Fig.17.13).

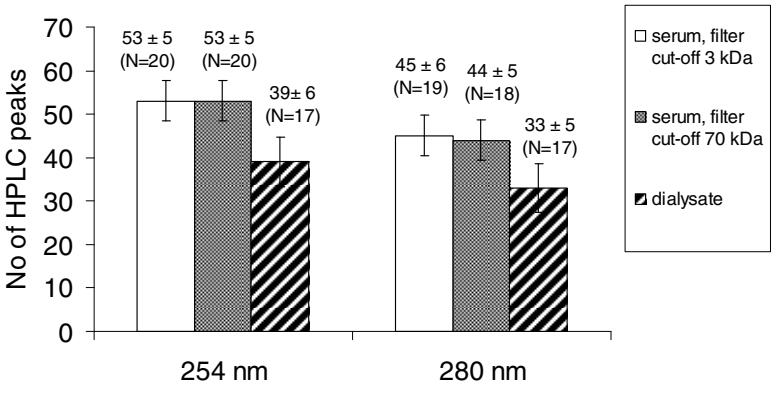


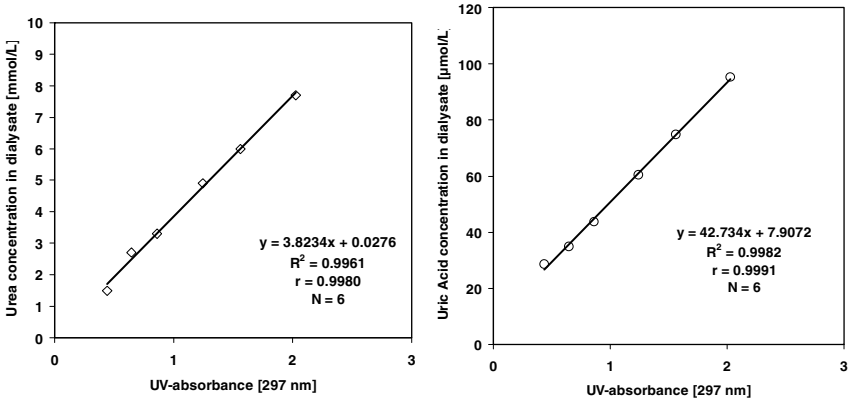

**Fig. 17.13** Number of detected HPLC peaks at wavelengths 254 nm and 280 nm in the serum (filter cut-off 3 kDa and 70 kDa, respectively) and in the spent dialysate.

The reduction ratio (RR) estimated by the total area of HPLC peaks at 254 nm and 280 nm in the serum and by the on-line UV absorbance at 280 nm was best related to the removal of small water-soluble non-protein bound solutes like urea, creatinine and UA (Lauri et al. 2010a). This indicates that the UV absorbance is following the behaviour of the UV absorbing compounds – the low-molecular-weight water-soluble non-protein bound uremic toxins, which contribute most to the total UV absorbance in the serum and in the spent dialysate (see Fig. 17.13).

#### 17.3.1.4 UV Absorbance and Uremic Solutes

Known from the HPLC studies, UV absorbance do not measure a single solute. The absorbance signal reflects contribution of several UV absorbing compounds in the spent dialysate, and the strongest influence comes from the low-molecular-weight water-soluble non-protein bound compounds (Lauri et al. 2010a). If a solute concentration is correlated with the total UV absorbance of the solutes then functional calibration

(transformation) models can be constructed for the solute. High correlation between UV absorbance at the wavelengths of 280-320 nm and concentration of some solutes in spent dialysate has been demonstrated such as urea, creatinine and uric acid (Fridolin et al. 2002). The correlations are close to 1.0 in every single treatment and even in several treatments of the same patient. The slope values are different for different solutes; single solutes have different relationships to the UV absorbing solutes that the UV-signal represents. Figures 17.14a and 17.14b show the correlation between UV absorbance and concentrations of urea and uric acid respectively in the same dialysis session.




(a) (b)

**Figs. 17.14** The correlation between concentrations of urea (17.14a), uric acid (17.14b) and UV absorbance respectively in a single treatment (the same treatment), r is high, but slope and intercept are different

The correlation is lower when several patients are included in the plot (see Fig. 17.15) due to different concentration of chromophores in the uremic fluids from different patients.

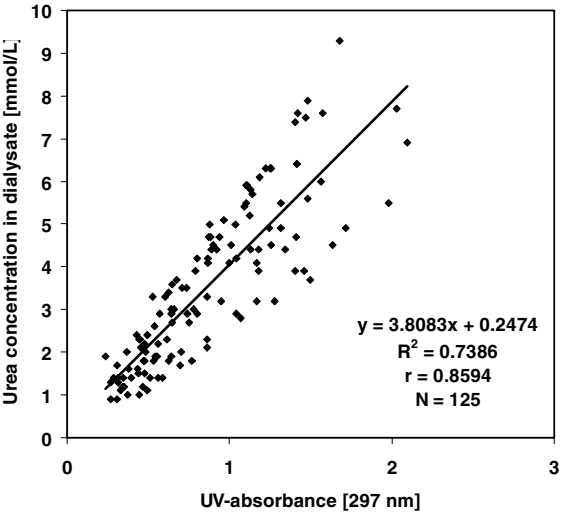



**Fig. 17.15** The correlation between urea concentration and UV absorbance in spent dialysate, in a group of 7 patients and 3 treatments each. The same type of dialyzer was used in all sessions

#### 17.3.1.5 Choice of Wavelength for Dialysis Monitoring

Studies of relation between UV and urea indicated that the wavelength range 280 to 320 should be preferred for on-line measurement when small water soluble molecules such as urea should be estimated (Fridolin et al. 2002). At this wavelength range a relatively strong linear relationship exists between the UV absorbance and concentrations of urea, creatinine and uric acid even for the larger patient groups. The wavelengths in this range, which have been mostly used in several studies, are 280 nm, 285 nm and 297 nm (Fridolin et al. 2002; Uhlin et al. 2003; Uhlin et al. 2006a; Jerotskaja et al. 2010a). The reason for this good relationship can be explained by the prevalent contribution of the low-molecular-weight water-soluble non-protein bound compounds to the total UV absorbance (Lauri et al. 2010a, b). Fig. 17.16 shows the sum of individual contribution to the absorbance signal of six waste solutes in the spent dialysate (Fridolin and Lindberg 2003).

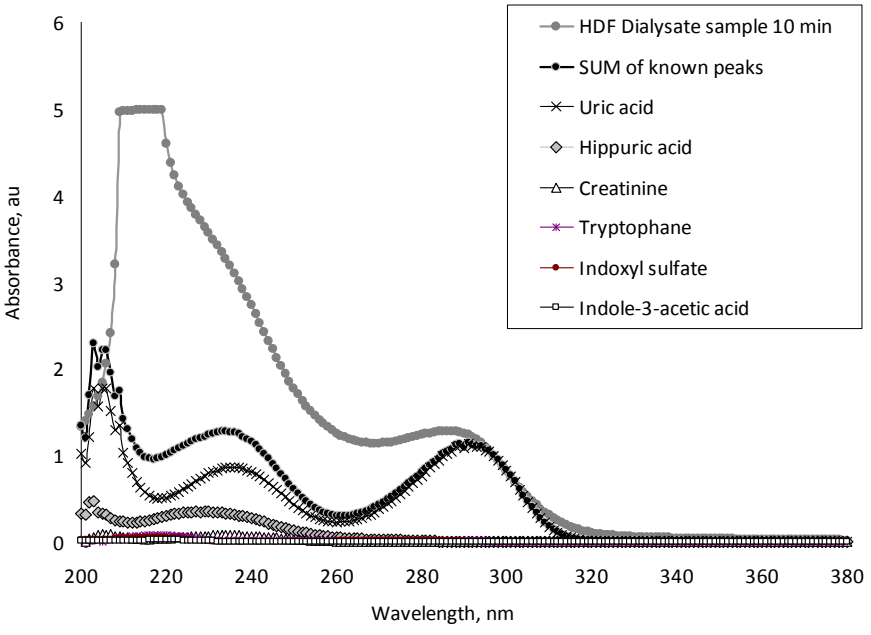



**Fig. 17.16** Solutes' individual contribution to the UV-absorbance signal

The remaining part of the total absorbance signal is the sum of other; partly unknown, contributing solutes (see Fig. 17.16). As mentioned earlier, uric acid has the highest contribution to the absorbance signal (see Fig. 17.12) and that urea does not absorb UV light in the chosen wavelength range. Other wavelengths can be also considered depending on particular uremic solutes (Jerotskaja et al. 2007). More advanced approaches, utilising multiple wavelengths to monitor uremic solutes, are shortly described later in this chapter.

### 17.3.2 Near Infrared Spectroscopy (NIRS)

Another method to measure urea in the spent dialysate using NIR radiation was firstly described in a PhD-thesis by Kupcinskas (2000), followed by the publications by Eddy and Arnold (2001), by Jensen and Bak (2002), and developed further by both last mentioned groups (Eddy et al. 2003; Jensen et al. 2004a; Olesberg et al. 2004; Cho et al. 2008). The method demonstrated to be able to perform online urea concentration measurements in the spent dialysate (Olesberg et al. 2004). No clinical study with dialysis dose calculated as Kt/V or URR using NIR radiation has been published so far.

Infrared energy is the electromagnetic energy of molecular vibration. Absorption of NIR light is based on molecular overtone and combination vibrations when NIR is passing through a sample. As a result, the molar absorptivity in the NIR region is typically quite small. Optical measurements of physiological solutes, often solved in water, utilizing NIR has usually water several orders of magnitude larger absorbance signal than the solute itself. The signal from the solute concentration could be far below the noise level of the measurement system. Despite of this promising attempts have been made to monitor an uremic solute like urea by NIR in the wavelength region of 12 500 – 8600 1/cm (0.80 – 1.16 microm) (Eddy and Arnold 2001), 6730 1/cm (1.486 microm) (Kupcinskas et al. 1998), 5000-4000 1/cm (2.0 – 2.5 microm) (Eddy and Arnold 2001; Olesberg et al. 2004; Cho et al. 2008) and mid IR band - region 1550-1000 1/cm (6.45 – 10.0 microm) (Jensen et al. 2004b). Since mostly the NIR wavelength range has been used, the common name "Near Infrared spectroscopy (NIRS)" was chosen for this approach. To eliminate the interfering factors during NIRS measurements somewhat more advanced technology has to be implemented than the standard double-beam spectrometer utilized during UV absorbance dialysis dose monitoring.

Two kinds of spectrometers have been utilized for the uremic solute determination by NIRS in the spent dialysate: 1) dual-beam interferometer-based spectrometer or so called Fourier transform near-infrared (FT-NIR) spectrometer (Eddy and Arnold 2001; Eddy et al. 2003; Olesberg et al. 2004; Jensen et al. 2004a); and 2) acousto optical tunable filter (AOFT) based spectrometer (Cho et al. 2008).

A FT-NIR spectrometer contents a Michelson interferometer, has high wavelength accuracy and instrumental signal-to-noise ratios. However, the interferometer-based spectrometers are sensitive to environmental parameters, such as temperature and vibrations, they are expensive to manufacture, and difficult to miniaturize (Cho et al. 2008).

An AOFT based spectrometer contents an acousto optical tunable filter, which uses pressure waves to create a periodic modulation of the refractive index in a tellurium dioxide crystal. The periodic index modulation creates a diffraction grating. The period of the grating, which determines the wavelength of light diffracted by the crystal, can be tuned by varying the frequency of the pressure wave (Tran 1992). Because AOTF is less expensive, more compact, and a solid state device that can be scanned fast (in milliseconds) over a wide wavelength range, cheaper and more robust NIR spectroscopic sensors could be constructed. At the same time the root mean square (RMS) noise level is higher for spectra collected with the AOFT spectrometers (Cho et al. 2008).

NIR-spectra consist of generally overlapping vibrational bands that may appear non-specific and poorly resolved. The use of chemometric mathematical data processing and multiple harmonics can be used to calibrate for qualitative or quantitative analysis despite these apparent spectroscopic limitations. In order to convert the optical signal into a solute concentration principal component regression and partial least squares regression analysis is usually carried out to establish a relationship between the measured optical signal and the solute concentration through multivariate calibration models (Eddy and Arnold 2001; Jensen et al. 2004b). For some solutes (phosphate, glucose) the second derivative spectra was utilized (Jensen et al. 2004b). To increase model robustness by excluding unimportant broad variations, that reduces the number of factors required for a multivariate calibration model, Savitzky-Golay smoothing filter was applied to the measured absorbance spectra (Olesberg et al. 2004).

#### 17.3.2.1 Clinical Setting during Monitoring by NIRS

The NIR method includes transmitting a selected band of NIR radiation through the spent dialysate. The instrumentation of the NIR method has varied in different publications and has been designed for a clinical use. The earlier instrumentation based on interferometers was not ideal for non-laboratory measurements due to the sensitiveness of environmental parameters e.g. temperature and vibrations. We will here present the set up from the latest publication of this method (Cho et al. 2008).

During the experiments, spent dialysate was drawn continuously from the outlet dialysate tube after passing the dialyzer. The dialysate was drawn though an optical cell with an optical path length of 1 mm at 30 mL/min by a peristaltic pump. Due to temperature variations are difficult to eliminate entirely in a flow-through system no active temperature stabilization was performed. The temperature was measured just downstream from the optical cell and varied between 28-32 ˚C. Spent dialysate sample were collected at predestinated times at 5, 15, 30, 60, 120, 180 and 240 min after start of dialysis treatment and later sent to laboratory for measurement of concentrations of urea creatinine, glucose and lactate. Spectra were collected using a FT-NIR spectrometer. The best analytic performance correspond top measurements within the combination of the spectral range, which extended from 2.0 to 2.5 μm (5000-4000 $cm^{-1}$). A tungsten halogen lamp, a beam splitter dividing source into a reference and sample channel, and a two-stage thermoelectrically cooled extended-wavelength photodiode detector. The dialysate sample was contained within a tube of thin-wall Teflon with an

inner diameter of 1.1 mm. NIR spectra was collected by focusing the incident light through the Teflon tubing flow-through cell (Cho et al. 2008).

#### 17.3.2.2 NIR Spectra of the Spent Dialysate and NIR Chromophores in Uremic Fluids

NIR is sensitive for variations of different origin that occur in spent dialysate during hemodialysis. Savitzky–Golay filtering is usually used for data smoothing e.g. to remove baseline variations and also high-pass filtering is used to remove the broad spectral features attributable to temperature variations while preserving the higher-frequency analyte signal. This smoothed baseline is then subtracted from the original spectrum; leaving only the high-frequency components (see Fig. 17.17)

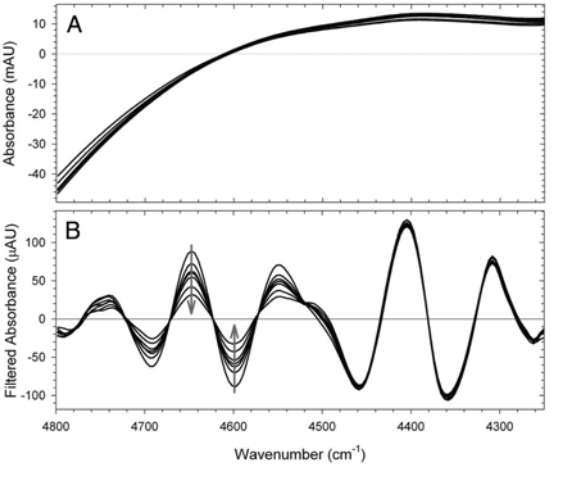



**Fig. 17.17** Online absorbance spectra of spent dialysate recorded during a dialysis treatment. (A), unfiltered spectra rationed to water; (B), spectra after the application of a second-order Savitzky–Golay filter of width 200 $cm^{-1}$. The features between 4700 and 4500 $cm^{-1}$ are primarily attributable to urea, whereas those between 4500 and 4300 $cm^{-1}$ are primarily attributable to glucose. The arrows in B indicate the direction of change with time. [Reprinted with permission from Clin Chem, Olesberg et al. 2004]

Subtraction of the smoothed baseline, local absorbance minima give negative absorbance features in the final absorbance spectra (see Fig. 17.17b) which then excludes unimportant broad variations and reducing the number of factors required for a multivariate calibration model.

The benefit of filtering is to increase model robustness rather than accuracy. The magnitudes of the spectral features in the filtered spectra (see Fig. 17.17b) are more than two orders of magnitude smaller than the broad variations attributable to sample temperature (see Fig. 17.17a). Filtered spectra of the NIR active dialysate components considered in Olesberg et al (2004) are shown in Fig. 17.18. Urea is absorbing in the NIR region. The urea absorption spectrum is distinct because it is dominated by features in the 4700–4500 $cm^{-1}$ range.

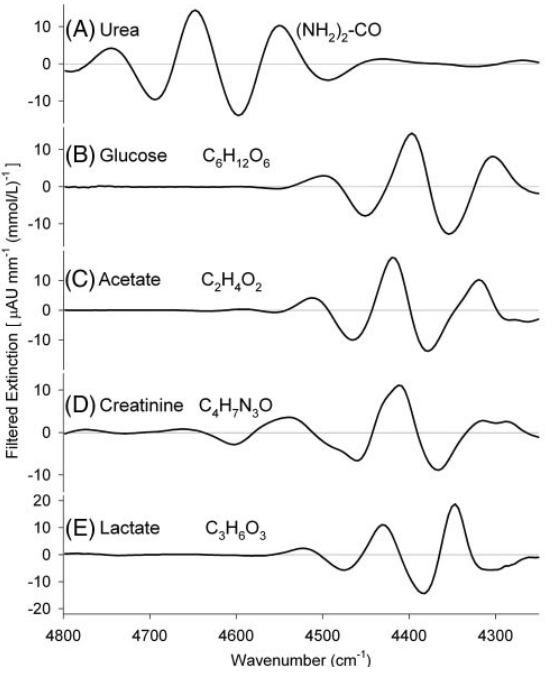



**Fig. 17.18** Filtered pure-component extinction spectra of the five principal solutes found in spent dialysate. [Reprinted with permission from Clin Chem, Olesberg et al. 2004]

These characteristics are attributable to nonlinear combinations of vibration modes of the N–H bond in the urea molecule, whereas the characteristics between 4500 and 4300 $cm^{-1}$ are attributable to combinations of C–H bond modes in Fig. 17.18. Only urea and creatinine contain N–H bonds, although the creatinine absorption spectrum is dominated by C–H characteristics (Olesberg et al., 2004). The shapes of the filtered online spectra, shown in Fig. 17.17b, are dominated by absorption of urea and glucose. The glucose concentration remains relatively constant, while the urea concentration

decreases by a factor of 3 during the dialysis treatment. According to existing infrared characteristics, the potential interfering substances with urea in the spent dialysate are glucose, creatinine, phosphate, lactate, bicarbonate and acetic acid (Eddy and Arnold 2001; Jensen and Bak 2002; Jensen et al. 2004b; Olesberg et al. 2004). Also, strong water absorption bands effect the dynamic measurement range and wavelength selection.

#### 17.3.2.3 NIRS and Uremic Solutes

Urea is the first and so far the only uremic solute that has been investigated and monitored on-line by NIRS in the spent dialysate. First a calibration model had to be built and verified by using a subset of spectra for the analytes whose concentrations are known. Then the model was tested for one dialysis treatment, not used when building the model, to calculate urea concentration over time (see Fig. 17.19) (Olesberg et al. 2004). Predicted urea concentrations in mmol/L from the NIR measurement, measured at once a minute, are shown as a solid line. The circles indicate the urea concentrations measured by the standard chemical assays, and show an excellent agreement (Olesberg et al. 2004).

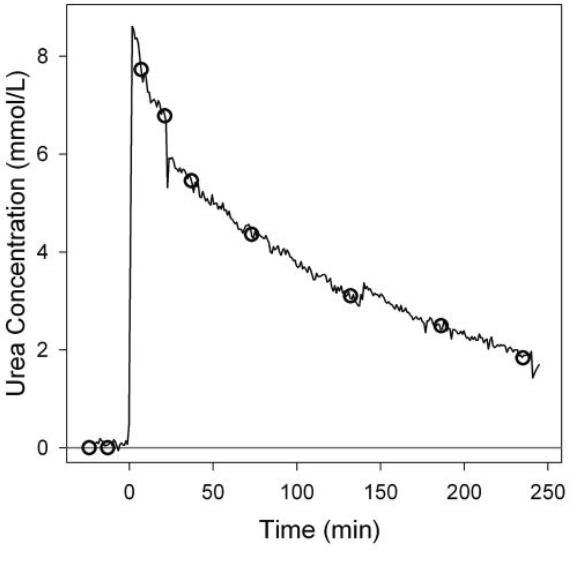



**Fig. 17.19** Concentration of urea in the spent dialysate stream at 1-min intervals during dialysis treatment and urea concentration measured using standard methods (circles). [Reprinted with permission from Clin Chem, Olesberg et al. 2004]

There are visible changes in the urea concentration at 20 and 140 min after the start of the treatment. This was due to changes of the blood flow rate. The blood flow rate was reduced from 330 to 260 mL/min at 20 min and later increased to 300 mL/min at 140 min because patient had problems with cramps. Predicted values from the NIR-method follow the expected trend of approximately exponential decrease in urea concentration over time. A direct calibration where the net analyte signal was computed by standard methods was utilized and no adjustment of the slope of the actual vs. predicted concentration line to match the online spectra (see Fig. 17.20) (Olesberg et al. 2004).

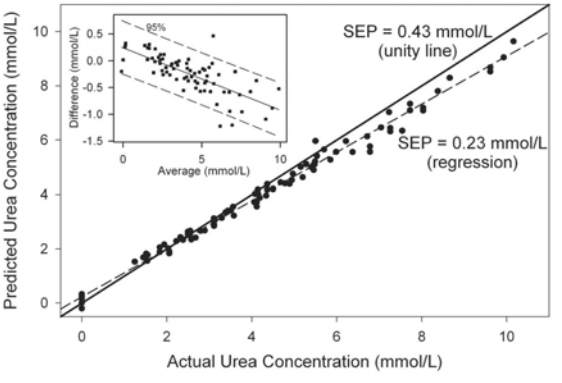



**Fig. 17.20** Predicted vs. actual urea concentration using the net-analyte signal calibration. The dashed line is a linear regression of the calibration and prediction points. (Inset), Bland–Altman plot comparing the optical and chemical assays, indicating a clear proportional error. The solid line in the inset is a regression line; the dashed lines represent the 95% confidence limits. [Reprinted with permission from Clin Chem, Olesberg et al. 2004]

The standard error of prediction (SEP) was 0.43 mmol/L (1.2 mg/dL urea nitrogen), which was larger (60%) than the standard error (SE) of the partial least squares regression (PLS) calibration model. In Figure 17.20 a Bland–Altman plot is also shown which presents that the error is attributable to a proportionality error. The proportionality error is probably a result of a combination of errors in the concentration of the reference urea solution, variations in the optical path length of the sample cell between collection of the pure component spectra and collection of the dialysate sample spectra, and unaccounted for solutes in the sample. A linear regression is used to correct for the proportionality error.

### 17.3.3 Pros and Cons of UV and NIR Spectroscopy

In this section three areas that distinguish the two methods are discussed.

#### 17.3.3.1 Signal Strength and Interfering Factors

Technically, the UV absorbance technique is practically easy to handle and the signal level is high for the uremic solutes in spent dialysate which makes influence of the interfering factors (e.g. temperature, pH, movement of water molecules etc.) minimal. The small absorptivities of biomolecules in the NIR spectral range generate relatively small absorbance values at clinically relevant concentrations (Cho et al. 2008), e.g. in mAU unprocessed intensity and microAU processed (e.g. Savitzky-Golay) intensity (Olesberg et al. 2004; Jensen and Bak 2002). This in turn results that the measurements regarding signal-to-noise ratio, determining accuracy of solute concentrations, are highly temperature sensitive. Thus, even the latest AOTF based technology seems to be overcome the need for thermostated samples utilised in earlier FT-NIR measurements, still the AOTF sensor and the detectors must be thermo-controlled (Cho et al. 2008) making the technology more complex and demanding.

#### 17.3.3.2 Selectivity to Solutes

The UV absorbance technology, as applied today, does not measure a single solute. Instead, the signal reflects the sum of all UV absorbing compounds in the spent dialysate. This makes difficult to select a specific uremic solute separately for monitoring in an easy way. On the other hand, the correlation is high to several water soluble solutes in spent dialysate, which gives the possibility to estimate the removal rate and amount of the particularly solute by satisfactory accuracy. By utilizing this good relationship between UV absorbance and a known solute, estimation of the removal is possible even when the solute is not UV-active at all e.g. in case of urea. Urea is absorbing in the IR region, which makes possible estimate urea removal by NIRS. According to existing IR characteristics, potentially interfering substances with urea in the spent dialysate are glucose, creatinine, phosphate, lactate, bicarbonate and acetic acid (Eddy and Arnold 2001; Jensen and Bak 2002; Jensen et al. 2004; Olesberg et al. 2004; Cho et al. 2008), which can be seen as a possibility to monitor several solutes by NIRS. Also, strong water absorption bands effect the dynamic measurement range and wavelength selection (Eddy and Arnold 2001). The spectral bands seen in the UV and NIR region are typically very broad, leading to complex spectra; it can be difficult to assign specific features to specific chemical components. Multivariate (multiple

wavelength) calibration techniques (e.g., principal components analysis, partial least squares, or artificial neural networks) are needed to extract the desired chemical information. Careful development of a set of calibration samples and application of multivariate calibration techniques is essential.

#### 17.3.3.3 Simplicity and Robustness

To implement NIR technology based on FT-NIR or AOTF sensor as a simple and robust is far more complicated because the underlying optical principle where interference or diffraction is utilized (Jensen and Bak 2002; Cho et al. 2008). UV- method is more straightforward and is not so demanding considering source and detector characteristics, and other technological modules. A simplified comparison of the advantages and disadvantages of the optical dialysis dose monitoring systems for UV and NIR spectroscopy is given in Table 17.1.

**Table 17.1** Comparison of the advantages and disadvantages of the optical dialysis dose monitoring systems for UV and NIR spectroscopy

| Method/Parameter | Signal strength, interfering factors | Selectivity to solutes | Simplicity, robustness |
|---|---|---|---|
| UV | + | - | + |
| NIR | - | + | - |

Finally, despite being not absolutely perfect, manifold additional values are created based on the advantages inherent with the optical dialysis dose monitoring technologies. In general, the optical systems allow the end user (the doctor) to evaluate the dialysis quality more precisely and diversely. This, in turn, will help to keep the dialysis patients healthier, prolong lifespan, and maintain ability to work. Since the treatment lasts for up to decades, the quality of the treatment in crucial to provide the patient with as long and complication-free life as possible. Also, decrease of complications offers economic frugality instead of hospital costs and treatment of after-effects.

## 17.4 CLINICAL PARAMETERS FROM OPTICAL DIALYSIS DOSE MONITORING

The two described optical techniques, UV absorbance and NIRS, have both investigated the possibility to estimate urea, the most commonly used representative marker for accumulated waste solutes, in dialysis patients.

In case of the NIR methodology studies have so far focused on validation of the method to measure urea concentration in the spent dialysate. No efforts have so far been made to calculate clinical parameters from NIR. In case of the UV methodology, some clinical parameters have been estimated and compared with existing standard methods. In this section we will present how clinical parameters based on urea such as Kt/V, URR, TRU and PCR/PNA can be estimated optically utilising UV absorbance.

### 17.4.1 Urea Kinetic Modelling Based on Optical Methods

Urea kinetic modelling (UKM), i.e. where urea is used in different equations, with the attempt to provide quantitative assessments of dialysis and nutrition adequacy in dialysis patients. The high correlation between urea concentration and measures of UV absorbance gives consequently the possibility to utilize the UKM equations for UV absorbance likewise. During the UV absorbance on-line measurements, the pure dialysate was used as the reference (see Beer-Lambert law $I_r$ = pure dialysate) and the wavelength was fixed for the entire treatment. The absorbance baseline level was, after the pure flowing dialysate had been stabilized in temperature and conductivity, set to zero when the pure dialysate was flowing through the cuvette prior treatment (baseline correction).

#### 17.4.1.1 How to Estimate Kt/V from UV Absorbance

From the differential equation, describing urea mass balance during a dialysis session, it can be determined that the average value of the urea clearance (K) in mL/min divided with urea distribution volume in the body (V) in mL (K/V) during a session may be approximated as the slope from the natural logarithm (ln) plot of the urea blood concentration in the blood versus time, $S_B$. In the same way, but instead of blood urea concentrations, the concentrations of urea in dialysate ($S_D$) can be used. Hence:

$$Kt / V \approx -S_B T \approx -S_D T \tag{17.12}$$

Where T is the dialysis session length in minutes. This equation would hold strictly if urea obeys fixed volume and single pool kinetics and no urea is generated during the session (Gotch and Keen 1991). In order to calculate Kt/V from the on-line UV absorbance, the slope of blood and dialysate urea concentration was replaced by the ln slope of the UV absorbance (Sa), Fig. 17.21, versus time (Kt/V ≈ - SaT), (Uhlin et al. 2003).

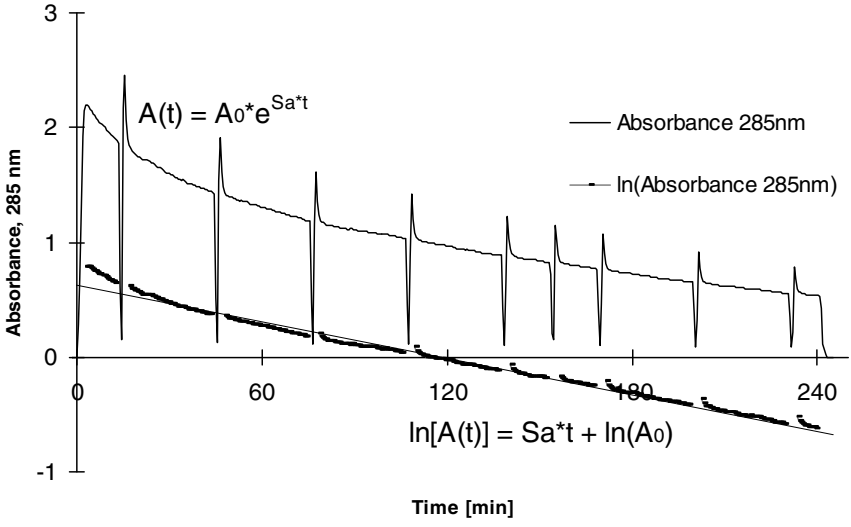



**Fig. 17.21** On-line absorbance curve during a single hemodialysis treatment where UV absorbance at the wavelength 285 nm is plotted against time. The corresponding natural logarithmic (ln) fitting line is also shown, used for Kt/V calculation

Assuming that urea is distributed in a single pool volume in the body, that urea generation rate and ultrafiltration are negligible during the session and that the ratio K/V remains constant over the dialysis the following equation holds (Barth 1988; Gotch and Sagent 1985):

$$\mathrm{Kt/V} = -\ln\frac{C_t}{C_0} \tag{17.13}$$

Where $C_t$ is the post and $C_0$ is the pre dialysis urea blood concentration respectively.

According to Eq. (17.12) we obtain from Eq. (17.13):

$$\frac{C_t}{C_0} \approx \exp\left(-\mathrm{Kt/V}\right) \approx \exp\left(S_B T\right) \approx \exp\left(S_D T\right) \approx \exp\left(S_a T\right) \tag{17.14}$$

If the slopes are used instead of the blood urea concentrations. This approximation is equivalent to the equation when two measuring points are used, and the previously mentioned assumptions are fulfilled. Using the

absorbance slope values ($S_a$), according to Eq. (17.14), the Daugirdas based monocompartmental (single pool, sp) Equation (Daugirdas 1995):

$$\mathrm{sp(Kt/V)} = -\ln\left(\frac{C_t}{C_0} - 0.008\frac{T}{60}\right) + \left(4 - 3.5\frac{C_t}{C_0}\right)\frac{UF}{BW} \qquad (17.15)$$

Equation 17.15 can be written as (Uhlin et al. 2003):

$$\mathrm{sp(Kt/Va)} = -\ln\left(\exp(S_a T) - 0.008\frac{T}{60}\right) + \left(4 - 3.5\exp(S_a T)\right)\frac{UF}{BW} \qquad (17.16)$$

Where UF and BW is the ultrafiltration volume in liters (L) and the patient's dry body weight in kg.

The equilibrated Kt/V from UV absorbance, eKt/Va, according to the rate adjustment method (Daugirdas 1995), is predicted from the rate of dialysis (K/V) and the sp(Kt/Va) as:

$$\mathrm{eKt/Va} = \mathrm{sp(Kt/Va)} - \frac{0.6}{(T/60)}\mathrm{sp(Kt/Va)} + 0.03 \qquad (17.17)$$

The rate adjustment method predicts that the urea rebound is related to the rate of dialysis or dialysis efficiency (Daugirdas et al. 1997).

### Example 17.2

During a dialysis session lasting 4.5 hours, the urea concentration in blood was 25.6 mmol/L at the start of dialysis and 9.1 mmol/L after dialysis. Weight of the patient was 89.0 kg before dialysis and the prescribed post dialysis weight was 87.0 kg, the estimated amount of fluid intake (drinking) during dialysis was 0.3 liters. Calculate sp(Kt/V) according to Daugirdas second generation formula (Daugirdas 1995) and according to Uhlin formula (Uhlin et al. 2003).

### Solution

The sp(Kt/V) according to Daugirdas second generation formula (Daugirdas 1995) is calculated according to Eq. (17.15) as follows:

$$\mathrm{sp(Kt/V)} = -\ln\left(\frac{9.1}{25.6} - 0.008\frac{270}{60}\right) + \left(4 - 3.5\frac{9.1}{25.6}\right)\frac{2.3}{87} = 1.22$$

In similar way sp(Kt/V) for UV absorbance, sp(Kt/Va) can be calculated using the ln slope of the absorbance values during dialysis.

$$\mathrm{sp(Kt/V)} = -\ln\left(\exp(-0.003835\cdot 270) - 0.008\frac{270}{60}\right) + \left(4 - 3.5\cdot\exp(-0.003835\cdot 270)\right)\frac{2.3}{87} = 1.22$$

K/V was determined as a linear fitting curve of the ln slope of the UV absorbance values = Sa, Fig. 17.21. In this example ln [A(t)] = - 0.003835 x + 0.7681, where Sa corresponds to 0.003835. Sa was then inserted into Eq. (17.16) to obtain sp(Kt/Va).

### 17.4.1.2 Simplified eKt/V Calculation from UV Absorbance

For determination of the dialysis dose from UV absorbance can be simplified when instead of the slope of UV absorbance only two values are utilized, similar to calculations from blood values. For example, when measured by the DIAMON prototype (Luman et al. 2009a), $eKt/V_{DIAMON}$, instead of the pre-and post-dialysis blood urea concentrations, the maximum UV absorbance value in the beginning and the minimum UV absorbance value at the end of dialysis ($A_0$ and $A_t$) were utilized. The sp(Kt/Va) was calculated as:

$$\mathrm{spKt/Va} = -\ln\left(\frac{A_t}{A_0} - 0.008\frac{T}{60}\right) + \left(4 - 3.5\frac{A_t}{A_0}\right)\frac{UF}{BW} \qquad (17.18)$$

sp(Kt/Va) was used to obtain the $eKt/V_{DIAMON}$ according to Eq. (17.17).

### 17.4.1.3 Estimation of Urea Removal Using UV Absorbance

One way to estimate Total Removed Urea (TRU), assuming that the dialysate flow, $Q_d(t)$, is constant and the total UF is known, is to use the following equation:

$$\mathrm{TRU(mmol)} = \overline{\mathrm{Urea}}\cdot\left(\mathrm{Qd}\cdot\mathrm{T} + \mathrm{UF}\right) \qquad (17.19)$$

where $\overline{\mathrm{Urea}}$ in mmol/L is the mean urea concentration in spent dialysate of a particular hemodialysis session (Raj et al. 1997). For the TRU calculations $\overline{\mathrm{Urea}} = D_{total}$ can be utilized as reference, where $D_{total}$ is the urea concentration in the collection tank, (Tank sample, Fig. 17.6), after end of dialysis. $Q_d$ is the rate of the dialysate flow in L/min, T is the

dialysis session length in minutes and UF is the total ultra-filtrated volume in L during the session.

Under the condition that a good correlation exist between UV absorbance and concentration of a urea (Fig. 17.14a and 17.15) it is possible to utilize this relationship. Therefore in a similar way TRU may be calculated from the on-line UV absorbance (TRUa) curve as (Uhlin et al. 2005):

$$\mathrm{TRUa(mmol)} = \left(\alpha \cdot \bar{A} + \beta\right) \cdot \left(\mathrm{Qd} \cdot \mathrm{T} + \mathrm{UF}\right) \tag{17.20}$$

Where the $\bar{A}$ is the mean of all UV absorbance (A) values from the start to the end of the dialysis, The regression line between the UV absorbance and concentration of in spent dialysate (Drain sample, Fig. 17.6) from on-line measurement gives the Slope (α) and the Intercept (β) inserted in Eq. (17.20) when determining TRUa from either an individual model (one for each patient, Fig 17.14a) or a general model (preferable) based on the entire group of patients (e.g. see Fig. 17.15). TRU from the Total Dialysate Collection (Fig 17.6), TDC (reference) was calculated as $D_{total}$ (mmol/L) multiplied with collected weight (kg), assuming that 1kg =1L of the dialysate. TRU from these methods was compared regarding mean values and showed no statistically significant difference (Uhlin et al. 2005).

### Example 17.3

According to example 17.2, we can get additional information from the UV absorbance curve namely; $\bar{A}$ = 1.279. A transformation/calibration model based on a group of seven dialysis patients distributed on 21 dialysis sessions gave the relationship (correlation) between urea concentration and UV-absobance in spent dialysate α = 3.8083 and β = 0.2474 (Fig. 17.15). Calculate TRUa for this particularly session.

### Solution

Total Removed Urea (TRU) is calculated according to Eq. (17.20) as follows:

$$\mathrm{TRUa(mmol)} = \left(3.8083 \times 1.279 + 0.2474\right) \times \left(0.5 \times 270 + 2.4\right) = 703.2$$

If we compare this result to the reference value; calculated as urea concentration in the collection tank after end of dialysis, $\overline{\mathrm{Urea}}$ = 5.2 mmol/L multiplied with the volume in the tank of 137.4 L (i.e. the last part of the formula; $Q_d \cdot T + UF$) we get a TRU value of 714.5, which is similar to the result estimated using UV absorbance.

### 17.4.1.4 Estimation of Nutrition Parameters from UV Absorbance

High blood concentration of urea is not necessarily related with a poor dialysis outcome if urea removal is sufficient (Blumenkrantz et al. 1982), but also protein-energy malnutrition is frequently present in patients undergoing hemodialysis therapy. Several studies have suggested that malnutrition is an important risk factor for morbidity and mortality in HD patients (Lindsay et al. 1994). In order to optimize the diet of patients with renal diseases, dietary protein intake has to be controlled. Protein nitrogen appearance (PNA), formerly protein catabolic rate (PCR) (European Best Practice Guidelines on Hemodialysis 2007), is easily obtainable from UKM and in patients who are not markedly catabolic or anabolic, the normalized PNA (nPNA) correlates closely with dietary protein intake (Flanigan et al. 1995, Keane and Collins 1994). These parameters can be calculated from TRU.

The PCR calculation, from TDC and UV absorbance, was based on a theory by Garred et al (1995), where a calculation of urea removal is expressed as a fraction of the week's urea generation. The fraction varies with the day of the week and was found to be essentially constant among patients on a given day (Garred et al. 1995). The amount of urea could therefore be approximated from measuring urea concentration from only one of the three treatments and PCR could be calculated as (Uhlin et al. 2005):

$$\mathrm{nPCRw} = \mathrm{Factor}_{1,\,2\text{ or }3}\left(\frac{\mathrm{TRU}_{1,\,2\text{ or }3}}{\mathrm{BW}}\right) + 0.17 \qquad (17.21)$$

Where TRU 1, 2 or 3 (expressed in grams of urea nitrogen)[1] is the TRU from the first (1), midweek (2) or last dialysis in week (3) and Factor 1, 2 or 3 is the fractional factor for the first (1), midweek (2) and last treatment (3) of the week respectively; factor 1 = 2.45; 2 = 2.89; 3 = 3.10 (Garred et al. 1995). Obligatory loss of dietary protein in stools and via skin shedding represents the constant term 0.17 (g protein/kg body weight/day). The dry body weight (BW) was used for normalization of PCR (nPCRw). Observe that these fractional factors relays to a treatment schedule of three times a

[1] First we have to convert urea in mmol into gram by multiplying with the molecule weight of urea, 60.06, and then divided with 1000. BUN (g) = TRU (g) 6.23/13.4.

week. More frequent dialysis treatments are more common today whereas the factors are not appropriate.

### Example 17.4

Using the same patient data as in Example 17.2; the dialysis treatment of this patient was performed on a mid-week. Calculate nPCRw according to Garred´s formula.

### Solution

Since the fractional factor for mid-week session is 2.89, then nPCRw can be calculated according to Eq. (17.21) as follows:

$$\text{nPCRw} = 2.89\left(\frac{19.64}{87}\right) + 0.17 = 0.82 \text{ g/kg/day}$$

#### 17.4.1.5 Dialysis Dose and Nutrition Mapping of the HD Patients

Simultaneous analysis of Kt/V, URR and nPNA permits to get a picture of: 1) the adequacy of dialysis treatment; and 2) dietary protein intake related to nutritional status of the patients. This enables the dialysis team to make a choice between increasing dialysis effectiveness, dietary counselling, or both. In order to take account those important parameters, UKM is suggested e.g. presenting the patients' status on a diagram incorporating Time-average concentration of urea (TAC), nPNA, and spKt/V (Lindsay et al. 1994). However, UKM is performed by tedious and time consuming calculations using special and complicated software. Recently, a new, simplified mapping of dialysis dose and nutrition was tested by using only two parameters: Kt/V and nPNA, Fig. 17.22, suitable for automatic and time-efficient way to review the performed HD strategy based on the data from on-line dialysate side dialysis monitors (Luman et al. 2009b).

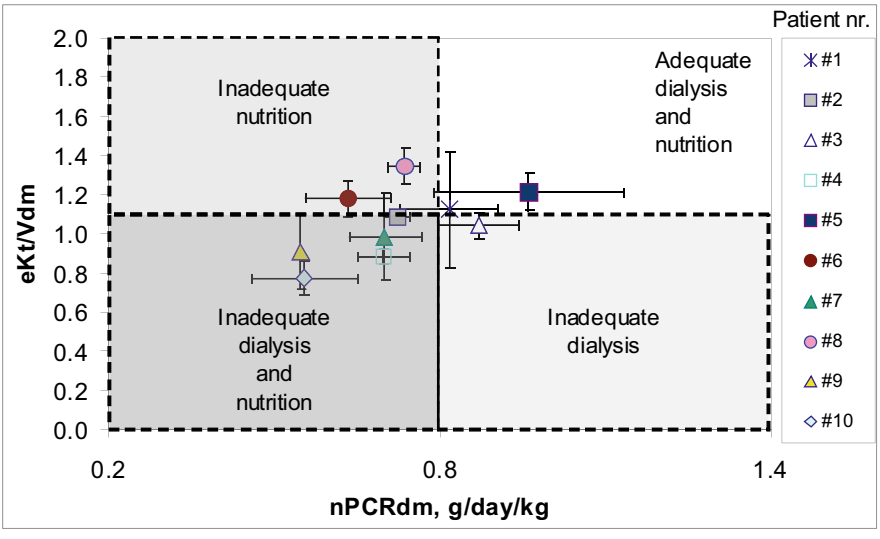



**Fig. 17.22** Simplified mapping of dialysis dose and nutrition applied by using only two parameters - Kt/V and nPNA, suitable for automatic and time-efficient way to review the performed HD strategy based on the data from on-line dialysate side dialysis monitor (dm)

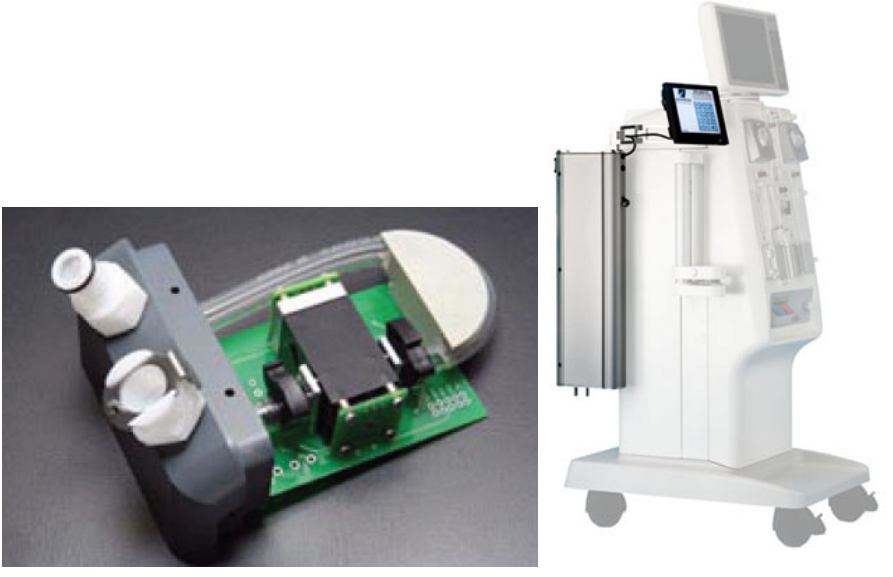
The eKt/V-nPNA plots yielded the results in concordance with the variable volume single-pool (VVSP) UKM presented as TAC = f (nPNA) for all patients and outlined similarly the critical patients regarding the delivered dialysis dose and nutrition.

#### 17.4.1.6 Current Commercial Systems for Optical Dialysis Dose Monitoring

The first commercial systems for optical dialysis dose monitoring are available today. Two kinds of the systems can be distinguished: 1) external, and 2) internal (integrated) modules; depending on if the systems have been designed either according to "stand-alone" or "built-in" architecture. The modules can currently estimate only urea based dialysis quality parameters, Kt/V and URR.

The first sensor for optical dialysis adequacy monitoring in the world is DiaSens, Fig. 17.23a (Ldiamon AS, Estonia). This is the main functional

element of DiaHub - an external "stand-alone" module which can be connected to dialysis machine and perform continuous on-line measurement of Kt/V and URR during the treatment, Fig. 17.23b (Ldiamon AS, http://www.ldiamon.eu/index.php?act=page&id=2).



(a) (b)

**Fig. 17.23** a) An optical sensor DiaSens. b) The external module DiaHub connected to a dialysis machine. [Reprinted with permission from Ldiamon AS]

The first integrated or "in-build" dialysis dose monitor in the world, utilising the UV-technology, is the Adimea system (Option Adimea, B.Braun Avitum AG) (B. Braun Avitum AG 2010). The heart of the Adimea system is the optical sensor DiaSens, integrated into the HD machine, delivering values of real-time Kt/V or URR for the dialysis team during a treatment (see Fig. 17.24).

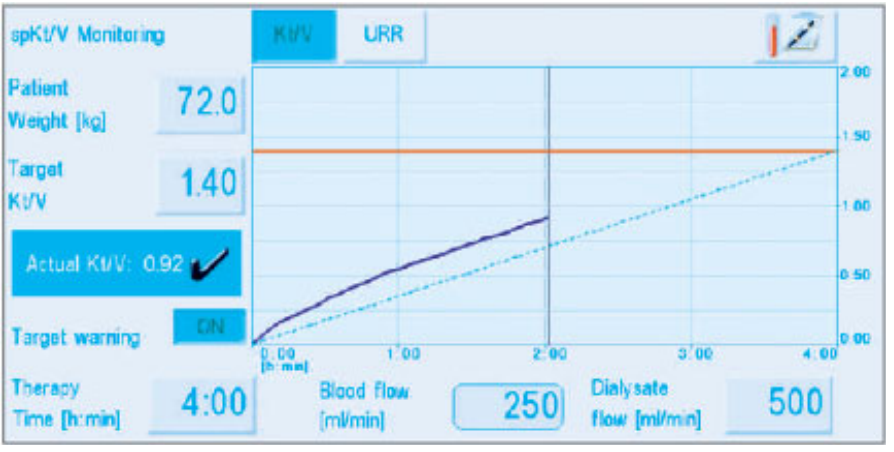



**Fig. 17.24** Graphic display to present dialysis dose monitoring progress by the Adimea system for clinicians [Reprinted with permission from BBraun Avitum AG]

The obtained data about the dialysis efficiency are available to be saved on the patient therapy card and the data management system. Validation studies of real-time Kt/V by the Adimea system have shown that the results by the UV-technology are indistinguishable from blood based Kt/V (Castellarnau et al. 2010).

## 17.5 MONITORING UREMIC TOXINS BEYOND UREA

The facts that: (i) urea is a nontoxic substance and only a marker for uremic retention solutes, and (ii) the European uremic toxins group (EUTox) has identified several more relevant uremic toxins utilizing optical analysis methods, arise a question connected to further development of optical techniques – "Could some of these identified uremic toxins be measured optical and on-line?". Of the 90 compounds that have been identified as uremic toxins by the EUTox group (Vanholder et al. 2003a, 2003b) we have, from spectroscopic databases, identified 36 to be UV absorbing and among them approximately 25 to be absorbing near 297 nm. Besides these 90 compounds mentioned as uremic toxins, there are even more solutes in the dialysate that are optically active at 297 nm and that add to the measured UV absorbance signal. Spent dialysate contains several different absorbing compounds and concentrations of solutes declines differently during a session for individuals. The UV absorbance curve may therefore be an individual “clinical print” of the patient’s sum of several UV

absorbing solutes and therefore a possible parameter for monitoring total solute removal during dialysis. Investigations still remain to find the single solute's individual contribution to the absorbance signal, which is also dependent on which wavelengths are used (Fridolin and Lindberg 2003). Earlier knowledge from the correlation analysis between UV absorbance and a few solutes-uremic toxins has shown that it is possible to estimate removal of such solutes which have a high correlation to UV absorbance. This removal beyond urea may have stronger impact on dialysis outcome compared to urea or urea alone.

### 17.5.1 Uric Acid

Uric Acid (UA) is a water–soluble compound (molecular weight of 168.1) that is the final metabolite of purine in humans. Elevated serum UA contributes to endothelial dysfunction and increased oxidative stress within the glomerulus and the tubulo-interstitium, with associated increased remodeling fibrosis of the kidney (Hayden and Tyagi 2004). A high level of serum UA, hyperuricemia, has been suggested to be an independent risk factor for cardiovascular and renal disease especially in patients with heart failure, hypertension and/or diabetes (Feig et al. 2008; Viazzi et al. 2006; Høieggen et al. 2004) and has been shown to cause renal disease in a rat model (Nakagawa et al. 2006). UA is mostly associated with gout but studies have implicated that UA affects biological systems (De Smet et al. 1997) and also could influence risks of higher mortality in dialysis patients (Perlstein et al. 2004) but the pathogenic role of hyperuricemia in dialysis patients is not completely established (Navaneethan and Beddhu 2009).

In previous studies a good correlation between UV absorbance in the spent dialysate and the concentration of several solutes both in the spent dialysate and in the blood of dialysis patients has been presented, indicating that the technique can be used to estimate the removal of retained substances (Fridolin et al. 2002). A study was performed in two dialysis centers in two different countries The purpose was to find out if it would be possible to create a specific model for UA while still using the same wavelength (285 nm) that earlier was used when urea removal was estimated (Uhlin et al. 2005). The fact that UA is a UV absorbing solute (Jerotskaja et al. 2007) made that study even more interesting. The results show the possibility to estimate Total Removed Uric Acid ($TR_{UA}$) by using UV absorbance technique generated transformation models in two different dialysis centers in two countries, Estonia and Sweden. The mean values of $TR_{UA}$ obtained using the UV-model were not statistically different to $TR_{UA}$ calculated from TDC (reference method) at the two centers (N=56) (see Fig. 17.25).

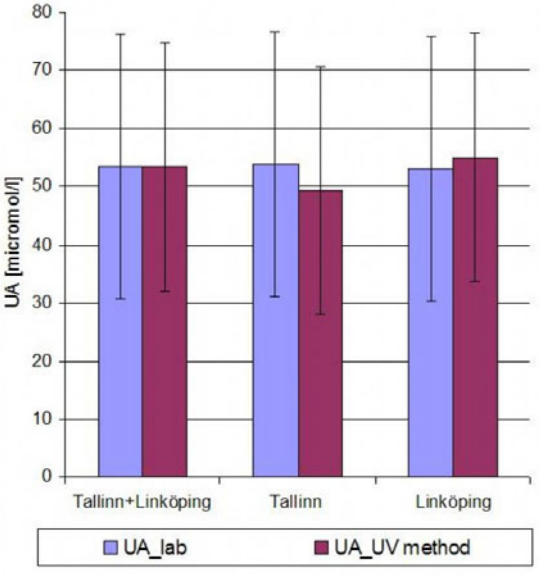



**Fig. 17.25** Mean values of UA for the total material and for different centers

Important issues to be considered, which have emerged from this study, are that the standardized optical parameters (wavelength, optical flow cuvette, optical path length, etc.) should be defined to build more accurate general models. Other areas that influence the measurements are type of dialyzer (ultrafiltration coefficient, surface area), and probably even some patient dependent parameters (Jerotskaja et al. 2010a). The high correlation between UV absorbance and UA in every single patient (Fig. 17.14B) could be explained by a dominant absorbance for UA, compared to other compounds in spent dialysate at the wavelength 280 nm (Jerotskaja et al. 2007). This is due to relatively high millimolar extinction coefficients of UA with three distinct maxima around 202, 235 and 292 nm and two minima around 220 and 260 nm in the wavelength range from 200 to 380 nm (Fridolin and Lindberg, 2003). The absorbance around 292 nm is characteristic for UA and is utilized for UA concentration determination by the enzymatic degradation method (Praetorius and Poulson 1953).

### 17.5.2 Creatinine

Beside the marker molecule urea-based dialysis patient nutrition parameter nPNA two promising alternative parameters (i) Creatinine index (CI); and (ii) Lean Body Mass (LBM), calculated from the small molecular

water soluble uremic retention solute – uremic toxin creatinine (Cr) have been proposed. CI and LBM are shown to be predictors of long-term survival in HDF patients (Desmeules et al. 2004). CI and LBM have several pros compared to the urea based dialysis quality and nutrition parameters:

- CI and LBM are related to the preservation of muscle mass and protein nutritional status and could be seen as markers of protein-energy malnutrition.
- CI and LBM predict survival better than Kt/V and nPNA.
- CI and LBM are more stable than nPNA which is highly dependent on protein intake and dialysis dose.

Recently, a new method to estimate LBM in hemodialysis patients by UV absorbance measurements in the spent dialysate was presented (Fridolin et al. 2010). A good linear relationship between UV absorbance and dialysate Cr concentration at the wavelength range of 230 - 300 nm was used for generating a model to estimate Cr concentration in the spent dialysate. The LBM using the blood samples (LBM_b), and LBM utilizing the Cr concentration values estimated by the UV absorbance (LBM_uv), were obtained according to the method described by Desmeules et al (2004). Comparison between the blood based lean body mass (LBM_b) and the UV absorbance method (LBM_uv) exhibited a good agreement (see Fig. 17.26).

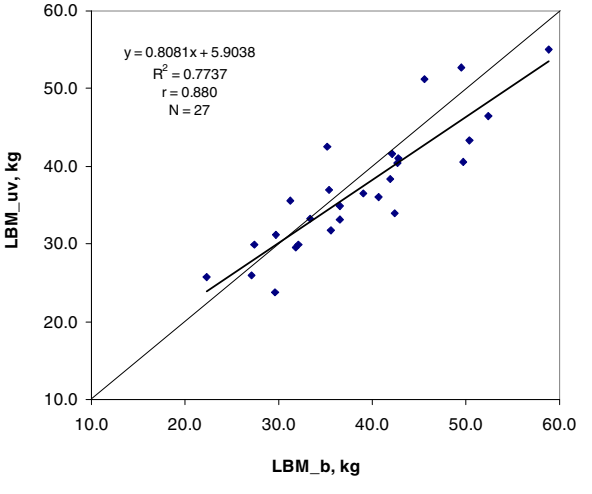



**Fig. 17.26** LBM_uv estimated by UV absorbance in the spent dialysate plotted against LBM_b estimated using the blood samples (number of HD sessions N = 27). The line of identity as a dashed line is also shown. Adapted from Fridolin et al (2010).

The mean ± SD of LBM_b estimated using the blood samples was 38.6 ± 8.77 kg (N = 27), and LBM_uv 37.9 ± 8.06 kg (N = 27). The mean value of LBM from blood samples were not statistically different from the corresponding value estimated by UV absorbance in the spent dialysate (P = 0.516).Those results encourage continuing in order to develop an optical technology enabling quickly and automatically estimate the muscle mass and protein nutritional status of the hemodialysis patients.

### 17.5.3 Middle Molecules

Urea shows a kinetic behavior that is not representative for all uremic retained solutes, yet including other water-soluble solutes (Vanholder et al. 2004). The retained organic compounds can be be divided into three groups, small, water soluble solutes with a molecule weight (MW) < 500 D (e.g. urea, uric acid and creatinine), protein-bound solutes (e.g. hippuric acid, indoxyl sulphate and P-cresol), and middle molecules MW > 500 D (e.g. β-2 microglobulin, Cystatin C, IL 6 and Leptin) (Vanholder et al., 2003a). Many of the solutes affecting metabolism have retention and elimination characteristics that are different from the traditional markers for uremia, urea and creatinine (Vanholder et al. 2004). β2-microglobulin has been suggested to be an excellent marker for the middle molecule range which is a "real" uremic toxin with an independent impact of patient outcome (Canaud et al. 2006). In a pilot study where correlation between concentration of β2-microglobuline in mg/L and UV absorbance at 297 nm was investigated in a number of 21 HemoDiaFiltration treatments, a high correlation was found (Uhlin et al. 2009a) similar to that of urea, uric acid and creatinine (see Fig. 17.27).

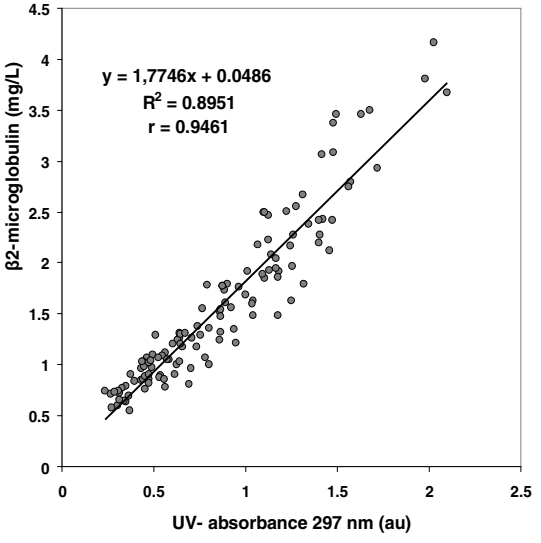



**Fig. 17.27** Correlation between concentration of β2-microglobulin and UV absorbance at 297 nm in spent dialysate, (Uhlin et al. 2009a)

This relationship can be utilized to estimate total removal of during dialysis β2-microglobulin in similar way as earlier have been described in case of urea.

## 17.6 FUTURE DIRECTIONS IN OPTICAL MONITORING

In this last section of the chapter we will present other approaches that could be used in order to obtain new parameters from UV absorbance or increase the accuracy of earlier presented parameters.

### 17.6.1 Other Approaches of UV Absorbance

There are two main areas which so far have been investigated by the UV method, area under curve and multiple wavelengths.

**17.6.1.1 Area under the UV Absorbance Curve** (AUCa) was recently introduced as a possible complementary parameter prospected to evaluate total solute removal during dialysis (Uhlin et al. 2009b). The results indicate a strong relationship between a patient's measured AUCa and the total removal of a few well-known low molecular weight solutes (urea, creatinine, urate and phosphate) during a given session, r = 0.967-1.000.

The relationship is less strong for the entire group of 15 patients (r = 0.919-0.957). AUCa is a less sensitive parameter for deviations during treatment compared to parameters based on the slope (e.g. Kt/V). Perhaps AUCa could add valuable information in combination with other parameters when evaluating dialysis treatments.

**17.6.1.2 Multiple Wavelengths** are an approach which has been tested for UA estimation to increase the accuracy (Jerotskaja et al. 2010c). The first results demonstrate that using two or three wavelengths of UV absorbance instead of one improves estimation of the UA noticeably (Table 17.2). Even more reliable results are achieved when derivative spectra is used instead of the original absorbance spectra (Jerotskaja et al. 2009; Jerotskaja et al. 2010b, c). The systematic and random errors were significantly different ($p \leq 0.05$) between the methods indicating that the 1st derivate and multi wavelength algorithm enables more accurate UA estimation.

**Table 17.2** Summary of results for the different methods to measure concentration of the uric acid (N=301), utilizing UV absorbance (UV_A) and derivate spectra (UV_D)

| Method | Concentration of UA ± SD [micromol/l] | Syst. Error [%] | Rand. Error [%] | $R^2$ |
|---|---|---|---|---|
| Lab | 52.91 ± 21.5 | - | - | - |
| UV_A_298 nm | 57.07 ± 23.6 | -8.89 | 16.5 | 0.87 |
| UV_A_298+312 nm | 54.15 ± 22.1 | -3.31 | 13.4 | 0.91 |
| UV_A_298+312+285 nm | 51.95 ± 21.1 | 1.16 | 10.0 | 0.94 |
| UV_D_307 nm | 54.96 ± 22.5 | -4.74 | 13.0 | 0.91 |
| UV_D_307+284 nm | 52.94 ± 21.7 | -0.61 | 10.4 | 0.94 |
| UV_D_307+284+214 nm | 52.78 ± 21.8 | -0.19 | 10.3 | 0.94 |

Multi wavelength systems, where several compounds with clinical impact could be measured simultaneously, are a vision for a time-to-come optical monitoring system, presenting a future for dialysis dose.

## 17.7 CONCLUSION

Optical technologies applied for dialysis dose monitoring have a potential to be a helpful tool for the dialysis team in evaluation of the dialysis process. Moreover, the optical methods offer new perspectives to ensure

dialysis adequacy and quality, aiming to be a practical toolkit for the clinicians and the dialysis team, which helps to obtain adequate dialysis targets and to meet the individual needs of each patient. This can lead to "personalized healthcare" within hemodialysis resulting decreased morbidity, longer life span and enhanced quality of life.

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## QUESTIONS

1. Which optical technology is found to be of clinical acceptance for monitoring dialysis dose?
2. What is the biological fluid used to measure optically elimination of uremic solutes? Why?
3. How can biological tissues and fluids be classified according to their optical properties?
4. How electromagnetic (EM) radiation is classified by wavelength?
5. Which are the UV-regions according to ISO standard on determining solar irradiances?
6. How the infrared (IR) part of the electromagnetic spectrum is divided?
7. How the "wave number" in the context of near infrared (NIR) spectroscopy is calculated?
8. How the term “Light” is defined?
9. Describe the main events occurring when photons propagate into a medium (e.g. into a biological fluid).
10. Describe the main events occurring when photons propagate inside a medium (e.g. inside a biological fluid).
11. Describe the main events occurring when photons propagate from a medium (e.g. from a biological fluid).
12. Describe the basic parts of a spectrophotometer.
13. How the Transmittance and Absorbance are calculated?
14. What does the Beer- Lambert law state? Give the mathematical equation.
15. Give the mathematical equation for the Beer- Lambert law for a medium containing several different absorbing compounds.
16. Which are the common assumptions to utilize absorbance calculated according to the Beer-Lambert law to determine concentration?
17. Describe the technical principle for on-line monitoring of dialysis dose by the UV absorbance.
18. Which information contains UV absorbance curve from on-line measurements of spent dialysate?

19. Which are the known predominant uremic toxins contributing to UV spectra between 200-400 nm.
20. Which uremic toxins on-line UV absorbance at 280 nm is mostly following?
21. How can concentration of a particular uremic solute be estimated by the total UV absorbance?
22. Which is the criterion according to a wavelength should be chosen to estimate optically concentration of a particular uremic solute?
23. Describe the technical principle for monitoring dialysis dose by the near infrared (NIR) spectroscopy.
24. Which are the known predominant uremic toxins contributing to filtered NIR spectra in the 4700–4500 $cm^{-1}$ range?
25. Describe the advantages and disadvantages of the optical dialysis dose monitoring systems for UV and NIR spectroscopy.
26. What marker is mostly used to evaluate dialysis dose today?
27. Which patient' status, this marker (in question 26) can also be used for, and why is it so?
28. Why is this marker (in question 26) not good enough and why efforts are being made to find additional markers?
29. Which is the fundamental difference between a single pool model and a double pool model when calculating dialysis dose?
30. Which parameters do you need when calculating Kt/V according to Daugirdas single pool model, give the mathematical equation?
31. When you are going to use UV absorbance to calculate Kt/V according to Daugirdas single pool model you have two options, which ones?
32. Calculate the sp(Kt/V) using the simplified calculation utilizing on-line UV absorbance measurements where the length of session was 4 hours, dialysate flow was 500mL/min, UF 2500mL and the patients post-dialysis weight was 95 kg . Readings from the UV absorbance curve you get the max and min absorbance value of 2, 17 and 0, 62 respectively.
33. What conditions must exist if solute removal should be estimated during dialysis utilizing an optical technique, and which constants do you need?

34. If total removed urea (TRU) is known for one single dialysis session of a patient, it's possible to estimate PCR both in case of blood and UV absorbance measurements. Which presumption concerning TRU is made if the PCR value is to be calculated?
35. Which method is used as reference during clinical studies when estimating TRU from UV absorbance? Can you think about potential risks of error with this reference method?
36. The correlation between urea concentration and UV absorbance in spent dialysate give the constants $\alpha = 3.8083$ and $\beta = 0.2474$. Calculate total removed urea (TRU) in mmol for a session where dialysate flow was 500mL/min, UF 1000mL during a dialysis lasting 3 hours. The mean absorbance value during this particularly treatment was $\overline{A} = 0.983$
37. The wavelength of 297 nm has been used in several studies using the UV absorbance technique in measurements of spent dialysate. The UV absorbance signal is not the signal of one single solute instead it's the sum of several UV absorbing solutes. How many UV-active solutes have so far been identified around this wavelength, approximately?
38. Recently, a new, simplified mapping of dialysis dose and nutrition status has been tested. What two parameters are used then?
39. What's the reason why the optical on-line curves from UV absorbance and NIR (and even concentrations of solutes) getting an exponential shape at the elimination during dialysis treatment?
40. Explain what happens to the UV absorbance signal if a decrease in blood flow occurs during dialysis, and why?
41. Explain what happens to the UV absorbance signal if decreases in dialysate flow occur during dialysis, and why?
42. If you are interested using a wavelength for on-line measurement of spent dialysate in the UV- range of approximately 240-260 nm, the UV-signal will probably be too high and reach a maximum level. How can this be solved?
43. Into which three groups are usually uremic waste solutes divided? Give one example from each group.

44. Uric acid is an absorbing solute in the UV-range; high serum level of uric acid is associated with some clinical manifestations, give examples?
45. Standardized optical parameters are important when using different set-up during studies, give expels of issues to consider in this field.
46. There has been demonstrated that the solute creatinine can be estimated using on-line UV absorbance measurements during hemodialysis. Which advantages may creatinine based parameters, such as creatinine index (CI) and lean body mass (LBM), have as a nutrition parameter compared to urea based parameters?.
47. What are the benefits by utilizing optical on-line monitoring of dialysis dose compared to monthly pre-and post-dialysis blood control of urea concentration that is the common used dialysis dose parameter today at dialysis units?
48. Give some examples about other approaches that could be used in order to obtain new parameters from UV absorbance or increase the accuracy of earlier presented parameters.
49. Calculate the absorbance A if the transmittance T is 1.0; 0.5; 0.1 and 0.01.
50. Calculate the transmittance T if the absorbance A is 4.0; 1.0; 0.5; and 0.1.
51. Which is the general benefit for the dialysis patients using the optical dialysis dose monitoring?

Chapter (18)

# Continuous Renal Replacement Therapy (CRRT)

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## CHAPTER OUTLINES

- History of CRRT and future directions.
- Choosing a renal replacement therapy in acute kidney injury (AKI).
- Complications of CRRT.
- Anticoagulation for Continuous Renal Replacement Therapy.
- Volume Management in Continuous Renal Replacement Therapy.
- Dialysate and Replacement Fluids.
- Vascular access in renal replacement therapies.
- Machine comparisons

## CHAPTER OBJECTIVES

- Describe the main modalities of renal replacement therapy in the treatment of acute kidney injury in the critically ill patient.
- Enumerate the pros and cons of each modality
- Describe the concepts of diffusion and convection and their application to fluid management and metabolic control
- List the desirable characteristics of the vascular access for CRRT to ensure safe delivery of an appropriate dialysis dose
- Describe the potential complications in the use of CRRT techniques.
- Enumerate the available anticoagulation modalities
- Compare the operational characteristics of the CRRT machines currently available to treat AKI

## KEY TERMS

- Acute Kidney Injury
- Continuous Renal Replacement Therapies, CRRT
- Intermittent Hemodialysis
- Extracorporeal
- Diffusion
- Convection
- Adsorption
- Hemofiltration
- Ultrafiltration
- Fluid Balance Errors
- Hemodynamics
- Vascular Access
- Anticoagulation
- Complications
- Replacement Fluid
- Ultrasound Guidance

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## ABSTRACT

This chapter will summarize current knowledge in renal replacement technologies in the treatment of critically ill patients with acute kidney injury. The mechanics of different treatment modalities with emphasis on continuous renal replacement therapies will be described, as well as the application of such technologies in the management of fluid overload and metabolic abnormalities. Appropriate composition of dialysate and replacement fluids, use of anticoagulation, choice of vascular access, and potential complications in the use of such technologies will be discussed. Finally, the chapter will compare the main features of the different currently available CRRT machines.

## 18.1 HISTORY OF CRRT AND FUTURE DIRECTIONS

This section briefly describes the history and future perspectives of the management of acute kidney injury (AKI) in the critically ill patient, utilizing extracorporeal technologies.

At the dawn of dialytic therapy, renal replacement therapy was seen as a way to temporarily support patients with acute renal failure until renal functional recovery. The development of external arteriovenous access by Scribner, and the arteriovenous fistula by Cimino and Brescia made repeated access to the circulation possible and focused the attention of the nephrologic world towards chronic renal disease. The challenge of end stage renal disease was resolved when -at least in Western countries- chronic dialysis was made widely available. Unfortunately, these events took AKI to a second place, both in terms of the number of patients treated as well as the development of specific dialytic therapies. For many years, instead of developing specific therapies it was felt that AKI patients should be treated with the same methodologies as patients with chronic renal disease. The persistently elevated mortality associated with AKI did not stimulate a critical analysis of the problem; rather, elevated mortality was attributed to high comorbidity or to the nature of the syndrome, instead of relating it to inadequate treatment. The strongly conservative management of AKI was also associated with extensive search into the pathogenesis and clinical presentation rather than on treatment, at a time when nephrology remained tightly linked with internal medicine. Towards the end of the seventies, clinical AKI began to change, together with the development of increasingly invasive and complex surgeries and the growth of intensive care therapies. In this context, the need for specific treatments of AKI became obvious.

Renal replacement therapies first evolved by the development of acute peritoneal dialysis, and later by extracorporeal technologies able to control blood flow and ultrafiltration rate. Newer machines were developed, with more adequate control of ultrafiltration and the use of bicarbonate buffers in the dialysis fluid. Unfortunately, such developments remained insufficient, and unable to confront the hemodynamic instability of the critical patient. Moreover, new problems became evident such as the need to utilize cumbersome water treatment systems, and the scant availability of dialysis facilities in smaller hospitals. At that time, the simultaneous development of newer high permeability dialysis membranes permitted the development of convective treatments such as hemoperfusion. With these, it became possible to provide renal functional substitution with the use of bagged replacement fluids, and without the need for dialysis fluid. In spite of such progress, there remained the problem of vascular access and the use of extracorporeal circulation in the intensive care unit (ICU) environment, at that time still lacking in expertise in such technologies. In 1977, Peter Kramer, while attempting to puncture the femoral vein, punctured the femoral artery by mistake (Kramer et al. 1977). He proceeded to advance the cannula into the artery and assembled a circuit utilizing a polysulphone Amicon 30 filter and venous return: continuous arteriovenous hemofiltration (CAVH) was born. The system had low efficiency and had to be applied continuously for 24 hours. Moreover, the low fluxes and the limited ultrafiltration regimens made CAVH the ideal treatment for unstable patients who could not even be considered candidates for intermittent hemodialysis (IHD). The absence of dialysis fluids, machines and extracorporeal pumps made this modality very popular in the intensive care setting. Towards the end of 1970's, first at Mount Sinai Medical Center in New York (under the direction of Juan Bosch) and later at the Hospital San Bortolo in Vicenza, Italy, many patients were treated with this modality. After that time, Ronco et al. started to disseminate the technology in Italy, not without significant resistance from colleagues.

In 1984 the first meeting on CAVH was organized; in those times, it was mostly a convention of a group of passionate physicians including Lee W. Henderson, Michael Lysaght, Robert Bartlett, Juan Bosch, Luciano Fecondini and many others. Luciano Fecondini, in particular, was the chief engineer at Amicon and this was the key to the development, during many sleepless nights on call at Vicenza, of filters specially dedicated to CAVH. The most important successes included the creation of a very low resistance filter with the use of special geometries and fibers, and the adaptation of a very novel minifilter dedicated to neonates. With the intensive use of CAVH many more severely ill patients were able to receive

treatment, thus creating the possibility of critically evaluating the results of the technique. Towards the end of the 1980's it became obvious that the dose of dialysis delivered by CAVH was insufficient by multiple reasons, including frequent clotting of the system and limited ultrafiltration rates. Contemporarily, newer double-lumen venous catheters were being developed and the use of a blood pump in the ICU was more widely accepted. Also, the newer filters had an additional port permitting the addition of slow-flow of dialysis fluid. This led to the development of continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF). All these techniques, originated in CAVH, were classified under the umbrella of continuous renal replacement therapies (CRRT), taking advantage of newer machine developments by industrial groups that saw the commercial potential of such devices. In the 1990's the collaboration between Dr. Claudio Ronco and Dr. Rinaldo Bellomo (an Italian who immigrated to Melbourne, Australia) led to important joint achievements and an extensive number of publications on CRRT (Ronco and Bellomo 1998). A crucial event in the development of the field was the publication of a 1600 page text on Critical Care Nephrology and the joint publication in Nephrology, Dialysis and Transplantation of an editorial[1] titled "*Critical care nephrology, the time has come"*, which led to newer concepts on diagnosis and interdisciplinary courses on the management of the critical patient with AKI. The desire to learn and the need to discuss critically clinical results, led to the organization of three international courses in Melbourne and Vicenza on Critical Care Nephrology, with enormous success. The courses in Vicenza were geared towards a multidisciplinary medical audience, with sporadic nursing participation. Conversely, other meetings such as the San Diego International Conference on CRRT had mixed participation of physicians, nursing and other allied health practitioners. The reassuringly good patient outcomes in critical patients treated with CRRT led to the development of randomized controlled trials which have helped to define indications and treatment guidelines. Thus, in the book Blood Purification in Intensive Care we stressed the need to find consensus in multiple fronts; such consensus was gathered around the ADQI (Acute Dialysis Quality Initiative, http://www.ADQI.net) conferences in New York and Vicenza, and later in the Acute Kidney Injury Network (http://www.akinet.org).

The possibility of removing solutes from blood to obtain blood purification has mainly focused over the years on classic hemodialysis. However, the characteristics of some solutes make their removal difficult, and the limited efficiency of some dialysis membranes have spurred a significant

interest in the use of further mechanisms of solute removal, hemadsorption. Materials with high capacity of adsorption (sorbents) have been utilized for about 50 years in extracorporeal blood treatments of acute poisoning or uremia. With the recognition of the role of cytokines in systemic inflammatory response syndrome (SIRS) and sepsis, and the fact that most cytokines are poorly removable by conventional diffusive or convective blood purification modalities, treatment of sepsis based on sorbent technique has recently been explored. Continuous treatments are currently being favorably applied to the management of multiorgan failure and sepsis, and the concept of Multiorgan Support Therapies (MOST) is being successfully developed, demonstrating that contemporary treatment modalities of AKI are always the fruit of interdisciplinary collaboration.

## 18.2 CHOOSING A RENAL REPLACEMENT THERAPY IN AKI

This section focuses on the different modalities of renal replacement therapy (RRT) and briefly reviews both the basic concepts and the newest approaches to the management of the critically ill patient with AKI. Intermittent hemodialysis, Slow Continuous Low Efficiency Dialysis (SLED/EDD) and Continuous Renal Replacement Therapies (CRRT) are modalities of renal functional replacement used to manage AKI in the critically ill patient. Depurative mechanisms include convection, diffusion and membrane adsorption utilizing low- or high-flux highly permeable biocompatible dialysis membranes. In hemofiltration, simultaneous infusion of replacement fluid permits fluid removal without intravascular contraction and provides better hemodynamic stability, metabolic control to almost normal parameters and removal of large-size toxins and cytokines. CRRT allows better long-term clearance of small and middle molecules than other dialysis modalities. Adjustments of RRT techniques to avoid exacerbation of hemodynamic instability and to decrease further renal injury are discussed, emphasizing the importance of RRT modality to ensure patient survival and renal functional recovery.

### 18.2.1 Introduction

Most hospital-acquired acute kidney injury occurs in the intensive care unit and is associated with elevated morbidity and mortality (Cerda et al. 2008a, b). A recent international survey (Uchino et al. 2007) showed that while 80% of patients with AKI in the ICU are treated with CRRT, 17% are managed with IHD and 3% with peritoneal dialysis or SLED. These novel techniques of renal substitution therapy have allowed a conceptual shift from renal “replacement” to renal “support” therapies (Mehta 2001),

whereby the strategies to treat AKI have become an integral part of the overall critically ill patient management, with 'renal' and 'non-renal' applications such as sepsis and acute respiratory distress syndrome (ARDS). Table 18.1 lists the characteristics of the ideal treatment modality of AKI in the ICU (Lameire et al. 1999). Although none of the currently available modalities of renal replacement therapy fulfills all the ideal characteristics, this chapter will discuss the best options in each patient scenario.

**Table 18.1** Characteristics of the "ideal" treatment modality of AKI in the ICU (Lameire et al. 1999)

| CHARACTERISTIC |
|---|
| Preserves Homeostasis |
| Does not increase co-morbidity |
| Does not worsen patient's underlying condition |
| Is inexpensive |
| Is simple to manage |
| Is not burdensome to the ICU staff |

The hemodynamic stability of the critically ill patient is the main determinant of the most appropriate dialysis modality (see Table 18.2):

**Table 18.2** Indications for Specific Renal Replacement Therapies (Murray and Hall 2000)

| Therapeutic Goal | Hemodynamics | Preferred Therapy |
|---|---|---|
| Fluid Removal | Stable | Intermittent Isolated UF |
| | Unstable | Slow UF |
| Urea Clearance | Stable | Intermittent Hemodialysis |
| | Unstable | CRRT |
| | | Convection: CAVH, CVVH |
| | | Diffusion: CAVHD, CVVHD |
| | | Both: CAVHDF, CVVHDF |
| Severe Hyperkalemia | Stable/Unstable | Intermittent Hemodialysis |
| Severe Metabolic Acidosis | Stable | Intermittent Hemodialysis |
| | Unstable | CRRT |
| Severe Hyperphosphoremia | Stable/Unstable | CRRT |
| Brain Edema | Unstable | CRRT |

When choosing the modality of renal replacement therapy most appropriate for each patient, multiple considerations must be kept in mind (see Table 18.3).

**Table 18.3** Considerations in Renal Replacement Therapy for AKI

| Consideration | Components | Varieties |
|---|---|---|
| Dialysis Modality | | |
| | Intermittent Hemodialysis | Daily, Every other day, SLED |
| | Continuous renal replacement therapies | AV, VV |
| | Peritoneal dialysis | |
| Dialysis Biocompatibility | Membrane characteristics | |
| Dialyzer Performance | | |
| | Efficiency | |
| | Flux | |
| Dialysis Delivery | | |
| | Timing of initiation | Early, Late |
| | Intensity of dialysis | Prescription vs. Delivery |
| | Adequacy of dialysis | Dialysis dose |

In addition to the patient's hemodynamic stability, the choice between the various renal replacement modalities rests on solute clearance goals; volume control and anticoagulation (see Table 18.4):

**Table 18.4** Advantages and disadvantages of various renal replacement modalities (Modified from Davenport 2008)

| Modality | Use in hemodynamically unstable patients | Solute clearance | Volume control | Anti-coagulation |
|---|---|---|---|---|
| PD | Yes | ++ | ++ | No |
| IHD | Possible | ++++ | +++ | Yes/no |
| IHF | Possible | +++ | +++ | Yes/no |
| Intermittent IHF | Possible | ++++ | +++ | Yes/no |
| Hybrid techniques | Possible | ++++ | ++++ | Yes/no |
| CVVH | Yes | +++/++++ | ++++ | Yes/no |
| CVVHD | Yes | +++/++++ | ++++ | Yes/no |
| CVVHDF | Yes | ++++ | ++++ | Yes/no |

HDF: Hemodiafiltration; CVVH: Continuous hemofiltration; CVVHD: Continuous hemodialysis; CVVHDF: Continuous hemodiafiltration; IHD: Intermittent hemodialysis; IHF: Intermittent hemofiltration; PD: Peritoneal dialysis.

For the purposes of this section, we will utilize the conventional view that RRT dose is a measure of the quantity of blood purification achieved by means of extracorporeal techniques (thoroughly discussed in Ricci, Bellomo and Ronco, 2005). As this broad concept is too difficult to measure and quantify, the operative view of RRT dose is that it is a measure of the quantity of a representative marker solute that is removed from a patient. This marker solute is taken to be reasonably representative of similar solutes, which require removal for blood purification to be considered adequate. This premise has several major flaws: the marker solute cannot and does not represent all of the solutes that accumulate in renal failure. Its kinetics and volume of distribution are also different from such solutes. Finally, its removal during RRT is not representative of the removal of other solutes. This is true for both end-stage renal failure and acute renal failure. However, a significant body of data in the end-stage renal failure literature suggests that, despite all of the above major limitations, single solute marker assessment of dose of dialysis seems to have a clinically meaningful relationship with patient outcome and, therefore, clinical utility.

This section will focus on RRT modalities, and review the basic concepts and the newest approaches to this technology and its application in the ICU. We intend to discuss convective and diffusive depurative mechanisms and address the use of membrane adsorption as an additional method of large molecule removal. Previous reviews (Palevsky et al. 2002; John and Eckardt 2007) have discussed the fundamental operational characteristics of CRRT.

Recently, the Acute Dialysis Quality Initiative (ADQI) (Kellum et al. 2008a) published a consensus on fluid (Gibney et al. 2008; Kellum et al. 2008b) and volume management (Gibney et al. 2008) which is relevant to the present discussion. A recent review (Cerda and Ronco 2009) discussed these issues in depth, and KDIGO guidelines will soon be available online http://www.kdigo.org/

### 18.2.2 Arterio-Venous or Veno-Venous Blood Circuits

Arterio-venous (AV) systems are not used except in emergent situations, when veno-venous (VV) systems are not available. AV system limitations include arterial damage, blood flow dependency on systemic hemodynamics and insufficient dialysis dose (Palevsky et al. 2002).

### 18.2.3 Choice of CRRT Modality

The different modalities of CRRT (see Fig 18.1) are defined by the main mechanism with which clearance is achieved: simple diffusion (continuous hemodialysis, CVVHD), convection (continuous hemofiltration, CVVH) or a combination of both (continuous hemodiafiltration, CVVHDF) (Ronco 2006).

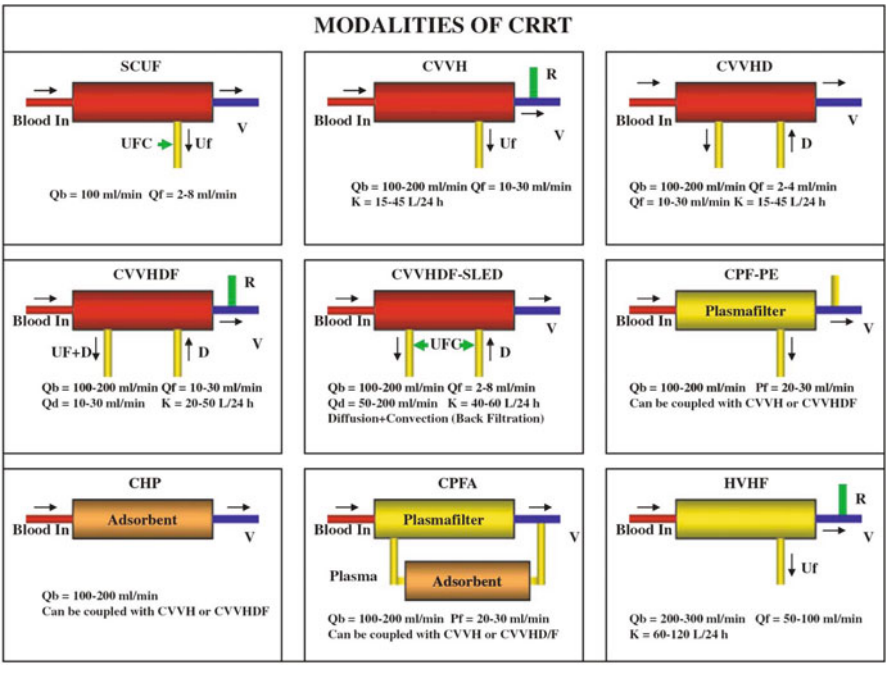



**Fig. 18.1** Modalities of CRRT (Modified from (Cerda and Ronco 2009; Ronco 2006)

These modalities differ in the magnitude of the clearance achieved by convection or diffusion, the vascular access and the need for fluid replacement (hemofiltration) (see Table 18.5).

**Table 18.5** Modalities of continuous renal replacement therapy

| Technique | Clearance | Mechanism | Vascular | Fluid |
|---|---|---|---|---|
| | Convection | Diffusion | Access | Replacement |
| SCUF | + | - | Large vein | 0 |
| CAVH | ++++ | - | Artery and vein | +++ |
| CVVH | ++++ | - | Large vein | +++ |
| CAVHD | + | ++++ | Artery and vein | +++ |
| CVVHD | + | ++++ | Large vein | +/0 |
| CAVHDF | +++ | +++ | Artery and vein | ++ |
| CVVHDF | +++ | +++ | Large vein | ++ |
| CAVHFD | ++ | ++++ | Artery and vein | +/0 |
| CVVHFD | ++ | ++++ | Large vein | +/0 |

CAVH=Continuous arteriovenous hemofiltration; CAVHD=Continuous arteriovenous hemodialysis; CAVHDF=Continuous arteriovenous hemodiafiltration; CAVHFD=continuous arteriovenous high-flux hemodialysis; CVVH=continuous venovenous hemofiltration; CVVHD=Continuous veno venous hemodialysis; CVVHDF=continuous venovenous hemodiafiltration; CVVHFD=Continuous venovenous high-flux hemodialysis; SCUF=Slow continuous ultrafiltration; 0=not required; +=negligible; ++=some; +++=marked; ++++=major

Given the absence of evidence of superiority among the different CRRT modalities, the choice rests on the available equipment (membranes, pump systems), and appropriate dialysate, and cost and conceptual considerations (Ricci et al. 2006).

#### 18.2.3.1 Dialysis Membranes for CRRT

The main features of convective treatments are:

- High flux membranes
- High permeability to water
- High permeability to low and middle MW solutes (1,000-12,000 Dalton)
- High “biocompatibility”

Dialysis devices are designated as:

- Dialyzers working predominantly in diffusion with a countercurrent flow of blood and dialysate,
- Hemofilters working prevalently in convection.
- Newer designs allow powerful simultaneous convection and diffusion (high flux dialysis, hemodiafiltration).

Although it is widespread opinion that when considering physiological outcomes convective treatments like high-flux hemodialysis, hemodiafiltration and hemofiltration offer a clinical advantage over standard dialysis, studies have not been able to demonstrate superiority of these techniques on morbidity, mortality or quality of life (Palevsky et al. 2002; Locatelli et al. 2002).

#### 18.2.3.2 Comparison between CRRT and Other Renal Replacement Modalities

CRRT techniques offer better long-term clearance of small and middle molecules than IHD or SLED. Modeling of these modalities shows (Liao et al. 2003):

- Small solute clearance is 8% and 60% higher with CVVH compared to SLED and IHD respectively
- CRRT and SLED allow effective azotemic control, while HD causes pronounced concentration peaks and poor time-averaged azotemic control
- Clearance results are even more different in the middle-molecule range of solutes, with superior middle-molecule clearance with CVVH compared with SLED or IHD
- The superior middle and large molecule removal for CVVH is due to a combination of convective clearance and continuous operation
- While on CRRT beta-2 microglobulin plasma concentration achieves steady state after 3 days, using SLED or IHD plasma concentration actually increases steadily, thus reflecting the inability of the latter modalities to clear large and middle molecular weight toxins.

The importance of the clearance of larger compounds is suggested by two treatment trials (Ronco et al. 2000) study and an earlier CRRT study (Storck et al. 1991) correlating convective dose (i.e. ultrafiltration rate) with survival. Large molecular clearance may have contributed substantially to the salutary effect of higher doses in these therapies. More recently,

studies (Saudan et al. 2006) have shown that the addition of diffusion to convective clearance resulted in further improvement in patient outcome.

Because the daily vs. every other day IHD study (Schiffl et al. 2002) was performed with high-flux dialyzers, the clearance of compounds significantly larger than urea may have played a role in the improved survival among the patients dialyzed daily. In spite of these suggestive findings, there is no firm evidence that enhanced removal of mid- or high-molecular weight patients leads to better patient outcomes (see below).

#### 18.2.3.3 Convection and Diffusion

Convection-based replacement techniques (hemofiltration and hemodiafiltration) using high-flux membrane filters are aimed at maximizing the removal of so-called medium and high-molecular weight solutes (higher than 1,000 kDa up to several thousand kDa), as opposed to the so-called low molecular weight toxins (Colussi and Frattini 2007; Vanholder et al. 2008; Ledebo 2005).

**Hemofiltration:** A predominantly convective technique, when compared to diffusion, hemofiltration removes larger quantities of hydrophilic large molecular weight (MW) compounds. It leads to greater cytokine removal by adsorption and convection. Removal of inflammatory mediators has been postulated (but not demonstrated) to benefit patient outcome.

**Hemodiafiltration:** Utilizes partially hydrophilic high-flux membranes. Membranes with have high sieving coefficient and reduced wall thickness, and combine diffusive and convective clearance. Accurate UF control systems make safe large volume removal possible. Newer machines permit separate control of dialysate and UF/reinfusion, and on-line production of ultrapure dialysate and replacement fluid has made possible to deliver safe and less costly treatments.

With current CRRT machines, solute exchanges can be obtained by convection, diffusion or both, with easier and more precise control over each component of the therapy. Blood ($Q_B$), dialysate ($Q_D$) and ultrafiltrate ($Q_{UF}$) flow rates can be controlled accurately with integrated pumps, and greater dialysate or convective flows –and therefore greater diffusive and convective solute fluxes- can be achieved. During CRRT, diffusion is limited by $Q_D$, in contrast to intermittent hemodialysis (IHD) (Brunet et al. 1999; Clark and Ronco 1999) the addition of convection may improve the clearances or middle-molecular weight solutes.

#### 18.2.3.3.1 Diffusion

The diffusivity of a solute, whether in solution or in an extracorporeal membrane, is:

- Inversely proportional to its molecular weight: as solute molecular weight increases, diffusion becomes a relatively inefficient dialytic removal mechanism and the relative importance of convection increases (Clark and Ronco 2004).
- Diffusion occurs whenever a concentration gradient (dc) exists for solutes not restricted in diffusion by the porosity of the membrane.
- Diffusion flux is also influenced by the characteristics of the membrane including:
  - Surface area (A)
  - Thickness (dx)
  - The temperature of the solution (T)
  - Diffusion coefficient of the solute (D).

The diffusion flux of a given solute ($J_x$) will therefore result from the equation (Clark and Ronco 2004):

$$J_X = D.T.A\left(\frac{d_C}{d_X}\right) \tag{18.1}$$

Other factors may influence the final clearance values including protein binding or electrical charges in the solute. Increased convection may contribute to greater solute transport, especially in the higher molecular weight range.

#### 18.2.3.3.2 Convection

Convection requires movement of fluid across the membrane driven by a transmembrane pressure gradient (TMP). The fluid transport is defined as ultrafiltration is described by the equation:

$$J_f = K_f.TMP \tag{18.2}$$

Where $K_f$ is the coefficient of hydraulic permeability of the membrane and $TMP = (P_b\text{-}P_{uf}) - \pi$, where $P_b$ is the hydrostatic pressure of blood, $P_{uf}$ the hydrostatic pressure of ultrafiltrate or dialysate and $\pi$ the oncotic pressure of plasma proteins. The convective fluid of a solute x will therefore depend on:

- The amount of ultrafiltration ($J_f$),
- The concentration of the solute in plasma water ($C_b$) and
- The sieving characteristics of the membrane for the solute (S):

$$J_X = J_f C_b (1-\sigma) = J_f C_b S \tag{18.3}$$

The sieving coefficient (S) is regulated by the reflection coefficient of the membrane σ according to the equation:

$$S = 1-\sigma \tag{18.4}$$

In clinical practice, however, because plasma proteins and other factors modify the original reflection coefficient of the membrane, the final observed sieving coefficient is smaller than expected from a simple theoretical calculation (Clark and Ronco 2004).

#### 18.2.3.4 Pre-dilution or Post-dilution

In hemofiltration, replacement fluid can be infused either before the hemofilter ("pre-dilution") or after the hemofilter ("post-dilution").

**In post-dilution CVVH**, a purely convective therapy, the three primary determinants of solute clearance are:

- Ultrafiltration rate,
- Membrane sieving coefficient and
- Dilution mode (Clark and Ronco 2004).

Convection occurs by "solvent drag": solutes are swept (dragged) across the membrane in association with ultrafiltered plasma water, such that

$$K = Q_F.S \tag{18.5}$$

Where K is clearance (ml/min), $Q_F$ is ultrafiltration rate (m/min) and S sieving coefficient. For small solutes, as S approaches unity clearance equals the ultrafiltration rate in post-dilution.

In post-dilution CVVH, filtration fraction (FF), the ratio of ultrafiltration rate ($Q_{UF}$) to plasma water flow rate is a limiting factor determined by blood flow ($Q_B$) rate and patient hematocrit (Htc):

$$F_F = \frac{Q_{uf}}{Q_b (1-H_{tc})} \tag{18.6}$$

Clinical practice indicates that a FF greater than 0.3 should be avoided because of hemoconcentration and protein-membrane interaction (Clark et al. 2003).

- Greater ultrafiltration rates require larger blood flows to avoid elevated FF and filter clotting and coating with accumulated proteins.
- Higher blood flows are usually difficult to reach with the temporary dialysis catheters and hemodynamic conditions commonly prevalent among critically ill patients. Reaching the higher doses recently demonstrated to affect survival are difficult to reach in post-dilution mode.

Pre-dilution mode has been introduced as a useful adjunct to prevent clotting of the extracorporeal circuit and to extend filter life, especially during high-volume CRRT, where filtration fraction would otherwise reach values greater than 0.3 and induce clotting and protein encroachment of the membranes.

**Pre-dilution CRRT** allows freedom from the constraints in blood flow and filtration rate imposed by pre-dilution. For small solutes dissolved in the water of the blood passing through the hemofilter (Brunet et al. 1999), clearance equals:

$$K = Q_F.S\left[\frac{Q_{BW}}{(Q_{BW} + Q_s)}\right] \tag{18.7}$$

Where $Q_{BW}$ is blood water flow rate and $Q_S$ the substitution (replacement) fluid rate.

At a given $Q_F$ value,

- Pre-dilution is always less efficient than post-dilution CVVH with respect to fluid utilization.
- While pre-dilution attenuates hemoconcentration-related effects, it simultaneously reduces the efficiency of the treatment.
- Thus, the larger $Q_s$ is relative to $Q_{BW}$, the smaller the entire fraction and the greater the loss of efficiency relative to post-dilution.

#### 18.2.3.5 Importance of Achieving a High Blood Flow $Q_B$

In CVVH, given the direct relationship between $Q_S$ and $Q_F$, great efforts are needed towards increasing the blood flow beyond that used traditionally in CRRT, usually close to 150 ml/min or less.

In pre-dilution mode, to attain doses of 35 ml/kg/h as described by Ronco et al (2000) it is necessary to achieve blood flows of 250 ml/min or higher, given that the decrease in efficiency inherent to pre-dilution mode can be as high as 35 to 40-45% for urea and creatinine respectively, when $Q_B$ is 125-150 ml/min and $Q_s$ is fixed at 75 ml/min (Troyanov et al. 2003).

Utilizing modeling analysis, (Clark et al. 2003) have shown that:

- As patient's weight increases, for low blood flow rates substitution fluid rates required to achieve this dose are impractically high in the majority of patients weighing more than 70 Kg.
- To achieve the dose target, the high ultrafiltration required determines high replacement fluid infusion rates, which in turn have a substantial dilutive effect on solute concentrations at low blood flows.
- Conversely, higher blood flows allow the delivery of higher doses without loss of efficiency.

Brunet et al (1999) studied the diffusive and convective solute clearances during CVVHDF at various dialysate and ultrafiltration rates. They demonstrated that convection is more effective than diffusion in removing middle-molecular weight solutes during CRRT, and that high convective flux should be applied if the goal is to remove middle molecules more efficiently.

#### 18.2.3.6 Interaction between Convection and Diffusion

At the slow flow rates normally utilized in CRRT, there is no interaction between diffusive and convective clearances. Recent studies (Saudan et al. 2006) have shown that the addition of a diffusive component to dialysis "dose" resulted in improved survival. Up until recently, dose data were mainly limited to diffusion (Schiffl et al. 2002) and convection (Ronco et al. 2000). The results of Ronco et al led to the definition of a "standard dose" of CRRT of 35 ml/kg/hr, which was applied indiscriminately to diffusive and convective continuous modalities.

More recently, Palevsky et al (2008) in the ATN study, utilizing a combined diffusive and convective modality (pre-dilution CVVHDF) or intermittent hemodialysis depending on hemodynamic stability, failed to demonstrate a beneficial effect of a higher dose of renal replacement therapy (daily IHD or CVVHDF at 35 ml/Kg/hour compared with three times/week IHD or CVVHDF at 20 ml/Kg/hour). It must be emphasized that the ATN study was *not* designed to evaluate the different RRT modalities, but

rather to evaluate the effects of dose on survival and renal recovery function. The RENAL study, led by (Bellomo 2006; Bellomo et al. 2009) addressed similar dose questions utilizing post-dilution CVVHD and equally found that a higher dose of CRRT (40 ml/Kg/h) did not result in improved 90-day patient survival when compared to 25 ml/Kg/h.

- The premise of those studies is that dose is a solute clearance-related parameter (Clark et al. 2003).
- The studies were not designed to determine which toxin clearance led to better survival. Although small solute clearance is a possible explanation, substantial clearance of relatively large molecular weight toxins may also explain the survival benefit in the high dose arm of the Ronco study (Ronco et al. 2000).

Basing on the dosing scheme of normalizing effluent flow rate to body weight, other forms of CRRT such as CVVHD and CVVHDF may provide equivalent or nearly equivalent small solute clearances as post-dilution CVVH, but for a given effluent flow rate, the diffusive component of these therapies limits their ability to clear larger molecular weight toxins relative to hemofiltration (Clark et al. 2003). Consequently, extrapolating Ronco's data to other forms of CRRT, especially for dosing purposes, should be done with caution.

### 18.2.4 Nutrition and Outcome

Better management of volume and body fluid composition is easily achieved with CRRT. Given the importance of nutrition on the outcome of critically ill patients with AKI (Cerda 2008; Cerda et al. 2007) CRRT could offer a theoretical advantage over IHD in this setting.

### 18.2.5 Hemodynamic Stability

Older (Davenport et al. 1993) and very recent (Ronco 2006) studies have consistently shown that the main advantage of continuous modalities is greater hemodynamic stability. In their recently published study, (Palevsky et al. 2008) chose CRRT (CVVHDF) as the modality of choice for hemodynamically unstable patients, a decision that reflects current practice in the US. In their study, although hemodynamically "stable" patients were allocated to IHD, hypotension occurred more frequently among patients treated with IHD than CRRT and may have had an impact on their lower rate of recovery of renal function.

CRRT is associated with better tolerance to fluid removal because:

- The rate of fluid removal is much slower in CRRT than in IHD
  - The main determinant of hemodynamic instability during RRT is the maintenance of intravascular compartment volume.
  - The volume of that compartment is the result of the balance between convective removal of fluid (ultrafiltration) from plasma and the rate of replenishment from the interstitium.
  - Therefore, whenever the UF rate exceeds the rate of interstitium-to-plasma flow (refilling), the patient will experience hypovolemia and hemodynamic instability (Gibney et al., 2008).

- In IHD rapid diffusion of urea creates a plasma-to-interstitium and interstitium-to-cell osmotic gradient that drives water to the interstitium and to the intracellular compartment, such that plasma volume decreases and cell edema (including neuronal edema) occurs.
  - With CRRT, the slower rate of urea clearance allows for equalization of urea concentrations between compartments and therefore, lessened water shifts and cell edema.
  - This is particularly important in patients with intracranial hypertension, such as head trauma and severe liver failure (Davenport et al. 1993, 1989; Ronco et al. 1999).

- A decrease in core temperature and peripheral vasoconstriction has been shown to decrease hypotensive episodes and may play a role in hemodynamic stability (Santoro et al. 2003).

- With either pre- or post-dilution hemofiltration, the magnitude of sodium removal is less than the amount of sodium removed with hemodialysis, a factor which may contribute to better cardiovascular stability in hemofiltration (Gibey et al. 2008; Kellum et al. 2008b; Di Filippo et al. 2003)

- Although hypovolemia is the first step in dialysis-related hypotension, the ultimate arterial pressure response to hypovolemia is the result of a complex interplay between active and passive mechanisms including decreased venous vessel capacity to sustain cardiac filling; increased arterial vascular resistances to ensure organ perfusion; and increased myocardial contractility and heart rate to maintain cardiac stroke volume (Santoro et al. 2003). Any factor

interfering with one or more of these compensatory mechanisms may foster cardiovascular instability. In this context, it is possible that convective removal of inflammatory mediators could contribute to hemodynamic stability, especially in the early phases of septic shock (see below).

### 18.2.6 Other Modalities of Renal Replacement Therapy

Modality selection for renal support in critically ill patients with acute kidney injury continues to be a controversial subject. Both intermittent hemodialysis and continuous renal replacement therapy are established therapies for such patients. While application of IHD to AKI patients is very similar to therapy delivery in end-stage renal disease (ESRD), CRRT was developed specifically to address the unique needs of critically ill AKI patients. A more recently proposed dialysis modality for the AKI population is sustained low-efficiency dialysis (SLED), also known as extended daily dialysis (EDD). This approach was first described in the mid-1990s as a "hybrid" therapy combining characteristics of both IHD and CRRT. In relation to CRRT, proponents have claimed that SLED is an equivalent modality, which can be provided at substantially lower treatment costs. The recent landmark ATN and RENAL trials consolidate the evidence base for the established modalities of CRRT and IHD. However, these trials add essentially nothing to the clinical community's understanding of the effect of SLED on AKI patient outcomes. Because an evidence base relating to the effect of SLED on patient outcomes is largely non-existent, the prescription of this modality continues to be based upon small and uncontrolled reports. In this era of evidence-based medicine, it would appear mandatory that randomized controlled trials assessing the effect of SLED on patient outcomes should be promptly designed and conducted. Until such trials provide relevant AKI patient outcome data, the argument that SLED is clinically equivalent to CRRT should be viewed with skepticism.

### 18.2.7 Renal Replacement Therapies in Special Situations

#### 18.2.7.1 Sepsis

##### 18.2.7.1.1 Hemofiltration of Large Molecules

- Middle molecules,
  - Mostly of peptides and small proteins with molecular weight in the range of 1,000 to 600,000 Daltons

- Accumulate in renal failure and contribute to the uremic toxic state (Vanholder et al. 2008; Tattersall 2007).
- Beta-2 microglobulin, with a molecular weight of 11,000 Dalton, considered a representative of these middle molecules (Gejyo et al. 1986), is not well cleared by low-flux dialysis
- High flux dialysis will clear middle molecules partly by internal filtration (convection); the convective component of high-flux dialysis can be enhanced in a predictable way by hemodiafiltration (Winchester and Audia 2006; Winchester et al. 2003).

In the last decade, it has been postulated that high convective dose therapies improve the management of sepsis (Ronco et al. 2000; Ledebo 2005; Ratanarat et al. 2006; Tetta et al. 2004; Silvester 1997; Ronco and Tetta 2007).

- Severe sepsis and septic shock are the primary causes of multiple organ dysfunction syndrome, the most frequent cause of death in intensive care unit patients.
- Many water-soluble mediators with pro- and anti-inflammatory action such as TNF, IL-6, IL-8, and IL-10 play a strategic role in the septic syndrome.
- In intensive care medicine, blocking any one mediator has not led to a measurable outcome improvement in patients with sepsis.
- CRRT is a continuously acting therapy, which removes pro- and anti-inflammatory mediators nonselectively. The *"peak concentration hypothes*is (Joannidis 2006; Ronco et al. 2003a, b) is the concept that cutting peaks of soluble mediators through continuous hemofiltration may help restore homeostasis.

This latter development proposes to use increased volume exchanges in hemofiltration or the combined use of adsorbent techniques.

- High volume hemofiltration (HVHF):
  - A variant of CVVH that requires higher surface area hemofilters and ultrafiltration volumes of 35 to 80 ml/kg/h.
  - Provides higher clearance for middle/high molecular weight solutes than simple diffusive transport (CVVHD) or convection-based transport at lower volumes (CVVH).
  - Associated with practical difficulties including machinery, replacement fluid availability and cost, and accurate monitoring systems to maintain safety (Gibney et al. 2008).

  - Studies utilizing this technique have shown preliminary evidence of benefit, but none of the studies are randomized trials of adequate statistical power to demonstrate effect conclusively.
  - Alternative technologies have utilized high cut-off hemofilters with increased effective pore size (Ronco 2006).
  - Drawbacks of such porous membranes include the loss of essential proteins such as albumin.

- Plasmafiltration coupled with adsorption (CPFA) has been recently utilized in septic patients (Bellomo et al. 2003).
  - In CPFA, plasma is separated from blood and the plasma is circulated through a sorbent bed; blood is subsequently reconstituted and dialyzed with standard techniques, thus achieving normalization of body fluid composition and increased removal of protein-bound solutes and high-molecular weight toxins.

- Recently, evidence has been obtained (Ronco et al. 2003a; Cole et al. 2002, 2001, 2004) that very high volume hemofiltration applied in pulses may improve the hemodynamic stability of septic patients in septic shock, but failed to show consistently improved survival.

#### 18.2.7.1.2 Use of Sorbent Technologies

The possibility of removing solutes from blood to obtain blood purification has mainly focused over the years on classic hemodialysis. However, both the characteristics of some solutes that make their removal difficult, and the limited efficiency of some dialysis membranes, have spurred a significant interest in the use of newer mechanisms of solute removal such as hemadsorption (Cruz et al. 2008; Joannidis 2006; Ronco et al. 2003b).

Materials with high capacity of adsorption (sorbents) have been utilized for about 50 years in extracorporeal blood treatments of acute poisoning or uremia. With the recognition of the role of cytokines in systemic inflammatory response syndrome and sepsis, and the fact that most cytokines are poorly removable by conventional diffusive or convective blood purification modalities, treatment of sepsis based on sorbent techniques has recently been explored.

Conventional blood purification has been shown to be poorly effective in the removal of pathogenic factors and mediators involved in the sepsis process. This has aroused interest in many innovative approaches such as

high-volume hemofiltration, the use of super-permeable membranes, and sorbent-based hemoperfusion using polymyxin B-immobilized adsorber (PMX) (Shimizu et al. 2009) to eliminate serum endotoxins.

Recent preliminary studies in septic patients have shown benefit in the use of sorbent technologies utilizing membrane-bound polymixin-B (the EUPHAS Trial) (Cruz et al. 2009). In this preliminary study, polymixin B hemoperfusion added to conventional therapy significantly improved hemodynamics and organ dysfunction and reduced 28-day mortality in a targeted population with severe sepsis and/or septic shock from intrabdominal gram-negative infection.

Larger multicentre evidence will be necessary before such techniques are widely implemented. If benefit is demonstrated, the use of very high volume hemofiltration and hemadsorption will require special equipment and very capable nursing able to manage such large volumes (i.e. up to 5-6 liters/hr) of ultrapure replacement fluid without error (Gibney et al. 2008).

#### 18.2.7.2 Hemofiltration in Congestive Heart Failure

The cardiorenal syndrome is a complicated and increasingly prevalent entity requiring a multidisciplinary approach. Renal replacement therapy in the form of slow ultrafiltration demonstrates promise for the treatment of acutely decompensated heart failure. Despite the lack of evidence for decreased mortality there is considerable short-term benefit in decreased re-hospitalizations and a restoration of diuretic responsiveness. Given the potential for improvement in quality of life and cost if hospitalizations are minimized, slow ultrafiltration should be considered in patients with repeated hospitalization for decompensated heart failure (Mathew and Cerda 2011).

#### 18.2.7.3 Acute Neurologic Injury

Acute neurologic injury is a highly unstable state requiring strict adherence to evidence based guidelines to achieve the best possible functional outcomes. With improved short-term survival, a greater burden of non-neurologic injury may hinder long-term functional recovery. Acute kidney injury is among such important considerations that can lead to worsened neurological injury. Careful application of continuous modalities of therapy, probably early in the course of illness to avoid intradialytic osmolar shifts and provide hemodynamic stability, will allow for unimpeded neurologic recovery. Newer evidence on dose and RRT modality on patients with acute and chronic brain injury will certainly add important knowledge to this field (Mathew and Cerda 2011).

#### 18.2.7.4 Extracorporeal Technologies in Patients with Liver Failure

Hepatorenal syndrome (HRS) type I is a unique form of acute kidney injury resulting from renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilation in patients with end stage liver disease. The only definitive treatment currently available is liver or liver-kidney transplantation. The goal of extracorporeal support (ECS) systems in HRS is to bridge eligible liver failure patients to transplantation or functional recovery by means of detoxification, assistance with biosynthesis of key metabolic products, and regulation of inflammation (Cerda et al. 2011). ECS systems in liver disease can be divided into two broad categories: cell-based and non-cell based systems. While cell-based systems aim to provide functions similar to those of normal hepatocytes, non-cell based systems do not incorporate tissue and provide detoxification utilizing membranes and adsorbents. There are no standard guidelines to the application of ECS systems. Published studies are too small and show considerable differences in primary indication, primary endpoint, and treatment protocols for 'intervention' and 'standard' treatment groups.

## 18.3 COMPLICATIONS OF CONTINUOUS RENAL REPLACEMENT THERAPIES

This section describes the complications of the CRRT procedure relating to the vascular access, the extracorporeal circuit, hematological and anticoagulation related problems, fluid balance errors, acid-base disorders, nutritional losses and problems dependent upon excessive removal of drugs such as antibiotics.

### 18.3.1 Vascular Access

#### 18.3.1.1 Infectious Complications

Central venous catheters (CVC) are the most common form of vascular access for patients undergoing CRRT. The estimated rate of infection is between 1.3 to 5.6 per 1000 catheter days (Edwards et al. 2009). Several mechanisms have been postulated (McGee and Gould 2003):

- Contamination of the catheter hub – leading to luminal colonization.
- Exit site infection – followed by migration of the organism along the external catheter surface.
- Hematogenous seeding of the catheter.

Infections have been classified as (McGee and Gould 2003):

- Catheter colonization – Growth of organisms from a catheter segment by either semi quantitative or quantitative culture.
- Catheter related blood stream infection (CRBSI) – Isolation of the same organism from a blood culture and from a catheter segment by either semi quantitative or quantitative culture accompanied by clinical symptoms of blood stream infections without any other apparent source.
- Exit-site infection – erythema, tenderness, induration or purulence within 2 cm of the exit site of the catheter.

Interventions to reduce infectious complications include stringent sterile placement techniques, appropriate catheter care, avoidance of femoral site and use of antimicrobial locking solutions when not in use (Vanholder et al. 2010).

#### 18.3.1.2 Mechanical Complications

The incidence of mechanical complications during catheter insertion varies between 5 and 19% based on the site selected (Merrer et al. 2001; Mansfield et al. 1994; Sznajder et al. 1986). Arterial puncture, hematoma, hemothorax, pneumothorax etc. are the major common complications reported. Arterio-venous fistulas, aneurysms, thrombus formation, pericardial tamponade, arrhythmias and retroperitoneal hemorrhage have also been reported (Oliver 2001).

#### 18.3.1.3 Thrombosis

Central venous thrombosis is a serious complication of CVCs. The incidence increases with the duration of catheterization. Various etiological factors have been implicated (Kaye and Smith 1988):

- Kink in catheter, tubing or tight sutures
- Catheter tip blockade by vessel wall
- Endothelial damage during procedure
- Insufficient / improper catheter lock
- Fibrin sheath or intraluminal clot
- Mural thrombus

An important factor to be considered is the site of catheterization. Femoral catheters carry the maximum risk of thrombosis when compared to subclavian or internal jugular venous catheters (Merrer et al. 2001).

#### 18.3.1.4 Access Recirculation

In a patient with AKI undergoing CRRT, dialysis dosing is a priority. An important factor to be considered is access recirculation because of temporary dialysis catheters. Studies have shown that recirculation may be as high as 22% in short femoral catheters and over 12% in long femoral catheters. Least recirculation is seen with subclavian catheters (Leblanc et al. 1996).

### 18.3.2 Extracorporeal Circuit Factors

#### 18.3.2.1 Air Embolism

Because of negative pressure in the venous side of the circuit, air embolism is possible. Even a small amount of air in the extracorporeal circuit can be fatal. It is usually manifested by chest pain, dyspnea, cough, cyanosis, hypoxia and cardiopulmonary arrest. Most modern machines have alarm systems that stop the flow of blood when air is detected within the circuit.

#### 18.3.2.2 Immune Activation

Prolonged exposure of blood to the filter and extracorporeal circuit can potentially activate several inflammatory mediators (Freyria et al. 1988).

#### 18.3.2.3 Hypothermia

During CRRT, the patient's blood leaves the body, travels along a plastic tube to a filter and is exposed to cooler ambient temperatures and CRRT fluids. Studies (Yagi et al. 1998; Matamis et al. 1994) have shown that a significant number of patients develop hypothermia while on CRRT. The resulting heat loss may increase daily energy requirements, mask fevers and delay the recognition of infection.

#### 18.3.2.4 Circuit Leaks

Rupture of the circuit may occasionally cause blood loss and contamination of the extracorporeal circuit. Circuit rupture may especially occur in the section of tubing in contact with the blood pump whenever the circuit is utilized for prolonged periods of time.

### 18.3.3 Hematologic

#### 18.3.3.1 Bleeding

Critically ill patients with multi-organ dysfunction syndrome develop a procoagulant state due to activation of the coagulation system by proinflammatory cytokines (Levi and Opal 2006). Therefore, anticoagulation of the extracorporeal circuit is usually required. The most commonly used anticoagulant is heparin. However, it is associated with the risk of excessive bleeding.

#### 18.3.3.2 Hemolysis

During CRRT, due to the effect of shearing forces generated by the roller pump or other parts of the extracorporeal circuit, a certain degree of hemolysis can occur. Treatment-related electrolyte imbalances such as hypophosphatemia, hypokalemia and hyponatremia can also promote hemolysis (Finkel and Podoll 2009). If clinically significant, hemolysis can delay recovery of renal function by causing pigment-induced nephropathy.

#### 18.3.3.3 Related to Anticoagulation

##### 18.3.3.3.1 Heparin Induced Thrombocytopenia (HIT)

Up to a quarter of patients experiencing repeated clotting of the extracorporeal circuit may have a positive HIT antibody (Lasocki et al. 2008). The diagnosis is primarily made on clinical grounds and serological confirmation. If not treated appropriately, it has devastating complications, including loss of limbs and even death(Arepally and Ortel 2006).

##### 18.3.3.3.2 Hypocalcemia

Regional anticoagulation using tri-sodium citrate is a good alternative to systemic heparinization. It chelates calcium in the extracorporeal circuit, providing effective anticoagulation. Asymptomatic hypocalcemia has been reported by several authors (Mehta et al. 1990; Kutsogiannis et al. 2000). The importance of close monitoring of $iCa^{++}$ levels cannot be overestimated. Critically ill patients who cannot metabolize citrate may require even more aggressive monitoring and repletion of calcium.

#### 18.3.3.3.3 Metabolic Alkalosis

In patients with normal liver function, each ion of citrate is converted to three bicarbonate ions by the liver. If not sufficiently cleared by dialysis, citrate overload may lead to metabolic alkalosis.

#### 18.3.3.3.4 Hypernatremia

When used as a 4% solution, trisodium citrate is hypertonic (560 mOsm/L) and hypernatremic (420 mmol/L) and can result in significant hypernatremia(Tolwani et al. 2001) unless baths of special composition (lower sodium) are used.

#### 18.3.3.3.5 Citrate Toxicity

Occasionally, patients may exhibit citrate toxicity characterized by low serum-ionized calcium levels and a high serum anion gap (Palsson and Niles 1999).

### 18.3.4 Fluid Balance Errors

One of the most common indications of CRRT is fluid overload. Most modern machines monitor the fluids within the system. However, some patients require significant pre- or postfilter replacement fluids. If these are not accounted for properly, gross volume imbalances can occur. It is also potentially dangerous to override fluid imbalance alarms because such situations can even result in patient death (Bagshaw et al. 2007; Ronco 2005; Gibney et al. 2008).

### 18.3.5 Acid-Base and Electrolyte Disturbances

Larger pore size and ongoing intercompartmental mass transfer commonly cause hypophosphatemia and hypomagnesemia in patients undergoing CRRT (Locatelli et al. 1998). Another common electrolyte imbalance is hypokalemia. These imbalances occur mostly because of inadequate monitoring and replacement (Fall and Szerlip 2010). The use of trisodium citrate as an anticoagulant can cause hypocalcemia, alkalosis, hypo and hypernatremia as described above.

### 18.3.6 Nutritional Losses

#### 18.3.6.1 Proteins

Critically ill patients on CRRT are hypercatabolic and have increased nutritional demands. In addition, the larger pore size of the membranes and large ultrafiltration rates result in significant protein and amino acid losses. It is estimated that 10 to 17% protein is lost in the effluent (Wooley et al. 2005). The impact of malnutrition as an important mortality risk factor is well known (Obialo et al. 1999).

#### 18.3.6.2 Trace Elements

Plasma levels of trace elements like zinc, selenium, copper, manganese and chromium are altered during CRRT (Wooley et al. 2005). These trace elements perform an important function in the body as antioxidants. However, the clinical impact of these losses is not well studied.

#### 18.3.6.3 Vitamins and Minerals

Water soluble vitamins can become depleted because they are readily filtered. Thiamin, vitamin C and vitamin E are all reported to be lost during CRRT. However, the clinical significance of these changes is unknown.

### 18.3.7 Drug Removal

In critically ill patients in the ICU, drug pharmacokinetics may be affected by the disease process. There may be altered protein binding, increased volume of distribution of water-soluble drugs and sometimes hyperdynamic circulation in early sepsis. In addition, extracorporeal drug removal also needs to be taken into account. The major factor affecting extracorporeal drug removal is either diffusion or convection. Other minor factors like drug charge, membrane adsorption and Gibbs-Donan effect also come into play (Schetz 2007a). Because of these issues, the clinician should resort to appropriate drug monitoring to ensure efficacy and to prevent toxicity.

## 18.4 ANTICOAGULATION FOR CONTINUOUS RENAL REPLACEMENT THERAPY

This section describes the different anticoagulation methodologies available for CRRT, including unfractionated heparin, regional heparinization, low-molecular weight heparin and heparinoids, thrombin antagonists, citrate anticoagulation and platelet inhibitor medications. The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring and pharmacy issues. There is no consensus on which anticoagulant should be first choice for all CRRT patients. However, citrate anticoagulation is gaining wide acceptance with the development of simpler and safer protocols. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications.

### 18.4.1 Introduction

CRRT commonly requires anticoagulation to prevent clotting of the extracorporeal circuit. Although CRRT without anticoagulation is feasible in patients with coagulopathy, most patients require some form of anticoagulation to ensure delivery of an appropriate dose of dialysis. The ideal anticoagulant should provide optimal anti-thrombotic activity with minimal bleeding complications and negligible systemic effects. It should be inexpensive, have a short half-life, and be easily reversed. Moreover, monitoring methods of the anticoagulant effect should be simple and readily available. The advantages and disadvantages of various reported methods of systemic and regional anticoagulation for CRRT are reviewed in this section.

### 18.4.2 Unfractionated Heparin

Unfractionated heparin (UFH), the most commonly used anticoagulant for CRRT, potentiates antithrombin III by a 1000-fold, resulting in inhibition of factors IIa (thrombin) and Xa. UFH is made up of heparin molecules of varied sizes (5-30 kDa). The larger fragments have predominantly anti-IIa activity and are cleared more rapidly than the smaller fragments. Anti-IIa activity is measured by the activated partial thromoboplastin time (aPPT). The smaller fragments principally inhibit Xa and may result in an anticoagulant effect in the setting of a normal aPPT due to its delayed clearance (Hirsh et al. 2001; Greaves 2002; Baker et al. 1997). UFH metabolites are eliminated by the kidneys. Plasma half-life is approximately 90 min but can increase up to 3 hours in the presence of renal insufficiency.

The advantages of UFH are that it is inexpensive, widely available and familiar to physicians, easy to administer, simple to monitor, and reversible with protamine. Disadvantages include the unpredictable and complex pharmacokinetics of UFH (resulting in dosing variability), the development of heparin-induced thrombocytopenia (HIT), heparin resistance due to low patient antithrombin levels, and the increased risk of hemorrhage (Hirsh et al. 2001). Considering all the administration methods of heparin, the incidence of bleeding episodes ranges from 10 - 50%, with mortality due to bleeding as high as 15% (Van de Wetering et al. 1996; Davenport et al. 1994; Martin et al. 1994).

Most of the publications using UFH in CRRT are small, non-randomized studies that used variable doses of heparin and variable aPTT targets (Hirsh et al. 2001; Davenport et al. 1994; Martin et al. 1994; Bellomo et al. 1993; Leslie et al. 1996; Tan et al. 2000). Circuit survival times ranging from 20 to 40 hours have been reported. UFH is generally administered as a bolus of 2000-5000 IU (30 IU/kg), followed by a continuous infusion of 5-10 IU/kg/hour into the arterial limb of the dialysis circuit. aPTT is maintained between 34 - 45 seconds, or aPPT of 1.5 - 2.0 times normal.

### 18.4.3 Regional Unfractionated Heparin-Protamine

Regional anticoagulation of the circuit is achieved by constant infusion of UFH into the hemofilter arterial line along with a constant infusion of protamine administered post-filter on the return line of the extracorporeal circuit. This approach requires measurement of both circuit and patient aPTT. The advantage of this method is that the anticoagulant effects of UFH are restricted to the extracorporeal circuit, thereby lowering the risk of systemic patient bleeding.

Regional heparinization is complicated because of the difficulty in estimating the amount of protamine required to antagonize post-filter heparin. For CRRT, an initial ratio of 100 between pre-filter heparin (in units) and post-filter protamine (in mg) has been recommended, with subsequent adjustment according to the aPTT. However, the amount of protamine needed to neutralize 100 IU of heparin varies substantially, making protocols cumbersome and difficult to standardize (Bellomo et al. 1993; Morabito et al. 2003; Biancofiore et al. 2003; Mehta et al. 1992; Kaplan and Petrillo 1987; Van der Voort et al. 2005). The heparin-protamine complex is taken up by the reticuloendothelial system and broken down, but then heparin and protamine are released back into the circulation. Protamine infusion is also associated with hypotension, anaphylaxis, cardiac depression,

leukopenia, and thrombocytopenia (Horrow 1985). In practice, UFH at 1000-1500 U/hour is infused pre-filter and neutralized with post-filter protamine at 10-12 mg/hour. Although several small studies have demonstrated that regional heparinization with protamine is feasible and safe, its efficacy in prolonging filter lifespan has been variable (Morabito et al. 2003; Biancofiore et al. 20036; Van der Voort et al. 2005).

### 18.4.4 Low Molecular Weight Heparins

Because of their reduced chain length, low molecular weight heparins (LMWHs) have higher anti-Xa/anti-IIa activity than UFH (Hirsh et al. 2001). The pharmacokinetics of LMWHs are more predictable than that of UFH because of less plasma protein binding. The advantages include a more reliable anticoagulant response and a lower incidence of HIT. Disadvantages include minimal reversal with protamine, prolonged duration in renal failure, need for special assays to monitor anti-Xa activity, and increased expense as compared to heparin.

Controlled studies of LMWHs in CRRT have utilized either fixed doses or doses based on anti-Xa levels (de Pont et al. 2000; Reeves et al. 1999; Journois et al. 1990; Joannidis et al. 2007). Studies have demonstrated mixed results as to whether anti-Xa levels correlate with circuit survival (de Pont et al. 2000; Reeves et al. 1999; Journois et al. 1990; Joannidis et al. 2007). Loading doses of 15-25 IU/kg of nadroparin and dalteparin have been used, with maintenance doses of 5 IU/kg/hour. Although some studies use LMWHs in a fixed dose, for safety reasons, monitoring of anti-Xa (target level 0.25-0.35 U/ml) is recommended with prolonged use. Levels of anti-Xa between 0.45 and 0.8 U/mL have been associated with bleeding complications (Jeffrey et al. 1993).

Four small randomized controlled trials (RCTs) have shown fixed-dose LMWHs to be as effective as, but not superior to, standard heparin in prolonging circuit life (Van der Voort et al. 2005; Reeves et al. 1999; Journois et al. 1990; Garces et al. 2010). One small RCT by Joannidis et al (2007) showed that enoxaprin (loading dose 0.15 mg/kg; maintenance dose 0.05 mg/kg/hour) extended circuit life, correlated with anti-Xa activity, and demonstrated less bleeding when compared to UFH.

### 18.4.5 Heparinoids

Danaparoid is a synthetic glycosaminoglycuron derived from pig intestine. It has a low-grade sulfation that reduces the incidence of platelet cross-reactivity with heparin-induced antibodies. It primarily has an anti-Xa,

rather than anti-IIa, effect. While danaparoid has been used for HIT, it has several disadvantages: cross-reactivity with heparin/platelet factor 4 (PF4) antibodies in 5-10% of patients; a prolonged half-life (up to 48 hours) in renal failure; and notably, no antidote.

For CRRT anticoagulation, danaparoid is administered as a bolus dose between 750 - 2500 U followed by a maintenance dose of 1-2 U/kg/hour. The dose is adjusted to achieve an anti-Xa level of between 0.25 and 0.35 IU/mL. One observational study of danaparoid in 13 patients on CRRT found a high rate of bleeding (46%) despite lower mean anti-Xa activity (0.4±0.2 U/ml) (Lindhoff-Last et al. 2001). Monitoring of anti-Xa activity is therefore critical with prolonged use.

### 18.4.6 Thrombin Antagonists

Recombinant (r) hirudin irreversibly inhibits bound and unbound thrombin independent of cofactors and PF4. The advantage is it can be used in patients with or suspected HIT. However the half-life of r-hirudin (normally 1-2 hours) is prolonged in patients with renal insufficiency since it is almost exclusively eliminated by the kidneys. Moreover, because it has a molecular weight of 6980 Da, it is negligibly removed by diffusion and variably removed with convection. No antidote exists. Since the anti-coagulation effect at higher doses of r-hirudin is not linearly related to the aPTT, the ecarin clotting time (ECT) is a more reliable test employed but not yet easily available (Nurmohamed et al. 1994; Potzsch et al. 1997). ECT uses the prothrombin-activating enzyme ecarin to monitor the concentration of r-hirudin plasma levels. Several authors have reported successful use of r-hirudin as an anticoagulant for CRRT in critically ill patients diagnosed with HIT (Fischer et al. 1999; Kern et al. 1999; Hein et al. 2001, 2004). For CRRT, it is administered either as a continuous infusion (0.005 – 0.01 mg/kg/hour) or delivered in bolus doses (0.002 g/kg) with a targeted ECT between 80-100 seconds (Wester 2004). In patients without HIT, two studies have demonstrated increased bleeding with continuous infusion, and less bleeding but a shorter circuit life with bolus doses (Hein et al. 2001, 2004). The use of hirudin as an anticoagulant in CRRT has been associated with hemorrhagic complications in up to 38% of patients (Kern et al. 1999; Hein et al. 2001).

Argatroban is a second generation direct thrombin inhibitor used in patients with HIT. Unlike hirudin, it is metabolized by the liver and has a 35 minute half-life in chronic dialysis (Murray et al. 2004). Furthermore, anti-coagulation can be effectively measured by aPTT levels. Similar to hirudin, no antidote exists. Studies are limited but describe a loading dose of

250 µg/kg and a maintenance dose of 0.5 – 2 µg/kg/minute with an aPTT 1-1.4 times normal (Reddy et al. 2005; Tang et al. 2005). Dose reduction is required in hepatic failure.

Compared to lepirudin and argatroban, bivalirudin is a thrombin inhibitor with a shorter half-life, reversible thrombin binding, and extrarenal and extrahepatic clearance mechanisms. A small RCT compared the safety and efficacy of bivalirudin to UFH for preventing CRRT hemofilter clotting and demonstrated prolonged circuit patency with no increase in bleeding (Kiser et al. 2010). Bivalirudin was administered at an initial rate of 2 mg/hr and titrated to maintain the prefilter aPTT to 1.5 to 2.5 times the patient's baseline aPTT. Bivalirudin may be a reasonable alternate to hirudin and argatroban in the setting of both renal and liver failure.

Recombinant human activated protein C (rhAPC) is a potent thrombin antagonist shown to reduce patient mortality in severe sepsis (Bernard et al. 2001). It inhibits thrombin formation by degrading coagulation factors Va and VIIIa. Few studies exist, and experience is limited. However, one study reported a mean circuit life of 55 ± 14 hours with rhAPC as compared to 66 ± 19 hours with UFH (de Pont et al. 2003).

### 18.4.7 Regional Citrate

Citrate is infused into the blood at the beginning of the extracorporeal circuit and provides anticoagulation by chelating ionized calcium ($iCa^{++}$). Optimal regional anticoagulation occurs when the $iCa^{++}$ concentration in the extracorporeal circuit is below 0.35 mmol/l (measured as the post-filter $iCa^{++}$ level). Since citrate is a small molecule, the majority of the calcium-citrate complex is freely filtered and lost in the effluent. Therefore, a systemic calcium infusion is necessary to replace the calcium lost with citrate. Any calcium-citrate complex remaining then returns to the patient and is metabolized to bicarbonate by the liver, kidney and skeletal muscle. Each citrate molecule potentially yields three bicarbonate molecules. Calcium released from the calcium-citrate complex helps restore normal $iCa^{++}$ levels. Advantages of citrate anticoagulation include the avoidance of systemic anticoagulation and HIT. The disadvantage is that citrate adds complexity and labor intensity to CRRT due to requirements for customized dialysate or replacement solutions. Frequent monitoring of electrolytes, $iCa^{++}$, and acid-base status is required, due to the potential for hypernatremia, metabolic alkalosis, and systemic ionized hypocalcemia. Patients with severe liver failure and lactic acidosis may have difficulty with citrate metabolism and develop citrate toxicity, which is characterized by low systemic $iCa^{++}$, elevated total serum calcium, metabolic acidosis, and an

increased anion gap (Apsner et al. 1997; Kramer et al. 2003; Meier-Kriesche et al. 2001; Bakker et al. 2006). If properly monitored, complications associated with regional citrate are uncommon.

A variety of methods of regional citrate anticoagulation are described in the literature (Palsson and Niles 1999; Gabutti et al. 2002; Mehta et al. 1990; Tolwani et al. 2001; Bagshaw et al. 2005; Monchi et al. 2004; Kutsogiannis et al. 2000, 2005; Brophy et al. 2005; Mehta et al. 1991; Thoenen et al. 2002; Hofmann et al. 2002; Tobe et al. 2003; Mitchell et al. 2003; Swartz et al. 2004; Cointault et al. 2004; Morgera et al. 2004; Egi et al. 2005; Naka et al. 2005; Bihorac and Ross 2005;Tolwani et al. 2006). Citrate is administered either as a separate citrate solution or added to a calcium-free pre-dilution replacement fluid. We have reported a simple citrate anticoagulation protocol with CVVHDF (Tolwani et al. 2006). By using an isotonic dilute-citrate based replacement solution and a commercially available physiologic calcium-free bicarbonate-based dialysate, the incidence of metabolic abnormalities is reduced.

Overall, studies of regional citrate anticoagulation, as compared to UFH, report better filter survival times and less bleeding (Palsson and Niles 1999; Gabutti et al. 2002; Mehta et al. 1990; Tolwani et al. 2001; Bagshaw et al. 2005; Monchi et al. 2004; Kutsogiannis et al. 2000, 2005; Brophy et al. 2005; Mehta et al. 1991; Thoenen et al. 2002; Hofmann et al. 2002; Tobe et al. 2003; Mitchell et al. 2003; Swartz et al. 2004; Cointault et al. 2004; Morgera et al. 2004; Egi et al. 2005; Naka et al. 2005; Bihorac and Ross 2005;Tolwani et al. 2006). There is also some evidence for improved biocompatibility by decreased activation of coagulation and leukocytes (Bos et al. 1997; Hofbauer et al. 1999). Five RCTs (Monchi et al. 2004; Kutsogiannis et al 2005; Betjes et al. 2007; Oudemans et al. 2009; Hetzel et al. 2011) report similar or longer circuit survival with citrate compared to heparin and less bleeding. Oudemans-van Straaten and colleagues (Oudemans-van Straaten et al. 2009) conducted a RCT comparing citrate to the LMWH nadroparin in 200 critically ill acute kidney injury patients on CRRT and found that citrate was better tolerated than heparin and improved patient and kidney survival, especially in patients after surgery, with sepsis, a high degree of organ failure or younger age. This mortality benefit, however, was not demonstrated in a similar RCT of 174 patients (Hetzel et al. 2011).

### 18.4.8 Platelet-Inhibiting Agents

Prostacyclin ($PGI_2$) and its synthetic derivative epoprostenol inhibit platelet aggregation and adhesion. Prostacyclin can cause hypotension

from vasodilation at doses of 20 ng/kg/minute. While the vasodilator half-life is 2 minutes, the antiplatelet effect remains for 2 hours. Prostacyclin has been investigated alone or in combination with UFH (Davenport et al. 1994; Langenecker et al. 1994; Kozek-Langenecker et al. 1998, 1999, 2002; Fiaccadori et al. 2002; Balik et al. 2005). The usual dose is 2 to 8 ng/kg/minute infused pre-filter. Monitoring is not required unless UFH is used. Its main drawbacks include the risk of hypotension and expense of the drug.

Most authors have reported only limited clinical experience with prostacyclin, and published reports on its safety and efficacy are scant (Davenport et al. 1994; Langenecker et al. 1994; Kozek-Langenecker et al. 1998, 1999, 2002; Fiaccadori et al. 2002; Balik et al. 2005). Langenecker et al. compared the efficacy and safety of $PGI_2$ as an alternative to and combined with UFH in a RCT. While $PGI_2$ increased circuit life, it was associated with more hemodynamic instability compared to heparin alone or heparin combined with $PGI_2$. The median filter life with prostacyclin as a sole agent was about 15-19 hours and extended to 20-22 hours when combined with low-dose UFH at 5-6 IU/kg/hour (Fiaccadori et al. 2002).

Nafamostat mesilate, a synthetic serine protease inhibitor, is a prostacyclin analog without the hypotensive activity. It is not available in the United States but typically administered at a dose of 0.1 mg/kg/hour. However, studies have demonstrated that levels of thrombin-antithrombin III complex and prothrombin activation fragment 1 + 2 increase, while protein C activity decreases, leading to circuit clotting (Ohtake et al. 1991; Nakae and Tajimi 2003). Several side effects (anaphylaxis, agranulocytosis, hyperkalemia) have been reported with use of nafamostat (Okada et al. 1992; Ookawara et al. 1996; Higuchi et al. 2000). Nafamostat has been widely used as an anticoagulant in Japan.

### 18.4.9 Conclusion

The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring and pharmacy issues. There is no consensus on which anticoagulant should be first choice for all CRRT patients. However, citrate anticoagulation is gaining wide acceptance with the development of simpler and safer protocols. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications.

## 18.5 VOLUME MANAGEMENT IN CONTINUOUS RENAL REPLACEMENT THERAPY

Fluid management with CRRT requires an understanding of the principles of fluid removal and fluid balance. Attention to fluid balance during CRRT is essential. Standardized order sets for prescription of the therapy, flow sheets for recording and monitoring fluid balance, and well trained nursing personnel are essential for the delivery of effective and safe CRRT. This section describes the hemodynamic implications of CRRT, the mechanics of fluid management, possible complications related to the procedure and the need for accurate recording to minimize such complications.

### 18.5.1 Introduction

Fluid management is a key component in the care of critically ill patients with AKI fluid overload represents one of the most frequent indications for the application of extracorporeal therapy in critically ill patients. Critically ill patients develop fluid overload in the setting of decreased urine output in AKI, congestive heart failure, sepsis, and other pathological conditions. Several observational studies, both in the pediatric and adult population (Foland et al. 2004; Gillespie et al. 2004; Goldstein et al. 2001; Payen et al. 2008; Bagshaw et al. 2008; Bouchard et al. 2009) suggest an association between fluid overload and increased mortality in critically ill patients with AKI.

Renal replacement therapies remove fluid from the intravascular compartment. Hemodynamic stability is dependent on refilling of the intravascular volume from the interstitial compartment. The plasma refill rate (PRR) limits fluid removal. In contrast to IHD, CRRT permits a slower and more constant fluid removal that can be targeted to match the PRR and minimize hemodynamic instability. Thus, CRRT techniques offer a significant advantage over IHD for fluid control in the critically ill patient. An understanding of the principles of fluid management with CRRT is necessary to ensure accurate management of fluid balance and prevent CRRT-related complications. Continuous clinical assessment of the patient's fluid status and adjustment of the CRRT prescription to optimize fluid balance are the keys to successful volume management with CRRT.

### 18.5.2 Fluid Removal in CRRT

The effluent is the total amount of fluid discarded by the CRRT device. It consists of the amount of fluid removed from the patient PLUS the

dialysate and/or replacement solution, depending on the modality of CRRT used. This is represented as follows: Total effluent = Replacement Fluid (RF) + Dialysate (D) + Fluid Removal (FR). The fluid removal rate is also known as the net ultrafiltrate. The replacement fluid and/or dialysate rate that is prescribed is automatically accounted for by the CRRT device and removed through the machine. In calculating the NET fluid removed from the CRRT device (or net ultrafiltrate), the dialysate and replacement fluid volumes should not be included in the calculation. In other words, the total effluent volume is NOT the net fluid removed from the patient. The fluid removal rate is the net amount of fluid the CRRT system removes from the patient each hour after accounting for any replacement fluid being used. Net fluid removal occurs whenever the operator sets the CRRT fluid removal rate to a value above zero. The CRRT device does not measure or account for non-CRRT sources of patient fluid intake (such as hyperalimentation, blood, or drug infusion) or fluid output (such as urine and wound drainage). It also does not account for anticoagulant solution infused via the anticoagulant syringe pump. The operator must account for these other sources when prescribing the patient fluid removal rate, as well as when calculating the patient's input/output totals. Overall fluid balance management in CRRT typically involves calculation of the patient's hourly total non-CRRT system intake (infusions, medications, etc.) minus the hourly total output. The hourly total output includes both the net fluid removal from the CRRT device and non-CRRT system output (urine, gastrointestinal losses, etc.). The patient fluid removal rate must be adjusted if the weight loss prescribed by the physician is changed or if the patient's non-CRRT fluid inputs or outputs change.

Patients on CRRT should have a complete assessment of the fluid status and the volume of fluid the patient is receiving each hour. Parameters for assessment include the patient's blood pressure, dosages of vasopressors, weight, presence of edema, central venous pressure (CVP), pulmonary artery occlusion pressures, cardiac index, and cardiac output if the patient has a pulmonary artery catheter in place. Other helpful measurements include arterial blood gases, arterial oxygen saturation, and mixed venous oxygen saturation.

Accurate CRRT-related fluid management requires the incorporation of a bedside CRRT flow sheet for calculating machine fluid balance. The flow sheet requires the recording of fluid balance changes and CRRT parameters on an hourly basis. Furthermore, the CRRT flow sheet should allow for a running hourly balance. The CRRT flow sheet ensures that treatment goals reflect 'machine' settings and 'patient' fluid inputs. For example, a treatment may be set for a 200 mL/hr fluid removal while the

intravenous inputs are also 200 mL/hr; this is considered patient 'even' or no net fluid loss. To achieve a patient negative fluid balance the machine fluid removal would need to exceed 200 mL/hr. A common misunderstanding and source of error is in prescribing fluid loss or determining desired negative fluid balance.

Scales or balancing chambers are used to manage the administration and removal of fluid through the CRRT device. If a scale system is used, the scales balance the weight of the volume of fluid programmed to be lost on the infusion scale and the weight gained on the output scale. In a balancing chamber system, the balance chambers empty and fill precisely, to balance the fluid volume programmed in and out, ensuring that the fluid volume desired is accurate. In either type of system, accuracy can be verified by monitoring the therapy history and comparing the volume of actual fluid removed at the end of each hour to the volume that was programmed. The volumes programmed to be infused and removed by the system should be within the manufacturer's error specifications of the system in use.

### 18.5.3 Management of Complications

When large net fluid removal rates are prescribed, ultrafiltration may exceed the refilling capacity of fluid movement into the intravascular compartment, resulting in hypotension, decreased CVP decreased pulmonary arterial wedge pressure, etc. Fluid removal should be decreased or stopped if these signs of hypovolemia occur. Excessive fluid removal, i.e. fluid removal greater than what is prescribed, has resulted in death and injuries when operators repeatedly overrode safety alarms intended to limit fluid removal when the gravimetric scales were being adjusted (Ronco et al. 2005). In these cases, an alarm called "incorrect weight change detected" was overridden without identifying the underlying cause. Most machines today are equipped with software that intervenes and stops the treatment after a fixed number of alarm overrides or when an absolute error in fluid balance has occurred. Regardless of this safety measure, a red alarm should never by overridden without identifying and correcting the cause of the alarm.

An increase in edema or weight gain may indicate that the therapy objectives are not being achieved or that the circuit is not functioning properly. Every time an alarm occurs, or the pumps stop on the system, the fluid removal is also stopped. Therefore, the programmed volume of fluid to be removed may not be the volume that was removed that hour. Frequent interruptions of therapy due to machine alarms may lead to extensive loss of treatment time and thus decreased fluid removal. Furthermore, adjustments

to the fluid removal prescription may need to be made if patients are off therapy for extensive amounts of time due to procedures or other issues. Prompt attention to fluid balance should always be a priority in patients treated with CRRT.

### 18.5.4 Conclusion

Fluid management with CRRT requires an understanding of the principles of fluid removal and fluid balance. Attention to fluid balance during CRRT is essential. Standardized order sets for prescription of the therapy, flow sheets for recording and monitoring fluid balance, and well trained nursing personnel are essential for the delivery of effective and safe CRRT.

## 18.6 DIALYSATE AND REPLACEMENT FLUIDS

A successful CRRT program is dependent on the proper and timely delivery of safe dialysate and replacement fluids. This section describes the composition of custom-made and commercially dialysate and replacement fluids currently available for CRRT. Fluids should be sterile and contain electrolytes in physiologic concentrations. Bicarbonate is the preferred buffer for CRRT solutions.

### 18.6.1 Introduction

CRRT solutions should restore acid-base balance and maintain physiological electrolyte concentrations while minimizing errors and maximizing safety. The U.S. drug Administration (FDA) classifies replacement solution as a drug since it is infused in the vascular space, and dialysate as a device. In general, there is little difference in the composition of dialysate and replacement fluids, and many commercially available dialysates are used off-label as replacement fluids. Whether replacement fluid or dialysate is utilized, the solution should be as pure as possible since significant backfiltration can occur with diffusive CRRT modalities. During backfiltration, dialysate flows from the dialysate compartment across the membrane into the blood compartment. Therefore, dialysate and replacement fluids need to be at least ultrapure and preferably sterile. Decisions regarding the generation and composition of CRRT solutions are discussed in this section.

### 18.6.2 Custom-Made versus Commercially Available Solutions

CRRT fluids can be custom-made by pharmacy, premade from a compounding company, or purchased prepackaged by a manufacturer. Customization of solutions, with subsequent adjustments based on or determined by patient clinical status, expends pharmacy resources and increases the risk for error. In 2004, two patients who were receiving CRRT died after potassium chloride, rather than sodium chloride, was added mistakenly to a custom-made dialysate (Johnston et al. 2004; Canada News Wire Group 2004). Because the FDA does not presently require batch testing for quality control, potentially hazardous CRRT solution errors may be unrecognized. Like customized pharmacy-made solutions, premade CRRT solutions obtained from a compounding company are associated with increased cost and a shorter shelf life as compared to commercially available prepackaged solutions. Furthermore, the quality and sterility of such fluids are questionable. As a result, the safest approach is to use commercially available CRRT fluids. These are significantly less expensive, have longer shelf life, available in 3 liter and 5 liter bags, and available from multiple manufacturers.

### 18.6.3 Electrolyte Composition

The Acute Dialysis Quality Initiative (ADQI) has published recommendations regarding the composition of CRRT solutions (Kellum et al. 2008b). These are reviewed below. In general, replacement and dialysate solutions should contain electrolytes in physiological ranges.

#### 18.6.3.1 Sodium

In most cases, the sodium concentration in CRRT solutions should be physiologic. Commercially available solutions contain sodium concentrations in the range of 130 to 145 meq/L. When hypertonic citrate solutions are used as anticoagulation for CRRT, hyponatremic replacement and/or dialysate fluids are often needed. Adjustments of the sodium concentration of CRRT fluids may also be necessary in patients with hypo- or hypernatremia.

#### 18.6.3.2 Potassium

CRRT fluids with potassium concentrations between 0 to 4 meq/L are commercially available. When initiating CRRT, potassium concentration of 0 to 2 meq/L may be needed in the setting of severe hyperkalemia. After steady state is reached with CRRT or the acute hyperkalemia resolves,

CRRT solutions with a potassium concentration of 4 meq/L should be used for maintenance.

#### 18.6.3.3 Calcium, Magnesium, Phosphorous

Calcium should be present in physiological concentrations in CRRT solutions. Exceptions include patients with severe hypo- or hypercalcemia and/or patients treated with citrate anticoagulation. When using citrate anticoagulation, the CRRT solutions should not contain calcium; instead, calcium is replaced to the patient by an intravenous infusion. Commercially available solutions contain calcium in the ranges of 0 to 3.5 meq/L.

Magnesium in commercially available CRRT fluids ranges between 1 – 1.5 meq/L. This level is not well studied but has been clinically successful in use without significant hypermagnesemia or hypomagnesemia. Intravenous magnesium may be needed if magnesium levels fall below normal or at lower ends of the normal reported range.

Although hyperphosphatemia is a frequent complication of AKI, the majority of patients on CRRT will develop hypophosphatemia after CRRT initiation. Phosphorus is not a standard component of replacement or dialysate fluids in CRRT. The most appropriate way to supplement phosphorus is to use higher phosphorous enteral feedings or phosphate addition to hyperalimentation. Hypophosphatemia may also be treated with intravenous supplementation. Several authors have described the safe addition of phosphorous to CRRT fluids (Troyanov et al. 2004, Broman et al. 2011).

#### 18.6.3.4 Glucose

Commercially available solutions contain glucose in the range of 0 to 110 mg/dL. Solutions with supraphysiologic glucose content should be avoided since they can induce hyperglycemia, which is associated with poorer outcomes. The predominate complications with the use of glucose-free solutions is hypoglycemia and inadequate nutritional supply.

#### 18.6.3.5 Buffer

CRRT fluids require a buffer anion due to substantial loss of bicarbonate in the effluent. Buffer options include acetate, lactate, bicarbonate, and citrate. Both acetate and lactate are converted by the liver into bicarbonate in a 1:1 ratio. Acetate has been associated with hemodynamic instability and decreased cardiac function in IHD. It has not been frequently

used as a buffer for CRRT (Morgera et al. 1997). Although controlled trials have demonstrated similar efficacy of lactate- and bicarbonate-based CRRT solutions in correcting metabolic acidosis (Thomas et al. 1997; Heering et al. 1999; Zimmerman et al. 1999), serum lactate levels are typically higher when lactate-based solutions are used and can confuse the clinical interpretation of blood lactate levels. Moreover, lactate solutions may worsen metabolic acidosis in patients with metabolic derangements and hepatic failure (Kierdorf et al. 1999). Bicarbonate-based solutions are preferred for patients with hepatic failure who cannot metabolize the lactate and are also more physiological than are lactate solutions. Recent studies have shown better control of metabolic acidosis with bicarbonate-based solutions as compared to lactate-based solutions (McLean et al. 2000). Both lactate-based and bicarbonate-based solutions are commercially available as CRRT fluids. Bicarbonate is currently the preferred buffer. Commercially available CRRT fluids contain bicarbonate in the range of 22 to 35 meq/L.

Citrate is used for anticoagulation and not solely as a buffer for CRRT. However, since citrate generates three moles of bicarbonate per mole of citrate, the concentrations of other buffers in CRRT solutions need to be adjusted or eliminated to prevent metabolic alkalosis. The acid-base complications of citrate are discussed in detail in the 'Anticoagulation' section of this chapter.

### 18.6.4 Conclusion

A successful CRRT program is dependent on the proper and timely delivery of safe dialysate and replacement fluids. Fluids should be sterile and contain electrolytes in physiologic concentrations. Bicarbonate is the preferred buffer for CRRT solutions.

## 18.7 VASCULAR ACCESS IN RENAL REPLACEMENT THERAPIES

This section discusses the characteristics of vascular access to be used for renal replacement therapy in patients with AKI. Dual lumen venous temporary catheters are the access of choice. Tunneled catheters can be used in patients with AKI if the anticipated need is more than one week, and insertion must be done under ultrasound guidance utilizing strict sterile technique, and preparing the skin with 2% chlorhexidine .The right internal jugular vein is the preferred site of insertion. The role of antibiotic

'locks' and antiseptics embedded into the catheter material is currently in question.

### 18.7.1 Introduction

Renal-replacement therapies are among the most invasive techniques used in the intensive-care units. Increased safety can be expected from interventions in several areas. Teaching and training are probably the more important due to the complexity of both techniques and devices (Journois and Schortgen 2008). Safe insertion and management of the hemodialysis access is key to ensure good patient outcomes. A well- functioning vascular access is an essential component of the equipment necessary to deliver adequate renal replacement therapy in AKI (Schetz 2007b).

The three main issues to be discussed in this section will include:

1. Insertion in the acute setting
2. Adequacy of dialysis in relation to the kind of catheter utilized
3. Prevention of angioaccess-related morbidity

### 18.7.2 Characteristics of Catheters and Procedures for Insertion

Most of hemodialysis catheters are made of plastic polymers, either polyurethane or silicone (Tal and Ni 2008). Polyurethane catheters are more rigid and therefore associated with greater risk of vessel injury, but their rigidity makes them easier to insert percutaneously. Conversely, silicone catheters are semi-rigid and become softer at body temperature: although less likely to injure blood vessels, these catheters require more complicated procedures for percutaneous insertion. For tunneled insertion, silicone soft cuffed catheters are preferable because they offer an additional barrier to the entry of bacteria (Siegel 2008). These catheters are generally inserted percutaneously via the right internal jugular vein, are larger than temporary catheters and provide better blood flow and less clotting complications. Tunneled catheters can be used in patients with AKI if the anticipated need is more than one week, but given the lack of predictors of duration of AKI, initial insertion of tunneled catheters is appropriate (Coryell et al. 2009). Tunneled catheters are equally adequate among elderly and young patients (Forauer et al. 2009).

The size of catheters is usually between 11 and 14 French. Structurally, catheters are double-lumen with variable catheter and tip design, attempting to minimize resistance to flow by ensuring maximal diameter and avoidance of recirculation between the outflow and inflow branches (Tal and Ni 2008). Reliable data directly comparing different designs and coatings are currently lacking.

Ultrasound guidance should be mandatory for catheter insertion. It reduces placement failure, decreases the number of placement complications and the number of attempts, and reduces the number of catheter associated infections (Randolph et al. 1996; Karakitsos et al. 2006; Hassan et al. 2008) (see Table 18.6)

**Table 18.6** Comparison of catheter placement complications with and without ultrasound guidance (Karakitsos et al. 2006)

| Complications | No U/S Guidance | U/S Guidance |
|---|---|---|
| Carotid Injury | 10.6% | 1.1% |
| Hematoma | 8.4% | 0.4% |
| Hemothorax | 1.7% | 0% |
| Pneumothorax | 2.4% | 0% |

#### 18.7.2.1 Site of Insertion

The preferred site of insertion is the right internal jugular vein, where the trajectory of the vein is direct towards the right atrium. Left internal jugular vein insertions tend to be more problematic because of the longer and more circuitous vein trajectory. Subclavian vein location should be avoided in order to minimize the chances of vein stenosis, considering possible future insertion of an arteriovenous fistula on the upper extremity. The place of insertion determines the required minimal length of the catheter (see Table 18.7 and Fig. 18.2).

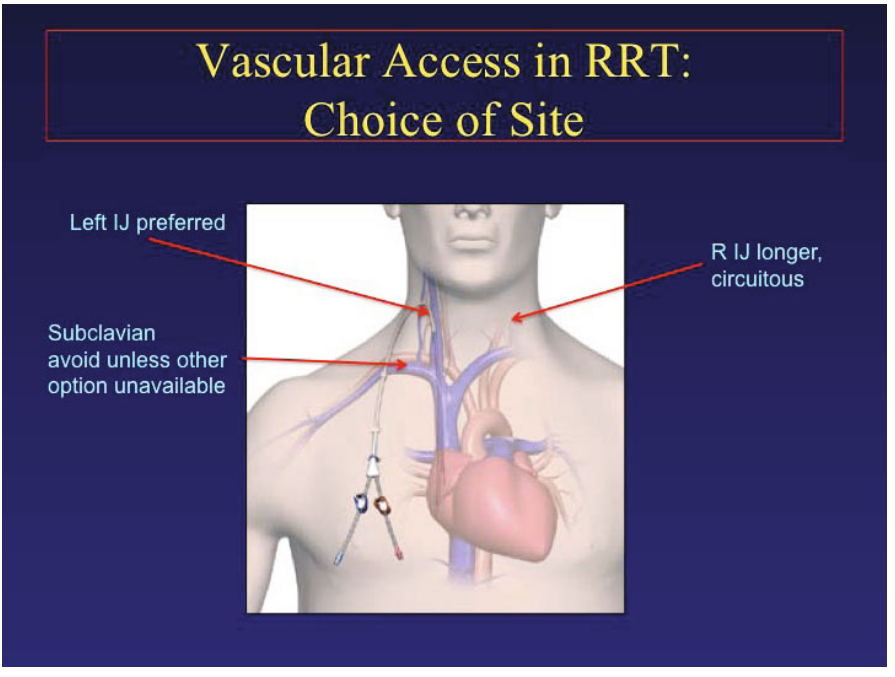



**Fig. 18.2** Vascular access in RRT: choice of site

**Table 18.7** Location of the dialysis line and preferred length of the catheter

| **Location** | | Preferred Length |
|---|---|---|
| Jugular | Right Internal | 15-16 cm |
| | Right Internal | 19-20 cm |
| Femoral | | 24-35 cm |

### 18.7.2.2 Complications from Insertion

The complications of temporary dialysis catheters occur either during placement or long term.

**During placement, complications include:**

- Bleeding, hematoma formation, arterial puncture and risk of hemomediastinum.
- Air embolism.
- Recurrent laryngeal nerve paralysis.
- Atrial perforation.

- Arrhythmia and cardiac arrest: the electrocardiogram must be continuously monitored during catheter placement.

**Long-term, complications include:**

- Catheter thrombosis.
- Venous thrombosis, especially with femoral catheters (Brzosko et al. 2008).
- Venous stenosis.
- Fibrin sheath formation (Faintuch and Salazar 2008).
- Infection: the reported risk of bacteremia in nontunneled catheters ranges between 3 and 10%.

### 18.7.3 Adequacy of Dialysis in Relation to the Kind of Catheter Utilized

Multiple studies have shown a significant discrepancy between the prescribed and delivered dose of dialysis (Venkataraman et al. 2002; Vesconi et al. 2009). The type and location of hemodialysis access plays a key role in the delivery of an adequate dose of dialysis (Liangos et al. 2004). Klouche et al (2007) studied the effects of dialysis catheters on dialysis dose and patient survival, to evaluate the potential benefit of tunneled silicone catheters in femoral vein location. In patients with AKI, silicone tunneled catheters minimize catheter-related morbidity and improves dialysis efficiency, when compared to conventional femoral access (see Table 18.8).

Catheter recirculation plays a significant role in the delivery of dialysis. Canaud et al showed that while internal jugular and subclavian vein catheters show an average 10% recirculation, femoral catheter recirculation is higher (average 20% [range 5-38%]) and the inversion of dialysis lines increases recirculation up to 20-30% (Canaud et al. 2004). Utilizing the saline dilution technique, temporary femoral catheters less than 20 cm in length show three times as much recirculation than longer catheters, while internal jugular lines show minimal recirculation (Little et al. 2000). More recently, Parienti et al conducted a randomized control trial of catheter dysfunction and dialysis performance in critically ill patients and showed that as long as the femoral lines reach the inferior vena cava, they are an acceptable alternative to jugular access in bed-bound adults in the ICU (Parienti et al. 2010).

**Table 18.8** Complications, effects on dialysis dose and survival of tunneled femoral catheters in acute kidney injury (Klouche et al. 2007)

| Complications | Tunneled silicone catheters | Non tunneled polyurethane catheters |
|---|---|---|
| Time for insertion | Longer | Shorter |
| Vein thrombosis | Lower | Higher |
| Catheter related infection | Lower | Higher |
| Venous pressure/$Q_b$ | Better | Worse |
| Recirculation | Same | Same |
| Dialysis dose (IHD or CRRT) | Higher | Lower |
| Catheter duration | Longer | Shorter |

### 18.7.4 Catheter Related Infections

Bacteremia and the development of sepsis syndrome is second only to cardiovascular disease as the leading cause of death in patients on renal replacement therapy (Thomson et al. 2007). Catheter related infections are the second most common major complication of dialysis lines. Infection usually occurs due to migration of skin bacteria, although hematogenous colonization is possible (NKF-KDOQI 2006). Catheter related infections are more common with uncuffed dialysis lines.

Catheter infections occur from three sources: from the lumen (infected catheter hub); from the skin, in progression from infected exit site leading to tunnel and later catheter infection; or hematogenous such as during episodes of transient bacteremia and bacterial endocarditis (see Fig. 18.3).

The commonest agents of infection include gram-positive staphylococcus (S Aureus or Coagulase Negative Staphylococcus Epidermidis), followed by gram negative bacilli, gram positive bacilli such as the skin contaminant Corynebacterium, and fungi (usually Candida Spp) (Parienti et al. 2008).

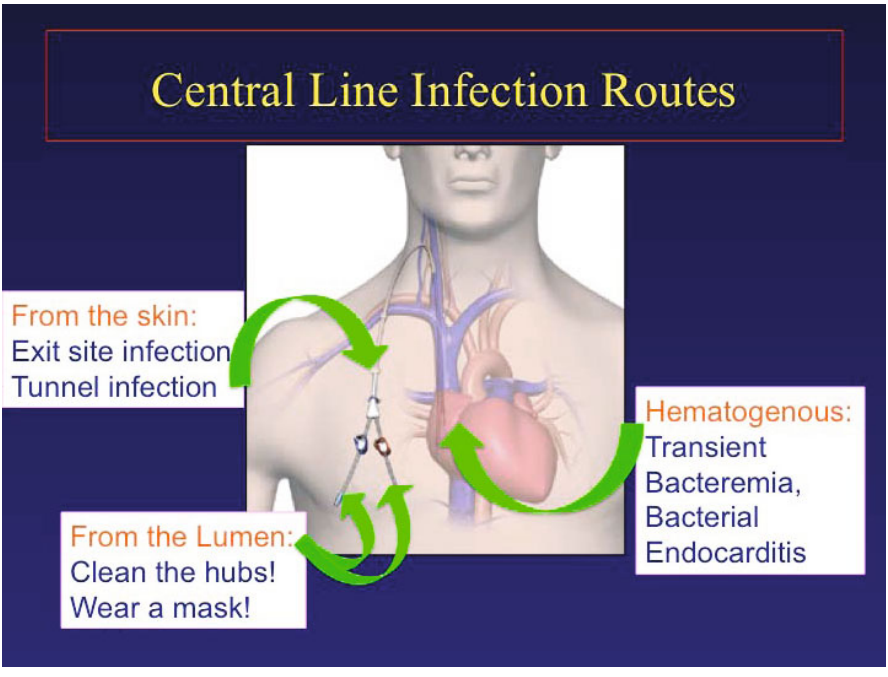



**Fig. 18.3** Central line infection routes

Although prevalent opinion is that femoral catheters become infected more commonly than jugular catheters, a recent large randomized controlled trial (Parienti et al. 2008) has shown that jugular venous catheterization does not reduce risk of infection compared with femoral access except in obese adults. Also, in contradistinction to prevalent wisdom, the same authors demonstrated that catheter colonization and infection are random events without a time threshold: the incidence of infection increases linearly with time without inflection at any given time. This finding indicates that the current policy of systematic predetermined catheter exchange after a certain period of time is not justified unless infection is demonstrated.

Best demonstrated practices to avoid catheter related infectious complications include:

- Use of maximal sterile barrier precautions during insertion
- Use of ultrasound guidance for insertion
- Use of chlorhexidine skin desinfection and chlorhexidine impregnated disks in the exit site

- Careful desinfection of the catheter hub whenever used
- Use of dialysis catheter only for dialysis, forbidding their use for other purposes such as iv infusions or blood draws
- Pre-scheduled routine catheter exchanges are not necessary unless infection is demonstrated
- Remember to remove lines when no longer needed

When to remove the dialysis catheter?

- When systemic bacteremic infection is demonstrated
- Exit site infection requires temporary catheter removal and placement of a new line at a separate location
- Tunneled catheters must be removed if there is tunnel infection
- Sole exit site infection may be managed with a trial of topical antibiotics such as mupirocin

Complications of catheter related bacteremia (Maya and Allon 2008) are:

- Less likely with tunneled than non-tunneled
- Frequency 2 to 5.5 episodes/1000 catheter-days
- Suspected with fever/chills; confirmed with positive Blood Cultures
- Serious complications 5-10%: bacterial endocarditis, osteomyelitis, epidural abscess, and death.
- Etiology: 60-70% gram positive cocci, 30-40% gram negative rods
- Uncomplicated catheter-related bacteremia requires 3 weeks of intravenous antibiotics
- Systemic antibiotics alone (without replacement of dialysis catheter) lead to 75% recurrent infection
- Catheter removal is mandatory with persistent fever or bacteremia while on antibiotics, or tunnel infection
- Guidewire exchange is possible if fever resolves on antibiotic therapy
- Catheter biofilm is a major source of catheter-related bacteremia
- Antibiotic lock may kill bacteria in the biofilm but variable success depends on organism: 90% with gram negative, 80% with coagulase negative staphylococcus, 45% in S. Aureus infections

A procedure-related complication is an unanticipated adverse event that requires therapy. In order to analyze frequency and severity of complications in the process of quality assurance, it is useful to have a classification of complications, indicating the type and severity. The Clinical Practice Committee of American Society of Diagnostic and Interventional Nephrology has developed a Classification of Complications relating to Hemodialysis Vascular Access Procedures, based on the system first proposed by Beathard in 2006 (Vesely et al. 2007). In this system, the "type" refers to the procedure being performed or vessel entered, and the "grade" is based on the intensity of medical care needed to address the complication. This publication describes 10 Types and 4 Grades of complications. Development of a quality assurance system in each center is essential to minimize complications and to optimize dialysis access use.

## 18.8 MACHINE COMPARISONS

This section will briefly discuss machine comparisons among currently available CRRT machines.

### 18.8.1 Characteristics of the Ideal CRRT Device

The main characteristics of the ideal CRRT device include:

- Inexpensive cost
- User friendly
- Flexible to adapt for multiple renal replacement modalities
- Accurate measures
- Safe
- Available thermoregulation
- Exchangeable components
- Biocompatible

Newer CRRT machines have incorporated multiple newer characteristics:

- Integrated blood modules
- Fluid balance controls with gravimetric or volumetric measurement devices

- Capacity for intermittent and continuous therapy applications
- Ability to increase blood flow up to 500 ml/min
- Increased dialysate and replacement fluid flow rates
- Highly permeable membranes
- Highly surface area dialyzers
- Simplified priming procedures
- Friendly user interface
- Data extraction capabilities and possibility of downloading data to centralized servers
- Automating data printing

Currently available CRRT machines include:

- Gambro Prisma
- Gambro Prismaflex
- Braun Diapact
- Baxter Aquarius
- NxStage
- Fresenius 2008 K

Table 18.9 incorporates a side-by-side comparison among the different available CRRT machines.

**Table 18.8** The main comparisons among different available CRRT machines

| Manufacturer | Baxter | Gambro | BBraun | Gambro | Fresenius | Fresenius | Infomed |
|---|---|---|---|---|---|---|---|
| Model | Aquarius | Prisma | Diapact | Prismaflex | Multifiltrate | 2008H, 2008K | HF 400 |
| Weight | | | | 75 kg | 80 kg | | |
| Dimensions (cm) | | H 145, W 41, D 30 | | H 162, W 49, D 30 | H 150 , W 46, D 60 | | H 160, W 72, D 66 |
| Battery backup | | None | Optional | 20 min | 15 min | | |
| Therapies provided | SCUF, CVVH, CVVHD, CVVHDF, TPE, IHD, IHFD | SCUF, CVVH, CVVHD, CVVHDF, TPE | SCUF, CVVH, CVVHD, | SCUF, CVVH, HVHF, CVVHD, CVVHDF, PEX | SCUF, CVVH, HVHF, CVVHD, CVVHDF, PEX | IHD, IHFD, SLED, SCUF, CVVHD | IHD, IHFD, IHF, SCUF, CVVH, CVVHD, CVVHFD, CVVHDF, PEX |
| Pumps | 4 | 4 | 3 | 5 | 4 | 1+3 | 4 |
| Display | Color, touchscreen | Monochrome, touchscreen | Monochrome | Color, touchscreen | Color, touchscreen | Color | Color, touchscreen |

**Table 18.8** (Continued)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Heater | Yes | Blood warmer | Yes | Yes, in-line | Yes, in-line | Yes | Yes |
| Heparin Pump | Yes | Yes | No | Yes | Yes | Yes | Yes |
| Reinfusion sites | Pre, Post, Pre-Post | Pre | Pre, Post | Pre, Post, Pre-Post | Pre, Post, Pre-Post | NA | Pre, Post, Pre-Post |
| Pressure sensors | 4 | 4 | 4 | 5 | 4 | 3 | 4 |
| Scales | 2 | 3 | 1 | 4 | 4 | Volumetric | 2 |
| RS-232 | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| USB | No | No | No | No | No | No | No |
| Printer | No | No | No | No | No | No | No |
| Qb | 0-450 | 0-180 | 10-500 | 0-450 | 0-500 | 0-500 | 0-450 |
| Qd | 0-165 | 0-40 | 0-400 | 0-133 | 0-70 | 0-300 | 0-200 |
| Replacement | | | 0-250 | 0-133 | 10-160 | NA | |
| Effluent | | | 0-300 | 0-33 | 0-100 | | |
| UF rate | | | 0-2000 g/h | 0-2000 ml/h | 0-100 | | |
| Sensor Accuracy | | | | | | | |

**Table 18.8** (Continued)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Access | | | -400 to +300 | -280 to +300 | | | |
| Return | | | 0 to +380 | -80 to +500 | | | |
| Pre-filter | | | 0 to +650 | 0 to +750 | | | |
| Filtrate | | | NA | NA | | | |
| Scale Range | 10L | | 25 L | 15L | 24L | NA | 12L |
| Air Detector | Yes | | Yes | Yes | Yes | Yes | Yes |
| Blood leak detector | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Remarks | | | | | | 3 pumps for dialysate & fluid replacement are positioned inside the hydraulic circuit of the monitor | |

Figures 18.4-18.13 describe the main characteristics, similarities and differences among the commonly used CRRT machines.

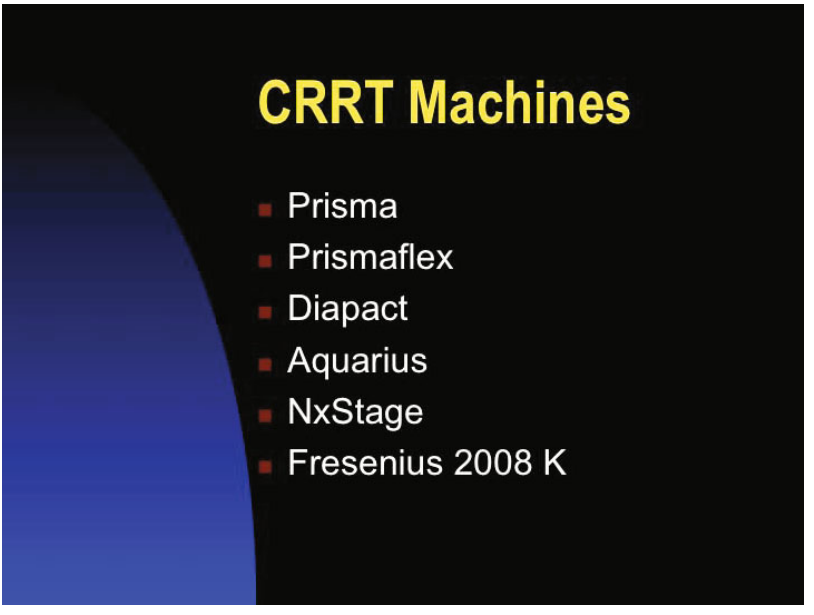



**Fig. 18.4**

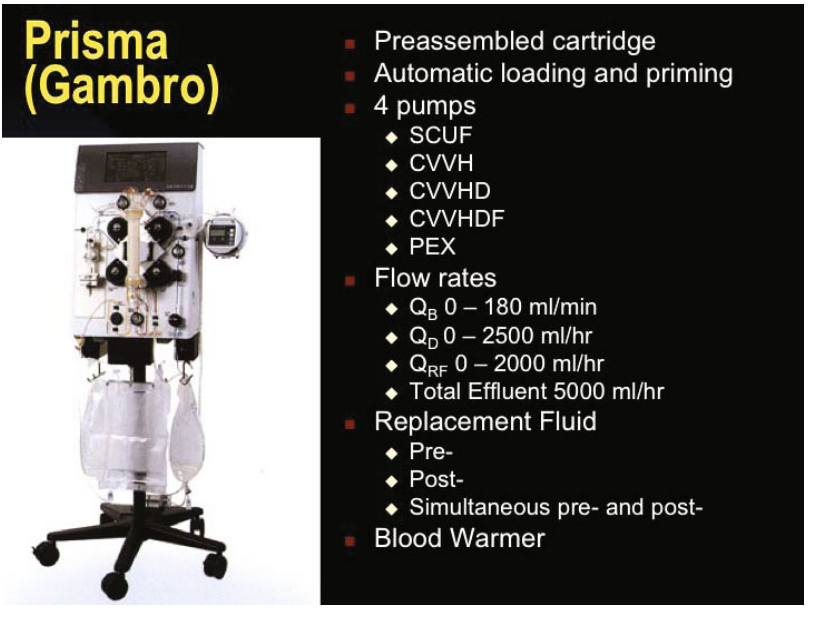
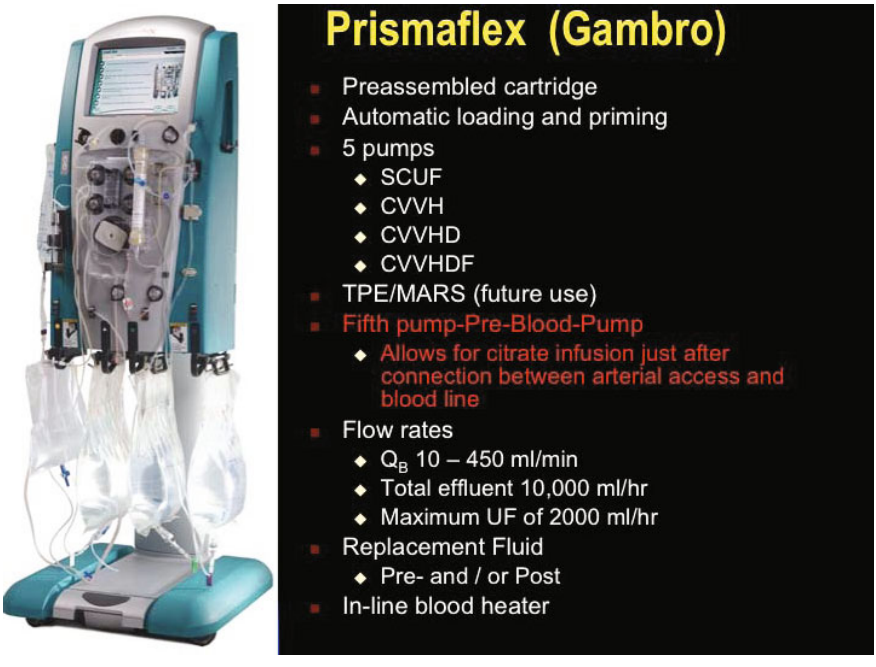



**Fig. 18.5**

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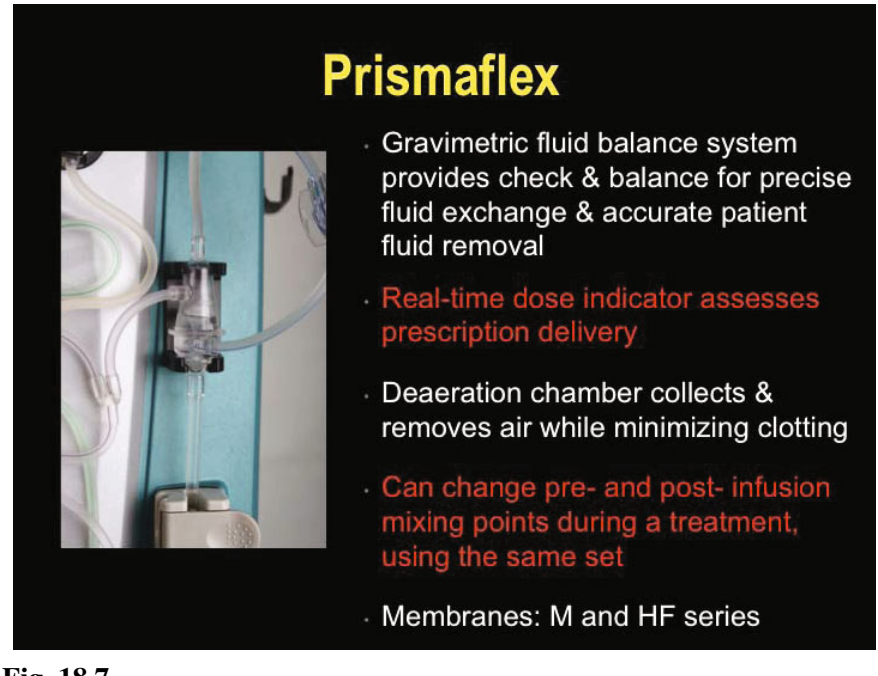


**Fig. 18.7**

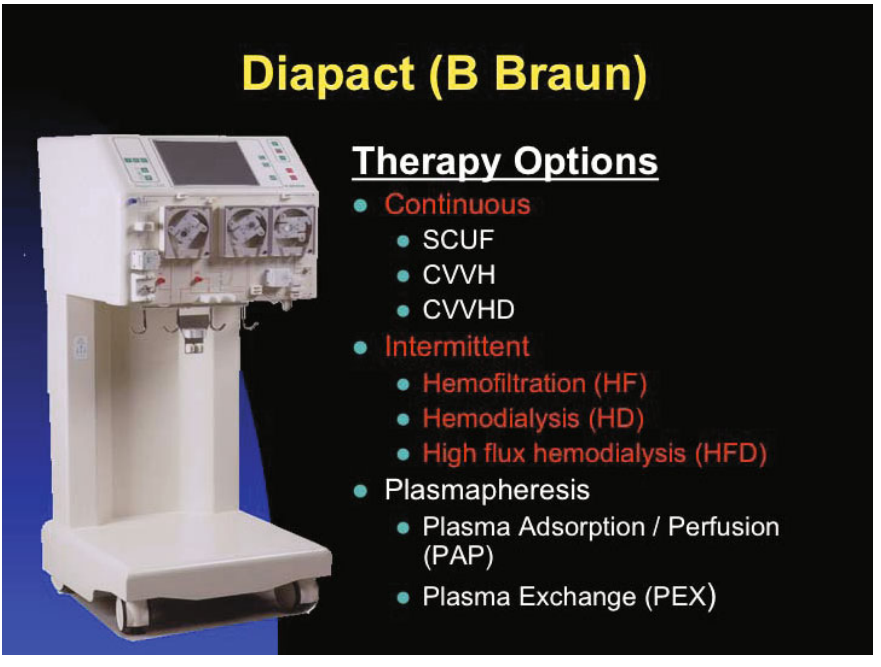


**Fig. 18.8**

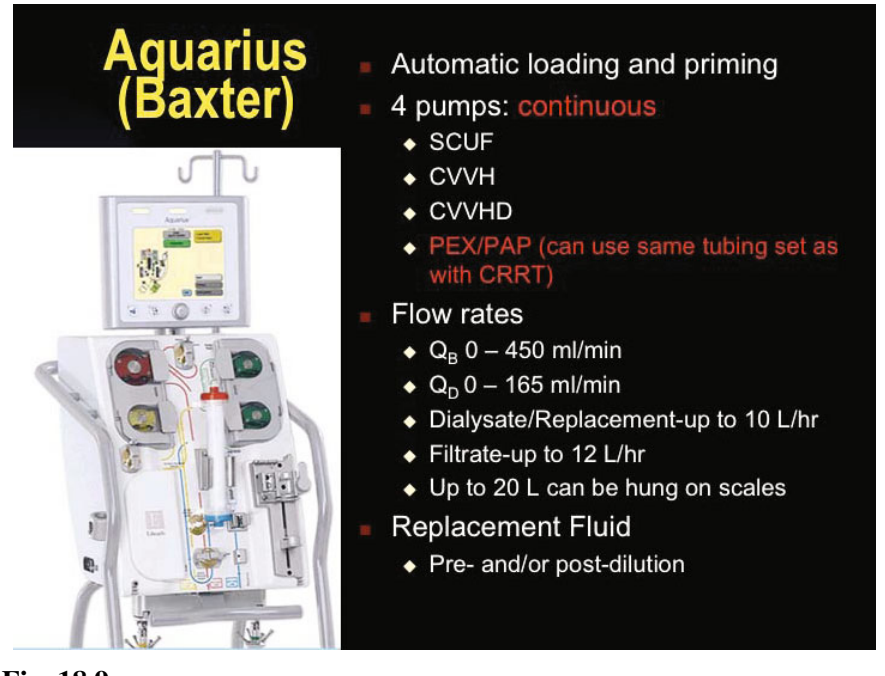


**Fig. 18.9**

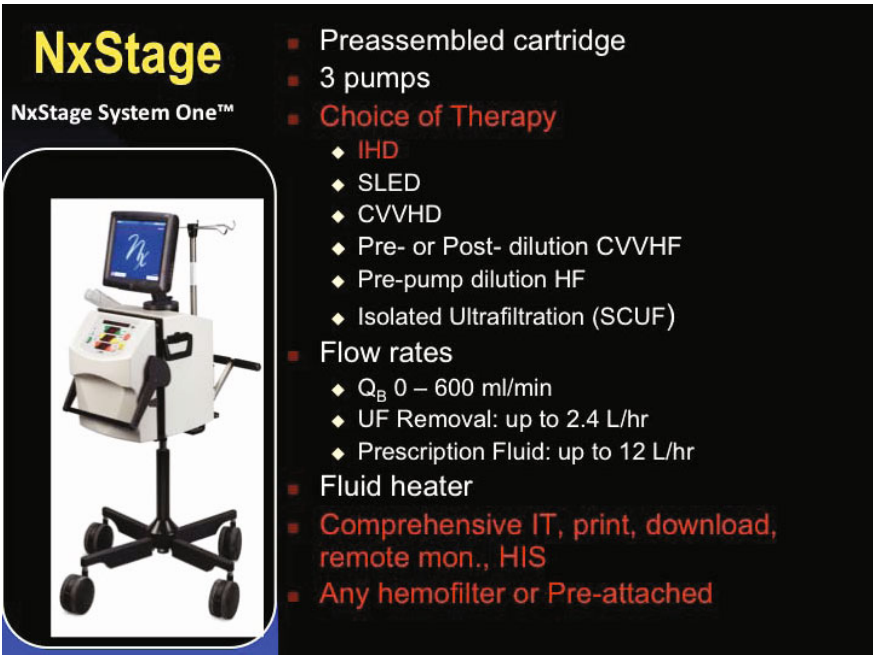


**Fig. 18.10**

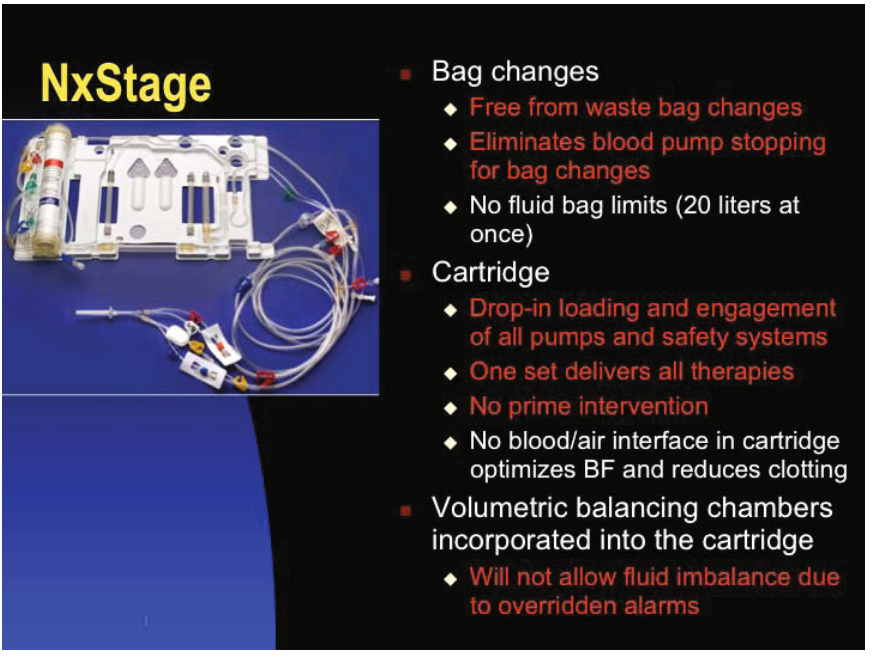


**Fig. 18.11**

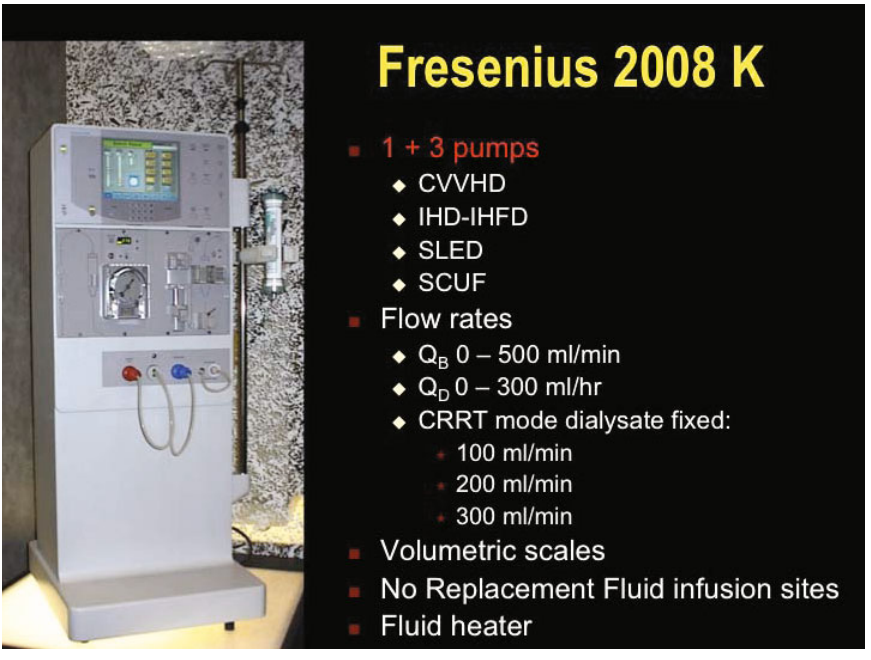


**Fig. 18.12**

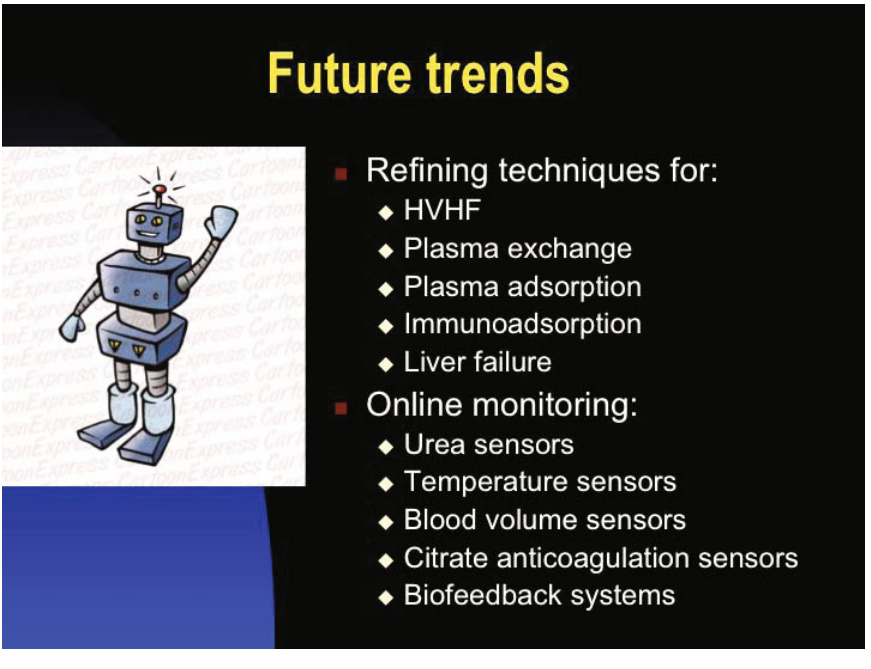


**Fig. 18.13**

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## ESSAY QUESTIONS

1. Comprehensively describe the concepts of diffusion and dialysis and their application to the different CRRT modalities
2. Describe the operational characteristics of the different CRRT modalities, including CVVH, CVVHD and CVVHDF, and their implications in terms of diffusive and convective clearance and the optimization of dialysis dose
3. List the pros and cons of the following anticoagulation modalities: a. Heparin; b. Citrate; c. Prostacycline
4. Describe the ideal vascular access for dialysis, including catheter characteristics depending on site of insertion, tunneled vs. non-tunneled, and the advantages of ultrasound -guided catheter insertion
5. List the reasons why intermittent hemodialysis is associated with greater risk of hemodynamic instability than CRRT modalities
6. Compare the operational characteristics of the currently available CRRT machines
7. Discuss the effects of different sodium concentration in the dialysis and replacement fluid in terms of loss or gain of fluid during CRRT
8. List the pros and cons of the use of lactate, acetate or bicarbonate buffers in the dialysis and replacement fluid
9. Discuss the implications of convective versus dialytic technologies in terms of risk of brain edema
10. Discuss the possible uses of CRRT in patients with severe sepsis

## MULTIPLE CHOICE QUESTIONS

### Choose the best answer

1. As the expert initiating a new CRRT program at your institution, you need thorough understanding of the evidence supporting the use of these new techniques. *That is why you are here!*

Please indicate which ONE of these statements is true:

A. Recent randomized controlled trials demonstrate that early initiation of renal replacement therapy is associated with improved patient outcomes.
B. The recent ATN trial (VA/NIH Acute Renal Failure Trial Network, Dr. Palevsky et al) was a "modality" study, which demonstrated that there is no difference in survival between CRRT and IHD
C. Recent studies (the ATN and the RENAL trials) have shown that either "high" or "low", the dose of dialysis is unimportant and is not a determinant of patient survival.
D. Retrospective trials have shown that intermittent Hemodialysis is associated with fluid gains and increased hemodynamic instability, when compared with CRRT
E. Recent randomized controlled trials have conclusively demonstrated that renal functional recovery is superior among patients treated with CRRT, as compared with IHD.

2. As a model for the prescription and management of CRRT in a critically ill patient, it is preferable that:

A. Orders and follow up of the procedure be managed by the ***intensivist***, who is in the unit all the time and is the overall manager of patient treatment.
B. Orders and follow up decisions be managed by the ***nephrologist*** exclusively, as he is best trained to do so and "knows best" about extracorporeal treatments.
C. Decisions can be made by "the team", depending on the circumstances: ***all the practitioners involved in care of the critically ill patient*** should be involved in the decisions on CRRT, but a leader must be clearly identified.

3. Recent surveys and single center studies have shown that, on average, the delivered dose (based on various forms of urea clearance) of renal replacement therapy (IHD, CRRT or SLED):

A. Is measured in the majority (more than 75%) of the surveyed institutions
B. Is consistently about 85% to 90% of the prescribed dose
C. Is close to 25-30 ml/kg/hour

4. All of these factors can affect the delivery of an adequate dose of CVVHDF, **EXCEPT**:

A. Inability to raise the dialysis fluid flow above 800 ml/min
B. Catheter dysfunction limiting blood flow to below 100 ml/min
C. Catheter dysfunction inducing a recirculation greater than 20%
D. Femoral catheter shorter than 20 cm

5. The following are potential complications resulting from the use of heparin anticoagulation **EXCEPT**:

A. Bleeding
B. Hemolysis
C. Ineffective anticoagulation due to deficiency of antithrombin III
D. Induction of heparin induced antiplatelet antibodies

6. Which of the following is indicative of adequate anticoagulation of citrate for CRRT?

A. CRRT circuit ionized calcium level of 0.25 mmol/L
B. Systemic ionized calcium level of 0.7 mmol/L
C. Serum citrate level of 1 mmol/L
D. Total calcium level of 2.2 mmol/L

7. Risks associated with Heparin anticoagulation include:

A. Hypocalcemia
B. Thrombocytopenia
C. Hypolipidemia
D. Hypotension

8. A patient is on CRRT with the following parameters:
Modality: CVVHDF
Post dilution Replacement Fluid: 1500 ml/hr
Dialysate: 2000 ml/hr
Blood flow: 150 ml/min
Fluid Removal: 200 ml/hr

What is the total effluent rate in ml/hr?

A. 1500 ml/hr
B. 3500 ml/hr
C. 3700 ml/hr
D. 3850 ml/hr

9. Select the statement that is most appropriate regarding input and output (I&O) calculations in patients receiving CRRT

A. All I&O calculations are performed by the CRRT machine
B. The nurse must always manually calculate dialysate and replacement fluid use
C. I&O is not necessary for these patients
D. The nurse must be aware of which calculations are performed by the CRRT equipment

10. A patient is about to be started on CRRT. The total fluid input in 24 hours is 3.9 L. The total fluid output in 24 hours is 0.7 L. You want the patient to be 1 liter negative on CRRT by the next 24 hours. What should you prescribe as your fluid removal rate, assuming that the patient's 24 hour input and output will remain unchanged?

A. 75 ml/hr
B. 100 ml/hr
C. 175 ml/hr
D. 200 ml/hr

11. A mechanically ventilated patient with fulminant hepatic failure and acute kidney injury is started on CVVH for severe metabolic acidosis. His pH is 7.3, bicarbonate 10 mmol/L, and lactate 4.5 mmol/L. Which buffer is the best choice for the CVVH replacement fluid?

A. Acetate
B. Lactate
C. Bicarbonate
D. Citrate

12. A patient has severe Acute Respiratory Distress Syndrome (ARDS) and oliguric acute kidney injury. He is on a sodium bicarbonate infusion. You are starting CVVHD with citrate anticoagulation. Patient's pH is 7.1, pCO2 70 mmHg, serum sodium 132 mmol/L, serum bicarbonate 15 mmol/L, and serum potassium 4.9 mmol/L. Which of the following options is the best choice for dialysate? (All electrolyte options are in mmol/L)

A. PrismaSate BK 0/3.5 (Na 140, Cl 109.5, K 0, Mg 0.5, Ca 3.5, Lactate 3.0, HCO3 32)
B. Accusol 35 5B9251 (Na 140, Cl 116.3, K 2.0, Mg 0.75, Ca 2.8, Lactate 0, HCO3 30)
C. Baxter Hemodiafiltration dialysate (Na 140, Cl 117, K 2.0, Mg 0.75, Ca 3.5, Lactate 30)
D. PrismaSate BGK 4/0/1.2 (Na 140, Cl 110.2, K 4.0, Mg 0.6, Ca 0, Lactate 3.0, HCO3 32)

13. An anuric 98 kg patient is on continuous dialysis with $Q_b$ 150, $Q_d$ 2300 ml/hour and $Q_{uf}$ 100 ml/hour. The patients small solute clearance is most nearly:
A. 145 ml/kg/hr
B. 40 ml/kg/hr
C. 30 ml/kg/hr
D. 25 ml/kg/hr

14. A 45 year old man with hepatitis C cirrhosis and hepatorenal syndrome is placed on Continuous Renal Replacement Therapy (CRRT) with no anticoagulation as a bridge to liver transplantation. He remains on CRRT for 7 days and his acid-base status is within normal limits prior to transplantation. He develops severe metabolic alkalosis immediately after liver transplantation. He is continued on CRRT intra- and post-operatively for persistent renal failure. The CRRT prescription has not changed from the pre-operative period.

Which ONE of the following is most likely to be responsible for the acid-base disturbance?
A. Transfusion of blood products
B. Increased ureagenesis by the transplanted liver
C. Increased urinary ammonium excretion
D. High bicarbonate CRRT solutions
E. Potassium depletion

15. Continuous renal replacement therapy is performed over a:
A. 3-4 hour period
B. 24 hour period
C. 6-8 hour period
D. 8-12 hour period

16. Continuous renal replacement therapy requires:
    A. A veno-venous central double lumen hemodialysis catheter
    B. An extracorporeal circuit and hemofilter
    C. A blood pump and effluent pump (dialysate and replacement pump, depending on therapy chosen)
    D. All of the above

17. Which therapy option does not require water hookup and hemodialysis nursing support?
    A. Continuous renal replacement therapy
    B. Sustained low efficiency dialysis
    C. Intermittent hemodialysis
    D. Intermittent hemofiltration

18. The movement of fluid through a semi-permeable membrane driven by a pressure gradient is called.
    A. Diffusion
    B. Convection
    C. Ultrafiltration
    D. Adsorption

19. The movement of solute from a higher concentration to a lower concentration is called:
    A. Convection
    B. Diffusion
    C. Ultrafiltration
    D. Adsorption

20. A 65 year-old man undergoes cardiac surgery with mitral valve replacement. His baseline serum creatinine is 2.7 mg/dl. Postoperatively he returns to the intensive care unit intubated and anuric on furosemide 20 mg/hr. His BP is 95/50 mmHg on vasopressin, dopamine, and norepinephrine infusions. He is mechanically ventilated and has an oxygen saturation of 90% on a fractional inspired oxygen of 0.8 with 15 cmH20 positive end-expiratory pressure. Central venous pressure (CVP) is 35 mmHg, and venous oxygen saturation is 50%. His weight has increased 12 kg from preoperatively, and the sternal wound has not been closed because of massive edema. His chest x-ray demonstrates bilateral pulmonary edema. His serum creatinine is 3.0 mg/dl. Other laboratory tests include sodium of 135 mEq/L, potassium of 5.1 mEq/L, chloride of 100 mEq/L. total CO2 of 12 mEq/L. blood urea nitrogen of 90 mg/dl and glucose of 80 mg/dl. The surgical team plans to transfuse 6 U of fresh-frozen plasma in preparation for

return to the operating room for sternal closure. You are asked to initiate emergent renal replacement therapy (RRT).

Which ONE of the following interventions is MOST appropriate in this setting?

A. Give intravenous boluses of 200 mg of furosemide with 500 mg of chlorothiazidc, and increase furosemide infusion to 40 mg/h.
B. Start a nesiritide infusion.
C. Initiate slow continuous ultrafiltration.
D. Initiate continuous venovenous hemofiltration (CVVH)

Chapter (19)

# Techniques and Kinetics of Hemodiafiltration

Luciano A. Pedrini - MD

**CHAPTER OUTLINES**

- Historical Notes
- Membranes for hemodiafiltration
- Water and solute transport in on-line HDF
- HDF Techniques and infusion modalities
- Kinetic modeling in hemodialysis and hemodiafiltration
- Biological Effects of HDF
- Clinical effects of HDF
- Effect of HDF on outcome
- Conclusion

**CHAPTER OBJECTIVES**

- To review present knowledge of materials, devices and technique of hemodiafiltration.
- To describe the most common mathematical models to simulate the solute kinetics during hemodiafiltration and to evaluate the efficiency of the treatment
- To review present evidence in favor of hemodiafiltration

**KEY TERMS**

- Hemodiafiltration
- Kinetic Models
- Mass transport
- High-flux membranes
- Diffusion
- Convection
- Adsoprption
- Dialyzer performance
- Ultrafiltration
- Patient outcome


## ABSTRACT

Medium–long-term application of on-line high-efficiency HDF compared to low- and high-flux HD results in enhanced removal and lower basal levels of small, medium and protein-bound uremic solutes, some of which are retained as markers or causative agents of several uremic derangements, mainly inflammation, secondary hyperparathyroidism, dyslipidemia and cardiovascular disease. Probably, many of the benefits attributed to HDF potentially result from a general reduction of the uremic toxicity. This might be the link with the clinical benefits reported in patients undergoing chronic


A.T. Azar (Ed.): Modeling and Control of Dialysis Systems, SCI 405, pp. 1011–1078.
springerlink.com 

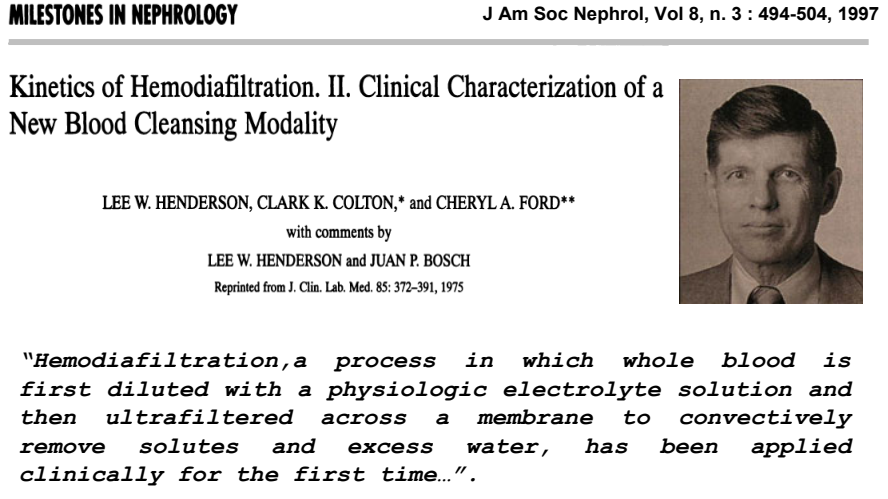
HDF which eventually contribute to improving patients survival, as suggested by published observational studies. However, In the absence of large randomized, prospective studies, it is reasonable to conclude that online HDF is a logical and safe therapy effective in maintaining the life and well-being of dialysis patients. Knowledge of the performance of materials, apparatus and devices used in HDF, and study of the solute transport mechanisms with the aid of modelling simulation will help to optimize this technique and obtain additional clinical benefits.

## 19.1 HISTORICAL NOTES

After the pioneering experiments conducted in dogs in 1947 (Malinow and Korzon 1947), a new blood-cleansing modality based on convection as a mechanism of uremic toxins removal was first applied in patients with end stage renal failure (ESRD) at the University of Pennsylvania and its rationale was published in 1967 by Henderson and colleagues (Henderson et al. 1967). The concept was inspired by the observation that ultrafiltration (UF) across the peritoneal membrane results in convective transport of urea and other small solutes (Henderson 1966), and the new technique was called ‘diafiltration’ to recognize the role of both diffusion and convection as transport mechanism. Parallel investigation on convective transport was also carried out in 1968 (Dorson and Markovitz 1968), and in 1972 (Quellhorst et al. 1972), but the original term 'hemodiafiltration' (HDF) was used by H.W. Leber from Germany, who was the first investigator to propose HDF as a new alternative treatment for ESRD (Leber et al. 1978).

Preliminary human studies on the new technique were started with great caution in the USA, hindered by regulatory requirements and the concern that some medium molecular weight compounds, critical for life, would be lost in the ultrafiltrate. As no adverse events were encountered, larger human application led the authors to deepen the focal points of their technique and to formulate the principles and the fundamental mathematical relationships for HDF (Colton et al. 1975; Henderson et al. 1975) (see Fig. 19.1). At the same time, HDF was applied clinically in Europe and the promising results of a series of studies in patients over a long time period were reported in 1983 by Quellhorst (Quellhorst 1983). From that time, continuous evolution of HDF took place until the more recent modalities of its application. Fundamental steps of this evolution were: 1) the introduction of bicarbonate-based dialysis fluid and replacement solution in substitution of the original fluids containing acetate or lactate, cause of relevant side-effects to the patients; 2) the application to dialysis machines

of UF control systems, primarily based on devices measuring differential flow between the outlet and inlet dialysate flow, which control body weight (BW) loss, balance UF and fluid replacement rates and adjust the trans-membrane pressure (TMP) in the filter; 3) on-line production of indefinite amount of ultrapure dialysate/infusion fluid al low cost, which avoided the cumbersome and expensive use of replacement fluids in sterile bags; 4) the availability of synthetic highly biocompatible and permeable membranes with selective cut-off, extended to small molecular weight proteins and beyond, and 5) the impressing technological development of dialysis machines, now specifically oriented towards convective techniques and equipped with advanced software devices, which are able to prescribe and monitor the achievement of the adequate dose of therapy with the use of conductivity apparatus, to enhance treatment efficiency by optimizing convective solute removal with ultrafiltration/trans-membrane pressure feed-back devices, to ensure better intradialytic stability also in critical patients with the use of software-guided profiles for UF, plasma sodium concentration and body temperature and to improve the safety of the sessions, automatically managed by the machine and easily controlled through a friendly user interface.


MILESTONES IN NEPHROLOGY J Am Soc Nephrol, Vol 8, n. 3 : 494-504, 1997

Kinetics of Hemodiafiltration. II. Clinical Characterization of a New Blood Cleansing Modality

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*"Hemodiafiltration,a process in which whole blood is first diluted with a physiologic electrolyte solution and then ultrafiltered across a membrane to convectively remove solutes and excess water, has been applied clinically for the first time…".*

**Fig. 19.1** Lee W. Henderson and his landmark publication in 1975, in which the principles and the fundamental mathematical relationships for HDF were formulated. The event was celebrated with a reprint of the article in the Journal of the American Society of Nephrology in 1997.

Nowadays, on-line HDF with high-flux membranes, combining diffusion and maximal convection, is the extracorporeal renal replacement technique which may ensure maximal solute removal in a wide spectrum of molecular weights.

## 19.2 MEMBRANES FOR HEMODIAFILTRATION

Cellulosic membranes have been used for many years on hemodialysis (HD). These symmetrical hydrophilic membranes granted efficient removal of small solutes by diffusion due to their thin-walled structure, usually in the range of 6-15 μm, and their porosity, more related to the high number of pores than to their size. However, the small diameter of pores limited their hydraulic permeability and achievement of high water fluxes, and the chemical structure of these membranes, including hydroxyl groups, was responsible for frequent incompatibility reactions (Clark et al. 1999a). This led to later chemical modifications of these membranes with reduction of their hydrophilic properties which resulted in substantial improvement of their biocompatibility and permeability to water fluxes. At the same time, synthetic highly biocompatible and permeable membranes took place, largely related to the interest in hemofiltration in the late 1970s. The first synthetic membranes (Amicon), made from precipitated polyelectrolyte and asymmetrical in structure, had a thin 1-2-μm skin supported by a thick spongy stroma which permitted very high UF and convective middle molecule (MM) removal but presented a significant barrier to diffusion due to their thickness (200 μm) (Colton and Lysaght 1966). Polyacrylonitrile (AN69®, Hospal) was also employed at that time (Funck-Brentano et al. 1972). This synthetic highly permeable membrane, symmetric in structure, coupled remarkable diffusion and convection properties and, in addition, favored the adsorptive process thanks to the net negative charge carried on its surface (Leypoldt et al. 1986).

Since that time, a number of other synthetic membranes have been deve1oped, mainly asymmetric, inc1uding polysulfone (Streicher and Schneider 1985), polyamide (Gohl et al. 1992), polymethylmethacrylate (Bonomini et al. 2004), polyethersulfone (Jaber et al. 1998) and polyarylethersulfone/polyamide (Ronco et al. 2003). These membranes were hydrophobic and had a very thin skin layer (approx. 1 μm) contacting the blood compartment lumen and surrounded by a microporous structure with a total thickness of 75-100 μm. Their large mean pore size and thick wall structure allowed the high ultrafiltration rates necessary in hemofiltration (HF) to be achieved at relative1y low TMP, but the marked thickness of the hollow fiber wall limited small solutes transfer by diffusion. This was

one of the reasons why, in the mid-1980s, the interest in HF fell as a chronic replacement therapy and highly permeable membranes started to be used in the diffusive mode as high-flux dialyzers. For this purpose, a new generation of synthetic polymers was produced with a combined hydrophilic-hydrophobic structure and a reduced wall thickness (30-35 μm). These membranes, constituted of the same polymers mixed in various proportions with hydrophilic compounds such as polyvinylpyrrolidone, realized an optimization of the combination of diffusion and convection and maximized the bidirectional water flux across the membrane (see Table 19.1).

**Table 19.1** High-flux membranes. Performance of some dialyzers for HDF

| Membrane | Dialyzer | Area, $m^2$ | $K_{UF}D$ ml/h/mmHg | Sieving Coeff. | | Clearance, ml/min | | |
|---|---|---|---|---|---|---|---|---|
| | | | | β2-m | albumin | urea | creatinine | P |
| polyamide | Polyflux S | 1.7 | 71 | 0.63 | < 0.01 | 254 | 229 | 223 |
| | Polyflux S | 2.1 | 83 | 0.63 | < 0.01 | 267 | 245 | 240 |
| purema | PF-170H | 1.7 | 74 | 0.8 | < 0.01 | 274 | 259 | 240 |
| | PF-210H | | 80 | 0.8 | < 0.01 | 285 | 272 | 253 |
| rexbrane | Rexeed 18A | 1.8 | 71 | 0.85 | 0.002 | 280 | 265 | 250 |
| | Rexeed 21A | 2.1 | 74 | 0.85 | 0.002 | 284 | 272 | 257 |
| helixone | FX80 | 1.8 | 59 | 0.8 | < 0.01 | 276 | 250 | 239 |
| | FX100 | 2.2 | 73 | 0.8 | < 0.01 | 278 | 261 | 248 |
| polyethersulfone | MD 190H | 1.9 | 90 | 0.8 | 0.005 | 276 | 264 | 257 |

Data from manufacturer's specification sheets. $K_{UF}D$, ultrafiltration coefficient, measured with bovine blood. $K_D$, whole-blood clearance, measured at $Q_B$ = 300 ml/min, $Q_D$ = 500 ml/min $Q_{UF}$ = 0.

More recently, Helixone, a new polysulfone based membrane assembled with sophisticated spinning nanotechnology procedures (Ronco and Bowry 2001) (see Fig. 19.2), was shown to promote greater MM removal by convection favored by a more regular and larger size of its pores (33 nm), while preventing significant albumin loss due to an extremely narrow distribution of the pore-size (Bowry and Ronco 2001) and minimal number of large pores. Moreover, the ability of this membrane to remove phosphate (P) was enhanced by modifying the composition and distribution of the polymer of the support region, critical for P transport, and improving the affinity between the low molecular weight (MW) compounds and the polymer matrix (Ronco et al. 2006).

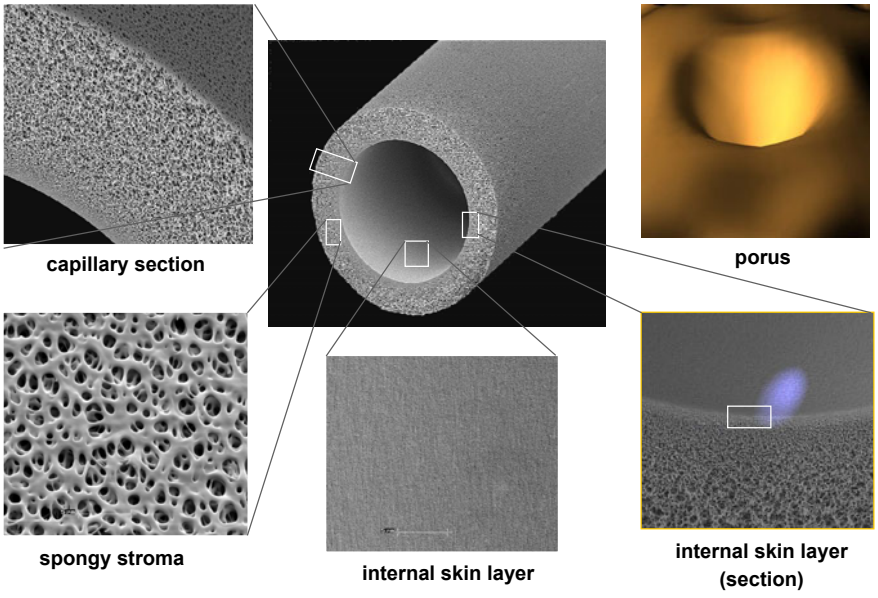



**Fig. 19.2** Polysulfone (Helixone) hollow fiber Fresenius. Different magnification (x 250, 800, 3000). Nano-controlled structure of the internal skin layer.

An alternative new class of dialysis membranes known as super-flux (SF) or protein-leaking membranes has been developed for HD in the last years (Ward 2005). These membranes have a larger pore size and hence provide greater clearances of low MW proteins and small protein-bound solutes than do conventional high-flux membranes by coupling diffusion with increased convection with the mechanism of back-filtration and internal filtration (DeSmet et al. 2007; Pellicano et al. 2008). Combined use of SF membranes and chemotherapy in patients with myeloma kidney and dialysis-dependent acute renal failure has been shown to reduce serum free light chain concentration and favour renal recovery (Hutchison et al. 2009). It is yet unproven whether SF membranes offer benefits beyond those obtained with high-flux membranes used in HDF or HF, and whether the considerable amount of albumin lost in the dialysate through their large pores can be tolerated by chronic patients in the long-term (Ward 2005).

## 19.3 WATER AND SOLUTE TRANSPORT IN ON-LINE HDF

### 19.3.1 Water Transport: Ultrafiltration (UF)

Plasma water ultrafiltration occurs as a consequence of a pressure gradient established across the dialyzer membrane. At every point of the

capillary length the driving force for water filtration is the resultant of the hydraulic pressure inside the fiber ($P_B$) and in the dialysate ($P_D$) and the oncotic pressure exerted by plasma proteins ($\pi$). An equation (Henderson 1989; Hoenich 2007) that relates the volumetric water flux ($J_f$) to the transmembrane pressure difference is:

$$\frac{J_f}{A} = L_P\left(\Delta P - \Delta\pi\right) \tag{19.1}$$

where $L_p$ is the hydraulic permeability of the membrane for water, i.e. the water flow rate per unit area of membrane (A) per unit pressure gradient (ml/min/cm$^2$/mmHg).

The average pressure gradient across a dialyzer membrane TMP is expressed with the Eq. (19.2):

$$TMP = \frac{\left(P_{Bin} + P_{Bout}\right)}{2} - \frac{\left(P_{Din} + P_{Dou}t\right)}{2} - \frac{\left(\pi_{in} + \pi_{out}\right)}{2} \tag{19.2}$$

where the suffix *in* and *out* indicate the inlet and outlet ports of the two dialyzer compartments.

In clinical practice, the ability of a dialyzer membrane to ultrafiltrate plasma water is defined with the ultrafiltration coefficient of the dialyzer ($K_{UF}D$, ml/hour/mmHg of TMP). The term $K_{UF}D$ expresses the hydraulic permeability of the overall membrane surface of the dialyzer and defines its class in terms of flux. A nominal $K_{UF}D > 40$ ml/hour/mmHg is a requisite for high-flux dialyzers.

$K_{UF}D$ is calculated in vitro by applying increasing TMP values in a defined experimental setting: the resulting ultrafiltration rate ($Q_{UF}$) is related linearly to the TMP up to a certain value (200-300 mmHg for high-flux membranes), and $K_{UF}D$ corresponds to the slope of the regression equation (Henderson 1989). Its value largely depends on the surface and characteristics of the membrane (mainly the pore radius), and on the dialyzer geometry. Lower than nominal $K_{UF}D$ values are found in vivo as a consequence of the protein layer formation on the inner face of the membrane (secondary membrane). Loss in hydraulic permeability is negligible and quite constant along low-flux HD sessions (Bosch et al. 1985) conducted at moderate $Q_{UF}$. Progressive and even substantial reduction in $K_{UF}D$ may be observed along HDF and HF sessions when higher $Q_{UF}$ and filtration fraction (FF) are usually applied, as an effect of the solute and protein polarization on the inner membrane surface and thickening of the secondary membrane (Rockel et al. 1986; Vilker et al. 1981). In addition, the colloid osmotic pressure exerted by the concentrated plasma proteins counteracts

the filtration pressure (Vilker et al. 1984). As a consequence, the relationship between TMP and $Q_{UF}$ becomes curvilinear and progressively increasing TMP is necessary to maintain the programmed filtration, until a plateau is reached, beyond which further increments in TMP are no more effective (Henderson 1989). The level of the plateau is mainly a function of the blood flow rate ($Q_B$) permeating the capillaries of the dialyzer. Therefore, high $Q_B$ is preferential for successful application of all convective therapies.

### 19.3.2 Solute Transport

Solute transport across the dialyzer membrane can occur in HDF via diffusion, convection and adsorption.

#### 19.3.2.1 Diffusion

Diffusion is the solute transport which occurs according to a first-order kinetics in the presence of a concentration gradient between blood and dialysis fluid. It is governed by Fick's law, expressed mathematically with Eq. (19.3):

$$\frac{J_D}{A} = -K_o \frac{dC}{dx} \tag{19.3}$$

where $J_D$ is the rate of solute diffusive flux per unit area (A), proportional to the concentration gradient (dC/dx), and $K_o$ is the solute diffusion coefficient (or, overall mass transfer coefficient) which characterizes the overall resistance to the solute flux across the membrane and is determined primarily by the property of the membrane and the solute.

Removal by diffusion is mainly influenced by $Q_B$ and dialysate flow ($Q_D$) and by the dialyzer surface, and the relative role of each factor depends on $K_o$. At constant $Q_{UF}$, increasing dialyzer surface results in moderate enhancement of the diffusion transport according to a curve that achieves its plateau faster for the small molecular solutes. The level of the plateau is a function of the diffusive permeability of the membrane. An increase in $Q_B$ up to 500-600 ml/min progressively increases diffusive removal of small solutes, while middle-high molecular weight solutes removal is scarcely affected by $Q_B$ values beyond 200-250 ml/min (Wizemann et al. 2001). An increase in $Q_D$ from 500 to 800 ml/min results in moderate enhancement of small solute removal by diffusion but not of the larger solutes (Hauk et al. 2000).

### 19.3.2.2 Convection

Solute transport by convection results from bulk movement of the solvent through the membrane in response to a hydrostatic pressure gradient. All solutes that are sieved by the membrane are carried along by the filtered fluid. In contrast to diffusive transport, convective transport is constant over a wide range of molecular weight solutes but decreases as the hydrated molecular size approaches that of the pores. The sieving property of a membrane determines what is removed, and its ability to remove a solute from plasma by convection is defined with an index, the sieving coefficient ($S_C$, dimensionless) for that solute. Sc, measured in vitro in a defined experimental setting and in the absence of diffusion, is the ratio between the solute concentration in the ultrafiltrate ($C_{uf}$) and its average plasma concentration within the dialyzer (Henderson 1989):

$$S_C = \frac{2C_{uf}}{\left(C_{in} + C_{out}\right)} \tag{19.4}$$

Thus, the mathematical equation that relates convective transport of a solute ($J_C$) to the rate of fluid transfer across the membrane $Q_{UF}$ and the solute plasma concentration (C) may be written as:

$$J_C = Q_{UF} \times C \times Sc \tag{19.5}$$

$S_C$ is a function of the membrane characteristics (electro-chemical properties and structure, pore radius and conformation) (Floege et al. 1989; Kim 1994; Morti and Zydney 1998; Ronco et al. 1997). Its value is inversely related to the solute molecular weight and varies between 0 for a freely permeable molecule and 1 for a completely impermeable molecule. The in vivo $S_C$ value (apparent sieving) for middle-molecular solutes such as beta2-microglobulin (β2-m) changes in accordance with the operating conditions similarly to $K_{UF}D$ and may approach zero in post-dilution hemofiltration (HF) at very high $Q_{UF}$ (David and Cambi 1992) as a consequence of the same events that affect the hydraulic permeability of the membrane. In general, the degree to which convection increases total solute removal is proportional to $Q_{UF}$ and to the molecular weight of the solute (Lornoy et al. 1998). The pore diameter, structure, and chemical properties of the membrane also play an important role (Floege et al. 1989; Kim 1994; Morti SM and Zydney 1998; Ronco et al. 1997).

### 19.3.2.3 Adsorption

Adsorption may be an additional mechanism which contributes to the overall solute removal from blood when membranes carrying electrical

charges are used. Electrochemical interaction between these membranes and certain hydrophobic compounds like peptides and proteins may cause them to adhere on the inner surface of the membrane within the pore structure (Clark et al. 1994). Therefore, the open pore structure of high-f1ux membranes affords more adsorptive potential than do low-f1ux membranes, and synthetic hydrophobic membranes are generally much more adsorptive than hydrophilic cellulosic membranes (Clark et al. 1995). Albumin coats the membrane immediately after exposure to blood, with the effect to reduce its in vivo permeability. Adsorption assumes relevance as a removal mechanism particularly in the case of some high-flux membranes, such as polyacrilonitrile and polymethyl-metacrilate (Bouman et al. 1998; Lonnemann et al. 1988) and may significantly enhance the dialyzer clearance of β2-m and of several cytokines. Adsorption capacity of cellulose triacetate and polyamide membranes is fairly small in face of the high diffusivity of the former, which extends to middle-molecular compounds (Bouman et al. 1998; Floege et al. 1989) and the combined effects of diffusion and convection of the latter (Bouman et al. 1998). Polysulfone membranes show minor absorptive capacity and remove middle molecule compounds mainly by convection (Clark et al. 1999a).

### 19.3.3 Dialyzers Performance

Mass removal capacity of a dialyzer can be quantified on the basis of the instantaneous mass balance in blood and dialysate compartments. At any time, the amount of a solute removed from blood must be found in the dialysate:

$$Q_{Bin}C_{Bin} - Q_{Bout}C_{Bout} = Q_{Dout}C_{Dout} - Q_{Din}C_{Din} \tag{19.6}$$

where $Q_{Bin}$ , $Q_{Bout}$ , $Q_{Din}$ , $Q_{Dout}$ , are whole-blood and dialysate flow rates at the inlet and outlet blood and dialysate compartments of the dialyzer, and $C_{Bin}$ $C_{Bout}$ $C_{Din}$ $C_{Dout}$ are the relative solute concentrations. If $Q_{UF}$ is the ultrafiltration rate, then:

$$Q_{Bout} = Q_{Bin} - Q_{UF} \tag{19.7a}$$

$$Q_{Dout} = Q_{Din} + Q_{UF} \tag{19.7b}$$

The dialyzer dialysance of a solute (D, ml/min) is the ratio of mass removal rate and incoming concentration driving force and determines the removal rate of a solute from blood. In all techniques, HD, HDF or HF, D

at a given time of the session can be calculated by rearrangement of equation 6 and integration with Eq. (19.7a):

$$D = Q_{Bin} \frac{(C_{Bin} - C_{Bout})}{(R_D C_{Bin} - C_{Din})} + \frac{Q_{UF} C_{Bout}}{(R_D C_{Bin} - C_{Din})} \tag{19.8}$$

Where $R_D$ (Donnan factor), the ratio between the ionic concentration in dialysate and blood must be taken into account.

The term dialyzer clearance ($K_D$, ml/min) applies to non-charged solutes not present in the dialysate and, in analogy with D, is the ratio of mass removal rate and incoming whole-blood concentration:

$$K_D = Q_{Bin} \frac{(C_{Bin} - C_{Bout})}{C_{Bin}} + \frac{Q_{UF} C_{Bout}}{C_{Bin}} \tag{19.9}$$

The concept of whole-blood clearance, assuming that the total volume of blood is cleared from the solute, overestimates the actual solute removal rate which only occurs from the aqueous part of blood. Moreover, larger solutes present in both red cells and plasma water are not freely diffusible across the cell membrane and may be retained in the intracellular space (Skalsky et al. 1978). The more appropriate approach is to consider the effective blood flow-rate ($Q_E$) of the solute under evaluation (Sargent and Gotch 1996), which can be calculated with knowledge of the hematocrit (Hct) and the fractions of plasma and red cell water ($F_P$ and $F_R$) as:

$$Q_e = Q_{Bin} \left[ F_P - \frac{Hct}{100} (F_P - F_R \gamma R_D) \right] \tag{19.10}$$

where $\gamma$ is a coefficient which expresses the resistance of a solute to transcellular transfer (being 1.0 for freely diffusible solutes and 0 for impermeable solutes). Theoretically, $K_D$ is constant during the treatment only under unchanged operating conditions of flow and membrane permeability. In vivo, minor reduction in $K_D$ may occur during HD sessions, while substantial reduction is possible during HDF, especially if very high $Q_{UF}$ are applied, due to reduction of the hydraulic and solute permeability of the membrane as a consequence of the secondary membrane forming on the surface of the membrane at a rate dependent on $Q_{UF}$ (Henderson et al. 1975).

### 19.3.4 Interactions between Diffusion and Convection

Solute removal occurs in HDF according to two simultaneous transport mechanisms, convection and diffusion, but the overall mass transport is

not the sum of the two separate components because of an interaction between them, which is more prominent at the high $Q_{UF}$ of HDF. Thus, the effects of the two transport mechanisms cannot be separated precisely, but several mathematical models have been proposed to determine their combined effect in term of solute removal. The simplest model is described by Eq. (19.11):

$$K_{HDF} = K_{diff} + Q_{UF}T \tag{19.11}$$

where $K_{diff}$ is the solute clearance in the absence of UF and T the transmittance coefficient, a parameter which is a function of the flow conditions and membrane properties.

Jaffrin et al (1990) proposed an expression for T that is universal for all solutes:

With $Q_{UF} < 70$ ml/min

$$K_{HDF} = K_{diff} + 0.46 Q_{UF} \tag{19.12}$$

With $Q_{UF} > 70$ ml/min

$$K_{HDF} = K_{diff} + 0.43 Q_{UF} + 0.00083 Q_{UF}^{2} \tag{19.13}$$

## 19.4 HDF TECHNIQUES AND INFUSION MODALITIES

### 19.4.1 Internal Filtration

When high-flux membranes are used in HD (high-flux HD), large water transfer occurs from blood to the dialysate compartment at the proximal end of the dialyzer according to a pressure gradient which results from the sum of hydrostatic, osmotic and oncotic pressures acting within the dialyzer compartments across the membrane. Water acts as solvent drag and favors removal of middle molecular compounds by convection. As a consequence of high UF, blood flow rate and hydraulic pressure within the capillaries drop progressively along the fiber length, while oncotic pressure increases with plasma protein concentration until, at a certain point of the dialyzer length, the pressure gradient across the membrane reverses its direction and, accordingly, water transfer occurs from the dialysate to the blood compartment (see Fig.19.3). This phenomenon, called 'back-filtration' or 'internal filtration' is the underlying principle of high-flux HD and its effect is an enhancement of small- and middle-molecular solute removal. Internal filtration flux taking place during high-flux HD may be

quantified by means of a mathematical model designed to supply the clinician with useful information about the contribution of convection to the efficiency of this treatment modality (Fiore et al. 2006).

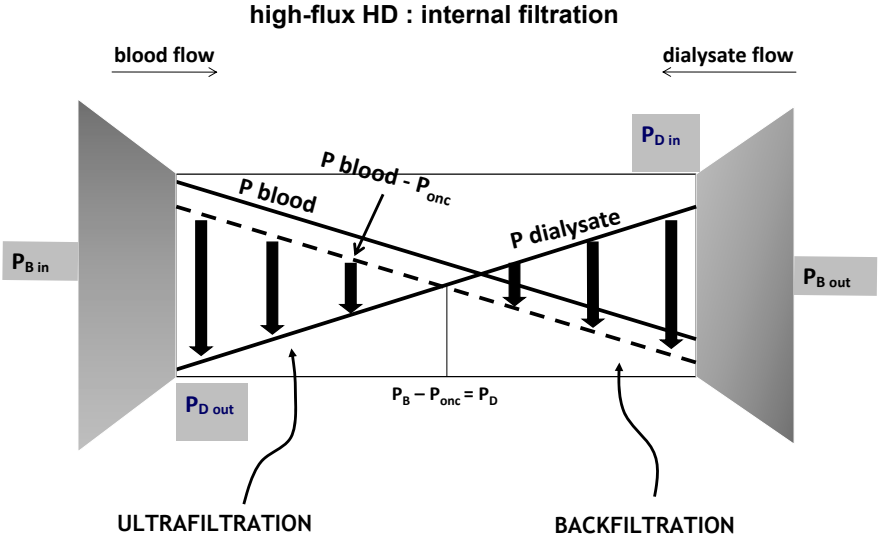



**Fig. 19.3** Schematic representation of internal filtration as a convective transport mechanism acting during high-flux HD.

In HDF, higher $Q_{UF}$ may be obtained in the absence of significant back-filtration. As a result of water filtration, solutes with diameter up to that of the membrane pores are dragged (convection) across the membrane independently of their molecular size. Pure convection (HF) promotes a higher rate of medium- and large-molecules removal than conventional HD but lesser removal of small-molecular compounds, which mainly occurs by diffusion. Combining both removal mechanisms into a single treatment (HDF) is undoubtedly the strategy enabling the high potential of hydraulic and solute permeability of synthetic membranes to be most properly exploited.

### 19.4.2 Post-dilution HDF

Post-dilution HDF (see Fig. 19.4A) is commonly held as the infusion mode in HDF that most efficiently removes middle molecules (Ahrenholz et al. 1997; Lornoy et al. 1998; Pedrini et al. 2000; Wizemann et al. 2001). Up to 5-6 liter of UF per hour may be obtained with appropriate pressure

regimen, thus maximizing removal by convection of uremic toxins, and the excess fluid loss of the patient is replaced with a sterile solution produced on-line from the dialysate and infused after the filter. However, when very high $Q_{UF}$ are applied in post-dilution HDF, hemoconcentration increases blood viscosity and resistance to flow inside the fibers, especially when high rates of weight loss are necessary to achieve the dry body weight and when the individual capacity to recruit fluid from the extra-vascular space during dehydration (refilling) is scarce. In these conditions, a critical reduction of the membrane permeability is likely to occur. In fact, progressive protein concentration contributes to a thickening of the secondary membrane layer so limiting its hydraulic and solute permeability (Rockel et al. 1986; Vilker et al. 1981). Moreover, plasma proteins exert an increasing oncotic pressure that resists UF (Vilker et al. 1984). As a consequence, increasingly higher TPM gradients are often reached in the attempt to maintain the planned $Q_{UF}$ but, beyond a certain limit, $Q_{UF}$ reduces and even stops. In order to better preserve the membrane permeability when high $Q_{UF}$ are applied, high $Q_B$ should be applied in order to increase the shear rate that stirs the protein layer formed on the blood side of the membrane.

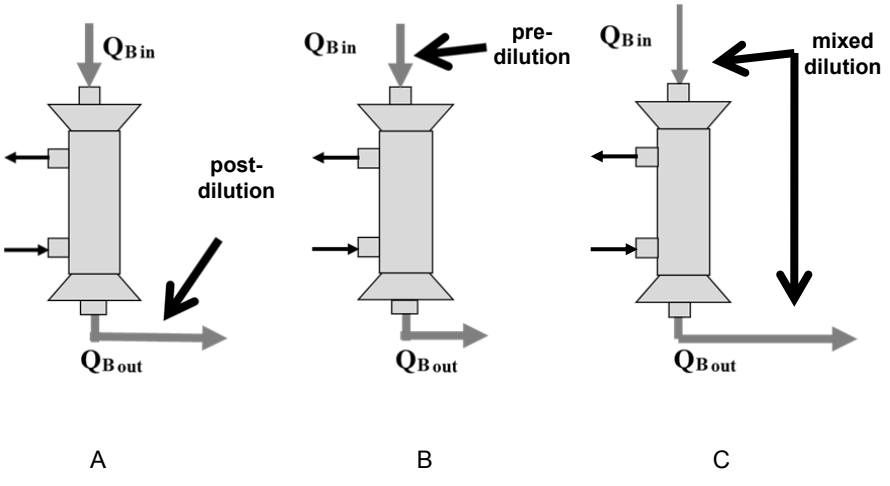



**Fig. 19.4** Infusion modalities in HDF. A, post-dilution HDF; B, pre-dilution HDF; C, mixed HDF.

### 19.4.3 Pre-dilution HDF

Pre-dilution HDF (see Figure 19.4B) partially prevents these drawbacks, by ensuring safer rheological and pressure conditions, and, thus, the possibility of higher infusion and $Q_{UF}$. In this modality, the replacement fluid solution is added to blood before the dialyzer, and the increased rate of diluted flow within the capillaries better preserves the permeability of the membrane by stirring the secondary protein layer. However, this advantage in terms of convective removal may be offset by the dilution of the plasma solutes concentration available for diffusion and convection, with consequent reduction of their cumulative transfer (Ahrenholz et al. 1997; Pedrini et al. 2000; Pedrini and Zerbi 2007; Wizemann et al. 2001), in spite of an accelerated extraction of the diffusible small solutes from the intracellular space, due to a more favorable transcellular gradient (Cheung et al. 1983; Colton et al. 1975). Loss in efficiency of pre-dilution HDF due to the above conditions may be limited by setting the infusion rate to a value approximately double with respect to post-dilution HDF (Ahrenholz et al. 1997; Wizemann et al. 2001).

### 19.4.4 Mixed (Pre and Post-dilution) HDF

Mixed HDF (see Figure 19.4C) is a newly developed modality of HDF in which the replacement fluid is simultaneously infused to a variable ratio at the inlet and outlet port of the dialyzer. The aim of this technique is to overcome limits and risks implicit in the traditional infusion modes in HDF while coupling their advantages (Pedrini et al. 2000, 2002, Pedrini and DeCristofaro 2003). The basic concept is that splitting the infusion between pre- and post-filter guarantees better rheological and hydraulic conditions within the dialyser and preserves the characteristics of water and solute transport of the membrane. Consequently, the highest fluid exchange rate may be achieved with enhanced solute removal by convection. In mixed HDF, variable amount of infusion is added in pre-dilution and balanced with that in post-dilution in order to ensure the highest possible filtration fraction, while simultaneously avoiding dangerous hydrostatic pressures within the dialyzer and excessive dilution of the inlet solute concentrations. Preliminary studies have shown that mixed HDF, performed under the control of a $TMP/Q_{UF}$ feedback system, achieved removal of small and large size solutes which was similar to post-dilution HDF when $Q_{UF}$ was matched for the two infusion modes (Pedrini et al. 2000). A more

recent study demonstrated that greater β2-m and phosphate removal may be safely obtained in on-line mixed HDF than in post-dilution HDF by further increasing the total infusion rate and forcing $Q_{UF}$ to achieve the most efficient convective transport (Pedrini et al. 2006; Pedrini and Zerbi 2007).

Mixed dilution may be of special advantage in patients with high predialysis hematocrit and an increased risk of filter clotting with post-dilution HDF due to hemoconcentration (Kuhlmann 2010).

### 19.4.5 Mid-dilution HDF (MD-HDF)

MD-HDF (see Figure 19.5A), a recently proposed HDF technique aimed at increasing convective solute transport (Krieter et al. 2005a), is based on the use of particular dialyzers (OLpur™ MD190 and MD220, Nephros, New York, USA) which include a U-shaped blood capillary bundle with a middle infusion port at the point where blood flow reverses direction. Blood and dialysate flow counter-current in the descending U branch of the capillaries where post-dilution is performed and co-currently in the ascending, pre-dilution U branch.

This infusion technique has been claimed to be of greater efficiency when compared to traditional pre- or post-dilution HDF (Krieter et al. 2005b). On the other hand, MD-HDF carried with it serious risks when applied as proposed in the original study because considerably high TMP in the post-dilution section of the filter was necessary to achieve the planned ultrafiltration of about 10 liter/hour (Feliciani et al. 2007). This problem was overcame by reversing the configuration of the blood tubing (Santoro et al. 2007). (reverse MD-HDF), but safer hydraulic conditions in MD-HDF was only shown with the use of the filter with the larger surface area (MD-220, 2.2 $m^2$) in reverse MD-HDF configuration (Pedrini et al. 2009). This system still lacks an efficient pressure control system with modulation of the infusion rate according to the operational conditions of the treatments, necessary to improve safety and performance in the routine clinical application of this technique.

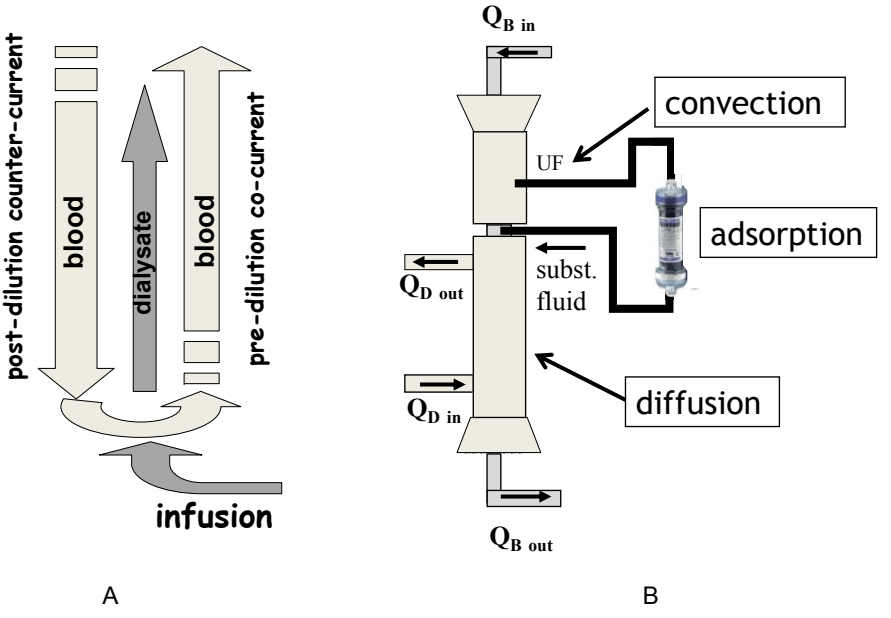



**Fig. 19.5** Schematic representation of Mid-dilution HDF (A) and HDF with endogenous reinfusion (B). Explanation in the text.

### 19.4.6 HDF with Endogenous Reinfusion (HFR)

HFR (see Figure 19.5B) is an HDF technique performed by means of a 2-chamber filter with a high-flux polyethersulfone membrane in the first chamber and a low-flux polyethersulfone in the second one (Ghezzi et al. 1991). The two filtration stages allow separation of the convective from the diffusive process. The ultrafiltrate produced in the first chamber is 're-generated' by a sorbent cartridge in a closed circuit and then used as an endogenous replacement solution infused in the second one. This system is claimed to prevent any problem of sterility and apyrogenicity (Tetta et al. 2002) of dialysis fluids and any loss of bicarbonate and amino acids (Borrelli et al. 2010). The sorbent cartridge contains a hydrophobic styrenic resin which has high affinity and adsorbs several uremic toxins and MM, such as β2-m, homocysteine, parathyroid hormone, and several cytokines, while electrolytes and small solutes such as urea, creatinine and uric acid are not adsorbed and are managed in the second, diffusive section of the dialyzer (Marinez de Francisco et al. 2000; Ghezzi et al. 1991).

### 19.4.7 Ultrafiltration Control in On-line HDF

On-line HDF has been shown to obtain substantial clinical benefits when performed with high volume exchange, thus fully exploiting its potential of convective solute removal (Canaud et al. 2006). Indeed, proportional increase in β2-m removal is achievable in post-dilution HDF with increasing $Q_{UF}$ ( Lornoy et al. 1998; Wizemann et al. 2001). For this reason, operating conditions should be set in order to achieve this goal by maximally exploiting the permeability of high-flux membranes. At any given blood flow the maximal efficiency in convective removal is obtained at the highest filtration fractions (Pedrini et al. 2000). The highest achievable FF may only be achieved in the post-dilution mode, but its value is often unpredictable, due to the events described above. At any given blood flow, TMP is exponentially related to the filtration fraction, and the slope of the curve is a function of the hydraulic permeability of the dialyzer (Pedrini et al. 2000). Above a certain level of TMP the system becomes unstable (Jenkins et al. 1992) and sudden dangerous pressure peaks are likely to result from small changes in blood flow or viscosity, venous pressure, or for clinical reasons (see Fig. 19.6), particularly in patients with cardiac failure, diabetes or hemodynamic instability. In such circumstances residual irreversible reduction in the performance of the dialyzer was observed, even after restoring safer pressure conditions. Historically, the limit beyond which the adverse events of high TMP levels and hemoconcentration may occur was set empirically at a FF of 0.5 (Henderson 1989). Setting the infusion rate purely on the basis of the in vitro $K_{UF}D$ may be misleading for several reasons. The present technology of HDF machines helps to automatically plan a session in order to accomplish this task safely with the use of feedback devices which modulate the infusion rate through the control of TMP. In mixed HDF a newly developed feedback system is able to automatically maintain TMP within the highest range of safety during the session, while at the same time ensuring a constant and maximal infusion rate, by optimizing the ratio between pre-filter and post-filter infusion (Pedrini et al. 2000, 2006, Pedrini and DeCristofaro 2003) (see Fig. 19.7A, B). It has been reported that with the use of the new TMP-UF feedback control an infusion rate similar to the plasma water flow rate, split between pre and post-dilution in order to achieve a FF as high as possible, resulted in β2-m removal that was significantly higher than that obtained in both post-dilution HDF and pre-dilution HDF

performed at the highest infusion rate (Pedrini and DeCristofaro 2003). In post-dilution HDF, TMP the infusion rate is set and maintained at the maximum level compatible with safe TMP values and is modulated through the session according to a preset algorithm that reduces the infusion rate if TMP increases beyond its maximum limit as a consequence of the progressive decline of the membrane permeability through the session (see Fig. 19.7C).

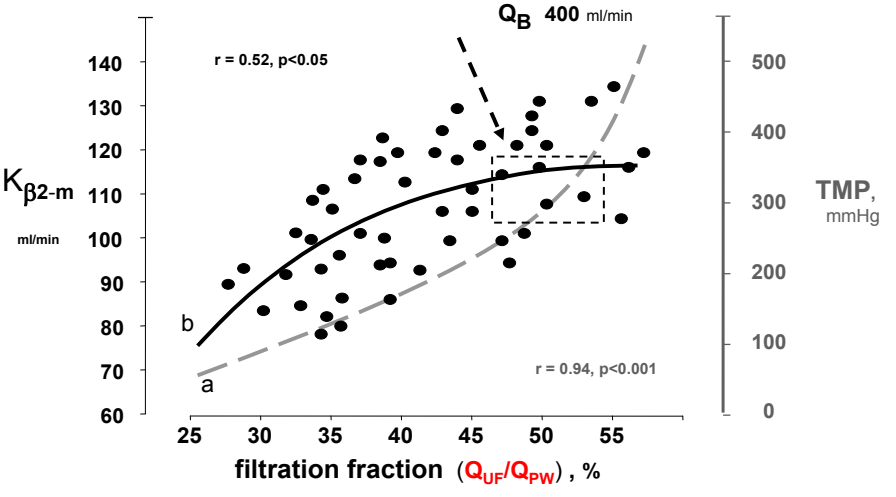



**Fig. 19.6** Dependence of the trans-membrane pressure (TMP, right y-axis, curve a) and β2-m clearance ($K_{\beta 2\text{-}m}$, left y-axis, curve b) on the filtration fraction (FF = $Q_{UF}$ /$Q_{PW}$, x-axis). Steep increase in TMP and stable $K_{\beta 2\text{-}m}$ values occur at a certain FF value between 50 and 55%. The domain included in the dotted square indicates the operating conditions of flow and pressure suitable to achieve safely maximal MM removal by convection in HDF. Data from Pedrini et al (2006).

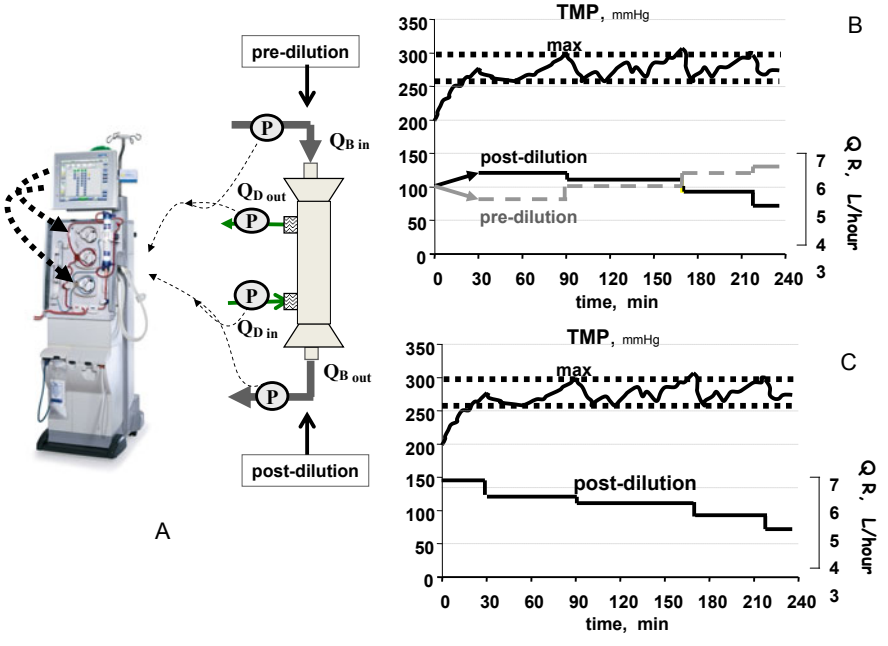



**Fig. 19.7** Schematic representation of the hardware for mixed HDF (A) implemented on the 5008 Fresenius system. Four pressure probes (P) placed at the inlet and outlet blood and dialysate compartments provide serial measurements (1200 per minute) from which the instantaneous mean TMP is calculated. Two infusion pumps work at variable speed to modulate and proportion the infusion rate at the inlet and outlet port of the blood compartment. The diagrams represent the mechanism by which the TMP/UF feedback system controls TMP in mixed dilution HDF (B) by modulating the total infusion and the ratio between post- and pre-dilution infusion, and in post-dilution HDF (C) by modulating the total infusion. More details in the text.

## 19.5 KINETIC MODELING IN HEMODIALYSIS AND HEMODIAFILTRATION

Kinetic modeling is an analytic technique based on the principle of conservation of matter and used to describe the time course of a solute concentration during and between dialysis treatments, which results from changes in the solute content of its distribution volume over

time (Gotch and Keen 2005; Sargent and Gotch 1996). A marker solute for toxins of similar molecular weight or kinetic behavior may be used to simulate the rate of change in concentration of all solutes of the group in the various compartments of the body, and to prescribe the dialysis dose regarded as "adequate" to control the clinical symptoms of the uremic syndrome (Gotch and Keen 2005).

A model formulation requires a rigorous mathematical definition of its parameters in order the relative effect of each of them and their interactions to be precisely assessed (Sprenger et al. 1983). Precise characterization is needed for: 1) the solute distribution volume in the body and, in the case of multiple compartment models, the relative volume of each compartment, the net rate of volume change with time, the inter-compartmental mass transfer coefficient of the solute, its distribution coefficient within each compartment, 2) the solute mass gain of the system, expressed by the rate (and site) of solute generation, 3) the rate of solute mass removal from the system through residual renal clearance and metabolic transformation (extra-renal clearance), and 4) the solute mass exchange through the dialyzer membrane (removal or gain), which depends on the transport properties of the dialyzer (dialysance or clearance) and the nature and concentration of the solute.

### 19.5.1 Single Pool Model

The single-pool model has been applied to simulate the kinetics of small molecules (mainly urea) during different dialysis techniques (Gotch and Keen 2005;Sargent and Gotch 1980; Sausse et al. 1974). A schematic representation is depicted in Fig. 19.8A. Its simplest version, the fixed-volume single-pool (FVSP) Urea Kinetic Model (UKM), assumes that urea is uniformly distributed in a single, homogeneous fluid compartment (V) coextensive with the total body water (TBW). The variable-volume (VVSP) UKM accounts for volume changes during the dialysis cycle. V changes occur at constant rate, estimated from the weight loss per unit of time during dialysis, and from the rate of weight gain between dialyses.

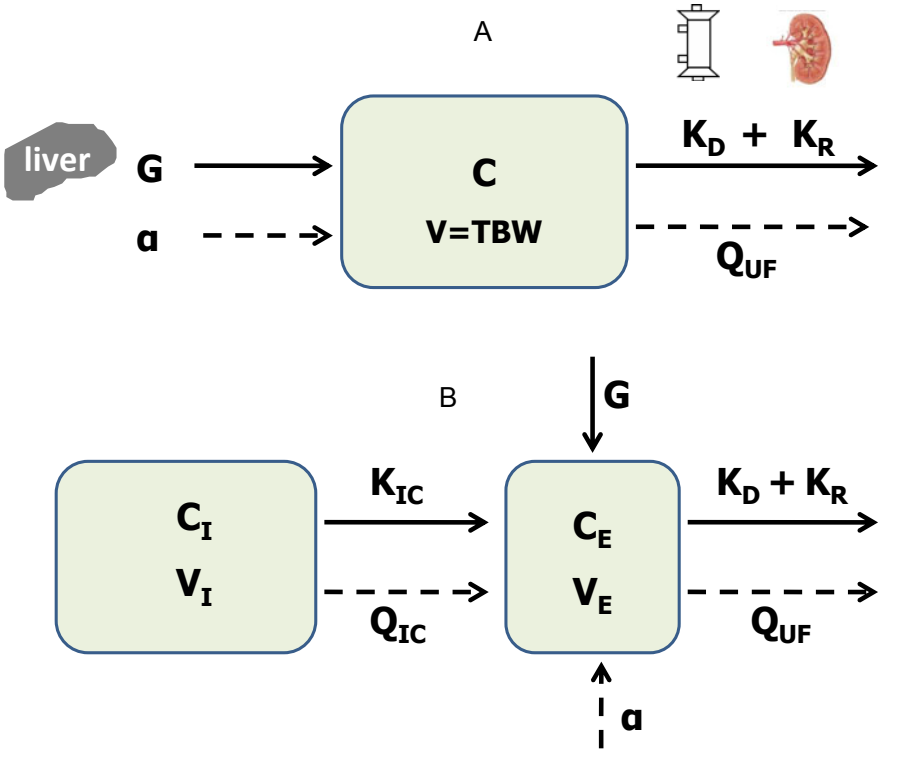



**Fig. 19.8** Schematic representation of the VVSP (A) and VVDP (B) kinetic models. Explanation in the text.

The solute mass gain of the system is expressed by the rate of urea generation (G, mg/min). Urea, the end product of protein catabolism, is added to the distribution pool V at a constant rate throughout the dialysis cycle and G may be quantified as the increase in urea content in V between sessions ($\Delta$ V $C_B$) divided by the length of the interdialytic interval ($t_{id}$), as:

$$G = \frac{\left[ V_{o2} C_{BO2} - VtC_{Bt} - K_R \frac{(C_{BO2} + C_{Bt})}{2} \right]}{t_{id}} \qquad (19.14)$$

where the suffix o, t and $_{O2}$ refer to the start and the end of the session and the start of the following session, respectively, and $K_R$ is the residual renal clearance of the solute.

The rate of solute mass removal from the system ($J_T$) is the product of the total solute clearance $K_T$ by its concentration ($C_B$):

$$J_T = C_B K_T = C_B \left( K_D + K_R \right) \tag{19.15}$$

$K_D$ (ml/min), as above defined, is the dialyzer clearance of a solute, i.e. the ratio of mass removal rate and incoming concentration and determines the removal rate of a solute from blood. In all techniques, HD, HDF or HF, $K_D$ at a given time of the session can be calculated with Eq. (19.9) substituting $Q_e$ for $Q_{Bin}$ as in Eq. (19.10).

Knowledge of $K_oA$, the overall mass transfer coefficient (per area) of the solute, provides an alternative method to estimate $K_D$ (Sargent and Gotch 1996). $K_oA$ is typical for a given dialyzer and constant at any blood and dialysate flow rate and solute concentration. The relationship between the diffusive $K_D$, $K_oA$ and flow rates is expressed by the Eq. (19.16):

$$K_D = Q_B \frac{\left\{ \exp\left[ \frac{K_o A}{Q_B} \left( \frac{1 - Q_B}{Q_D} \right) \right] - 1 \right\}}{\left\{ \exp\left[ \frac{K_o A}{Q_B} \left( \frac{1 - Q_B}{Q_D} \right) \right] - \frac{Q_B}{Q_D} \right\}} \tag{19.16}$$

The equation is valid for counter current flow and only with $Q_{UF}$ null or minimal. $Q_{UF}$ typical on HD (up to 10 ml/min) has a trivial effect on $K_D$ of urea and highly diffusible solutes, while it may substantially increase $K_D$ of larger solutes.

$K_R$ (ml/min) contribution to removal should not be neglected because even very low values may significantly affect blood concentration of solutes, particularly in the middle molecular weight range. $K_R$ is usually calculated by collecting and measuring urine volume ($V_u$) and its concentration ($C_u$) over an entire interdialytic interval and taking the average of blood urea concentration at the beginning and the end of urine collection, with the assumption of a linear increase in $C_B$:

$$K_R = \frac{\left( C_u \times V_u \right)}{\left[ \frac{\left( C_{Bt} + C_{Bo2} \right)}{2} \times t_{id} \right]} \tag{19.17}$$

With these premises, the rate of change in body content of urea during a dialysis treatment is described mathematically from the following general equation of the FVSP-UKM (Sargent and Gotch 1996):

$$VC_B\left(\frac{d}{dt}\right) = -K_T C_B + G \tag{19.18}$$

While, the general equation of the VVSP-UKM is:

$$\left(\frac{d}{dt}\right)\left[V(t)C_B(t)\right] = -K_T(t)C_B(t) + G \tag{19.19}$$

Integration and rearrangement of the VVSP model equation Eq. (19.19) allows calculation of V and G on the basis of measured values for $K_D$, $C_{Bo}$, $C_{Bt}$, $C_{Bo2}$, $t_d$, $t_{id}$ and the constant rate of change in V during dialysis ($Q_{UF}$) and the interdialytic period (α):

$$V_t = Q_{UF} \times t_d \left\{ \left[ 1 - \left( \frac{G - C_{Bt}(K_T - Q_{UF})}{G - C_{Bo}(K_T - Q_{UF})} \right)^{\frac{Q_{UF}}{K_T - Q_{UF}}} \right]^{-1} - 1 \right\} \tag{19.20}$$

$$G = \frac{(K_r + \alpha)\left[ C_{BO} - C_{Bt}\left( \frac{V_t + \alpha t_{id}}{V_t} \right)^{-\frac{K_r + \alpha}{\alpha}} \right]}{1 - \left( \frac{V_t + \alpha t_{id}}{V_t} \right)^{-\frac{K_r + \alpha}{\alpha}}} \tag{19.21}$$

Equations (19.20) and (19.21) may be solved iteratively for the end-session V ($V_t$) and G until unique solution for $V_t$ and G is found. Once individual estimate of the variables $V_t$, and G has been achieved, then the actual time course of the concentration changes during dialysis and the end-session concentration ($C_{Bt}$) may be obtained on the basis of the initial solute concentration ($C_{Bo}$) by solving the Eq. (19.19) for $C_{Bt}$ (Sargent and Gotch 1996):

$$C_{Bt} = C_{Bo}\left[ \frac{V_o - Q_{UF} t_d}{V_o} \right]^{\frac{(K_T - Q_{UF})}{Q_{UF}}} + \left[ \frac{G}{K_T - Q_{UF}} \right] \times \left[ 1 - \frac{V_o - Q_{UF} t_d}{V_o} \right]^{\frac{(K_T - Q_{UF})}{Q_{UF}}} \tag{19.22}$$

while, plasma solute concentration at the start of the following session ($C_{BO2}$) may be obtained as :

$$C_{BO2} = C_{Bt}\left[\frac{(V_t + \alpha t_{id})}{V_t}\right]^{-\frac{(K_R+a)}{a}} + \left\{\frac{G}{(K_R+a)} \times \left[1 - \frac{(V_t + \alpha t_{id})}{V_t}\right]^{-\frac{(K_R+a)}{a}}\right\} \quad (19.23)$$

Since equations (19.22) and (19.23) are discontinuous when $Q_{UF}$ or $\alpha = 0$, assumption of a very small value for V changes is necessary to solve the equations in this case without affecting the final result.

The weekly course of the solute concentration simulated by the VVSP model for thrice/weekly HD schedule is represented in Fig. 19.9

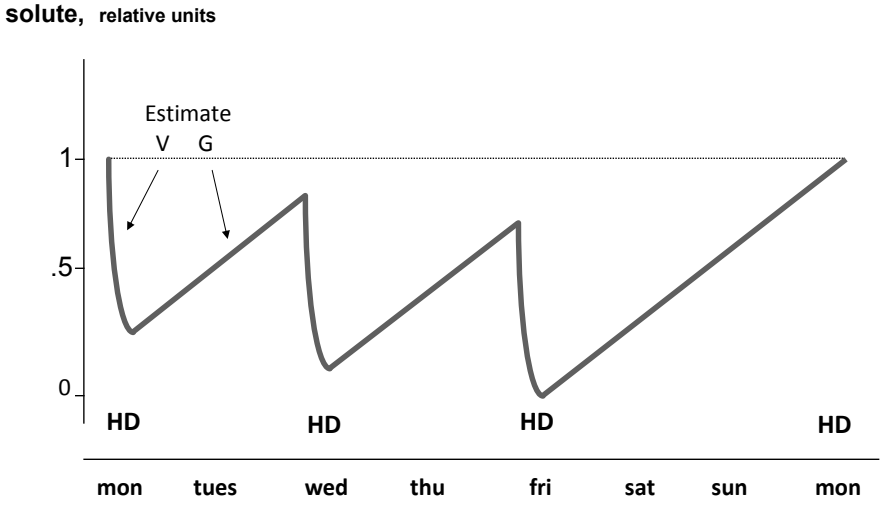



**Fig. 19.9** Weekly time course of urea concentration simulated by the VVSP-UKM model in steady state condition.

Clinical application of this model requires three determinations of urea concentration from two consecutive dialyses. A simpler method, which only requires knowledge of Co and Ct from a single dialysis (Depner and Cheer 1989; Gotch and Keen 2005)., is based on iterative solution of the model equations over a weekly dialysis schedule and adjustments of Vt and G values until a unique solution for Co is found.

The SPVV-UKM provides a method for quantifying the amount of delivered dialysis dose and for monitoring the quality of the prescribed therapy with an index, the $K_D$ t / $V_t$ , which expresses the fractional urea clearance of the session.

### 19.5.2 The Variable Volume Double-Pool Model (VVDP)

The VVSP model assumes a single body compartment as a solute distribution volume and does not simulate precisely the intradialytic kinetics of solutes which do not cross freely the body compartment barriers. The actual distribution volume of low MW compounds, such as urea, creatinine and phosphate includes the intracellular ($V_I$) and the extracellular space ($V_E$), the latter divided in turn into interstitial ($V_i$) and intravascular ($V_P$) space. The capillary bed is highly permeable to most small solutes and concentration equilibrium between $V_P$ and $V_i$ is achieved instantaneously. Hence, in this case the two compartments are retained as a single extracellular pool $V_E$ (Schindhelm and Farrell 1978). A schematic representation of the VVDP model is depicted in Fig. 19.8B.

A concentration disequilibrium between $V_I$ and $V_E$ may be generated during dialysis when a solute is cleared from plasma water at a faster rate than its transfer rate across the cell wall membrane. This imbalance between concentrations triggers a solute movement between $V_I$ and $V_E$ according to a diffusion concentration gradient. The magnitude of transfer depends on the resistance opposed by the cell membrane, which is expressed by the solute inter-compartment mass transfer coefficient ($K_{IC}$, inter-compartmental clearance) and is typical for the solute (null for large impermeable molecules and large for freely diffusible small molecules). At the end of the session solute removal from blood ceases, but its transfer from the inner to the outer compartment continues until the respective concentrations re-equilibrate. This phenomenon appears as a rapid increase of plasma concentration immediately after the end of dialysis (post-dialysis rebound) (Pedrini et al. 1988) and its magnitude and duration are inversely proportional to the solute $K_{IC}$ (see Fig. 19.10).

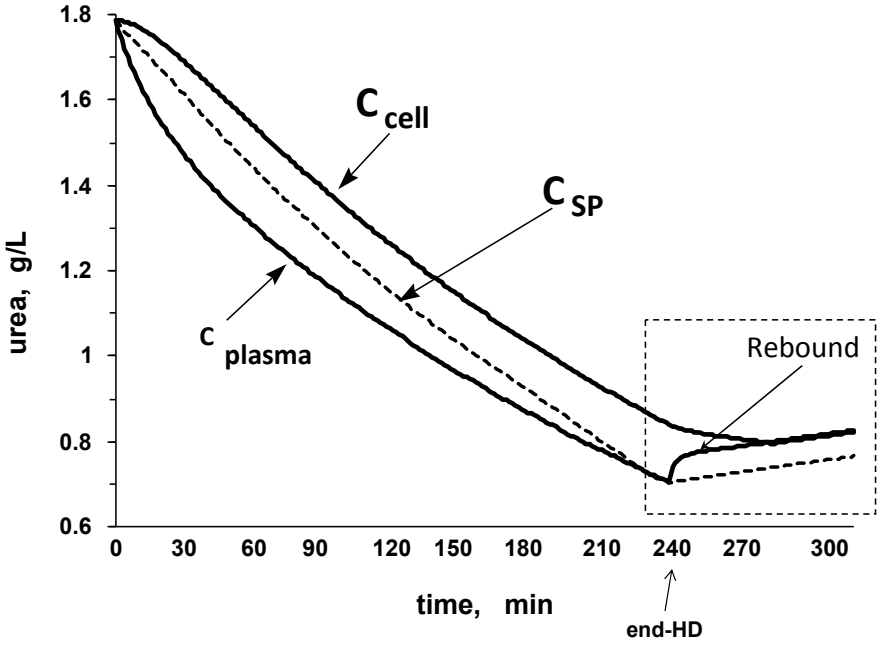



**Fig. 19.10** Time course of plasma and intracellular urea concentration during a session of HDF and during the rebound period, as simulated by the VVDP-UKM model. The dotted line represents the VVSP-UKM simulation obtained at the same operating conditions.

Not accounting for these events, the single pool model does not simulate accurately the kinetic behavior of most solutes, but the error is small when urea or other solutes freely diffusible are modeled (Rastogi et al. 1968). HDF has the main objective to remove middle molecular compounds, which are retained in the inner body compartment to a variable extent according to their molecular weight and may exhibit a post-dialysis rebound of up to 50% (Popovich et al. 1975). Thus, two- or multiple pool models simulate more reliably the kinetics of small solutes not freely permeable, such as creatinine and phosphate, and their application is mandatory for reliable simulation of the kinetics of larger molecules such as β2-m.

#### 19.5.2.1 The Variable Volume Double-Pool Urea Kinetic Model (VVDP-UKM)

The most consistent VVDP-UKM provides simultaneous modeling of urea, sodium (Na) and fluid volume changes (Gotch and Keen 2005; Gotch et al. 1980; Sargent and Gotch 1980, 1996). In this model, urea V corresponds to

the TBW, which is divided in two compartments, $V_I$ and $V_E$. Sodium distribution space is $V_E$ but its osmotic power regulates the water content of both $V_E$ and $V_I$ compartments by driving water shifts across the cell membranes. Therefore, a consistent assumption for modeling purposes is that the distribution volume of Na activity extends to the TBW, and that extracellular Na activity is counterbalanced in $V_I$ by the cation osmotic activity (C+), assumed to be constant and corresponding to the intracellular K+ concentration (Edelman et al. 1958).

Solute removal from the system occurs from $V_E$ at a rate determined by $K_T$ (ml/min), as in VVSP model. Urea is assumed to be generated in $V_E$ (Gotch and Keen 2005) or in both compartments according to other authors (Rastogi et al. 1968). The original formulation of the VVDP-UKM is based on the following mass balance equations for urea (C, concentration), Na and water (Gotch 1995):

**For Urea:**

$$\frac{d}{dt}\left(V_E C_E\right) = K_{IC}\left(C_I - C_E\right) + G - \left[K_T\left(1 - \frac{Q_{UF}}{Q_E}\right) + Q_{UF}\right] C_E \quad (19.24)$$

$$\frac{d\left(V_I C_I\right)}{dt} = -K_{IC}\left(C_I - C_E\right) \quad (19.25)$$

The initial intracellular urea concentration $C_I$ can be estimated from $C_E$ and the distribution coefficient $\chi$, that is the ratio of a substance in two compartments at equilibrium ($C_E = \chi\, C_I$).

**For Na:**

$$\frac{\mathrm{d}}{\mathrm{dt}}\left(\mathrm{V_E Na_E}\right) = \mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right)\mathrm{Na_{Di}} - \left[\mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right) + \mathrm{Q_{UF}}\right]\mathrm{Na_E} \quad (19.26)$$

$$\frac{d}{dt}\left(V_I C^{+}{}_I\right) = 0 \quad (19.27)$$

where D is Na dialysance [see Eq. (19.8)] and $Na_{Di}$ is the inlet dialysate Na concentration. Trans-compartmental water flow is driven by the osmotic

gradient which results from the combined difference in concentration/activity of urea and anions between VI and VE and is limited by the trans-cellular transfer coefficient for water ($K_{CW}$):

**For Water:**

$$\frac{d}{dt}V_E = K_{CW}\left[\left(C_E - C_I\right) + \left(Na_E - C^+{}_I\right)\right] - Q_{UF} \tag{19.28}$$

$$\frac{\mathrm{d}}{\mathrm{dt}}\left(\mathrm{V_E Na_E}\right) = \mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right)\mathrm{Na_{Di}} - \left[\mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right) + \mathrm{Q_{UF}}\right]\mathrm{Na_E} \tag{19.29}$$

Mathematical solution of the VVDP-UKM requires the exact definition of at least five parameters (G, $V_I$, $V_E$, $K_{IC}$ and $K_{CW}$), which could only be calculated individually on the basis of serial blood sampling for urea and Na and numerical integration of the model equations (Gotch and Keen 2005), for instance with the Runge-Kutta method. Thus, estimate of parameters for clinical model application are often assumed from the literature, with the drawback that inaccurate simulation may result from incorrect assumptions.

The relative magnitude of V, $V_I$ and $V_E$ spaces has been estimated with various kinetic models and radioisotopic injection methods in accordance with physiological measurements, usually in patients with normally functioning kidneys (Popovich et al. 1975; Rastogi et al. 1968; Schindhelm et al. 1978; Watson et al. 1980). Urea $K_{IC}$ may be calculated with a series of measurements of blood concentrations during dialysis and post-dialysis rebound. Values reported by several authors are ranging from 500 to 860 ml/min (Clark et al. 1999b; Frost and Kerr 1977; Gotch and Keen 2005; Pedrini et al. 1988; Popovich et al. 1975;Schindhelm and Farrell 1978). In general, $K_{IC}$ decreases with increasing MW of different solutes. $K_{IC}$ is the limiting factor in mass transport because of its magnitude which is least an order lower than that of the trans-capillary transfer coefficient. An estimate of 0.2 ml/min per mmHg for $K_{CW}$ has been reported (Gotch 1995). The distribution coefficient $\chi$ for urea was estimated to be 0.86 by (Colton et al. 1975), but a value equal to 1 resulted from measurements on uremic erythrocytes, implying concentration equilibrium between compartments (Nolph et al. 1978). In the latter case, $\chi$ may be ignored in pool calculations.

## Example 19.1

**Simulate the time course of plasma and intracellular urea concentration (U) in a patient on chronic extracorporeal treatment during HD and high-efficiency HDF and post-session rebound simulated using VVDP model, and comparative estimate (Kt/V) of the efficiency of the two sessions.**

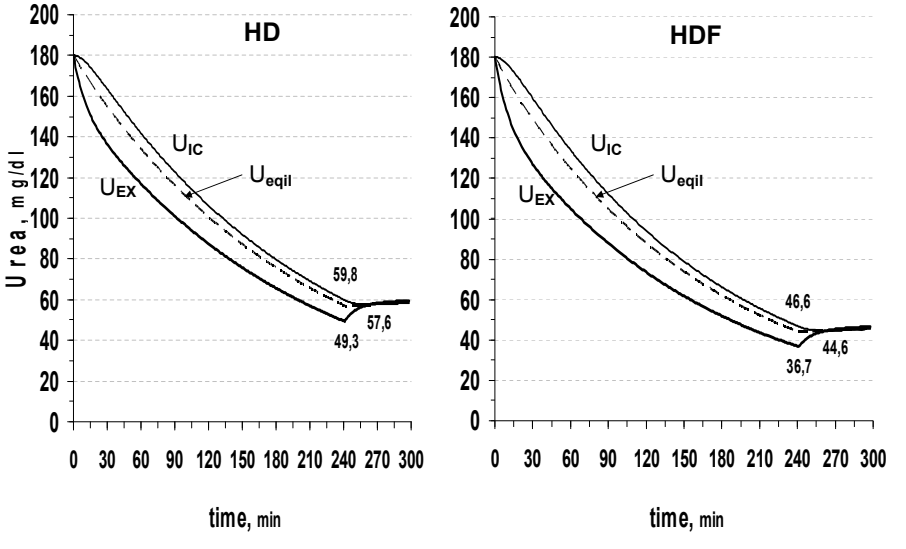
| *Known/measured patient parameters* | *value* |
|---|---|
| Age, *years* | 70 |
| Height, *cm* | 175 |
| Dry BWt, *kg* | 70.0 |
| Hct , *%* | 35.0 |
| Tot Prot, *g/dl* | 6.0 |
| Urea start session , *mg/dl* | 180 |

| *Treatment parameters* | *value* | *note* |
|---|---|---|
| Session time, *min* | 240 | |
| $Q_B$ , *ml/min* | 400 | |
| $Q_{UF}$ (on HD), *ml/min* | 10 | |
| $Q_{UF}$ (on HDF) , *ml/min* | 122 | Set to achieve FF= $Q_{UF}/Q_{PW}$ = 0.5. $Q_{PW}$ from Eq. (19.31). |
| $Q_{subs.fluid}$ (on HDF), *ml/min* | 112 | |

### *Solution*

***Step 1: estimate of patient and treatment parameters to be included in calculations***

| *Estimated Parameter* | *value* | *method of estimate* |
|---|---|---|
| Urea G , *mg/min* | 12.0 | *Eq.(19.14) applied to a pilot session.* |
| $K_{Renal}$ , *ml/min* | 2.0 | *Eq.(19.17) applied to a previous interdialytic interval.* |
| TBW ($V_E$ +$V_I$) | 39 | *Watson equation (Watson 1980)* |
| $V_I/V_E$ | 2.0 | *Assumed from Gotch (see Table 19.2)* |
| $K_{IC}$ , *ml/min* | 70 | *Assumed from Gotch (see Table 19.2)* |
| $K_D$ on HD, *ml/min* | 230 | *Nominal in vivo value from the Manufacturer* |
| $K_D$ on HDF, *ml/min* | 291 | *From Eq. (19.13)* |



| HD | |
|---|---|
| $U_{EX}$ *end-session, mg/dl* | 49.3 |
| $U_{eq}$ *, mg/dl* | 57.6 |
| *Rebound, %* | 14.4 |
| Session time, *min* | 240 |
| TBW ($V_E$ +$V_I$), *Liter* | 39 |
| $K_D$ on HD, *ml/min* | 230 |
| Kt/V | 1.42 |

| HDF | |
|---|---|
| $U_{EX}$ *end-session, mg/dl* | 36.7 |
| $U_{eq}$ *, mg/dl* | 44.6 |
| *Rebound, %* | 17.7 |
| Session time, *min* | 240 |
| TBW ($V_E$ +$V_I$), *Liter* | 39 |
| $K_D$ on HD, *ml/min* | 291 |
| Kt/V | 1.79 |

### 19.5.3 Kinetic Modeling of β2-microglobulin in HDF

In clinical practice, a simplified approach based on a single-pool kinetic was used in the past to quantify β2-m removal from its percent reduction (RR, %) in plasma concentration from the start to the end of the session (Floege et al. 1989; Jorstad et al. 1988).

$$RR = \left( \frac{1 - C_t}{C_o} \right) \times 100 \tag{19.30}$$

This approach entails significant imprecision given that it assumes a fixed single distribution space for β2-m ($V_E$) and but neglects its dimension, renal and non-renal clearance and generation rate of the solute, duration of the treatment (Leypoldt et al. 1997), and the effect of hemoconcentration on the end-session β2-m concentration (Bergstrom and Wehle 1987). Actually, a VVDP model is mandatory to simulate the actual β2-m kinetics during the dialysis cycle. A schematic representation of the β2-m VVDP model is depicted in Fig. 19.11. The VVDP-UKM model by Gotch (Gotch et al 2005) applies to β2-m kinetics with appropriate recognition of the inherent parameters and reciprocal relationships. However, problems with its clinical application are of the same nature as for urea, in that the necessary estimate of several unknown parameters is too cumbersome from only the time dependence of β2-m plasma concentration. Thus, values from the literature are often assumed for some key parameters (Clark et al. 1999b; Floege et al. 1991; Floege et al. 1988; Gotch et al. 1989; Kanamori and Sakai 1995; Karlsson et al. 1980; Maeda et al. 1990; Odell et al. 1991; Stiller et al. 2002; Ward et al. 2006), as reported in Table 19.2.

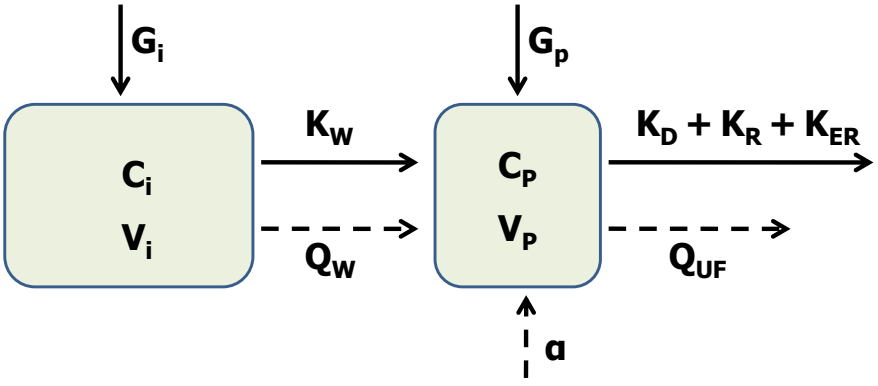



**Fig. 19.11** Schematic representation of the VVDP kinetic model for β2-m. Explanation in the text.

The total distribution space for β2-m is $V_E$, divided in two homogeneous sub-compartments: $V_P$ (plasma) and $V_i$ (interstium). Resistance to β2-m transfer from $V_i$ into $V_P$ is large enough to generate substantial concentration disequilibrium between the two spaces during dialysis and a rapid increase in plasma concentration at its end, as an effect of the inter-compartmental re-equilibration (Leypoldt et al. 1999). Especially during convective treatments with high-flux filters, β2-m removal rate from plasma approaches and often exceeds the rate of diffusive transfer into $V_P$ ($K_{IC}$) (Ward et al. 2006), and β2-m rebound after the sessions may last one to two hours with an increase in plasma concentration up to 50% (Leypoldt et al. 1999; Maeda et al. 1990). Fluid removal during dialysis is assumed to occur from $V_E$ (Gotch et al. 1989), and distributes in both $V_P$ and $V_i$ proportionally to their size. $Q_{UF}$ determines the rate of $V_P$ changes while trans-capillary water shifts follow the osmotic gradient created by changes in plasma protein concentration and are limited by the trans-capillary water coefficient ($K_W$). Water removal from both $V_I$ and $V_E$ is assumed by other authors (Lian et al. 1993), based on the fact that Na is the most powerful osmotic agent in plasma and water shifts between compartments are mainly consistent with changes in its concentration/activity. Continuous β2-m G is assumed to occur at a constant rate. According to different views the site of G is the interstitial compartment (Gotch et al. 1989), the intravascular fluid (Kanamori and Sakai 1995; Karlsson et al. 1980), or both compartments (Ward et al. 2006). β2-m G may be independently measured in the interdialytic interval in analogy with urea generation by adapting the equation (19.14). Removal of β2-m occurs from plasma through three different pathways: residual renal ($K_R$) and extra-renal ($K_{ER}$) clearance

assumed to be continuous along the dialysis cycle, with values independently measured in the interdialytic interval in the former case (see Eq. 19.17) and measured (Xu et al. 2001) or assumed from the literature in the latter case, and dialyzer clearance ($K_D$) acting only during therapy. $K_D$ can be measured at any time of the session by substituting the appropriate parameters into Eq. (19.9) and using the effective β2-m blood flow rate, which corresponds to plasma water flow rate ($Q_{PW}$):

$$Q_E = Q_{PW} = Q_B \left( \frac{1 - Hct}{100} \right) F_p \tag{19.31}$$

**Table 19.2** Values for some key parameters of ß2-m VVDP model assumed from the literature.

| Author | year | patients/method | G (mg/hr/kg) | $K_{IC}$ (ml/min) | $V_E$ = % TBW | $V_i/V_p$ | $K_{ER}$ (ml/min ) |
|---|---|---|---|---|---|---|---|
| **Karlson** | 1980 | 6 normal $^{125}$I β2-m | **0.131** ± 0.023 | | **58.8** ml/kg normal<br>**52.3** ml/kg IRC | | **1.0** |
| **Odell** | 1991 | 5 HD pts | **0.159** ± 0.041 | **42.9** ± 6 | **200** ± 30 ml/kg | **2.78** ± 0.8 | **2.96** ± 0.35 |
| **Floege** | 1991 | 11 HD $^{131}$I β2-m | **0.129** ± 0.033 | **65.8** ± 12.8 | **0.24** x BWt | **4.3** | **3.40** ± 0.7 |
| | | 5 normal $^{131}$I β2-m | **0.1** ± 0.028 | | | | |
| **Kanamori** | 1995 | simulation | **0.131** ± 0.023 | | **200** ml/kg | | **1.64** |
| **Maeda** | 1990 | CKD pts | **0.130** ± 0.029 | | | | |
| | | HD pts | **0.152** ± 0.016 | | | | |
| **Gotch** | 1989 | simulation | **0.131** | **5 ml x Lit VE** | **33%** | **3.0** | |
| **Clark** | 1999 | simulation | **0.170** | **40** | **33%** | | **3.0** |
| **Stiller** | 2002 | 8 HD pts | **0.104** ± 0.027<br>(0.065 - 0.155) | **56.3** ± 25.2<br>(26 -140 ) | **28.4** ± 3.1<br>(23.7 - 35.7) | **4.6** ± 1.8<br>(2.5 - 10) | **3.16** ±0.57 |
| **Ward** | 2006 | 10 HD pts | **0.113** ± 0.021<br>(0.0076 - 0.152) | **82.5** ± 21<br>(53 -108) | **14.3** ± 0.7% | **3.0** | **3.0** |

An equation has been derived with the aim to provide a prompt quantification of the efficiency of a technique/dialyzer in removing β2-m. This approach was described by (Leypoldt et al. 1997), based on the observation that the normalized intra-dialytic reduction in β2-m plasma concentration depended primarily on β2-m Kt/V ($K_D$ × treatment time / distribution volume $V_E$ at end-treatment), and on the rate of fluid removal. Leypoldt's equation allows calculation of $K_D$ for β2-m from the pre- and post-dialysis β2-m concentration, an estimate of $V_E$, treatment time, and the total amount of fluid removed during

therapy. Only β2-m G during dialysis, $K_R$ and $K_{ER}$ are not considered in this analysis. This equation was used to define the dialyzer clearance β2-m and the flux intervention in the HEMO study (Eknoyan et al. 2002).

$$K_D = Q_{UF}\left[\frac{1-\ln\left(\frac{C_t}{C_o}\right)}{\ln\left(1+Q_{UF}\,t\,V_{Et}\right)}\right] \tag{19.32}$$

As for urea, solution of the β2-m VVDP model is only possible by numerical integration of the model equations. However, this method is rather cumbersome to be applied in clinical practice as it requires several measurements of the solute concentration during and after the session and estimates of the parameters according to the best fit of the model curves. More practical approaches have been taken to solve the model equations by different authors, who reduced the number of the parameters left unknown. Gotch (Gotch et al. 1989) and Lian (Lian et al. 1993) left three parameters (G, $K_D$ and $K_{IC}$) to be determined by fitting. Other authors evaluated β2-m G and $K_{ER}$ in dialysis patients (Xu et al. 2001).

Based on the above relationships and assumptions, the equations of the β2-m VVDP model may be written in accordance to Ward (Ward et al. 2006) and with reference to other authors (Gotch et al. 1989; Kanamori and Sakai 1995). Change in β2-m mass in the two compartments as a function of time can be described as:

$$\frac{d\left(V_P C_P\right)}{dt} = V_P G + K_{IC}\left(C_i - C_P\right) - \Theta K_D C_P - \left(K_R + K_{ER}\right)C_P + \Theta V_i Q_{UF} C_i - \left(1-\Theta\right)V_i a C_P \tag{19.33}$$

$$\frac{d\left(V_i G\right)}{dt} = V_i G + K_{IC}\left(C_P - C_i\right) - \Theta V_i Q_{UF} C_i + \left(1-\Theta\right)V_i a C_P \tag{19.34}$$

where Θ is a constant which assumes the value of 1 during dialysis and 0 during the interdialytic period. β2-m G, calculated according to Eq. (19.14), is assumed to occur in both compartments in proportion to their volumes. Assumed values for the initial $V_i/V_P$ ratio and for $K_{ER}$ are those reported in Tab. 19.2.

Change in $V_I$ and $V_P$ are proportional to their relative volumes and can be described as:

$$\frac{d}{dt}\left(V_p\right) = -\Theta\, V_P\, Q_{UF} + \left(1-\Theta\right)V_P\, \alpha \tag{19.35}$$

$$\frac{d}{dt}(V_i) = -\Theta V_i \, Q_{UF} + (1-\Theta) V_i \, \alpha \tag{19.36}$$

Equations (19.33) to (19.36) may be solved with numerical methods (i.e. Runge-Kutta method) with the assumed parameters value and estimate of the unknown variables (i.e. KIC and $V_P$ or $V_i$) by fitting the model equations to serial measured β2-m concentrations.

The time course of plasma and interstitial β2-m concentration during a HDF session and the post-session rebound as simulated by the VVDP model in a hypothetical patient is represented in Fig. 19.12

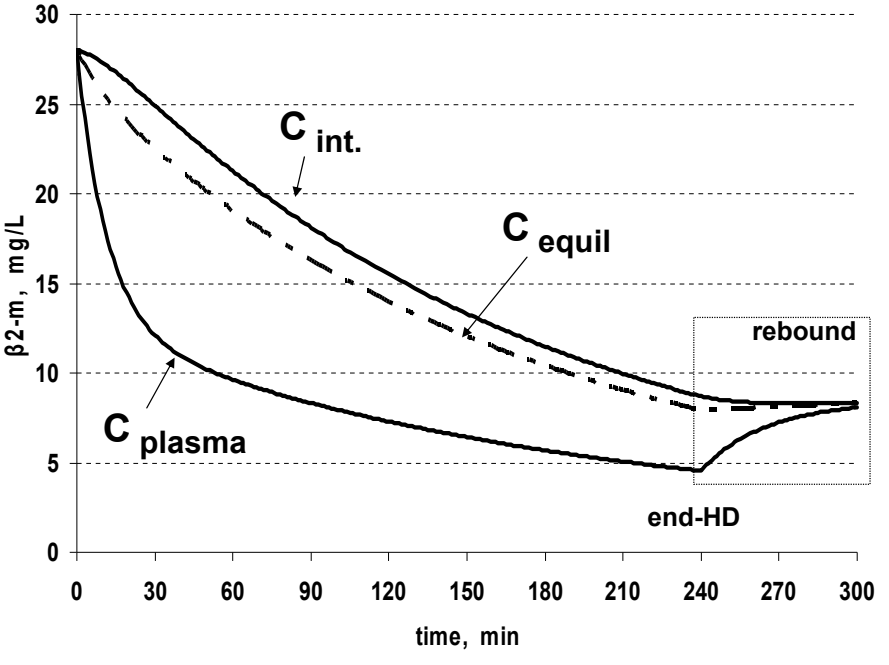


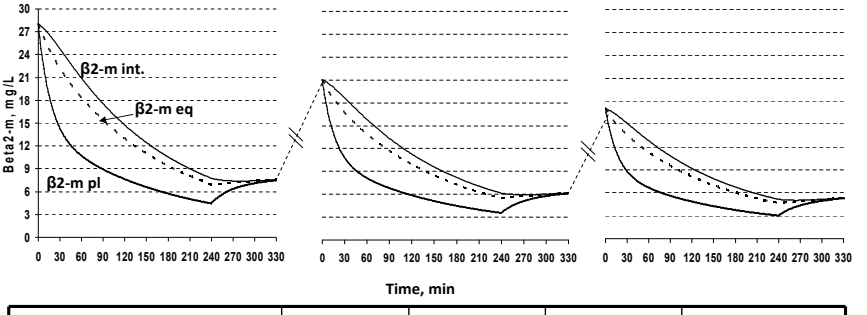

**Fig. 19.12** The time course of plasma and interstitial β2-m concentration during a HDF session and the post-session rebound as simulated by the VVDP model.

## Example 19.2

A patient on chronic HD treatment is shifted to high-efficiency HDF treatment with a substitution fluid rate set in order to achieve a FF of 50%. The pre-dialysis steady-state plasma β2-m concentration of the first session of the week on standard HD is 28 mg/L. Which will be the corresponding value on high-efficiency HDF according to the prediction of a 2-pool kinetic variable volume of β2-m ? The following parameters have been calculated/derived from the HD treatment.

| *Known/measured patient parameters* | *value* | |
|---|---|---|
| **Age,** *years* | **70** | |
| **Height,** *cm* | **175** | |
| **Dry BWt,** *kg* | **70.0** | |
| **Hct ,** *%* | **35.0** | |
| **Tot Prot,** *g/dl* | **6.0** | |
| **β2-m start 1° HD ,** *mg/L* | **28** | |
| **β2-m G ,** *mg/min* | **0.12** | *Eq.(19.14) applied to a pilot session.* |
| **β2-m $K_{Renal}$ ,** *ml/min* | **2.0** | *Eq.(19.17) applied to a pilot session* |
| **β2-m $K_{ExtraRenal}$ ,** *ml/min* | **3.0** | *Assumed (see Table 19.2)* |
| **$V_{EX}$ = 1/3 TBW ,** *L* | **13** | *TBW (Watson 1980), $V_{EX}$ (Table 19.2)* |
| **$V_i/V_P$** | **4.3** | *Assumed from Gotch (see Table 19.2)* |

| *HDF treatment parameters* | *value* | *note* |
|---|---|---|
| **Session time,** *min* | **240** | |
| **$Q_B$ ,** *ml/min* | **400** | |
| **$Q_{UF}$ (Δ BWt),** *ml/min* | **10** | |
| **$Q_{UF\ TOTAL}$ ,** *ml/min* | **122** | *Set to achieve FF= $Q_{UF}/Q_{PW}$ = 0.5. $Q_{PW}$ from Eq. (19.31).* |
| **$Q_{subst.fluid}$ ,** *ml/min* | **112** | $Q_{UF\ TOT}$ - *ΔBWt* |
| **$K_{IC}$ ,** *ml/min* | **82.5** | *Assumed (Ward 2006, see Table 19.2)* |
| **β2-m $K_D$ on HD,** *ml/min* | **30** | *Nominal in vivo value from the Manufacturer* |
| **β2-m $K_D$ on HDF,** *ml/min* | **99.6** | *Predicted from Eq. (19.13)* |




| **B2-m concentr., mg/L** | | **1° session** | **2° session** | **3° session** | **Steady-state** |
|---|---|---|---|---|---|
| **start** | | **28** | **20.7** | **17** | **19.8** |
| **end** | **plasma** | **4.4** | **3.4** | **3** | |
| | **Interst.** | **7.8** | **5.6** | **5.2** | |
| **plasma equilibrated** | | **7.6** | **5.8** | **5.3** | |
| **time of equilibrium** | | **88 min** | **90 min** | **85 min** | |
| **% rebound** | | **42** | **41.3** | **43,3** | |

### 19.5.4 Phosphate Kinetics

Phosphate (P) clearance is generally lower than urea clearance for any dialyzer membrane, due to a higher diffusive resistance for P in whole blood, with blood cells acting as diffusion barrier (Kuhlmann 2010). Past studies have shown that P removal is scarcely affected by increasing blood flow rates (Gutzwiller et al. 2003) and not significantly different in high-flux HD compared to low-flux HD with membranes of similar surface area (Chauveau et al. 1991; Kerr et al. 1999). Membrane surface area itself has a potentially important impact on phosphate mass removal, as reported by studies showing increasing P clearances with dialyzers with increasing membrane surface areas (Jindal et al. 1989; Zucchelli and Santoro 1987). More recently, several studies have demonstrated the ability of HDF to enhance P removal and reduce plasma P concentrations (Davenport et al. 2010; Lornoy et al. 2006; Minutolo et al. 2002; Pedrini et al. 2011; Penne et al. 2010; Vaslaki et al. 2006).

Phosphate has a molecular weight of 96 Da and falls into the category of water-soluble small toxins. However, due to its hydrophilic characteristics, P molecule is surrounded by an aqueous cover, which increases its effective molecular weight. Phosphate distribution volume is assumed to be TBW but it is mainly distributed in $V_I$ and shows a slow intercompartmental transfer rate. These characteristics, which are more similar to those of middle molecules, determine the particular 2-phase kinetics of P during HD, with a steep decline of its concentration in the first half of the treatment and removal proportional to the initial concentration (Man et al. 1991; Sugisaki et al. 1982). Then, P concentration tends to level off or even to increase despite ongoing P removal during the second half of the treatment, and rebounds to almost pre-dialysis values after the end of the session (Gotch et al. 2003). The intradialytic decline of P concentration does not significantly change between HD and HDF despite the different removal (Minutolo et al. 2002). This behavior may be explained by the multi-compartmental kinetics of P, which is first removed predominantly from the extracellular plasma compartment and then from the intracellular space with a plasma P rate of change which is limited, in the second half of the session, by its transfer rate from the inner compartment(s) (Spalding et al. 2002).

HDF succeeds in enhancing P removal by convection in the first part of the treatment session. This leads to a greater reduction of P levels than during conventional HD, and a greater mobilization of phosphate from the inner compartment. This, in turn, results in a more pronounced rise of serum P levels in the second part of treatment and greater post-dialysis P rebound

in HDF compared to HD. However, cumulative P removal is greater in HDF and significant reduction of basal P levels is a possible long term effect of this convective technique (Minutolo et al. 2002).

For its characteristics, P kinetics during and after dialysis cannot be precisely simulated with the two-pool kinetic model of use in the case of most uremic marker solutes (Heaf et al. 1998). A comprehensive view of the limits of this model when applied to P kinetics has been provided by Spalding et al (2002), who compared the results of the application of different kinetic models, a two-pool, a three pool model and a four compartment model, to 29 patients on standard HD and HDF (see Fig. 19.13). In this study, the two pool model formulation was similar to the classical one, with a total distribution space for P coextensive to the TBW and divided into $V_I$ and $V_E$. In the three-pool model, a third compartment was added and P transfer from this pool to $V_E$ was supposed to occur when the intracellular P concentration dropped below an intracellular target concentration. In the four compartment model, the additional compartment released P in $V_I$ when intracellular P concentration fell to a critically low concentration. In the author's experiments, the two- and three-pool models failed in most cases to explain P kinetics, while the four-compartment model was able to fit all experimental data of HD and HDF treatments.

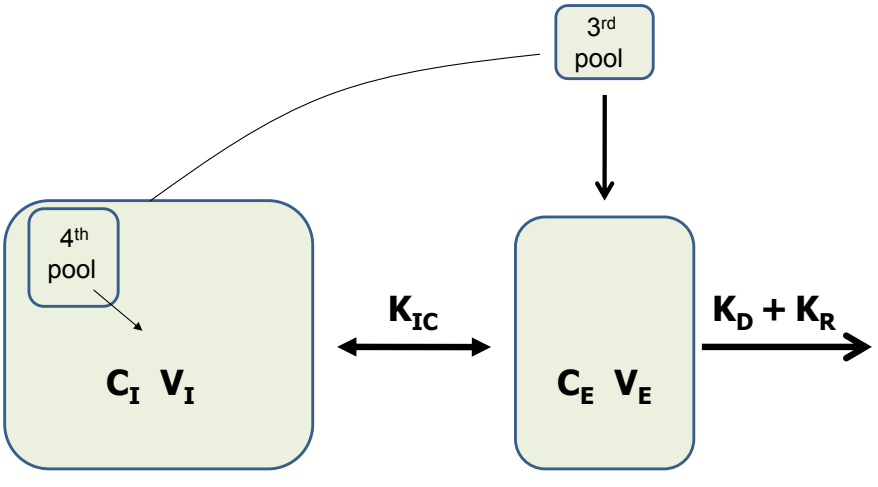



**Fig. 19.13** Schematic representation of the four-compartment kinetic model of phosphate proposed by Spalding et al (2002). The perfused and non-perfused compartments are VE and VI, respectively. The third compartment releases P into VE when P in VI drops below an intracellular target concentration. The fourth compartment releases P in VI when P in VI falls to a critically low concentration.

## 19.6 BIOLOGICAL EFFECTS OF HDF

The uremic syndrome includes a constellation of symptoms and metabolic derangements attributed to the retention in the body of a large number of compounds which are normally excreted by the healthy kidneys and can be toxic per se or only at the high concentration found in uremia. These compounds are called uremic toxins, when they interact negatively with biologic functions. Knowledge of the dependence of uremic abnormalities on specific toxic solute concentrations is still incomplete, so it is difficult at this time to define the precise role of all compounds in uremic derangements. A systematic classification of uremic solutes has been compiled by the European Uremic Toxin Work Group (EUTox) according to their characteristics, molecular weight and/or electro-chemical binding that potentially influence their removal pattern during dialysis (Vanholder et al. 2008; Vanholder et al. 2003). Three main physico-chemicals group of uremic toxins have been recognized: 1) free water-soluble low-molecular-weight solutes (MW <500 D), such as urea, creatinine, uric acid and several guanidine compounds; 2) middle-molecular solutes, (MW >500 D up to 30 kD), among which several peptides such as β2-microglobulin, myoglobin, cystatin C, clara cell protein, retinol-binding protein and cytokines such as interleukins and tumor necrosis factor α are included; 3) protein-bound solutes, mostly characterized by a MW <500 D, such as pentosidine, homocysteine, hippuric acid, p-cresylate, indoxyl sulphate, and others.

### 19.6.1 Free Water-Soluble Low-Molecular-Weight Solutes

Urea (MW 60 D) is a recognized marker of this category of toxins for its biological and metabolic characteristics and easiness to be detected and measured in blood. The fractional excretion index of urea removal during dialysis (Kt/V) has become the most used index of adequacy of dialysis treatment (Gotch and Sargent 1985). Removal of urea and of all free small molecular weight solutes mainly occurs by diffusion and, thus, it is very effective during low- and high-flux HD. However, online HDF has been shown to further increase urea (Lin et al. 2001b; Maduell et al. 2002; Pedrini et al. 2003) and creatinine (Lornoy et al. 2000; Ward et al. 2000) removal, and higher $Kt/V_{urea}$ has been reported on HDF treatment compared to HD at matched treatment duration and operational conditions (Lin et al. 2001b; Pedrini et al. 2011).

Phosphate molecule falls into the category of water-soluble low-molecular weight toxins (MW 96 D) but, for its hydrophilic characteristics, it is surrounded by an aqueous cover which considerably increases its

effective molecular weight. Moreover, P is mainly distributed within cells and is not freely diffusible into the extracellular space. For these reasons its elimination characteristics are different from those of urea and other small-molecular weight toxins and its intradialytic kinetics is more similar to that typical of middle molecules (Spalding et al. 2002).

HDF as compared to standard HD has been shown to increase P removal during single treatment sessions and to establish lower basal level in the medium-long term. This was demonstrated in several controlled studies and in large data base observational experiences (Davenport et al. 2010; Lornoy et al. 2006; Minutolo et al. 2002; Pedrini et al. 2011; Penne et al. 2010; Vaslaki et al. 2006) (see Table 19.3). Post-dilution HDF has been shown to be more effective than pre-dilution HDF and mixed-dilution HDF has shown a significant advantage over post-dilution HDF in regard of P removal (Feliciani et al. 2007).

**Table 19.3** Studies comparing the effect of HDF on basal P levels versus low-flux HD

| Author | year | comparison | study | n. of patients | follow-up | effect of high-flux HD | significance (p) |
|---|---|---|---|---|---|---|---|
| Minutolo | 2002 | low-flux HD vs HDF | RCT | 12 | 3 months | reduced levels on HDF | 0.05 |
| Pedrini | 2011 | low-flux HD vs HDF | RCT | 69 | 6 months | reduced levels on HDF | 0.008 |
| Penne | 2010 | low-flux HD vs HDF | RCT | 493 | 6 months | reduced levels on HDF | 0.001 |
| Vaslaki | 2006 | low-flux HD vs HDF | RCT | 70 | 6 months | reduced levels on HDF | <0.05 |
| Davenport | 2010 | low-flux HD vs HDF | audit | 5366 | - | reduced levels on HDF | <0.001 |

### 19.6.2 Middle-Molecular Solutes

Beta2-microglobulin (β2-m, 11.800 D) has been recognized as the most suitable marker of middle molecular uremic toxins of similar molecular weight by the European Best Practice Guidelines Expert Group (The EBPG 2002). Its pre-dialysis level was shown to predict mortality in the randomized Hemodialysis (HEMO) study (Cheung et al. 2006) and in a Japanese prospective trial (Okuno et al. 2009).

It has been demonstrated that β2-m removal is greater during a session of HDF than on low-flux and high-flux HD (Floege et al. 1989; Lornoy et al. 2000; Maduell et al. 2002; Pedrini et al. 2003). On HDF, β2m removal correlates with the convection volume of the session (Lin et al. 2001b; Lornoy et al. 2000). While β2m basal level is reported to progressively increase with time in chronic patients on RRT with low-flux HD, observational and randomized studies have shown that β2m level remains stable (Locatelli et al. 2009) or may be reduced (Locatelli et al. 1996) in patients on high-flux HD, and even significantly decreases with time in patients switched to online HDF (Lin et al. 2001b; Locatelli et al. 1996; Pedrini et al. 2011) or HF (Beerenhout et al. 2005; Santoro et al. 2008). This effect is most pronounced when residual renal function is absent (Fry et al. 2007).

Besides β2-m, other uremic compounds of the larger molecular spectrum were removed to a greater extent in HDF with all the available highly permeable and biocompatible membranes. This was shown for myoglobin (17.2 kD) (Maduell et al. 2002), factor D (24 kD) (Beerenhout et al. 2005; Ward et al. 2000). A complement fraction abnormally elevated in patients with renal failure, other complement fractions, such as fraction Ba (33 kDa) (Kaiser et al. 1995), C3a (8,9 kD) and C5a (11 kD), (Jorstad et al. 1988). Online HDF has also been associated with increased removal and/or reduced production of pro-inflammatory cytokines such as TNF-α (17 kD)( Carracedo et al. 2006; Gil et al. 2003), interleukins 1-6-8 (17 kD) (Bouman et al. 1998; Carracedo et al. 2006; Gil et al.2003; Goldfarb and Golper 1994;Panichi et al. 2008) and proinflammatory CDl4+ CD16 + cells (Carracedo et al. 2006)., and with improvement of variables related to endothelial dysfunction (Ramirez et al. 2007), oxidative stress, and antioxidant capacity (Calo et al. 2007; Filiopoulos et al. 2008). Moreover, two randomized crossover studies demonstrated a potent effect of high-flux membranes on lipoprotein and lipid profiles (Wanner et al. 2004) and a significant reduction in triglycerides and increase in high-density lipoprotein concentration as a long-term effect of on-line HDF with high-flux membranes, not shown with standard HD (Pedrini et al. 2011).

**19.6.3 Protein-Bound Solutes** follow during dialysis a multicompartmental kinetics similar to that of the middle molecules in spite of their generally low molecular weight, as a possible consequence of their protein binding and metabolic transformation. Substantial part of removal of these compounds occurs by diffusion. As such, pentosidine (379 D) was removed to a similar extent (70%) with low-flux and high-flux membranes and long-term lower basal levels were only observed in patients on high-flux polysulfone, possibly as a consequence of reduced oxidative stress

promoted by this membrane (Jadoul et al. 1999). On the contrary, high-flux and low-flux polysulfone resulted in similar plasma level of homocysteine (135 D) in a 3-month longitudinal study, despite the greater removal per session obtained with the high-flux membrane (House et al. 2000). More recently, observational and randomized controlled studies have shown that internal HDF and on-line HDF applied in the long term were both able to reduce homocysteine level to a greater extent than low-flux HD (Beerenhout et al. 2005; Eiselt et al. 2010; Pedrini et al. 2011; Righetti et al. 2010). Variable reduction ratios have been reported for asymmetric dimethylarginine (ADMA, 202 D) during low-flux HD and HDF, but without significant long-term change of its basal level with both techniques (Beerenhout et al. 2005; Eiselt et al. 2010; Pedrini et al. 2011).

Convection was shown to positively impact protein-bound toxin removal because HDF was able to increase p-cresol clearance without leading to excessive albumin loss (Bammens et al. 2004). Similar removal (40% to 50%) of p-cresyl sulphate (MW 187 D, protein binding ±95%) and indoxyl sulphate (MW 212 D, protein binding ±90%) was reported during HD and HDF sessions with high-flux membranes (Krieter et al. 2010; Lesaffer et al. 2000) . On HDF, removal of different solutes was inversely proportional to the percentage of protein binding and ranging from 4% in the case of carboxy-methyl-propyl-furanpropanoic acid (CMPF, MW 240 D, protein binding ±100%) to 74% in the case of hippuric acid (MW 179 D, protein binding ±50%) (Meert et al. 2009). A clear effect of flux on such compounds, as well on homocysteine, was shown with the use of large pore "superflux" polysulfone and triacetate cellulose membranes (DeSmet et al. 2007; van Tellingen et al. 2001) at the expense, however, of significant albumin leakage. The longitudinal application of online post-dilution HDF was recently shown to result in consistent and progressive decline of the basal level of some protein-bound uremic solutes, particularly those with the strongest protein binding (p-cresylsulfate and CMPF), and this effect was not observed in the patients group on high-flux HD (Meert et al. 2010).

## 19.7 CLINICAL EFFECTS OF HDF

Several protein-bound and middle-molecular solutes have a pathogenic role or are markers of the most frequent long-term complications and causes of death in HD patients. Data from a number of clinical studies suggest that the use of online HDF may be associated with enhanced removal and reduced basal levels of these compounds that might be of relevance in the

pathogenesis of uremic and cardiovascular complications. So, HDF may promote a whole array of potential beneficial effects which individually are believed to improve clinical outcome.

Beta2-microglobulin accumulation and oxidation is retained as the main cause of dialysis related amyloidosis. Lower basal β2-m level, established in patients treated for long time with high-flux membranes and on-line HDF, not only resulted in lower incidence and progression of this invalidating systemic disease (Koda et al. 1997; Locatelli et al. 1999; Van Ypersele de Strihou 1996) but, outstandingly, it has been associated to a significant lower risk of mortality in HD patients, independent of treatment duration, diabetes, malnutrition and chronic inflammation (Cheung et al. 2006; Okuno et al. 2009). As well, lower phosphate level achieved in patients on long-term convective treatments (Davenport et al. 2010; Pedrini et al. 2011; Penne et al. 2010; Vaslaki et al. 2006) supported by appropriate pharmacological therapy may help to prevent the progression of mineral metabolic disorders caused by secondary hyperparathyroidism(Pedrini et al. 2011)., and of the accelerated athero- arteriosclerotic lesions which are the main cause of morbidity and mortality of uremic patients. Indeed, phosphate level has been associated with mortality in several authoritative studies (Block et al. 2004; Covic et al. 2009). Thus, online HDF may lead with time to a potentially improved outcome, given that the amount of β2-m and phosphate removal is greater than in high-flux therapy and leads with time to lower basal levels of these uremic toxins.

Several protein-bound solutes have been found to be toxic in vitro (Dou et al. 2004; Dou et al. 2007; Schepers et al. 2007)., and some of them have also been associated with adverse outcomes in dialysis patients, such as atherosclerosis (Taki et al. 2007)., cardiovascular disease (Meijers et al. 2008) , infectious disease (DeSmet et al. 2003), and neurological abnormalities (Deguchi et al. 2006). The free p-cresol serum concentration predicts overall mortality in HD patients group (Bammens et al. 2006). P-cresyl sulfate, the main in vivo metabolite of p-cresol, promotes vascular disease in uremia as a consequence of its pro-inflammatory effect on unstimulated leucocytes leading to oxidative stress and, consequently, atherosclerosis (Schepers et al. 2007). Since, convective strategies can result in significantly reduced plasma levels of these protein-bound compounds (Bammens et al. 2004; Meert et al. 2009), they may be beneficial for patients outcome.

Both uncontrolled and randomized studies have reported decreased erythropoietin resistance and reduced need for its administration in patients

treated with online HDF (Lin et al. 2002; Maduell et al. 1999; Pedrini et al. 2011; Vaslaki et al. 2006) possibly as an effect of the increased removal of middle molecular inhibitors of erithropoiesis (Bonomini et al. 2004; Le Meur et al. 2001). In this respect, also favored by the use of ultrapure dialysis fluid, HDF may play a role in the control of anemia in uremic patients by creating a more biocompatible environment with less toxic and inflammatory stimuli.

Intradialytic hypotension is frequently observed during HD and is associated with regional wall motion abnormalities of the left ventricle and myocardial stunning (McIntyre 2010). Repeated episodes can contribute to myocardial damage and cardiomyopathy. Online HDF and HF have been associated with improved hemodynamic stability and blood pressure control in some studies (Altieri et al. 2001; Lin et al. 2001a; Locatelli et al. 2010), but not in others (Karamperis et al. 2007). However, this effect, rather than to increased removal of unknown hypertensive factors, seems mainly due to the large amount of cooler substitution fluid infused in online HDF which causes thermal energy loss within the extracorporeal system and so avoids vasodilatation caused by heat accumulation (Donauer et al. 2003).

## 19.8 EFFECTS OF HDF ON OUTCOME

The hypothesis that the enhanced removal of larger solutes obtained with high-flux membranes might result in improvement of hard clinical end points, has been confirmed in a number of observational studies, and in two large data-base randomized trials. The HEMO study showed no difference in survival between low- and high-flux HD in the overall study population (Eknoyan et al. 2002). However, a reduced rate of death for cardiac causes (Eknoyan et al. 2002) or cerebrovascular disease (Delmez et al. 2006) in patients treated with high-flux membranes, as well as longer survival in patients undergoing high-flux HD for >3.7 years were observed in post hoc subgroups analyses. Similarly, a primary analysis of the European Membrane Permeability Outcome (MPO) study showed improved survival of high-flux HD patients with albumin level ≤4 g/dL and of diabetic patients in a secondary analysis (Locatelli et al. 2009). Moreover, a post-hoc analysis of the German 4D study (Krane et al. 2007) and a large observational French study (Chauveau et al. 2005) showed a superior survival in patients treated with high-flux as compared to low-flux HD (see Table 19.4).

**Table 19.4** Studies comparing mortality risk in low-flux HD versus high-flux HD.

| Author | year | comparison | study | n. of patients | follow-up, years | effect of high-flux HD |
|---|---|---|---|---|---|---|
| Eknoyan (HEMO Study) | 2002 | low-flux vs high-flux HD | RCT | 1846 | 2.8 (mean) | reduced death risk 8% , n.s. (main outcome)<br>reduced cardiac death risk 32% , p<0.05 (secondary outcome)<br>reduced death risk for patients on high-flux for > 3.7 years, p<0.005 (secondary outcome) |
| Locatelli (MPO Study) | 2009 | low-flux vs high-flux HD | RCT | 738 | 3.0 ± 1.9 | reduced death risk 24% , ns (main outcome)<br>reduced death risk with albumin < 4.0 g/dl 37%, p<0.01 (main outcome)<br>reduced death risk diabetes 37%, p=0.056 (subgroup analysis) |
| Krane (4-D Study) | 2007 | low-flux vs high-flux HD | RCT | 648 | 4 .0 | reduced death risk 63% , p<0.001 (post-hoc) |
| Chauveau | 2005 | low-flux vs high-flux HD | observ. | 650 | 2.0 | reduced death risk 38% , p<0.01 |

The evaluation of the impact of HDF on hard clinical end points is still underway. However, the available evidence is suggestive for a definite benefit of convective treatments as compared to low- and high-flux HD at least in some categories of patients and/or treatment modalities (see Table 19.5). A small Italian randomized study showed better survival in patients on HF compared to low-flux HD over a 3-years period (Santoro et al. 2008). Some observational and registry studies reported similar findings: in a retrospective analysis of the European Dialysis Outcomes and Practice Patterns Study (DOPPS), Canaud et al. reported a significant 35% lower mortality risk in patients on high-efficiency HDF (volume exchange 15–25 liter per session), compared to low- and high-flux HD (Canaud et al. 2006). In a British study by Vilar et al., a reduced hazard for death of 0.66 was reported in 232 patients who were treated solely by HDF compared with 637 patients who solely used high-flux HD (Vilar et al. 2009). In the RISCAVID prospective study a survival benefit was associated with online HDF over standard HD; however, only 4.9% of the HD population used high-flux membranes (Panichi et al. 2008; Jirka et al. 2006) also reported similar results from data collected through the EuCliD network with a mortality reduction of 35.3% compared with an HD group (Jirka et al. 2006). It was not specified what proportion of the HD group used high-flux membranes.

Most recently, two large database prospective studies have been closed and results made public. The CONTRAST Study (Grooteman et al. 2011) did not show any benefit in terms of survival and fatal or not fatal cardiovascular events in 358 patients submitted to on-line HDF compared to a matched group of patients undergoing low-flux HD for a 3-years period. In analogy, the "Turkish HDF Study" (Ok et al. 2011), comparing high-flux HD and on-line HDF, found similar risk of death and composite cardiovascular risk in the overall study population (782 prevalent patients) after a 2-years follow-up. However, secondary subgroup analysis of both studies suggested benefit among patients treated with high convection volumes on cardiovascular and overall survival compared to HD. In the CONTRAST Study, HDF with over 20 liter/treatment was associated with a 34% reduction of mortality risk. In the Turkish Study, the subgroup of 195 HDF patients treated with a volume exchange of more than 17.4 liter/session showed better cardiovascular and overall survival than both the subgroups of HDF patients with substitution volume less than 17.4 liter session (p=0.03) and the HD patients (p=0.002). Even if secondary analyses entail reduced statistical power, the results obtained with high volume exchanges in HDF are impressing.

**Table 19.5** Studies comparing mortality risk in low- and high-flux HD versus HDF

| Author | year | comparison | study | n. of patients | follow-up years | reduced death risk with HDF , % | significance (p) |
|---|---|---|---|---|---|---|---|
| Grooteman | 2011 | low-flux HD vs HF | RCT | 714 | 3.0 | 9.0 | ns |
| Ok | 2011 | high-flux HD vs HDF | RCT | 782 | 2.0 | - | ns |
| Santoro | 2008 | low-flux HD vs HF | RCT | 64 | 3.0 | 41.6% | <0.05 |
| Canaud | 2006 | low-flux HD vs HDF | observ. | 2165 | 3.0 | 35% | 0.01 |
| Vilar | 2009 | high-flux HD vs HDF | observ. | 858 | 10 | 34% | 0.014 |
| Panichi | 2008 | low-flux HD vs HDF | observ. | 757 | 2.5 | 22% | 0.01 |
| Jirka | 2006 | low-flux HD vs HDF | observ. | 2564 | 1 | 35% | <0.05 |

## 19.9 CONCLUSION

Medium–long m term application of on-line high-efficiency HDF compared to low- and high-flux HD results in enhanced removal and lower basal levels of small, medium and protein-bound uremic solutes, some of which are retained as markers or causative agents of several uremic derangements, mainly inflammation, secondary hyperparathyroidism, dyslipidemia and cardiovascular disease. Probably, many of the benefits attributed to HDF potentially result from a general reduction of the uremic toxicity. This might be the link with the clinical benefits reported in patients undergoing chronic HDF which eventually contribute to improving patients' survival, as suggested by published studies. However, in the absence of, a definite evidence, it is reasonable to conclude that online HDF is a logical and safe therapy effective in maintaining the life and well-being of dialysis patients. Knowledge of the performance of materials, apparatus and devices used in HDF, and study of the solute transport mechanisms with the aid of modelling simulation will help to optimize this technique and obtain additional clinical benefits.

## APPENDIX A: GLOSSARY

| | |
|---|---|
| A | Surface Area Of A Membrane |
| BW | Body Weight |
| C | Concentration |
| D | Dialyzer Dialysance |
| ESRD | end-stage renal disease |
| FF | filtration fraction |
| $F_P$, $F_R$ | fractions of plasma and red cell water |
| G | rate of solute generation |
| HD, HDF, HF | hemodialysis, hemodiafiltration, hemofiltration |
| Hct | hematocrit |
| KoA | overall mass transfer coefficient of the solute (per area) |
| $K_{UF}D$ | ultrafiltration coefficient of a dialyzer |
| $K_D$, $K_R$, $K_{ER}$, $K_T$ | dialyzer clearance, residual renal clearance, extra-renal clearance, total clearance ($K_D + K_R + K_{ER}$ ) |
| $K_{IC}$ | solute inter-compartment mass transfer coeffi-cient (inter-compartmental clearance) |
| $K_{CW}$ , $K_W$ | Water transcellular and transcapillary coefficient |
| Lp | hydraulic permeability of the membrane for water |
| MW | molecular weight |
| MM | middle molecule |
| P | phosphate |
| $P_B$ , $P_D$ | hydraulic pressure within the blood/ dialyzer compartment |
| $Q_B$ , $Q_E$, $Q_D$ | whole-blood, effective blood and dialysate flow rate |
| $Q_{UF}$ | ultrafiltration rate |
| $R_D$ | Donnan factor |
| SF | super-flux (membranes) |
| $S_C$ | sieving coefficient |
| t, $t_d$ , $t_{id}$ | time, duration of the dialysis session and the inter-dialytic period |
| TMP | trans-membrane pressure |
| UF | ultrafiltration |
| α | constant rate of change in V during the interdialytic period |

## APPENDIX A (Continued)

| | |
|---|---|
| β2-m | beta2-microglobulin |
| Π | colloid osmotic pressure |
| χ | ratio of a substance in two compartments at equilibrium ($C_E = \chi C_I$) |
| γ | coefficient which expresses the resistance of a solute to trans-cellular transfer |

## APPENDIX B: Suffix

| | |
|---|---|
| B, D, UF | blood, dialysate, ultrafiltrate |
| *in*, *out* | inlet and outlet ports of blood and dialysate compartments of the dialyzer. |
| o, t | start and end of the treatment session |

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## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. The scarce biocompatibility of cellulosic membranes was mainly related to…
   A. Their hydrophilic properties.
   B. The hydroxyl groups included in the chemical structure of these membranes.
   C. Their thin-walled structure.

2. Diffusion of small molecular weight solutes across a dialyzer membrane is favored by…
   A. The reduced thickness of the capillary wall and the porosity of the membrane.
   B. The large size of the pores.
   C. Low dialysate flow.

3. The hydraulic permeability of high-flux synthetic membranes is mainly related to…
   A. The pore size (diameter)
   B. Thickness of the inner layer of the membrane.
   C. Thickness of the spongy stroma of the membrane.

4. Earlier high flux membranes allowed high ultrafiltration rates but limited small solutes transfer by diffusion. What was the reason?
   A. The large pore diameter.
   B. Their chemical composition.
   C. The marked thickness of the whole hollow fiber wall.

5. The main characteristics of super-flux membranes are…
   A. They have pores with larger size than high-flux membranes.
   B. They provide greater clearances of low molecular weight proteins and small protein-bound solutes than do conventional high-flux membranes.
   C. They allow considerable amount of albumin loss in the dialysate.
   D. All of the above answers.

6. Plasma water ultrafiltration across a dialyzer membrane occurs as a consequence of…
   A. A pressure gradient established across the dialyzer membrane.
   B. A solute concentration gradient established across the dialyzer membrane.
   C. As an effect of the oncotic pressure of blood.

7. An index which expresses the ability of a dialyzer membrane to ultrafiltrate plasma water is…
   A. The Sieving coefficient for albumin.
   B. The ultrafiltration coefficient of the dialyzer ($K_{UF}D$, ml/hour/mmHg of TMP).
   C. The ultrafiltration rate in the absence of a pressure gradient across the membrane.

8. The ultrafiltration coefficient of the dialyzer ($K_{UF}D$)…
   A. Is the slope of the linear regression equation which relates the ultrafiltration rate ($Q_{UF}$) to the trans-membrane pressure (TMP) up to a certain TMP value (200-300 mmHg)
   B. Reduces progressively in vivo through a HDF session as a consequence of the protein layer formation on the inner surface of the membrane.
   C. Must be greater than 40 ml/hour/mmHg of TMP for high-flux dialyzers.
   D. Largely depends on the characteristics of the membrane (the pore radius).
   E. All of the above answers.

9. Removal of small solutes by diffusion is mainly influenced by…
   A. The blood flow rate ($Q_B$).
   B. The dialysate flow rate ($Q_D$).
   C. The trans-membrane pressure.

10. Removal of middle molecular solutes is mainly influenced by…
   A. The blood flow rate ($Q_B$).
   B. The overall surface area of the membrane.
   C. The dialysate flow rate ($Q_D$)

11. The sieving coefficient ($S_C$, dimensionless) is…
    A. Characteristic for a solute irrespective of the membrane.
    B. Characteristic for a membrane irrespective of the solute.
    C. Typical for a defined solute and a defined membrane.

12. The sieving coefficient ($S_C$)…
    A. Is a function of the membrane characteristics (electro-chemical properties and structure, pore radius and conformation.
    B. Is inversely related to the solute molecular weight and varies between 0 for a freely permeable molecule and 1 for a completely impermeable molecule.
    C. Reduces similarly to $K_{UF}D$ through the session in the case of middle molecular compounds and may approach zero in convective treatments at excessively high $Q_{UF.}$
    D. All of the above answers.
    E. None of the above answers.

13. Adsorption of solutes into the inner membrane surface…
    A. May occur when membranes not carrying electrical charges are used.
    B. Does not contribute to the overall solute removal from blood.
    C. Occurs to a greater extent on hydrophilic cellulosic membranes than on synthetic hydrophobic membranes.
    D. Albumin adsorption reduces the in vivo permeability of a membrane.

14. Whole-blood clearance of solutes not freely diffusible across the erythrocyte membrane…
    A. Underestimates the actual solute removal rate.
    B. Overestimates the actual solute removal rate.
    C. Determines the actual solute removal rate.

15. The Donnan factor ($R_D$), i.e. the ratio between the ionic concentration in dialysate and blood applies to…
    A. Positively charged solutes.
    B. Negatively charged solutes.
    C. Both of them.

16. During HDF, the total solute removed…

A. is the sum of diffusive and convective transfer.
B. Occurs by both transport mechanisms but it is lower than their algebraic sum due to negative interactions between them.
C. Only occurs by convection.

17. Internal filtration is a transport mechanism acting on…
A. Post-dilution HDF.
B. Mixed HDF.
C. Mid-dilution HDF.
D. high-flux HD.

18. During high-flux HD, water flow reverses its direction (internal filtration) within the dialyzer when…
A. The algebraic sum of hydrostatic and colloid osmotic blood pressure matches the hydrostatic pressure in the dialysate compartment.
B. The hydrostatic pressure in the dialysate compartment becomes positive.
C. The algebraic sum of hydrostatic blood and dialysate pressure becomes null.

19. During post-dilution HDF, very high ultrafiltration rates may result in…
A. Risky trans-membrane pressure.
B. Excessive haemoconcentration.
C. High blood viscosity.
D. Reduction of solute and water permeability of the dialyzer membrane.
E. All of them.
F. None of them.

20. When the above condition occur during post-dilution HDF, it is necessary to…
A. Reduce ultrafiltration rate.
B. Increase dialysate flow rate.
C. Stop the treatment session and substitute the dialyzer.
D. Reduce blood flow rate to the dialyzer.

21. At similar ultrafiltration rates pre-dilution HDF is less efficient than post-dilution HDF due to…
    A. Reduced convective power.
    B. Reduced diffusion of solutes.
    C. Dilution of blood entering the dialyzer and diluted concentration of solutes available for both diffusion and convection of solutes.

22. Middle molecular solutes are removed during HDF with endogenous reinfusion…
    A. By diffusion.
    B. By adsorption through the passage in a sorbent cartridge.
    C. By convection.
    D. All combined transport mechanisms.

23. Maximal infusion rate is maintained in mixed HDF by…
    A. Modulating the ratio between post- and pre-dilution.
    B. Increasing/decreasing the total infusion rate according to the expansion/contraction of circulating blood volume.
    C. Maintaing the trans-membrane pressure within an optimal range of values to get maximal filtration.
    D. All mechanisms.

24. Which of the following sentences is/are correct…
    A. The inter-compartment mass transfer coefficient ($K_{IC,}$ ml/min ) of a solute is the inter-compartmental clearance of the solute.
    B. $K_{IC}$ changes in accordance with the rates of blood and dialysate flow.
    C. $K_{IC}$ depends on the resistance opposed by the cell membrane to the solute transfer.
    D. $K_{IC}$ is null for large impermeable molecules and large for freely diffusible small molecules.

25. Which of the following sentences is/are correct…
    A. Post-dialysis rebound of a solute is mainly the expression of concentration re-equilibration between the distribution pools of the solute.
    B. Magnitude and duration of post-dialysis rebound are inversely proportional to the solute $K_{IC.}$
    C. Post-dialysis rebound of a solute is mainly the expression of the solute generation during the interval between dialyses.

D. Not accounting for post-dialysis rebound leads to an overestimate of the distribution volume for urea in single-pool urea kinetic model.

26. The distribution space assumed for sodium (Na) in two-pool model formulation is…
A. Total body water (TBW). Na is anatomically confined to the extracellular space but its osmotic power extends to the TBW.
B. The extracellular space.
C. The intracellular space.

27. The total distribution space for β2-microglobulin is…
A. The total body water (TBW).
B. The extracellular space ($V_E$).
C. The intravasculat space ($V_P$).

28. Which of the following sentences is/are correct…
A. Phosphate is a small molecular weight solute and its kinetics may be reliably simulated with a single-pool kinetic model.
B. HDF has scarce effect on phosphate removal and on its basal level.
C. Phosphate kinetics is more reliably simulated with a multiple-pool model.

29. The HEMO Study demonstrated that chronic HD patients treated with high flux membranes survive longer than those treated with low-flux membranes?
A. Yes, definitely.
B. No difference was shown in survival between low- and high-flux HD in the overall study population, but some sub-groups analyses were highly suggestive for longer survival of patients on high-flux HD.
C. No, definitely.

30. The European Dialysis Outcomes and Practice Patterns Study (DOPPS) reported a significant 35% lower mortality risk in patients on HDF compared to low- and high-flux HD when HDF was performed with volume exchange of…
A. At least 10 liter per session.
B. Between 15 and 25 liter per session.
C. Greater than 25 liter per session.
D. Irrespective of the amount of exchanged volume.

# Part III

# Biofeedback Systems and Soft Computing Techniques of Dialysis

Chapter (20)

# Biofeedback Systems and Their Application in the Hemodialysis Therapy

Antonio Santoro, Elena Mancini, and Ahmed Taher Azar

**CHAPTER OUTLINES**

- Introduction
- The Biofeedback Concept
- Monitoring and controlling hemodialysis
- Biochemical monitoring and control
- Conclusion

**CHAPTER OBJECTIVES**

- Define the concept of Biofeedback system.
- Discuss various Types of Biofeedback systems.
- Understand the importance of on-line monitoring devices.

**KEY TERMS**

- Biofeedback
- Open-loop Control System
- Closed-Loop Control System
- Multi-Input Multi-Output systems
- Actuators
- Adaptive Controllers
- On-line monitoring
- Blood volume
- Body temperature
- Ultrafiltration
- Blood Pressure
- Biochemical
- Hemodynamic

## ABSTRACT

The traditional control of the dialysis session comes about by means of an open-loop system. At the beginning of the session some parameters are set, such as the kind of dialyzer, the blood flow, the ultrafiltration rate, the dialysate conductivity and the dialysate temperature. Generally speaking, these parameters are not modified unless there occur complications in the patient that call for adjustments to be made. The biofeedback concept, which is synonymous with a closed-loop control of biological variables, presupposes, on the other hand: the continuous measurement of a variable thanks to a specific sensor its evaluation by a sort of expert system - the

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so-called controller and a series of means - the actuators - that allow the behavior of the variable to be directly or indirectly influenced. In clinical practice, different biofeedback systems are emerging, addressed to the control of blood volume, body temperature, and blood pressure. Each one of these systems has been successfully utilized, especially in the management of "difficult" patients unstable from the hemodynamic point of view. However, the future will be an integrated system that sees a complex adaptive, multi-input, multi-output controller which, with a great simplicity of use and low costs, will allow renal replacement therapy to be increasingly physiological and more efficient.

## 20.1 INTRODUCTION

The progressive increase in the mean age and the growing conditions of co-morbidity, especially of cardiovascular pathologies and diabetes, has significantly worsened the patients' clinical status and tolerance to the hemodialysis (HD) treatment. On the other hand, the demand for short treatment times enhances the risk for hemodynamic instability as well as for inadequate depuration.

The traditional management of the dialysis session, setting of predefined treatment parameters, with active therapeutic interventions only in the event of complications, is definitely unsuitable for short-lasting treatments, often complicated by hemodynamic instability, especially in critical patients.

The first step to improve the management of the dialysis session is the utilisation of continuous and uninvasive monitoring systems for hemodynamic or biochemical parameters involved in the dialysis quality. Special sensors for the continuous measurement of blood volume, blood temperature, blood pressure, heart rate, electrolytes, have been realized throughout the last 10 years. As a second step, some of these devices have been implemented in the dialysis instrumentation, mainly with a view to preventing cardiocirculatory instability but also to control the dialysis efficiency (biofeedback control systems).

The basic components of a biofeedback system are: the plant, the sensors, the actuators and the controller. The plant is the biological process that we need to control, while the sensors are the devices used for measuring the variables under control. The actuators are the working arms of the controller. The controller is the mathematical model that continuously sets the measured output variable against the reference input and modifies the actuators in order to reduce any discrepancies.

Yet, in practice there are a number of conceptual, physical and technological difficulties to be overcome. In particular, the behaviour of what is to be controlled may be non-linear and time-varying, with interactions between the actuators and the controlled variable. In these cases, more sophisticated control systems are needed, which must be capable of identifying the behaviour of the process, and continuously up-date information data while the control is on. These complex systems are called adaptive controllers.

At present, there are three biofeedback systems routinely used in clinical dialysis (Santoro et al. 2003a; Locatelli et al. 2005; Azar 2008). All of them are aimed to improve the cardiovascular stability during HD, that is, at present, one of the main problem limiting on the one hand the tolerance to treatment by the patient, and on the other hand, the quality of HD in itself. One is the biofeedback control of blood volume, one is the biofeedback control of thermal balance, and the third is the biofeedback control of blood pressure.

Renal replacement therapies have enjoyed an exceptional development in the past few decades. Indeed, there has been a shift away from treatments aimed solely at the survival of the patient to systems capable of interacting with the various functions of the organism to such an extent as to be capable of addressing attention also to the patient's rehabilitation and quality of life.

Today we have the chance to view dialysis treatment from a more all-inclusive standpoint, oriented to the "patient-system" through the application of methods and techniques more typical of bioengineering and through a wider use of sensors and computers. The time has come to redefine the concept of the artificial "kidney" organ endowing it with the capacity to adapt the functions of the device to the physiological, hemodynamic and metabolic needs of the organism it has to interact with. In practice, it is now necessary to think in terms of biofeedback, which is a mechanism capable of measuring a physical-chemical status of the organism and react automatically to maintain it, or to bring it back to a condition of equilibrium.

The human organism is an extremely complex system of controls integrated with one another that operate at different hierarchical levels in order to maintain internal homeostasis also when faced with substantial variations in the environmental conditions in which it made to live. Historically speaking, bioengineering is a science that has set itself the primary objective of studying and reproducing the various organs and their main functional principles by means of non-organic devices. The concept

of being able to substitute the diseased organ, besides merely being able to heal it, has brought about an outright revolution in the therapeutic and rehabilitative field.

## 20.2 THE BIOFEEDBACK CONCEPT

Ever since the dawning of human kind, control has always meant a form of power over man's environment. Although control is sometimes equated with the notion of feedback control (involving the transmission and return of information), modern usage tends to favour a broader meaning of the term. For instance, the control and regulation of machines, the control of prosthetic devices, general aspects of co-ordinated activity in the social sphere, such as the optimisation of business operations, the control of economic activity by means of government policies and even the control of political decisions by means of democratic procedures.

In the language of engineering, a control system is the set of interconnected components capable of providing the desired response by a given system. As a function of the configuration of the components, control systems are subdivided into two large categories: direct action controls (so called 'feed-forward' or open chain) and 'feedback' control. Examples of such control systems are present in many human activity applications: in the car sector all the anti-sliding control systems (ABS), the traction control and the speed cruise, as well as in the sector of heating and cooling (air-conditioning) or in the control of industrial processes. Some of these systems are in actual fact already present on the dialysis monitors: the temperature of the dialysis bath, the conductivity or the ultrafiltration are variables controlled by feedback systems. In order to understand the need to extend such control techniques to biological systems it is necessary to recall some salient characteristics of the control systems in open-chain or feedback.

The open-chain systems are generally easier to manufacture industrially, they do not necessarily require a sensor to measure the controlled variable, but have as a downside a less accurate regulation and a greater sensitivity to the variations in the environmental conditions in which they operate (noise) if the laws that govern the system to be controlled are not known in detail.

Given, therefore, the law that describes the controlled variable as a function of time and the control variable ($y = f(t,u)$), it is sufficient to apply the forcing action $u_0$ to obtain the desired response $y_0$. For example, having to warm up a room, if the external temperature and the thermal

resistance to the passage of the heat towards the outside are known, it is enough to apply a fixed thermal power in order to take the temperature internal to room to the desired value. However, if there appears a variation in the external temperature or a thermal resistance of the room, the law describing the system is modified; thus, with thermal power being equal, the internal temperature will be different.

The feedback systems function according to the principle of error minimisation between the desired value of the variable to be controlled and its direct measurement (see Fig. 20.1). These are more complex systems to be manufactured industrially, and require a sensor for the measurement of the controlled variable. However, they do not require a detailed knowledge of the laws governing the system to be controlled, they are more insensitive to the noise and guarantee a greater accuracy and control precision. For these reasons, the feedback techniques are more promising in the applications to biological systems, in that the law governing the system is not always known, the system parameters to be controlled are time-variable, the initial conditions in which the biological system functions are not known. Going back to the previous example, a thermoregulation system is definitely more effective in that also in the presence of variations in the external temperature or in the thermal resistance they are always capable of reaching the desired internal temperature.

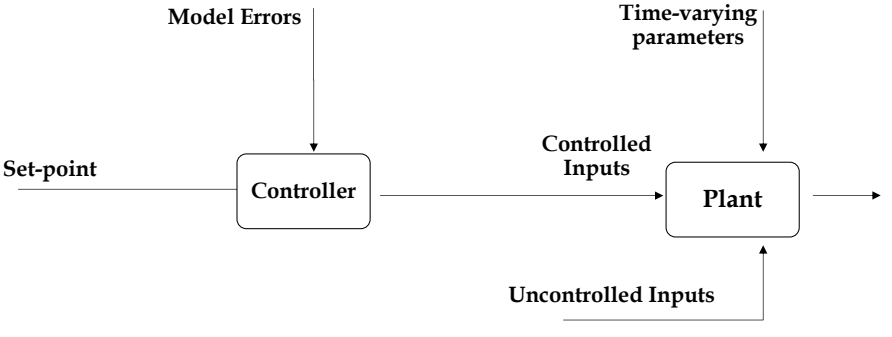


**Fig 20.1** Schematic representation of an open-loop control system. The control parameters are set at the beginning of the process in order to obtain a desired change in the plant. However, model errors or time-varying parameters or uncontrolled inputs can modify the plant response during the process control and thus the result.

Biofeedback is widespread in nature and, in physiology; the term is synonymous of a servosystem, which controls a biological process such as muscular co-ordination and metabolism. A classic example is that of body

temperature regulation, which is kept constant independently of the external temperature. Thermoreceptors continuously measure the core and surface temperatures and send this information to the integration centres. The integration centres, via descending pathways, control the state of the effectors, the skin blood flow, the sweat rate and shivering, and keep the body temperature constant in spite of large changes in the outside temperature. Learning a lesson from nature, bioengineering has codified the basic components of a biofeedback: the process, the sensing elements, the actuators and the controller.

The process is the system that we would like to control, while the sensing elements are devices for measuring the output variable. This is the variable that is measured and compared to the input, i.e. the output's reference value. The controller consists of a mathematical model that continuously sets the measured output variable against the reference input and modifies the actuators in order to reduce the differences between them.

The scientific formulation of a control problem is based on two kinds of information: a) the behaviour must be described in a mathematically accurate way; b) the purpose of the control and the environment (noise) must be specified, again in a mathematically accurate way. This is the theory, while, in practice, the development of feedback systems has several conceptual, physical and technological difficulties to overcome. Often the process to be controlled and the quantification of the desired effects may not be wholly understood. Indeed, the behaviour of what is to be controlled may be non-linear and time-varying and, lastly, the controlled variable may interact with the actuators.

A problem that is posed in the biofeedback systems is that of the system's stability. If indeed the size of the biofeedback is too low (the ring gain is small) the control can prove to be ineffective, whereas if it is too high, the control can prove to be unstable and give rise to unwanted behaviours.

In dialysis, over the last few years, it has been relatively easy to realise some biofeedback systems, since a series of sensors have been developed for the online monitoring (Santoro 1995). The dialysis machines have become increasingly sophisticated and capable of providing accurate adjustments and this has turned them into powerful actuators. Furthermore, the internal computers are equipped with are also capable of hosting complex controllers of a multi-input and multi-output type.

## 20.3 MONITORING AND CONTROLLING HEMODIAYSIS (HD)

The need of new systems to check and possibly improve the quality of the dialysis treatments mainly derives from the characteristics of the present patient population on chronic dialysis treatment. In fact, the progressive increase in the mean age and the growing conditions of co-morbidity, especially of cardiovascular pathologies and diabetes, has significantly increased the patient's critical status. On the other hand, the demand for short treatment times enhances the risk for hemodynamic instability as well as for inadequate depuration.

The traditional management of the dialysis session presupposes the setting of pre-defined session parameters, and the active therapeutic interventions are limited to those situations in which complications occur. At the end of the pre-set time, often without taking account of the so-called recovery times and with no chance to check the "quality" of the depuration, the treatment is interrupted. Its efficacy is occasionally checked or else only when belated clinical complication appear. This kind of approach, acceptable in conventional treatments lasting 4-5 hours, is instead definitely unsuitable for short-lasting treatments, especially if they are complicated by phases of hemodynamic instability, or they are used in critical patients.

A technological response has followed, namely in the development of systems for on-line intradialytic monitoring, aiming to prevent critical situations and to continuously measure various physiological parameters of the patient, both of a hemodynamic kind and of a biochemical kind. The on-line monitoring systems have been most useful in high-efficiency, short-lasting dialysis techniques, since the risk of being "unphysiological" is so much greater when the treatment times are shortened while at the same time increasing the efficiency. In such conditions and in critical patients there is the need to have a continuous flow of information that guarantees at least two objectives:

- the adequacy of the cardiocirculatory *response* in terms of the progressive withdrawal of the fluids that guarantee a certain degree of hemodynamic stability;
- the overlapping of the actually delivered dialysis dose with the scheduled one;

An essential pre-requisite for reaching these objectives is that of disposing of adequate measurement devices and "sensors" for continuous measures during the dialysis sessions. Thus, besides a high degree of reliability and the continuity and accuracy of the measure, essential characteristics are relative simplicity of use, sterility and biocompatibility (for the sensors

that come into direct contact with the blood), the possibility to interface the measurement system with a computer and, lastly, an acceptable cost that will not further inflate dialysis treatment costs that are already high enough. But the indispensable pre-requisite for a sensor to be used in hemodialysis is its absolute non-invasiveness and utmost tolerability on the part of the patient.

Some devices for continuous hemodynamic or biochemical monitoring can be implemented in the dialysis instrumentation with a view to preventing cardiocirculatory instability (acute hypotension, arrhythmias) or controlling and improving the dialysis efficiency.

Hemodialysis is in fact no doubt the best area of application of the new servo-control systems, since it is not a static but a rather dynamic process, with rapid and continuous changes in both the solute and fluid distribution, as well as in the acid-base balance and hemodynamics. This kind of process needs a continuous monitoring of a number of parameters (both of a biochemical and a hemodynamic kind) to improve surveillance, but also needs a retroactive control aiming to keep the process back to an equilibrium state and reduce the unphysiology of the treatment.

However, the development of a biofeedback system for hemodialysis is not at all easy, because it presupposes a deep knowledge of the variables to be controlled, the construction of suitable sensors, the definition of the actuators and the realisation of an expert system overlooking, that is managing all the variables involved (input and output variables). In other words, they should be true and proper adaptive controllers.

In actual fact, the feedback systems that have ended up having a practical routine application are substantially three: the blood volume biofeedback, the temperature biofeedback and the arterial pressure biofeedback.

### 20.3.1 Blood Volume (BV) Biofeedback

The BV behaviour during dialysis has been extensively described mathematically (Kimura et al. 1984) and several factors influencing and modifying BV changes throughout dialysis treatment have been identified (Scheneditz et al. 1992).

Ultrafiltration and changes in the dialysate sodium concentration are, however, the major and the most important dialysis variables in the control of volemia during dialysis treatment (Mancini et al. 1993). On the other hand, ultrafiltration profiling can have a beneficial impact on blood pressure behaviour during hemodialysis.

However, models based on ultrafiltration alone are limited to adapting the rhythm of plasma water removal to the patient's refilling capacities. The major limitation to these models is their inability to maintain control over the total planned weight loss within the pre-defined treatment times (Santoro et al. 1992; Mann et al. 1990). Increased dialysate sodium can promote greater fluid mobilisation from the extra-vascular compartment, thereby reconstituting a greater portion of the plasma volume lost during ultrafiltration (Kouw et al. 1991) helping the reduction in the desired body-weight loss.

Moreover, on the one hand the modification of the intra-vascular sodium concentration can increase plasma refilling, while, on the other, it can increase the activity of the Autonomic Nervous System, with a consequently better hemodynamic response from the peripheral vascular resistances. In this light, we have recently modified, along with the Gambro-Hospal research group, our first automatic BV control system based on variable ultrafiltration (Santoro et al. 1994). The new feedback control system is based on an adaptive controller, capable of forcing the spontaneous volemia trends along pre-selected trajectories by means of both ultrafiltration as well as sodium. From a modelling point of view, the model proposed is an example of a *closed loop system* (see Fig. 20.2), with a dependent output variable or controlled *variable*, i.e. volemia, and two independent or control variables, i.e. ultrafiltration and conductivity (Santoro et al. 1998).

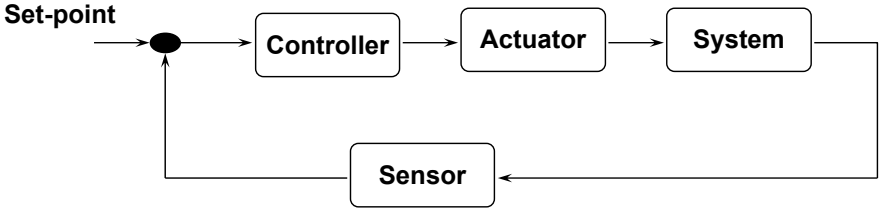


**Fig. 20.2** Schematic representation of a closed-loop system

As shown in Fig. 20.2, in a closed-loop system, the variable to be controlled is continuously measured by a sensor and the action on the controller is determined by the difference between the desired and the measured value of the system variables. In this case, it is not necessary to know in detail the model of the system to achieve the desired point. Often, only the knowledge of a simplified input-output relationship is sufficient. This way is in general much less sensitive to external noise as well as to internal system variations, because the deviations from the imposed set values are first

measured then compensated for by the action of the controller on the system inputs.

The relative BV changes are measured continuously during dialysis by an optical absorbance system (Paolini et al. 1995). At the same time, the following parameters are continuously calculated:

i. The mathematical coefficients that link the controlled variable to the control variables;
ii. The instantaneous errors in the actual BV trajectory as compared with the ideal one;
iii. The differences in the body weight loss first prescribed and then achieved and their relationships with BV reductions.

In the presence of substantial errors, the model is able to automatically update both the ultrafiltration and the conductivity with a view to minimising any discrepancies there may be between the ideal volemia trajectories and the experimentally obtained ones, as well as any relevant errors in the patients' body weight reductions. At the core of the system is a MIMO, multi-input, multi-output controller in which all the branches are linearly controlled with adapted parameters (see Fig. 20.3).

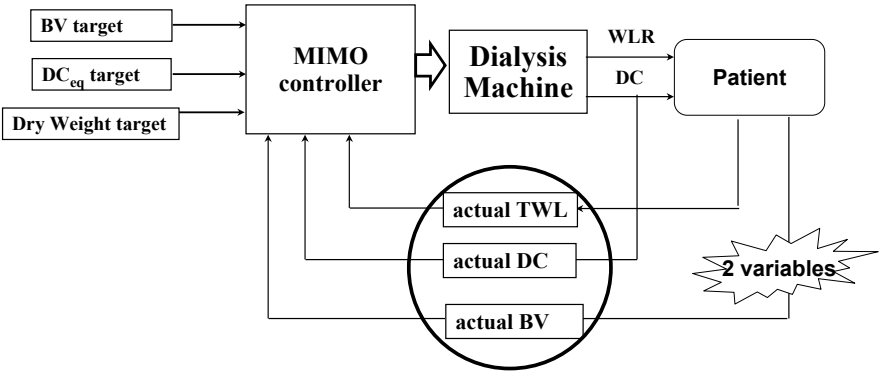


**Fig. 20.3** The blood volume biofeedback with the multi-input and multi-output controller (MIMO controller)

As shown in Fig. 20.3, the BV biofeedback system consists in the setting of 3 clinical objectives:

- The Total Weight Loss (TWL) for the restoration of the dry weight;
- The variation of the blood volume (BV) for the preservation of cardiovascular stability;

- The equivalent dialysate conductivity (DC) to maintain a desired sodium balance.

According to the biofeedback architecture, similar parameters are continuously measured: variations in the blood volume, total weight loss and equivalent conductivity. With this information the physiological controller adjusts continuously the ultrafiltration rate and the dialysate conductivity.

The adaptive controller manages three kinds of error; errors on the volemia, but also ones on the total weight loss and dialysate conductivity. For greater safety during the treatment, ultrafiltration and conductivity, i.e. the two independent variables, can fluctuate only within a well-defined range, established at the start of the treatment according to the patients' clinical characteristics (see Fig. 20.4).

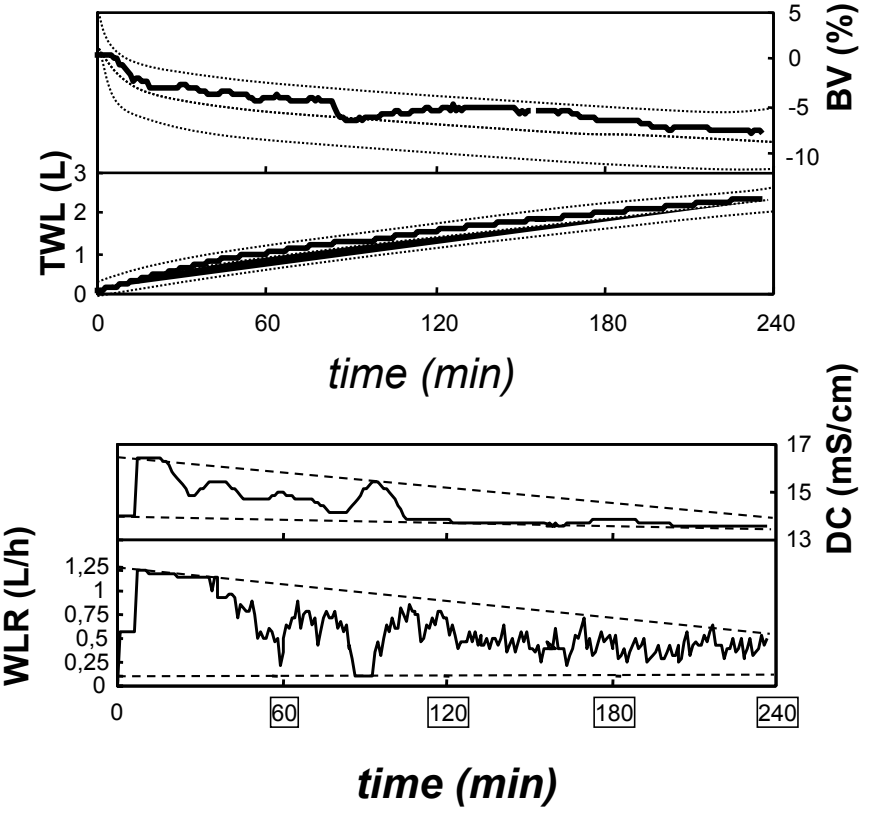


**Fig. 20.4** Time course of the blood volume reductions (BV, %), total weight loss (WL, Kg), dialysate conductivity (DC, mS/cm) and weight loss rate (WLR, L/h) during a dialysis session with the biofeedback control of blood volume.

As shown in Fig. 20.4, according to the desired pattern for blood volume and total weight loss (the thin dashed line in the top plot), the weight loss rate and the dialysate conductivity change time by time to reduce the error between the desired and observed values. The WLR and DC are in any case constrained within safety limits (dotted lines in the bottom plot).

Moreover, the overall system, apart from allowing for the regulation of the BV profile according to desired trajectories, makes it possible to prescribe adequate ultrafiltration in order to achieve the ideal body weight in the individual patients along with personalised intradialytic sodium balance. From a clinical point of view, biofeedback in BV regulation has several aims:

i. To avoid reaching serious and major contractions in BV; reductions over 25% should be avoided owing to the greater risk of intradialytic hypotension;
ii. Modelling the volemia curves in patients with plasma refilling instability and non-homogeneous and non-linear plasma volume trends during dialysis;
iii. To avoid, in patients with cardiovascular instability, the reaching of critical hypovolemia thresholds independently of their absolute value;
iv. To modulate the sodium balance and the patient's dehydration.

Biofeedback blood volume controlled HD is now possible with this system in routine dialysis, allowing the delivery of a more physiologically acceptable treatment. The largest clinical validation of Blood Volume Tracking is represented by a multicenter study protocol involving our Centre, where the system was born and experienced, and other 9 italian Nephrology Units. In this study (Santoro et al. 2002) carried out in 36 patients with a high degree of cardiovascular co-morbidity and suffering from frequent dialysis-induced hypotensive episodes, the cardiocirculatory stability during dialysis was compared in two different treatments: conventional dialysis (A treatment) and dialysis with Blood Volume Tracking (B treatment). Each patient served as his/her own control, and was randomly assigned either to a sequence A-B-A-B or B-A-B-A, each period lasting 4 weeks. At the end of the study a 30% reduction of dialysis hypotension incidence resulted in dialysis with the BVT system. The effect was particularly evident in patients with the highest number of hypotensive events in conventional dialysis (in these patients the reduction of hypotension was up to 65%). The results concerning the treatment hemodynamic tolerance were reinforced by the observation of a 10% overall reduction in interdialysis

symptoms (thirst, cramps, fatigue, etc.). Body weight gain, pre-dialysis blood pressure, and Kt/V did not differ between the two treatments.

A confirmation of our results comes from Basile's experience (Basile et al. 2001) who also compared conventional bicarbonate dialysis with biofeedback equipped dialysis in 19 HD patients, in the short-medium term. He found out a reduction of both acute hypotension and muscle cramps and a significant difference in post-dialysis asthenia. The residual percentage reduction in BV divided by the percentage change in extracellular fluid volume (measured by a bioimpedance technique) was significantly higher during HD with biofeedback, suggesting a better capacity of refilling in dialysis with BV control. Once again the BVT systems proves less "unphysiological" compared to conventional treatment. The continuous adaptation of both theultrafiltration rate and dialysate conductivity to the instant vascular refilling capacity preserves more water in the interstitital fluid compartment or reduces the intracellular shift: vascular refilling is in any case maximally safeguarded and enhanced.

Ronco et al (2000), besides observing similar results in terms of hypotension prevention, reported also better values of equilibrated Kt/V in BV controlled HD, with a striking reduction in post-dialysis percentage urea rebound (6.4 $\pm$ 2.3 % *vs* 14.2 $\pm$ 2.7 %, in BV controlled and standard HD, respectively). Hence, the better hemodynamic stability obtained thanks to the biofeedback, reflects positively in terms of HD efficacy: it reduces solute compartmentalisation and favours a better blood flow distribution within the body. As a consequence, the amount of urea accessible to the dialyser is greater, and greater is the amount actually removed. McIntyre et al (2003) have applied blood volume biofeedback to 15 stable, non-hypotension-prone HD patients and they found an increasing tolerability, reducing intradialytic fluid gains and enhancing urea clearance.

### 20.3.2 Body Temperature Biofeedback

Apart from blood volume, intradialytic hemodynamics can now be improved thanks to a blood temperature monitor. The theoretical assumption for such a system is that the thermal exchange processes between blood and heated dialysate may have an impact on different hemodynamic parameters of patients undergoing HD.

The standard dialysate temperature setting of approximately 37°C does not take into account that most uremic patients tend to be slightly hypothermic. Consequently, in several HD treatments, an unwanted positive

thermal energy balance is applied to patient, which in a certain number of cases, may provoke or contribute to symptomatic hypotension by eventually forcing the thermoregulatory system of the patient into a redistribution of the available blood volume from the central vassal system into the peripheral circulatory system.

In earlier studies by Maggiore et al (1985) an improved vascular response was observed during cooled dialysate or during isolated ultrafiltration in comparison with conventional hemodialysis. Recently, Rosales et al (2000) have shown that the amount of thermal energy to be removed for an isothermic HD correlates with ultrafiltration. The prevalence of symptomatic hypotension is comparable in hemodialysis and isolated ultrafiltration, if the core temperature is stabilized.

Unlike uraemic solutes, which accumulate between treatments, there is some potential for thermal energy to accumulate within a hemodialysis treatment. Basically, there are three possibilities for intradialytic heat accumulation: i) delivery of thermal energy by the extracorporeal system; ii) increase in the metabolic rate; iii) decreased dissipation of heat from the body surface during hemodialysis and ultrafiltration.

The reduced transfer of metabolic heat from the body core to the body shell is essentially caused by cutaneous vasoconstriction as a compensation for ultrafiltration-induced hypovolemia. However, if the heat accumulation increases beyond a critical threshold, the increase in the thermoregulatory drive will lead to an increase in cutaneous blood flow and blood volume which will reduce peripheral resistances, leading to a fall in blood pressure, and an increased risk of intradialytic morbid events. This additional cardiovascular stress can be avoided by the controlled adaptation of dialysate temperature to the individual needs of an individual patient. According to the present knowledge the target should be a negative extracorporeal heat balance throughout the treatment. A manual adjustment of the dialysate temperature is not practical for routine application. However, the availability of microprocessor controlled equipment permits the development of closed loops to influence the extracorporeal thermal balance in a defined way according to the medical prescription.

The dialysate temperature should then be individualized and chosen with regard to actual patient temperature, blood flow and treatment modality. Above all, it is not sufficient to maintain a constant dialysate temperature throughout the treatment, but to continuously adjust the dialysate temperature to keep a pre-defined patient temperature. In practice, it is necessary to realise a biofeedback system. A practical realisation is now available with the BTM, short for blood temperature monitor, by Fresenius. Short sections

of the extracorporeal circulation are inserted into arterial and venous measuring heads equipped with sensors to measure arterial and venous temperature (see Fig. 20.5).

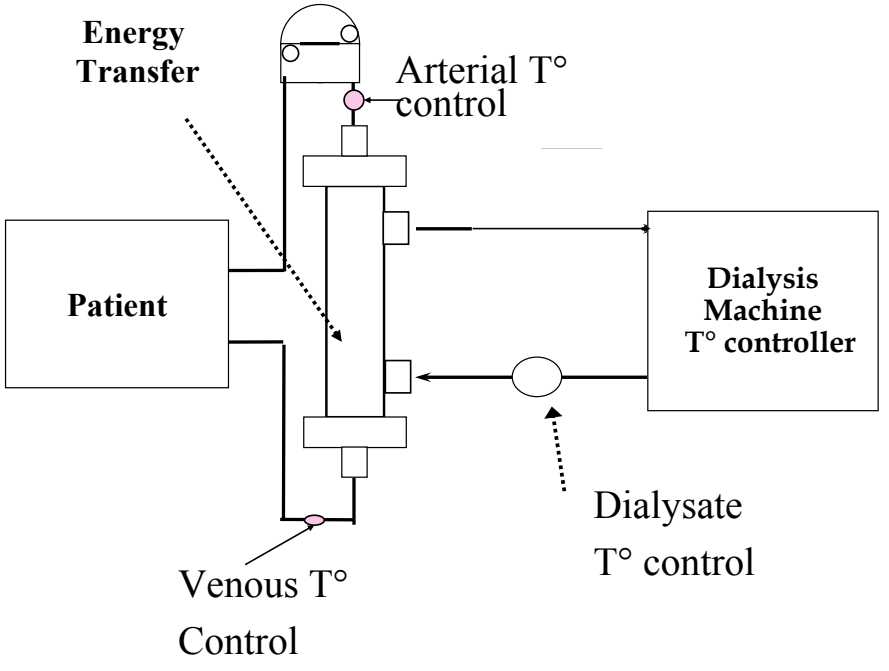


**Fig. 20.5** The extracorporeal circuit of the blood temperature monitor which shows the measuring points of the temperature and the temperature controller.

The function of body temperature control is exerted by a controller. The controller uses the error signals between the desired and actual changes in temperature to actuate a bounded change in dialysate temperature which changes the temperature of the venous blood returning to the patient, thereby changing the extracorporeal heat flow.

Two active operational modes are possible with the BTM used as a closed-loop device: E-control and T-control. In the E-control modality the BTM controls the thermal energy balance of the extracorporeal circuit. A positive energy balance means transferring energy into the patient; on the contrary, a negative energy balance represents heat removal (cooling) and a zero extracorporeal heat balance means that the thermal state of the patient is not at all influenced by the extracorporeal circuit. The desired energy balances are keyed into the BTM by selecting a certain heat flux in KJoule/hour over the treatment time (internal limits: -500 kJ/h and +200 kJ/h). From the

therapeutical point, E-control with a set parameter of 0 kJ/h is a useful tool, if the medical intention is to exclude any thermal influence from an extracorporeal circuit.

In T-control mode, the BTM tries to influence the patient's body temperature directly by assessing the body temperature of the patient and applying the respective dialysate temperature changes according to a pre-set temperature goal. This goal can be keyed into the BTM's panel by setting a certain body temperature change per time ($\pm$ x°C/h; internal limits: -2°C/h and +1°C/h). Setting the BTM goal to $\pm$ 0°C consequently stabilizes the patient's body temperature at the temperature level which was present when the active control program was started.

In a prospective study (on 95 hypotension-prone patients), (Maggiore et al. 2002) have documented the hemodynamic benefits in terms of reduction of hypotension episodes of isoenergetic dialysis as compared with the thermo-neutral treatment mode. In isoenergetic treatment the patient temperature was keep constant throughout the treatment. Moreover, patients with left ventricular hypertrophy (LVH) seem to have more benefit from "cold" hamodialysis compared to patients without. In fact, a reduction in the dialysis hypotension incidence was observed in as much as 86% of the patients with LVH (left ventricular mass > 125 gr/m$^2$), and in 62 % of the patient without LVH, which was a statistically significant different (see Fig 20.6) (personal unpublished observations).

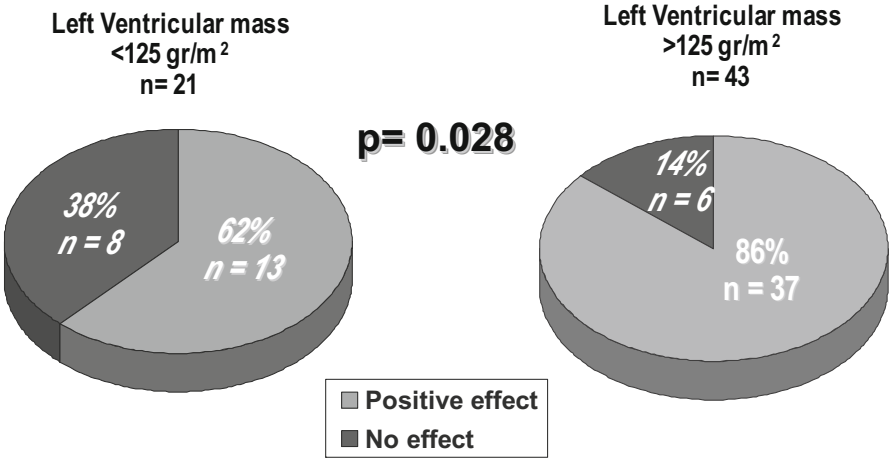


**Fig. 20.6** Comparison of the effect the "cold" dialysis on the incidence of dialysis hypotension in patients without and with left ventricular hypertrophy (LVH). The positive effect was significantly higher in patients with LVH compared to patients without.

A hypothesis for this different effect could be seen in the fact that hypertrophic ventricle may present, during HD with concomitant UF, an inadequate filling, secondary to impaired relaxion. The reduced peripheral venous pooling, due to the cold-induced increase in venous tone, may favour the venous return to heart and the filling of the cardiac chambers, thereby maintaining an adequate cardiac output (which, on the contrary, could decrease to a critical level), and blood pressure. Different thermal balance characterizes convective and diffusive treatments, with the more negative one observed in cold hemodialysis (dialysate 35.5°C) and post-dilution hemofiltration (infusate 37°C) (Santoro et al. 2003b).

### 20.3.3 Arterial Blood Pressure Biofeedback

The arterial pressure control is definitely the most ambitious objective in the management of a dialysis session. Unfortunately, in order to exert a feedback control online, the essential prerequisite is the continuous measurement of the variable that should be controlled and in this case it is necessary to measure the arterial pressure. The continuous arterial pressure systems are, however, at least until now, only of an invasive kind and it is not thinkable that they can be applied in the routine dialysis and on a day patient. So we must be content with the oscillometric systems with external cuff that is periodically deflated and inflated in order to monitor the height and the width of the sphygmic wave. Many patients, however, do not like this continuous disturbance during the dialysis session and so we are only able to have the measures at pre-set time intervals that are no longer than a quarter of an hour. The company B Braun have created a measuring system of arterial pressure that is a little more sophisticated than the normal cuff instruments and a feedback control of arterial pressure based on ultrafiltration as the actuator.

The feedback control provides for the measurement of arterial pressure and its trend during the treatment and an accurate regulation of ultrafiltration finalised to the maintenance of an adequate blood volume. The system controller is based on fuzzy logic. Fuzzy logic does not work on the binary logic but allows for continuous and gradual transitions from 0 to 1. The fuzzy controller allows the modulation of ultrafiltration proportionally to the variation trend in the arterial pressure and so small variations in blood pressure are matched by small variations in ultrafiltration or the maintenance of a constant ultrafiltration, while large pressure variations are matched by large variations in the ultrafiltration. As reported in Fig. 20.7, when the controller highlights a negative trend in the blood pressure it reduces the ultrafiltration to the extent of reducing it to zero when there is no pressure recovery.

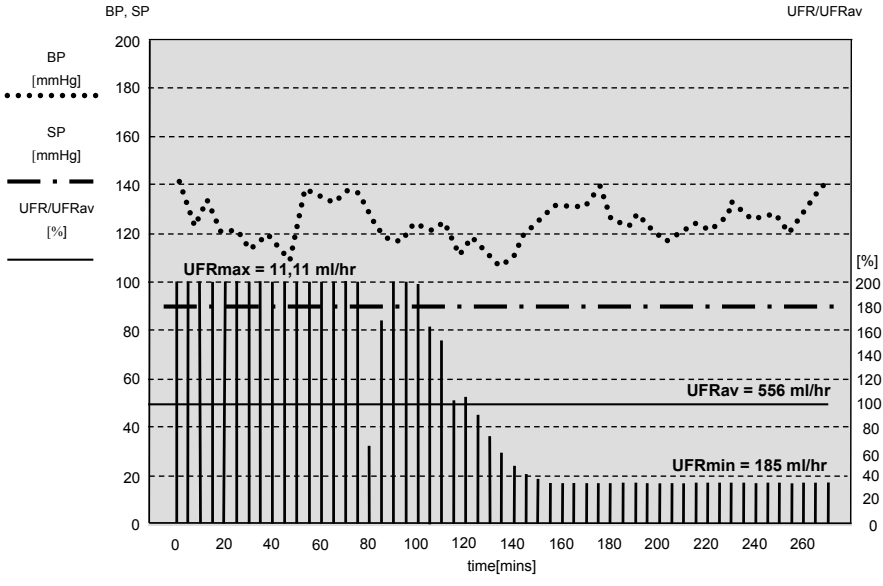


**Fig. 20.7** The figure shows the behaviour of the Ultrafiltration rate (UFR, vertical bars) and blood pressure (BP, dotted line) trend during a dialysis session with the automatic blood pressure stabilisation system. The critical systolic pressure (SP, dashed line) set-point was 90 mmHg (top horizontal line) and was not changed since BP never reached that level. The UFR was maintained constant (1111 ml/h) until a BP reduction was recorded (80 minutes), when it was automatically reduced. During the 3rd and 4th hour the UFR was progressively reduced until a minimum value of 185 ml/h (bottom horizontal line). The mean UFR resulted equal to 556 ml/h (middle horizontal line).

Obviously, a system limitation may be, having to respond categorically to given constrains such as the duration of the session and the total ultrafiltration (total patient fluid loss). If rigid limits are set upon these parameters, then in some patients the control becomes more difficult by the system. We are performing a clinical multicenter, prospective, controlled, randomised trial, based on the application of this system, better known as APBS (Automatic Blood Pressure Stabilisation System) in a group of patients with pressure instability. Although the study is not yet complete, the preliminary results show an efficacy of the system vis-à-vis symptomatic intradialytic hypotension. In particular (see Fig. 20.8), the most severe hypotensive episodes are significantly statistically reduced; this is likely to be linked to the large reductions in the blood volume (Mancini et al. 2003).

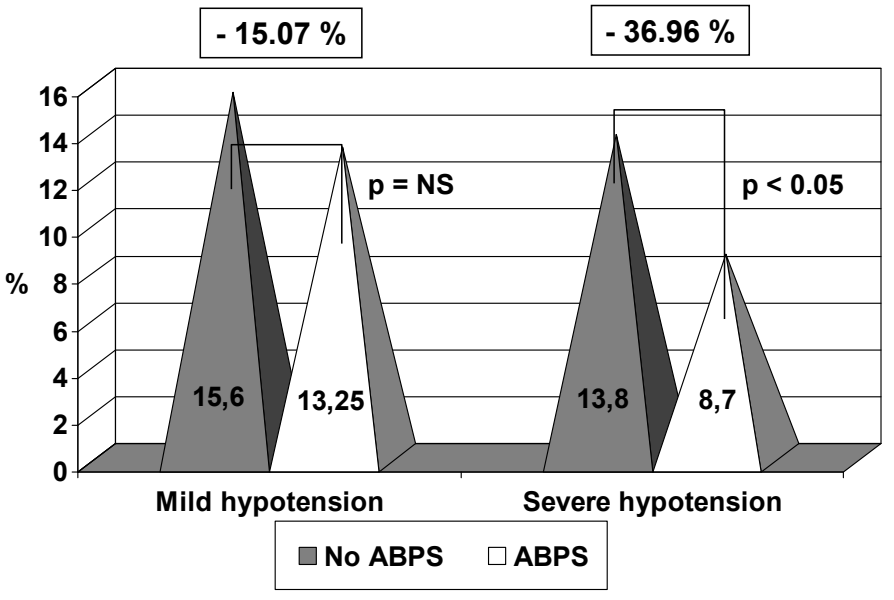


**Fig. 20.8** Comparison of the frequency of hypotension episodes (severe and mild) in dialysis sessions without and with the automatic blood pressure stabilisation system (ABPS). A significant difference between the two modalities was observed in the appearance severe hypotension events (-36.96% in ABPS dialysis).

## 20.4 BIOCHEMICAL MONITORING AND CONTROL

The need to verify the quality of the actually delivered treatment can only be satisfied by the use of systems aimed at the real-time monitoring of actual urea clearance (dialysis efficiency) and solute removal (dialyzer performance), using special biosensors.

An indirect measurement of the urea clearance can be obtained with the ionic dialysance (total effective dialysance) that can be measured conducimetrically. Conducimetric dialysance measured by the conductivity technique in the dialysate represents the effective dialyzer clearance, which does not take the vascular access and cardiopulmonary recirculation into account, so it can be usefully used to monitor the fluctuations in the clearance.

Further possibilities for monitoring dialysis efficiency, with indirect measurements of the effective clearance, can only be superseded by the

real-time monitoring of urea concentration, made possible by using dedicated urea sensors measuring urea directly on the extra-corporeal circuit.

Continuous urea monitoring can now be carried out on the ultrafiltrate by means of a devised that can only be used during Paired Filtration Dialysis, a dialysis technique in which there is a continuous production of ultrafiltrate (UF), and where the urea concentration is wholly comparable to the plasma water concentration. The measurement system consists of:

i. a conductivity cell measuring UF conductivity;
ii. a urea sensor containing urease, an enzyme inducing the complete hydrolysis of UF urea with production of ammonium ions;
iii. a second conductivity cell which detects the UF conductivity changes induced by the ammonium ions.

The conductivity difference between the two cells correlates well to the UF urea concentration. The continuous intradialytic measurement of the urea concentration allows us to calculate kinetic parameters, such as Kt/V and dialytic time averaged urea concentration. Hence, there is this is a true and “quality control" of the treatment, with the possibility to check, in real-time, that the prescribed and the administered dialysis dose do actually overlap, and, eventually, modify the parameter prescription in order to avoid situations of underdialysis.

## 20.5 CONCLUSIONS

The technological innovation that has come about in the dialysis field in the past few years has allowed for the realisation of sophisticated biofeedback systems, based on the continuous measurement of the physical variables such as body temperature or haemodynamic variables such as the blood volume and the arterial pressure. These systems have been implanted and used successfully in the day-to-day dialysis practice, above all in the management of the “difficult” and unstable patients.

In our opinion, however, the future must look to an integration of the already existing system and the completion with other physical and chemical variables that are essential for a physiological dialysis (see Fig. 20.9).

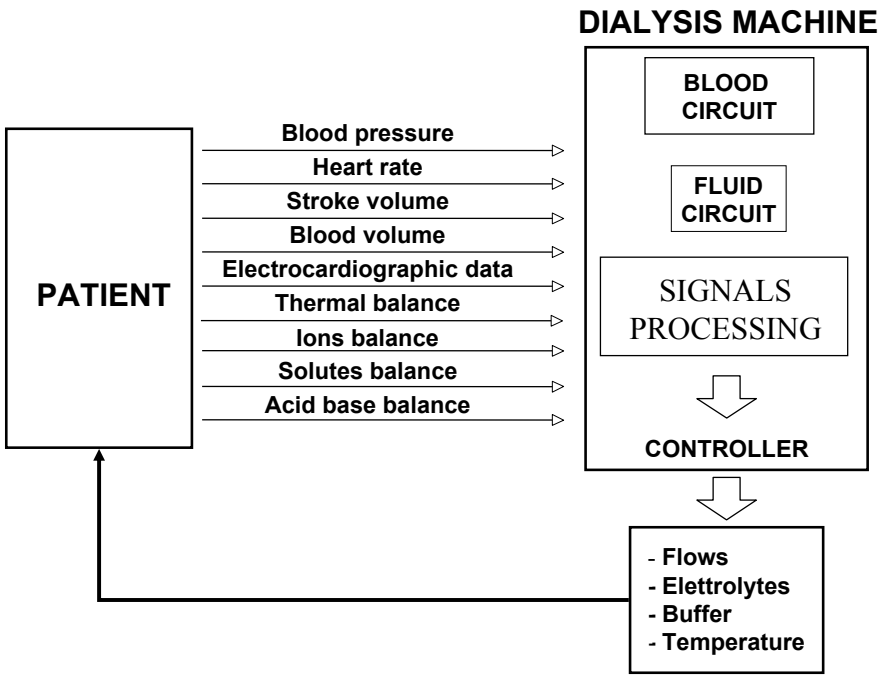


**Fig. 20.9** Integrated adaptive control with a schematic view of the monitored variables and the controller dedicated to signal processing and dialysis machine control.

Only by means of a more accurate and complete monitoring and adaptive control of the patient during the dialysis session will it be possible to make the process of renal replacement therapy more physiological, with traditional times and methods. A similar system, integrated into the dialysis machine, is today impossible to create. However, the challenge that industry and researchers must face and conciliate is the technological complexity of the system with an extreme simplicity of use and extremely low running costs. The alternative, which however does not exclude a careful "instrumental" surveillance of the patient, is the recourse to dialysis techniques with a greater weekly frequency (such as daily dialysis) or with a longer duration (diurnal or nocturnal long-duration dialysis) that come closer to the continuous physiological purification ensured over the 24 hours by the human kidney.

Unfortunately, the continuous increase in demand for R.R.T. and the even lower availability of economic resources hamper the diffusion of long dialyses and extremely frequent ones, so it is quite likely that we should increasingly look to technology for a helping hand.

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## ESSAY QUESTIONS

1. Define the concept of biofeedback system
2. List the basic components of a biofeedback system
3. Define the plant, the actuators and the controller.
4. List the two kinds of information which the scientific formulation of a control problem is based on.
5. List the major types of biofeedback systems routinely used in clinical dialysis.
6. What are the most important dialysis variables for controlling volemia during dialysis treatment?
7. What is the main problem of the biofeedback systems?
8. What is the major limitation of BV Biofeedback models based on ultrafiltration alone?
9. What are the main objectives of the BV biofeedback system?
10. List the main possibilities for intradialytic heat accumulation.
11. Differentiate between the active operational modes of the BTM.

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. In a biofeedback system what is a sensor?

A. A device used to define the changes in the work of the actuators
B. A device used to measure the variable under control
C. A device used to calculate the distance between the target and the actual value

2. In a biofeedback system what is the role of the "actuators"?

A. They are the arms of the control process and actually work to reach the target
B. They are the systems to measure the variations of the variable under control
C. They are the heart of the mathematical model

3. Which one of the following is not a characteristic of a sensor dedicated to dialysis?

A. Continuity and accuracy of the measure
B. Non-invasiveness
C. Off-line continuous measurement

4. Which one of the following is a target for biofeedback systems for chronic hemodialysis patients?

A. Improve the efficacy of anticoagulation
B. Improve the cardiovascular stability
C. Improve the functioning of the vascular access

5. In the biofeedback system controlling blood volume changes during hemodialysis which one of the following is an actuator used to pilot blood volume?

A. Dialysate temperature
B. Dialysate sodium concentration
C. Dialysate flow rate

6. Besides blood volume, what are the other goals for the blood volume biofeedback system?

A. Kt/V and urea reduction
B. Water removal and equivalent conductivity
C. Electrolyte mass removal

7. How is the trend of the ultrafiltration rate during a dialysis session with the biofeedback control system of blood volume?

A. Continuously changing, higher at the beginning
B. Continuously changing, lower at the beginning
C. Continuously changing with a step profile (ups and downs)

8. What is the vascular refilling rate?

A. The rate of the fluid shift from the vessels to the interstitium
B. The rate of the fluid shift from the interstitium to the vessels
C. The rate of the fluid shift from the interstitium to cells

9. What is the effect on the blood volume trend of increasing the dialysate conductivity?

A. Favouring fluid mobilisation towards the cells
B. Favouring fluid mobilisation towards the circulation
C. Favouring fluid mobilisation towards the heart

10. In many uremic patients the body temperature tends to be…

A. Lower than in non-uremic subjects
B. Higher than in non-uremic subjects
C. Comparable to non-uremic subjects

11. The cutaneous vasoconstriction induced by ultrafiltration-induced hypovolemia is responsible for…

A. Enhanced dissipation of the heat accumulated
B. Reduced dissipation of the heat accumulated
C. No relationship between heat and blood volume

12. BTM stands for…
    A. Blood temperature monitor
    B. Body temperature modifier
    C. Blood temperature maintenance

13. During a dialysis session with BTM, which temperatures are measured?
    A. Arterial and venous
    B. Arterial, venous and dialysate
    C. Venous and dialysate

14. During a dialysis session with BTM, where is the first effect of the change in the dialysate temperature?

    A. In the arterial line of the extracorporeal circuit
    B. In the venous line of the extracorporeal circuit
    C. In the vascular access

15. During a dialysis session with BTM, setting the BTM goal to 0°C implies:
    A. Isothermic dialysis
    B. Isoenergetic dialysis
    C. Isovolemic dialysis

16. Which one of the following dialysis strategies has the more negative thermal balance?
    A. Bicarbonate dialysis dialysate 36.5°C
    B. Post-dilution Hemodiafiltration, infusate 37°C
    C. Pre-dilution hemodiafiltation, infusate 37°C

17. One of the following is not a feature of the BTM system…

    A. Temperature control
    B. Energy control
    C. Volume control

18. The system called ABPS is dedicated to…

    A. The prevention of acute hypotension
    B. The prevention of insufficient depuration
    C. The prevention of vascular access problems

19. What are the actuators in ABPS?

A. Dialysate sodium concentration and dialysate temperature
B. Dialysate sodium concentration and ultrafiltration
C. Ultrafiltration alone
D. Dialysate sodium concentration alone

20. A real-time monitoring of urea concentration in the extracorporeal circuit may help to…

A. Monitor the dialysis efficiency
B. Prevent cardiovascular instability
C. Monitor the reduction in plasma volume

Chapter (21)

# Clinical Applications of Biofeedback Systems in Hemodialysis

Judith J. Dasselaar and Casper F.M. Franssen

**CHAPTER OUTLINES**

- Introduction.
- Dialysis hypotension.
- Biofeedback apparatus
- Conclusions and future directions

**CHAPTER OBJECTIVES**

- Basic understanding of the pathophysiology of dialysis hypotension.
- Knowledge of functioning, clinical results and limitations of currently available biofeedback systems for hemodialysis.

**KEY TERMS**

- Hemodialysis.
- Dialysis hypotension.
- Blood volume.
- Blood pressure.
- Ultrafiltration.
- Dialysate sodium concentration.
- Biofeedback systems.
- Dialysate temperature.

**ABSTRACT**

Despite the tremendous progress in hemodialysis technology over the past decades, hemodynamic instability during hemodialysis is still a frequent complication. This is caused by the fact that in most patients large amounts of fluid are being removed over a short period of time, in combination with an increasingly higher proportion of (elderly) patients with significant cardiovascular co-morbidity. In recent years various closed-loop techniques have been developed to prevent hemodynamic instability during hemodialysis. These techniques differ with respect to the input and output parameters but have in common that they are based on current concepts of the pathophysiology of dialysis hypotension. In this chapter we will outline the pathophysiology of dialysis hypotension and discuss the various closed-loop techniques for hemodialysis that are currently available.

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## 21.1 INTRODUCTION

In 1943 the first human hemodialysis (HD) treatment was performed by Willem J. Kolff in Kampen, the Netherlands (Kolff 1946). In the early years, HD was only feasible as a short-term life-saving procedure for patients with acute renal failure pending recovery of renal function. In the following decades, HD also evolved as a life-sustaining long-term therapy for patients with chronic renal failure (Kloppenburg 2002) (see Fig. 21.1).

The major goals of HD treatment are the regulation of the extracellular volume by the removal of excess fluid and sodium and the clearance of uremic waste products. The removal of a large volume of fluid (usually 2 to 4 liters per session) and solutes over a short period of time (usually 3 to 5 hours) is not physiological and has a major impact on the cardiovascular system. Moreover, the HD procedure induces a bioincompatibility reaction as a result of the interaction between the blood and the material of blood lines and dialyser (Grooteman and Nubé 1998; Friedrich et al. 2006). The resulting systemic inflammatory reaction can cause symptoms such as fever and can negatively affect organ function (Mårtensson et al. 1990; van Teijlingen et al. 2003).

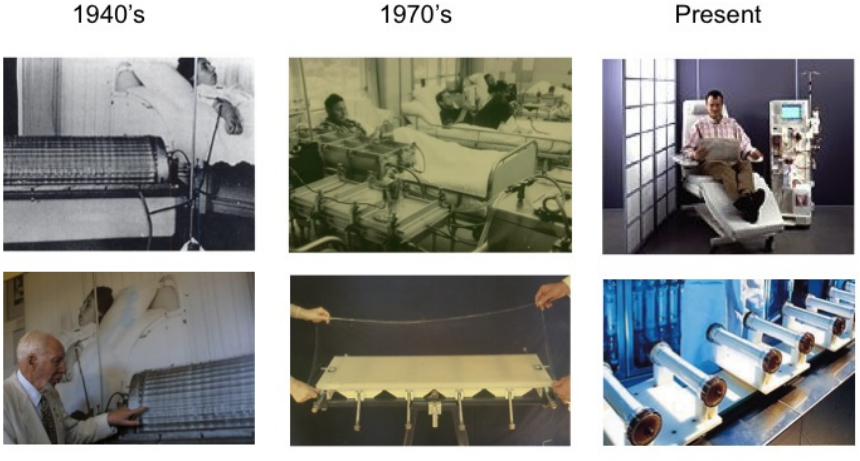


**Fig. 21.1** Evolution in dialysis techniques over time

Progress in HD equipment, dialysate composition (bicarbonate), and dialysis access, as well as the development of more biocompatible blood lines and dialysers, has helped enormously in improving the tolerance to HD since the early days of dialysis. Nevertheless, hemodynamic instability is still one of the most frequent complications occurring during the HD procedure. This is largely explained by the change in the characteristics of the dialysis population over time. In the past decades the proportion of

older patients and patients with diabetes and significant cardiovascular co-morbidity has increased considerably (Locatelli et al. 1999). Since especially these patients are prone to hemodynamic instability, the HD procedure should be as tolerable and physiological as possible.

In recent years various closed-loop techniques have been developed to prevent hemodynamic instability during HD. These techniques differ with respect to the input and output parameters, but have in common that they aim to intervene in those factors that are thought to have a crucial role in the pathophysiology of dialysis hypotension. Although some of these techniques have also been used to reduce the extracellular volume in hypertensive dialysis patients, the focus in this chapter is on the prevention of dialysis hypotension. We will first outline the pathophysiology of dialysis hypotension. Next, we will discuss the principles, clinical results and major advantages and limitations of the various closed-loop techniques for HD that are currently commercially available (see Table 21.1).

**Table 21.1** Overview of Biofeedback Techniques

| Biofeedback technique (manufacturer) | Input parameter | Output parameter | Clinical studies (references) |
|---|---|---|---|
| **Blood volume based** | | | |
| Blood Volume Monitor (Fresenius) | BV | UF-rate | Garzoni et al. 2007; Sentveld et al. 2008; Gabrielli et al. 2009 |
| Hemocontrol (Gambro-Hospal) | BV | UF-rate & DC | Santoro et al. 1994; Mancini et al. 1995; Santoro et al. 1998; Basile et al. 2001; Santoro et al. 2002; Begin et al. 2002; Ronco et al. 2002; Wolkotte et al. 2002; McIntyre et al. 2003; Franssen et al. 2005; Moret et al. 2006; Selby et al. 2006a; Dasselaar et al. 2007a; Deziel et al. 2007; Nesrallah et al. 2008; Winkler et al. 2008 |

**Table 21.1** (Continued)

| | | | |
|---|---|---|---|
| **Blood pressure based** | | | |
| Biologic RR (B. Braun) | Systolic BP | UF-rate | Schmidt et al. 2001; Mancini et al. 2007. |
| **Temperature based** | | | |
| Blood Temperature Monitor (Fresenius) | Blood temperature | Blood temperature | Levin et al. 1996; Schneditz et al. 1997; Kaufman et al. 1998; Maggiore et al. 2002; Beerenhout et al. 2004; van der Sande et al. 2005; van der Sande et al. 2009 |
| **Sodium based** | | | |
| Diacontrol (Gambro-Hospal) | Plasma conductivity | Plasma conductivity | Bosetto et al. 1999; Locatelli et al. 1998; Di Giulio et al. 1998; Moret et al. 2006; Selby et al. 2007 |

BV: Blood Volume; UF-rate: Ultrafiltration Rate; DC: Dialysate Conductivity: BP: blood pressure.

## 21.2 DIALYSIS HYPOTENSION

### 21.2.1 Definition and Symptomatology

Dialysis hypotension is one of the most frequent complications of HD. It is estimated to occur in about 20% of HD sessions (Daugirdas 2001) but the actual prevalence varies with the definition used. Nowadays, dialysis hypotension is usually defined as a decrease in systolic blood pressure of ≥20 mmHg or a decrease in mean arterial pressure of ≥10 mmHg in combination with hypotensive symptoms and a treatment intervention by the dialysis nurse (Kooman et al. 2007). The symptoms of dialysis hypotension vary from fatigue, yawning, muscle cramps, nausea and vomiting to angina pectoris and loss of consciousness. The symptoms are generally transient but dialysis hypotension can also cause permanent damage, such as a myocardial infarction, a cerebrovascular accident, intestinal ischemia or an acute occlusion of the arteriovenous fistula (John et al. 2000; Schreiber Jr 2001). Frequent dialysis hypotension may also cause chronic overhydration and

underdialysis, since HD sessions are often prematurely terminated when patients develop symptomatic hypotension. Consequently, the actual duration of HD is too short for the adequate removal of fluid and uremic waste products (Daugirdas 2001, Schreiber Jr 2001). Finally, frequent dialysis hypotension is associated with an increased mortality risk (Shoji et al. 2004). The prevention of dialysis hypotension, therefore, is an important challenge to the dialysis staff.

### 21.2.2 Ultrafiltration and Blood Volume Changes

Most dialysis patients produce little or no urine. Therefore, the excess fluid that is accumulated between dialysis sessions must be eliminated during HD. Most of the excess fluid is accumulated in the interstitial tissues whereas the volume of the intravascular space is generally only modestly increased. During HD, fluid is ultrafiltered from the intravascular space in the artificial kidney and, at the same time, the excess fluid in the interstitial tissues moves to the intravascular space. Importantly, the rate at which fluid is removed from the circulation (the ultrafiltration rate or UF-rate) is higher than the rate at which the fluid moves from the interstitial tissues into the circulation (the plasma refill rate). The difference between the UF-rate and the plasma refill rate inevitably results in a drop of blood volume during HD. In other words, the change in blood volume during HD is the resultant of the difference between the UF-rate and the (lower) plasma refill rate.

The fall in blood volume is generally believed to be the initiating event in dialysis hypotension (Daugirdas 2001). The degree of the blood volume decrease during HD varies significantly from patient to patient, but also between different HD sessions in the same patient (Krepel et al. 2000). Part of this variation is probably explained by differences in the degree of fluid excess at the start of HD (Koomans et al. 1984; Wizeman et al. 1995). This is because the plasma refill rate is higher when the patient is more overhydrated. The intra-HD course of blood volume is also affected by various other factors like changes in posture (Ookawara et al. 2001), exercise (Banerjee et al. 2004), and food intake during HD (Shibagaki and Takaichi 1998).

### 21.2.3 Cardiovascular Compensation Mechanisms

Although a reduction in blood volume is believed to be the initiating event in dialysis hypotension, frank dialysis hypotension only occurs when the cardiovascular compensatory mechanisms can no longer compensate for the reduction in blood volume (Daugirdas 2001). The major

cardiovascular compensatory mechanisms are a reduction of the venous capacity by venoconstriction of the capacitance vessels, active increases in arterial tone, and increases in heart rate and contractility (Daugirdas 2001). Venous constriction promotes venous return that helps to maintain systemic filling pressure whereas arteriolar vasoconstriction helps to maintain blood pressure directly (Ligtenberg et al. 1998). In addition, arteriolar vasoconstriction lowers capillary pressure, which facilitates vascular refill (Ligtenberg et al. 1998). Some authors consider plasma refill as a cardiovascular compensatory mechanism and not merely as a passive event (Daugirdas 2001). The transition of fluid from the interstitial tissues to the intravascular space is governed by Starling forces. It follows that the plasma refill rate can be enhanced by increasing the plasma osmolality through an increase of the plasma sodium concentration (vide infra).

Various patient factors are associated with an inadequate function of the compensatory mechanisms. For example, patients with systolic or diastolic left ventricular dysfunction and left ventricular hypertrophy are prone for dialysis hypotension since these patients are less capable of maintaining the cardiac output under circumstances of underfilling (Ruffmann et al. 1990). Patients with autonomic neuropathy, often the result of longstanding diabetes mellitus, are also at risk for dialysis hypotension since the detection of a fall in blood volume and/or blood pressure, as well as the activation of the cardiovascular compensatory mechanisms, is mediated by the autonomic nervous system. Various classes of drugs can interfere with the function of the compensatory mechanisms as well, e.g. the use of vasodilating agents such as calcium antagonists or ACE-inhibitors will disrupt the compensatory mechanism of arteriolar vasoconstriction.

The HD procedure itself can also interfere with the function of the compensatory mechanisms. Patients that are being dialysed with a relatively high dialysate temperature (even only 37 to 38°C), for example, respond with vasodilatation, especially in the skin, in order to prevent an increase in body temperature (van der Sande et al. 1999). This vasodilatation predisposes to hypotension since it opposes the compensatory mechanism of venous and arteriolar vasoconstriction.

### 21.2.4 Blood Pressure, the Resultant of the Blood Volume and the Compensatory Mechanisms

A simplified concept of dialysis hypotension is schematically depicted in Fig. 21.2. It summarises that the major factors in the development of dialysis hypotension are a reduction in blood volume and an inadequate function of the compensatory mechanisms. It also depicts that patients will

usually experience clinical symptoms of hypotension if the blood pressure falls below an individual threshold. Although this simplified scheme is helpful in understanding the basic concept of dialysis hypotension, it should be noted that the clinical reality is more complex. For instance, patients can develop profound hypotension during HD without a fall in blood volume. This may be caused by heart rhythm disturbances or by HD-induced cardiac ischemia which may occur even in the absence of ultrafiltration (McIntyre et al. 2008; Dasselaar et al. 2009). Figure 21.2 also suggests that patients first will develop hypotension and, only after some time has passed, experience symptoms of hypotension. This time window offers the opportunity to intervene at that point in time during which the blood pressure has decreased but the patient is not yet symptomatic. Unfortunately, this is not always the case. Some patients develop symptomatic hypotension very suddenly without previous warning or a documented fall in blood pressure.

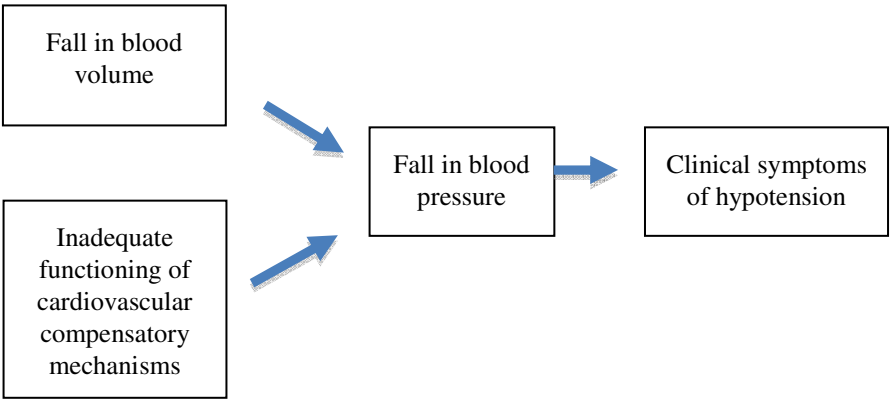


**Fig. 21.2** Simplified scheme of the chain of events leading to dialysis hypotension. It should be noted that clinical symptoms may develop acutely without a prior drop in blood pressure.

### 21.2.5 Management of Dialysis Hypotension

In the acute stage, the treatment of dialysis hypotension consists of measures aimed at raising the blood pressure to an acceptable level as rapidly as possible in order to guarantee blood flow to the vital organs. Since a drop in blood volume plays a crucial role in the development of dialysis hypotension, most of the measures are aimed at increasing the blood volume: temporary cessation of ultrafiltration and the intravenous administration of physiological saline or colloids. Sometimes, hypertonic NaCl is used in or-

der to increase the plasma refill rate. Placing the patient in the Trendelenburg position increases the venous return to the heart. As a result, the filling pressure in the left ventricle is increased and the cardiac output will rise. Obviously, other possible causes of the hypotension must be taken under consideration as well, certainly if the patient does not respond rapidly to the measures listed above. Hypotension may be caused by a primary cardiac event (ischemia or cardiac rhythm disorders) but also by a bacteremia or hemorrhage (e.g., in the digestive tract).

Standard measures to prevent the recurrence of dialysis hypotension include careful assessment of dry weight, limitation of fluid and salt intake, reduction of the dialysate temperature, abstinence from food during HD, use of bicarbonate instead of acetate as buffer in the dialysate, avoidance of low sodium and low calcium dialysate, and adjustment of the dosage and/or time of administration of anti-hypertensive drugs. Several classes of drugs have been reported to decrease the incidence of dialysis hypotension: e.g. the selective alpha-1 adrenergic agonist midodrine (Prakash et al. 2004). Notably, one of the most effective strategies to prevent dialysis hypotension is to increase the dialysis duration and/or the dialysis frequency, e.g. by short daily HD (Fagugli et al. 2001) or frequent nocturnal (home) HD. However, not all patients can be motivated to undergo more frequent and/or longer dialysis. Finally, the severity of dialysis hypotension can sometimes be decreased by biofeedback techniques. Such techniques, however, should not replace the other measures but are an additional possibility if the measures described above fail to have the desired effect.

## 21.3 BIOFEEDBACK APPARATUS

### 21.3.1 Relative Blood Volume Based Biofeedback

The initiating factor in the pathogenesis of dialysis hypotension is a decrease in blood volume, which results from an imbalance between the UF-rate and the plasma refilling rate (van der Sande et al. 2000a). Based on this concept, devices that continuously and non-invasively monitor relative blood volume (RBV) changes during HD have been developed. Nowadays, most manufacturers have incorporated a RBV monitor in their dialysis apparatus and two manufacturers have designed a biofeedback system that controls intra-dialytic RBV changes. The goal of RBV based biofeedback systems is to prevent a severe or abrupt decrease in blood volume, which should prevent the development of dialysis hypotension. There are several non-invasive RBV devices but since the main focus of this chapter is RBV based biofeedback, we will only discuss the two devices that are part of a

biofeedback system. At the moment two RBV based biofeedback techniques are available: the Blood Volume Monitor (BVM, Fresenius, Bad Homburg, Germany) and Hemocontrol (Gambro-Hospal, Lund, Sweden).

When fluid is withdrawn from the circulation, the concentration of those intra-vascular constituents that are too large to be removed by HD increases. Based on this principle, the relative change in blood volume during HD can be calculated from changes in the concentration of hemoglobin (Hb) or total protein concentration (TPC). The change in blood volume is calculated by means of the following Equation:

$$\text{Blood volume change (\%)} = \left[\frac{\text{Intra-vascular constituent}_{\text{start HD}}}{\text{Intra-vascular constituent}_{\text{during HD}}} - 1\right] \times 100 \quad (21.1)$$

**Example 21.1**

At the start of the HD session the Hb concentration is 10 g/l. One hour into the session 600 ml of fluid is withdrawn and the Hb concentration has risen to 10.5 g/l. Calculate the relative change in blood volume.

**Solution**

RBV has now declined 5% since ((10 / 10.5) – 1) x 100 = -5%.

The BVM calculates RBV by continuously monitoring changes in TPC during the HD treatment. The system is based on the principle that the velocity of ultrasonic sound waves in blood depends on the TPC, which is the sum of plasma proteins and Hb (Schneditz et al. 1990; Johner et al. 1998). Alternatively, Hemoscan (Gambro-Hospal, Lund, Sweden) calculates RBV from changes in Hb. Hemoscan measures Hb every minute by determining the optical absorbance of monochromatic light (Mancini et al. 1993; Paolini et al. 1995).

It is important to realize that both RBV systems only measure the relative change in blood volume in comparison with the start of HD. These systems are not capable of providing information on (changes in) absolute blood volume.

#### 21.3.1.1 The Blood Volume Monitor

At the start of the HD session the blood volume is, by definition, set at 100%. If a patient is considered for HD with BVM, first several HD sessions are performed during which the course of RBV throughout the

session is monitored. The staff needs to observe and take note of the changes in RBV in relation to the patients' condition and blood pressure. These observations must be written down since these parameters cannot be stored or printed out.

After the staff has gained a good insight in the RBV curve in relation to the patient's blood pressure and/or complaints, a co called $RBV_{crit}$ can be set. The $RBV_{crit}$ stands for the critical RBV level below which hypotensive episodes become more frequent (Fresenius Medical care). The goal of the BVM system is to keep the actual RBV at the safe side of the $RBV_{crit}$. Of course, the $RBV_{crit}$ can be adjusted over time.

During HD, the UF-rate is adapted by the BVM according to certain algorithms. At the start of the session the BVM divides the allowed decline in RBV into a green, yellow and red area depending on the $RBV_{crit}$ level. In the green zone, the UF-rate starts at twice the average UF-rate. Thereafter, the UF-rate is continuously linearly reduced. When the RBV decline is halfway the individual $RBV_{crit}$, the yellow zone is reached and the UF-rate decreases faster. The red zone indicates that the $RBV_{crit}$ has been reached and the UF-rate is lowered to a minimum. As a general rule, the UF-rate will increase when RBV rises. If the prescribed UF-volume cannot be removed, since the $RBV_{crit}$ is reached, the HD apparatus sounds an alarm. In Fig. 21.3, a HD session with the BVM is shown.

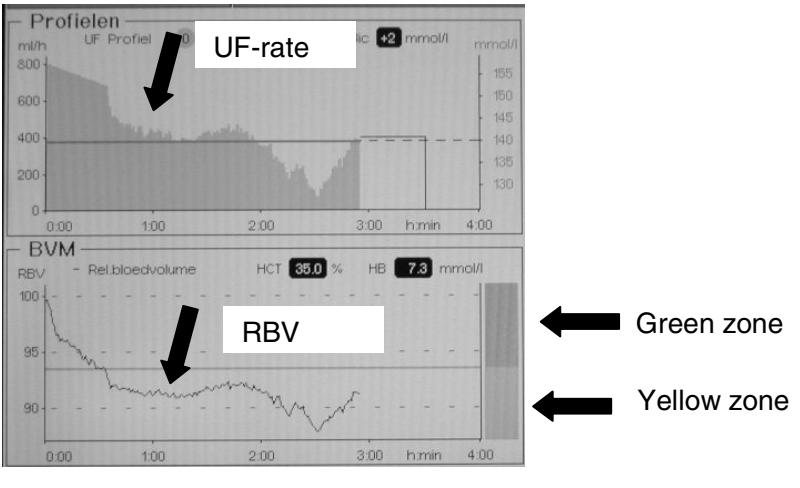


**Fig. 21.3** An example of a HD treatment with the BVM. On the top of the graph the UF-rate is shown. On the bottom of the graph the RBV curve is shown. The UF-rate decreases when the RBV decreases below the green zone, and increases again when RBV rises.

At present, there are a limited number of studies on the clinical results of this technique on hemodynamic stability in hypotension-prone (Garzoni et al. 2007; Gabrielli et al. 2009) and non-hypotension-prone (Sentfeld et al. 2008) patients. Garzoni et al (2007) studied 56 hypotension-prone patients in a cross-over design and reported that slightly fewer intra-dialytic morbid events (mostly hypotension) occurred during dialysis with BVM compared with standard HD but the difference was not statistically significant. However, a subgroup of 31 patients with the highest frequency of intra-dialytic morbid events, experienced a modest but significant event reduction (from 1.2 to 1.0 events per treatment) during dialysis with the BVM system compared to standard HD. Gabrielli et al (2009) studied 26 hypotension-prone patients, again in a crossover design, and found that dialysis with BVM was associated with a significant reduction in the proportion of dialysis sessions that were complicated by intra-dialytic morbid events (32% versus 40%). However, in that study, the average change in blood pressure and heart rate from the start to the end of the HD session did not differ significantly between dialysis with BVM and standard HD. Sentfeld et al (2008) performed a crossover study, comparing BVM and standard HD in 19 non-hypotension-prone patients. They found no difference in the occurrence of decreases in systolic blood pressure of >30 mmHg, or subjective complaints, during or after treatment, between both dialysis modalities. This group also studied the patients' quality of life and found no consistent differences between BVM and standard HD.

#### 21.3.1.2 Hemocontrol

The RBV at the start of HD (measured by Hemoscan) is set at 0%. Hemocontrol guides the measured RBV along a pre-programmed so-called ideal blood volume trajectory, by continuously adjusting the dialysate conductivity and UF-rate. The ideal blood volume trajectory has an exponential form and its final level is based on an individual value for the ratio 'RBV decrease divided by total weight loss and (BV/TWL). Since TWL varies between sessions, the final RBV level varies as well (see Fig. 21.4). The BV/TWL ratio is determined on the basis of a number of HD sessions in which the changes in RBV are monitored in relation to the changes in the patients' condition and blood pressure (Dasselaar and Franssen 2006). The test HD sessions can be stored electronically in a specific software system (the Exalis system), thus allowing thorough evaluation of the HD session.

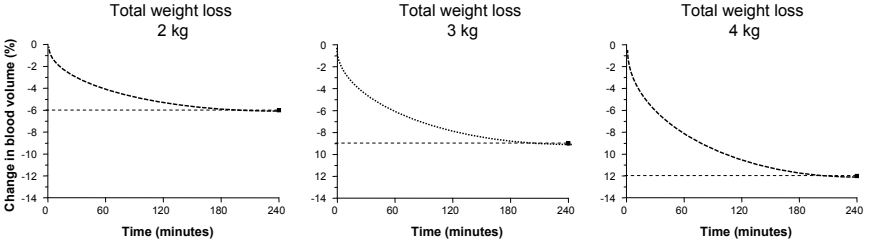


**Fig. 21.4** Hemocontrol: The Final RBV varies with the total UF-volume. The target (and hence the level) of the ideal blood volume trajectory varies according to the amount of fluid that must be withdrawn. A patient with a BV/TWL value of -3%/kg therefore may decline 6% in blood volume with a TWL of 2 kg (left), 9% with 3 kg (middle) and 12% with 4 kg (right), in order to achieve the target weight.

The Hemocontrol system has three targets that have to be achieved during HD: 1) keeping the RBV at the ideal blood volume trajectory (within certain limits (tolerance)), 2) removing the prescribed total UF-volume, and 3) achieving a pre-set equivalent conductivity in order to avoid a sodium overload. Hemocontrol adjusts the UF-rate and dialysate conductivity continuously throughout the HD session. At the start of the session the UF-rate is 1.8 times the average UF-rate and the dialysate conductivity initially rises to the maximum allowed conductivity (usually 16.0 mS/cm). As the RBV starts to decline at a steeper angle than the RBV trajectory allows, the UF-rate will decrease and dialysate conductivity will remain high. When the RBV rises, the UF-rate will increase while the dialysate conductivity decreases. Notably, if the RBV declines at the end of the session, the dialysate conductivity will not increase much since Hemocontrol must end the HD treatment with a pre-set conductivity equivalent (usually set at 13.8 mS/cm) which is determined on an individual basis so that the patient does not end the HD session with a too high plasma sodium level. The HD machine will sound an alarm when one of the three targets, or the 3 combined, deviate too much from the targets. In Fig. 21.5, a HD session with Hemocontrol is shown.

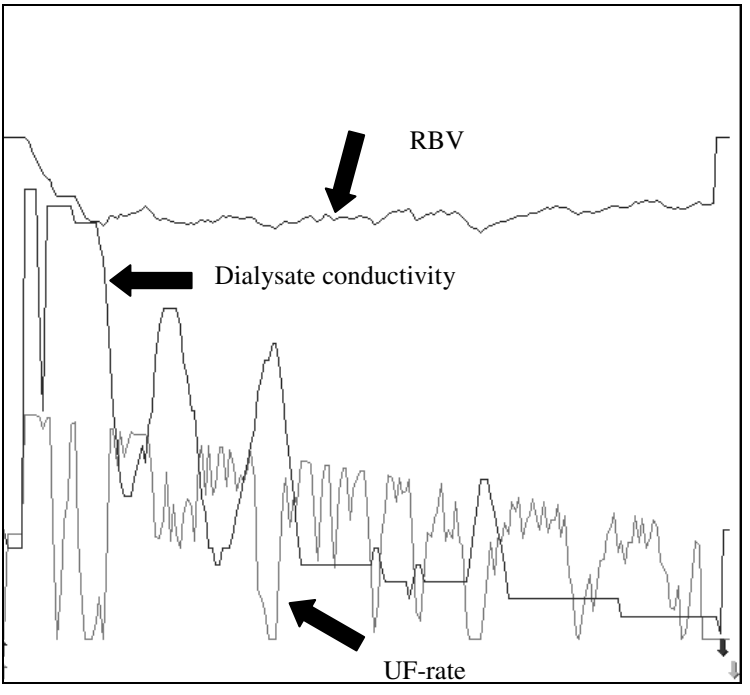


**Fig. 21.5** An example of a HD treatment with Hemocontrol. The line on the top of the graph represents the RBV, the 2nd line the dialysate conductivity and bottom line the UF-rate. When RBV decreases the UF-rate decreases while the dialysate conductivity increases, when RBV rises the UF-rate rises as well and dialysate conductivity declines.

The effect of Hemocontrol on hemodynamic stability has been studied by several groups, both in hypotension-prone (Santoro et al. 1994; Mancini et al. 1995; Santoro et al. 1998; Basile et al. 2001; Santoro et al. 2002; Begin et al. 2002; Ronco et al. 2002; Wolkotte et al. 2002; McIntyre et al. 2003; Franssen et al. 2005; Selby et al. 2006a; Moret et al. 2006; Winkler et al. 2008) and non-hypotension-prone patients (Wolkotte et al. 2002; McIntyre et al. 2003). A limited number of studies have also investigated the usefulness of Hemocontrol in the optimisation of dry weight and/or blood pressure via a reduction of the target weight in hypertensive dialysis patients (Dasselaar et al. 2007a; Deziel et al. 2007; Nesrallah et al. 2008). Some studies will now be discussed briefly with the emphasis on studies in hypotension-prone patients.

In 1995, Mancini et al were among the first to describe the results of HD with Hemocontrol (Mancini et al. 1995). They treated five hypotension-prone patients with standard HD and Hemocontrol in a cross-over trial, and observed a less pronounced fall in systolic blood pressure during Hemocontrol compared with standard HD. Three years later, the same group published the results of a cross-over study in 8 patients who frequently experienced dialysis hypotension (Santoro et al. 1998). The systolic blood pressure decreased less with Hemocontrol than during standard HD and the number of episodes of severe dialysis hypotension was lower with Hemocontrol. Ronco et al (2000) studied 12 patients with frequent dialysis hypotension and basically found the same results as those of the two studies described above. In addition, they reported that the removal of uremic waste products was significantly higher with Hemocontrol than with standard HD. The authors hypothesized that the improved hemodynamic stability with Hemocontrol would benefit tissue perfusion and thus the transfer of uremic waste products from the interstitial tissue to the blood. This hypothesis, however, remains to be proven. Basile et al (2001) also found a reduced frequency of dialysis hypotension with Hemocontrol compared with standard HD. In addition, they found that the fatigue was less severe after dialysis sessions with Hemocontrol than after standard HD. Franssen et al (2005) studied 12 hypotension-prone patients and compared the intra-, and the post-dialysis blood pressure course with 24 h ambulatory blood pressure measurements between standard HD and 3 and 9 weeks of dialysis with Hemocontrol. The intradialytic systolic blood pressure was significantly better preserved at 3 and 9 weeks of dialysis with Hemocontrol compared with standard HD. Following dialysis with Hemocontrol, the systolic blood pressure remained significantly higher during the first 16 hours after the end of the HD session than after standard HD. The higher systolic blood pressure following dialysis with Hemocontrol may explain the decrease in the severity of post-dialysis fatigue reported by Basile et al (2001), as discussed above.

Overall, the available studies in hypotension-prone patients show that dialysis with Hemocontrol is associated with a reduction in both the frequency and severity of dialysis hypotension episodes. One would expect that the increased hemodynamic stability with Hemocontrol would be related to less reduction in blood volume in comparison with standard HD. Interestingly, we and others found that the better hemodynamic stability and the reduction of symptoms with Hemocontrol was not paralleled by better RBV preservation in comparison with standard HD (Basile et al. 2001; Wolkotte et al. 2002; Franssen et al. 2005). However, it is possible that treatment with Hemocontrol exerts its favourable hemodynamic effect

by avoiding rapid RBV fluctuations, as has been suggested previously (Santoro et al. 1994; Mancini et al. 1995; Franssen et al. 2005). Alternatively, Hemocontrol may favourably affect the cardiovascular compensatory mechanisms, e.g. by stimulation of the sympathetic activity as a result of the increased plasma sodium concentration during the first half of the HD session. However, this hypothesis is still speculative and awaits further study.

A limited number of studies have investigated the application of Hemocontrol in the optimisation of dry weight and/or blood pressure via a gradual reduction of the target weight in hypertensive dialysis patients (Dasselaar et al. 2007a; Deziel et al. 2007; Nesrallah et al. 2008). Dasselaar et al (2007a) randomized 28 hypertensive HD patients to a 12-week treatment period with either Hemocontrol or standard HD. Dialysis with Hemocontrol was associated with a significant reduction in predialysis blood pressure. At the same time, the frequency of intra-dialytic hypotensive episodes decreased significantly. Deziel et al (2007) randomized a total of 44 patients to a 6-month period with either Hemocontrol or standard HD and found that the blood pressure management (recorded by the patient at home) did not differ significantly between Hemocontrol and standard HD. At the same time, the number of HD sessions that required nursing intervention decreased and health-related quality of life increased significantly with Hemocontrol compared with standard HD. Nesrallah et al (2008) randomized 60 overhydrated patients (defined as an extracellular fluid >45% of total body water as measured with multifrequency bioelectric impedance analysis) to a 6-month period of dialysis with Hemocontrol (29 patients) or standard HD (31 patients). At 6 months there was no difference in hydration state between Hemocontrol and standard HD.

#### 21.3.1.3 RBV Measurements and RBV Based Biofeedback: Influencing Factors

There are some important differences between the Blood Volume Monitor and Hemocontrol. First off all, the two monitors differ in the type of blood constituents that they use for the measurement of blood volume changes and they differ in the method of measuring the change in concentration of these constituents. In a recent study, we compared the results of continuous RBV measurements from both devices, and we found that both systems yielded results that differed systematically from the RBV results obtained from laboratory-derived Hb changes (Dasselaar et al. 2007b). Consequently, the RBV results from these devices should be considered as a rough estimate of the 'real' change in RBV. Furthermore, this study

showed that RBV results from different devices are not interchangeable, which is an important finding for centers that use hemodialysis monitors from different manufacturers. Second, the output parameter of the BVM system is UF-rate, whereas the Hemocontrol system uses both UF-rate and dialysate conductivity as output parameters. Third, the manufacturers have a completely different approach for the prescription of the individual blood volume course, based on different concepts of the relation between fluid removal and blood volume. Hemocontrol uses the concept of a variable end–HD RBV, (see Fig. 21.4), that varies with the total UF-volume, whereas the BVM uses a fixed $RBV_{crit}$ regardless of the UF-volume that has to be ultrafiltered during that HD session. At present, it is difficult to compare the two methods with respect to efficacy in diminishing the occurrence and/or the severity of HD hypotension, since there has been no direct comparison between the two systems.

In one multi-centre study the concept of an individual fixed $RBV_{crit}$ was studied. The hypothesis was that HD patients have an individual $RBV_{crit}$ below which HD hypotension will occur (Barth et al. 2003). Results indicated that in 47.2% of their patients the SD of the critical RBV threshold was greater than 4%. In a patient with a mean $RBV_{crit}$ of 90%, and a SD of 4%, this implies, by definition (normal distribution), that one third of the critical RBV threshold values of this patient will be outside the 86% to 94% range. With this variability, it would be difficult to use a $RBV_{crit}$ for the prevention of dialysis hypotension in about half of their patients (Franssen et al. 2004).

#### 21.3.1.4 Conceptual Limitations of Relative Blood Volume

The current generation non-invasive RBV devices are able to continuously measure Hb, Ht or total protein concentrations during HD. The reliable use of these measurements in clinical practice depends on their accuracy in reflecting the change in total blood volume (TBV). RBV devices are based on the assumptions that the total mass of the blood constituent in the vascular space is constant and that there is uniform mixing throughout the vascular space (Dasselaar et al. 2005). This, however, is not true since whole-body hematocrit (Ht) is lower than central Ht and during HD the ratio between whole-body to central Ht (F cell ratio) rises (Dasselaar et al. 2007b). This suggests that during HD, blood translocates from the microcirculation to the central circulation, probably as a cardiovascular compensatory mechanisms. As a result, RBV measurements significantly underestimate the total blood volume decrease during HD.

In other words, RBV measurements do not adequately reflect the real intravascular volume changes during HD.

Other known factors that influence the accuracy of total protein-based RBV devices, are the intravenous administration of albumin or other protein-containing fluids. Of course, infusion of erythrocytes (packed cells) will also be interpreted as a decline in RBV (see Fig. 21.6) by the Hb-based systems and - to a lesser extent - by the total protein-based systems. In addition, food intake during HD, as well as exercise and changes in body position, e.g. from upright to the supine position, all exert effects on the measured RBV during HD (Dasselaar et al. 2005). Given the many factors that influence Hb and Ht during HD, it is not surprising that the observed RBV course is so variable in many patients.

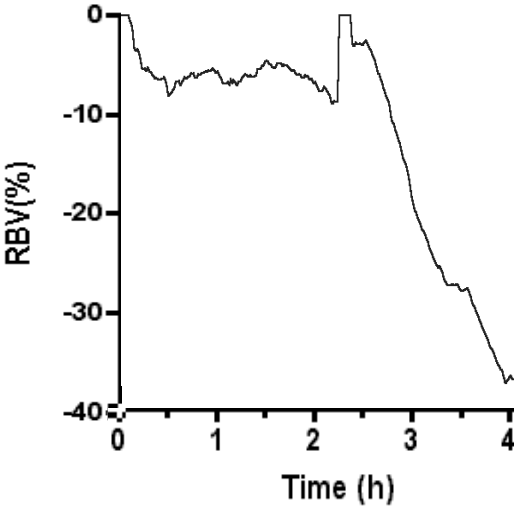


**Fig. 21.6** The effect of erythrocyte infusion on the RBV course. After 2½ hours of dialysis two units packed erythrocytes were given to this patient. In the remaining 1½ hours of the dialysis session the addition of erythrocytes to the circulation increased the hematocrit and hemoglobin concentration. The RBV device interpreted the rise in Hb as a decline of the RBV whereas in fact the blood volume increased. [Adapted from: Dasselaar et al (2005), with permission].

### 21.3.2 Blood Pressure Biofeedback

The ultimate target of any form of biofeedback is blood pressure (BP) preservation. As discussed, BVM and Hemocontrol aim to preserve BP

indirectly by means of RBV control. One biofeedback system aims to influence the systolic blood pressure itself: The bioLogic RR device (RR stands for Riva Rocci) is implemented in the Dialog Advanced dialysis machine (B. Braun, Melsungen, Germany).

The device 'retroactively' aims to control BP during dialysis, by automatically adapting the UF-rate in response to changes in BP with the so called automatic blood pressure stabilization system (ABPS) (Mancini et al. 2007). The feedback control of BP is achieved by means of fuzzy logic (FL), as shown in Fig. 21.7. This system is based on learning about the patient's BP behavior during the treatment (Nordio et al. 1995).

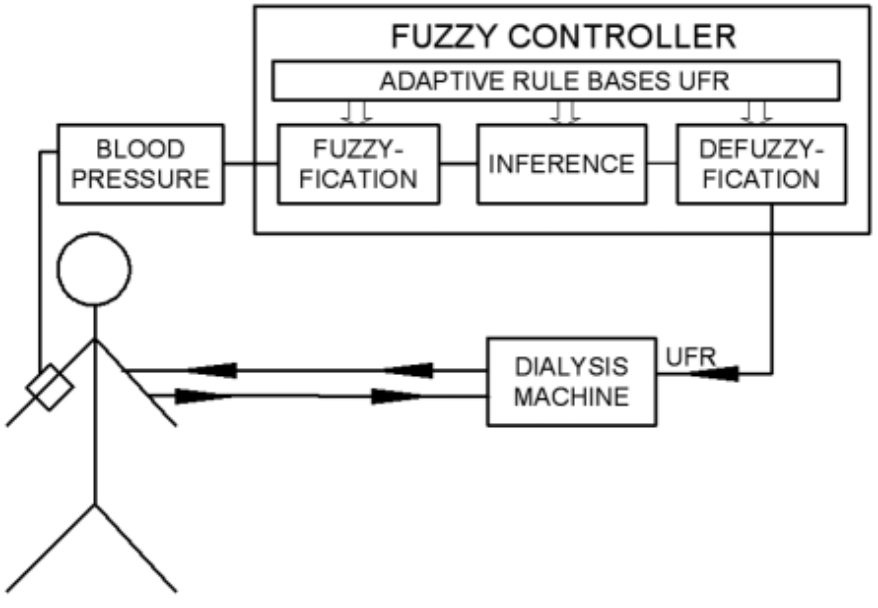


**Fig. 21.7** Technical scheme of the closed-loop system for the fuzzy control of the UF-rate.

The system requires two input parameters:

- The UF-rate maximum, chosen by the operator and defined as the maximum UF-rate to be applied in a specific patient. This parameter is expressed as a percentage value of the UF-rate used in a conventional dialysis with a constant UF-rate;

- The critical systolic BP set point, defined as the systolic BP level at which a patient generally presents his/her complaints (e.g. dizziness, yawning, pallor).

In order to be sufficiently precise, the system needs a frequent evaluation of the BP. For this purpose, BP is measured before the start of dialysis and throughout the whole HD treatment at 5-min intervals with an oscillometric manometer (Dinamap 1846 SX, Critikon, Norderstedt) that is incorporated in the machine. This system automatically adapts the cuff's inflating pressure to the patient's BP level. At the first measurement, it reaches 200 mmHg, whereas after that, it inflates up to the level of the last measurement plus 30 mmHg, thus reducing inconvenience to the patient. In addition, the system can use stored BP profiles of previous sessions for use in future treatments. In this mode, the system performs BP measurements every 5 minutes during the first 45 minutes of the session. Next, it reads the card's memory to determine the most similar previous blood pressure course. This course forms the basis for the time interval at which the BP will be measured, for the remainder of the treatment. During the dialysis session, regular BP measurements are performed and additional measurements can be programmed by the staff to ensure that this blood pressure profile is adapted to the current blood pressure of the patient (B. Braun 2009).

Since vascular instability is most prominent during the second half of the HD session, the BP Biofeedback system uses relatively low UF-rates during this phase of the session. Therefore, the UF-rate is highest at the start of the HD session and, next, it is subsequently 'retroactively' reduced and adapted, depending on the BP variations and on how much and how fast the BP declines in comparison to its BP set point (Mancini et al. 2007). The so-called UF-rate maximum can be set individually and may be as high as 200% of the average UF-rate. Likewise, the critical systolic BP (set point) is selected. Both parameters are to be programmed into the dialysis apparatus prior to starting the treatment. Usually, set points of 90–100 mmHg are used for patients having initial systolic blood pressures of 90 mmHg or higher. For patients with initial systolic pressures <90 mmHg the initial value itself is chosen as 'set point' in most cases (Schmidt et al. 2001). If the BP set point is reached, then UF stops automatically. It re-starts, once the critical hemodynamic moment has been overcome. Figure 21.8 displays an example of a HD treatment with Blood pressure Biofeedback.

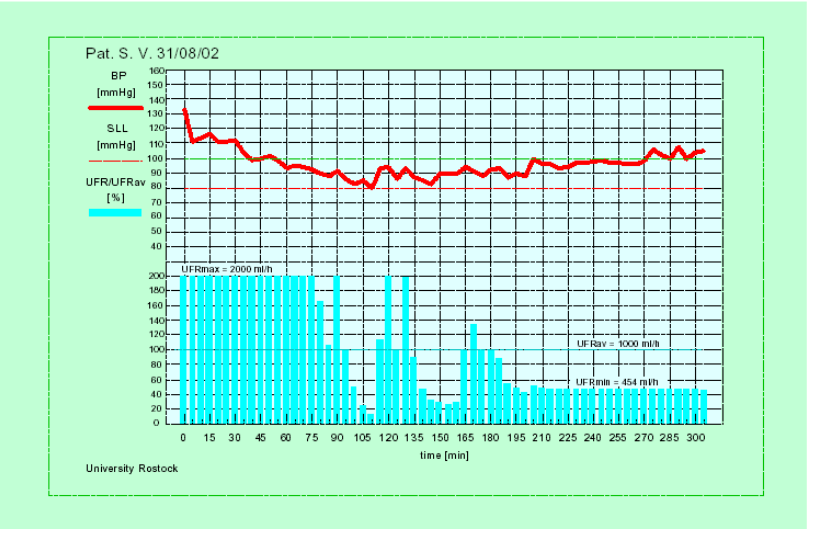


**Fig. 21.8** An example of a HD treatment with Blood pressure Biofeedback. The thick red line represents the blood pressure. The aquamarine bars depict the UF-rate. When the BP drops, the UF-rate diminishes. When the BP rises again, so does the UF-rate.

At present there are two publications on the clinical effects of this system (Schmidt et al. 2001; Mancini et al. 2007). Schmidt et al (2001) studied this system during 237 HD treatments in a total of 7 hypotension-prone patients and found that the frequency of dialysis hypotension episodes decreased significantly with blood pressure biofeedback. Mancini et al (2007) performed a multicenter study in 55 hypotension-prone dialysis patients. Sessions with blood pressure feedback and sessions with standard HD were alternated and an average of 30 HD sessions per patient was studied. Dialysis hypotension was significantly less frequent during BP feedback (8.3%) compared with standard HD (13.8%).

The impact of this technique on patient acceptance or quality of life has not been reported yet. These aspects should be studied since the frequent measurement of blood pressure is a potential burden for the patient.

### 21.3.3 Blood Temperature Monitor

The rationale of temperature control is to prevent the heat accumulation that occurs during HD (Schneditz et al. 2003). An increase in body temperature is associated with an increase in blood flow to the cutaneous

circulation to provide cooling, an increase in cardiac output, a decrease in total peripheral resistance, and a reduction in blood pressure (Gotch et al. 1989; Daugirdas 2001). This decrease in blood pressure may be prevented by temperature control.

Body temperature and thermal balance during HD can be controlled by the blood temperature monitor (BTM) (Fresenius Medical Care, Bad Homburg, Germany) (Kramer and Polaschegg 1992). The BTM measures the core temperature (CT) at the arterial blood line and calculates central venous blood temperature by correcting for fistula and cardiopulmonary recirculation. This correction is necessary because the temperature of the arterial blood is determined by the CT as well as by the temperature of the recirculated venous blood. Recirculation is measured by the BTM using the thermodilution method (Schneditz et al. 2003). Changes in temperature are recorded by the venous sensor head of the BTM and by the arterial sensor head (van der Sande et al. 2000b). Pre-dialytic CT is defined as the first reliable temperature obtained (within 5 min) after the start of HD. The system has demonstrated to accurately measure CT (Schneditz et al. 2003).

The BTM can be operated in two control modes. In the isothermic HD (T-control) mode, the device can modulate dialysate temperature in order to maintain an unchanged body temperature. In the thermoneutral (E-control) mode, the aim is to achieve an unchanged energy flow rate across the extracorporeal circuit (Schneditz et al. 2003). This is accomplished through the feedback loop connecting the arterial and venous blood temperature sensor with the dialysate thermostat in the machine (Kaufman et al. 1998). The BTM module is discussed in detail in Chapter 20.

Several groups have studied the clinical effects of this system in hypotension-prone (Maggiore et al. 2002; van der Sande et al. 2009) and non-hypotension-prone (Beerenhout et al. 2004; van der Sande et al. 2005) patients; in three other studies the patient characteristics with regard to intra-dialytic hemodynamic stability were not clearly specified (Levin et al. 1996; Schneditz et al. 1997; Kaufman et al. 1998).

In the largest clinical study with biofeedback dialysis techniques thus far, Maggiore et al (2002) compared the effect of isothermic dialysis and thermoneutral dialysis on intra-dialytic hemodynamic stability in 95 patients in a crossover design. Following a screening period of 4 weeks with standard HD patients underwent isothermic and thermoneutral HD (each period lasting 4 weeks) in randomized order. During the screening phase, 50% of HD sessions were complicated by symptomatic hypotension. With isothermic dialysis, body temperature did not change significantly whereas

it increased by 0.47°C during thermoneutral dialysis. Isothermic dialysis was associated with a significantly lower proportion of HD sessions that were complicated by hypotension (25% of treatments) compared with thermoneutral dialysis (50% of treatments). The dialysis efficiency with regard to the removal of urea did not differ between both treatments. Isothermic dialysis was well tolerated by this patient population.

Selby et al (2006b) have performed a systematic review on clinical effects of reducing dialysate temperature, and performed separate analyses of studies that used a fixed reduced dialysate temperature and studies using the blood temperature monitor. The latter analysis included most studies on this technique that are currently available (Levin et al. 1996; Schneditz et al. 1997; Kaufman et al. 1998; Maggiore et al. 2002; Beerenhout et al. 2004; van der Sande et al. 2005). Dialysis with the blood temperature monitor was associated with a significant reduction of symptomatic hypotension episodes. At the same time, dialysis efficiency, defined as urea removal, did not differ between dialysis with the blood temperature monitor and standard HD. This is relevant since there has been concern that cooling the dialysate might lead to a reduction in dialysis adequacy due to peripheral solute sequestration as a result of greater vasoconstriction (Selby et al. 2006b). Another important conclusion of the systematic review was that most studies had not adequately reported the patient's acceptance with regard to frequency and severity of thermal-related symptoms.

Recently, van der Sande et al (2009) compared 2 settings of the blood temperature feedback system in 14 hypotension-prone patients: isothermic dialysis and 'cooling' dialysis in which the biofeedback system was set to decrease the patient's core temperature by 0.5 C. Blood pressure was better preserved during cooling dialysis compared with isothermic dialysis; three patients complained of shivering during cooling dialysis.

At present there are no randomized trials that have compared the long-term effects of the blood temperature monitor and a fixed reduction of the dialysate temperature with regard to hemodynamic stability.

### 21.3.4 Diacontrol

Complete removal of the interdialytic accumulation of sodium is a key requirement of hemodialysis. Failure to do so leads to greater thirst, increased interdialytic weight gains and hypertension, which in turn affects cardiovascular outcomes (Sang et al. 1997).

Empirical reduction of the dialysate sodium concentration to below the plasma sodium level, enhances sodium removal by diffusion and may lead to a reduction in total body sodium. However, in the initial phase of the HD session, this may result in an excessive reduction in plasma tonicity with symptoms like e.g. hypotension. In addition, the greatest benefits are seen at the lowest dialysate sodium conductivities (13.0 mS/cm), however, they were only achievable in a limited number of patients due to intradialytic symptoms (Lambie et al. 2005). Diacontrol (Gambro-Hospal, Lund, Sweden) is a plasma conductivity targeted biofeedback system. This software, incorporated in dialysis machines, is equipped with conductivity measurement cells placed at the dialysate inlet and outlet part of the dialyzer. It has the ability to alter the dialysate inlet conductivity and it can calculate dialysance.

Dialysance (D) is a surrogate marker for effective solute clearance. It is determined by briefly changing the inlet conductivity by 1 mS/cm, and measuring the resultant change in dialysate outlet conductivity (Cd) according to Polaschegg (1993):

$$D = -Q_d \times \left[ 1 - \frac{(Cd_{out2} - Cd_{out1})}{(Cd_{in2} - Cd_{in1})} \right] \tag{21.2}$$

Where $Q_d$ is the dialysate flow, $Cd_{out}$ and $Cd_{in}$ represent the dialysate conductivity at the outlet and inlet, respectively, 1 and 2 indicate the measurements before and after the temporary increase in $Cd_{in}$, respectively. Dialysance (D) is assessed every 30 min (Bosetto et al. 1999; Moret et al. 2002; Petitclerc et al. 1995).

Furthermore, the system can estimate ionic mass balance (IMB), a surrogate for net sodium removal (Petitclerc 1999; Bosetto et al. 1999), by constant measurement of the conductivity in the dialysis outlet and inlet according to Moret et al (2006):

$$IMB = \left[ (Qd_{in} \times Cd_{in})(Qd_{out} \times Cd_{out} \right] \times 10 \times \text{time (min)} \tag{21.3}$$

$Qd_{out}$ and $Qd_{in}$ are dialysate flow at the outlet and inlet, respectively; $Cd_{out}$ and $Cd_{in}$ are dialysate conductivity at the outlet and inlet, respectively. A positive IMB reflects net sodium removal from the patient, a negative IMB means net sodium transfer from the dialysate to the patient.

Plasma conductivity (PC), a surrogate for plasma sodium concentration, can be determined when ionic Dialysance (D), dialysate inlet ($Cd_{in}$) and

outlet ($Cd_{out}$) conductivities, and dialysate ($Q_d$) and UF flow rates are known according to Moret et al (2006):

$$PC = \frac{\left[ Cd_{out} - \left( 1 - \frac{D}{Q_d} \right) \times Cd_{in} \right]}{D/Q_d} \tag{21.4}$$

By means of assessment of ionic mass balance (IMB) and changes in pre-dialytic PC, it is possible to assess sodium balance during dialysis therapy in a non-invasive way during every dialysis treatment (Moret et al. 2006). Through serial plasma conductivity monitoring and appropriate adjustments in dialysate conductivity, Diacontrol makes it possible for the operator to set the desired post-dialysis plasma conductivity. Therefore, the interdialytic sodium can be completely removed even when pre-dialysis sodium levels vary (Locatelli et al. 2000; Bosetto et al. 1999; Di Giulio et al. 1998). In addition, this may be of relevance since PC-controlled treatments with fixed pre-set targets (such as a post-dialytic PC of 13.8 mS/cm) may lead to a reduced sodium removal in those patients with low pre-dialytic plasma sodium levels.

Diacontrol has been shown to achieve the prescribed end-dialysis plasma conductivity within very tight limits (Locatelli et al. 1995; Moret et al. 2006). There are a limited number of studies that have investigated the clinical effects of Diacontrol on hemodynamic stability during HD (Bosetto et al. 1999; Locatelli et al. 1998; Di Giulio et al. 1998; Moret et al. 2006). Early studies suggested improved hemodynamic stability with Diacontrol compared with standard HD (Bosetto et al. 1999; Locatelli et al. 1998; Di Giulio et al. 1998) but this was not confirmed in subsequent studies (Moret et al. 2006; Selby et al. 2007). Moret et al (2006) did not observe a reduced frequency of hypotensive episodes with Diacontrol compared with standard HD in their randomized crossover study in 10 hypotension-patients. Importantly, this is also the first and only study that has compared different biofeedback techniques with regard to their efficacy to reduce the frequency of dialysis hypotension. They found that Hemocontrol was associated with the lowest frequency of hypotensive episodes (8%) whereas hypotension occurred in 16% of standard HD sessions and in 17% of dialysis sessions with Diacontrol. However, the differences were not significant. Selby et al (2007) compared Diacontrol and standard HD, in 10 non-hypotenion-prone patients in a cross-over design. They used a progressive reduction of the (target or fixed conductivity for Diacontrol and standard HD, respectively) dialysate conductivity in both groups. Diacontrol did not have a clinical advantage over standard HD

with regard to the frequency of hypotensive episodes or the course of blood pressure.

## 21.4 CONCLUSIONS AND FUTURE DIRECTIONS

Dialysis hypotension is a frequent and serious side effect of a HD treatment. Based on the simplified concept of the pathophysiology of dialysis hypotension (a combination of a fall in blood volume and an inadequate response of compensatory mechanisms leads to hypotension and clinical symptoms), several closed-loop biofeedback systems have been developed to intervene in the chain of events that leads to dialysis hypotension. Clinical studies have demonstrated that some of these techniques indeed reduce the frequency and severity of dialysis hypotension and may even improve the patient's quality of life. At the same time, it should be realized that none of the current biofeedback systems is able to reduce the frequency of dialysis hypotension episodes with more than 50% compared to standard HD. Even more so, it is unlikely that any current or future system can completely eliminate hemodynamic instability during HD given the patient characteristics (many elderly patients and patients with cardiovascular comorbidity) and given the dialysis schedule of the vast majority of patients worldwide that require the removal of a large volume of fluid within a relatively short period of time. At present, studies that have compared the various biofeedback systems with regard to their clinical efficacy, side effects and patient tolerability are scarce. Moreover, there are no prospective randomized trials that have studied the effect of any of the biofeedback techniques on hard end point such as cardiovascular event rate and mortality. Such studies are required to single out the most effective system(s) with regard to the reduction of patient symptomatology and prognosis.

## DISCLAIMER

**Conflict of interest:** The authors have received a research grant in 2003 from Gambro-Hospal, the manufacturer of one of the biofeedback systems described in this chapter. In addition, they have written a book for Gambro-Hospal on the subject of dialysis hypotension and Hemocontrol.

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## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. Which input parameter is currently not used as a basis of a Biofeedback technique?
   A. Ultrafiltration volume
   B. Relative blood volume
   C. Plasma conductivity

2. Relative blood volume is calculated based on…
   A. Changes in total red cell volume
   B. Changes in the concentration of certain intra-vascular constituents
   C. Changes is plasma conductivity

3. An $RBV_{crit}$ is in 95-100% of hemodialysis sessions accurate in preventing dialysis hypotension
   A. True
   B. False

4. Hemocontrol prevents hemodialysis hypotension in 1/3 of the cases.
   A. True
   B. False

5. Hemocontrol has three targets, which of the ones below isn't one of them
   A. Total Ultrafiltration volume
   B. Equivalent conductivity
   C. Final Blood volume
   D. Allowed Relative blood volume decline in relation to the total UF volume

6. A concern in using Hemocontrol long term is…
   A. Not achieving the needed amount of total ultrafiltration; hereby inducing volume overload.
   B. The use of high dialysate sodium concentrations which may induce sodium loading in the patient thus inducing volume overload.

7. The BVM and Hemocontrol have several differences. Which of the following is not one of them?
   A. The type of blood constituents the systems use
   B. The use of ultrafiltration profiling
   C. The use of sodium profiling
   D. The use of relative blood volume as the input parameter

8. Which of the following situations would induce the largest relative blood volume decline?
   A. Removing 5 litres of ultrafiltration volume
   B. Allowing unlimited RBV decline (by not activating the biofeedback modus)
   C. Administering 1 unit (300 ml) of red blood cells
   D. Administering 300 ml of saline

9. Blood pressure biofeedback has one output parameter which is…
   A. Ultrafiltration rate
   B. Blood pressure
   C. Dialysate sodium concentration

10. BP biofeedback requires the blood pressure to be measured every…
   A. 1 minute
   B. 2 minutes
   C. 5 minutes
   D. 20 minutes

11. The rationale of temperature control during hemodialysis is to prevent…

A. Heat accumulation
B. An increase in cardiac output,
C. A decrease in total peripheral resistance,
D. A reduction in blood pressure

12. The BTM has a different application besides measuring and controlling body temperature; this feature is…

1. Determining plasma sodium concentration
2. Determining plasma erythrocyte concentration
3. Determining fistula recirculation

13. Early reduction of dialysate sodium concentration may lead to dialysis hypotension

1. True
2. False

14. What does 'Ionic mass balance' stand for?

1. The amount of sodium removed during a hemodialysis treatment
2. The amount of sodium to be removed during a hemodialysis treatment
3. The amount of sodium to be administered during a hemodialysis treatment

15. At which point in the dialysis system does the BTM measures the temperature?

1. At the inlet of the artificial kidney
2. In the artificial kidney
3. At the arterial side of the fistula
4. At the venous side of the fistula

16. What is the effect of administering 100 ml of saline (NaCl 0.9%) on the measurement of ionic dialysance during this measurement.

A. It has no effect: the outcome of the measurement is reliable.
B. It has a severe effect: the outcome of the measurement is unreliable
C. The measurement does not take place since the necessary increase in dialysate conductivity induced by the machine does not take place.

17. The BTM's T-control mode is used to control body temperature.
    A. True
    B. False

18. The majority of hemodialysis hypotension episodes occurs:
    A. In the first hour of dialysis
    B. In the second hour of dialysis
    C. In the third hour of dialysis
    D. In the fourth hour of dialysis

19. The success of biofeedback treatment during hemodialysis relies the most on…
    A. The medical status of the patient
    B. The knowledge of the systems operator on biofeedback apparatus
    C. The amount of fluid to be removed

20. Input parameters for Blood pressure biofeedback are…
    A. Blood pressure and total ultrafiltration volume
    B. Blood pressure and ultrafiltration maximum
    C. Blood volume and total ultrafiltration volume
    D. Blood volume and ultrafiltration maximum

21. Dialysis hypotension occurs in 15% of hemodialysis sessions
    A. True
    B. False

22. Most of the excess fluid in a dialysis patient is accumulated in the intravascular space.
    A. True
    B. False

23. Dialysis hypotension is initiated mostly by…
    A. The removal of sodium and waste products like urea
    B. The decrease in blood volume caused by ultrafiltration
    C. The administration of bicarbonate
    D. The rise in body temperature

24. What is the first measure taken in the acute stage of dialysis hypotension
    A. Increase in dry weight
    B. Administration of hypertonic NaCl
    C. Cessation of ultrafiltration

25. Which of the below mentioned strategies is the most effective is diminishing the occurrence of dialysis hypotension

A. Increase dialysis duration and frequency
B. Increasing the ultrafiltration rate
C. Abstinence of food during hemodialysis
D. Reduction of the dialysate temperature

26. In de early years of renal replacement therapy, dialysis was possible only in acute renal failure for a short period of time.
A. True
B. False

27. Progress in dialysis technology has helped improving HD tolerance. Which of the following is not part of this aforementioned progress?
A. Bicarbonate dialysate
B. Dialysis access
C. Biocompatible bloodlines
D. Dialysis duration

28. A difference between the BVM and Hemocontrol is that the BVM uses changes in total protein concentrations for the calculation of the RBV whereas Hemocontrol uses Hb measurements for this purpose.
A. True
B. False

29. Patients with co-morbidity are prone to develop intra-dialytic hypotension. Which of the following is likely to contribute the most to this risk.
A. Family history of orthostatic hypotension
B. Neurogenic claudication
C. Diabetes Mellitus
D. Ejection fraction of 55%

30. The F-cell ratio rises during Hemodialysis
A. True
B. False

Chapter (22)

# Artificial Neural Networks Applications in Dialysis

Elmer A. Fernández, Rodolfo Valtuille, and Mónica Balzarini

**CHAPTER OUTLINES**

- Neural Networks
- Artificial Neural Networks
- Neural Networks in hemodialysis
- Discussion and conclusion

**CHAPTER OBJECTIVES**

- To introduce main ideas of Artificial Neural Networks
- To describe an application of neural networks in Hemodialysis

**KEY TERMS**

- Artificial Neural Networks
- Multilayer Perceptron
- Backpropagation
- Levenberg-Marquardt
- Regression/Prediction
- Urea removal
- Dialysis Dose
- Equilibrated Urea Concentration
- Urea Rebound

**ABSTRACT**

Artificial Neural Networks are mathematical models resembling the brain behavior. They have the ability to "learn" from the "environment" and produce responses as a consequence of this learning process. They were broadly used in medicine both as a classification model as well as a prediction tool. In hemodialysis they were used for molecular modeling in the estimation of equilibrated urea concentration, as a monitoring strategy for online treatment analysis and also for bed side models for hemodialysis adequacy evaluation. In this chapter the basic concepts of artificial neural models are introduced and a complete application in equilibrated urea estimation in hemodialized patients is presented.

A.T. Azar (Ed.): Modeling and Control of Dialysis Systems, SCI 405, pp. 1145–1179.
springerlink.com 

## 22.1 A NEURAL NETWORK

All the brain tasks such as reasoning, memory and so on are able thanks to the function of neurons. A neuron is and electrically excitable cell that processes and transmits information by electrical and chemical signaling. A typical neuron possesses a cell body (soma), dendrites, and an axon. The neuron is electrically excitable and keeps an ion based voltage gradient across their membrane. Changes in this voltage can be achieved by excitatory or inhibitory signals through the dendrites, filaments arising from the cell body, or the soma itself. If the incoming signals are excitatory enough the voltage sufficiently changes to produce an all-or-none electrochemical pulse, "the action potential", which will actively propagate through the axon (a special cellular filament emerging from the cell body at a site called the axon hillock). In essence a neuron is a simple processing unit that integrates input information and, if it is high enough, produces an output. So, why the brain can perform complex tasks through such simple processing units? It can do that because of the massive and parallel interconnections of its constitutive neurons. The human brain has a huge number of neuron interconnections i.e. synapses. Each of neuron has on average 7,000 synaptic connections to other neurons which yields to approximately $(1 - 5) \times 10^{14}$ synapses (100 to 500 trillions) (Drachman 2005). In this sense, the brain is a complex computational structure, highly non-linear and parallel with the capacity to organize neurons to perform different tasks (Haykin 1999).

### 22.1.1 The Neuron Model

As mentioned, a neuron is a simple processing unit that receives one or several input signals, integrate them and an output signal is generated and propagated. In Fig. 22.1 a translation from a neuron cell to a neuron graphical model can be seen. In the latter one the following four parts can be identified (as depicted in Fig. 22.2):

1. A set of connections and its associated weight coefficient resembling synapses. Each input "$x_i$" is weighted by its corresponding weight coefficients $w_i$ with i=1..p. Where "p" is the number of inputs or input dimension.
2. An integrator ($\Sigma$) that sums all the weighted inputs yielding the "net input effect" (nie) onto the neuron.
3. An activation function *f(...)* which decides according to the nie if the neuron "fires" an output signal.
4. An output signal that propagates through the axon to other connected neurons.

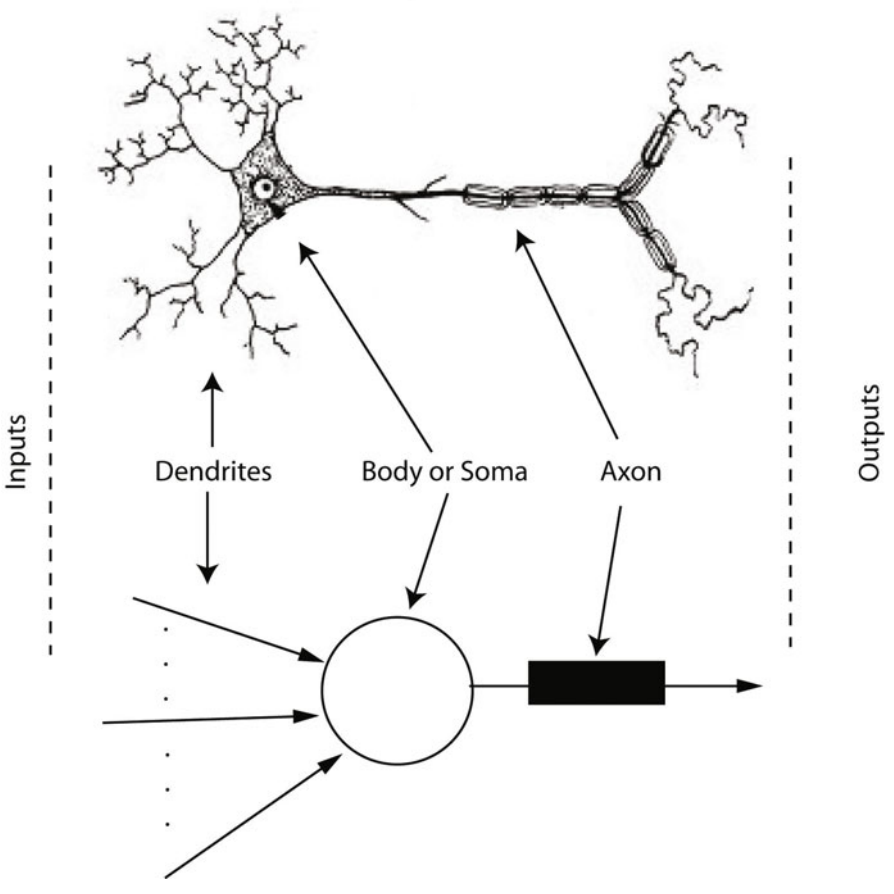


**Fig. 22.1** The neuron cell and its graphical model.

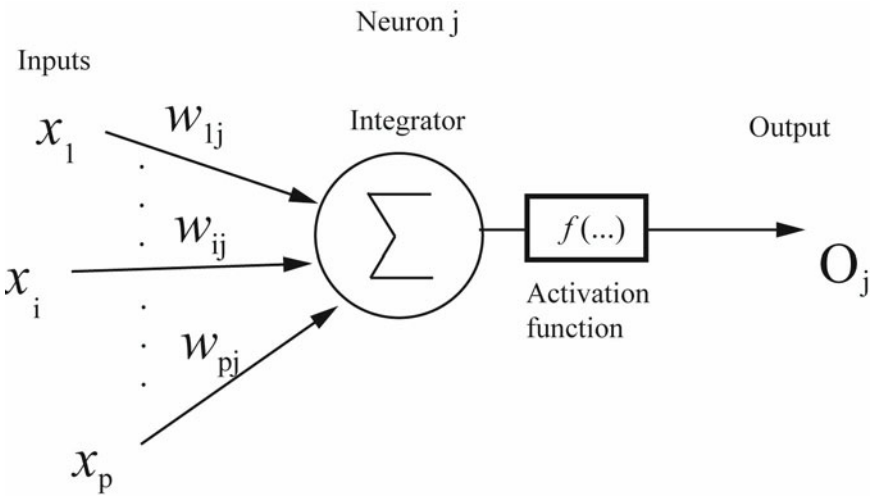


**Fig. 22.2** The Artificial Neuron Model

In summary, the neuron processes the input data and propagates them in the following way: Let's assume the j-th neuron is fed with an input vector $\boldsymbol{X}$ of dimension "p" $\mathbf{X}^p = \{x_1, x_2, ...., x_i, ..., x_p\}$. Each input is weighted and summed algebraically as follows:

$$x_1 \cdot w_{1j} + x_2 \cdot w_{2j} + .. + x_i \cdot w_{ij} + ... + x_p \cdot w_{pj} = \sum_{i=1}^{p} x_i \cdot w_{ij} = nie_j \quad (22.1)$$

This equation can be expressed in matrix form as (Haykin 1999; Kosko 1992):

$$nie_j = \mathbf{X} \cdot \mathbf{W}_j^T \quad (22.2)$$

In a neuron cell if the incoming signals are excitatory or high enough, an output signal is propagated through the axon. This means that if the nie is higher than a threshold, then an output is generated. In general, the activation function is a continuous, bounded non-linear function, thus $output_j = O_j = f(nie_j)$ where $\boldsymbol{f}$ is some "activation" function as those listed in Table 22.1.

**Table 22.1** Artificial neuron Activation Functions

| Activation Function | Equation | Output Range |
|---|---|---|
| Identity or linear | $O_j = nie_j$ | $\{-\infty, \infty\}$ |
| Threshold | $O_j = \begin{cases} 1 & if\ nie_j \geq b_j \\ 0 & if\ nie_j < b_j \end{cases}$ | (0, 1) |
| Piecewise-linear | $O_j = \begin{cases} 1 & if\ nie_j \geq k \\ nie_j & -k < nie_j < k \\ 0 & if\ nie_j \leq -k \end{cases}$ | (0, 1) |
| Sigmoid | $O_j = \frac{1}{1+e^{-a \cdot nie_j}}$ with $a>0$ | {0, 1} |
| Hyperbolic Tangent | $O_j = \frac{e^{nie_j} - e^{-nie_j}}{e^{nie_j} + e^{-nie_j}}$ | {-1, 1} |

The $b_j$ coefficient in the Threshold function can be incorporated as a new synaptic weight with a constant input $\boldsymbol{x_0=1}$. The constant $k$ in the piecewise linear is a user defined constant and the $\alpha$ coefficient in Sigmoid function is a user defined constant that model the speed of the function transition.

## 22.2 ARTIFICIAL NEURAL NETWORK

Artificial Neural Networks (ANN) are models that try to emulate the organizational and functional behavior of the Brain. An ANN consists of a set of simple and basic computational units (artificial neurons) or nodes and a set of connections linking such nodes. Each connection has a weight coefficient associated to it (Barro and Mira 1995; Haykin 1999). The assembling of nodes in the net, the connections and the weights defines the model behavior.

The following definition for an ANN will be used in this text (Haykin 1999):

*A Neural Network is a massively parallel distributed processor made up of simple processing units, which has a natural propensity for storing*

*experimental knowledge and making available for use. It resembles the brain in two aspects:*

1. Knowledge is acquired by the network from its environment through a learning process
2. Interneuron connection strengths, known as synaptic weights, are used to store the acquired knowledge.

The procedure to perform the learning process is called "learning algorithm" which modify the synaptic weights of the network in such a way to satisfy a desired design objective.

### 22.2.1 Network Architecture

The architecture or structure of the network refers to the spatial organization of the nodes. There are networks with nodes arranged in layers such as Multilayer Perceptron (see Fig. 22.3A) (Rumelhart et al. 1986), Monolayers networks such as Hopfield network (see Fig. 22.3B) (Hopfield 1982) and bidimensional array of nodes such as Kohonen network (see Fig. 22.3C) (Kohonen 1997).

The first architecture is also known as feed-forward neural network, where the data flow from input to output units is strictly feed-forward. The data processing can extend over "$l$" layer of units (hidden layers) with $l$=1,..L, but no feedback connections are present, that is, connections extending from outputs to inputs of units in the same layer or previous layers. The second case, is also known as recurrent neural networks that do contain feedback connections. The dynamical properties of this network are important. In some cases, the activation values of the units undergo a relaxation process. The neural network will evolve to a stable state in which these activations do not change anymore. In the later model, dynamical behavior constitutes the output of the neural network. The change of the activation value of the output neurons is significant, providing contextual information.

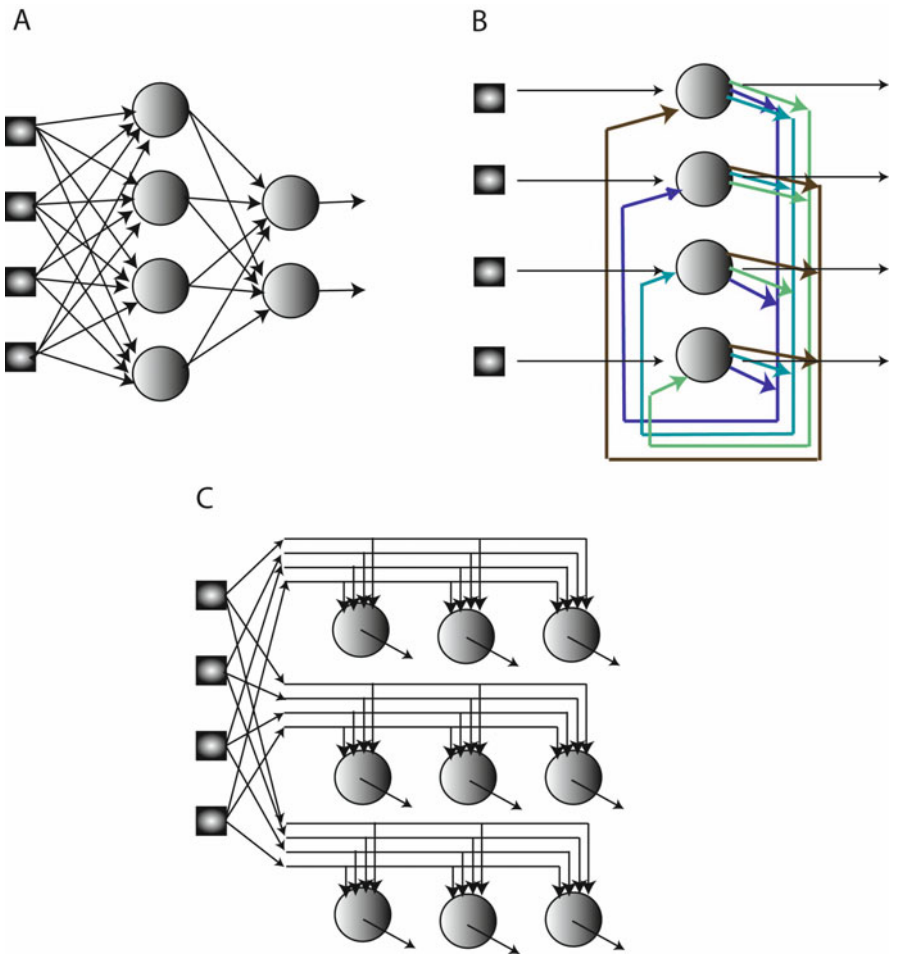


**Fig. 22.3** Neural Network architecture. **A)** Multilayer Network, **B)** Monolayer Network and **C)** Bidimensional array of nodes.

### 22.2.2 Neural Network Dynamics

An ANN always has an input or sensor layer that by pass the signal, usually, to the first nodes layer of the network architecture. Then, the node outputs are propagated to the network accordingly to its architecture. If the layer is the output layer, usually, the node output is the output of the neural network. For example, in Fig. 22.4 a two layer (L=2) neural network, with two inputs, two nodes in layer $l$=1 and one node in the output layer ($l$=L=2) is shown. Once the input vector $X = \{x_1, x_2\}$is presented to the

first layer *l*=1, the "net input effect" for each node is computed as follows:

$$\begin{aligned} nie_{lj} &= \sum_{i}^{N} x_i w_{ij} \\ nie_{11} &= x_1 w_{11}^{l=1} + x_2 w_{21}^{l=1} \\ nie_{12} &= x_1 w_{12}^{l=1} + x_2 w_{22}^{l=1} \end{aligned} \tag{22.3}$$

where $nie_{lj}$ is the net input effect for the *j-th* neuron in the *l-th* layer and $w_{ij}$ is the "i-th" weight of the *j-th* neuron for the "i-th" input $x_i$ . Then the output for the nodes $nr_{11}$ and $nr_{12}$ from the first hidden layer *l*=1 are computed as:

$$\begin{aligned} nr_{11} &= f\left(nie_{11}\right) \\ nr_{12} &= f\left(nie_{12}\right) \end{aligned} \tag{22.4}$$

and propagates to the next layer (the Output layer in this case). The net input for the Output layer is $nie_{21} = net_o = nr_{11} w_{11}^{l=L} + nr_{11} w_{12}^{l=L}$ . Then the neural network output is $O_{21} = f\left(nie_{21}\right)$

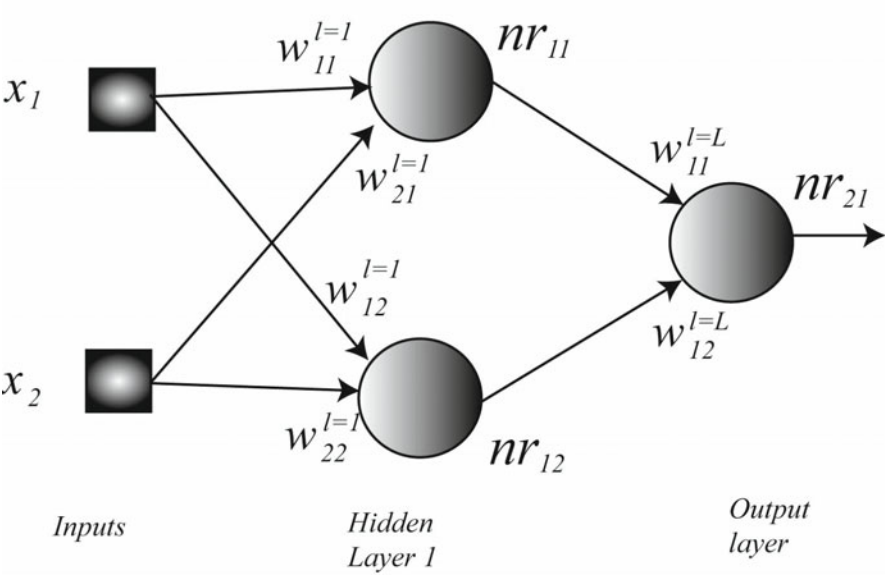


**Fig. 22.4** A feed-forward network with two input nodes, one hidden layer with two nodes $\{nr_{11}, nr_{12}\}$ and one output node O ($nr_{21}$).

### 22.2.3 The Neural Network Learning

The learning process of a neural network is the algorithm by means the weights are modified in order to keep environmental knowledge in the net. There are three main learning process categories:

- Supervised learning or associative learning in which the network is trained by providing it with input and matching output patterns. These input-output pairs can be provided by an external teacher, or by the system which contains the neural network (self-supervised).
- Unsupervised learning or self-organization in which the net self-organize the output according to some local rules. In this paradigm the system is supposed to discover statistically salient features of the input signals. Unlike the supervised learning paradigm, there is no a priori set of categories into which the patterns are to be classified; rather the system must develop its own representation of the input stimuli.
- Reinforcement learning, in which the learning may be considered as an intermediate form of the above two types. Here the learning machine does some action on the environment and gets a feedback response from the environment. The learning system grades its action good (rewarding) or bad (punishable) based on the environmental response and accordingly adjusts its parameters. Generally, parameters adjustment is continued until an equilibrium state occurs, following which there will be no more changes in its parameters.

In general, the learning process is an iterative procedure which inspects one input vector at a time from the training set of samples $S^N = \{\mathbf{X}_s\}_{s=1}^N$. At each discrete time, a new vector from the S set is drawn and propagated through the net. Then the output is compared to some desired output (in case of supervised learning) or used for some local rules to update the weights as follows $w[t+1] = w[t] - \eta \Delta w[t]$ where $\eta$ is a learning rate factor and $\Delta w$ is the amount of weight change at discrete time "$t$". The form of $\Delta w$ depends on the learning algorithm and network architecture (Barro and Mira 1995).

### 22.2.4 Benefits of ANNs

The main benefit of a neural network derives, fundamentally, from its massively parallel and distributed structure and in its ability to learn and

generalize. *Generalization* refers to a neural network producing reasonable outputs for new inputs not viewed during learning. In addition, a neural network provides the following properties and capabilities (Haykin 1999):

- Non-linearity: Spite that a neuron can be linear o nonlinear, the neural network is basically a non linear processor because of its distributed and fully interconnected nature.
- Input-Output mapping: As a special case of the supervised learning strategy, the network learns from input-output pairs thus building an input-output mapping for the problem at hand.
- Adaptivity: Neural Networks have the ability to change synaptic weights when stimulated by the surrounding environment. Moreover it can be retrained as many times is required to deal with minor changes in the environmental conditions.
- Evidential Response: In a pattern classification task, the neural network can be designed to provide a "confidence" in the decision made. This information can be used to reject ambiguous data and improve the classification performance.
- Contextual information: Contextual information is naturally deal through a neural network by its structure. Any neuron potentially affect the response of the others neurons.

## 22.3 NEURAL NETWORKS IN HEMODIALYSIS

Neural Networks have been widely applied to study different problems in End Stage Renal Disease (ESRD) patients. One of the first neural network application in Hemodialysis was proposed by Smith et al. in 1998 to predict and prevent blood clotting in the extracorporeal circuit, they used a Multilayer Perceptron (MLP) with tangent activation function in the hidden layer. The MLP was feed with different kind of variables such as patient weight, heparine dose, gender, hematocrit etc. The MLP model provided greater precision, had fewer outliers in its prediction and it did not require any distributional assumptions as usual statistical models.

One of the hemodialysis problems that receive a lot of attention in the last years was to quantify the delivered dialysis dose in a reproducible manner. Measurement of dialysis dose has been based on estimation of clearance of the small, water soluble, nitrogenous waste product urea and hence the mathematical model was referred as urea kinetic modeling. This approach assumes that urea is distributed in a well mixed pool (explained by single or the most complex double pool) and also assumes that urea is generated by protein metabolism at a constant rate and removed at a constant rate by dialysis and residual renal function.

Several urea kinetic based approaches have been developed in the last years to provide an efficient and objective way to monitor the quality of the treatment and to correlate with clinical outcomes (specially mortality). They are based on different measures of Urea as a surrogate biomarker during the hemodialysis session. It has been widely accepted that current quality, Urea based, indexes such as Kt/V (a dimensionless ratio representing urea clearance "K", duration of the dialysis treatment session "t" and volume of the urea distribution V) and Urea Reduction Ratio (the recommended adequacy indexes) provides an accurate value once the equilibrated Urea value is provided. Equilibrated Urea differs from the end session value due to the rebound phenomena, where the Urea concentration continuously grows for the following 30-60 minutes after the session ends. The rebound effect is produced by solute disequilibrium between compartment and different organ fluxes. Several formulas (Daugirdas and Schneditz 1995; Daurgidas 1995; Smye et al. 1992, 1993, 1994; Tattersall et al. 1996; Maduell et al. 1997; Bhaskaran et al. 1997; Canaud et al. 1997) (termed equilibrated Kt/V) have been developed in last decades by adjusting the Kt/V for the rebound in urea. Frequent changes in blood flow, clotting of membranes or hypotension during dialysis procedure are not considered by the classical kinetic approach.

Different neural networks were applied to predict the equilibrated Urea (Ghu et al. 1998; Fernández et al. 2001), to provide equilibrated indexes (Goldfarb-Rumyantzev et al. 2003; Gabutti et al. 2004a) or to estimate Urea rebound (Azar et al. 2010). In the first case Ghu et al (1998) uses a self-organizing system called aiNet which is a NN derived from the probabilistic approach. They predict 60 minutes post-dialysis equilibrated Urea using a NN with 3 inputs ($U_0$, arterial $U_{pos}$ and low flow $U_{pos}$ (taken after 3 minutes of blood flow reduction to 50ml/min). This approach achieves very good results with a correlation coefficient of 0.96 and a mean absolute percentage error of 8.2 ± 0.8% on 74 patients. A Multilayer Perceptron was first used to predict equilibrated Urea by Fernández et al (2001). The NN was fed by three Urea concentration ($U_0$, $U_{mid=120}$ and $U_{pos}$) and two anthropometric data (pre-dialysis Body weight and Ultrafiltration). In this case the correlation coefficient was 0.88 with a mean percentage error of -7.62 ± 21.19%. Both methods outperform the usual Smye method (Smye et al. 1993) which is based on a simplification of the constant volume compartment model. Unfortunately these neural Network approaches are not comparable because the populations studied were very different. The 74 patients in Ghu et al (1998) were very homogeneous, they shown lower concentration values than in the Fernandez work. In Ghu et al (1998) the rebound phenomena was fairly similar for all the patients (28.6% ± 2%) meanwhile in Fernandez et al (2001)

the rebound was 20.8% ± 24.1%. The later shows greater dispersion and also included patients from two different centers.

Gabutti and coworkers (Gabutti et al. 2004b) used Multilayer Perceptrons to predict Kt/V, follow-up dietary protein intake and occurrence of hypotension during treatment. Nutritional, anthropometric, biological and dialysis quality variables were used as inputs to the NN. The NN was both used as a predictor (estimate the index value) and as a classification or diagnostic tool (Kt/V is grater than 1.3? yes/no, Hypotension episode? yes/no). The use of ANN significantly improves the ability of experienced nephrologists to estimate the Kt/V, the follow –up PCR, detect a Kt/V < 1.30 and the occurrence of intradialytic hypotension.

A similar approach as in Fernandez et al (2001) was used by Azar et al (2010) to predict equilibrated Urea and post dialysis Urea rebound 30 minutes after the end of dialysis session. The model was tested on a larger and multicenter population of 310 patients. The ANN results were significantly better than the usual Smye approach.

Azar and Wahba (2011) have demonstrated in their study the ability of Artificial Neural Network (ANN) to accurately predict the equilibrated post-dialysis BUN ($C_{eq}$) with the corresponding benefits for the true dose calculations for HD patient without the need for intradialytic sample. The ANN model is more accurate than the Smye formula because the ANN model showed, from a Bland– Altman point of view, lower mean and standard deviation errors. The analysis of % error against the % of urea rebound showed that the ANN is very robust to the level of urea rebound. The intrinsic nonlinearities involved in the ANN model render this approach very promising to directly estimate the $_{eq}$(Kt/V) without the previous estimation of the $C_{eq}$. The results presented in the study of Azar and Wahba suggest that the ANN, based on limited clinical parameters, is an excellent alternative method to other traditional urea kinetic models (UKM) for accurately predicting equilibrated urea concentrations and urea rebound in HD patients.

A Multilayer Perceptron was also used for on-line monitoring of dialysate-side urea kinetics. The MLP was able to predict hemodialysis adequacy at mid-session time, provides warning for bad treatment allowing correction actions during session (Fernandez et al. 2003).

Total body water (TBW) is an important parameter involved in the evaluation of dry weight and dialysis dose. Many anthropometric formulas were built in last years to predict TBW. Chiu et al (2005) tested several neural network models for TWB prediction in hemodialysis patients. The

best model was a Generalized Regression Neural Network (GRNN) which is a kind of probabilistic neural model where the neuron transfer function is a distance based Gaussian model. The GNRR developed model outperforms all the anthropometric methods.

Neural Networks are currently available methods to build plenty of hemodialysis tools to being used in daily hemodialysis centers. Available softwares/Languages such as Matlab® (www.mathworks.com) or R (www.r-project.org) made them easy to apply and ready for use.

### 22.3.1 Illustrating an Estimation of Equilibrated Urea Concentration by a Neural Network

It has been shown that mortality in End Stage Renal Disease (ESRD) patients is lower when sufficient hemodialysis treatment are provided [KDOQI]. Both the US National Kidney Foundation, by means of the Dialysis Outcome Quality Initiative (DOQI) guidelines, and the European Renal Association (ERA), by means of the European Best Practice Guidelines for hemodialysis (HD) (EBPGH), have recommended the routine measurement of hemodialysis dose and have set standards for adequacy of dose. Those guidelines suggest the use of two well know dose indexes, the single pool Kt/V (a dimensionless ratio which includes clearance of dialyzer plus residual clearance of patient (K), duration of treatment (T) and volume of total water of the patient (V)) and the Urea Reduction Ratio (URR). Both of them are calculated at the end of the dialysis session using pre and immediate post session Urea concentrations.

One of the main problems on using immediate post Urea concentrations is the increase of the blood molecular concentrations following the dialysis session ("Urea rebound") mainly due to non mono-compartment behavior of Urea distribution during dialysis session, recirculation and Urea sequestration in different body compartments (Smye et al. 1994; Daugirdas et al. 1995; Alloati et al. 1998). The Urea rebound UR is a critical problem, which influences the calculation of all dose indexes thus increasing the risk of malestimation of the true dose of dialysis (Alloati et al. 1998). For instance, Kt/V and URR are greater than that actually achieved in the patient, when calculated using the immediate post-dialysis blood urea concentration (Gotch and Sargent 1985).

It is well known that blood urea (U) concentration continuously grows after dialysis session reaching an equilibration level after 30–60 min. The measurement of the true dialysis dose would require the measurement of the true equilibrated Urea ($_{eq}$U) 60 min after dialysis. In this case, the single-pool

based urea kinetic model may still be used to calculate Kt/V and/or URR because this model gives an accurate measurement of the amount of urea removed independent of the number of distribution compartments, provided equilibration has occurred (Gotch and Sargent 1985). The simplest way to do this would be to retain the patient for 30 or 60 min after dialysis and then measure the $_{eq}$U. However, this is clearly inconvenient for the patient and not practical on a day-to-day basis in a busy dialysis unit thus an accurate equilibrated Urea prediction method would be very beneficial.

Over the last few years different approaches have been used to predict equilibrated indexes. Smye et al (1994) and Kaufman et al (1995) predicted $_{eq}$U concentration using the principle of mass conservation and then employed this eqU to calculate the equilibrated dialysis dose ($_{eq}$Kt/V or $_{eq}$URR). Daugirdas et al (1995) proposed an even simpler method where a single-pool Kt/V is modified according to the speed of dialysis (K/V) to obtain a double-pool estimate of Kt/V. These two approaches make some biological assumptions that are not always true but remain the most accepted models.

Here a supervised Artificial Neural Network (ANN) model to predict the $_{eq}$U 60 min after the end of HD is proposed. The ANN used here is the well-known multilayer perceptron (MLP) trained with the Levenberg-Marquardt algorithm (Hagan and Menhaj 1994). Different input parameter combinations were tried in order to find the most predictive ones and all the results were compared to the Smye and Daugirdas models. MLPs are very appropriate to deal with this kind of problem because they can handle the intrinsic nonlinearities involved in these types of biological systems.

One hundred and thirty-three stable patients were selected from two dialysis units as follows: 61 from Unit 1 (mean age 56 ± 3.5 years and mean time on dialysis (MTD) 32 ± 12.3 months) and 48 from Unit 2 (mean age 58 ± 18.0 years and MTD of 42 ± 23.5 months). All patients were from Buenos Aires, Argentina and were subjected to chronic HD treatment for at least 3 months. The selection criteria to include patients in the study were: (1) patients without infection or hospitalization in the last 30 days; (2) patients with an A-V fistula (70% autologous fistula and 30% prosthetic fistula) with a blood flow rate ($Q_B$) of ‡300 mL/ min; and (3) patients having consented to participate in the study. The study protocol complied with the Helsinki Declaration and was approved by the Ethical Committee of the Catholic University of Cordoba, Argentina. All patients received HD three times a week with Baxter® machines (model 1550) using variable bicarbonate and sodium. Hollow-fiber polysulfone (Fresenius F6 and F8) and cellulose diacetate (FB170 and 210, Nissho Corp.) dialyzers

were used. For the purpose of this study, all patients were dialyzed over 240 min and the flows of blood ($Q_B$) and dialysate ($Q_D$) were fixed at 300 and 500 mL/min, respectively. It is known that hemodialysis dose is influenced by several factors including dialysis time, hemodialysis schedule, and blood and dialysate flow. In order to decrease the complexity, such variables were handled externally, fixing their values to control their effects on the equilibrated urea prediction model.

### 22.3.2 Inputs and Outputs Variables

Blood samples were obtained at the mid-week HD session. They were taken from the arterial line at different times to obtain urea determinations: (1) pre-dialysis urea (U0), at the beginning of the procedure; (2) intra-dialysis urea (U120), in the middle of the HD session (at 120 min from the beginning); (3) post-dialysis urea (U240), at the end of the HD session. For the intra-dialysis urea (U120) and post-dialysis urea (U240), QB was slowed to 50 mL/min and blood was sampled 15 s later. At this point, access recirculation ceased and the dialyzer inlet blood reflected the arterial urea concentration. Regarding the protocols for intradialysis samples, it is worth noting that originally Smye et al. proposed taking them within 60 min from the beginning of the session and at 20 min before its finalization. However, it was decided to take the intra-dialysis sample 120 min after the beginning of the HD session (U120), which allowed us to compare our results with those reported by Ghu et al (1998) and because Smye et al (1994) originally proposed that the intradialysis sample be obtained between 60 min after the beginning of the session and before the last 20 min of the end of HD.

Urea (U) determinations were performed in triplicate on each blood sample, using two autoanalyzers (Hitachi 704 in Unit A and Technicon RA 1000 Bayer in Unit B). The urea averages were calculated and recorded with an accuracy of 1% for both machines. For information about the pre- and post-treatment status of the patient, the pre- and post-dialysis body weights (BW0, BW240) were used. Both variables are commonly used in clinical practice to decide the treatment schedule as well as to calculate the treatment dose. These variables were recorded in the same dialysis session when the blood samples were taken. The output variable was the equilibrated urea. For the purpose of this study, the patients were retained one hour in the dialysis center and the "true" equilibrated urea levels ($_{eq}U$) were extracted 60 min after the end of HD. In Fig. 22.5 the variables relationships (pairs plots) and distribution (histograms) are displayed. The correlation ($R > 0.4$) is shown in the upper panels of the Fig. 22.5. The summary statistics for the input and output variables are shown in Table 22.2.

**Table 22.2** Summary statistics of the studied population

| Center | n | M/F | Age (Years) | Mean time on HD (months) | Body weight (Kg) | Uf (l) |
|---|---|---|---|---|---|---|
| A | 71 | 49/22 | 56.0 ± 13.5 | 32 ± 12.3 | 70.9 ±17.8 | 2.7 ± 1.3 |
| B | 58 | 42/16 | 58.6 ± 18.0 | 42 ± 23.5 | 69.0 ±12.1 | 2.7 ± 1.2 |

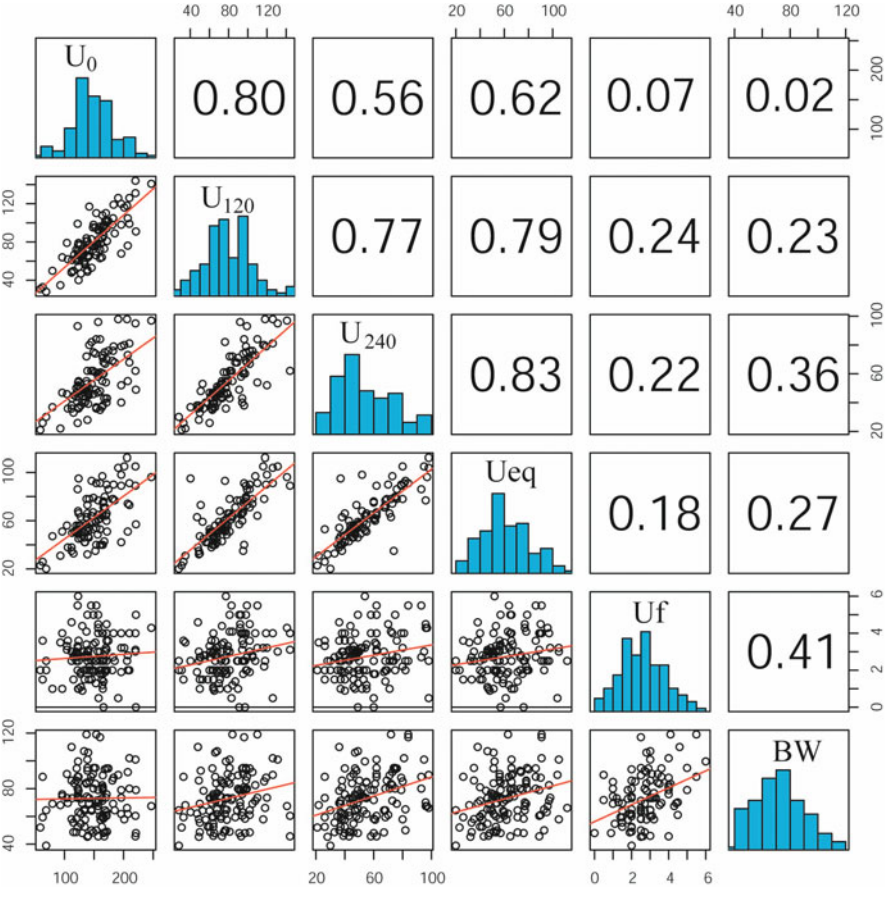


**Fig. 22.5** Pairs plot for all the measured variables. The lower diagonal panels show dispersion plots with the regression line (in red) between variables. The diagonal panels show the variable histogram and the upper panels display the correlation coefficient.

In Fig. 22.6 the box plots for the urea concentration levels are shown where it is possible to see highly symmetrical distributions.

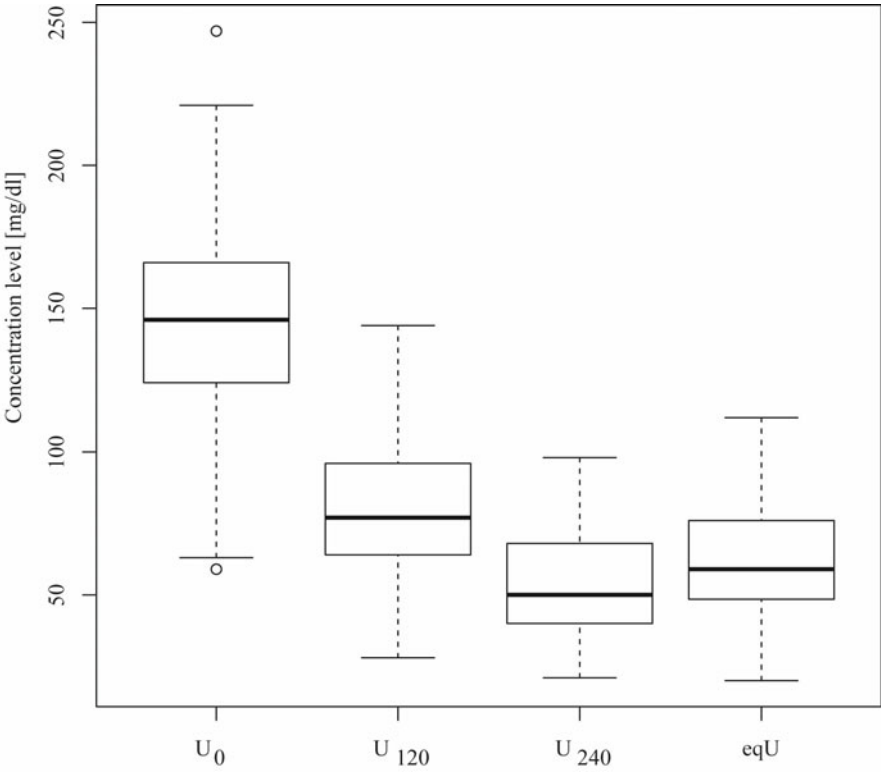


**Fig. 22.6** Urea concentration levels distribution for each measured time.

The true $_{eq}U$ was used as a 'gold standard' for post-dialysis $_{eq}U$. Urea Rebound (UR) was calculated as:

$$UR = 100 \times \frac{^{eq}U - U_{240}}{U_{240}} \tag{22.5}$$

In Fig. 22.7 the UR vs. the true equilibrated Urea ($_{eq}U$) is shown. It is possible to see zero and negative rebound values. It was reported (Daugirdas et al. 1997) that negative rebound values are frequently found in daily hemodialysis centers due to measurement errors in approximately 20% of the cases. In the used data base 15% of negative rebound cases were found.

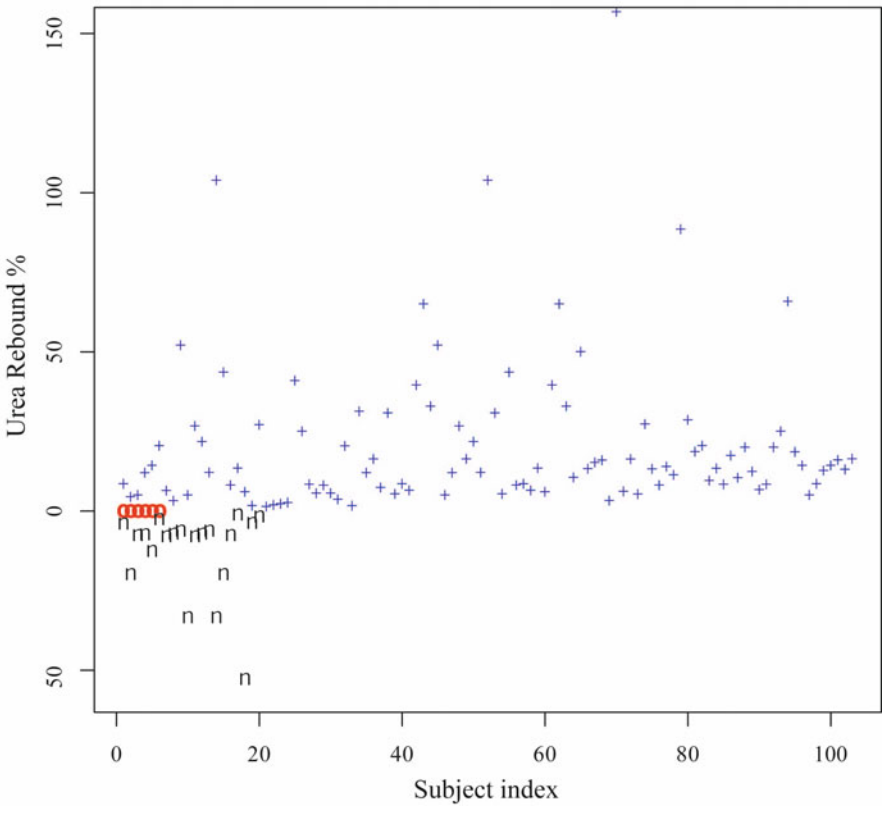


**Fig. 22.7** Urea Rebound. "+" UR > 0 , "o" UR = 0 and "n" UR < 0

The Multi-Layer Perceptron (MLP) is described as a set of sensory units (input or sensory nodes equal in number as the amount of input variables used in the analysis) with one or more hidden layers of computational nodes (neurons) and an output layer of nodes. Each layer is connected by numerical coefficients called 'weights' which resemble neuronal synapses. The input signal propagates through the network in a forward direction, on a layer-by-layer basis. The most popular algorithm to update the weights (learning process) is this type of NN is the "*error back-propagation algorithm*" based on the error correction rule (Haykin 1999). In this algorithm two passes through the different layers of the network can be identified:

1. A forward pass where an activity pattern (input signal) is applied to the sensory units and propagates forward (neuron by neuron) through the network and emerges at the output end of the network as an output signal. This output signal is presumed to

be some useful function/task by means the propagation of the input signal through the network. During this pass the synaptic weights of the network are all fixed.

2. The backward pass, which only take place during the learning time of the network, where the synaptic weights are updated in accordance to an error correction rule. In essence, an error signal (difference between the actual network output and a desired (target) response) is backward propagated against the synaptic direction and the synaptic weights are changed in order to make the actual response closer to the expected one (the desired network response).

Briefly, the basic Back-Propagation algorithm can be summarized as follows:

Assume a data set of *N* input-output samples pairs $S = \{\mathbf{X}_s, \mathbf{D}_s\}_{s=1}^{N}$ where **X** is a *N*×*p* matrix with *N* samples of *p* variables and **D** their corresponding *N*×*o* output matrix. In this particular hemodialysis case *N=129, p=5* and *o=1*, the algorithm implies:

1. Initialization: A random (usually a uniform distribution) assignment of the synaptic weight values with zero mean and standard deviation assuring that the values lie inside the linear part of the current activation function
2. Training samples presentation: Pick a vector sample from S, $(\mathbf{x}_s, \mathbf{d}_s)$, at time "*t*" and present them to the input layer.
3. Forward computation: The $\boldsymbol{x}_s$ sample vector is presented to the sensory layer and the corresponding desired $\mathbf{d}_s$ response is presented to the computational output nodes. Then the "nei" at time "*t*" for neuron "*j*" in layer "*l*" is:

$$nie_j^l(t) = \sum_{j^{l-1}=0}^{m_0} w_{j\,j^{l-1}}(t)\, y_{j^{l-1}}^{l-1}(t) \tag{22.6}$$

where $y_{j^{l-1}}^{l-1}(t)$ is the output activation (function) signal of neuron "$j^{l-1}$" in the previous layer *l-1* at iteration (discrete time) "*t*" and $w_{ji}^l(t)$ is the synaptic weight of neuron "*j*" in layer "*l*" which is fed from neuron "*i*" in layer *l-1*. For i=0, $y_i^{l-1}(t) = +1$

and $w^{l}_{j\,j^{l-1}}(t) = b^{l}_{j}(t)$ is the bias applied to neuron "*j*" in layer *l*. Then, the output signal of neuron "*j*" in layer "*l*" is:

$$y^{l}_{i}(t) = \begin{cases} x_{j}(t) & if \quad l = 0 \\ f\left(nie^{l}_{j}(t)\right) & if \quad 0 < l < L \\ f\left(nie^{l}_{j}(t)\right) = O_{j}(t) & if \quad l = L \end{cases} \tag{22.7}$$

where *l=0* is the sensory layer and *l=L* is the output layer. In the output layer the error signal is computed as:

$$e_{j}(t) = d_{j}(t) - O_{j}(t) \tag{22.8}$$

4. Backward propagation: Compute the local gradients ($\delta$) as

$$\delta^{l}_{j}(t) = \begin{cases} e^{L}_{j}(t) f'\left(nie^{L}_{j}(t)\right) \\ f'\left(nie^{l}_{j}(t)\right) \sum_{k} \delta^{l+1}_{k}(t) w^{l}_{kj}(t) \end{cases} \tag{22.9}$$

where *f'* refers to the derivative with respect to the argument and *L* to the output layer. Then adjust the synaptic weights of the layer *l* according to:

$$w^{l}_{ji}(t+1) = w^{l}_{ji}(t) + \eta \cdot \delta^{l}_{j}(t) \cdot y^{l-1}_{j^{l-1}}(t) \tag{22.10}$$

where $\eta$ is the learning rate parameter.

5. Iterate: Iterate from 2 to 4 pick, sequentially or randomly, samples from the *S* data set until the stopping criteria is met.

In the current illustration a modified version of the backpropagation algorithm, the Levenberg-Marquardt (LM) training algorithm was used. It is an intermediate optimization algorithm between the Gauss-Newton method and gradient descent algorithm addressing the shortcomings of each of those techniques. LM uses gradient descent to improve on an initial guess for its parameters and transforms to the Gauss-Newton method as it approaches the minimum value of the cost function. Once it approaches the minimum, it transforms back to the gradient descent algorithm to improve the accuracy (Hagan and Menhaj 1994; Beale et al. 2010).

The net was trained to predict the $_{eq}U$ from the following independent variables: U pre-dialysis ($U_0$), U intra-dialysis ($U_{120}$), U post-dialysis ($U_{240}$), pre-dialysis body weight ($BW_0$), and ultrafiltration (*Uf*, the difference between pre- and post-dialysis body weights). Basic codes are shown in Table 22.3.

**Table 22.3** Matlab ® code to train the MLP

```
%preprocessing the inputs. Set them in a -1,+1 range
[pn,minp,maxp,t,mint,maxt]=premnmx(p,yd);

%net initialization
net=newff(minmax(pn),[2 1],{'logsig','purelin'},'trainlm');

%setting training parameters
net.trainParam.lr=.04;
net.trainParam.epochs=100;
net.trainParam.goal=0.001;
net.trainParam.show=net.trainParam.epochs;
%==============================================
net=init(net);%weight initialization
net,tr]=train(net,pn,t);%training
```

Spite MLP is a widely used method for function approximation model, the definition of the number of hidden layers/nodes remains as an art process. There is no theory that can lead us to a definition of the net size and/or structure. Automatic pruning methods for ANN size optimization are difficult to implement and hardly found in available ANN software. Thus, in order to look for the most appropriate number of hidden nodes different net sizes were tested. The process was done using the complete data from both HD centers. They were randomly mixed and two training/test set pairs were built as follows: (A) training: first 60% of the samples test: last 40% of the samples; (B) training: last 60% of the samples, test: first 40% of the samples. The mean squared error (MSE) between the net's output and the $_{eq}U$ from a ten-fold cross-validation process (five for each training/test set pair) was averaged. The net size which achieved the lowest MSE was selected (see Table 22.4). In all cases logistic sigmoid function was used as the activation function for hidden layers and an output layer with a single node with identity activation function.

**Table 22.4** Means square error of prediction for ANNs for different number of nodes in the hidden layer

| Nodes in the hidden layer | MSE | | | |
|---|---|---|---|---|
| | Min | Mean | Sd | Max |
| 2 | 111.54 | 216.71 | 129.77 | 477.05 |
| 3 | 90.89 | 245.34 | 217.06 | 726.84 |
| 4 | 111.55 | 393.25 | 579.21 | 1978.10 |
| 5 | 112.90 | 755.64 | 1023.19 | 3110.30 |
| 6 | 149.00 | 345.85 | 218.90 | 690.28 |

A single-pool Daugirdas formula (Daugirdas 1993) is used to calculate the single- pool Kt/V ($Kt/V_{sp}$):

$$Kt/V = -Ln(R - 0.008 \times t) + (4 - 3.5 \times R) \cdot \frac{Uf}{BW} \qquad (22.11)$$

Where R is the ratio of the post-dialysis to pre-dialysis BUN, t is the length of the dialysis session in hours, UF is the ultrafiltration volume in liters, W is the post-dialysis weight in kg.

The Urea Reduction Ratio is calculated as (Lowrie and Lew 1991):

$$URR = 100 \times (1 - R) \qquad (22.12)$$

where for the standard approach $R = U_{240}/U_0$ , for the "gold standard" $R_{eq} = eqU/U_0$ and for the predicted equilibrated Urea $R_{NN} = eqU_{NN}/U_0$ .

The NN approach was also compared with the widely used Smye formula $eqU_{Smye} = U_0 \cdot e^{-\alpha \cdot Td}$ where $\alpha = \Delta t_{Um}{}^{-1} \cdot Ln(U_m/U_{pos})$ , $\Delta t_{Um}$ is the difference in minutes of total session length and time of intra-dialysis Sample $U_m$ (in our case $U_m = U_{120}$ , $\Delta t_{Um} = 120$) and $R_{Smye} = eqU_{Smye}/U_0$ .

The effects on the dialysis dose indexes of all the equilibrated urea estimation methods (the selected ANN and the Smye method) were compared. As a "gold standard indexes" the "true" $_{eq}U$ measured from the blood samples taken at 60 min after the end of the HD session into the dose equations was used. The models were tested with three different sets of data: (1) all the patients, (2) only those patients with UR > 0% (excluding patients with zero and negative rebound), and (3) only those patients with UR ≥ 0% (excluding only those patients with negative rebound).

In all cases the following coefficients were used: (i) correlation: index of direct association between two methods and (ii) Bland-Altman agreement method (Bland and Altman 1986): this method is based on the analysis of the average and the standard deviation of the difference between the model and the 'gold standard', against the true value ('gold standard'). This difference was called Error (Error = $_{eq}U - {}_{eq}U_{estimated}$).The average error is an index of systematic bias of one method with respect to the true value, while the standard deviation error is an index of the model accuracy. The percentage error (% Error = 100*Error/$_{eq}U$) was also analyzed.

The method for net size selection was based on the MSE, which is the most typical one in the ANN field. The ANN which achieved the lowest MSE was selected as the best model. Table 22.4 shows the results with different net sizes (more precisely different number of hidden nodes). The mean, standard deviation, minimum and maximum values of the MSE of

each training were analyzed. From this, an ANN with two hidden nodes was selected, because it achieved the lowest MSE (216.7 $[mg/ml]^2$) and the lowest standard deviation of the MSE (129.7 $[mg/ml]^2$), which means that this size is robust to different initialization procedures of the ANN initial weights. This characteristic is also evident in the smaller difference between the minimum (111.54 $[mg/ml]^2$) and maximum (477.05 $[mg/ml]^2$) MSE values. The decision of selecting a NN with two hidden nodes was also supported by the lower standard deviation achieved by this number of hidden neurons (HN) which gives an idea of the robustness of this model to the different initialization values in the node's weights. A net with 3 HN achieved a lower MSE (90.894 mg/dl) and a mean MSE similar to a net with 2 HN, but the net with 3 HN shows not only a higher standard deviation but also a higher difference in the extreme MSE achieved (726.84 – 90.894 =635.946 mg/dl (3HN) vs. 477.05 – 111.54 = 365.51 mg/dl (2 HN). This means that the net with 2 HN is more robust to the initialization procedures than the other architectures.

Of 129 patients, 20 and 6 had negative and zero rebound respectively. In the final prediction process by the ANN, the training method used was the 'early stopped' method which improved the generalization (Beale et al. 2010). In all cases the ANN model shows better results than the Smye method, showing a lesser bias (see mean difference and mean % Error in Table 22.5) and also best accuracy (lesser standard deviation) (see standard deviations in Table 22.5).

**Table 22.5** Equilibrated true Urea and predicted by Smye formula and by an ANN results.

| | Patients | Average [mg/dl] | *r* | Error [mg/dl] | % Error |
|---|---|---|---|---|---|
| True $_{eq}$U | All | 60.03 ±18.93 | | | |
| | UR > 0 | 60.38 ±18.89 | | | |
| | UR ≥ 0 | 62.83 ±18.51 | | | |
| Smye formula | All | 73.93±31.33 | 0.55 | -11.99 ± 26.06 | -25.10 ± 52.63 |
| | UR > 0 | 70.02 ±29.55 | 0.61 | -7.23 ± 23.15 | -13.75 ± 34.98 |
| | UR ≥ 0 | 70.87±28.87 | 0.62 | -6.87 ± 22.54 | -12.68 ± 34.30 |
| ANN | All | 60.83 ±14.56 | 0.84 | -0.80 ± 10.37 | -6.09 ± 24.58 |
| | UR > 0 | 62.20 ±14.71 | 0.88 | -1.83 ± 9.2 | -7.62 ± 21.19 |
| | UR ≥ 0 | 63.44 ±14.77 | 0.84 | -0.59 ± 10.12 | 4.85 ± 21.42 |

The ANN shows, in all cases, the best correlation coefficient ($r$). For all the patients (including those with negative and zero rebound) the ANN achieves a correlation coefficient of 0.84 ($p < 0.0001$) while the Smye method yielded $r = 0.55$ ($p < 0.0001$); when patients with negative and zero rebound where excluded the $r$ for ANN was 0.84 ($p < 0.0001$) and 0.62 for Smye ($p < 0.0001$) and finally when only those patients with negative rebound were excluded, ANN achieved an $r$ value of 0.88 ($p < 0.0001$) against 0.61 ($p < 0.0001$) of the Smye method.

The percentage errors of the Smye method were bigger than the percentage errors achieved by the neural net models for both mean and standard deviation, more than double in most cases. For both methods, best results were achieved excluding data with negative and zero rebound.

In all cases the neural net shows lower dispersion between the estimated and measured equilibrated Urea (see Fig. 22.8). Residual analysis showed no systematic errors in the comparison Smye and ANN methods compared to the true equilibrated Urea. The error distribution shows a better behavior for the ANN model. The distribution is thinner (less standard deviation) and more Gaussian like (suggesting random error distribution) than in the Smye case

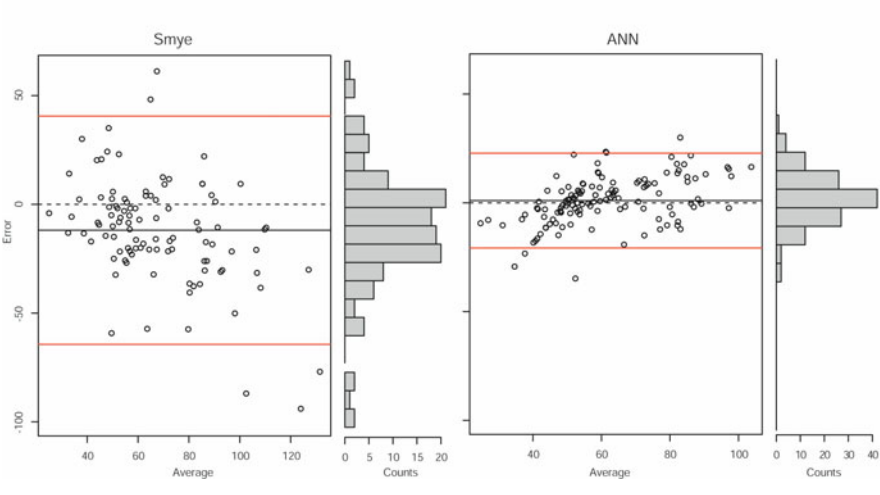


**Fig. 22.8** Bland-Altman plots of residual vs. average between true and predicted equilibrated urea values

In Figure 22.9 the dispersion plots are shown for both estimation methods. In continuous line the regression $eqU = a \cdot eqU_{estimated} + b$ is shown. where ${}_{eq}U={}_{eq}U_{Smye}$ or ${}_{eq}U={}_{eq}U_{ANN}$, "$a$" is the line slope and "$b$" the intercept. In Figure 22.8 it is possible to see that Smye estimation do not follow

very well the expected behavior, the intercept is quite high (35.6 mg/dl) and the slope (0.36) is far from the expected value of one. On the ciontrary, the ANN estimation provides good estimations, the slope is 1.06 and the intercept (-2.65) is not statistically different from cero.

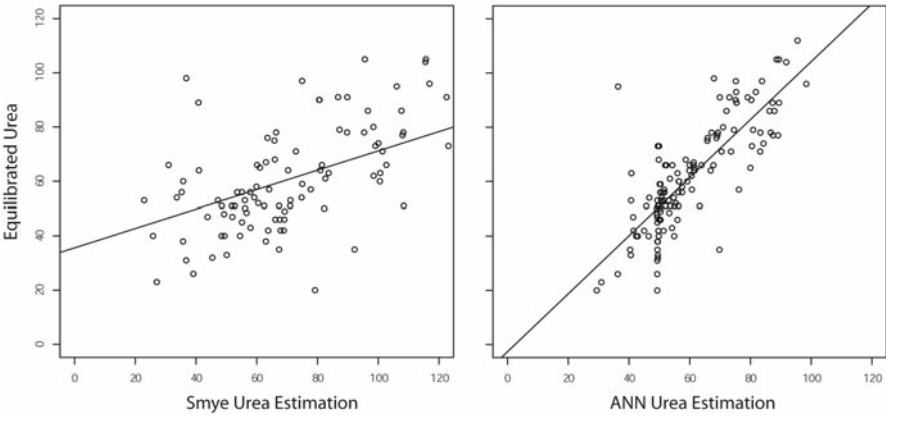


**Fig. 22.9** Dispersion plots between equilibrated Urea ($_{eq}U$) and Estimated equilibrated Urea by both Smye ($_{eq}U_{Smye}$) and ANN ($_{eq}U_{ANN}$)

In Fig. 22.10 the percentage error vs. Urea Rebound is plotted for both methods. In both cases the under-estimation of equilibrated urea is achieved for high UR values, but in any case the percentage error is much less for the ANN approach.

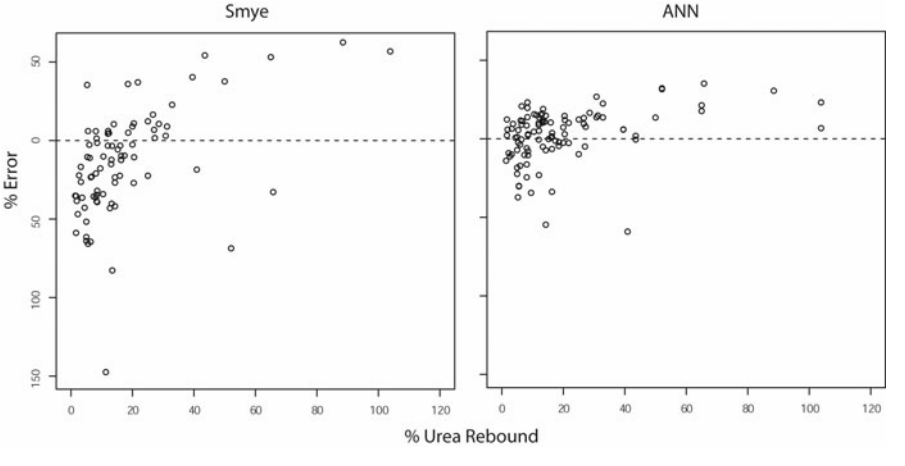


**Fig. 22.10** Percentage error vs. Urea rebound

When the ANN was trained with the patients belonging to one center and testing with the patients from the other center, i.e cross-center evaluation, In both cases the ANN were accurate with a mean estimation error of 4.28 ($p<0.01$) in center B (trained with patients from center A) and -1.95 -1.95 with a non significant p-value in center A. It is possible to see that the ANN trained with patients from center A tends to systematically under-estimate the true equilibrated Urea of patients from center B. When the ANN is trained from patients of center B the over-estimation is not significant. In Fig 22.11, the ANN errors by center box plots are shown.

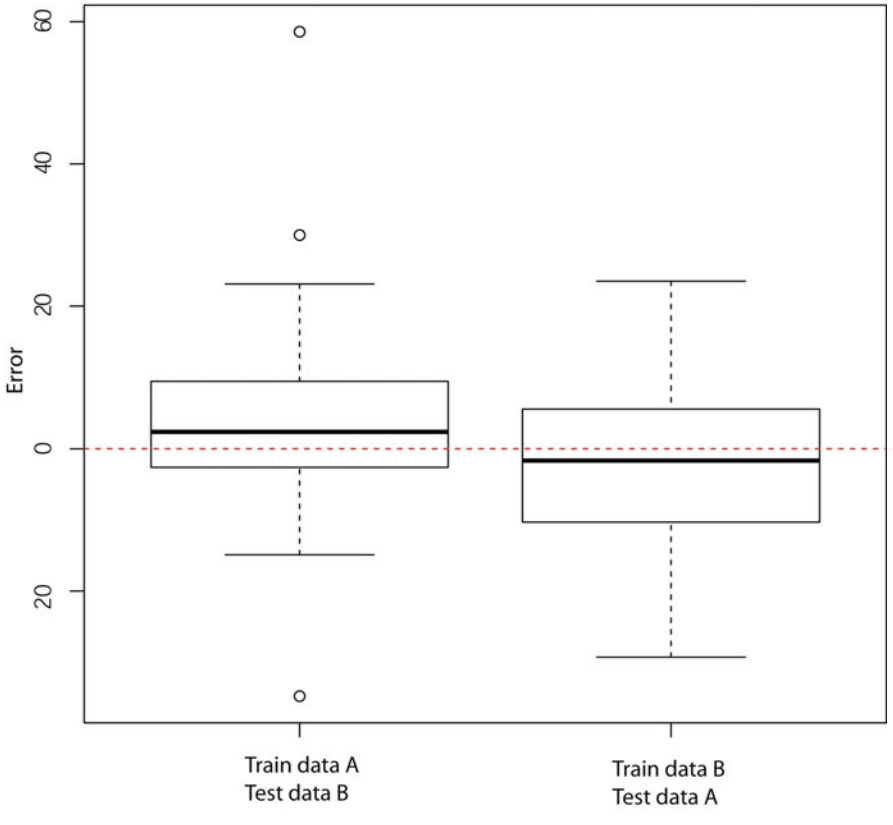


**Fig. 22.11** ANN error distribution for cross-center evaluation

## 22.4 DISCUSSION AND CONCLUSION

Urea removal dynamics are very complex, being affected by recirculation phenomena and sequestration of urea volumes in different body compartments (Daugirdas et al. 1995; Kauffman et al. 1995). The Smye formula

(Smye et al. 1996) is derived from a bicompartment model but it makes assumptions that are not always true (Ghu et al. 1998), yielding to under- or overestimation of the real urea concentrations after the end of the HD session. The miss-estimation of the true post-dialysis urea results in an inadequate HD prescription, with predictably poor clinical outcome for the patients. It is well known that the dynamics of physiological processes are highly nonlinear, so a nonlinear model seems to be a good tool for modeling. ANN has been successfully applied in many biomedical problems and their ability to accurately predict the $_{eq}U$ was shown with the corresponding benefits for the true dose calculations for each patient.

If the patients with negative and zero rebounds are regarded as bad or noisy data, from tables 4–6 it is possible to see that the ANN model is more robust to noisy inputs than the Smye method. The ANN is more accurate than the Smye formula because the ANN model shows lower mean and standard deviation error (see Fig. 22.8). It is well known that urea kinetics has two exponential components, the fast and the slow one. Smye used this information to derive his formula, so this method needs an intradialysis urea sample which contains information about both components. This intradialysis urea sample is likely to be taken at 30–40% of elapsed treatment time. In this illustration it was chosen to draw the interdialisys measurement 120 min from the beginning of the treatment. It is 50% of the total treatment time, and the reason was for comparison purposes against the other published neural network model (Ghu et al. 1998), but according to the poor results achieved by the employment of the Smye method, it is possible that 120 min was too late and the fast component could have vanished, making the use of the Smye formula inappropriate.

The ANN also shows high efficiency in urea estimation when used in the cross-center study, which means that the ANN could be trained from data collected in one center and used in another one thanks to the generalization capabilities of the ANN. However, a slightly different behavior was found when trained and tested with patients from different hemodialysis centers, suggesting that center specific ANN models would a better approach for this problem.

The supervised ANN used in this work showed most of the main characteristics of these models to solve prediction problems: (1) robustness to noisy inputs; it was able to accurately predict the $_{eq}U$ when patients with negative and zero rebound were included in the training sets. (2) generalization properties; the ANN was accurate in the cross-center evaluation when the net was trained with data belonging to one HD center and tested with the data belonging to the other center. The results are similar to those achieved with the mixed data pool, (3) nonlinear modeling. This work also

shows better results than those presented by Guh et al (1998). but the inexistence of a database makes the comparison between different intelligent data analysis methods impractical, so the development of a database to be used in the analysis of methods applied to different applications in HD (mortality risk, and dose predictions) it would be very beneficial.

Neural networks are very promising analysis tools to be applied in the HD field. ANN shows to be successful compared to other hemodialysis adequacy evaluation methods (Fernandez et al, 2005a, 2005b). More work should be done on the use of this technique in order to provide incentives for the use of intelligent analysis techniques in real medical problems and improve the confidence of the physicians in the use of them

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## ESSAY QUESTIONS

1. Describe the main learning algorithms of neural network
2. What are the main differences between learning algorithms?
3. List the main properties and capabilities of artificial neural network
4. What is the network architecture?
5. Assuming a sigmoid transfer function for all the net nodes, calculate the output of the ANN of Fig. 22.12.
6. Repeat the problem 4 with a linear output node.
7. If the desired output is 0.2, calculate the updated weights of the output node.
8. Why do you think that MLP is superior to the Smye formula for equilibrated urea estimation?
9. A Knowledge engineer said that if you train several times the same MLP architecture with the same training parameters the weights will not be necessary the same after each training process. Do you agree with this asseveration? Justify the answer
10. In a dialysis center, they want to build a predictor for total body volume. Based on the following variables: Age, Pre-dialysis Weight, Ultrafiltration, Gender, Body Mass Index. From a total population of 395 patients, they decide to use 60% of them. What is the other required variable that they should measure in order to build the predictor based on a MLP?
11. How many input nodes of MLP in question 10? And Outputs?

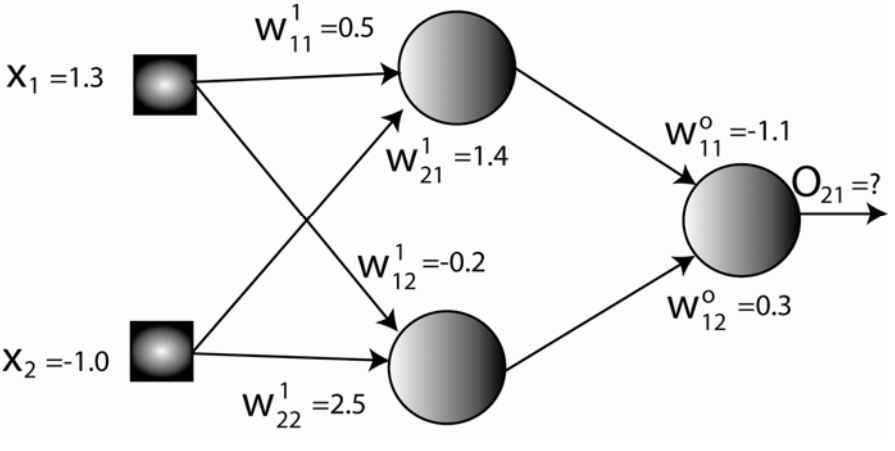


**Fig. 22.12** ANN Architecture and weights configuration for Questions 4, 5 and 6

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1 Assuming a specific ANN architecture, a training data set S, a fixed number of training steps and a fixed learning rate, why it is possible to get different ANN weights in different trainings?

A) The solution is non linear
B) The weights initialization is random in each training
C) The weight adaptation rule is non linear

2 The learning algorithm for a Multilayer Perceptron is…

A) Supervised
B) Non Supervised
C) Reinforced

3 The number of input nodes is defined by…

A) The problem complexity
B) The output dimension
C) The number variables in the input vector

4 If the output signal is in the range ± 5, which of the following output transfer function is appropriate…
A) Threshold
B) Sigmoid
C) Linear

5 In the MLP learning algorithm, the weight update rule requires that the node's transfer function be differentiable. Which of the following transfer function are not allowed for the algorithm
A) Hiperbolic-Tangent
B) Sigmoid
C) Threshold
D) None of the previous ones

6 Which of the following learning procedures requires the desired output?
A) Reinforced
B) Supervised
C) Self- Organized

7 Why the threshold function could not be used in the Backpropagation algorithm?
   A) Its output is in the wrong range
   B) It is not derivable
   C) It is not linear

8 The Bland-Altman plot is used to evaluate
   A) Correlation between MLP output and true value?
   B) To evaluate agreement of the evaluated methods?
   C) To compare the performance of MLP vs. Smye method?

9 An MLP model of 2 nodes in the hidden layer was chosen in the illustration example because it achieves:
   A) The lowest error value
   B) The lowest mean error over a cross validation test
   C) The lowest difference between minimum and maximum error

10 The gradient $\delta$ of the output layer requires:
   A) The error and the actual weight value
   B) Only the error and the actual net input effect of the output
   C) The actual net input effect of the output and the gradient of the other hidden layers

11 If a continuous MLP output is required, which output activation function is appropriate?

   A) Sigmoid
   B) Threshold
   C) Identity

12 In a Sigmoid activation function, if the following condition for the $a$ coefficient holds: $a_1 > a_2$, the transition between the output ranges for $a_1$ (compared to $a_2$) is…

   A) Slower
   B) Faster
   C) Equal

13 In an artificial neuron, a inhibitory synaptic will have a…weight value
   A) Negative
   B) Positive
   C) Zero

14 A biological neuron is slower than a computational counterpart to process and propagates the information, but the brain can, for instance, recognize a face much faster than the ANN. The reason for this is…

A) The activation function
B) The weigh synaptic values
C) The massive interconnection of neuron cells
D) The different cell structures in the brain

15 The ANN architecture is defined by…

A) The learning algorithm
B) The ANN output
C) The nodes organization

16 During the estimation process of the eqU, the backpropagation step of the algorithm is used…
A) To update the weights
B) To estimate the output
C) It is not used

17 What "Generalization" means for an ANN?

A) Small error during training phase
B) God performance for new data
C) Appropriate output when using a training data
D) None of them

18 The "Net Input Effect" is…

A) The net output
B) The node output
C) The weighted total node input
D) The activation function

19 In table 22.4, an NN with 3 nodes/neurons in the hidden layer achieves the lowest error, however an ANN with 2 nodes was chosen. The reason was…

A) The range between minimum and maximum errors was the lowest one
B) The averaged cross validation MSE was the lowest
C) The standard deviation of the cross validation MSE was the lowest
D) Only B is true
E) B and C are true

20 In which case the output of a node is equal to their "Net Input Effect"
A) For a sigmoid transfer function
B) For a linear transfer function
C) When the node is an output node
D) When the node is an input node

Chapter (23)

# Fuzzy Logic Control for Dialysis Application

Silvio Giove, Ahmad Taher Azar, and Maurizio Nordio

**CHAPTER OUTLINES**

- Introduction
- Modeling paradigms
- Fundamental of fuzzy control
- Fuzzy logic models
- Fuzzy control of dialysis session
- Comparison with other approaches
- Clinical results
- Diffusion of dialysis control system
- Future directions
- Conclusion

**CHAPTER OBJECTIVES**

- To understand the principles of fuzzy control.
- To understand hemodynamic instability in dialysis.
- To apply fuzzy control to prevent dialysis hypotensive episodes.

**KEY TERMS**

- Modeling paradigms
- Fuzzy logic
- MIMO system
- Fuzzy logic controller
- Hemodialysis
- Blood pressure
- Blood volume
- Ultrafiltration rate
- Conductivity
- Plasma refilling

**ABSTRACT**

This chapter introduces the fuzzy control approach for a dialysis session. Due to the complexity of the human system, the classical control methods, like PID, can fail to reach the target, mainly for what it concerns the stabilization of the system, which can induce sudden and undesired hypotensive collapses. To this purpose, a heuristic strategy based on expert rules, as fuzzy logic control, can help to reach the desired performances, reducing undesired collateral effects and increasing the potentiality of the dialysis session.

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springerlink.com 

## 23.1 INTRODUCTION

Automate control of many manual activities is nowadays possible and advisable, thanks both to great progress in hardware evolution and the relative cost fall-down, and to the availability of powerful algorithms for optimization and control of complex multi-dimensional systems, included the human body and many clinical operations that can be applied. To this purpose, in the following paragraphs, an innovative controller which has been applied by some Medical Center to optimize the dialysis parameters will be described. This system is based on fuzzy logic, a “new way” of thinking and managing with non probabilistic uncertainty (Bellazzi et al. 1994; Degani and Pacini 1980; Kageyama et al. 1990; Linkens et al. 1996; Mitra 1994; Moller 1993; Roy and Biswas 1992). After a brief introduction on fuzzy logic based control, the fuzzy logic hierarchical controller for hemodialysis will be described. This system will automatically optimize time by time the values of the therapeutic variables used during a dialysis session.

## 23.2 MODELING PARADIGMS

Models are developed to facilitate the solving of real world problems. Modeling is also a part of the learning process. It is an iterative, continual process of formulating hypotheses, testing and revision, of both formal and mental models (Sterman 2000). Modeling is not an individual effort. It requires active involvement of the decision makers and the individuals who are familiar with the system. Inputs from these subject matter experts ensure the integrity of the model structure with the actual system structure. The modeled interrelationships among variables depict mental models of the decision makers on which the decisions are based in the real world. Modeling activity has to follow a systematic step by step approach else our efforts can very easily digress from the main problem under consideration. Predictive modeling, also called predictive learning, consists in estimating an unknown dependency from known observations. Once the dependency has been estimated, it can be used to predict the response for future input data. Therefore, the basic objective of a predictive modeling procedure is to seek a model, using only a finite set of resources, with low prediction error. The prediction error is usually called generalization error, since it measures the capacity of the model to generalize, i.e. to return a good prediction of the output for input values not used during the modeling process. Inferring a predictive model from data is inherently an "ill-posed" problem due to the lack of knowledge about the underlying dependency and the finiteness of available data. This means that many models can often fit a

given finite data set, and yet these models might generalize very differently on new data drawn from the same distribution. To make the modeling problem well-posed, one needs to somehow calibrate the complexity of the model to the amount and quality of available sample data. This is described by the bias/variance tradeoff which states that the number of free parameters should be kept to a minimum in the model, thus reducing the fit to the noise on the data. To find the best balance between accuracy and complexity of the model, a search is necessary in the space of all possible models belonging to a fixed family. This search for the best model involves three main tasks: choosing the best structure, choosing the best set of parameters given the structure, and validating the resulting model. Actually, the generalization capability is heavily reliant on the model's structure, and hence structure identification is arguably the most important task in a modeling process. Instances of structure identification include the problem of choosing the degree of a polynomial model or the problem of determining the best number of hidden nodes in a neural network.

Finding the best structure requires a search over all possible structures. However, exhaustive search over the space of model structures is computationally infeasible and motivates the use of heuristic strategies that dramatically reduce the search complexity by employing directed search algorithms. Examples are pruning/growing algorithms that start with a large/small structure and then prune/grow it to obtain a smaller/larger one. The second modeling task, i.e. finding a good set of parameters, is typically accomplished by minimizing an objective function. Examples of parametric identification procedures are linear least-squares for linear models and gradient-descent techniques. After the apparently best model has been found, its quality must be evaluated through a model validation procedure which returns the estimate of the generalization error on the basis of the finite training set. Examples of validation techniques are resampling methods, such as the holdout, the cross-validation and the bootstrap. Alternatively, the ability to generalize can be measured through complexity-based criteria that penalize the accuracy of the model by its size, hence adhering to the principle of parsimony. Therefore, if the model assessed on the basis of the estimate produced by the validation step is found inadequate, then the selected structure should be revised and the modeling process is repeated until a valid model is found. Hence the model should also be interpretable, so that the user can gain insight and improved understanding about the process that produced the data. To this end, the modeling process should attempt to induce a parsimonious representation of the available input-output data. However, accurate (and hopefully interpretable) predictive models are not necessarily simple to identify. Model construction is

typically a non-trivial task especially for complex high-dimensional problems. Models of phenomena found in everyday life are usually derived from two fundamental sources: numerical data acquired from observation and a priori knowledge about the phenomenon. These two knowledge sources are invaluable in any modeling process, where all available a priori knowledge should be utilized, while inadequacies found in this knowledge can be compensated by the ability to learn from data. Depending on the extent to which these two kinds of knowledge are exploited, three basic levels of model synthesis can be defined (Ljung 1999):

- **White Box.** The model is completely constructed from a priori knowledge and physical insight. Here, empirical data are not used during model identification and are only used for validation. Complete a-priori knowledge of this kind is very rare, because usually some aspects of the distribution of the data are unknown.
- **Gray Box.** An incomplete model is constructed from a priori knowledge and physical insight, then available empirical data are used to adapt the model by finding several specific unknown parameters.
- **Black Box.** No a priori knowledge is used to construct the model. The model is chosen as a flexible parameterized function, which is used to fit the data.

The different modeling paradigms are summarized in Table 23.1 (Babuska 1998). In such a case, the most suitable approach is expected to be the gray-box one, even though none of the three modeling approaches can be easily applied, due to the lack of knowledge.

**Table 23.1** Different modeling paradigms (Babuska 1998).

| Modeling Approach | Source of Information | Method of Acquisition | Example | Deficiency |
|---|---|---|---|---|
| Mechanistic (white-box) | Formal knowledge and data | Mathematical | Differential equations | cannot use "soft" knowledge |
| Black-box | Data | Optimization (learning) | Regression, neural network | cannot at all use knowledge |
| Fuzzy (grey box) | Various knowledge and data | Knowledge-based + learning | Rule-based model | “curse” of dimensionality |

Actually, these three modeling paradigms are not as distinct as this classification suggests, and a general rule of thumb is to employ both qualitative a priori knowledge and empirical data to derive a model. Thus, the important requirement for any modeling technique is the ability to exploit available a priori knowledge. When such knowledge relies on some physical information describing some input-output behavior, an expert can often describe such behavior using natural language. A linguistic model is a knowledge-based representation of information; its rules and input-output variables are described in a linguistic form which can be easily understood and handled by humans. The fuzzy set theory formulated by Zadeh in 1965 provides an appropriate method for handling linguistic terms and human concepts (Zadeh 1965). Zadeh's proposal to build models based on such linguistic descriptions through fuzzy values (fuzzy sets) rather than crisp numbers led to fuzzy systems. In recent years, fuzzy logic based modeling, and more generally linguistic modeling of complex processes, as a complement to conventional modeling techniques, has become an active research topic and found successful applications in many areas (Harris 2006; Ross 2004; Terano et al. 1994). The main advantage of fuzzy systems is that they can provide simple intuitive for interpretation and prediction in the form of fuzzy rules. However, due to vagueness and subjectivity of natural language statements, fuzzy rules based on qualitative knowledge alone can adequately model only very simple processes. Fuzzy models consist of a series of linguistic rules, which can easily be understood and constructed by humans.

## 23.3 FUNDAMENTAL OF FUZZY CONTROL

The basis for proposing fuzzy logic was that humans often rely on imprecise expressions like big, expensive or far. But the "comprehension" of a computer is limited to black-white, everything-or-nothing, or true-false modes of thinking. In this context, Lofti Zadeh emphasises that humans easily let themselves be dragged along by a desire to attain the highest possible precision without paying attention to the imprecise character of reality (Zadeh 1973). The basic idea of fuzzy sets introduced by Lofti Zadeh in 1965 is quite easy to comprehend. In a classical set, this is a collection of distinct objects in which dichotomize the elements of the universe of discourse into two groups, then:

$\mu_A(x) = 1$, if $x$ is an element of the set A, and
$\mu_A(x) = 0$, if $x$ is not an element of the set A

On the other hand, fuzzy sets eliminate the sharp boundaries that divide members from nonmembers in a group. In this case, the transition between

full membership and nonmembership is gradual (a fuzzy membership function) and an object can belong to a set partially. The degree of membership is defined through a generalized characterized function called the membership function. The membership degree allows obtaining a desired level of smoothness about the threshold (set-points). Mathematically, a fuzzy set A is represented by a membership function defined on a domain X, called universe of discourse, given by:

$$\mu_A(x): X \rightarrow [0, 1]$$

Where A is the fuzzy label or linguistic (value) term describing the variable x. The values of the membership function are real numbers in the interval [0,1], where 0 means that the object is not a member of the set and 1 means that it belongs entirely to the set. Each value of the function is called a membership degree. Consider the fuzzy variable temperature, which can be described by many different adjectives each with its own fuzzy set. A typical partition of the universe of discourse, 0-40°C, is shown in Fig. 23.1, where the fuzzy sets cold, warm and hot are defined. In this example, the crisp temperature 20°C has a grade of membership of 0.5 for both the cold and the warm fuzzy sets i.e. $\mu_{cold}(20°C) = \mu_{warm}(20°C) = 0.5$. It is clear that the definition of fuzzy sets is non-unique for the nature of language, but it is very context-dependent and user specific (e.g. this definition may seem inappropriate to an Eskimo!). On specifying a membership function $\mu_A(x)$ in its present context the vague fuzzy label A is precisely defined.

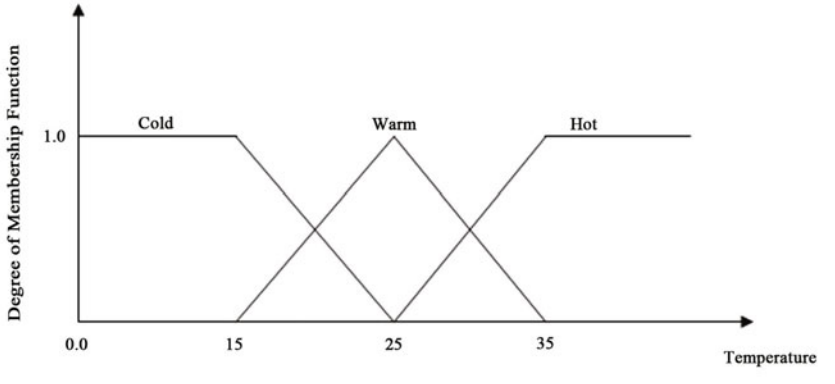


**Fig. 23.1** Typical fuzzy sets defined for a variable.

Hence fuzzy sets can be thought as measuring the inherent vagueness of language precisely. The properties of these fuzzy sets play an important role in the modeling capabilities of the fuzzy system, and for a model to be

truly transparent these sets should sensibly represent terms that describe the input and output variables. It is up to the system designer to determine the shape of the fuzzy sets. In most cases, however, the semantics captured by fuzzy sets is not too sensitive to variations in the shape; hence it is convenient to use simple membership functions. The membership function choice is the subjective aspect of fuzzy logic, it allows the desired values to be interpereted appropriatly. The most common membership functions are the triangular, the trapezoidal, and the Gaussian function. Fig. 23.2 shows some typical shapes of membership functions and described in detail in Appendix A. Fuzzy sets form a key methodology for representing and processing uncertainty.

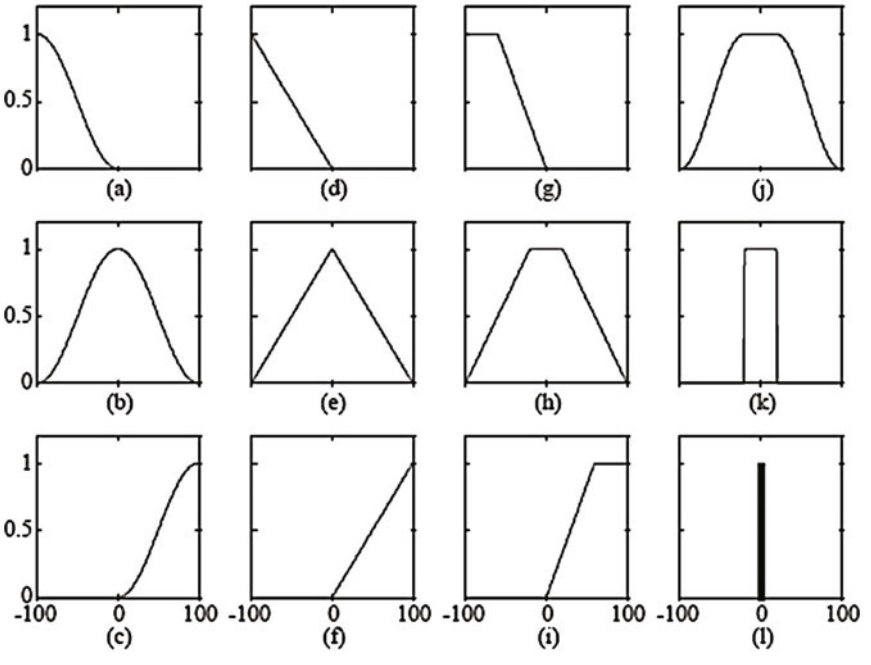


**Fig. 23.2** Examples of membership functions (Fuller 2000). Read from top to bottom, left to right: (a) S-function, (b) gaussian-function, (c) Z-function, (d-f) triangular versions, (g-i) trapezoidal versions, (j) gbell-function, (k) rectangle, (l) singleton.

As such, fuzzy sets constitute a powerful approach not only to deal with incomplete, noisy or imprecise data but also to develop models of the data that provide smarter and smoother performance than traditional modeling techniques. The popularity and practicality of fuzzy systems derives from

their ability to express complex relations in terms of linguistic rules. Thus, fuzzy systems have advantages of excellent capabilities to describe a given input-output mapping. The second important property to be considered concerns function approximation: fuzzy systems have been proved to be universal approximators (Kreinovich et al. 1998; Castro and Delgado 1996; Castro 1995), i.e. they are able to uniformly approximate continuous functions to any degree of accuracy on closed and bounded (compact) sets, a property they share with feed-forward neural networks. Moreover, in contrast with other universal approximators (e.g. neural networks) fuzzy systems are uniquely suited to incorporate linguistic information in a natural and systematic way. These two important properties qualify fuzzy systems as excellent candidates for predictive modeling tasks.

With these properties, the main disadvantage of fuzzy systems, however, is that they do not have much learning capability to tune their fuzzy rules and membership functions. Normally, fuzzy rules are decided by experts or operators according to their knowledge or experiences. However, when the fuzzy system model is designed, it is often too difficult (sometimes impossible) for human beings to define all the desired fuzzy rules or membership functions in an optimized way, due to the ambiguity, uncertainty or complexity of the identifying system. Also, fuzzy systems do not have any learning capability in which their fuzzy rules, along with their corresponding membership function, could be automatically tuned in order to reach the desired optimal fuzzy rules and membership functions.

### 23.3.1 Design of Fuzzy Logic Controller

Fuzzy Control System (FCS) is based on *heuristic* rules, acting on a set of input variables by means of *linguistic variables* to produce one or more control variables (as for Multiple Input – Multiple Output systems, MIMO for brevity). For this reason, it is not so easy to obtain some general rules for stability, overshoot, response time, etc., as for linear control systems. Some attempts were done in the past, and some results were obtained only for particular situation. Moreover, not only the fuzzy control is strongly not linear, but, it depends on many design choice, like the form of the fuzzy sets, which represent the linguistic variables, the choice of the aggregation operators for the rules, the number of the rules, and so on. Again, the mathematical analysis of a fuzzy control system is not easy in general, and in most cases it can be carried on with numerical simulations.

The basic structure of a fuzzy system, as described by Mamdani and Assillian (1975), is shown in Fig. 23.3 (Tanaka and Wang 2001). There are four main building blocks of the fuzzy logic system: the fuzzification

interface, fuzzy logic rule base, inference engine and the defuzzification interface. A fuzzy system processes crisp data at the input and produces crisp data at the output through inference from a fuzzy rule base. Therefore a fuzzifier is used at the front of the system to convert crisp data to fuzzy sets, and a defuzzifier is used at the output of the system to convert fuzzy sets into crisp values. A rule-base is a set of If-Then rules, which contains a fuzzy logic quantification of the expert's linguistic description of how to achieve good control. The fuzzy inference engine combines the rules in the rule base according to approximate reasoning theory to produce a mapping from fuzzy sets in the input space to fuzzy sets in the output space. Hence a fuzzy system provides a computational scheme describing how rules must be evaluated and combined to compute a crisp output value (vector) for any input crisp value. One can therefore think of a fuzzy system simply as a parameterized function that maps real vectors to real vectors.

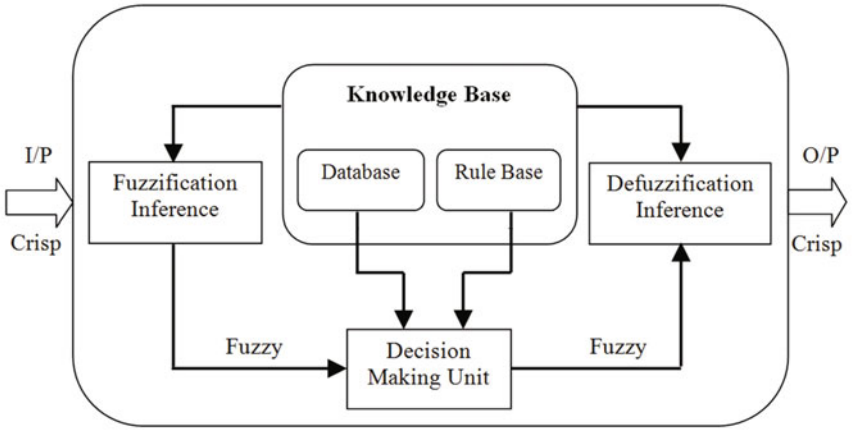


**Fig. 23.3** The basic structure of a fuzzy system.

Unlike conventional control which uses a model of the controlled process and applies specific techniques to satisfy as best as possible the desired closed-loop behavior, fuzzy control tries to replicate an expert strategy, as usually done by human operator. As a matter of fact, if the model is unavoidable, or too much expensive to be obtained, or if the model itself is strongly not nonlinear, a mathematical analysis can fail, and it is preferable to use expert knowledge. At the same time, a linear control, like a classical PID controller, is not appropriate for a non linear plant. Moreover, for MIMO control the aggregation of different types of information and sources can be easily performed by a human operator, but the same cannot easily be done using a mathematical tool. Thus the idea of

*fuzzy* control relies on this main reason: to capture in an efficient way the human expertise, from one or more process operators, and to use this knowledge to implement a performing control law. Technically, this task can be achieved by defining a set of rules over the logical combination of input variables, using some linguistic terms (*term-sets* like LOW, MEDIUM, HIGH, BAD, GOOD, etc.) in such a way that, for each combination of input variables, some rules fire with different degree. The firing degree will depend on the true degree of the antecedent, and on the logical combination of the linguistic degrees of true. Subsequently the outputs of each rule are combined, weighting more the ones for which the membership degree is higher, thus obtaining the values of the output variables. In this sense, we can speak of *rule-based fuzzy* control. Thus every FRCS (Fuzzy Rule Control System) is characterized by a suitable set of (fuzzy) *if-then* rules. For what above pointed out, the antecedent of each rule is formed by the logical disjunction of some elementary proposition, each of them referring to a single input variable. Such elementary propositions are in the following form: "$X_i$ is $A_{i,j}$", where $X_i$ is the numerical value of the i-th input variable, and $A_{i,j}$ is the term-set for the i-th variable in the j-th rule. Every term-set, which is linguistically expressed in the form of an attribute of the natural language, is represented by a suitable *fuzzy set* (Klir and Yuan 1995; Coletti and Scozzafava 2004) which defines its meaning. In the case of a control system, the input variables can be the error, its derivative or its integral. The same is done for the control variables. Each rule can be written as an inference condition, where in the antecedent part the logical conjunction of the input variables appears, while in the consequent part the control actions are described. For instance, a rule of a MIMO FCS with 3 input variables and 2 control variables can be written in the following way:

$$\text{IF } X_1 \text{ is } A_{1,j} \text{ AND } X_2 \text{ is } A_{2,j} \text{ AND } X_3 \text{ is } A_{3,j} \text{ THEN } C_1 \text{ is } B_{1,j} \text{ AND } C_2 \text{ is } B_{2,j}$$

where $X_i$, i=1,2,3 is the i-th input variables, $A_{i,j}$, i=1,2,3, is the linguistic term-set referring to the i-th input variable in the j-th rule, $C_i$ , i=1,2 is the i-th control variables, and $B_{i,j}$, i=1,2, is the linguistic term-set referring to the i-th output variable. The complete FCS can be represented by a set of such rules: the Rule Data Set (RDS for brevity in the sequel). More in general, a RDS can be formally represented as follows:

$$\left\{ \bigcap_{i=1,..,n} A_{i,j}(x_i) \rightarrow \bigcup_{k=1,..,m} B_{k,j}(y_k) \right\}, j = 1,..,NR$$

where NR is the number of inference rules. $A_{i,j}(x_i), B_{k,j}(y_k)$ are the values of true of the propositions $x_i$ is $A_{i,j}$, $y_k$ is $B_{k,j}$, and are computed by means of suitable pre-defined functions (*membership degree*) assigned by the user.

## 23.4 FUZZY LOGIC MODELS

Depending on the types of fuzzy reasoning and fuzzy if-then rules employed, most fuzzy inference systems can be classified into three types (Babuska 1998). From a technical point of view, the two most used FCS implementations are based on the *Mamdani* FCS, usually used as a *direct* closed-loop controller, and the *Takagi-Sugeno-Kang (TSK)* fuzzy controllers, more often used as a *supervisory* controller (Yager and Filev 1994)[1].

### 23.4.1 Mamdani Fuzzy Models

This method was introduced by Mamdani and Assilian in 1975 as an attempt to control a steam engine and boiler combination by synthesizing a set of linguistic control rules obtained from experienced human operators (Mamdani and Assillian 1975). This is first vision of fuzzy models, and by far the most innovating one, assumes to represent an input/output mapping by means of a collections of IF-THEN rules whose antecedents and consequences utilize fuzzy values, i.e.:

$$R_k : \text{IF (x is } A^k\text{) THEN } (y_1 \text{ is } B_1^k\text{) AND....AND } (y_m \text{ is } B_m^k)$$

The use of linguistic terms in consequent parts makes these models very intuitive and understandable. This class of fuzzy models uses fuzzy reasoning and forms the basis for qualitative modeling, which describes an input-output mapping by using a natural language. The Mamdani model form falls into this category. When adopting this perspective, which pursuits the ultimate goal of fuzzy logic, i.e. "computing with words", the emphasis is put essentially on the readability of the model, rather than on computational cost and accuracy of the model (i.e. fine quality of approximation, classification or control). The advantages of the Mamdani fuzzy inference system: it's intuitive, it has widespread acceptance and it's well suited to human cognition. However, fuzzy models of this class tend to become complex, requiring too many parameters, hence they can become heavy to

[1] Mamdani and TSK, are not only used for implementing a FCS, but more in general to represent a fuzzy-rules data base.

run, to maintain and to manually tune. This leads to the prepositions of other types of fuzzy inference systems. The fuzzy reasoning procedure for Mamdani model is shown in Fig. 23.4.

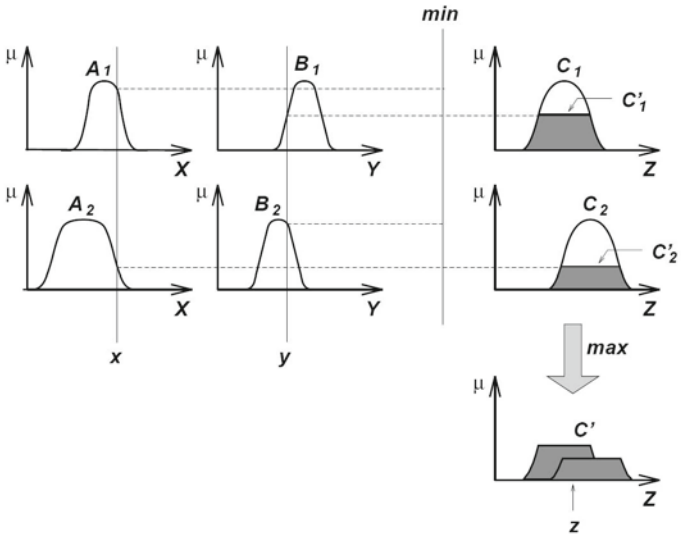


**Fig. 23.4** Mamdani fuzzy inference system using the min and max operators (Adapted from Jang JSR, Sun CT (1995) Neuro-Fuzzy Modeling and Control. Proceedings of IEEE; 83(3): 378-406, with permission from IEEE)

For a MIMO controller, the i-th rule of the rule data base appears as follows:

$$\text{IF } x_1 \text{is } A_{i,1} \text{AND } x_2 \text{is } A_{i,2} \ldots \text{ AND } x_n \text{is } A_{i,n} \text{THEN } y_1 \text{is } B_{i,1} \ldots \text{ AND } y_m \text{is } B_{i,m}$$

where $i = 1, 2, \ldots, R$ ; $A_{ij}$ is the term-set of the j-th input variable for the i-th rule; $B_{k,i}$ is the term-set of the k-th output variable and $R$ is number of inference rules.

Both $A_{ij}$ and $B_{k,i}$ are represented by suitable fuzzy numbers. To obtain the value of the crisp output $y_1 \ldots y_m$, the steps are the following:

1) Compute the *degree of truth* of the elementary propositions: $x_j$ is $A_{ij}$; if $\mu_{ij}(z)$ is the membership function concerning the linguistic term set $A_{ij}$, it is sufficient to compute $\mu_{ij}(x_j)$,

2) Compute $\tau_i$, the degree of truth of the compounded proposition $x_1$ is $A_{i1}$ ..... AND $x_n$ is $A_{in}$, that is the logical conjunction of n elementary propositions; this task is performed by a suitable aggregation operator $\otimes$ (see the comments below):

$$\tau_i = \mu_{i,1}(x_1) \otimes \mu_{i,2}(x_2) \otimes ... \otimes \mu_{i,n}(x_n),$$

3) Compute the fuzzy quantity $\eta_{k,i} = \tau_i \wedge B_{k,i}$, the minimum between the crisp number $\tau_i$ and the fuzzy number $B_{k,i}$,

4) For each k, compute the fuzzy quantity $\xi_k = \eta_{1,k} \oplus \eta_{2,k} \oplus ... \oplus \eta_{R,k}$, that is the logical disjunction, or other aggregation operator, as the generalized mean. This is the fuzzy output for the k-th output variable,

5) Finally, to obtain a crisp number for all the m output variables, the *defuzzification* task is activated, obtaining a crisp value (a real number) from the fuzzy output, which encompasses all the available information obtained by the data and by the inference mechanism. To this purpose, many methods were proposed in the literature, the most commonly used in the "center of gravity" approach (Yager and Filev 1994).

Some comments are in order:

a) The conjunction $\otimes$ is a logical operator which can be extended from the *boolean* case to the continuous one through the so called *triangular norm* operators, T-norm for brevity (Klement et al. 2000), a monotonic function defined in $[0,1]^n \rightarrow [0,1]$, which is also commutative and associative, with one as the neutral element. The upper bound of the class of all the T-norm is the minimum operator, but other choices are possible, like the product or the Łukasiewicz T-norm, see the above quoted reference;

b) Similarly, the logical disjunction $\oplus$ can be represented by a triangular co-norm (S-norm for brevity), with the same property as for the T-norm, except the last one, since the neutral element is zero. The lower bound of the class of all the T-conorm is the maximum operator, but other possibilities exist, like the probabilistic sum, or

the bounded sum[2]. Every S-norm is the dual operator of a T-norm, and namely the biunivocal relationship is:

$$S(x,y) = 1 - T(1-x, 1-y);$$

c) An important family of T-norm (S-norm) is formed by the *Hamacher* T-norm, which depends continuously on a tuning parameters which permit to obtain a wide range of T-norm (S-norm).

Note that for a Mamdani FCS, the following data need to be assigned:

i. Membership functions ,

ii. Rules (rule data base),

iii. T-norm and the S-norm used for the conjunction and disjunction respectively (sometimes other aggregation operators can be used).

Even if many, possibly, infinite, choices exist for the T-norm (S-norm) the most common are the min and the max operators respectively. The type of the inference rules, on the other side, is usually performed with an Expert (or more) of the application domain. Together with the memberships functions, the assignment of a T-norm (S-norm) and of the rule data base can be a long and stressing phase; sometimes a neuro-fuzzy algorithm could help if many input-output data are available, i.e. a collection of instances (we have in this case a non linear regression problem to be solved).

The Mamdani controller can be used to implement a fuzzy version of a classical PID controller, in this case, the input variables are the error, its derivative, and its integral.

### 23.4.2 Takagi-Sugeno-Kang (TSK) Fuzzy Models

The "Sugeno fuzzy model" (also known as the "TSK fuzzy model") was proposed by Takagi, Sugeno and Kang in an effort to develop a systematic approach to generate fuzzy rules from a given input-output data set (Takagi and Sugeno 1985). These models use fuzzy rules with fuzzy antecedents and functional consequent parts, thereby qualifying them as mixed fuzzy or non-fuzzy models. Such models can represent a general class of static or dynamic nonlinear mappings via a combination of several linear models. The whole input space is decomposed into several partial fuzzy spaces and

[2] The averaging operators, as the weighted mean, the generalized mean, the OWA operators, the Choquet integral with non additive measures are in between the min and the max operators; the family of the T-norm is a contiguous class of operators with furnishes lower values, while the family of the S-norm is a contiguous class of operators with furnishes higher values (w.r.t. an averaging operators).

each output space is represented with a linear equation. The resulting models are referred to as TSK models and are represented by a series of fuzzy rules of the form:

$$R_k : \text{IF } (x \text{ is } A^k) \text{ THEN } (y_1 = h_1^k(x)) \text{ AND....AND } (y_m = h_m^k(x))$$

Where $h_j^k(x)$; $j$ =1,…,m are polynomial functions of the inputs and represent local models used to approximate the response of the system in the region of the input space represented by the antecedent $\mathbf{A}^k$. When $h_j^k(x)$; is a first order polynomial, the resulting fuzzy inference system is called a "first order Sugeno fuzzy model". When *y* is constant, the resulting model is called "zero-order Sugeno fuzzy model", which can be viewed either as a special case of the Mamdani inference system, in which each rule's consequent is specified by a fuzzy singleton, or a special case of the Tsukamoto fuzzy model (to be introduced next) in which each rule's consequent is specified by a MF of a step function center at the constant. The Sugeno fuzzy type of knowledge representation does not allow the output variables to be described in linguistic terms, which is one of the drawbacks of this approach. Hence, this class of fuzzy models should be used when only performance is the ultimate goal of predictive modeling. Each of these fuzzy models has inherent drawbacks. For Mamdani fuzzy models the defuzzification process may be time-consuming, and systematic fine tuning of the parameters is not easy.

For TS fuzzy models it is hard to assign appropriate linguistic terms to the rule consequence part, which does not use fuzzy values. Readability and performance thus appear as antagonist objectives in fuzzy rule-based systems. Some form of compromise can be found by using simplified fuzzy rules of the form:

$$R_k : \text{IF } (x \text{ is } A^k) \text{ THEN } (y_1 \text{ is } b_1^k) \text{ AND....AND } (y_m \text{ is } b_m^k)$$

Where $b_j^k$ are fuzzy singletons (see def. A.6). Fuzzy models relying on such rules are referred to as singleton fuzzy models. This class of fuzzy models can employ all the other types of fuzzy reasoning mechanisms because they represent a special case of each of the above-described fuzzy models. More specifically, the consequent part of this simplified fuzzy rule can be seen either as a singleton fuzzy set in the Mamdani model or as a constant output function in TS models. Thus the two fuzzy models are unified under this simplified fuzzy model. Another interesting aspect of the simplified fuzzy model is its functional equivalence to the Radial Basis Function (RBF) network. This equivalence is established when Gaussian

membership functions are used to describe the antecedents of rules. Sugeno system is suited for modeling nonlinear systems by interpolating between multiple linear models. Because it is a more compact and computationally efficient representation than a Mamdani system, the Sugeno system lends itself to the use of adaptive techniques for constructing fuzzy models. These adaptive techniques can be used to customize the membership functions so that the fuzzy system best models the data. Figure 3.9 shows the fuzzy reasoning procedure for a first-order Sugeno model. Since each rule has a numeric output, the overall output is obtained via "weighted average", thus avoiding the time-consuming process of defuzzification required in a Mamdani model. In practice, the weighted average operator is sometimes replaced with the "weighted sum" operator (that is, $w_1z_1 + w_2z_2$ in Fig. 23.5) to reduce computation further specially, in the training of a fuzzy inference system (Castillo and Melin 2001). However, this simplification could lead to the loss of MF linguistic meaning unless the sum of firing strengths (that is, $\sum w_i$) is close to unity.

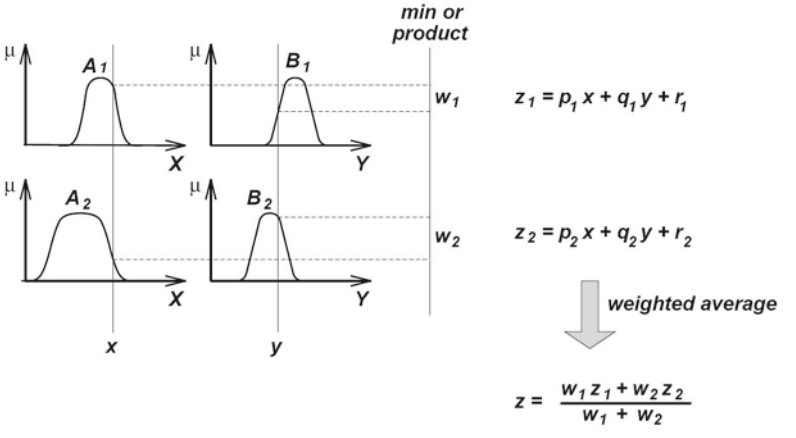


**Fig. 23.5** First-order Sugeno fuzzy model (Adapted from Jang JSR, Sun CT (1995) Neuro-Fuzzy Modeling and Control. Proceedings of IEEE; 83(3): 378-406, with permission from IEEE)

Thus, the main difference between Mamdani and Sugeno is that the Sugeno output membership functions are either linear or constant. Also the difference lies in the consequents of their fuzzy rules, and thus their aggregation and defuzzification procedures differ suitably. The number of the input fuzzy sets and fuzzy rules needed by the Sugeno fuzzy systems depend on the number and locations of the extrema of the function to be

approximated. In Sugeno method a large number of fuzzy rules must be employed to approximate periodic or highly oscillatory functions. The minimal configuration of the TS fuzzy systems can be reduced and becomes smaller than that of the Mamdani fuzzy systems if nontrapezoidal or nontriangular input fuzzy sets are used. Sugeno controllers usually have far more adjustable parameters in the rule consequent and the number of the parameters grows exponentially with the increase of the number of input variables. Far fewer mathematical results exist for TS fuzzy controllers than do for Mamdani fuzzy controllers, notably those on TS fuzzy control system stability.

### 23.4.3 Tsukamoto Fuzzy Models

In the "Tsukamoto fuzzy models", the consequent of each fuzzy if-then rule is represented by a fuzzy set with a monotonical MF, as shown in Fig. 23.6 (Tsukamoto 1979; Castillo and Melin 2001). As a result, the inferred output of each rule is defined as a numeric value induced by the rule firing strength. The overall output is taken as the weighted average of each rule's output. Figure 23.6 illustrates the reasoning procedure for a two-input two-rule system. Since each rule infers a numeric output, the Tsukamoto fuzzy model aggregates each rule's output by the method of weighted average and thus avoids the time-consuming process of defuzzification. However, the Tsukamoto fuzzy model is not used often since it is not as transparent as either the Mamdani or Sugeno fuzzy models (Castillo and Melin 2001).

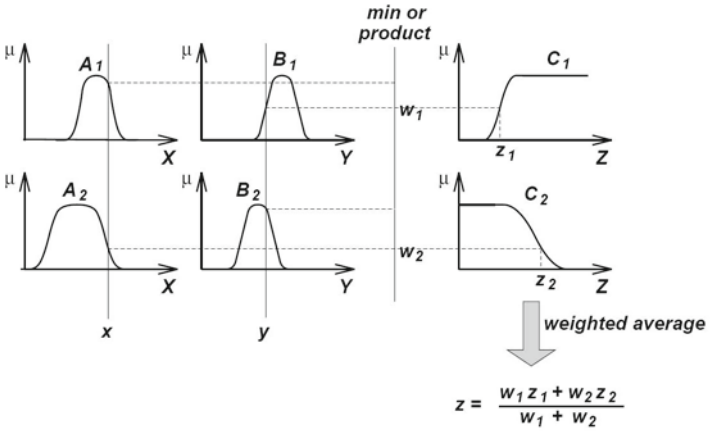


**Fig. 23.6** Tsukamoto fuzzy model (Adapted from Jang JSR, Sun CT (1995) Neuro-Fuzzy Modeling and Control. Proceedings of IEEE; 83(3): 378-406, with permission from IEEE)

## 23.5 FUZZY CONTROL OF DIALYSIS

### 23.5.1 Automatic Control of Dialysis Session

A dialysis session lasts more or less four hours, in this period the removal of toxic substances must be sufficient to obtain a grade of renal insufficiency compatible with life; hyperkaliemia, metabolic acidosis and water overload must be corrected. This means that in few hours urea concentration drops of about 65%, serum potassium halves, bicarbonate rises of about 25% and at least 2 or 3 liters of water are removed. The impact of these alterations on body physiology is not negligible; as a matter of fact a hemodynamic instability often occurs during the dialysis session.

Water is primarily removed from blood, determining a reduction in circulating blood volume. This process is counteracted by the refilling from interstitial fluid that transfers water from the extracellular compartment to the intravascular one, thus restoring blood volume. This flow is primary determined by the increased osmotic pressure due to hemoconcentration. A pivotal role is due to serum proteins and sodium concentration that are the two most important osmotic agents. The physiologic response to hypovolemia involves also an increase in heart rate and a constriction of the arterial bed that causes an increase in vascular resistance. When these mechanisms fail, hypotension occurs.

In general mean arterial pressure is determined by cardiac output and systemic vascular resistance according to the law:

$$\mathrm{MAP} = \mathrm{CO} \times \mathrm{SVR} \tag{23.1}$$

where MAP is mean arterial pressure, CO is cardiac output and SVR means systemic vascular resistance. Cardiac output reduction induced by hypovolemia may be corrected by fluid infusion or tempered by increasing Na concentration that enhances plasma refilling and/or slowdown of ultrafiltration rate. Systemic vascular resistance may be increased by the reduction of body temperature or by eliminating any vasodilators in the dialysis bath (acetate free dialysis bath) or by administering vasoconstrictor agents (rarely used).

Owing to the possibility of the described side effects, dialysis procedure usually requires a strict medical supervision, since it often produces severe undesired side effects. Hypotensive episodes are mainly caused by the unbalanced flow between ultrafiltration (UFR) and plasma refilling rate (PRR). An excessive sodium extraction or excessive UFR cannot be compensated by a proportional PRR, thus the blood volume (BV) is reduced, determining hypotension. Conversely, a too high sodium load or a too low UFR can

originate a fluid overload followed by heart failure. Hence, it is necessary to obtain the best compromise. Usually, a doctor adjusts the two control variables, UFR and the *sodium conductivity* (Na) in the dialysate, aiming to satisfy some therapy targets, the most important of which are:

- The decrease of body weight to a pre-defined value, i.e. the removal of a predetermined excess of water,
- The desired sodium balance during and at the end of the session
- To avoid at the same time severe hypotension episodes, cramps and other undesired effects, while guaranteeing the removal of some toxic substances.

To avoid the fluid unbalance, the doctor tries to achieve a sufficient PRR (Churchill 1996). In so doing, medical experience is quite important to obtain the fulfillment of the objectives, on the other side, the manual control is resource consuming, and subject to personal consideration brought to human errors, due for instance to inattention or tiredness. To this aim, some model-based tools were developed to control the process, but the results were not completely satisfactory, because the models cannot account for the physiological processes involved in hemodynamic stability not directly measurable (Daugirdas 1991). Conversely an approach based on a fuzzy rule based control system is different and more suitable for real clinical applications (Giove 1998; Giove et al. 1993; Nordio et al. 1995, 1999). The most important feature of this method is that even the trend can be taken into account, because a frequent sampling is possible, thus predictive action can be implemented to avoid sudden changes.

The advantages of a fuzzy based approach are the following:

- instead of using a model-based approach, this method captures, implements, and replays the medical experience,
- it is almost completely model free, because only a predetermined weight reduction and sodium removal are fixed,
- the clinical knowledge is implemented using a MIMO fuzzy rule data base,
- it is based on a *hierarchical* strategy, and on a *heuristic* knowledge.

The diagram of the fuzzy logic support system for the dialysis session is depicted in Fig. 23.7.

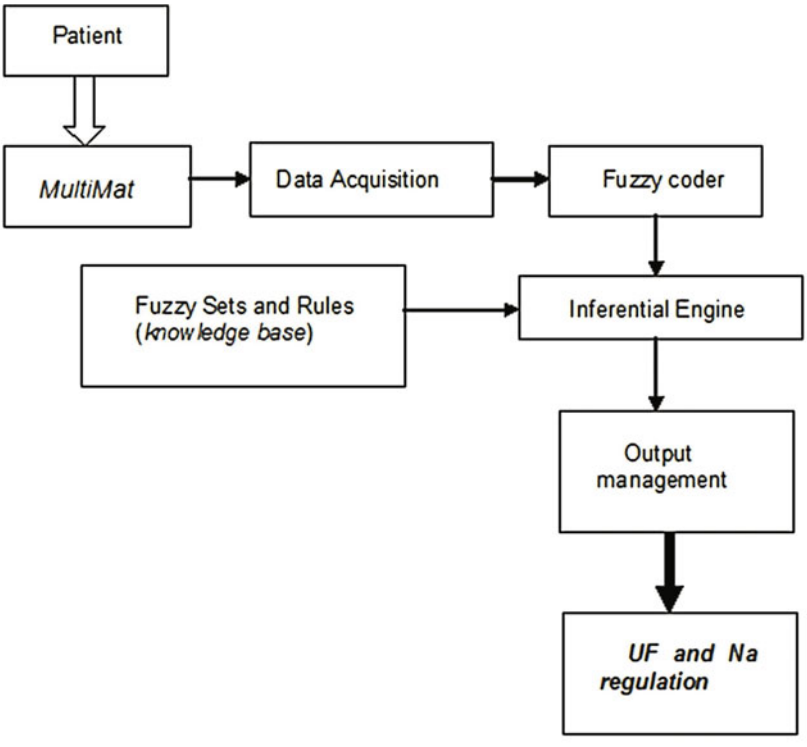


**Fig. 23.7** Diagram of the UF and Na fuzzy regulation. MultiMat is a dialysis machine by Bellco (Mirandola, Italy) used in the Nineties to perform paired filtration dialysis.

### 23.5.2 Data Acquisition

The fuzzy control described in this section was performed using a particular technique of hemodiafiltration named "paired filtration dialysis" (PFD) in which the convective component occurs in a little hemofilter separated from the dialysis filter. The plasmatic water collected during the convective process was used to measure continuously the conductivity (and hence plasma sodium concentration). In a classical hemodialysis procedure the measurement of plasmatic sodium conductivity may be substituted by ionic dialysance with little changes in the rules.

A dialysis PFD machine has been used to collect the sampled data, namely blood pressure, blood volume, sodium conductivity, body weight, recorded in a PC every minute (except for blood pressure, acquired every 10 minutes), and processed every 10 min. The on-line sodium balance is computed by the measurements of plasma conductivity and dialysate

conductivity, using a well-known mathematical model (Di Filippo et al 1996). A pre-elaboration procedure computes the trend using different methods (least squares, or the average on the last observed values, and other ones), and fuzzify the variables. The trend measures the tendency to increasing or decreasing. For instance, Fig. 23.8 reports the interpolating line of the sampled blood volume values; the trend is nothing else but the linear coefficient of the interpolating line.

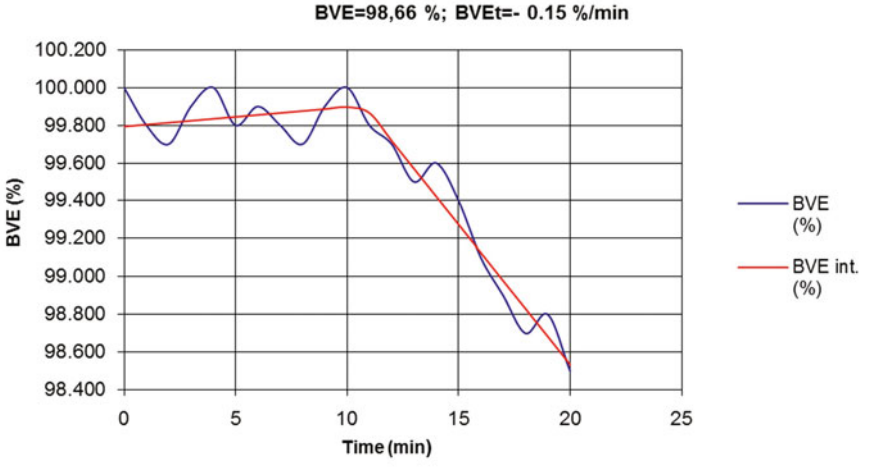


**Fig. 23.8** Blood Volume Trend (BVE = blood volume error).

The variables and the relative trends are fuzzyfied. To this purpose, *trapezoidal* fuzzy sets were used, since they are easy to be obtained by expert's judgments using only 4 points; in fact a trapezoidal fuzzy sets [a,b,c,d] splits the real line into subsets where the linguistic term is completely true, completely false or uncertain. In particular, in all the points below a, and in all the points above d, the membership is null (the linguistic term in false), in all the points in between b and c the linguistic term in completely true, while in the two intervals [a,b] and [c,d] there is uncertainty, that is, the considered value belongs to the fuzzy set with membership linearly increasing from a to b, and linearly decreasing from c to d[3].

[3] The trapezoidal fuzzy number are particular case of L-R type fuzzy numbers (Klement et al. 2000), that are characterized by an increasing behaviour, followed by a constant interval, the *core* (possibly degenerating into a single point) and finally by a decreasing part. Triangular fuzzy numbers are trapezoidal numbers whose core is formed by a single point. Many other L-R type fuzzy numbers exist in the literature, like the Gaussian type, etc. Anywise, from many simulations it can be verified that the performances of a FIS do not significantly change if Gaussian type are used instead that trapezoidal, mainly if many variables and rules are involved.

This formalism is easy to explain to the Clinician and he/she can fulfill a sheet where the four points representing all the fuzzy sets, i.e. for each linguistic terms, can be easily be inserted.

Moreover, in this heuristic approach, there is not the necessity to introduce a tuning strategy, as in neuro-fuzzy controller (even if it could be done of course), since the required knowledge is directly extracted from the Clinician's expertise, and tested by off-line simulations.

Fig. 23.9 reports the fuzzy sets for the variables SBP (systolic blood pressure) and SBPt, its trend; the labels "VL, L, G, H, VH", and "N, Z, P", stand for "Very Low", "Low", "Good", "High", Very High" and "Negative", "Zero", "Positive" respectively.

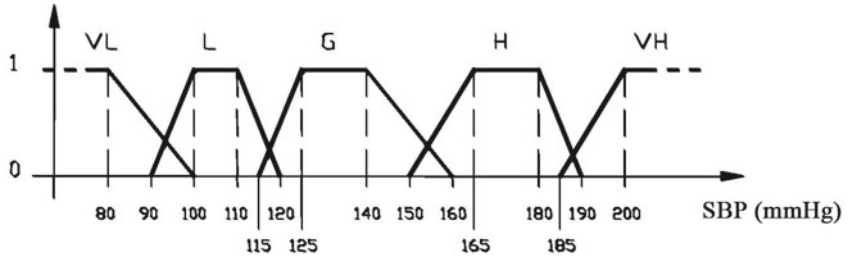


**Fig. 23.9** (a) Fuzzy sets for systolic blood pressure

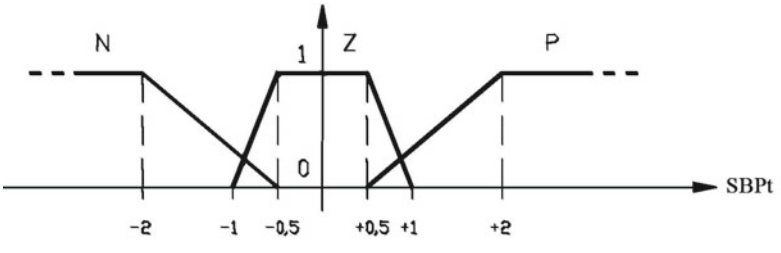


**Fig. 23.9** (b) Fuzzy sets for systolic blood pressure trend

The input variables are (with the number of corresponding fuzzy sets within parenthesis): systolic blood pressure SBP (5) and its trend SBPt (3), blood volume changes BVC (3) and its trend BVCt (3), sodium balance error NaEr (3) and body weight error BWEr (3)

The output variables are the change of UFR, ΔUFR, and the change of dialysate conductivity, ΔDC, computed by the fuzzy engine, in order to achieve the desired performances.

### 23.5.3 The Fuzzy Logic Controller

The fuzzy rule system is a TSK-type inference MIMO controller, because it acts on the error and the error trend of several state variables to determine the optimal strategy[4]. It uses a *hierarchical* approach, defined by a fuzzy *meta*-rule data base. To this purpose, 4 sub-systems are defined; one for each controlled variable, and then the supervisory control determines the optimal mix of each sub-module proposed control values, taking the most important control objective into account. The control action is applied every 10 min., when all the state variables are collected, and the control values remains constant within each sampling interval $[T_i, T_{i+1}]$. The outputs of each rule are crisp singletons, like the ones in Fig. 23.10 for the variable ΔUFR.

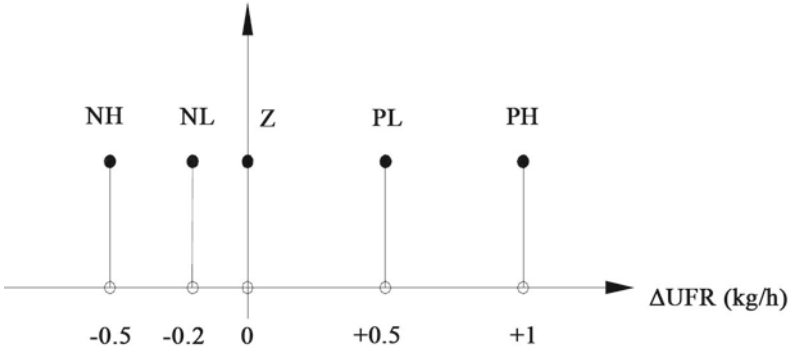


**Fig. 23.10** ΔUFR crisp consequents

All the rules, in the form of an inference "if.., then" rule are collected in a tabular form, and can be modified by the user (he can also select all other optional parameters and items, like the T-norm). Table 23.2 reports the rules for pressure control. For instance, the four column-third row rule means "IF SBP is High AND SBPt is Positive THEN ΔUFR is Positive Low AND ΔCD is Negative Low". The outputs of each subsystem are subsequently aggregated by a super-visor rule block, using a defined priority strategy.

[4] In this sense, it is not properly a PID controller, but it is very similar in the conceptual philosophy.

**Table 23.2** SBP and SBPt Rule Table

| SBP→<br>SBPt ↓ | Very Low | Low | Good | High | Very High |
|---|---|---|---|---|---|
| Negative | ΔUFR=NH<br>ΔCD=PH | ΔUFR=NH<br>ΔCD=PL | ΔUFR=NL<br>ΔCD=Z | ΔUFR=PL<br>ΔCD=Z | ΔUFR=PL<br>ΔCD=NL |
| Zero | ΔUFR=NH<br>ΔCD=PH | ΔUFR=NL<br>ΔCD=PL | ΔUFR=Z<br>ΔCD=Z | ΔUFR=PL<br>ΔCD=Z | ΔUFR=PH<br>ΔCD=NL |
| Positive | ΔUFR=NH<br>ΔCD=PL | ΔUFR=NL<br>ΔCD=Z | ΔUFR=PL<br>ΔCD=Z | ΔUFR=PL<br>ΔCD=NL | ΔUFR=PH<br>ΔCD=NH |

### 23.5.4 The Priorities and the Integrated System

The priority of the actions to be performed was given by a set of weights computed using, again, a decision table of fuzzy rules. When both SBP and BVE were satisfactory, the tables for NaEr and BWEr were used to gain the objectives of the correct Na balance (predetermined by the doctor) and the dry weight of the patient. If SBP or BVE were not good, their proper actions were preferred. Anywise SBP had the maximal priority, followed, in order, by BVE, NaEr, and BWEr. For instance, referring to BWEr (characterized by the lowest priority), its weight is negligible if at least one of the other variables (SBP, BVE, NaEr) has a high weight. The aggregation of the outputs was obtained using a weighted sum:

$$\Delta UFR = \sum_{i=1}^{4} w_i \Delta UFR(i), \qquad \Delta DC = \sum_{i=1}^{4} w_i \Delta CD(i) \tag{23.2}$$

where ΔUFR(i) and ΔCD(i) are the output of each rule table and $w_i$ are the weights calculated by the priority table (see Table 23.3). The values SBPB, SBPG, BVEB, BVEG (SBPB stand for "SBP is Bad", SBPG stands for "SBP is Good", and so on) are computed from the relative sub-module decision tables. For instance, the value SBPB is the maximum activation degree of the rules implemented in the Table 23.2, except the element in second row and third column (corresponding to "SBP is Good, SBPt is Zero"). The system was tested in 10 sessions, and all the patients gained the prescribed dry weight with a correct sodium balance. No hypotension episode was observed. In four cases the dry weight and a correct sodium balance were obtained reducing the dialysis time without significant changes in blood pressure.

**Table 23.3** Priority Management Table

| Pressure | Volemia | Output weighs | Output |
|---|---|---|---|
| SBPB | | $W_1$ = SBPB | TabP |
| SBPG | BVEB | $W_2$ = min{SBPG,VVEB} | TabV |
| SBPG | BVEG | $W_3$ = min{SBPG,VVEG} | TabNa |
| SBPG | BVEG | $W_4$ = min{SBPG,VVEG} | TabDBW |

TabP, TabV, TabNa and TabDBW are the outputs from the rule tables respectively of blood pressure, blood volume, conductivity and blood volume change.

### 23.5.5 Other Fuzzy Controllers

An alternative fuzzy controller was developed by Schmidt and others (Schmidt et al. 2001). In this case the input parameter is blood pressure, measured as relative difference of systolic pressure and pre-adjusted set point pressure, short term pressure trend (15 min) and long term pressure trend (25 min). The numeric values are fuzzified into linguistic variables described by trapezoidal or triangular fuzzy sets. Specific rules are used to obtained the corresponding fuzzy sets of UFR and the infusion rate of hypertonic saline (the output variables), finally converted into crisp outputs for adaptation of the variables to patient's actual blood pressure behavior. The control is provided by the transmission of these outputs both to the dialysis machine for UFR change and to a programmable infusion pump for hypertonic saline infusion. The underlying strategy is to establish a set point systolic blood pressure (90 – 100 mmHg) and a starting UFR (150% of the average UFR) in order to avoid excessive loss of water in the last part of the session. If the actual systolic blood pressure comes close to the set point, the system reacts first with injection of 20% saline, if blood pressure does not stabilize, then UFR is lowered. In the final phase the main reaction is to decrease UFR and sodium injection is avoided, to avoid a positive Na balance. This system was subsequently improved by substituting the hypertonic saline infusion pump with dialysate conductivity changes (Hickstein et al. 2009).

This system is conceptually simple: it looks for the signs of an incipient collapse and it reacts by increasing plasma refilling with an osmotic solution, if this maneuver fails, then UFR is considered excessive and consequently decreased. The system proposed by Nordio et al (1995) is more complex because both systolic blood pressure and blood volume changes are considered and weighted with rules that give the maximal priority to heavy blood pressure changes. The underlying strategy is to look for the best UFR

profile for each patient. As a matter of fact some hypotensive-prone patients show a drop in blood pressure at the beginning of the dialysis session, in this case the problem is given by a inappropriate sympathetic response to UFR that corresponds to inadequate vasoconstriction. In this situation sodium is given and UFR is reduced in the meanwhile hemodynamic stabilization is obtained, at this point, with a stable blood pressure (SBPt near zero), UFR restarts. If blood pressure holds in the first and medium parts of the dialysis session the two fuzzy control systems are equivalent.

## 23.6 COMPARISON WITH OTHER APPROACHES

In order to better understand the flexibility and the advantages of a fuzzy controller, a comparison with a classical adaptive controller is proposed.

The controller targets prescribed are total body weight loss, equivalent dialysate conductivity and relative BV change (Santoro et al. 1996). The input parameters for the controller are the monitored discrepancies between the instantaneous actual value and the instantaneous desired target for BV change, dialysate conductivity and weight loss. The control variables (output parameters) are the instantaneous dialysate conductivity and weight loss rate, which can vary from instant to instant to reach the desired targets. This system aims at driving the BV reduction curve over time along a pre-set trajectory balancing the classical goals of removal of sodium and water excess (total body weight and equivalent conductivity targets) with the new goal of (relative BV change target).

The core of this closed-loop bio-feedback software is an error-based mathematical model. The net result produced by this system is that the three target parameters (relating to water balance, sodium balance and desired BV reduction curve), decided by the operator at the beginning of the sessions, are smoothly driven, during the HD session, through a precise three-dimensional curve that represents the best compromise among the targets themselves. This operation is performed with a given range of tolerances for each parameter, decided by the operator as a safety feature.

The control system acts as a BV controller that continuously modifies the instantaneous UF rate and dialysate conductivity, while guaranteeing sodium and water balance. The rationale of this system is to smooth out the acute and sudden reductions in BV that can appear during HD sessions, consequent to a transient imbalance in the patient's vascular refilling capacity, in order to try to reduce the incidence of intra-HD hypotension episodes.

Both the fuzzy and the classical system just described are MIMO controller. The input variables of the fuzzy system are systolic blood pressure SBP and its trend, blood volume, blood volume changes, sodium balance error and weight error. The classical adaptive system input variables are the discrepancies between the instantaneous actual value and the instantaneous desired target for BV change, dialysate conductivity and weight loss. The true target of the adaptive control, that is blood pressure, cannot be treated, because BP is not easily modeled. Thus, only hypotensive episodes due to BV changes may be predicted and corrected, and nothing can be made for hypotension due to vasodilatation. The fuzzy controller works better with hypotension due to BV reduction, but it is able to account also for hypotensive episodes due to other causes, since SBP is an input variable.

## 23.7 CLINICAL RESULTS

In the clinical practice both systems works, allowing for a reduction in hypotensive episodes in a similar percentage (Santoro et al. 2002; Mancini et al. 2007; Hickstein et al. 2009). This means that the policy to control dialysis related hypotension by modulation of dialysate sodium conductivity and ultrafiltration rate is only partially effective. These results may be someway expected. In all the control systems described (and available), the response to blood pressure or blood volume reduction is given by sodium infusion (given directly or indirectly by an increase in sodium dialysate) or by UFR reduction. These responses are proper if the cause of the hemodynamic instability is only inadequate refilling, but when the problem is inadequate vascular reaction to blood volume reduction, no correct response is available. In this case a particular attention should be devoted to temperature control system (Schneditz et al. 2003) that aims to maintain blood pressure by minimizing vasodilatation due to thermal unbalance.

An integration of BV/ultrafiltration/conductivity and temperature control system should be desirable. This integration is problematic using model based controller, while may be feasible with a fuzzy logic controller since tables of rules may be easily performed.

## 23.8 DIFFUSION OF DIALYSIS CONTROL SYSTEMS

Three dialysis companies implemented in their dialysis machines the dialysis control systems. In particular, a company implemented thermal balance, another one the classical adaptive controller and the last one the fuzzy controller. This policy is due to two main reasons: first of all each

dialysis company promoted research, engineering and trade, thus linking a single system to a particular machine with the aim to increase the sale of the final product owing to the additional benefit implemented; second, since the control systems strictly interacts with the machine hardware (UFR and conductivity control), the software is integral part of the machine. The market of dialysis machines is only partially linked to innovative technologies, since it is governed in part by private companies that are often the same producers of the machines and thus they use their products and in part by public health systems that pay attention to a balance between costs and innovation.

By an epidemiologic point of view, symptomatic intradialytic hypotension is an important but not overwhelming problem, as a matter of fact it occurs in about 20% of diabetic patients and 15% of non-diabetic patients (Davenport et al. 2008). Other researches suggest that a correct definition of the dry body weight (Agarwal et al. 2010), and sodium and/or ultrafiltration profiling are able to avoid a large part of hypotensive episodes without having recourse to sophisticated tools.

These considerations explain why these systems are not so widespread in clinical practice.

## 23.9 FUTURE DIRECTIONS

All available control systems are probably not effective in optimizing sodium removal, especially in patients highly hypotension prone. No study gives evidence that biofeedback works better than conductivity and UFR profiling and randomized studies are lacking. Biofeedback systems are tightly linked to machines, profiling is independent on machines. An interesting alternative should be offline profiling optimization. This objective requires various steps: pattern recognition of blood pressure and/or blood volume during the dialysis session, adjustment of conductivity an UFR profiling according to specific patterns, implementation of an expert system able to perform this task.

Expert driven fuzzy systems or, better, neuro-fuzzy system should be suitable methods to give the better conductivity and UFR profile for each patient's blood pressure pattern. Both patterns and profiles could be stored in servers linked to the machine, now widespread in many dialysis facilities, thus this decision support system should be independent on machines.

## 23.10 CONCLUSION

Hemodialysis is often complicated by hypotensive episodes that lead to chronic hyperhydration and determine suffering for the patients. Excessive decrease of blood volume is probably the most important cause of dialysis induced hypotension. It is due to the unbalance between water removal and plasma refilling. Mathematical models that links blood volume changes to ultrafiltration rate and plasma conductivity are available; as a consequence control systems that adapt these variables to obtain a desired slope of blood volume decrease may be performed. Unfortunately, the physiology of blood pressure is much more complex, since it includes not only factors related to blood volume, but also to cardiac performance and to vascular reactivity. A quantitative model that links all these variables is not available owing to the rough knowledge of the whole systems, but a qualitative knowledge, expressed in linguistic terms, is possible. Fuzzy logic is suitable to solve this kind of problems.

The two fuzzy control systems use directly blood pressure and its trend as input variable, this is not possible with a classical PID controller since the quantitative relationships between blood pressure and the control variables are not known. In the fuzzy control system the relationships are described in tables that link the linguistic description of the input variables with the appropriate adaptive response. One may expects that fuzzy controllers work better than classical PID controllers, but this has not been demonstrated, also if a direct comparison between the two methods has not been performed. This result is probably explained by the fact that the adaptive control is assigned to the same variables: changes in ultrafiltration rate and in dialysate conductivity. These variables can only act on plasma refilling.

Fuzzy controllers allows future improvements because they allow to implement other control variables such as temperature, infusion of drugs that acts on heart performance or vascular reactivity, concentration of K or Ca in the dialysate and so on. It is sufficient to create tables with the corresponding rules and the hierarchy of intervention.

## APPENDIX A: FUZZY SETS

### A.1 MEMBERSHIP FUNCTIONS

Although the underlying purpose of the membership functions is to represent vague linguistic terms, they should also possess other important properties making the fuzzy system more suitable for predictive modeling. For example, the output of membership functions should be computationally cheap to be evaluated as this is one of the most frequently performed operations in fuzzy systems. Common choices fall into the following families of parameterized functions (Pedrycz and Gomide 1999):

- Triangular function:

$$\mu_A(x) = \begin{cases} 0 & \text{if } x \le a \\ \dfrac{x-a}{c-a} & \text{if } x \in [a,c] \\ \dfrac{b-x}{b-c} & \text{if } x \in [c,b] \\ 0 & \text{if } x \ge b \end{cases}$$

Where c is a modal value, and a and b denote the lower and upper bounds, respectively, for nonzero values of $\mu_A(x)$. Sometimes it is more convenient to use the notation explicitly highlighting the function's parameters:

$$\mu_A(x;a,b,c) = \max\left\{0, \min\left[\frac{(x-a)}{(c-a)}, \frac{(b-x)}{(b-c)}\right]\right\}$$

- Trapezoidal function:

$$\mu_A(x) = \begin{cases} 0 & \text{if } x < a \\ \dfrac{x-a}{c-a} & \text{if } x \in [a,c] \\ 1 & \text{if } x \in [c,d] \\ \dfrac{b-x}{b-c} & \text{if } x \in [d,b] \\ 0 & \text{if } x > b \end{cases}$$

$$\mu_A(x;a,b,c,d) = \max\left\{0, \min\left[\frac{(x-a)}{(c-a)}, \frac{(b-x)}{(b-d)}\right]\right\}$$

- Gaussian function:

$$\mu_A(x) = e^{-k(x-c)^2}$$

where k > 0. Typically k = $1/a^2$ where $a^2$ reflects the width (spread) of $\mu_A(x)$.

- Bell-shaped function:

$$\mu_A(x) = \frac{1}{1 + k(x-c)^2} \quad \text{with } k > 1$$

## A.2 CHARACTERISTICS OF FUZZY SETS

Fuzzy sets are characterized in more detail by referring to the concepts of support, core, normality, convexity, etc. Let $F(X)$ denote the set of all possible fuzzy sets defined on the universe of discourse $X$. For a fuzzy set $A \in F(X)$ we can give the following definition (Pedrycz and Gomide 1999).

**Definition A.1** (*support*) *The support of A, denoted by supp(A), is a fuzzy set of X whose elements all belong to A with nonzero degree:*

$$\text{supp}(A) = \{x \in X | \mu_A(x) > 0\}$$

**Definition A.2** *(core) The core of A, denoted by core(A), is a fuzzy set of X whose elements exhibit a full membership degree in A:*

$$\text{core}(A) = \{x \in X | \mu_A(x) = 1.0\}$$

**Definition A.3** *(α-cut) The α-cut of A, denoted by* $[A]^\alpha$ *with α > 0:0, is a non-fuzzy set of X consisting of those elements whose membership values exceed the threshold level α:*

$$[A]^\alpha = \{x \in X | \mu_A(x) \geq \alpha\}$$

**Definition A.4** *(empty fuzzy set) A is an empty fuzzy set if* $\mu_A(x) = 0.0$, $\forall x \in X$ *that is if Supp(A) = Φ.*

**Definition A.5** *(universal fuzzy set) A is a universal fuzzy set if* $\mu_A(x) = 1.0$, $\forall x \in X$ *, that is if Core(A) = X.*

**Definition A.6** *(fuzzy singleton) A is a fuzzy singleton if supp(A) = {$x_0$} and we use the notation A =* $\overline{x}_0$.

**Definition A.7** *(normal fuzzy set) A is said normal if its membership function attains 1, that is* $\sup_x \mu_A(x) = 1.0$. *The supremum is the height of A. Hence A is normal if its height is equal to 1. If the height is less than 1, then A is called subnormal.*

**Definition A.8** *(convex fuzzy set) A is said convex if its membership functions is such that:*

$$\mu_A(\lambda x_1 + (1-\lambda)\, x_2 \geq \min\left[\mu_A(x_1), \mu_A(x_2)\right]$$

*For any* $x_1$, $x_2 \in X$, *and* $\lambda \in [0,1]$. *Equivalently, it can be said that A is normal if* $[A]^{\alpha}$ *is a convex subset of* $X \forall \alpha \in [0,1]$.

**Definition A.9** *(Compact fuzzy set) A is said compact if supp(A)* $\subset X$.

### A.2.1 Basic Relationships between Fuzzy Sets

As in set theory, we can define generic relations between two fuzzy sets, such as inclusion and equality. Let $A \in F(X)$ and $B \in F(X)$ be fuzzy sets (Pedrycz and Gomide 1999).

**Definition A.10** *(inclusion) We say that A is included in B, denoted by A* $\subseteq$ *B ,iff*

$$\mu_A(x) \leq \mu_B(x), \ \forall x \in X .$$

**Definition A.11** *(equality) A and B are said to be equal, denoted by A = B, iff*

$A \subset B$ *and* $B \subset A$. *Of course A = B iff* $\mu_A(x) = \mu_B(x), \ \forall x \in X$ .

Another relationships between two fuzzy sets is similarity expressed in terms of a distance function between their membership functions which is treated as an indicator of their closeness. The more similar the two fuzzy sets, the lower distance between them. For this reason, it can be convenient to normalize the distance function so as to obtain a similarity measure by straight complementation of the normalized distance. In general, the distance between A and B can be defined as:

$$d(A,B) = \left[ \int_x \left| \mu_A(x) - \mu_B(x) \right|^p dx \right]^{1/P}$$

Where $P \geq 1$. Specific cases typically encountered in applications are:

$$\text{Hamming distance } (p = 1): d(A,B) = \left[ \int_x \left| \mu_A(x) - \mu_B(x) \right| dx \right]$$

$$\text{Euclidean distance } (p = 2): d(A,B) = \left[ \int_x \left| \mu_A(x) - \mu_B(x) \right|^2 dx \right]^{1/2}$$

### A.2.2 Operations on Fuzzy Sets

In this section the operations on fuzzy sets are defined, which come from an extension of the classical set theoretic operations from ordinary sets. Logical fuzzy operations are defined through triangular norms and triangular conorms, referred to as the T-norm and T-conorm (or S-norm) in the literature and here denoted by $\top(\cdot)$ and $\sigma(\cdot)$, respectively.

**Table A.1** The most popular choices for the T-norm and T-conorm (Pedrycz and Gomide 1999).

| norm | T-norm | T-conorm |
|---|---|---|
| truncation | $T(a,b) = \min\{a, b\}$ | $\sigma(a,b) = \max\{a, b\}$ |
| algebraic | $T(a,b) = ab$ | $\sigma(a,b) = a + b - ab$ |
| bounded | $T(a,b) = \max\{a + b - 1, 0\}$ | $\sigma(a,b) = \min\{a + b, 1\}$ |

**Definition A.12** *(Triangular norm) A t-norm is a binary mapping*

$$\top : [0,1] \times [0,1] \rightarrow [0,1]$$

*Satisfying the following properties: commutativity, associativity, monotonicity and one*-identity (i.e. $\top(x,1)=x, \forall x \in [0,1]$)

**Definition A.13** *(Triangular conorm) A s-norm is a binary mapping*

$$\sigma : [0,1] \times [0,1] \rightarrow [0,1]$$

*satisfying the following properties: commutativity, associativity, monotonicity and zero-identity (i.e.* $\sigma(x,0)=x, \ \forall x \in [0,1]$ *)*

These norms provide a wide range of suitable operators but the most popular are the algebraic and truncation operators as summarized in table (A.1). that the truncation operators may produce model outputs with discontinuous derivatives, while the algebraic operators produce smooth outputs ideal for modeling and control. For this reason algebraic operators are preferred.

Let $A \in F(X)$ and $B \in FX)$ be fuzzy sets.

**Definition A.14** *(Complement) The complement of A, denoted by* $\neg A$*, is a fuzzy set of X with membership function:*

$$\mu_{\neg A}(x) = 1 - \mu_A(x), \forall x \in X$$

**Definition A.15** *(Intersection) The intersection of A and B is a fuzzy set of X with membership function:*

$$\mu_{A \bullet B}(x) = \top(\mu_A(x), \mu_B(x)), \ \forall x \in X$$

**Definition A.16** *(Union) The union of A and B is a fuzzy set of X with membership function:*

$$\mu_{A \cup B}(x) = \sigma(\mu_A(x), \mu_B(x)), \ \forall x \in X$$

**Definition A.17** *(Possibility measure) The possibility measure of A with respect to B, denoted by Poss (A,B) is defined as*

$$Poss(A,B) = \sup_{x \in X} [\top(\mu_A(x), \mu_B(x))]$$

*It quantifies the extent to which A and B overlap*

**Definition A.18** *(Necessity measure) The necessity measure of A with respect to B, denoted by Nec(A,B) is defined as*

$$Nec(A,B) = \inf_{x \in X} [\sigma(\mu_A(x), 1-\mu_B(x))]$$

*It quantifies the degree to which B is included in A*

**Definition A.19** (*Fuzzy Relation) Let X and Y be nonempty sets. A fuzzy relation is a fuzzy subset of* $X \times Y$ *i.e.* $R \in F(X \times Y)$

**Definition A.20** *(Composition of Fuzzy Relations) If* $R \in \mathcal{F}(X \times Y)$ and $S \in \mathcal{F}(Y \times Z)$ *are fuzzy relations, the composition of R and S is a fuzzy relation in* $X \times Z$ *denoted by* $R \circ S$ *and is defined by:*

$$\mu_{R \circ S}(x,z) = \sup_{y \in Y} [\top (\mu_R(x,y), \mu_S(y,z))]$$

**Definition A.21** (Cartesian Product) If A and B are fuzzy sets defined on X and Y, respectively, the Cartesian product $A \times B$ is a fuzzy relation in the product space $X \times Y$ with membership function

$$\mu_{A \times B}(x,y) = \top (\mu_A(x), \mu_B(y))$$

**Definition A.22** *(Fuzzy Implication) Let* $A \in \mathcal{F}(X)$ *and* $B \in \mathcal{F}(Y))$ *be fuzzy sets. The fuzzy implication* $A \rightarrow B$ *is a fuzzy relation* $A \times B$.

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## ESSAY QUESTIONS

1. Compare between the basic levels of model synthesis.
2. What is fuzzy logic?
3. What does fuzzy set mean?
4. List some applications of fuzzy logic systems
5. List the main building blocks of the fuzzy logic system
6. What is a fuzzy inference rule?
7. Define the defuzzification process

8. Is FCS a linear controller?
9. Describe the main differences between Mamdani and Sugeno fuzzy models
10. What is Fuzzy Control System (FCS)?
11. What is the difference between fuzzy logic and probabilities?
12. Can we affirm that the proposed approach for the fuzzy logic controller is a Decision Support System, rather than a fuzzy control system for a dynamic system?
13. Describe the mechanisms involved in maintaining hemodynamic stability during hemodialysis.
14. Describe the main differences between a fuzzy blood pressure controller and a classical blood volume adaptive controller in dialysis.

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. Who is the founder of fuzzy logic?
   A. Mamdani
   B. Sugeno
   C. Lotfi Zadeh
   D. Tsukamoto

2. What are the following sequence of steps taken in designing a fuzzy logic machine?
   A. Fuzzification→Rule evaluation→Defuzzification
   B. Rule evaluation→Fuzzification→Defuzzification
   C. Fuzzy Sets→Defuzzification→Rule evaluation
   D. Defuzzification→Rule evaluation→Fuzzification

3. Fuzzy logic has rapidly become one of the most successful of today's technologies for developing sophisticated control systems. The reason for this is…
   i. Fuzzy logic resembles the human way of thinking.
   ii. Fuzzy logic enables the ability to generate precise solutions from certain or approximate information.
   iii. Fuzzy logic is easy to implement.

A. i & ii & iii
B. i & ii
C. ii & iii only
D. none of the above

4. “Fuzzy logic” is…
A. A “new type” of logic
B. A different name of probability calculus
C. A logic with incomplete information
D. A way to reason with non-probabilistic uncertainty

5. A fuzzy control system is…
A. A linear control law
B. A control law which uses empirical knowledge
C. An optimal control law
D. A control law based on zero-pole allocation

6. A FIS is useful…
A. To implement expert knowledge for many application fields
B. To solve nonlinear differential equations
C. To build a neural net
D. To solve logistic problems

7. Defuzzification consists of…
A. Process reasoning to infer a conclusion from a rule data set
B. Computing the membership degree of the antecedent part in a FIS
C. Obtain a crisp number from a fuzzy number
D. Computing a T-norm between two membership degree

8. The proposed FCS for dialysis control…
A. if formed by a Mamdani control
B. it is an adaptive PID controller
C. it is a DSS for determining the optimal values of UFR and Na
D. it is a SISO control (Single Input-Single Output)

9. Trapezoidal fuzzy numers are…
   A. A different representation of complex numbers
   B. Particular probability distributions
   C. Linearly increasing and decreasing fuzzy numbers (with possibly a constant part)
   D. A way to represent S-norms

10. The priorities in the integrated FCS systems serve to…
   A. Introduce a feedback action
   B. Analyse the stability
   C. Select the "best" rules to be applied
   D. Modify the Sodium Balance

11. A T-norm is…
   A. A particular type of membership function
   B. A conjunction logical operator
   C. A disjunction logical operator
   D. A method to defuzzify a fuzzy number

12. In the fuzzy controller described in the chapter, the input variable with the higher priority was…
   A. Blood pressure
   B. Blood volume changes
   C. Blood pressure trend
   D. Blood volume trend

13. The fuzzy controller and the classical adaptive controller share as input variables…
   A. Blood pressure
   B. Blood volume changes
   C. A and B
   D. other

14. Fuzzy rules are…
   A. rules for synapsis computation in neural nets
   B. an algorithm to optimize an adaptive control
   C. a way to represent not probabilistic uncertain inference
   D. other

15. The proposed fuzzy support system for dialysis regulation is…
    A. a PID controller
    B. a dynamic adaptive control
    C. an optimal control system
    D. an inference rule based system

16. Triangular fuzzy numbers are…
    A. Probability density
    B. Fuzzy numbers with infinite support
    C. Gaussian type fuzzy numbers
    D. L-R type fuzzy numbers

17. A TSK controller is…
    A. a non linear controller
    B. a discrete time stable controller
    C. a predictive controller
    D. a Mamdani type controller

18. A FCS for the dialysis session…
    A. Is based on the medical experience
    B. uses a model-based approach
    C. is necessarily stable
    D. can be applied only for SISO systems

19. A FIS is…
    A. A dynamic system identifier
    B. An inference system based on fuzzy rules
    C. A way to check if a dynamic system is stable
    D. A stable control rule

20. Fuzzy identification from a…modeling point of view
    A. White-box
    B. Grey-Box
    C. Black Box

Chapter (24)

# Neuro-Fuzzy Applications in Dialysis Systems

Ahmad Taher Azar

**CHAPTER OUTLINES**

- Introduction
- Classification of Neuro-Fuzzy Systems
- Adaptive Neuro-Fuzzy Inference System (ANFIS)
- Modeling with neuro-fuzzy systems
- Interpretability Versus Accuracy Of Neuro-Fuzzy Models
- Adaptive-Neuro-Fuzzy Inference System as a novel approach for post-dialysis urea rebound prediction
- Other Neuro-Fuzzy Models for Dialysis Patients
- Conclusion

**CHAPTER OBJECTIVES**

- Understand the concept of Neuro-fuzzy systems
- Describe the Neuro-Fuzzy system Architectures
- Discuss the modeling methodology of neuro-fuzzy systems.
- Discuss the applications of Neuro-fuzzy systems in dialysis

**KEY TERMS**

- Fuzzy logic
- Artificial Neural Network
- Neuro-fuzzy system
- Adaptive Neuro-Fuzzy Inference System (ANFIS)
- Hemodialysis
- Hemodialysis adequacy
- Equilibrated Kt/V
- Equilibrated urea concentration
- Post-dialysis Urea rebound (PDUR)
- Transductive reasoning systems
- Coactive Neuro-Fuzzy Inference System
- Parathyroid hormone

## ABSTRACT

Soft computing techniques are known for their efficiency in dealing with complicated problems when conventional analytical methods are infeasible or too expensive, with only sets of operational data available. Its principal constituents are fuzzy logic, Artificial Neural Network (ANN)

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and evolutional computing, such as genetic algorithm. Neuro-fuzzy controllers constitute a class of hybrid soft computing techniques that use fuzzy logic and artificial neural networks. The advantages of a combination of ANN and Fuzzy Inference system (FIS) are obvious. There are several approaches to integrate ANN and FIS and very often it depends on the application. This chapter gives an overview of a neuro-fuzzy system design with novel applications in dialysis using an adaptive-network-based fuzzy inference system (ANFIS) for the modeling and predicting important variables in hemodialysis process.

## 24.1 INTRODUCTION

One benefit of fuzzy systems (Zadeh 1965; Ruspini et al. 1998; Cox 1994) is that the rule base can be created from expert knowledge, used to specify fuzzy sets to partition all variables and a sufficient number of fuzzy rules to describe the input/output relation of the problem at hand. However, a fuzzy system that is constructed by expert knowledge alone will usually not perform as required when it is applied because the expert can be wrong about the location of the fuzzy sets and the number of rules. A manual tuning process must usually be appended to the design stage which results in modifying the membership functions and/or the rule base of the fuzzy system. This tuning process can be very time-consuming and error-prone. Also, in many applications expert knowledge is only partially available or not at all. It is therefore useful to support the definition of the fuzzy rule base by automatic learning approaches that make use of available data samples. This is possible since, once the components of the fuzzy system is put in a parametric form, the fuzzy inference system becomes a parametric model which can be tuned by a learning procedure. Fuzzy logic and artificial neural networks (Haykin 1998; Mehrotra et al. 1997) are complementary technologies in the design of intelligent systems. The combination of these two technologies into an integrated system appears to be a promising path toward the development of Intelligent Systems capable of capturing qualities characterizing the human brain. Both neural networks and fuzzy logic are powerful design techniques that have their strengths and weaknesses.

Table 24.1 shows a comparison of the properties of these two technologies (Fuller 2000). The integrated system will have the advantages of both neural networks (e.g. learning abilities, optimization abilities and connectionist structures) and fuzzy systems (humanlike IF-THEN rules

thinking and ease of incorporating expert knowledge) (Brown and Harris 1995). In this way, it is possible to bring the low-level learning and computational power of neural networks into fuzzy systems and also high-level humanlike IF-THEN thinking and reasoning of fuzzy systems into neural networks. Thus, on the neural side, more and more transparency is pursued and obtained either by pre-structuring a neural network to improve its performance or by possible interpretation of the weight matrix following the learning stage. On the fuzzy side, the development of methods allowing automatic tuning of the parameters that characterize the fuzzy system can largely draw inspiration from similar methods used in the connectionist community. This combination does not usually mean that a neural network and a fuzzy system are used together in some way.

The neuro-fuzzy method is rather a way to create a fuzzy model from data by some kind of learning method that is motivated by learning procedures used in neural networks. This substantially reduces development time and cost while improving the accuracy of the resulting fuzzy model. Being able to utilize a neural learning algorithm implies that a fuzzy system with linguistic information in its rule base can be updated or adapted using numerical information to gain an even greater advantage over a neural network that cannot make use of linguistic information and behaves as a black-box. Equivalent terms for neuro-fuzzy systems that can be found in the literature are neural fuzzy or sometimes neuro-fuzzy networks (Buckley and Eslami 1996). Neuro-fuzzy systems are basically adaptive fuzzy systems developed by exploiting the similarities between fuzzy systems and certain forms of neural networks, which fall in the class of generalized local methods. Hence, the behavior of a neuro-fuzzy system can either be represented by a set of humanly understandable rules or by a combination of localized basis functions associated with local models (i.e. a generalized local method), making them an ideal framework to perform nonlinear predictive modeling. Nevertheless, one important consequence of this hybridization between the representational aspect of fuzzy models and the learning mechanism of neural networks is the contrast between readability and performance of the resulting model.

**Table 24.1** Properties of neural networks and fuzzy Systems [Adapted from Fuller R (2000) Introduction to Neuro-Fuzzy Systems. Advances in Soft Computing Series, Springer-Verlag, Berlin/Heildelberg, with permission]

| Skills | Type | Fuzzy Systems | Neural Nets |
|---|---|---|---|
| Knowledge acquisition | Inputs | Human experts | Sample sets |
| | Tools | Interaction | Algorithms |
| Unceratinity | Information | Quantitative and Qualitative | Quantitative |
| Reasoning | Cognition | Heuristic approach | Perception |
| | Mechanism | Low | Parallel Computation |
| | Speed | low | High |
| Adaption | Fault-tolerance | Low | Very high |
| | Learning | Induction | Adjusting weights |
| Natural language | Implementation | Explicit | Implicit |
| | Flexibility | High | Low |

Summarizing, neural networks can improve their transparency, making them closer to fuzzy systems, while fuzzy systems can self-adapt, making them closer to neural networks (Lin and Lee 1996). Fuzzy systems can be seen as a special case of local modeling methods, where the input space is partitioned into a number of fuzzy regions represented by multivariate membership functions. For each region, a rule is defined that specifies the output of the system in that region. The class of functions that can be accurately reproduced by the resulting model is determined by the nonlinear mapping performed by the multivariate fuzzy membership functions. This impressive result allows comparison to be drawn between fuzzy systems and the more conventional techniques referred to as generalized local methods. In particular, if bell-shaped (Gaussian) membership functions are used, then a Takagi-Sugeno (TS) fuzzy system is equivalent to a special kind of Radial Basis Function (RBF) network (Jang and Sun 1993).

Theorems and analysis derived for local modeling methods can directly be applied to fuzzy systems. Also, due to this similarity, fuzzy systems allow relatively easy application of learning techniques used in local methods for identification of fuzzy rules from data. On the other side,

fuzzy systems distinguish from other local modeling techniques, for their potentiality of an easy pre-structuring and a convenient integration of a priori knowledge. Many learning algorithms from the area of local modeling, and more specifically techniques developed for some kind of neural networks, have been extended to automatically extract or tune fuzzy rules based on available data. All these techniques exploit the fact that, at the computational level, a fuzzy system can be seen as a layered architecture, similar to an artificial neural network. By doing so, the fuzzy system becomes a neuro-fuzzy system, i.e. special neural network architecture. In 1991, Lin and Lee have proposed the very first implementation of Mamdani fuzzy models using layered feed-forward architecture (Lin and Lee, 1991). Nevertheless, the most famous example of neuro-fuzzy network is the Adaptive Network-based Fuzzy Inference System (ANFIS) developed by Jang in 1993 (Jang 1993), that implements a TS fuzzy system in a network architecture, and applies a mixture of plain back-propagation and least mean squares procedure to train the system.

## 24.2 CLASSIFICATION OF NEURO-FUZZY SYSTEMS

There are several ways to combine neural networks and fuzzy logic. Efforts at merging these two technologies may be characterized by considering three main categories: neural fuzzy systems, fuzzy neural networks and fuzzy-neural hybrid systems.

### 24.2.1 Neural Fuzzy Systems

Neural fuzzy systems are characterized by the use of neural networks to provide fuzzy systems with a kind of automatic tuning method, but without altering their functionality. One example of this approach would be the use of neural networks for the membership function elicitation and mapping between fuzzy sets that are utilized as fuzzy rules as shown in Fig. 24.1. In the training process, a neural network adjusts its weights in order to minimize the mean square error between the output of the network and the desired output. In this particular example, the weights of the neural network represent the parameters of the fuzzification function, fuzzy word membership function, fuzzy rule confidences and defuzzification function respectively. In this sense, the training of this neural network results in automatically adjusting the parameters of a fuzzy system and finding their optimal values. This kind of combination is mostly used in control applications. Examples of this approach can be found in (Wang and Mendel 1992; Nomura et al. 1992; Nauck 1994; Shi and Mizumoto 2000a, b; Yager and Filev 1994; Cho and Wang 1996; Ichihashi and Tuksen 1993).

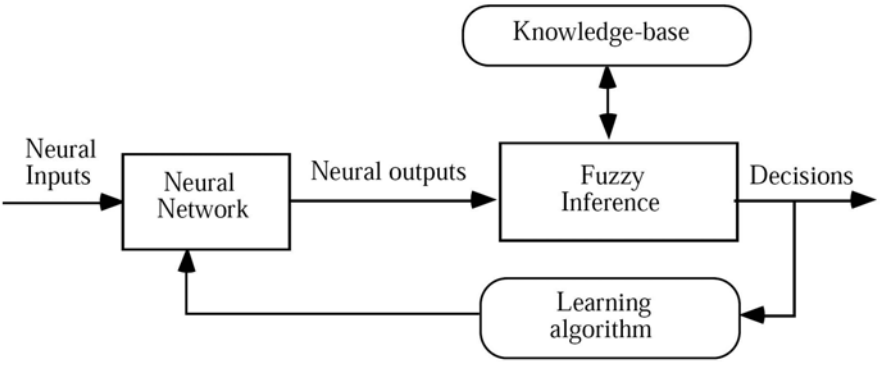


**Fig. 24.1** Neural fuzzy system [Adapted from Fuller R (2000) Introduction to Neuro-Fuzzy Systems. Advances in Soft Computing Series, Springer-Verlag, Berlin/Heildelberg, with permission]

### 24.2.2 Fuzzy Neural Systems

The main goal of this approach is to 'fuzzify' some of the elements of neural networks, using fuzzy logic (see Fig. 24.2). In this case, a crisp neuron can become fuzzy. Since fuzzy neural networks are inherently neural networks, they are mostly used in pattern recognition applications. In 1996, for instance, Lin and Lee presented a neural network composed of fuzzy neurons (Lin and Lee 1996). In these fuzzy neurons, the inputs are non-fuzzy, but the weighting operations are replaced by membership functions. The result of each weighting operation is the membership value of the corresponding input in the fuzzy set. Also, the aggregation operation may use any aggregation operators such as min and max and any other t-norms and t-conorms.

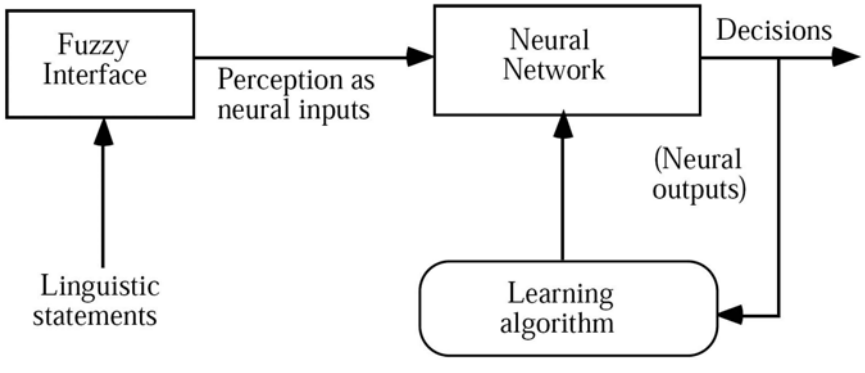


**Fig. 24.2** Fuzzy neural system [Adapted from Fuller R (2000) Introduction to Neuro-Fuzzy Systems. Advances in Soft Computing Series, Springer-Verlag, Berlin/Heildelberg, with permission]

### 24.2.3 Hybrid Neuro-Fuzzy Systems

In this approach, both fuzzy and neural networks techniques are used independently, becoming, in this sense, a hybrid system. Each one does its own job in serving different functions in the system, incorporating and complementing each other in order to achieve a common goal. This kind of merging is application-oriented and suitable for both control and pattern recognition applications. The idea of a hybrid model is the interpretation of the fuzzy rule-base in terms of a neural network. In this way the fuzzy sets can be interpreted as weights, and the rules, input variables, and output variables can be represented as neurons. The learning algorithm results, like in neural networks, in a change of the architecture, i.e. in an adaption of the weights, and/or in creating or deleting connections. These changes can be interpreted both in terms of a neural net and in terms of a fuzzy controller. This last aspect is very important as the black box behaviour of neural nets is avoided this way. This means a successful learning procedure results in an explicit increase of knowledge that can be represented in form of a fuzzy controller's rule base. Hybrid neuro-fuzzy controllers are realized by approaches like ARIC (Berenji 1992), GARIC (Bersini et al. 1993), ANFIS (Jang 1993) or the NNDFR model (Takagi and Hayashi 1991). These approaches consist all more or less of special neural networks, and they are capable to learn fuzzy sets.

## 24.3 ADAPTIVE-NEURO-FUZZY INFERENCE SYSTEM: ANFIS

Adaptive Neuro-Fuzzy Inference System (ANFIS) is one of the most successful schemes which combine the benefits of these two powerful paradigms into a single capsule proposed by Jang (Jang 1993). An ANFIS works by applying neural learning rules to identify and tune the parameters and structure of a Fuzzy Inference System (FIS). There are several features of the ANFIS which enable it to achieve great success in a wide range of scientific applications. The attractive features of an ANFIS include: easy to implement, fast and accurate learning, strong generalization abilities, excellent explanation facilities through fuzzy rules, and easy to incorporate both linguistic and numeric knowledge for problem solving (Jang and Sun 1995; Jang et al. 1997). According to the neuro-fuzzy approach, a neural network is proposed to implement the fuzzy system, so that structure and parameter identification of the fuzzy rule base are accomplished by defining, adapting and optimizing the topology and the parameters of the corresponding neuro-fuzzy network, based only on the available data. The network can be regarded both as an adaptive fuzzy inference system with the capability of learning fuzzy rules from data, and as a connectionist architecture provided with linguistic meaning. A typical architecture of an

ANFIS, in which a circle indicates a fixed node, whereas a square indicates an adaptive node, is shown in Figure 24.3. In this connectionist structure, there are input and output nodes, and in the hidden layers, there are nodes functioning as membership functions (MFs) and rules. This eliminates the disadvantage of a normal feedforward multilayer network, which is difficult for an observer to understand or to modify. For simplicity, we assume that the examined FIS has two inputs and one output. For a first-order Sugeno fuzzy model, a typical rule set with two fuzzy "if-then" rules can be expressed as follows:

*Rule 1*: If $x$ is $A_1$ and y is $B_1$, then $f_1 = p_1 x + q_1 y + r_1$
*Rule 2*: If $x$ is $A_2$ and y is $B_2$, then $f_2 = p_1 x + q_2 y + r_2$

Where x and y are the two crisp inputs, and $A_i$ and $B_i$ are the linguistic labels associated with the node function.

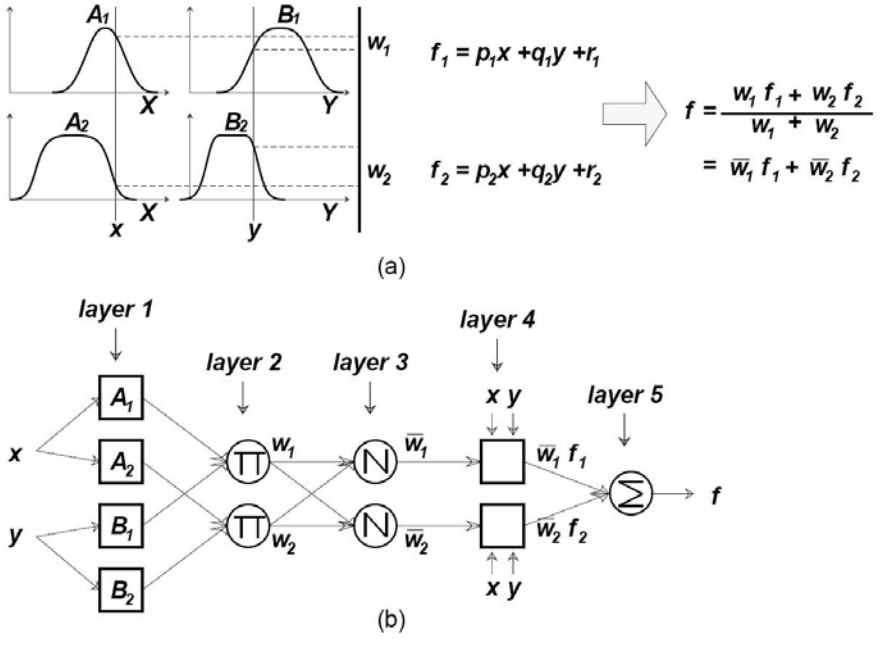


**Fig. 24.3** First order Sugeno ANFIS architecture (Type-3 ANFIS) (Adapted from Jang JSR, Sun CT (1995) Neuro-Fuzzy Modeling and Control. Proceedings of IEEE; 83(3): 378-406, with permission from IEEE)

As indicated in Fig. 24.3, the system has a total of five layers. The functioning of each layer is described as follows (Jang 1993).

**Input node (Layer 1):** Nodes in this layer contains membership functions. Parameters in this layer are referred to as premise parameters. Every node *i* in this layer is a square and adaptive node with a node function:

$$O_i^1 = \mu_{A_i}(x) \qquad \text{For } i = 1, 2 \tag{24.1}$$

Where *x* is the input to node *i*, and $A_i$ is the linguistic label (small , large, etc.) associated with this node function. In other words, $O_i^1$ is the membership function of $A_i$ and it specifies the degree to which the given x satisfies the quantifier $A_i$.

**Rule nodes (Layer 2):** Every node in this layer is a circle node labeled II, whose output represents a firing strength of a rule. This layer chooses the minimum value of two input weights. In this layer, the AND/OR operator is applied to get one output that represents the results of the antecedent for a fuzzy rule, that is, firing strength. It means the degrees by which the antecedent part of the rule is satisfied and it indicates the shape of the output function for that rule. The node generates the output (firing strength) by cross multiplying all the incoming signals:

$$O_i^2 = w_i = \mu_{A_i}(x) \times \mu_{B_i}(y), \quad i = 1, 2 \tag{24.2}$$

**Average nodes (Layer 3):** Every node in this layer is a circle node labeled N. The $i^{th}$ node calculates the ratio between the $i^{th}$ rule's firing strength to the sum of all rules' firing strengths. Every node of these layers calculates the weight, which is normalized. For convenience, outputs of this layer are called normalized firing strengths.

$$\overline{w}_i = \frac{w_i}{w_1 + w_2}, \quad i = 1, 2 \tag{24.3}$$

**Consequent nodes (Layer 4):** This layer includes linear functions, which are functions of the input signals. This means that the contribution of ith rule's towards the total output or the model output and/or the function defined is calculated. Every node *i* in this layer is a square node with a node function:

$$O_i^4 = \overline{w}_i f_i = \overline{w}_i (p_i x + q_i y + r_i) \tag{24.4}$$

Where $\overline{w}_i$ is the output of layer 3, and $\{p_i, q_i, r_i\}$ is the parameter set of this node. These parameters are referred to as consequent parameters.

**Output node (Layer 5):** The single node in this layer is a fixed node labeled $\sum$, which computes the overall output by summing all incoming signals:

$$O_i^5 = \text{overalloutput} = \sum_i \overline{w}_i f_i = \frac{\sum_i w_i f_i}{\sum_i w_i} \tag{24.5}$$

## 24.4 MODELING WITH NEURO-FUZZY SYSTEMS

Whatever may be the adopted vision of fuzzy model, two different phases must be carried out in fuzzy modeling, designated as structural and parametric identification. Structural identification consists of determining the structure of the rules, i.e. the number of rules and the number of fuzzy sets used to partition each variable in the input and output space so as to derive linguistic labels. Once a satisfactory structure is available, the parametric identification must follow for the fine adjustment of the position of all membership functions together with their shape as the main concern. As seen before, to overcome the limitations of using expert knowledge in defining the fuzzy rules, data driven methods to create fuzzy systems are needed. With such methods both structure and parameters are derived from scratch relying only on the training data. There are several ways that structure learning and parameter learning can be combined in a neuro-fuzzy system. They can be performed sequentially: structure learning is used first to find an appropriate structure of the fuzzy rule base, and then parameter learning is used to identify the parameters of each rule. In some neuro-fuzzy systems the structure is fixed and only parameter learning is performed. Algorithms inspired by neural network learning often do parameter learning. Structure learning on the other hand is usually not from neural networks. Indeed, many different approaches exist to automatically determine the structure of neural networks, but none of them is appropriate to perform structure identification in neuro-fuzzy models. In the following, different methods are presented that used for structure and parameter identification in neuro-fuzzy systems. There may be a lot of structure/parameter combinations which make the fuzzy model to behave satisfactorily; hence the search for the best model is not an easy task.

As a rule, simple fuzzy models should be preferred to complex ones; hence in the search for the best model two main objectives must be taken into account: good accuracy and minimal complexity.

### 24.4.1 Parametric Identification

Two types of parameters characterize a fuzzy model: those determining the shape and distribution of the input fuzzy sets and those describing the output fuzzy sets (or linear models). Many neuro-fuzzy systems use direct nonlinear optimization to identify all the parameters of a fuzzy system. Different optimization techniques can be used to this aim. The most widely used is an extension of the well-known back-propagation algorithm implemented by gradient descent. A very large number of neuro-fuzzy systems are based on backpropagation. One limitation of using gradient descent techniques is that the membership functions and all functions that take part in the inference of the fuzzy rule base must be differentiable. As a consequence, gradient descent learning can be more easily applied to identify the parameters of a TS model, because only the product operator is used for intersection and the output is computed as a weighted sum. Recent neuro-fuzzy approaches choose to implement back-propagation by simple heuristics instead of gradient descent to identify the parameters of a Mamdani-type fuzzy model (Nauck and Kruse 1999). The general idea of such heuristics is to slightly modify the membership functions of a fuzzy rule according to how much the rule contributes to the overall output of the fuzzy system. From the proposed type-3 ANFIS architecture (see Fig. 24.3), it is observed that given the values of premise parameters, the overall output can be expressed as a linear combinations of the consequent parameters. More precisely, the output f in Fig. 24.3 can be rewritten as:

$$\begin{aligned} f &= \frac{w_1}{w_1 + w_2} f_1 + \frac{w_2}{w_1 + w_2} f_2 = \bar{w}_1 f_1 + \bar{w}_2 f_2 \\ &= (\bar{w}_1 x) p_1 + (\bar{w}_1 y) q_1 + (\bar{w}_1) r_1 + (\bar{w}_2 x) p_2 + (\bar{w}_2 y) q_2 + (\bar{w}_2) r_2 \end{aligned} \tag{24.6}$$

which is linear in the consequent parameters ($p_1$, $q_1$, $r_1$, $p_2$, $q_2$ and $r_2$). Therefore the hybrid learning algorithm can be applied directly. More specifically, in the forward pass of the hybrid learning algorithm, functional signals go forward till layer 4 and the consequent parameters are identified by the least squares estimate (LSE). In the backward pass, the error rates propagate backward and the premise parameters are updated by the gradient descent. Table 24.2 summarizes the activities in each pass.

**Table 24.2** The two passes in the hybrid learning algorithm (Jang and Sun 1995).

| | **Forward Pass** | **Backward pass** |
|---|---|---|
| Premise Parameters | Fixed | Gradient Descent |
| Consequent parameters | Least-squares estimator | Fixed |
| Signals | Node Outputs | Error Signals |

As mentioned earlier, the consequent parameters thus identified are optimal (in the consequent parameter space) under the condition that the premise parameters are fixed. However, it should be noted that the computation complexity of the least squares estimate is higher than that of the gradient descent. In fact, there are four methods to update the parameters, as listed below according to their computation complexities (Jang 1993):

- Gradient Descent Only: All parameters are updated by the gradient descent.
- Gradient Descent and One Pass of LSE: The LSE is applied only once at the beginning to get the initial value of the consequent parameters and then the gradient descent takes over to update all parameters.
- Gradient descent and LSE: This is the proposed hybrid learning rule.
- Sequential (Approximate) LSE Only: The ANFIS is linearized with respect to the premise parameters and the extended Kalman filter algorithm is employed to update all parameters.

The choice of above methods should be based on the trade-off between computation complexity and resulting performance. Other approaches to parameter learning of fuzzy models that do not require gradient computations, and hence differentiability, are reinforcement learning which requires only a single scalar evaluation of the output, and Genetic Algorithms (GAs) that perform a random search in the parameter space, using a population of individuals, each coding the parameters of a potential fuzzy rule base (Seng et al. 1999). One problem with GAs is that with conventional binary coding, the length of individuals increases significantly with the number of inputs, the number of fuzzy sets and the number of rules. Evolution Strategies (ES) are more suitable techniques to tune the fuzzy rule parameters due to their direct coding scheme (Jin et al. 1999). GA's and ES allow also a simultaneous identification of the

parameters and the structure (rule number) of a fuzzy model, but in such a case these evolutionary techniques are computationally demanding since very complex individuals need to be manipulated. The identification of the whole set of parameters by nonlinear optimization techniques may be computationally intensive and requiring long convergence rates. To speed up the process of parameter identification, many neuro-fuzzy systems adopt a multi-stage learning procedure to find and optimize the parameters. Typically, two stages are considered. In the first stage the input space is partitioned into regions by unsupervised learning, and from each region the premise (and eventually the consequent) parameters of a fuzzy rule are derived. In the second stage the consequent parameters are estimated via a supervised learning technique. In most cases, the second stage performs also a fine adjustment of the premise parameters obtained in the first stage using a nonlinear optimization technique.

### 24.4.2 Structural Identification

Before fuzzy rule parameters can be optimized, the structure of the fuzzy rule base must be defined. This involves determining the number of rules and the granularity of the data space, i.e. the number of fuzzy sets used to partition each variable. In fuzzy rule-based systems, as in any other modeling technique, there is a tradeoff between accuracy and complexity. The more rules, the finer the approximation of the nonlinear mapping can be obtained by the fuzzy system, but also more parameters have to be estimated, thus the cost and complexity increase. A possible approach to structure identification is to perform a stepwise search through the fuzzy model space. Once again, these search strategies fall into one of two general categories: forward selection and backward elimination.

- Forward selection. Starting from a very simple rule base, new fuzzy rules are dynamically added or the density of fuzzy sets is incrementally increased (Royas et al. 2000).
- Backward elimination. An initial fuzzy rule base, constructed from a priori knowledge or by learning from data, is reduced, until a minimum of the error function is found (Yen and Wang, 1999). The structure of the fuzzy rules can also be optimized by GA's so that a compact fuzzy rule base can be obtained (Seng et al. 1999).

The learning algorithm is an example of structure adaptation in neuro-fuzzy systems. Rules are dynamically recruited or deleted according to their significance to system performance, so that a parsimonious structure with high performance is achieved. When initial fuzzy rules are generated

by clustering, the number of cluster (i.e. of rules) must be specified before clustering. If no prior knowledge is available that suggests the number of clusters, automated procedures can be applied. For example the number of clusters can be found by evaluating a given validity measure, i.e. a criterion that assesses the quality of the clusters, and selecting the number of clusters that minimizes (maximizes) the validity measure. Another approach is cluster merging, that starts with a high number of clusters and reduces them successively by merging compatible clusters until some threshold is reached and no more clusters can be merged.

## 24.5 INTERPRETABILITY VERSUS ACCURACY OF NEURO-FUZZY MODELS

As seen in the previous sections, neuro-fuzzy systems are essentially fuzzy systems endowed with learning capabilities inspired (not only) by neural networks. Fuzzy systems join the advantages of modeling methods oriented to provide suitable models for both prediction and understanding. It must be considered whether these advantages of fuzzy systems for predictive modeling are preserved when they are transformed into neuro-fuzzy systems. The twofold face of neuro-fuzzy systems leads to a trade-off between readability and accuracy (see Table 24.3).

**Table 24.3** Interpretability vs. accuracy in fuzzy systems.

| | **Interpretability** | **Accuracy** |
|---|---|---|
| **No. of parameters** | Few Parameters | More Parameters |
| **No. of fuzzy rules** | Few Rules | More Rules |
| **Type of Fuzzy logic Model** | Mamdani Models | TSK models |

Fuzzy systems can be forced to arbitrary precision, but it then loose interpretability. To be very precise, a fuzzy system needs a fine granularity and many fuzzy rules. It is obvious that the larger the rule base of a fuzzy system becomes, the less interpretable it gets (Nauck and Kruse 1998a, b).

To keep the model simple, the prediction is usually less accurate. In solving this trade-off the interpretability (meaning also simplicity) of fuzzy systems must be considered the major advantage and hence it should be pursuit more than accuracy. In fact fuzzy systems are not better function approximators or classifiers than other approaches. If we are interested in a very precise prediction, then we are usually not so much interested in the interpretability of the solution. In this case we use just one feature of fuzzy

systems: the convenient combination of local models to an overall solution. For this, Sugeno-type models are more suited than Mamdani-type models because they offer more flexibility in the consequents of the rules. However, if optimal performance is the main objective, we should consider whether a fuzzy system is the most suitable approach and an exhaustive and deep comparison with related methods (local methods and generalized local methods) has to be done, in terms of pure performance, computational cost and practicability. Briefly put, fuzzy systems should be used for predictive modeling if an interpretable model is needed that can also be used to some extent for prediction. Interpretability of a fuzzy model should not mean that there is an exact match between the linguistic description of the model and the model parameters. This is not possible anyway, due to the subjective nature of fuzzy sets and linguistic terms. Usually it is not important that, for example, the term approximately zero be represented by a symmetrical triangular fuzzy set with support [-1, 1]. Interpretability means that the users of the model can accept the representation of the linguistic terms, more or less. The representation must roughly correspond to their intuitive understanding of the linguistic terms. Furthermore, interpretability should not mean that anybody could understand a fuzzy model. It means that users who are at least to some degree experts in the domain where the predictive modeling takes place can understand the model. Since interpretability itself is a fuzzy and subjective concept, it is hard to find an explicit and exhaustive list of conditions which, when violated, make the fuzzy model to lose its readability.

Traditional neuro-fuzzy modeling techniques, and in general data-driven methods for learning fuzzy rules from data, are aimed to optimize the prediction accuracy of the fuzzy model. However, while the accuracy improves, the transparency of the fuzzy models after learning may be lost. The overlap of the membership functions typically increases and peculiar situations may occur, when some membership functions are contained in the others or membership functions swap their positions. This hampers the interpretability of the final model. For the sake of interpretability, the learning procedure should take the semantics of the desired fuzzy system into account, and adhere to certain constraints, so that it cannot apply all the possible modifications to the parameters of a fuzzy system. For example the learning algorithms should be constrained such that adjacent membership functions do not exchange positions, do not move from positive to negative parts of the domains or vice versa, have a certain degree of overlapping, etc. The other important requirement to obtain interpretability is to keep the rule base small. A fuzzy model with

interpretable membership functions but a very large number of rules is far from being understandable. By reducing the complexity, i.e. the number of parameters, of a fuzzy model, not only the rule base is kept manageable (hence the inference process is computationally cheaper) but also it can provide a more readable description of the process underlying the data. Also the use of a simple rule base contributes to decrease the overfitting, thus improving generalization. So far, few data-driven fuzzy rule learning methods aiming at improving the interpretability of the fuzzy models in terms of both small rule base and readable fuzzy sets have been proposed.

## 24.6 ADAPTIVE-NEURO-FUZZY INFERENCE SYSTEM AS A NOVEL APPROACH FOR POST-DIALYSIS UREA REBOUND PREDICTION

### 24.6.1 Problem Statement

Kinetic models of urea concentration are now widely used to manage hemodialysis (HD) patients. The calculation Kt/V (where K is the dialyzer clearance, t is the time of treatment, and V is the urea distribution volume), is now widely used to quantify HD treatment (Depner 1994, 1999). The Kt/V calculation is commonly determined from measurements of the pre- and post-HD blood urea nitrogen (BUN) concentrations (Gotch and Sargent 1985). However, because the rapid removal of BUN during HD causes a concentration disequilibrium between intracellular and extracellular fluid spaces, BUN increases immediately following HD. This phenomenon is well known as the urea rebound, and is due to the multiple-pool nature of the human body, and mass transfer resistance of the biological membranes and variations in regional blood flows (Schneditz and Daugirdas 2001; Yashiro et al. 2004). Since Kt/V calculation is based in part on the post-hemodialysis BUN level (Daugirdas 1993), urea rebound has a significant impact upon the calculation of the delivered dose of hemodialysis. While single-pool kinetic modeling ($_{sp}$Kt/V) uses a convenient 30-second post-dialysis BUN sample, it does not take urea rebound into account, which leads to a 12 to 40% of the true equlilibrated dialysis dose ($_{eq}$Kt/V). Double-pool modeling ($_{eq}$Kt/V) uses an equilibrated BUN ($C_{eq}$) and is the best reflection of the true urea mass removed by hemodialysis. Because a delay of 30 to 60 minutes after dialysis before sampling the urea is inconvenient for both the clinician and patient, several methods have been devised to predict the PDUR in order to estimate the equilibrated Kt/V. The first is based on the standard single-pool Daugirdas Kt/V model that takes into account the dialysis time, which evolved into a double-pool Kt/V ($_{eq}$Kt/V) formula (Daugirdas and Schneditz 1995). The

second, according to Smye (Smye et al. 1994), Daugirdas (Daugirdas et al. 1996), Tattersall (Tattersall et al. 1996), and Maduell (Maduell et al. 1997), is based on an intradialytic urea sample at 33% of the session time. Other methods use a urea sample taken 30 minutes before the end of the hemodialysis session, which corresponds to the 30-minute PDUR (Bhaskaran et al. 1997; Canaud at al. 1997). Finally, Artificial Neural Network (ANN) method was used as a predictor of equilibrated post-dialysis blood urea concentration ($C_{eq}$) (Guh et al. 1998; Azar et al. 2010; Azar and Wahba 2011). All of these methods still overestimate the urea rebound and underestimate the equlilibrated dialysis dose ($_{eq}Kt/V$).

### 24.6.2 Subjects and Methods

The study was carried out at four dialysis centers. BUN was measured in all serum samples at a central laboratory. The overall study period was 5 months from August 1, 2008 to December 31, 2008. No subjects dropped out of the study. The study subjects consisted of 310 hemodialysis patients that gave their informed consent to participate. They are 165 male and 145 female patients, with ages ranging 14-75 years (48.97±12.77, mean and SD), and dialysis therapy duration ranging 6-138 months (50.56±34.67). The etiology of renal failure was chronic glomerulonephritis (65 patients), diabetic nephropathy (60 patients), vascular nephropathy (55 patients), hypertension (51 patients), interstitial chronic nephropathy (45 patients), other etiologies (18 patients) and unknown cause (16 patients). The vascular access was through a native arteriovenous fistula (285 patients), and a permanent jugular catheter (25 patients).

Patients had dialysis three times a week, in 3-4 hour sessions, with a pump arterial blood flow of 200-350 ml/min, and flow of the dialysis bath of 500-800 ml/min. The dialysate consisted of the following constituents: sodium 141 mmol/l, potassium 2.0 mmol/l, calcium 1.3 mmol/l, magnesium 0.2 mmol/l, chloride 108.0 mmol/l, acetate 3.0 mmol/l and bicarbonate 35.0 mmol/l. Special attention was paid to the real dialysis time, so that time-counters were fitted to all machines for all sessions, to record effective dialysis duration (excluding any unwanted interruptions, e.g. due to dialysis hypotensive episodes). All patients were dialyzed with 1.0 $m^2$ Polyethersulfone low flux dialyzer, 1.2 $m^2$ cellulose-synthetic low flux dialyzer (hemophane), 1.3 $m^2$ Polyethersulfone low flux dialyzer, 1.3 $m^2$ low flux polysulfone dialyzer, 1.6 $m^2$ low flux polysulfone dialyzer and 1.3 $m^2$ high flux polysulfone dialyzer. The dialysis technique was conventional hemodialysis, no patient being treated with hemodiafiltration. A Fresenius model 4008B and 4008S dialysis machine equipped with a

volumetric ultrafiltration control system was used in each dialysis. Fluid removal was calculated as the difference between the patients' weight before dialysis and their target dry weight. Pre-dialysis body weight, blood pressure, pulse rate and axillary temperature were measured before ingestion of food and drink. Pre-dialysis BUN ($C_{pre}$) was sampled from the arterial port before the blood pump was started. Post-dialysis BUN ($C_{post}$) was obtained from the arterial port at the end of HD with the blood flow rate unchanged. Equilibrated post-dialysis BUN ($C_{eq}$) was obtained from the peripheral vein 30 and 60 minutes after HD. It was then corrected for urea generation. This corrected $C_{eq}$ was used as a "gold standard" or the reference method.

### 24.6.3 ANFIS Architecture for Equilibrated Blood Urea Concentration Prediction

To overcome the problem of overestimating urea rebound, Adaptive Neuro-Fuzzy Inference System (ANFIS) is developed by Azar et al (2008) in the form of a zero-order Takagi-Sugeno-Kang fuzzy inference system to predict equilibrated urea ($C_{eq}$) taken at 30 ($C_{eq30}$) and 60 ($C_{eq60}$) min after the end of the hemodialysis (HD) session in order to predict post dialysis urea rebound (PDUR) and equilibrated dialysis dose ($_{eq}$Kt/V) (Azar 2009). The developed neuro-fuzzy hybrid approach is more accurate and doesn't require the model structure to be known a priori, in contrast to most of the modeling techniques. Also, this system doesn't require 30- or 60-minute post-dialysis urea sample (Azar 2011). The proposed ANFIS can construct an input-output mapping based on both expert knowledge (in the form of linguistic rules) and specified input-output data pairs and the least squares estimate (LSE) to identify the parameters (Jang et al. 1997). The ANFIS is a multilayer feed-forward network uses ANN learning algorithms and fuzzy reasoning to characterize an input space to an output space. The architecture of the proposed ANFIS realizes the inference mechanism of zero-order Takagi-Sugeno-Kang (TSK) fuzzy models (Takagi and Sugeno 1985). The first-order Sugeno models have more freedom degrees and therefore the approximation ability is higher, together with a higher risk to overfit. The use of less freedom degrees is helping to control overfitting for the problem. Then, in this particular problem it is better zero-order. On the other hand, zero-order are more interpretable than first-order (depending on the number of rules required). Therefore, the selection of TSK model type depends on the necessities for the problem and the possibility to overfit the system (if it is important or not to have an interpretable model).

For an n-dimensional input, m-dimensional output fuzzy system, the rule base is composed of a set of fuzzy rules formally defined as:

$$R_k : \text{IF } (x_1 \text{ is } A_1^k) \text{AND} \ldots \text{AND } (x_n \text{ is } A_n^k) \text{ THEN } (y_1 \text{ is } B_1^k) \text{ AND} \ldots \text{AND } (y_m \text{ is } B_m^k) \quad (24.7)$$

Where x = ($x_1$, . . . $x_n$) are the input variables and $y = (y_1, \ldots y_m)$ are the output variables, $A_i^k$ are fuzzy sets defined on the input variables and $B_j^k$ ($j$ =1,…,m) are fuzzy singletons defined on the output variables over the output variables $y_j$. When $y$ is constant, the resulting model is called "zero-order Sugeno fuzzy model", which can be viewed either as a special case of the Mamdani inference system (Mamdani and Assilian 1975), in which each rule's consequent is specified by a fuzzy singleton, or a special case of the Tsukamoto fuzzy model (Tsukamoto 1979), in which each rule's consequent is specified by a MF of a step function center at the constant. Figure 24.4 illustrate the reasoning mechanism for zero-order Sugeno model. This class of fuzzy models should be used when only performance is the ultimate goal of predictive modeling as in the case of our modeling methodology. This class of fuzzy models can employ all the other types of fuzzy reasoning mechanisms because they represent a special case of each of the above described fuzzy models. More specifically, the consequent part of this simplified fuzzy rule can be seen either as a singleton fuzzy set in the Mamdani model or as a constant output function in TS models. Thus the two fuzzy models are unified under this simplified fuzzy model. Different types of membership functions can be used for the antecedent fuzzy sets. In this work, the membership functions have been tested based on error analysis (calculation of average error). The membership function with minimum error is selected and that will be the suitable membership function to estimate the model. Therefore, triangular-shaped membership functions are used for zero-order TSK based models in this study. Based on a set of K rules, the output for any unknown input vector $x(0)$ is obtained by the following fuzzy reasoning procedure:

- Calculate the degree of fulfillment for the k-*th* rule, for k = 1,…,K, by means of Larsen product operator:

$$\mu_k(X) = \prod_{i=1}^{n} \mu_{ik}(x_i), \qquad k = 1,\ldots\ldots,K \quad (24.8)$$

  Note that when computing the activation strength of a rule, the connective AND can be interpreted through different T-norm operators: typically there is a choice between product and min

operators. Here we choose the product operator because it retains more input information than the min operator and generally gives a smoother output surface which is a desirable property in any modeling application.

- Calculate the inferred outputs $\hat{y}_j$ by taking the weighted average of consequent values $B_j^k$ with respect to rule activation strengths $\mu_k(x)$:

$$\hat{y}_j = \frac{\sum_{k=1}^{K} \mu_k(X)\, b_{jk}}{\sum_{k=1}^{K} \mu_k(X)}, \qquad j = 1,....,m \tag{24.9}$$

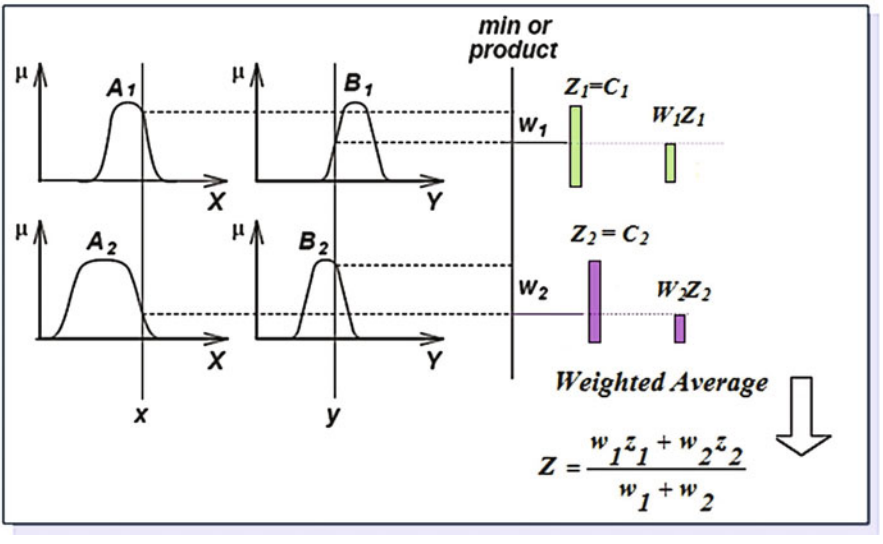


**Fig. 24.4** Zero-order TSK fuzzy inference system with two inputs and two rules [Adapted from Castillo O, Melin P (2001). Soft Computing for Control of Non-Linear Dynamical Systems. 1st edition, Physica-Verlag Heidelberg, Germany, with permission from Springer].

### 24.6.3.1 Parameter Selection for the System

For a real-world modeling problem, it is not uncommon to have tens of potential inputs to the model under construction. An excessive number of inputs not only impair the transparency of the underlying model, but also increase the complexity of computation necessary for building the model. Therefore, it is necessary to do input selection that finds the priority of

each candidate inputs and uses them accordingly. Specifically, In order to build a reasonably accurate model for prediction, proper parameters must be selected. The MATLAB function '*exhsrch*' performs an exhaustive search within the available inputs to select the set of inputs that most influence the desired output. The first parameter to the function specifies the number of input combinations to be tried during the search. Essentially, exhsrch builds an ANFIS model for each combination and trains it for one epoch and reports the performance achieved. The following are some practical considerations in parameter selection:

- Remove some irrelevant inputs such as the type of dialysate, dialysate temperature, blood pressure of patients, probability of complications, blood volume of patients, intercompartmental urea mass transfer area coefficient, fraction of ultrafiltrate from ICF and access blood flow. This was performed based on the recommendations of an expert in the hemodialysis field. This expert is the medical consultant who supervises the dialysis sessions throughout the research.
- Remove inputs that can be derived from other inputs.
- Make the underlying model more concise and transparent.
- The reduction of the number of parameters results in the reduction of the time required for model construction.
- The selected parameters must affect the target problem, i.e., strong relationships must exist among the parameters and target (or output) variables .
- The selected parameters must be well-populated, and corresponding data must be as clean as possible.

The proposed input selection method is based on the assumption that the ANFIS model with the smallest RMSE (root mean squared error) after one epoch of training has a greater potential of achieving a lower RMSE when given more epochs of training. This assumption is not absolutely true, but it is heuristically reasonable. For instance, if we have a modeling problem with ten candidate inputs and we want to find the most three influential inputs as the inputs to ANFIS, we can construct $C_3^{10}$ =120 ANFIS models, each with different combination of inputs and train them with a single pass of the least-squares method. The ANFIS model with the smallest training error is then selected for further training using the hybrid learning rule to tune the membership functions as well. Note that one-epoch training of 120 ANFIS models in fact involves less computation than 120-epoch training of a single ANFIS model, therefore the input selection procedure is not really as computation intensive as it looks. Therefore, five inputs are selected as the

data set for $C_{eq}$ predictor. They are, urea pre-dialysis (Cpre, mg/dl) at the beginning of the procedure, urea post-dialysis ($C_{post}$, mg/dl), Blood flow rate (BFR, dl/min), desired dialysis Time ($T_d$, min) and Ultrafiltration rate, the removal of excess water from the patient (UFR, dl/min). All blood samples were obtained from the arterial line at different times for urea determinations. The ANFIS output is the equilibrated post-dialysis BUN ($C_{eq}$) which was obtained 30 and 60 minutes after HD. Two triangular membership functions (MFs) are assigned to each linguistic variable as shown in Fig. 24.5. The ANFIS structure containing $2^5 = 32$ fuzzy rules and 92 nodes. Each fuzzy rule is constructed through several parameters of membership function in layer 2 with a total of 62 fitting parameters, of which 30 are premise (nonlinear) parameters and 32 are consequent (linear) parameters. To achieve good generalization capability, it is important that the number of training data points be several times larger than the number parameters being estimated. In this case, the ratio between data and parameters is five (310/62). Once the FIS structure was identified, the parameters that had to be estimated (Triangular input MF parameters and output constants) were fitted by the hybrid-learning algorithm.

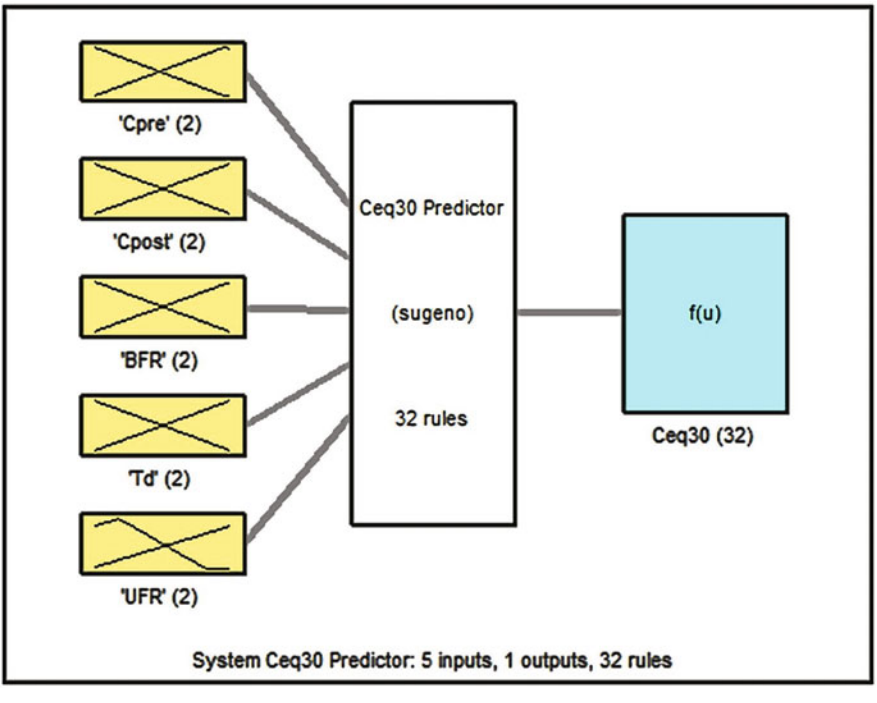


**Fig. 24.5** Fuzzy rule architecture of the triangular-shaped MF for equilibrated blood urea concentration ($C_{eq}$) prediction (see online version for colours)

### 24.6.4 Training Methodology of the Developed ANFIS System

The core of the ANFIS calculations was implemented in a MATLAB environment. Functions from the Mathwork's MATLAB Fuzzy Logic Toolbox (FLT) were included in a MATLAB code programmed by the author[1] to solve the input-output problem with different numbers of input MFs, using all data available. An estimate of the mean square error between observed and modeled values were computed for each trial, and the best structure was determined considering a trade-off between the mean square error and the number of parameters involved in computation.

Input MFs were linked by all possible combinations of if-and-then rules defining an output constant for each rule. The flow chart of proposed training methodology of ANFIS system is shown in Fig. 24.6. The modeling process starts by obtaining a data set (input-output data pairs) and dividing it into training and checking data sets. Training data constitutes a set of input and output vectors. The data is normalized in order to make it suitable for the training process. This normalized data was utilized as the inputs and outputs to train the ANFIS. To avoid overfitting problems during the estimation, the data set were randomly split into two sets: a training set (70% of the data; 220 samples), and a checking set (30% of the data; 90 samples). When both checking data and training data were presented to ANFIS, the FIS was selected to have parameters associated with the minimum checking data model error. In other words, two vectors are formed in order to train the ANFIS, input vector and the output vector (see Fig. 24.6). The training data set is used to find the initial premise parameters for the membership functions by equally spacing each of the membership functions. A threshold value for the error between the actual and desired output is determined. The consequent parameters are found using the least-squares method. Then an error for each data pair is found. If this error is larger than the threshold value, update the premise parameters using the gradient decent method. The process is terminated when the error becomes less than the threshold value. Then the checking data set is used to compare the model with actual system. A lower threshold value is used if the model does not represent the system. Training of the ANFIS can be stopped by two methods. In the first method, ANFIS will be stopped to learn only when the testing error is less than the tolerance limit. This tolerance limit would be defined at the beginning of the training. It is obvious that the performance of a ANFIS that is trained with lower tolerance is greater than ANFIS that is trained with higher

[1] The ANFIS source code developed by the author for training the system is copyright protected and not authorized for sharing.

tolerance limit. In this method the learning time will change with the architecture of the ANFIS. The second method to stop the learning is to put constraint on the number of learning iterations.

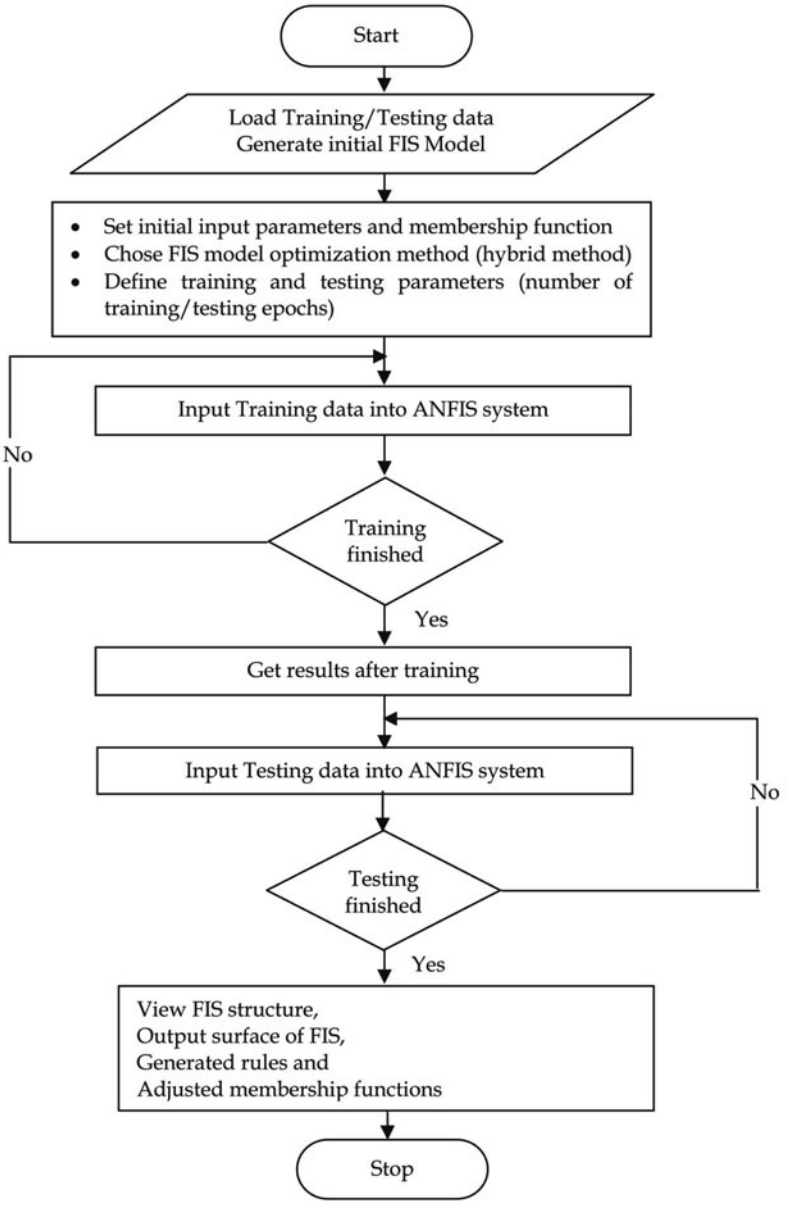


**Fig. 24.6** Flow chart of training methodology of ANFIS system.

### 24.6.5 Testing and Validation Process of the Developed ANFIS

Once the model structure and parameters have been identified, it is necessary to validate the quality of the resulting model. In principle, the model validation should not only validate the accuracy of the model, but also verify whether the model can be easily interpreted to give a better understanding of the modeled process. It is therefore important to combine data-driven validation, aiming at checking the accuracy and robustness of the model, with more subjective validation, concerning the interpretability of the model. There will usually be a challenge between flexibility and interpretability, the outcome of which will depend on their relative importance for a given application. While, it is evident that numerous cross-validation methods exist, the choice of the suitable cross-validation method to be employed in the ANFIS is based on a trade- off between maximizing method accuracy and stability and minimizing the operation time. In this research, the hold-out cross-validation method is adopted for ANFIS because of its accuracy and possible implementation. The choice of the hold-out method is attributed to its relative stability and low computational time requirements. A major challenge in applying the temporal cross-validation approach is the need to select the length of the checking data set utilized. Different lengths of the cross-validation data set ranging from one tenth to one third of the window size were examined. Apparently, choosing one third of the original data lead to short data set for the training process that may cause difficulty to reach the error goal.

While choosing 20% of window size lead to weakness in detecting the features of the expected data set in prediction stage since it leads to relatively short data set for the cross-validation procedure. Therefore, it was decided to select the length of data set for cross-validation utilized in our study to be 30% of the original data-set. Two pair sets were made with different combinations of 70% and 30% of the samples to improve the generalization properties of the adopted ANFIS as follows:

- Pair set 1: training set first 70%; test set last 30%
- Pair set 2: training set last 70%; test set first 30%

For each pair set, two ANFIS models of the same size, but differing in initialization weights, were trained to study the stability and robustness of the each model. The best weights (giving minimum mean-squared error) of two different training sessions over each input/output training set were chosen as the final ANFIS models. The performances of the ANFIS models both training and testing data are evaluated and the best training/testing data set is selected according to mean absolute error

(MAE), mean absolute percentage error (MAPE), Root Mean Square Error (RMSE) and normalized root mean squared error (NRMSE). Prediction accuracy is calculated by comparing the difference of predicted and measured values. If the difference is within tolerance, as in $|C_{eq}$ predicted-$C_{eq}$ measured$| \leq \varepsilon$, accurate prediction is achieved. The tolerance $\varepsilon$ is defined based based on the recommendations of an expert in the hemodialysis field. In equilibrated blood urea concentration ($C_{eq}$) prediction, errors of ±1.5% are allowed. So the prediction accuracy is defined as follows:

$$\text{Accuracy} = \frac{\left|C_{eq}^{predicted} - C_{eq}^{measured}\right| \leq \varepsilon}{|\text{predicted set}|} \tag{24.10}$$

For the five input parameters, each one was assigned two fuzzy sets, i.e. low and high. The membership function $\mu(k)$ for each input parameter is divided into two regions, low and high. The number and type of parameters for training ANFIS are shown in Table 24.4.

**Table 24.4** Training parameters of $C_{eq30}$ ANFIS prediction model.

| ANFIS parameter type | Value |
|---|---|
| TSK Type | Zero-order |
| Numbers of Rules | 32 |
| Number of Training Epochs | 50 |
| Number of nodes | 92 |
| Total fitting parameters | 62 |
| • premise (nonlinear) parameters | 30 |
| • consequent (linear) parameters | 32 |
| Number of Membership functions | Traingular-2 |
| Defuzzification Method | Weighted average |
| Initial step size, $k_{ini}$ | 0.07 |
| Step increasing rate, $\eta$ | 1.6 |
| Step decreasing rate, $\gamma$ | 0.1 |

The collection of well-distributed, sufficient, and accurately measured input data is the basic requirement in order to obtain an accurate model. The data set is divided into separate data sets- the training data set and the test data set. The training data set is used to train the ANFIS, whereas the test data set is used to verify the accuracy and effectiveness of the trained ANFIS. The ANFIS was tuned using a hybrid system that contained a combination of the back propagation and least-squares-type methods. An error tolerance of 0 was used and the ANFIS was trained with 50 epochs.

After training and testing, the RMSE became steady, the training and testing were regarded as converged as shown in Fig. 24.7. RMSE from each of the validating epochs was calculated and averaged to give the mean RMSE. The network error convergence curve achieved mean RMSE values of 0.2978 and 0.3125 for training and testing, respectively. It is noted from error curves that the ANFIS model performed well and it is obvious that the error between the actual and the predicted output of the model is very insignificant.

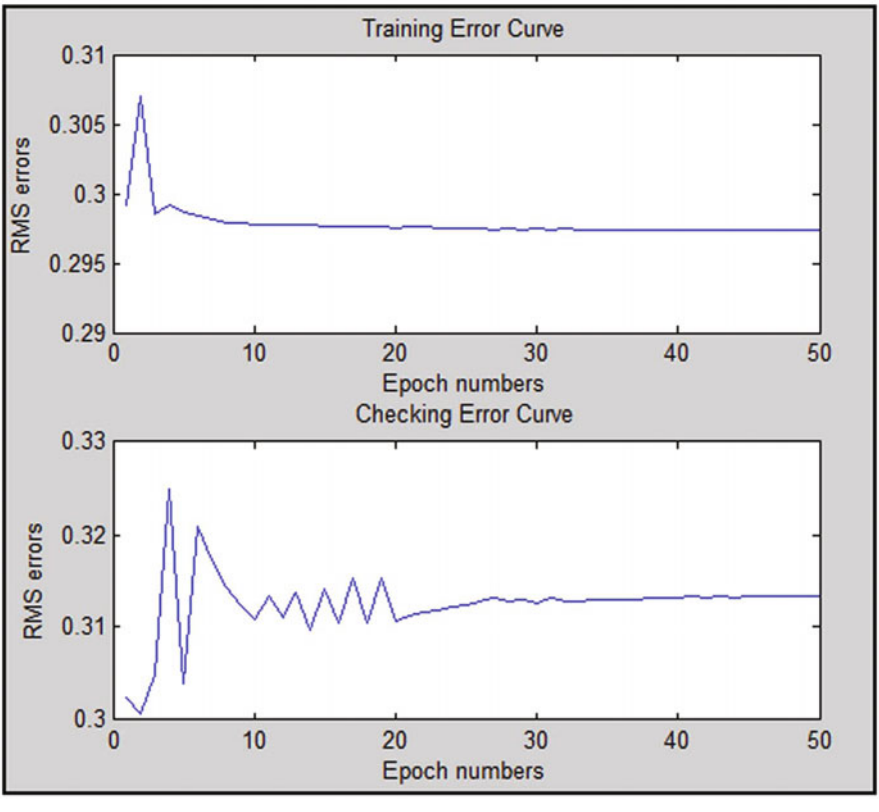


**Fig. 24.7** Training and checking errors obtained by ANFIS for predicting $C_{eq30}$.

The final member functions of the five inputs are changed through supervised learning. In a real world domain, all the features described may have different levels of relevancy. Moreover, human-determined membership functions are seldom optimal in terms of producing desired

outputs. Therefore, the training data are sufficient to provide the available input-output data necessary for fine-tuning the membership function. Figure 24.8 shows the final membership functions of the input parameters derived by training via the triangular membership function. Considerable changes happened in the final membership function after training especially for ultrafiltration rate (UFR) input. After the training process, the model is validated by comparing the predicted results against the experimental data. The validation tests between the predicted results and the actual results for both training and testing phases are summarized in Table 24.5. The statistical analysis demonstrated that there is no statistically significant difference was found between the predicted and the measured values. The percentage of MAE and RMSE for testing phase is 0.44% and 0.61% respectively.

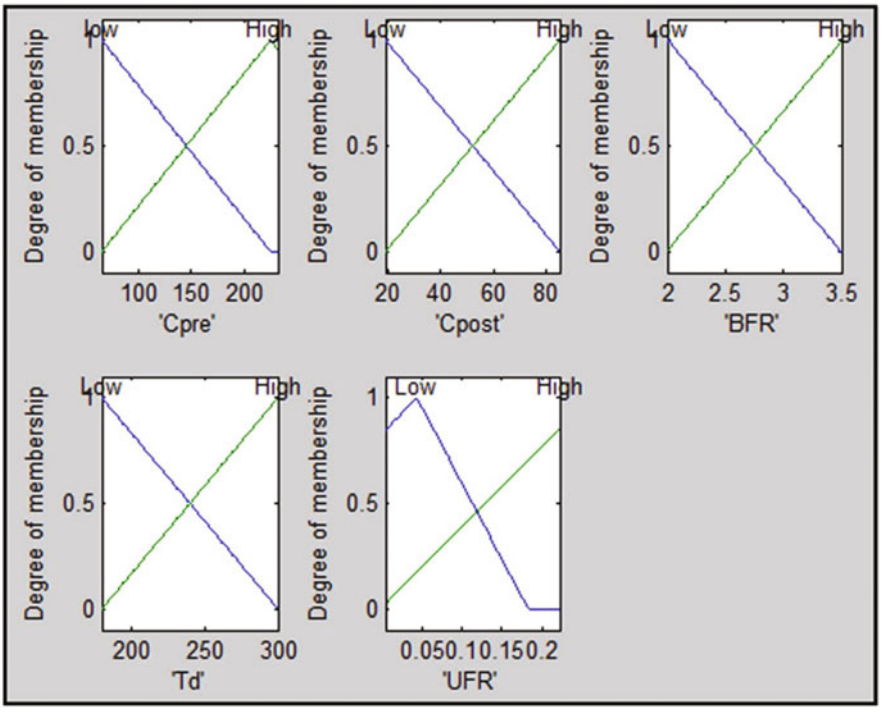


**Fig. 24.8** The final membership functions of selected inputs for $C_{eq30}$ predictor.

**Table 24.5** Validation tests between the measured $C_{eq30}$ as a reference and the predicted one by the ANFIS system.

| Agreement Comparison | $C_{eq30\text{-measured}}$ versus $C_{eq30\text{-ANFIS}}$ | |
|---|---|---|
| | Training Phase | Testing Phase |
| Mean Absolute Error (MAE) | 0.2383 | 0.2425 |
| Mean Absolute Percentage Error (MAPE) | 0.0044 | 0.0044 |
| Root mean square error (RMSE) | 0.2978 | 0.3125 |
| Normalized root mean square Error (NRMSE) | 0.0040 | 0.0061 |
| Median algebraic difference Δ | 0.2347 | 0.0113 |
| Median absolute difference \|Δ\| | 0.6529 | 0.3143 |

The same data set were used for predicting equilibrated urea concentration at 60 min ($C_{eq60}$) post-dialysis session. The $C_{eq60}$ model achieved RMSE values of 0.2707 and 0.3125 for training and testing, respectively. The results obtained indicate that ANFIS is a promising tool for predicting equilibrated urea concentration at 30 min ($C_{eq30}$) and 60 min ($C_{eq60}$) post-dialysis session. Both $C_{eq30}$ and $C_{eq60}$ models had very low MAE and RMSE values for both training and testing. This model was conducted to determine how the equilibrated urea concentration ($C_{eq}$) could be predicted without having to take a final urea sample an hour after the patient had completed the dialysis session.

### 24.6.6 Verification of System Output

Testing, validation and verification is inevitable part of any modeling process. These processes help modelers and other stakeholders build confidence in the appropriateness and usefulness of the model. Whatever modeling paradigm or solution technique is being used, the performance measures extracted from a model will only have some bearing on the real system represented if the model is a good representation of the system. Of course, what constitutes a good model is subjective, but from a performance modeling point of view our criteria for judging the goodness of models will be based on how accurately measures extracted from the model correspond to the measures which would be obtained from the represented system. Verification is like debugging-it is intended to ensure that the model

does what it is intended to do. It is important to remember that validation does not imply verification, nor verification imply validation. However, in practice, validation is often blended with verification, especially when measurement data is available for the system being modeled. If a comparison of system measurements and model results suggests that the results produced by the model are close to those obtained from the system, then the implemented model is assumed to be both a verified implementation of the assumptions and a valid representation of the system. Verification of the proposed system is divided into two phases to examine the output behavior of the model:

- A comparison between PDUR calculated by the model and other methods.
- A comparison between $_{eq}$(Kt/V) calculated by the model and other traditional methods.

#### 24.6.6.1 Comparison of Estimated Urea Rebound By ANFDIAC[2] and Other Traditional Methods

Post-dialysis urea rebound was calculated as the percentage of increase in serum urea level at 30 or 60 minutes compared with urea immediately post-dialysis. There are several methods for calculating PDUR as described in chapter 13. In order to verify the accuracy of the proposed NF system, the estimated urea rebound by the model was compared with various methods to determine how frequently these methods would lead to different prescription management. In Table 24.6 the different methods to determine the PDUR using 30 min post-dialysis sample are compared to the referring reference sample.

[2] The developed ANFIS by the author is referred to as ANFDIAC, which stands for adaptive neuro-fuzzy system for dialysis control.

**Table 24.6** Comparisons of Urea rebound calculated by different methods with the true urea rebound determined using the 30-min sample $(PDUR)_{30}$.

| Agreement Comparison | Comparisons with true PDUR at 30 min post-dialysis | | |
|---|---|---|---|
| | **True $PDUR_{30}$ vs. $PDUR_{Smye}$** | **True $PDUR_{30}$ vs. $PDUR_{Daugirdas}$** | **True $PDUR_{30}$ vs. $PDUR_{30\text{-}ANFDIAC}$** |
| Mean ± SD | 17.4196±4.1149 vs. 23.70 ± 4.3896 | 17.4196±4.1149 vs. 19.926 ± 3.4908 | 17.4196±4.1149 vs. 17.5774 ±3.9124 |
| Mean Bias | -6.2030 ± 2.1368 | -2.5067 ±1.6362 | -0.1577 ± 0.1209 |
| MAE | 0.3818 | 0.1699 | 0.0668 |
| RMSE | 6.5596 | 2.9920 | 1.2786 |
| NRMSE | 0.3175 | 0.1448 | 0.06189 |
| P-value of T-test | <0.0001 | <0.0001 | 0.6251 |
| Median | 17.5 vs. 24.28 | 17.5 vs. 19.7125 | 17.5 vs. 17.5007 |
| Median difference Δ | -6.78 | -2.2125 | -0.0007 |
| Median \|Δ\| | 0.5246 | 0.4725 | 0.4407 |
| Pearson $R_p$ | 0.8557 | 0.9204 | 0.9511 |
| Pearson $R^2_p$ | 0.7322 | 0.8471 | 0.9046 |
| Spearman $R_s$ | 0.8517 | 0.9155 | 0.9473 |
| Concordance $R_c$ | 0.4227 | 0.7465 | 0.9492 |

The percent of true PDUR using 30 min post-dialysis sample (true $PDUR_{30}$) was 17.4196% ± 4.1149% (median 17.5%) with a coefficient of variation (CV) of 23.6%. PDUR estimated by Smye, Daugirdas and ANFDIAC system were 23.70% ± 4.3896%, 19.926% ± 3.4908% and 17.5774% ± 3.9124% respectively. The box plot comparison between PDUR methods is shown in Fig. 24.9. The box plot is a convenient way of graphically depicting groups of numerical data through their five-number summaries (the smallest observation (sample minimum), lower quartile, median, upper quartile, and largest observation (sample maximum).

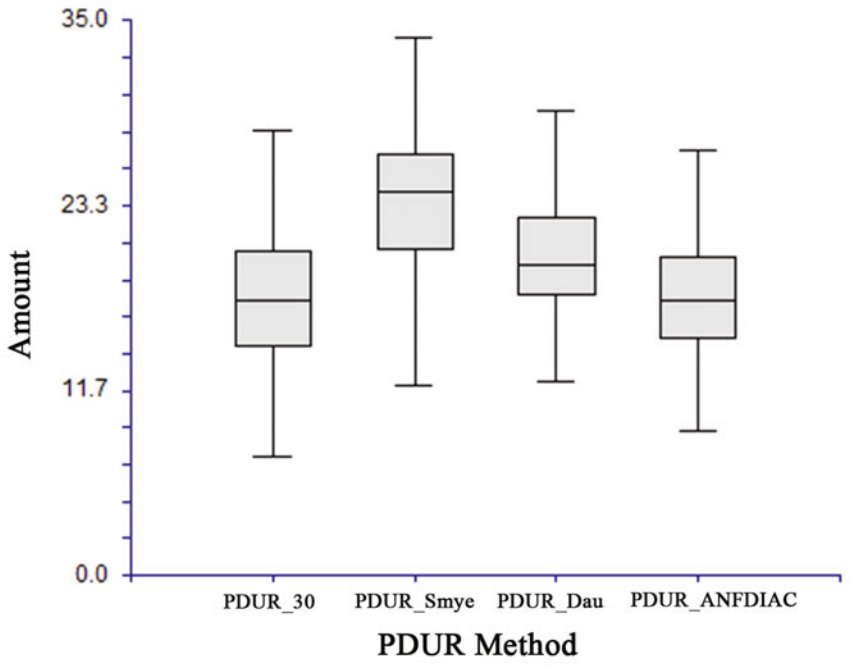


**Fig. 24.9** Box plot comparison between True $PDUR_{30}$ and other prediction methods.

Statistically significant differences were found between true $PDUR_{30}$ and $PDUR_{Smye}$ ($P < 0.0001$). Also, comparisons between true $PDUR_{30}$ and $PDUR_{Dugirdas}$ showed significant difference ($P < 0.0001$). There is no statistically significant difference was found between true $PDUR_{30}$ and $PDUR_{ANFDIAC}$ ($P = 0.6251$). The Smye and Daugirdas methods used in the experimental design slightly overestimated the urea rebound (median $\Delta$=-6.78 and $\Delta$ =-2.2125 respectively), leading to an underestimation of $_{eq}$(Kt/V). The Smye method resulted in a relatively large absolute error of PDUR than Daugirdas method (0.3818 vs. 0.1699) respectively. There was significant correlation between true $PDUR_{30}$ and $PDUR_{Smye}$ ($R_p$=0.8557 & $R_s$=0.8517), true $PDUR_{30}$ and $PDUR_{Dugirdas}$ ($R_p$=0.9204 & $R_s$=0.9155). Strong positive correlation was found between true $PDUR_{30}$ and $PDUR_{ANFDIAC}$ ($R_p$=0.9511 & $R_s$=0.9473) as shown in Fig. 24.10. The regression analysis between $PDUR_{30}$ and other methods are summarized in Table 24.7.

**Table 24.7** Regression analyses between true urea rebound determined using the 30-min sample $(PDUR)_{30}$ and other methods.

| Parameter | Regression analysis between $PDUR_{30}$ and other methods | | |
|---|---|---|---|
| | **True $PDUR_{30}$ vs. $PDUR_{Smye}$** | **True $PDUR_{30}$ vs. $PDUR_{Daugirdas}$** | **True $PDUR_{30}$ vs. $PDUR_{30\text{-}ANFDIAC}$** |
| **Intercept (SE)** | 7.3675 (0.5252) | 6.3256 (0.3383) | 1.8247 (0.2995) |
| | T-value = 14.0290 | T-value = 18.6981 | T-value = 6.0934 |
| | P-value < 0.0001 | P-value <0.0001 | P-value < 0.0001 |
| **Slope (SE)** | 0.9332 (0.0293) | 0.7808 (0.0189) | 0.9043 (0.0167) |
| | T-value = 31.8021 | T-value = 41.3064 | T-value = 54.0464 |
| | P-value < 0.0001 | P-value = 0.0001 | P-value < 0.0001 |
| **Regression Equation** | $PDUR_{Smye}$ = 7.3675 + 0.9332* $PDUR_{30}$ | $PDUR_{Daug}$ = 6.3256 + 0.7808 * $PDUR_{30}$ | $PDUR_{30\text{-}ANFDIAC}$ = 1.8247+0.9043*$PDUR_{30}$ |

SE: Standard Error

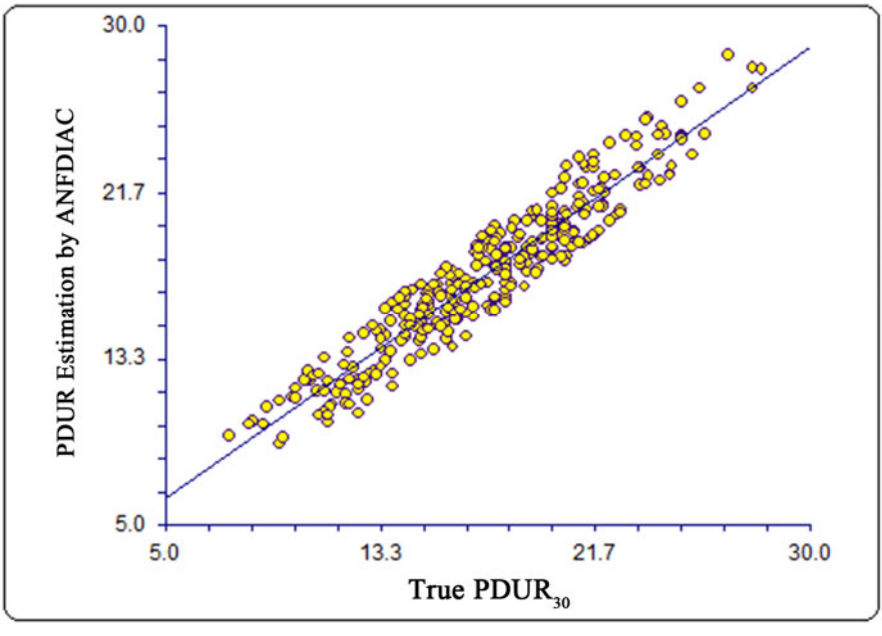


**Fig. 24.10** Association between the true $(PDUR)_{30}$ and the calculated PDUR by ANFDIAC.

Measurement biases of -6.203, -2.5067 and -0.1577 were observed for $PDUR_{Smye}$, $PDUR_{Dugirdas}$ and $PDUR_{ANFDIAC}$ respectively. Limits of agreement for $PDUR_{ANFDIAC}$ (-2.6 to +2.3) was comparably lesser than those for $PDUR_{Smye}$ (-10.4 to -2.0) and $PDUR_{Dugirdas}$ (-5.7 to +0.7). The limits of agreement indicate a possible error of minus 10.4% to minus 2% when using $PDUR_{Smye}$ instead of the measured $PDUR_{30}$, which is unacceptable from a routine point of view as shown in Fig. 24.11. When $PDUR_{Dugirdas}$ is used instead of the measured $PDUR_{30}$, error would fall between -5.7% and +0.7% as shown in Fig. 24.12, and if $PDUR_{ANFDIAC}$ is used, it would be -2.6% and +2.3% as shown in Fig. 24.13, which falls into acceptable margins for routine estimation. The concordance agreement correlation coefficient for Daugirdas method and the estimated bias correction factor is higher than Smye method. The agreement coefficients $R_p$, $R_s$, and $R_c$ were significantly higher and med $|\Delta|$ significantly smaller ($P < 0.05$) for the ANFDIAC than for the Smye and Daugirdas methods. Our results suggest that use of the proposed neuro-fuzzy system to estimate urea rebound is a useful means of estimating the $_{eq}$(Kt/V).

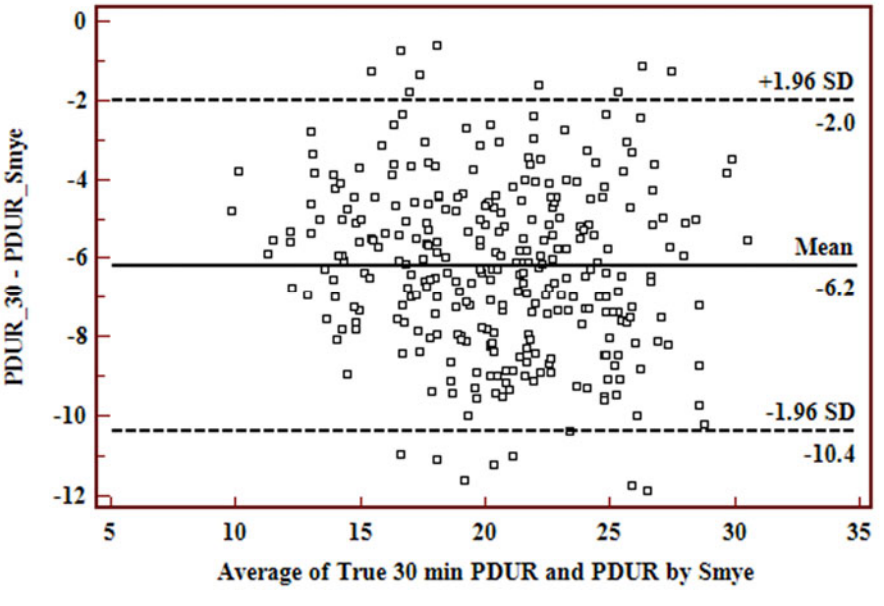


**Fig. 24.11** Bland-Altman plot showing the mean of ($PDUR_{30}$ and $PDUR_{Smye}$) compared with the difference between means.

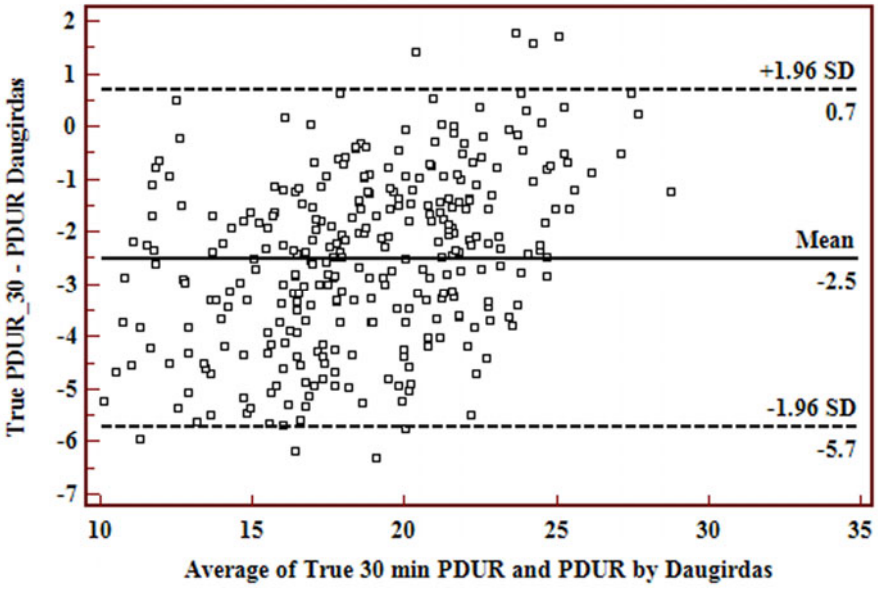


**Fig. 24.12** Bland-Altman plot showing the mean of ($PDUR_{30}$ and $PDUR_{Dau}$) compared with the difference between means.

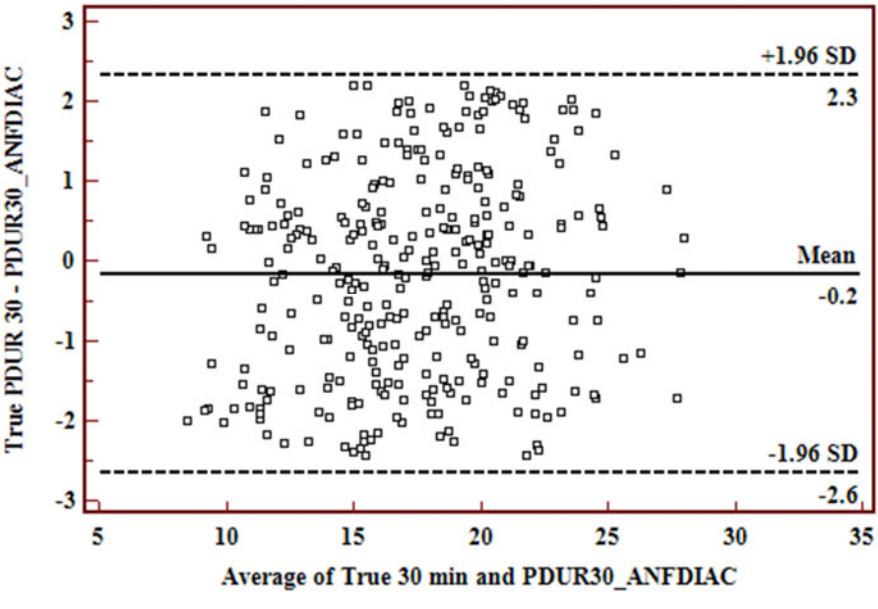


**Fig. 24.13** Bland-Altman plot showing the mean of ($PDUR_{30}$ and $PDUR_{30\text{-}ANFDIAC}$) compared with the difference between means.

### 24.6.6.2 Comparison of Estimated $_{eq}$(Kt/V) by ANFDIAC and Other Traditional Methods

Since Kt/V calculation is based in part on the post-hemodialysis BUN level, urea rebound has a significant impact upon the calculation of the delivered dose of hemodialysis. While single-pool kinetic modeling $_{sp}$(Kt/V) uses a convenient 30-s post-dialysis BUN sample, it does not take urea rebound into account. Double-pool modeling $_{eq}$(Kt/V) uses an equilibrated BUN ($C_{eq}$) and is the best reflection of the true urea mass removed by hemodialysis. However, it is inconvenient for patients and costly to the dialysis unit to wait 30 min or 1 hour post-dialysis to obtain a $C_{eq}$ sample. Several formulas have been developed to approximate double-pool equilibrated Kt/V without obtaining a measured $C_{eq}$. The different $_{eq}$(Kt/V) calculations were compared with true $_{eq}(Kt/V)_{30}$ which was considered to be the reference method as shown in Table 24.8. $_{eq}(Kt/V)_{30}$ was 1.179±0.1682 and had been compared with (a) $_{eq}(Kt/V)_{Smye}$, 1.127±0.1681; (b) $_{eq}(Kt/V)_{Dau}$, 1.1686±0.1635; (c) $_{eq}(Kt/V)_{30\text{-}ANFDIAC}$, 1.1864±0.1675; (d) $_{eq}(Kt/V)_{Mad}$, 1.1617±0.1571; and (e) $_{eq}(Kt/V)_{Tatt}$, 1.1884±0.1651. The box plot comparison between $_{eq}$(Kt/V) methods is shown in Fig. 24.14. Statistically significant difference were found between true $_{eq}(Kt/V)_{30}$ and $_{eq}(Kt/V)_{Smye}$ (P=0.0001). There are no statistically significant differences were found when using $_{eq}(Kt/V)_{Dau}$ (P = 0.4331), $_{eq}(Kt/V)_{30\text{-}ANFDIAC}$ (P = 0.5842), $_{eq}(Kt/V)_{Mad}$ (P = 0.1863) and $_{eq}(Kt/V)_{Tatt}$ (P = 0.4819) for predicting true $_{eq}(Kt/V)_{30}$. In an attempt to answer the question of which is the best simplified formula, we first tried to catalogue the methods yielding the greatest differences. It is observed from table 5 that a good correlation does not (necessarily) a good biological agreement make. Therefore, for the first time this question is addressed using the correct statistical approach. A more stringent test is to analyze how well the difference between single-pool Kt/V and $_{eq}$(Kt/V), or the ΔKt/V, can be predicted from each method. So, which formula can be recommended? For the group as a whole the biggest difference from true $_{eq}(Kt/V)_{30}$ mean value was obtained using Smye method (0.0520 ± 0.0231).

**Table 24.8** Comparisons of equilibrated Kt/V $_{eq}$(Kt/V) derived from different methods with the true equilibrated Kt/V determined using the 30-min post-dialysis sample $_{eq}(Kt/V)_{30}$.

| **Agreement** | **Comparisons with true eq(Kt/V)$_{30}$** | | | | |
|---|---|---|---|---|---|
| **Comparison** | **$_{eq}(Kt/V)_{30}$ vs. $_{eq}(Kt/V)_{Smye}$** | **$_{eq}(Kt/V)_{30}$ vs. $_{eq}(Kt/V)_{Dau}$** | **$_{eq}(Kt/V)_{30}$ vs. $_{eq}(Kt/V)_{30\text{-}ANFDIAC}$** | **$_{eq}(Kt/V)_{30}$ vs. $_{eq}(Kt/V)_{Mad}$** | **$_{eq}(Kt/V)_{30}$ vs. $_{eq}(Kt/V)_{Tatt}$** |
| **Mean±SD** | 1.179 ± 0.1682 vs. 1.127 ± 0.1681 | 1.179 ± 0.1682 vs. 1.1686 ± 0.1635 | 1.179 ± 0.1682 vs. 1.1864 ± 0.1675 | 1.179 ± 0.1682 vs. 1.1617 ± 0.1571 | 1.179 ± 0.1682 vs. 1.1884 ± 0.1651 |
| **Mean Bias** | 0.0520 ± 0.0231 | 0.01045 ± 0.0178 | -0.0074 ± 0.0157 | 0.0173 ± 0.0257 | -0.01 ± 0.0176 |
| **ΔKt/V** | 0.2422 ± 0.0397 | 0.2007 ± 0.0348 | 0.1829 ± 0.0367 | 0.2075 ± 0.0349 | 0.1908 ± 0.0325 |
| **MAPE** | 0.0450 | 0.0142 | 0.0124 | 0.0210 | 0.0144 |
| **RMSE** | 0.0568 | 0.0206 | 0.0173 | 0.0309 | 0.0198 |
| **NRMSE** | 0.0648 | 0.0235 | 0.0197 | 0.0353 | 0.0226 |
| **P-value of T-test** | 0.0001 | 0.4331 | 0.5842 | 0.1863 | 0.4819 |
| **Median** | 1.2005 vs. 1.1381 | 1.2005 vs. 1.1847 | 1.2005 vs. 1.2047 | 1.2005 vs. 1.1777 | 1.2005 vs. 1.1991 |
| **Median Δ** | 0.0624 | 0.0158 | -0.0042 | 0.0228 | 0.0014 |
| **Median \|Δ\|** | 0.0044 | 0.0027 | 0.0024 | 0.0043 | 0.0031 |
| **$R_p$** | 0.9906 | 0.9947 | 0.9956 | 0.9898 | 0.9946 |
| **$R^2_p$** | 0.9812 | 0.9894 | 0.9912 | 0.9797 | 0.9892 |
| **$R_s$** | 0.9811 | 0.9903 | 0.9921 | 0.9763 | 0.9896 |
| **$R_c$** | 0.9452 | 0.9923 | 0.9946 | 0.9819 | 0.9928 |
| **$C_{bias}$** | 0.9542 | 0.9976 | 0.9989 | 0.9921 | 0.9982 |

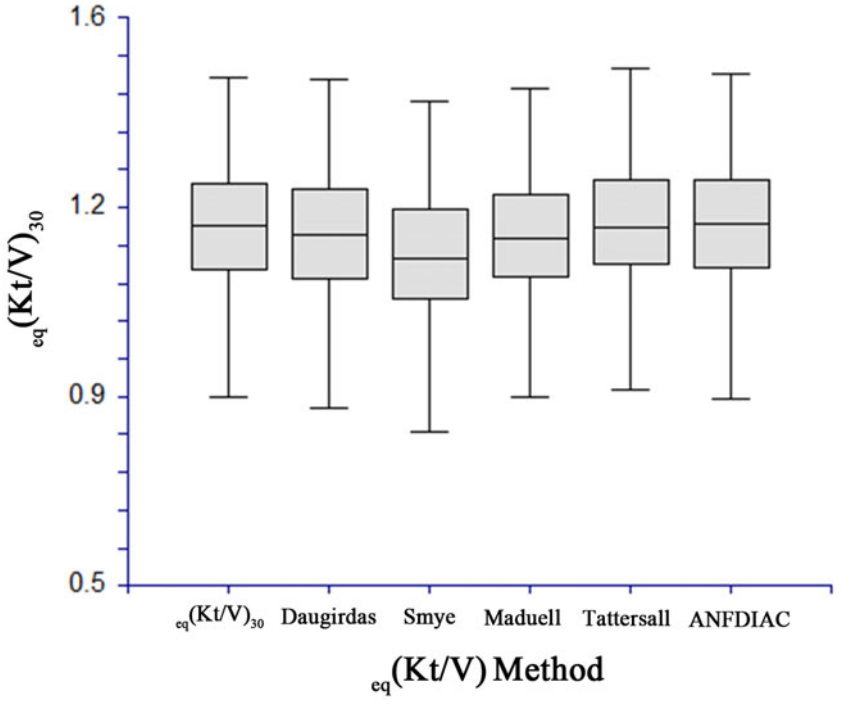


**Fig. 24.14** Box plot comparisons of equilibrated Kt/V derived from different methods with the true equilibrated Kt/V at 30-minute post-dialysis.

The best agreement was found with ANFDIAC system $_{eq}(Kt/V)_{30\text{-}ANFDIAC}$ because it achieved the lowest MAE and RMSE which implies that the two methods may be used interchangeably. Also, the agreement coefficients $R_p$, $R_s$, and $R_c$ were significantly higher and med |Δ| significantly smaller ($P < 0.05$) for the ANFDIAC system. The Bland and Altman agreement analysis shows that one can expect a minimum difference from true $_{eq}(Kt/V)_{30}$ values of 0.006–0.097 using Smye method, -0.024 to 0.045 using Daugirdas method as shown in Fig. 24.15, -0.038 to 0.023 using ANFDIAC system as shown in Fig. 24.16, -0.033 to 0.068 using Maduell method and limit of agreement from -0.044 to 0.025 using Tattersall method. The mean value of ANF-DIAC system was almost 1.24% higher than true $_{eq}(Kt/V)_{30}$ but this difference was not statistically significant. The Smye method result in significant overestimation of the true $C_{eq}$, and as a consequence a significant underestimation of the true $_{eq}(Kt/V)_{30}$ value. The mean ΔKt/V (difference between single-pool and equilibrated Kt/V) for the five different methods for calculating $_{eq}(Kt/V)$

(Smye, Daugirdas, ANFDIAC, Maduell and Tattersall) were respectively 0.2422±0.0397, 0.2007±0.0348, 0.1829±0.0367, 0.2075±0.0349 and 0.1908±0.0325. It is noted that the largest ΔKt/V was found using Smye method and the smallest ΔKt/V was found using ANFDIAC and Tatersall methods. The statistical analysis also revealed that it is reasonable to say that the Tattersall and Daugirdas methods consistently more closely approached the true $_{eq}$(Kt/V) results. The Daugirdas rate equation is simple and can be easily solved using only a standard calculator, which makes it practical for use in both very small and large dialysis units. The high correlation ($R_p$=0.9947 and $R_s$= 0.9903) between the true $_{eq}(Kt/V)_{30}$ and the rate equation in our study indicates that PDUUR is a function of the rate of dialysis (K/V). As shown, Kt/V uncorrected for rebound significantly overestimated effective dialysis dose, particularly with high efficiency regimens, whereas, the use of either equilibrated urea concentration or its estimate using intradialytic sample allowed accurate estimation of double-pool Kt/V.

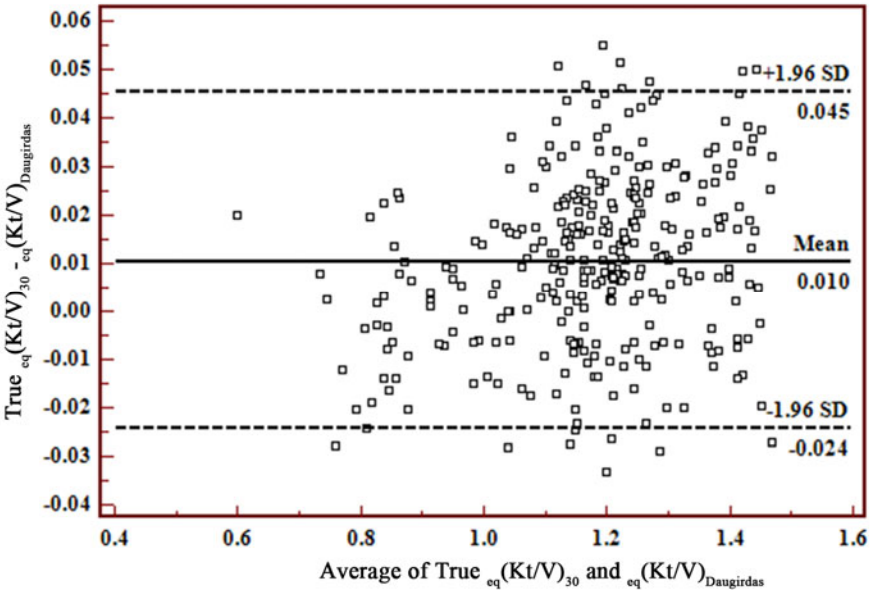


**Fig. 24.15** Bland-Altman plot showing the mean of {$_{eq}(Kt/V)_{30}$ and $_{eq}(Kt/V)_{Daugirdas}$} compared with the difference between means

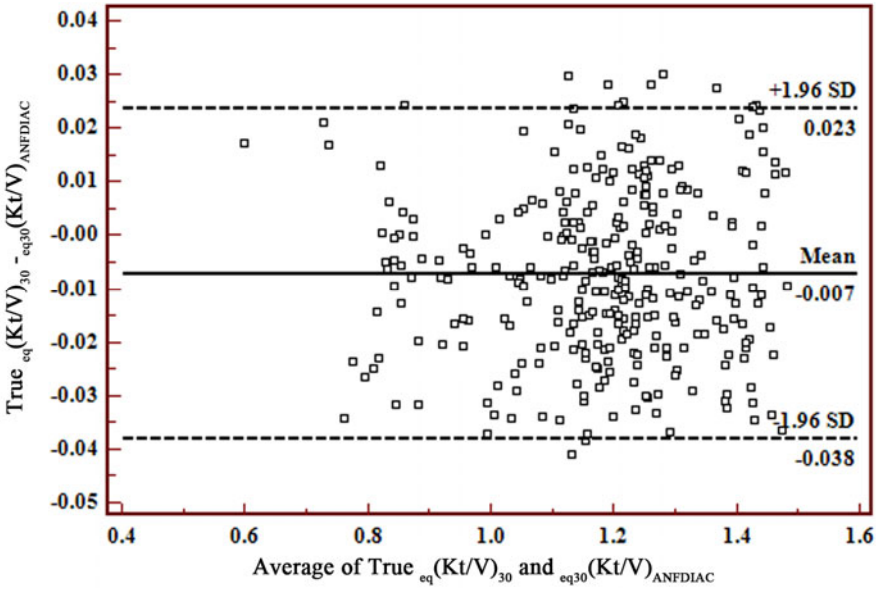


**Fig. 24.16** Bland-Altman plot showing the mean of ($_{eq}Kt/V_{30}$ and $_{eq}Kt/V_{30\text{-}ANFDIAC}$) compared with the difference between means.

## 24.7 OTHER NEURO-FUZZY MODELS FOR DIALYSIS PATIENTS

Song and Kasabov developed a novel neural fuzzy inference method - NFI for transductive reasoning systems (Song and Kasabov 2005, 2006). The transductive NFI method is applied for the prediction of the Glomerular filtration rate (GFR) to determine renal function. The accurate evaluation of renal function is fundamental to sound nephrology practice. The early detection of renal impairment will allow for the institution of appropriate diagnostic and therapeutic measures, and potentially maximize preservation of intact nephrons. However, the prediction of GFR with the use of the existing formulas that constitute global and fixed models, can be misleading as to the presence and progression of renal disease (Levey et al. 1999). Therefore, the transductive NFI method is applied for the prediction of the GFR through the construction of an individual model for each new patient. Transductive inference methods estimate the value of a potential model (function) only in a single point of the space (the new data vector) utilizing additional information related to this point (Vapnik 1998). This approach seems to be more appropriate for clinical and medical applications of learning systems, where the focus is not on the model, but

on the individual patient (Song and Kasabov 2005). Song and Kasabov used the NFI on a GFR data set (447 samples), collected from hospitals in New Zealand and Australia and they have obtained more accurate results than with the use of the MDRD formula or the use of other connectionist and statistical techniques.

Chen et al (2007) constructed a coactive neuro-fuzzy inference system (CANFIS) (Mizutani and Jang 1995), which is an advanced combination technology of fuzzy logic and neural network to investigate the feasibility of quantitatively predicting plasma parathyroid hormone concentration for hemodialysis patients. The CANFIS model integrates adaptable fuzzy inputs with a modular neural network to rapidly and accurately approximate complex functions. Patients enrolled in the study were 121 stable hemodialysis patients from an independent dialysis unit of Buddhist Dalin Tzu Chi General Hospital, Chiayi County, a teaching hospital in western Taiwan. These patients served as the training group (Unit A). In addition, 32 stable hemodialysis patients from an independent dialysis unit of Taitung Hospital, Taitung City, a general hospital in eastern Taiwan were enrolled as the test group (Unit B). Chen et al used NeuroSolutions 4.32 (NeuroDimension, Inc., Gainesville, FL, USA) to construct a CANFIS network using a training set of patients from dialysis unit. Plasma PTH concentration for each patient predicted by CANFIS (PTH-CANFIS) was compared with the actual PTH measurement at dialysis unit B measured by radioimmunoassay (RIA). Plasma PTH concentrations measured by RIA and predicted by CANFIS were 179.04 ± 38.18 ng/l and 179.34 ± 37.76 ng/l, respectively ($p = 0.15$). The CANFIS was able to precisely estimate plasma PTH concentrations in hemodialysis patients. These results suggest that the neuro-fuzzy technology, based on limited clinical parameters, is an excellent alternative to RIA for accurately predicting plasma PTH concentration in hemodialysis patients.

## 24.8 CONCLUSION

Predictive modeling is the process of identifying a model of an unknown or complex process from numerical data. Due to the inherent complexity of many real processes, conventional modeling techniques have proved to be too restrictive. Recently, the hybrid approach to predictive modeling has become a popular research focus. A novel hybrid system combining different soft computing paradigms such as neural networks and fuzzy systems has been developed for predictive modeling of dialysis variables in order to estimate the equilibrated dialysis dose ($_{eq}$Kt/V), without waiting for 30-60 min post-dialysis to get the

equilibrated urea sample which is inconvenient for patients and costly to the dialysis unit. The aim of using a neuro-fuzzy network is to find, through learning from data, a fuzzy model that represents the process underlying the data. In neuro-fuzzy models, connection weights, propagation and activation functions differ from common neural networks. Although there are a lot of different approaches, the term neuro-fuzzy is restricted to systems which display the following properties:

- A neuro-fuzzy system is a fuzzy system that is trained by learning algorithm (usually) derived from neural network theory. The (heuristic learning procedure operates on local information, and causes only local modifications in the underlying fuzzy system. The learning process is not knowledge based, but data driven.
- A neuro-fuzzy system can be viewed as a special 3-layer feedforward neural network. The units in this network use *t*-norms or *t*- cononrms instead of the activation functions usually used in neural networks.
  The first layer represents input variables, the middle (hidden) layer represents fuzzy rules and the third layer represents output variables. Fuzzy sets are encoded as (fuzzy) connection weights. Some neuro-fuzzy models use more than 3 layers, and encode fuzzy sets as activation functions. In this case, it is usually possible to transform them into 3-layer architecture. This view of fuzzy systems illustrates the data flow within the system and its parallel nature. However this neural network view is not a prerequisite for applying a learning procedure, it is merely a convenience.
- A neuro-fuzzy system can always (i.e. before, during and after learning) be interpreted as a system of fuzzy rules. It is both possible to create the system out of training data from scratch, and it is possible to initialize it by prior knowledge in form of fuzzy rules.
- The learning procedure of a neuro-fuzzy system takes the semantical properties of the underlying fuzzy system into account. This result in constraints on the possible modifications of the system's parameters.
- A neuro-fuzzy system approximates an n-dimensional (unknown) function that is partially given by the training data. The fuzzy rules encoded within the system represent vague samples, and can be viewed as vague prototypes of the training data. A neuro-fuzzy system should not be seen as a kind of (fuzzy) expert system, and it has nothing to do with fuzzy logic in the narrow sense.

Besides accuracy, model transparency is the most important goal of the proposed modeling methodology, which supports this feature at different levels. The first level of transparency supported is the ability to represent the knowledge characterizing the relations between the data in a natural manner, e.g. as a series of linguistic fuzzy rules, which is common to all neuro-fuzzy approaches. The second level of transparency required to models derived from data is a simple structure. Indeed, the use/reliability of a fuzzy model can become limited with too many fuzzy rules. Hence a compromise between model complexity and model accuracy should be found by identifying parsimonious structures, which aid handling and comprehension of the fuzzy rule base. Simple structures also could be beneficial in improving the model generalization capabilities. A further level of model transparency is a truly linguistic representation of the produced fuzzy rules. By supporting these various levels of transparency, the proposed neuro-fuzzy modeling methodology significantly aids the process of knowledge discovery and model validation. With a data-driven methodology, like the proposed one, fundamental to the success of the modeling process is the availability of good empirical data. When data is limited and/or poorly distributed, the modeling task can easily become unmanageable. This reinforces the importance of the human for injecting a priori knowledge, expert judgment and intuition in to the modeling process. The developed methodology enables the incorporation of a-priori knowledge into the modeling process so as to compensate for the lack of data. When a-priori knowledge provided by the expert takes the form of qualitative descriptions of the process underlying the data, it can be easily inserted into the modeling process by building and pre-weighting the neuro-fuzzy network, giving an initial model which can be later refined in the presence of training data. These are the more appealing features of the proposed methodology.

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## ESSAY QUESTIONS

1. Discuss the properties of neural networks and fuzzy Systems
2. List the main classification of neuro-fuzzy systems
3. What does ANFIS stand for?
4. What are the features of ANFIS?
5. List the different phases that must be carried out in fuzzy modeling
6. Comprae between the two passes in the hybrid learning algorithm
7. What are the two used techniques in ANFIS for updating parameters and searching for the optimum?
8. How big should the set of training data be?
9. Describe some of the common methods for updating parameters in neuro-fuzzy systems.
10. List some of practical considerations in parameter selection for neuro-fuzzy models.

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. Who is the founder of ANFIS?
   A. Mamdani
   B. Sugeno
   C. Jang JSR
   D. Tsukamoto

2. In the a typical architecture of an ANFIS, a circle indicates...
   A. Fixed node
   B. Adaptive node

3. In the a typical architecture of an ANFIS, a square indicates...
   A. Fixed node
   B. Adaptive node

4. First order Sugeno ANFIS architecture has a total of...
   A. 2 layers
   B. 3 layers
   C. 4 layers
   D. 5 layers

5. The first hidden layer in ANFIS is responsible for...
   A. Normaliztion of the rules strengths
   B. Mapping of the input variable relatively to each membership functions.
   C. Calculating the antecedents of the rules
   D. Calculating the consequents of the rules

6. The...hidden layer of ANFIS normalizes the rules strengths
   A. First
   B. Second
   C. Third
   D. Forth
   E. Fifth

7. The operator T-norm is applied in the...hidden layer of ANFIS to calculate the antecedents of the rules.
   A. First
   B. Second
   C. Third
   D. Forth
   E. Fifth

8. The consequents of the rules are determined in the...hidden layer of ANFIS
   A. First
   B. Second
   C. Third
   D. Forth
   E. Fifth

9. A neuro-fuzzy system can be viewed as a special…feedforward neural network.
   A. 2-layer
   B. 3-layer
   C. 4-layer
   D. 5-layer

10. In the sstructural identification phase of neuro-fuzzy modelling...
    A. The number of rules is determined
    B. The number of fuzzy sets used to partition each variable in the input and output space is determined so as to derive linguistic labels.
    C. Fine adjustment of the position of all membership functions together with their shape is obtained.
    D. A and C
    E. A and B
    F. B and C
    G. A, B, C

11. In the parametric identification phase of neuro-fuzzy modelling...
    A. The number of rules is determined
    B. The number of fuzzy sets used to partition each variable in the input and output space is determined so as to derive linguistic labels.
    C. Fine adjustment of the position of all membership functions together with their shape is obtained.
    D. A and C
    E. A and B
    F. B and C
    G. A, B, C

12. In the forward pass of a hybrid learning algorithm, the algorithm uses...method to identify the consequent parameters on the layer 4.
    A. Backpropagation
    B. least-squares
    C. gradient descent

13. In the backward pass of a hybrid learning algorithm, the errors are propagated backward and the premise parameters are updated by...
    A. Backpropagation
    A. least-squares
    B. gradient descent

14. The computation complexity of the least squares estimate is…than that of the gradient descent.

A. Higher
B. Lower

15. If five inputs are selected as the data set for ANFIS and three membership functions (MFs) are assigned to each linguistic variable, then the ANFIS structure will contain...fuzzy rules.

A. 32
B. 64
C. 128
D. 243

16. If four inputs are selected as the data set for ANFIS and three membership functions (MFs) are assigned to each linguistic variable, then the ANFIS structure will contain...premise parameters..

A. 32
B. 36
C. 46
D. 64

17. If four inputs are selected as the data set for ANFIS and two membership functions (MFs) are assigned to each linguistic variable, then the ANFIS structure will contain...consequent parameters..

A. 32
B. 36
C. 16
D. 64

18. For interpretable neuro-fuzzy model, the following should be considered...

A. More Parameters
B. More Rules
C. TSK models
D. All of the above
E. Non of the above

19. For accurate neuro-fuzzy model, the following should be considered...
    A. Few Parameters
    B. Few Rules
    C. Mamdani Models
    D. All of the above
    E. Non of the above

20. ANFDIAC system is is developed by Azar et al (2008) in the form of a…fuzzy inference system.

    A. Zero-order Takagi-Sugeno-Kang
    B. First-order Takagi-Sugeno-Kang
    C. Mamdani

Chapter (25)

# Renal System Dynamics Modeling

Geoff McDonnell, Ahmad Taher Azar, and J. Chris White

**CHAPTER OUTLINES**

- A brief overview of systems change, concept maps and computer models.
- Models of systems as theory and data.
- A brief overview of system dynamics modeling.
- The tools of system dynamics.
- The system dynamics modeling methodology
- A system dynamics model of dialysis and transplant patients.
- Conclusion and future directions for SD models in renal disease management.

**CHAPTER OBJECTIVES**

- Describe the concept of system dynamics.
- Discuss the modeling methodology of system dynamics approach.
- Discuss a system dynamics model of dialysis and transplant patients

**KEY TERMS**

- System dynamics
- Policy Resistance
- Modeling Methodology
- Mental models
- Feedback
- Causal loop diagram
- Stock and Flow diagram
- Model Validation
- Dialysis
- Transplant
- Hemodiadynamics
- Kidney replacement therapy
- Chronic Kidney Disease

**ABSTRACT**

System dynamics (SD) is a powerful simulation method that is ideal for modeling human processes, as well as many processes that occur within the healthcare system. The SD approach has been used and validated extensively in a wide array of fields and industries. This chapter will provide an overview of the SD modeling and simulation methodology as well as provide more detailed steps related to building and validating SD models. Finally, this chapter will show a specific set of SD models related to dialysis, Kidney and Transplant Patients, Hypertension Patient Flow, and Organ Donation and Transplantation.

A.T. Azar (Ed.): Modeling and Control of Dialysis Systems, SCI 405, pp. 1275–1320.
springerlink.com 

## 25.1 A BRIEF OVERVIEW OF SYSTEMS CHANGE, CONCEPT MAPS AND COMPUTER MODELS

**System** is derived from the word for composition and can be thought of as a collection of interactions among component parts (Blanchard and Fabrycky 1998). There is a reason or purpose for the system. Systems are described by their structure (what they are) and behaviour (what they do), caused by the interactions among their component parts and the environment in which the system operates. Systems include subsystems, which are also fully functioning systems. Therefore a system has parts, and can also be part of a system. The structure and behaviour of systems help us make sense of the world we live in. They exhibit some common properties as shown in Table 25.1.

**Table 25.1** Common Systems Characteristics

| Most systems, including health systems, are: | |
|---|---|
| ▸ Self-organizing | ▸ Non-linear |
| ▸ Constantly changing | ▸ History dependent |
| ▸ Tightly linked | ▸ Counter-intuitive |
| ▸ Governed by feedback | ▸ Resistant to change |

## 25.2 MODELS OF SYSTEMS AS THEORY AND DATA

Models can be considered as a mix of theoretically linked concepts and empirical data from real world observations (see Fig. 25.1). Concepts are perceived patterns or regularities based on past experience to describe objects or explain events. Concepts are linked to form propositions that describe structures often in terms of parts and relationships. They can also explain observed patterns of events or change in terms of deeper understanding of how things work or why things change.

### 25.2.1 Concept and Mind Maps

Over the past four decades concept and mind maps have organized the knowledge that can be used to answer focused questions about the world. There are no separate systems. The world is a continuum. Where to draw a boundary around a system depends on the questions to be asked.

**Mind maps** are a simple tree of linked concepts where the links are usually unlabeled. They highlight hierarchies rather than networks of concepts and linking words.

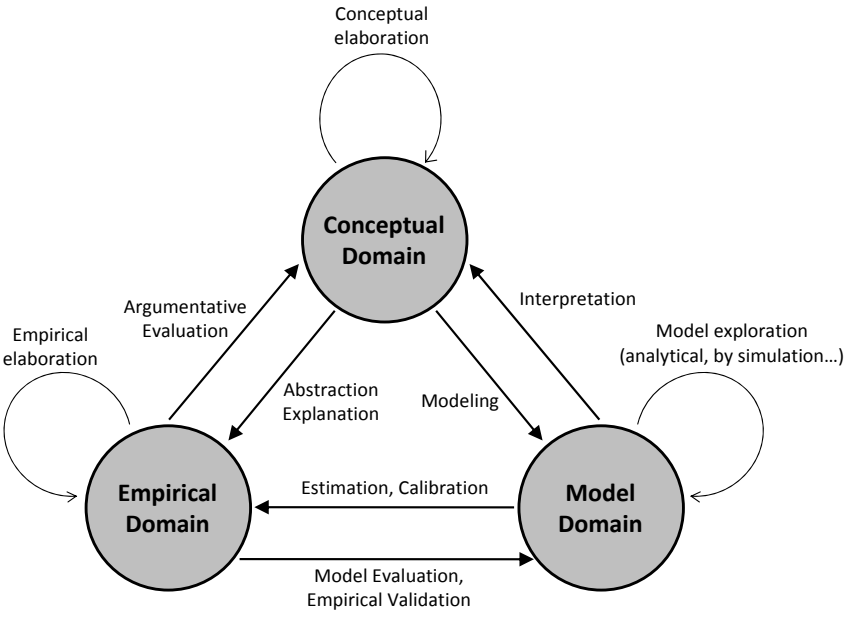



**Fig. 25.1** Models as a mix of theoretically linked concepts and empirical data from real world observations.

### 25.2.2 Mental Models

Mental models are organized knowledge structures that allow individuals to interact with their environment. Information about the structure and relationships in dynamic systems can be gleaned from mental models (Doyle and Ford 1998). Specifically, mental models allow people to predict and explain the behavior of the world around them, to recognize and remember relationships among components of the environment, and to construct expectations for what is likely to occur next (Rouse and Morris 1986). Furthermore, mental models allow people to draw inferences, make predictions, understand phenomena, decide which actions to take, and experience events vicariously (Johnson 1983). Formal representations in maps make it easier to share and improve mental models. This becomes important when facing surprises that can't be explained well by the current mental models. A related problem, common in healthcare, is disagreement among groups about the causes and solutions to chronic persistent problems. Methods and tools to surface mental models and locate the differences in perceptions, beliefs and values offer a way to improve social, technical and personal systems of health and healing. Models are

considered to be as arguments, used to persuade people to take common effective action to improve or sustain the future. Climate change modeling offers a cogent example of this process and difficulties in modeling to produce effective actions of groups with different beliefs values and incentives.

### 25.2.3 Computational Models

Computer models take conceptual map structures and convert them into behavior, i.e. moving from static snapshots to videos of changes over time. This provides a logical, consistent framework for translating structure into behaviour. Logical constructs of linked concepts can be built up piece by piece from simple propositions or hypotheses to a more complex theory of multiple propositions. Then sets of virtual experiments can be run which play out the results of future actions based on theories of causation and perception of the current situation and context (see Fig. 25.2). Rather than just predicting a train wreck, models help to decide how to intervene to avoid or mitigate the train wreck. This is the difference between scientific predictive models and models for designing and performing interventions that shape the future.

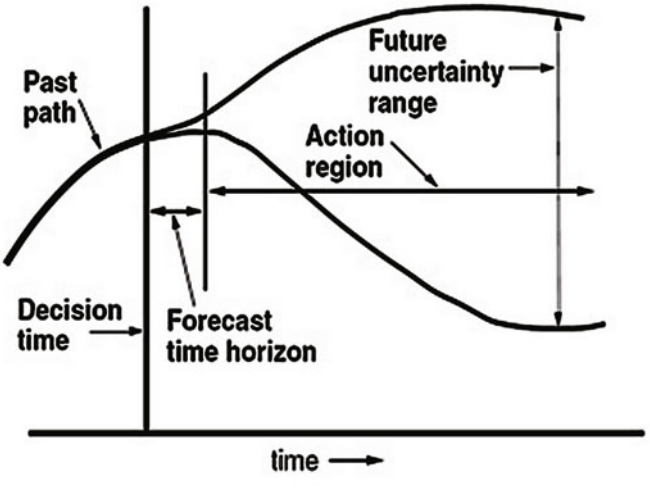



**Fig. 25.2** Watching versus shaping the future.

### 25.2.4 What Is a Good Model?

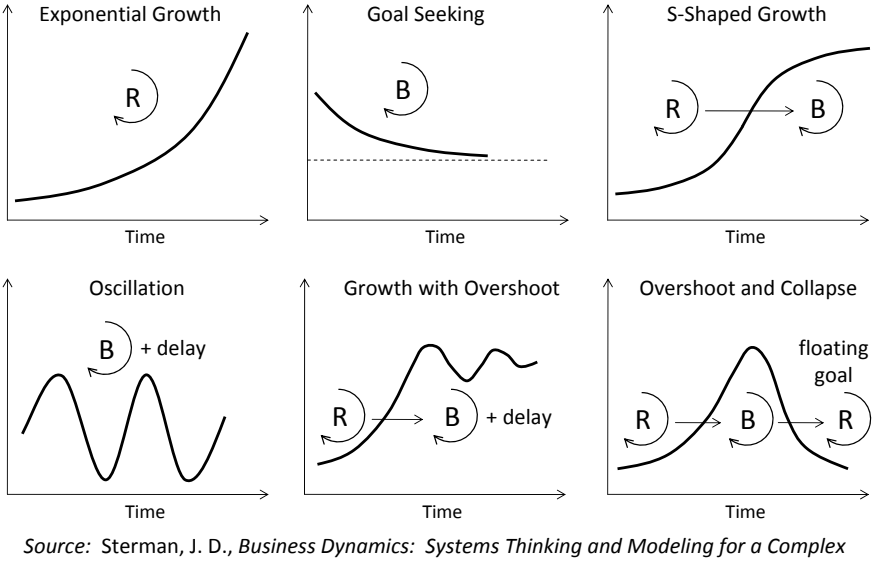
A good model is one that fits the purpose it was designed for. Common uses of models are:

- To show insights
- To build theory
- To predict the consequences of action or inaction
- To work out what data to collect in information studies
- To analyse data (including parameter estimation)

A good model has the right breadth (scope or boundary) and depth (level of detail) for its intended purpose. Sterman (2000) describes common features of good models of persistent problems that produce effective action as:

- Includes structures for all relevant causes within the model
- Explain dynamic changes over time
- Include human behavioural responses
- Show important differences (acknowledging heterogeneity)
- Are grounded in empirical testing in many settings, including learning laboratories and the real world
- Combine both quantitative and qualitative knowledge and concepts
- Have a broad boundary, a "zoom out" view
- Integrate perspectives from multiple disciplines

A good model explains puzzling behaviours as shown in Fig. 25.3.




*Source:* Sterman, J. D., *Business Dynamics: Systems Thinking and Modeling for a Complex World*, ©2000, Irwin McGraw-Hill, Boston, MA.

**Fig. 25.3** Dynamic hypothesis and fundamental models of dynamic behaviour.

## 25.3 A BRIEF OVERVIEW OF SYSTEM DYNAMICS MODELING

### 25.3.1 Systems Principles and Perspective

System dynamics (SD) is an approach to problem solving initially developed at MIT by Jay Wright Forrester in the 1950s with the establishment of the MIT System Dynamics Group (Forrester 2007a). He had a background in computer hardware and feedback control systems based on servo-mechanisms for gun and missile guidance. During the late 1950s and early 1960s, Forrester and a team of graduate students moved the emerging field of system dynamics from the hand-simulation stage to the formal computer modeling stage (Forrester 1961; 1969). In 1983, the International System Dynamics Society was formed (http://www.systemdynamics.org). Even though the Society was officially acclaimed into existence in 1983, it took some years to get its operations in order (Andersen et al. 2007). Since the early 1980s, SD applications have expanded to a very wide spectrum, including supply chains, project management, educational problems, energy systems, sustainable development, politics, psychology, internal medicine, health care and many other areas (Forrester, 2007a). Significant methodological advances have also been made in the last two decades. Perhaps the most significant one in the 1980s was the emergence of user-friendly simulation software with advanced graphical user interfaces such as STELLA (www.iseesystems.com), Powersim (www.powersim.com), and Vensim (www.vensim.com). Interactive simulation games have been effectively used by John Sterman and others (Sterman 1994) to test various decision rules by direct experimentation. Games can be used in many different ways to facilitate learning. They can be used to give participants a shared vocabulary or common experience of some dynamic problem. They can illustrate the dynamics of specific systems and show the importance of particular causal mechanisms. They give participants a chance to practice communicating with each other and working together, developing more effective team skills. They can, under very special circumstances, even be used to predict the future behavior of essentially closed systems or to predict the results of different decisions (Meadows 2007). Such "management flight simulators" have also been a door opener to introduce system dynamics to business managers. Some of the generic simulation models/games have been developed into "simulation-based case studies", an enhanced version of the traditional case studies often used in management education.

Early applications of SD in health included hospital management and medical technology, human services delivery and narcotic addiction, body

system models, diffusion of medical technologies and capacity planning. With the advent of microcomputer SD software, the application of system dynamics to health has expanded across the world since the early 1990s. Improving health is a dynamically complex problem with many contributing factors and time delays between the implementation of policy and when results are observed. A health system is "*all actors, institutions and resources that undertake health actions - where the primary intent of a health action is to improve health*" (Murry and Evans 2003). More recently there has been activity in public health, chronic disease, tobacco policy, polio eradication, as well as some process-centric simulation addressing patient flows (Wolstenholme 1999a; Gray et al. 2006; Homer and Hirsch 2006; Lane and Husemann 2007; Paich et al. 2009). Learning environments and serious games for health have become more widespread and online community learning environments using interactive web-based simulations are now available. Climate change and environmental modeling and systems biology, including the physiome project, continue to accelerate the development of virtual experiments in a variety of health and health care problems.

Simulation and modeling is now firmly established in public health, systems biology, infectious diseases, physiology and clinical skills training. Recent events include special issues of the American Journal of Public Health on systems thinking and modeling and tobacco control, seminars, video casts and an annual Institute on Systems Science and Health by the National Institutes of Health (NIH) Center for Disease Control (CDC) including system dynamics with a number of other behavioural and social sciences methods. There is growing use of SD in mental health, clinical activities and other worldwide activities publicized and encouraged by the Health Policy Special Interest Group (SIG) of the System Dynamics Society since 2003 (http://hpsig.com/index.php/Main_Page).

There has been some strengthening of systems approaches in traditional disciplines, including the areas of health policy and health economics, complex interventions in complex systems, program evaluation using critical realism frameworks (realistic evaluation), process and systems improvement in quality and safety led by Don Berwick's IHI (http://www.ihi.org/ihi) Systems frameworks for health care performance, and the social determinants of health in the WHO and funded activities in emergency preparedness and bio-security. Systems science is now recognised as a requirement for the education of the future medical professional.

In 2007, Forrester restated the goals of system dynamics in the following way (Forrester, 2007a):

> "Through an appropriate simulation model, one should know the structure causing the problem, should know how the problem is created, should have discovered a high-leverage policy that will alter behavior, should understand the reasons why the low-leverage policies will fail, should be able to explain how strongly defended policies within the system are actually the cause of troubles, and should be able to argue for better alternative policies."

The argument is often stated in terms of causal loop diagrams (CLDs), a type of influence diagram.

System dynamics is now considered as a branch of systems science which emphasizes designing better policies and management control structures based on an understanding of dynamic complexity. This explicit handling of time includes attention to sequences of actions, the pattern of forces that influence actions and time lags and delays in information processing feedbacks that affect stability. The field of system dynamics has spread very widely, but very thinly (Forrester, 2007b). Many academic programs have been started around system dynamics and have stagnated at the level of introductory courses and educational programs taught to students who have no expectation of developing expertise in the powerful professional field of nonlinear feedback systems (Kainz and Ossimitz 2002; Pala and Vennix 2005; Raia 2005; Lyneis and Stuntz 2008; Hovmand and O'Sullivan 2008; Schaffernicht and Madariaga 2010). These courses and educational programs focus on the causal structures that students develop mentally in order to understand the dynamics of complex systems (Plate 2010). Developing an appropriate mental map of cause and effect is a fundamental step in understanding the dynamics of a system (Lane 2007; Lagnado et al. 2007). At present, with system dynamics on a rather aimless plateau, the field seems to be catching its breath. The field is pursuing practices of the last many decades, but there is little evidence of a strong reach into new territory.

Donna Meadows has expressed the key features of the system dynamics view and approach in her 2008 (posthumous) book (Meadows 2008). A good system dynamics model focuses on explaining a specific problem or situation. The situation is best described by a puzzling trend over time that requires explanation and corrective action. It describes interactions among parts, especially information feedback interactions. All relevant assumptions are made explicit in the structure of the model. It takes an endogenous view

of the problem, usually by zooming out from the immediate issue, so there is a causally closed boundary involving feedbacks (rather than forcings by exogenous time series). It integrates multiple stakeholder perspectives and its key aim is to design better policies so individuals and groups can learn to take effective action. System dynamics specifically adds the dynamic dimension to the systemic perspective, with a focus on feedback and introduces the concepts of stocks and flows.

### 25.3.2 Information Feedback and Circular Causation

People perceive states of the world and act on this information based on their beliefs or mental models, including understanding of causes and effects. The logic people use to make decisions (converting information into action) that make sense in one part of a system may not be reasonable or desirable within a broader context. So the bounded rationality of each actor in a system may not lead to decisions that further the welfare of the system as a whole. The system dynamics method aims to avoid these unintended consequences of clinical policy and management interventions due to their feedback effects. These feedback effects are sometimes described as vicious or virtuous circles or cycles. Feedback is an important concept in SD (Richardson 1992). A feedback loop is a closed chain of causal connections from a stock, through a set of decisions or rules or physical laws or actions that are dependent on the level of the stock, and back again through a stock to change the stock. There are two basic types of feedback loops – positive (self-reinforcing) loops and negative (balancing) loops.

#### 25.3.2.1 Negative Feedback

Balancing or negative feedback loops are equilibrium-seeking or goal-seeking structures in systems and are both sources of stability and sources of resistance to change. This explains why large interventions can have small effects, particularly in social systems. This gridlock is called policy resistance. In the human body this resistance to change is described as homeostasis (e.g., when blood pressure or blood sugar level is kept within a narrow range despite large fluctuations in food intake and exercise).

#### 25.3.2.2 Positive Feedback

Conversely, positive feedback loops allow small interventions to have large effects. This is described as a leverage point in the systems. A common example is the trim-tab rudder in a boat, where a large rudder is made easier to move by using a small rudder. The exponential growth of a population of

rabbits in a large meadow is another example. These positive feedback effects are called runaway loops or reinforcing feedback. Reinforcing feedback loops are self-enhancing, leading to exponential growth or to runaway collapses over time.

### 25.3.3 Causal Loop Diagrams (CLDs)

Causal loop diagrams (CLDs) are an important tool for displaying the cause-and-effect interactions among key variables when developing the model of a dynamic system (Randers 1980; Richardson 1999; Sterman 2000; Binder et al. 2004). The first step when developing a CLD is to identify the key variables that describe the problem (Kim 1992). Causal loop diagrams consist of two or more causal links that connect the various elements in the model. Each link is assigned a polarity, as shown Fig. 25.4, to indicate the direction of change of the affected element with respect to the causing element (Richardson 1995).


(a) Positive link polarity


(b) Negative link polarity

**Fig. 25.4** Polarity of a causal link

The direction of the arrow indicates the direction of causality for a pair of variables. The variable at the head of the arrow is the dependent variable; the variable at the tail is the independent variable for the given pair of variables. A plus (+) sign indicates a "positive" association between the variables while a minus (−) sign indicates a "negative" association. A positive association means that an increase in the value of the independent variable leads to an increase in the value of the dependent variable. Similarly, a decrease in the value of the independent variable leads to a decrease in the value of the dependent variable. The change is in the same direction. A negative association means that an increase in the value of the independent variable leads to a decrease in the value of the dependent variable (Richardson 1995), and vice versa, a decrease in the value of the independent variable leads to an increase in the value of the dependent variable. The change is in the opposite direction. [Note: Because of the "same" and "opposite" impacts, some people prefer to label positive associations with a "S" and negative associations with an "O".] In addition to the signs on each link, a complete loop also is given a sign. The sign for a particular

loop is determined by counting the number of minus (−) signs on all the links that make up the loop. Specifically, A feedback loop is called ***positive***, indicated by a + sign in parentheses, if it contains an *even number* of negative causal links. A feedback loop is called ***negative***, indicated by a − sign in parentheses, if it contains an *odd number* of negative causal links. Thus, the sign of a loop is the algebraic product of the signs of its links (Kirkwood 1998). Often a small looping arrow is drawn around the feedback loop sign to more clearly indicate that the sign refers to the loop, as shown in Fig. 25.5.

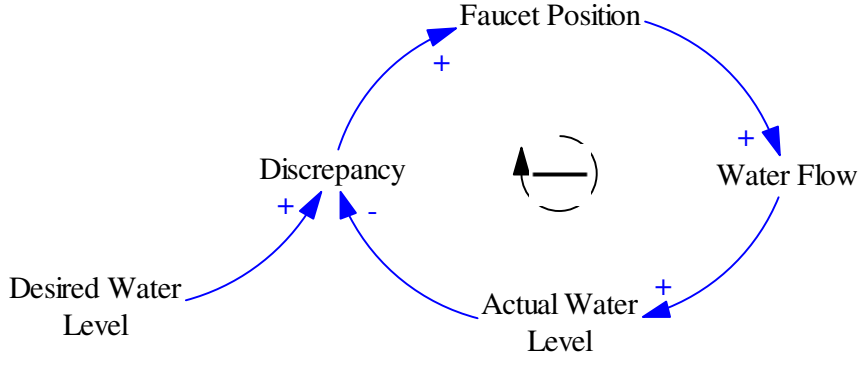



**Fig. 25.5** Example of a causal loop diagram (Kirkwood 1998)

Note that in this diagram there is a single feedback (causal) loop, and that this loop has one negative sign among its links. Since one is an odd number, the entire loop is considered a negative feedback loop.

### 25.3.4 Stock and Flow Diagram (SFD)

Haraldsson (2004) and others propose to use CLDs for brainstorming and then to switch to a SFD which models the system exactly. This at once raises the question how CLDs can be used as a base for an SFD (Binder et al. 2004). Causal loop diagrams are inherently weak because it is impossible, in principle, to determine the behavior of a system solely from the polarity of its feedback loops, because stocks and flows create dynamic behavior, not feedback. The drawbacks of CLDs are discussed in detail in Richardson (1986; 1997).

There are two basic components of the SFD. They are rates (flows) and levels (stocks). Levels are state variables that represent the accumulation of resources or “things” in the system. They denote the state of the system

at specific points in time. For example, population and level of liquid in a tank are state or level variables. Rate variables represent the change of a variable per unit time. For example, births, deaths and fluid flow rate are rate variables. Rate variables affect changes in the level variables. The general structure of a stock and flow is shown in Fig. 25.6 (Sterman 2000). Clouds at the origin of the inflow arrow and at the end of the outflow arrow represent the source and sink respectively. Stocks basically generate the information on which decisions and actions are based. As with a causal loop diagram, the stock and flow diagram shows relationships among variables which have the potential to change over time.

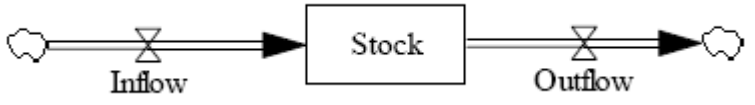



**Fig. 25.6** General structure of a stock and flow

Stocks are accumulations of material or information that has built up in a system over time. A good example is an accumulation of water in a bathtub (e.g. 150 litres) (Sweeney and Sterman, 2000) or the number of people with a disease (e.g., prevalence). Flows are rates per unit time, such as the rate of water flowing into a bath through a tap (e.g. 2 litres per minute) or the amount of water flowing out of a bath through a drain or plug-hole (e.g., 1 litre per minute). In the disease example, it is the number of new cases of a disease per year (incidence rate). The hydraulic metaphor of stock and flow is shown in Fig. 25.7.

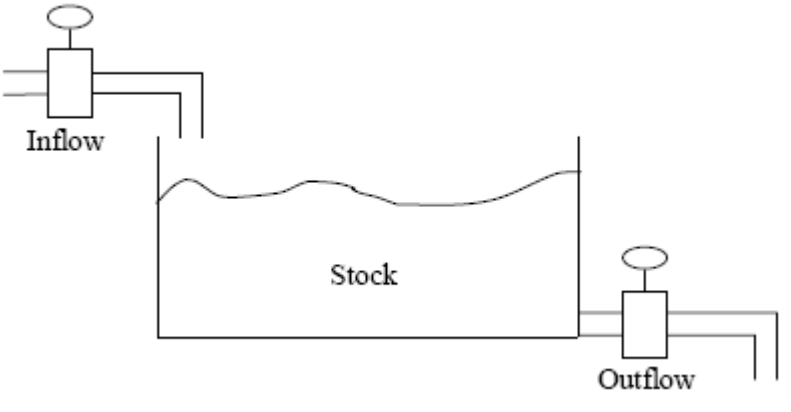



**Fig. 25.7** Hydraulic metaphor of stock and flow

Mathematically, equations for the stock element can be formulated as follows:

$$\text{Stock}(t) = \int [\text{Inflow}(s) - \text{Outflow}(s)]\, ds + \text{Stock}(t_0) \qquad (25.1)$$

Thus, the value of stock at time t is the sum of the value of stock at time $t_0$ and the integral of difference between inflow and outflow rates from $t_0$ to t. In other words, it can be stated that the rate of change in stock at any point in time is equal to the difference between inflow and outflow at that point. Stock and flow networks undoubtedly follow the laws of conservation of material. The contents of the stock and flow networks are conserved in the sense that items entering a stock remain there until they flow out. When an item flows from one stock to another, the first stock loses exactly as much as the second one gains. The number of level variables in a feedback loop determines the order of the differential equations describing the feedback loop. For example, if there are *n* level variables in a feedback loop then the mathematical model for that feedback loop would be an $n^{th}$ order differential equation. Auxiliary variables are the variables used in the feedback loop that are a function of time, other than the level and rate variables. They are used to simplify the model by avoiding complex level equations. The absence of auxiliary variables may increase the complexity of the rate equation and obscure the meaning of the model.

Suppose someone asked you to explain how the number of people on long term renal replacement therapy will change over the next 20 years. How would you answer?

This is the way a system dynamics thinker and modeller might answer. You can consider the number of people now on dialysis as a bathtub of water with an inflow tap of new dialysis patients per year and an outflow drain of deaths per year on dialysis (see Fig. 25.8). Similarly, consider the current number of transplanted patients as the level of water in another bathtub. Most people who flow into the transplant bathtub are an outflow drain from the dialysis bathtub. Some people may also be transplanted without being dialysed, particularly live donor transplants. This extra inflow into transplants is represented as a tap of transplants with no dialysis flowing in each year. Now the outflow from the transplant bathtub can again be transplant deaths per year. But people with transplants can also flow back to the dialysis bathtub at the rate of the number of graft failures per year. This bathtub thinking, called stock-flow thinking is a key component of system dynamics.

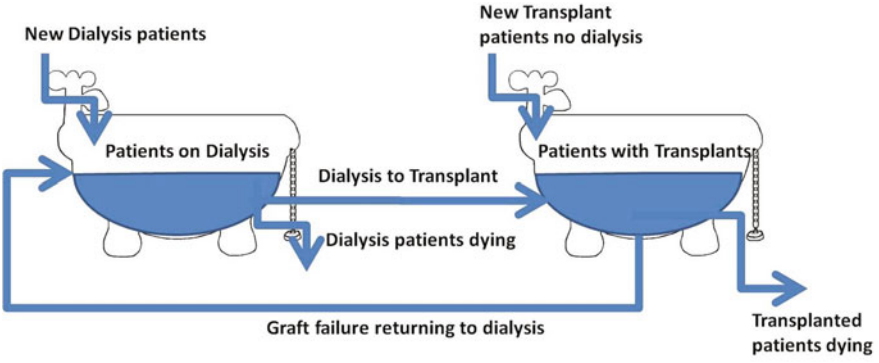



**Fig. 25.8** Bathtub thinking of dialysis

### 25.3.4 Delays

The information delivered by a feedback loop can only affect future behaviour and actions and their effects are often delayed. Delays make a system likely to oscillate (e.g., changes in the size of the health workforce or building boom-and-bust cycles). Changing the length of a delay may make a large change in the behaviour of the system. Where there are long delays in feedback loops, some foresight is essential.

### 25.3.5 Putting It All Together

Complex behaviours of systems often arise as relative strengths of feedback loops shift, causing first one loop and then another to dominate behaviour. This is described as *feedback loop dominance*. Accumulations, delays and feedback structures cause *nonlinear behaviour*. Non-linear relationships between causes and interventions and effects are those in which the cause does not produce a proportional effect. System dynamics models explore possible futures and ask "what-if" questions. The usefulness of a model depends on relevance and plausibility. Confidence in the model is based more on structure than coefficient accuracy.

## 25.4 THE TOOLS OF SYSTEM DYNAMICS

The system dynamics method produces formal computer models of real world problems which represent a theory of how system structure produces change. This theory is a synthesis of several hypotheses or causal process propositions. Indeed James Hansen, often called the "climate change modeler," states that the "model is a word for people who can't

spell hypothesis." These models are refined using the scientific method with best practice tools and techniques which focus on building user confidence and acceptance of the structure as a useful explanation to guide future actions (Lyneis 2008). These computable models are related to the implicit informal mental models people use to think, learn and make sense of the world. The method often uses tools of feedback systems thinking including causal loop diagrams to help develop, use and explain the results obtained from formal models. There is a certain viewpoint adopted when applying the system dynamics method that involves zooming out on a problem, focusing on structure, and considering past and possible future trends and patterns rather than events. From this viewpoint decisions are represented as patterns of how information is translated into action.

There is a balance between theory (represented by the model structure) and data (represented by parameter values and calibration) to achieve the right mix of rigour and relevance in order to produce effective action. Unfortunately, this approach leads us into the world of non-linear relationships that can require unfamiliar techniques for careful analysis and testing. There are excellent examples of moving from linear event-oriented thinking to pattern-oriented feedback thinking in the general, business and environmental literature (e.g. Morecroft (2007), McLeroy (2006), Sterman (2000), Richmond (1993), Meadows (2008), Ford (2009)). These texts are excellent introductions to system dynamics modeling. This section of the chapter will offer a brief introduction to the tools so health domain readers can get started with understanding and refining simple models, using STELLA/ithink (www.iseesystems.com) software and emerging online packages. They include a language to represent structure and change over time, a modelling process, a software toolkit and technical tips and tricks required for successful computational modeling.

One tool already mentioned, which can be useful for clarifying concepts and their relationships, is the concept map, or a simpler tree version, the mind map. This is a popular way to make mental models explicit so the concepts themselves, the language used to describe them, and their relationships can be clarified. In system dynamics "the abstractions from experience are arranged in mental models which form knowledge that one wants to improve in order to make better decisions." Representing these mental models as formal models of causation to explain observations using abstractions of real world mechanisms leads to better policies and actions, particularly avoiding unintended consequences. Confidence in these

models is based more on the structure of the model than the accuracy of the parameters in the model.

Mental models guide the way people think and talk about a problem. Formal computer models provide a logical consistent framework including explicit handling of time, which helps clarify concepts and mechanisms. These formal computer models can be used with other tools to clarify thinking, including causal loop diagrams and concept maps. In this way there is movement from discourse to conceptual maps to computational models. Online environments for supporting this transition are now becoming available, such as systemswiki (*www.systemswiki.org)*, Insightmaker (*insightmaker.com)*, and Simgua (www.simgua.com).

## 25.5 THE SYSTEM DYNAMICS MODELING METHODOLOGY

SD Modeling is a process of learning and persuading, which produces a useful model. The purpose of the model might be to be more confident that the focus is on the right problem, to persuade ourselves and others to implement the right solution in the right way, or to check that intended actions or policies do not make things worse in the future. The quality of the model produced is judged by its adequacy and suitability for a particular purpose. It is a tool for clarifying thoughts, and involves abductive, deductive and inductive inference. During the process one can represent and test theoretical concepts relevant to a problem, play out the consequences of mental model assumptions, and search for mechanisms to explain puzzling general regularities. The modeling process can be divided into a spiral of phases with different functions, activities and methods.

Based on Bloom's taxonomy, to successfully learn SD there is a progression through the stages of knowing, understanding, applying, analysing, creating and evaluating SD modeling skills (Schaffernicht and Madariaga 2010).

### 25.5.1 Steps in the Modeling Process

The steps of modeling process were defined by Sterman (2000) and can be summarized in Table 25.2. Modeling, as a part of the learning process, is iterative and continual process of formulating hypothesis, testing, and revision of both formal and mental models (Sterman 2000).

**Table 25.2** Steps of Modeling Process

- Formulate problem or issue as a puzzling behaviour over time & set objectives (reference mode).
- Develop a dynamic hypothesis or structure to explain the puzzle, based on participants' mental models and knowledge of system structure and behavior.
- Build and test conceptual model of explicit system theories and assumptions maps that can be converted into computational models using appropriate tools.
- Extensive policy analysis and design to experiment with changing structures and policies and interventions including decisions on where to intervene.
- Translate into computer model, then calibrate and test the model hypotheses against data and observations.
- Perform virtual experiments and test against real system results in order to persuade people to act effectively.
- Convince a group of people to act effectively. To do this people need to be involved in the modeling process and scientific principles need to be used throughout the process.

### 25.5.2 Important Elements of System Dynamics Model Validation

Validation is the task of demonstrating that the model is a reasonable representation of the actual system: that it reproduces system behavior with enough fidelity to satisfy analysis objectives. Validation and verification of the model seeks to enable experts and modelers to have a better understanding of the system and share their views (Sargent 2009). This step involves testing of the model as to whether it replicates the behavior of the real-world system. Another important task of validation and verification is to verify whether the variables and parameters of the model have a meaningful concept in the real world (Balci 1995). When models are subjected to extreme conditions, their robustness is determined. A model should not just be a means to mirror field data exactly. In addition, its elements should have a sound conceptual basis for being in the model. According to Law and McComas (2001), validation can be done for all simulation models regardless of whether their corresponding systems exist presently or would

be built in future. Also, Kleijnen (1999) gives insight on validation of simulation models using statistical techniques and reasoned that the technique applied would depend on the availability of data in the real system. Shreckengost (1992) has described some tests to validate the SD models. There are mainly two types of tests (Shreckengost 1992):

#### 25.5.2.1 Model Structure Tests

These tests check the validity of the structure of the model compared to the real system being modeled. They depend upon experience, intuition, and judgment as opposed to data. Model structure tests are summarized in Table 25.3 (Shreckengost 1992).

**Table 25.3** Model Structure Tests (Shreckengost 1992)

| Validation Test | Description |
|---|---|
| Model Parameter | The model parameters are tested against historical data. |
| Boundary Adequacy | This is a subjective test and depends upon the purpose of the model. As the purpose changes, the model's boundaries shift. |
| Extreme Conditions | The ability of the model to function properly under extreme conditions contributes to its utility as a policy evaluation tool and also boosts user confidence. These tests may expose structural faults or inadequacies and incomplete or erroneous parameter values. |

#### 25.5.2.2 Model Behavior Tests

These tests are less technical and more appealing and convincing than the structural tests. They are summarized in Table 25.4 (Shreckengost 1992).

**Table 25.4** Model Behavior Tests (Shreckengost 1992)

| Validation Test | Description |
|---|---|
| Behavior replication | Model behavior is compared to system behavior. When quantitative data is not available, the test may be one of reasonableness. |
| Anomalous behavior | This test is particularly useful when a model behaves well except for a particular period. In such cases, the model structure or parameter values may not be incorrect but the error may lie in the data. This test helps in resolving discrepancies and bolsters validity. |
| Behavior Sensitivity | Small, reasonable changes in the model parameters should not produce unreasonable, radical changes in model behavior, unless expected. |
| Behavior Prediction | Confidence in the model is reinforced if the model not only replicates long-term historical behavior but also responds similarly to existing systems in which various policies have been implemented. |
| Family Member | When SD models are generic (applicable to family of similar situations), it may be validated for similar systems. |
| Behavioral Boundary | By the previous tests, the boundary conditions may be modified. This test helps check if the model includes the necessary modifications. |

#### 25.5.2.3 Other Tests

Table 25.5 summarizes other validation tests (Shreckengost 1992).

**Table 25.5** Other Validity Tests (Shreckengost 1992)

| Validation Test | Description |
|---|---|
| Policy implication | This includes system improvement, changed behavior prediction, boundary adequacy, and policy sensitivity tests. These deal with whether the real system's response to a policy change would replicate the response to that policy change as predicted by a model, i.e., whether perturbations given to parameters bring about output changes that are expected out of the system. |
| Dimensional consistency | This test verifies whether all equations are dimensionally constant. Errors in dimensional consistency might be introduced due to adjustments during other tests. |
| Surprising behavior | There are certain unknown facts revealed by the model about the system. Such discoveries help reinforce confidence in the model. |

### 25.5.3 Summary of the SD Method

David Lane places system dynamics in the general structure agency approach of the social sciences. He also emphasizes that confidence in the models stems from the ability of the structure to explain puzzling behavior over time, rather than the accuracy of estimating the parameters in the model. A good SD model can perhaps be described to adapt Aristotle's definition of knowledge as a justified true belief to a socially justified improvable belief. It provides a way to explicitly arrange and present knowledge, or a working theory of multiple complex causality, used to explain patterns of behaviour in a way that convinces people to act effectively. This explanation of a pattern of behaviour is referred to as a dynamic hypothesis. Virtual experiments can be used to test beliefs, as well as iteratively modify and improve the presentation of these beliefs. The purpose is to learn to take more effective actions in similar situations. This leads to a collection of generic structures and behaviours than can be used to guide the search for explanations and corrective actions when faced with puzzling situations.

Formal computer models are constructed following the scientific method. SD models:

- Focus on better policies and explanations of problems
- Explain causal structure of a problem or situation
- Explain how the problem is created by this structure
- Explain why one policy has high impact while others do not
- Explain how established and defended policies are the underlying cause of the problem behaviour
- Argue in favour of better policies

## 25.6 A SYSTEM DYNAMICS MODEL OF DIALYSIS AND TRANSPLANT PATIENTS

Returning to the two bathtub example of dialysis and transplant, a simple computer model based on real world data will be constructed. A stock flow representation has been used by the Australasian dialysis and transplant data registry, ANZDATA (*www.**anzdata**.org.au)*, for many years in their annual reports, as a patient flow diagram (see Fig. 25.9).

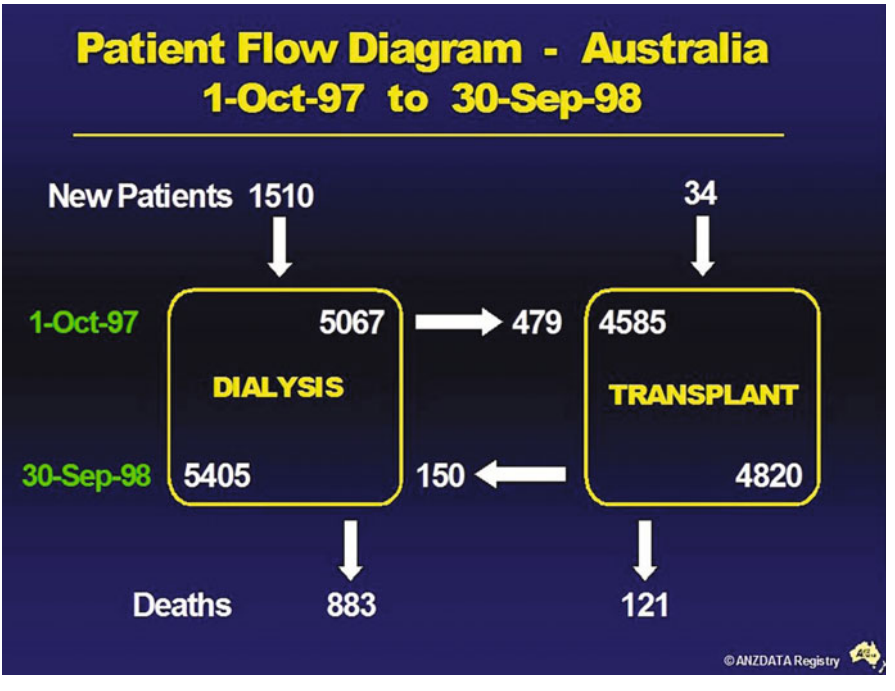



**Fig. 25.9** Patient flow diagram for dialysis and transplant

The calculations are as follows:

- The stock of dialysis patients at the end of year (5405) = Number at beginning of year (5067) plus inflows of new patients during the year (1510) plus inflows from transplant to dialysis during the year (150) minus the outflows of Deaths during the year (883) minus the outflows from dialysis to transplant during the year (479)
- 5045=5067+ (1510+150-883-479)
- This can be written as a differential equation:

DIALYSIS (t) = DIALYSIS (t - dt) + (New_Patients + Tx_Failures - Deaths_Dx - Dx_to_Tx) * dt (25.2)

Several SD modeling tools are available to convert stock flow maps into model equations. Figure 25.10 shows a stock-flow map of Renal Replacement Therapy produced using ithink/STELLA software.

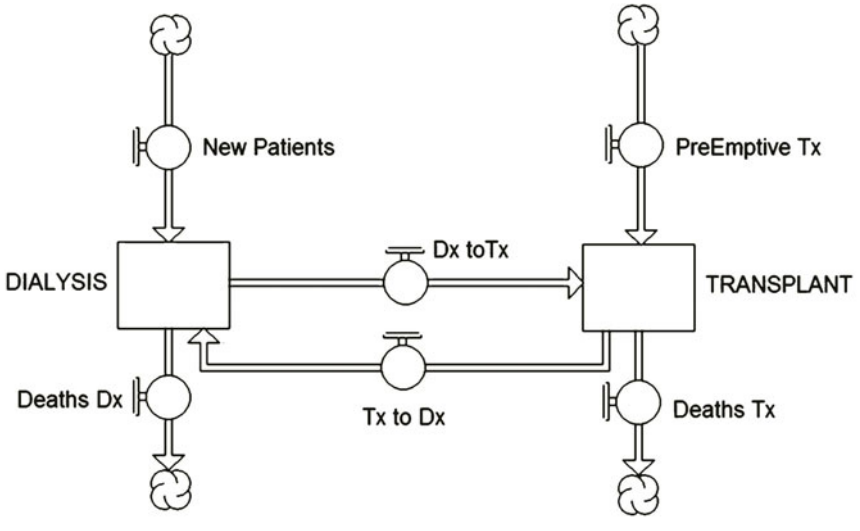



**Fig. 25.10** Stock and flow diagram of dialysis and transplant patients: First Step

This pattern of calculations can be generalized by calculating the flows in terms of the fractional change in the relevant population. *New patient* and *Transplant* rates are usually reported in rates per million of the general population per year and death and graft failure rates are usually reported as fractions of the stock of dialysis or transplant patients per year. Connectors (between stocks) and converters (which alter the flow rates) are used to show these relationships on the stock flow map (see Fig. 25.11).

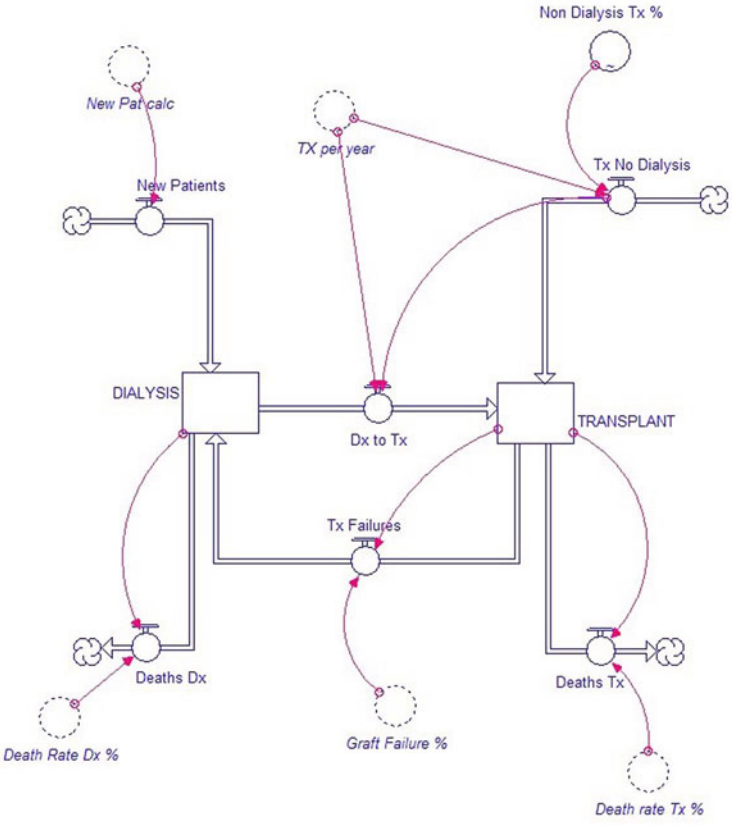



**Fig. 25.11** Stock and flow diagram of dialysis and transplant patients: Second Step

Additional structure can be added to perform calculations of these key parameters. For example, a population stock and population increase flow have been added to calculate the size of the future population (the formulae generated by the connectors and converters are found in the appendix) (see Fig. 25.12). Calibrating the model initial stock and parameter values from historical data since 1994 provides us with an executable model that produces behaviour over time.

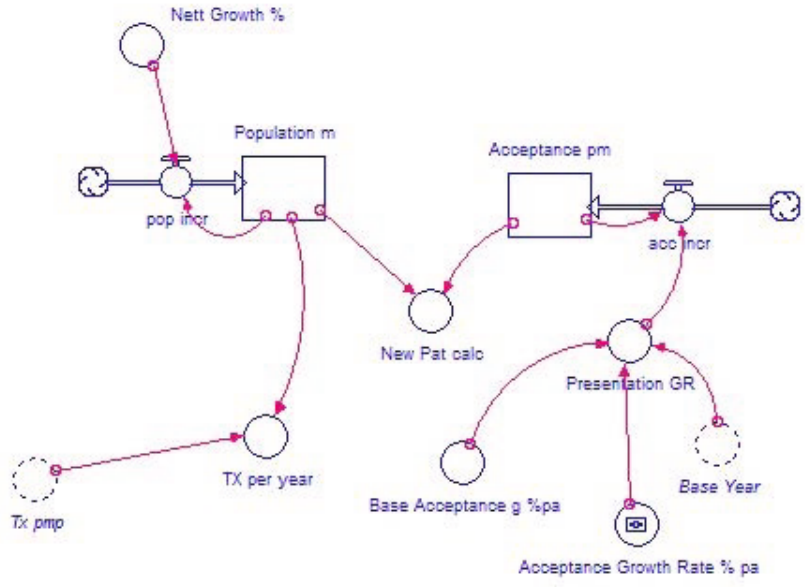



**Fig. 25.12** Stock and flow diagram of dialysis and transplant patients: Third Step

A user interface can then be added with sliders to vary the parameters in the model and to conduct what-if virtual experiments. The results of two sets of virtual experiments are show below.

First, explore the effect of varying the percentage growth in the Acceptance rate above and below the historical rate of 6% per year from 2003. There are four simulation runs shown (see Fig. 25. 13 and Fig. 25.14)

1. No change 6% growth rate (the base case) (blue)
2. Decrease to 3% growth rate (brown)
3. Decrease to 0% growth rate (mauve)
4. Increase to 10% growth rate (green)

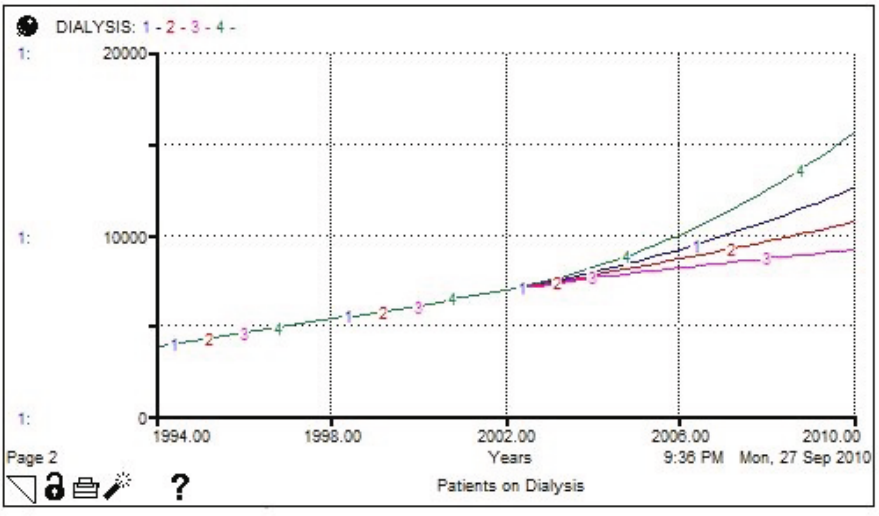



**Fig. 25.13** Number of patients on dialysis after varying the percentage growth in the acceptance rate above and below the historical rate of 6% per year from 2003.

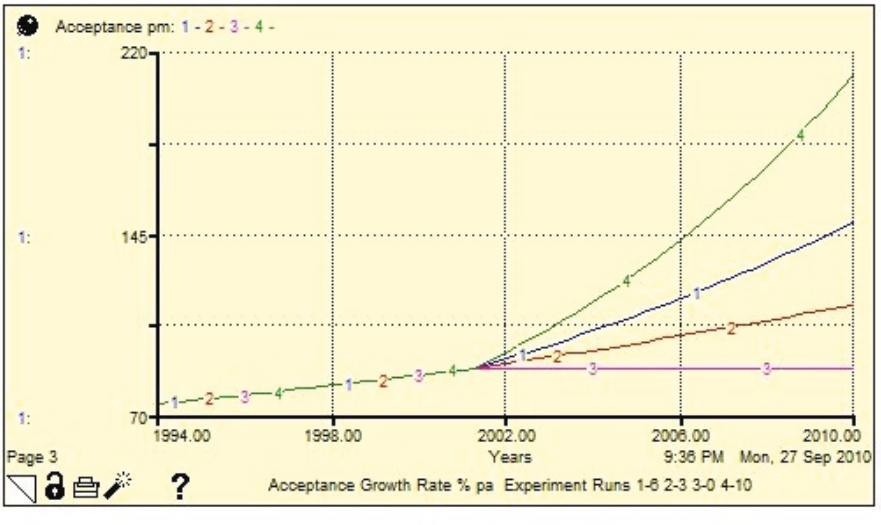



**Fig. 25.14** Acceptance growth rate after varying the percentage growth in the acceptance rate above and below the historical rate of 6% per year from 2003.

The results from these four runs show a spread of numbers on dialysis at mid-2010 from 8,000 to 16,000 and a spread of Acceptance per million populations in 2010 from 90 to 210 per year.

In another set of virtual experiments the *Transplant* rate is varied, taking a period of five years to reach the new rate. The four simulation runs shown are (see Fig. 25.15 and Fig. 25.16):

1. No change in the rate of 26 kidney transplants per million population pa (blue)
2. Increase to 34 kidney transplants per million population pa (brown)
3. Increase to 50 kidney transplants per million population pa (mauve)
4. Decrease to 17 kidney transplants per million population pa (green)

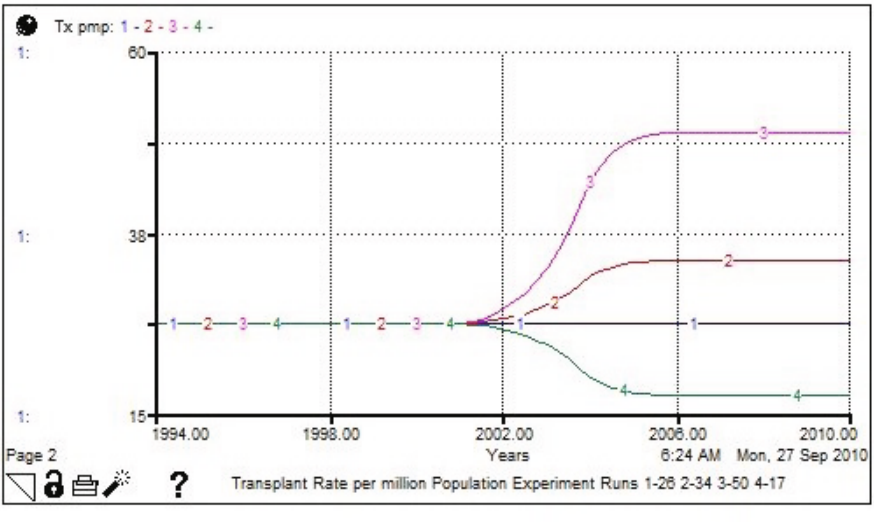



**Fig. 25.15** Transplant rate per million population Experiment runs

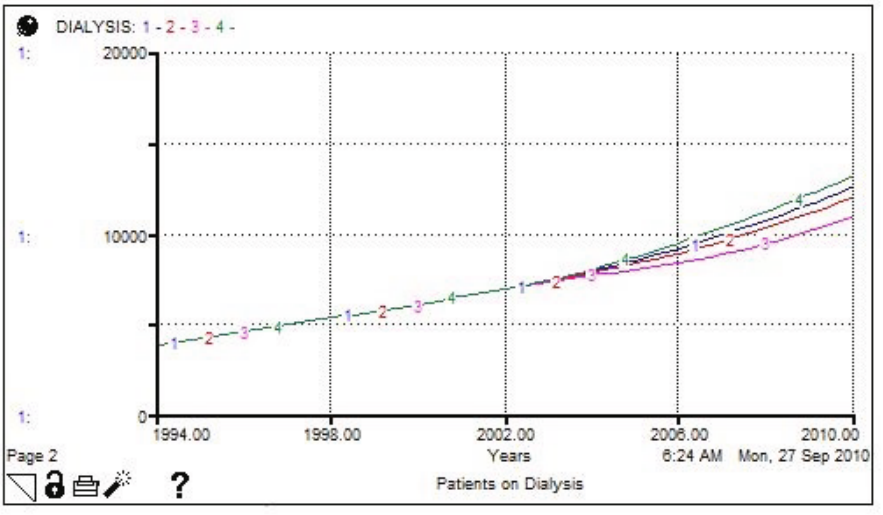



**Fig. 25.16** Number of patients on dialysis after varying Transplant rate

If the quality of life and annual cost of treatment are better for transplanted patients than patients on dialysis then the better course to follow is to increase the kidney transplant rate. The full model equation listing used to produce these runs appears in the Appendix.

### 25.6.1 Causal Loop Diagram Representation of the Dialysis and Transplant Model

The stock-flow model of renal replacement therapy can be represented as a causal loop diagram, using the online tool Insightmaker (http://insightmaker.com/insight/317). Firstly, construct the individual links inherent in the above bathtub model (see Fig. 15.17). Note that an inflow has a same link to its stock and outflow has an opposite link to its stock.

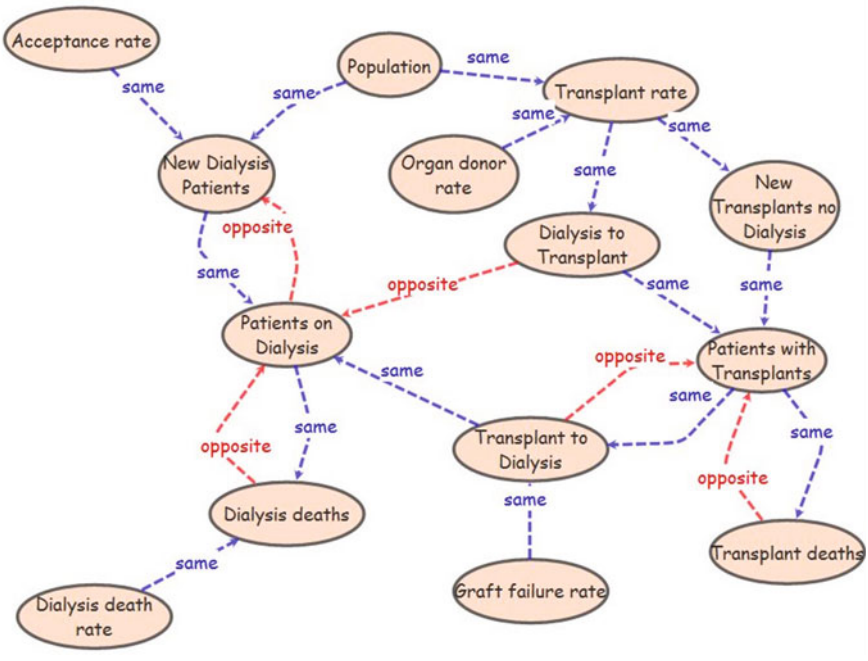



**Fig. 25.17** Causal loop diagram representation of the Dialysis and Transplant model: First Step

Note in Fig. 25.17, taken from SD model, the dialysis death rate and the acceptance rate are represented as exogenous time trends or forcings. Can you identify any other exogeneous causes or variables in the diagram? (Graft failure rate, Organ donor rate and Population)

Another key feature of a good SD model is that all changes are endogeneous. Another way to describe this is that the model is causally closed. For example, one can simply hypothesise that an increase/decrease in dialysis death rate will tend to reduce/augment the acceptance rate as dialysis becomes less/more attractive. Here is one way to close some of the loops, keeping the focus on deaths in this diagram. Figure 25.17 suggests some additional possibilities for producing a causally closed system, by considering the influences that might change organ donor rates and the links between acceptance rate and dialysis death rate. These extra loops can be considered as dynamic hypotheses, and the exact loops explored depend on the surprising situation that is being explained. For instance, in Australia

the growth in acceptance rate slowed and the number of new transplants with no dialysis increased more than expected. Closing the loops can provide potential explanations of these non-linear effects (see Fig. 25.18). This plausible explanation is described as a dynamic hypothesis.

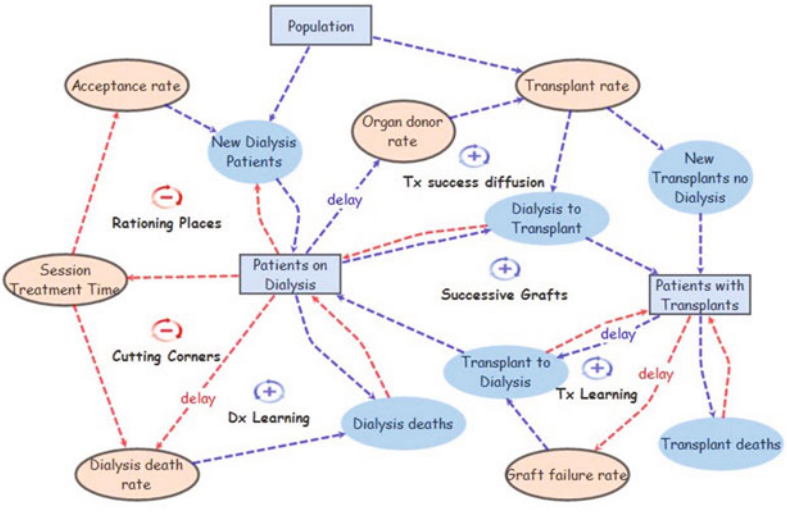



**Fig. 25.18** Causal loop diagram representation of the Dialysis and Transplant model: Second Step

Some plausible balancing loops and reinforcing loops have been explicitly labelled as possible explanations for observed non-linear trends in people on renal replacement treatment. Several other simple balancing loops are left unlabelled. Note that the stocks are explicitly shown as boxes.

#### 25.6.1.1 Labelled Reinforcing Loops

Dialysis and Transplant learning effects: The dialysis death and graft failure rates fall over time as the techniques improve with experience. This increases the number of people on renal replacement therapy over time. Another reinforcing loop is the possibility of successive grafts, which tends to increase the number of people on both dialysis and transplant. The final reinforcing loop is the delayed effect on organ donation rate of the number of people living with transplants, labelled as Transplant success diffusion.

#### 25.6.1.2 Labelled Balancing Loops

To explain what limits the number of people on dialysis, the concepts of session treatment time as the limiting resource have been introduced. To manage this resource one can either ration the number of people accepted on to dialysis, labelled as rationing places, or one can reduce the time spent on dialysis for each patient, labelled as cutting corners.

These causal loop diagrams can be used to explain the results of our models or to develop plausible dynamic hypotheses which can guide future extensions to the model and data gathering to test these models empirically. However, there are many other concepts that could be used to represent the dynamics of this complex system. Zooming out would include people with progressing chronic kidney disease prior to being accepted on to a dialysis program. People involved in the technical detail of dialysis might want to explore the contribution of dialysis adequacy. Therefore, the purpose of the model is an important determinant of the way the dynamics of a system are represented.

### 25.6.2 Chronic Kidney Disease Dynamics

Of course the need for dialysis is mostly driven by the number of people who have progressive forms of kidney disease, including glomerulonephritis and diabetes. The flow of people through early and late stages of chronic disease can also be represented using system dynamics models.

The key chronic kidney diseases that produce end stage renal failure in many countries are glomerulonephritis and diabetic nephropathy and their onset and progression can be delayed by screening and effective management of risk factors including hypertension, proteinuria and glycaemic control. The above generic pattern can be adapted to these specific diseases and interventions, similar to Motohashi and Nishi (1991). Rather than the original stock flow diagram, the model here is represented as causal loops and explicit stocks (see Fig. 25.19) (available online at http://insightmaker.com/insight/336)

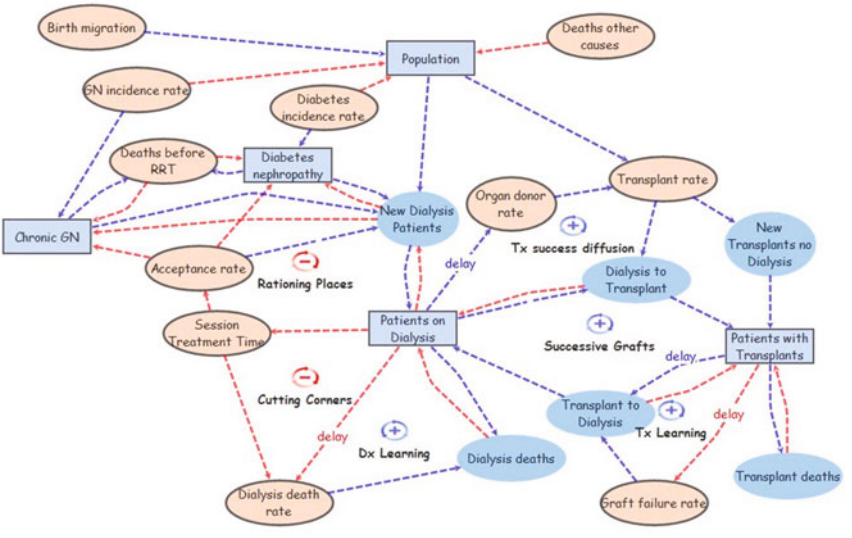



**Fig. 25.19** Kidney replacement therapy dynamics: causal loop diagram of the kidney dialysis and transplant model extended to Chronic Kidney Disease from Motohashi and Nishi (1991).

The reader may wish to identify flows and label more loops and add the effects of other limited resources, such as funding.

### 25.6.3 People with Treatable Diseases Flowing though Diagnosis and Treatment

A useful model for generic patient flow is found in Paich et al (2009) is shown in Fig. 25.20 and also available online at Insightmaker (http://insightmaker.com/insight/305), where virtual experiments using sliders can be performed.

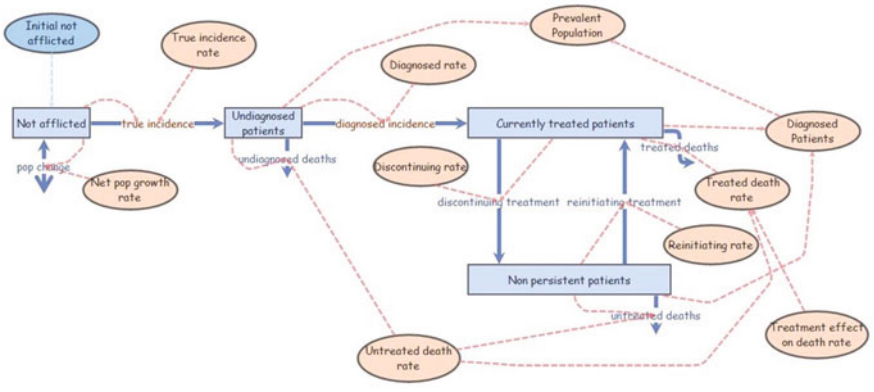



**Fig. 25.20** Stock and flow diagram of Hypertension Generic Patient Flow.

A causal loop diagram of the same stocks and flows, with some additional potential feedback mechanisms is shown in Fig. 25.21 and also available at http://insightmaker.com/insight/315

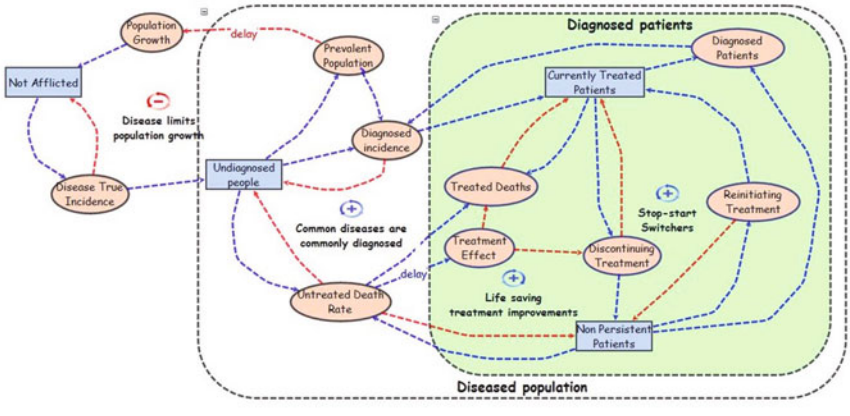



**Fig. 25.21** Hypertension Generic Patient Flow causal loop diagram.

### 25.6.4 Organ Donation and Transplantation Dynamics

Where possible the preferred renal replacement therapy seems to be a combination of self-managed dialysis and kidney transplantation. Of course the transplantation rate is limited by the availability of live and deceased donors. Here a slightly different conceptualisation will be introduced to explore ways to increase the transplantation rate. In this view the stock of transplantable organs in the general population is considered.

These can be added to by births and in migration of transplantable organs or by advances in technology that make more organs capable of being transplanted. Perhaps transplantable organs may also be grown from stem cells in the future. These organs mostly become no longer transplantable by the organs ageing beyond the time they are considered transplantable, or by dying without being donated. This pool of transplantable organs in people is also depleted by organs failing and people becoming potential transplant recipients. This stock of organs failed in transplantable recipients can be removed by death or by replacing organs. By the act of donating by live and deceased donors, organs can flow outside the body, be potentially stored and then flow into the bodies of recipients. They will remain there until the death of the recipient or the failure of the graft. Graft failure takes the organ back to the organs failed in transplantable recipients, where they are again removed by dying or being retransplanted. Figure 25.22 shows these organ flows and the potential feedback effect of increasing donor age reducing the life of the transplanted organ (from http://insightmaker.com/insight/323).

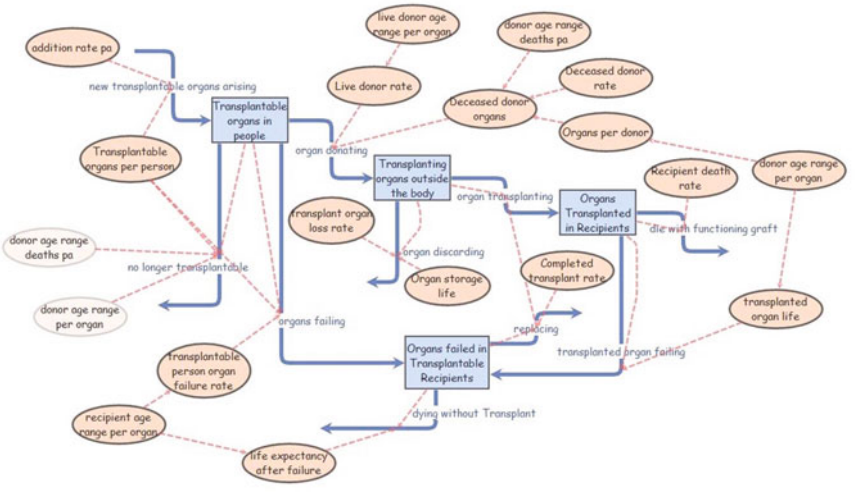



**Fig. 25.22** Stock and flow diagram of Organ Donation and Transplantation

This organ flow representation shows the ways transplantable organs are generated and are consumed by aging, death and organ failure. Transplantable organs can flow from a donor to a recipient, with a variable time spent outside the body. This forms a basis for discussing places to intervene to promote the flow of organs to recipients and to increase the time organs spend as functioning and transplantable entities.

### 25.6.5 Zooming in on Dialysis Modality Selection

Azar et al (2006) developed Hemodiadynamics which is a novel system dynamics software used to analyse and identify the important implications for a successful implementation of a Hemodialysis session Performance. Hemodiadynamics can be considered as a novel urea kinetic modelling system used for monitoring and assessing dialysis efficiency online (Azar 2011). The developed system focuses on analysing and highlights factors which may alter the delivered dose and may lead to session degradation. This will help increase the achievement of adequate Hemodialysis to a level consistent with or higher than National Adequacy Statistics, in order to reduce the Morbidity rate of the Hemodialysis patient.

The broad context, as previously shown, includes understanding the drivers of demand for dialysis, including both population dynamics and kidney disease dynamics including diabetes and other risk factors. On the supply side, the availability and configuration of resources, including technologies, specialised staff and funding determines the quality of services and therefore the patient and medical preferences for different dialysis options. Key decisions include provision of shared facilities, the availability of resources for prevention of progression of chronic kidney disease, early specialist referral and vascular access surgery which interact with the age, comorbidity and social conditions of the population that need dialysis. Again, the availability of live and deceased kidney donors will also affect dialysis treatments and outcomes. At a more detailed level, dialysis adequacy affects the morbidity, quality of life and mortality and attractiveness of different modality options. Intradialytic session length and filtration interact with interdialytic management of fluid balance, nutrition and anaemia. Some of these concepts are included in Fig. 25.23.

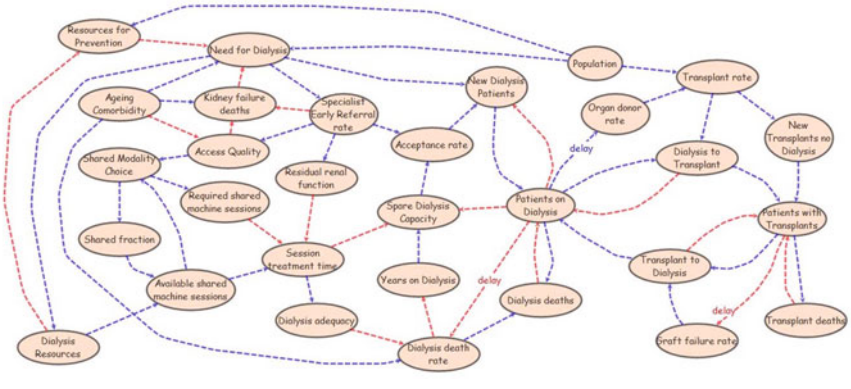



**Fig. 25.23** Kidney replacement therapy dynamics extended to dialysis management.

Another constraint which could be added to Fig. 25.23 is the interaction between costs benefits and resources. This is indicated above by the links among population, resources for prevention and dialysis resources. The reader may wish to modify this diagram to add loops, stocks and flows (Available at http://insightmaker.com/insight/318).

### 25.6.6 More Detailed Models

The models already presented contain only a few stocks. Like all compartmental models, perfect mixing within each stock is assumed. If the differences within stocks are of interest, the stock can be divided or arrayed into multiple dimensions. One common way to array stocks is by age and gender, since in epidemiology and public health the detailed data by age and gender are often available. This increases the accuracy of our model, but it may detract from understanding the feedback dynamics of the situation. Age-specific mortalities are important in quantifying costs and benefits, particularly using quality adjusted life years and health adjusted life expectancy as measures of population health. Specifically modelling policies for accepting elderly people on dialysis may require this more detailed level of analysis. Other problems may require zooming out to include a much broader context, including both drivers of demand and constraints on supply. In general, the interacting components include the population, people with health conditions, patients in care, clinical services workload, workforce, facilities, technology and funding sources (Masnick and McDonnell 2010).

## 25.7 CONCLUSION AND FUTURE DIRECTIONS FOR SD MODELS IN RENAL DISEASE MANAGEMENT

The advantages of dynamic modeling are that it can provide leadership, co-ordination and inform planning in a real world context. There are opportunities to combine system dynamics modeling with other health system science methods such as process-centric discrete event models, network science and agent based modeling. Multi-scale, multi-level models can link physiological models, clinical practice and health policy. There are examples of this in obesity, infectious diseases modeling and public health. There may also be a place for SD to link multiple interventions into a broader policy context, so indirect feedback effects among multiple programs can be managed in a more coherent way. Currently single interventions are modeled separately using Markov chain Monte Carlo methods and SD has the potential to provide a more synthetic approach. Finally

other decision modeling tools including behavioral modeling , entropy models and complexity science and engineering methods can be combined to help renal disease understanding and decision making at the practice, health service and policy level.

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## ESSAY QUESTIONS

1. Define Mind Maps and Mental Models.
2. How does one build a good model?
3. What is system dynamics (SD)?
4. List some applications of systems dynamics approach.
5. What is a causal loop diagram (CLD)?
6. Discuss the drawbacks of causal loop diagrams.

7. Describe the two types of feedback loops found in SD.
8. List the main steps of the SD Modeling Process.
9. List the main tests of SD model validation
10. What is the main function of the Hemodiadynamics software?

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. Who invented system dynamics (SD)?
   A. John Sterman
   B. John Morecroft
   C. Jay W. Forrester
   D. David Ford

2. According to the founder of SD, an appropriate simulation model should help someone know which of the following:

   A. A high-leverage policy that will alter behaviour
   B. A low-leverage policy that will improve behaviour
   C. How the problem is created
   D. A and C
   E. B and C

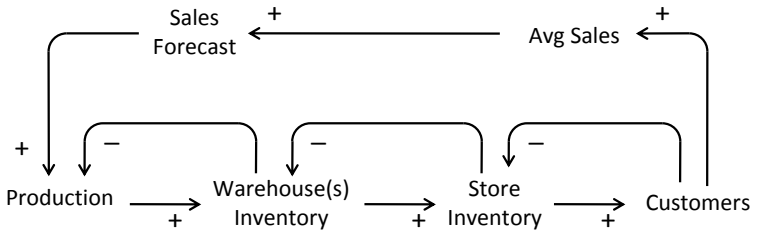
3. Which type of feedback loop has an even number of – (minus) signs?

   A. Positive feedback loop
   B. Negative feedback loop

4. Which type of feedback loop causes change in the same direction?

   A. Positive feedback loop
   B. Negative feedback loop

5. How many feedback loops are in the following CLD?




A. 5
B. 4
C. 3
D. 2

6. Which type of variable represents an accumulation of resources or things in a system?
A. Rate
B. Level
C. Auxiliary

7. Suppose a bathtub was holding 100 litres. If the faucet into the bathtub is turned on at a rate of 10 litres per minute and the drain for the bathtub is opened so that water flows out at a rate of 5 litres per minute, how many litres of water would be in the tub at the end of 5 minutes?
A. 75
B. 90
C. 100
D. 110
E. 125

8. A traditional "S" curve is an example of a shift in feedback loop dominance. For an "S" curve, what is the order of dominance of the two feedback loops?

A. Positive feedback loop first, then a negative feedback loop
B. Negative feedback loop first, then a positive feedback loop

9. Which of the following equations represent a non-linear system?
A. $y = x$
B. $y = -x$
C. $y = 2x$
D. $y = x^2$

10. Which of the following steps is NOT commonly used in the SD modeling process?

A. Build and test conceptual model of explicit system theories
B. Construct focus group survey
C. Formulate problem or issue as a puzzling behaviour
D. Convince a group of people to act effectively

11. What are the most common SD model validation techniques?

A. Structure
B. Model behavior
C. Statistical
D. Boundary
E. A and B
F. C and D

12. The construction of SD simulation models often follows which method?
A. Scientific method
B. Statistical method
C. Agent method
D. Theoretical method

13. What are some of the stocks in the SD model of Dialysis and Transplant Patients presented in this chapter?

A. Dialysis patients
B. Transplant patients
C. New patients
D. Dying patients
E. A and B
F. C and D

14. Which of the following is NOT a positive (reinforcing) feedback loop in the Dialysis and Transplant Patients SD model presented in this chapter?

A. Dialysis death and graft rates fall over time as the techniques improve with experience
B. The possibility of successive grafts tends to increase the number of people on dialysis
C. Session time is a limiting resource for the number of people on dialysis
D. The delayed effect of number of people living with transplants on organ donation rate

15. What is an SD-based modeling tool that is considered a novel urea kinetic modeling system used for monitoring and assessing dialysis efficiency online?

A. Kidney and Transplant Patients
B. Peritonealdiadynamics
C. Kidney dynamics
D. Hemodiadynamics

16. In what timeframe was SD initially developed?

A. 1940's
B. 1950's
C. 1960's
D. 1970's

17. According to Sterman (2000), what are common features of good models?

A. Explains dynamic changes over time
B. Includes structure for exogenous variables
C. Limits concepts to qualitative knowledge
D. Focuses on details
E. A and B
F. C and D

18. What tool highlights hierarchies rather than networks of concepts?

A. Computational models
B. Mental models
C. Mind maps
D. Statistical models

19. A key feature of a good SD model is that it is causally _____?

A. Open
B. Equal
C. Connected
D. Closed

20. If a team used both a causal loop diagram (CLD) and a stock and flow diagram (SFD) on a SD model development project, which tool would most likely be used first?

A. Causal loop diagram (CLD)
B. Stock and flow diagram (SFD)

## APPENDIX: Model Equations for Simple Dialysis and Transplant Model

Acceptance_pm(t) = Acceptance_pm(t - dt) + (acc_incr) * dt
INIT Acceptance_pm = 74
INFLOWS:
acc_incr = Acceptance_pm*Presentation_GR/100
DIALYSIS(t) = DIALYSIS(t - dt) + (New_Patients + Tx_Failures - Deaths_Dx - Dx_to_Tx) * dt
INIT DIALYSIS = 3705
INFLOWS:
New_Patients = New_Pat_calc
Tx_Failures = TRANSPLANT*Graft_Failure_%/100
OUTFLOWS:
Deaths_Dx = DIALYSIS*Death_Rate_Dx_%/100
Dx_to_Tx = TX_per_year-Tx_No_Dialysis
Population_m(t) = Population_m(t - dt) + (pop_incr) * dt
INIT Population_m = 17.5
INFLOWS:
pop_incr = Population_m*Nett_Growth_%/100
TRANSPLANT(t) = TRANSPLANT(t - dt) + (Tx_No_Dialysis + Dx_to_Tx - Deaths_Tx - Tx_Failures) * dt
INIT TRANSPLANT = 3855
INFLOWS:
Tx_No_Dialysis = TX_per_year*Non_Dialysis_Tx_%/100
Dx_to_Tx = TX_per_year-Tx_No_Dialysis
OUTFLOWS:
Deaths_Tx = TRANSPLANT*Death_rate_Tx_%/100
Tx_Failures = TRANSPLANT*Graft_Failure_%/100
Acceptance_Growth_Rate_%_pa = 6
Base_Acceptance_g_%pa = 2.5
Base_Dx_Death_%_pa = 16
Base_Graft_failure_% = 3.5
Base_Tx_Death_rate = 2.5
Base_Tx_rate = 26
Base_Year = 2001
Death_Rate_Dx_% = if time >Base_Year then Dx_Death_Rate_% else Base_Dx_Death_%_pa
Death_rate_Tx_% = if time >Base_Year then Tx_Death_Rate_% else Base_Tx_Death_rate
Delta_Tx = Max_Tx_Rate-Base_Tx_rate
Dialysis_Historical = GRAPH(time)

(1994, 3705), (1995, 4100), (1996, 4529), (1997, 4893), (1998, 5197), (1999, 5549), (2000, 6021), (2001, 6410), (2002, 6850), (2003, 7265), (2004, 7723), (2005, 8008), (2006, 8634), (2007, 9251), (2008, 9642), (2009, 10062), (2010, 0.00)

Dia_Correlation = if Dialysis_Historical>0 then DIALYSIS/Dialysis_Historical*100 else 0

Dx_Death_Rate_% = 16

D_to_T_ratio = DIALYSIS/TRANSPLANT

Graft_Failure_% = if time >Base_Year then Gx_Failure_Rate_% else Base_Graft_failure_%

Gx_Failure_Rate_% = 3.5

Max_Tx_Rate = 26

Nett_Growth_% = 1.4

New_Pat_calc = Population_m*Acceptance_pm

Non_Dialysis_Tx_% = GRAPH(time)

(1994, 5.00), (1996, 5.00), (1997, 5.00), (1999, 5.00), (2000, 10.0), (2002, 10.0), (2004, 10.0), (2005, 10.0), (2007, 10.0), (2008, 10.0), (2010, 10.0)

Presentation_GR = if time >Base_Year then Acceptance_Growth_Rate_%_pa else Base_Acceptance_g_%pa

T&D_Total = DIALYSIS+TRANSPLANT

take_up_years_% = take_up_yr/Years_to_Max*100

take_up_yr = max(0,time-Base_Year)

Tx_correlation = if Tx_Functioning_Historical>0 then TRANSPLANT/Tx_Functioning_Historical*100 else 0

Tx_Death_Rate_% = 2.5

Tx_Functioning_Historical = GRAPH(time)

(1994, 3855), (1995, 4045), (1996, 4210), (1997, 4413), (1998, 4649), (1999, 4856), (2000, 5053), (2001, 5250), (2002, 5454), (2003, 5750), (2004, 5982), (2005, 6267), (2006, 6523), (2007, 6837), (2008, 7109), (2009, 7541), (2010, 0.00)

TX_improve_tx = GRAPH(take_up_years_%)

(0.00, 0.00), (10.0, 2.50), (20.0, 8.00), (30.0, 15.5), (40.0, 29.5), (50.0, 48.5), (60.0, 74.5), (70.0, 89.5), (80.0, 96.5), (90.0, 99.0), (100, 100)

TX_per_year = Population_m*Tx_pmp

Tx_pmp = Base_Tx_rate+Delta_Tx*TX_improve_tx/100

Years_to_Max = 5

# Part IV

# Overview of Peritoneal Dialysis and Modeling Techniques

Chapter (26)

# Overview of Peritoneal Dialysis

Rajnish Mehrotra, John Crabtree, and Pranay Kathuria

**CHAPTER OUTLINES**

- Historical review of development of peritoneal dialysis
- Types of peritoneal dialysis
- Peritoneal Dialysis Access
- Peritoneal Dialysis Solutions
- Complications of peritoneal dialysis
- Conclusions

**CHAPTER OBJECTIVES**

- To understand different types of peritoneal dialysis
- To understand the devices and solutions that allow us to use the peritoneal membrane for dialysis
- To understand the limitations and complications of peritoneal dialysis

**KEY TERMS**

- Peritoneal dialysis
- End-stage renal disease
- Peritoneal equilibration test
- Tenckhoff catheter
- Glucose degradation products
- Icodextrin
- Peritonitis
- Encapsulating peritoneal sclerosis

**ABSTRACT**

It is estimated that there are over one million patients with end-stage renal disease (ESRD) treated with dialysis around the world. While the overwhelming majority of these patients are treated with extra-corporeal therapies in dialysis units (hemodialysis), over 10% perform their dialysis treatments at home – virtually all these patients use peritoneal dialysis (PD). In at least two countries – Hong Kong and Thailand – end-stage renal disease patients are eligible for governmental financial support for dialysis services only if they begin treatment with PD. In PD, a naturally occurring membrane, the peritoneal membrane, is used as dialysis membrane and over the years, the therapy has developed such that it allows successful removal of sufficient amount of solutes and fluid required to sustain life even in individuals without any residual kidney function. PD involves the instillation of dialysate fluid through an indwelling abdominal catheter and allowing it to dwell for variable periods of time before exchanging it with fresh dialysate. Most patients require dialysis to be performed continuously – 24 hours a

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springerlink.com 

day, seven days a week. Recent studies from different parts of the world show that the 5- and 10-year mortality of patients treated either with in-center hemodialysis or peritoneal dialysis are remarkably similar. In this chapter, we present an overview of the development of the therapy, key components that allow the therapy to be performed in its current form, and the complications of the therapy.

## 26.1 HISTORICAL REVIEW OF THE DEVELOPMENT OF PERITONEAL DIALYSIS

### 26.1.1 Initial Development of Peritoneal Dialysis

The initial concept of peritoneal lavage may have evolved as early as the 1740's. Christopher Warrick treated a patient with recurrent ascites by draining the ascitic fluid and then instilling Bristol water and Claret wine into the patients' peritoneum through a leather pipe (Warrick 1744). Reverend Stephen Hales recommended a modification to Warrick's technique suggesting placement of 2 trocars on either side of the abdomen to allow the "liquor" to flow in and out of the abdomen (Hales 1744). Early anatomists and surgeons described the size and features of the peritoneal membrane but failed to discover its detailed structure or function. In 1862, Friedrich Daniel von Recklinghausen published the first scientific description of the peritoneum's cellular composition (Von Recklinghaussen 1863). In 1877, G. Wegner from Germany performed the first animal experiments to observe the metabolic transport processes occurring through the peritoneum (Wegner 1877). He noted that ultrafiltration could be altered based upon changes in the infused sugar solutions. In 1894, two Englishmen, Ernest Henry Starling and Alfred Herbert Tubby, discovered that fluid removal through the peritoneum was effected by the number of blood vessels in the membrane (Starling and Tubby 1894). Tracy Putnam in 1923 performed elegant experiments in dogs and characterized the peritoneum as a dialyzing membrane (Putnam 1923). He established the concept of osmotic equilibrium between peritoneal fluid and plasma and concluded that mass transfer was driven by passive concentration gradients rather than active membrane transport.

The first peritoneal dialysis performed for uremia is credited to Georg Ganter from the University of Würzburg in 1923 (Ganter 1923). He treated a patient with post-partum renal failure with exchanges of 1 to 3 liters of solution which was allowed to dwell for 30 minutes to 3 hours. Though the patient died, Ganter's work established some of the basic principles of dialysis: the need for appropriate access and sterile dialysate, the fluid

removal being dependent on dextrose concentrations and the effect of dwell time and fluid volume effecting solute clearances. In 1936, Wear, Sisk and Trinkle from the Wisconsin General Hospital reported the successful use of peritoneal lavage in treating a patient with obstructive uropathy (Wear et al. 1938).

During the Second World War, thousands of cases of acute renal failure died because of uremia. Fine, Frank and Seligman at the Beth Israel Hospital in Boston were charged with finding a method to treat renal failure for military trauma patients. They performed elegant studies in nephrectomized and non-nephrectomized uremic dogs to determine suitable peritoneal access, optimal use of continuous flow peritoneal irrigation, and proper irrigation fluid (Fine et al. 1946). Encouraged by their experimental work, they successfully treated a patient with renal failure due to sulfa overdose by 'intermittently continuous irrigation'. By 1948, they had treated a total of 18 patients with four survivors (Frank et al. 1948). At first, they employed continuous lavage through the peritoneal cavity to a sump but later devised a double lumen tube made of ordinary rubber and stainless steel, which was surgically implanted in the abdominal wall and pelvis, and which could be used for continuous or intermittent irrigation.

Arthur Grollman published his experience with intermittent peritoneal lavage in nephrectomized dogs and 5 patients in 1952 (Grollman et al. 1951a, b). He described the use of a one liter container with a cap that connected to a piece of plastic tubing and attached to a polyethylene catheter. He suggested that the fluid be instilled by gravity and allowed to dwell for thirty minutes and then drained out into the same container. This technique was to be repeated on an hourly basis until the patient's chemistries returned to normal. His work is a classic in that it described the method of peritoneal dialysis that we use today.

### 26.1.2 Intermittent Chronic Peritoneal Dialysis and Peritoneal Dialysis Catheters

The relative success of intermittent peritoneal dialysis led to its eventual application in end stage renal disease. In 1959, Morton Maxwell collaborated with industry and developed sterile dialysate packaged in glass bottles (Maxwell et al. 1959). He described a simplification of Grollman's technique using commercial dialysate, disposable tubing and a semi-rigid nylon catheter, which was placed in the lower peritoneal cavity through a small trocar. Two liters were introduced, retained for 0.5 to 1 hour and then siphoned off into the original bottles - an "exchange" It was a completely closed system, but a fresh set of tubing and bottles was required for

each "exchange". Paul Doolan developed a polyvinyl chloride peritoneal catheter with a straight intra peritoneal segment with multiple side holes, transverse ridges, and spiral grooves to avoid kinking and omental obstruction (Doolan et al. 1959). Richard Reuben is credited with performing the first chronic treatment of a patient with peritoneal dialysis in 1959. He used the Doolan catheter which was left indwelling and had to be changed only once in a 7 month period.

A major step forward in creating a permanent peritoneal access was made in 1964. Gutch noticed lower protein losses with silicon rubber catheters as compared to those with polyvinyl ones, which suggested less irritation of the peritoneum with a new material (Gutch 1964). About the same time, Palmer, with the help of Wayne Quinton, developed a catheter which is a prototype of currently used coiled catheters (Palmer et al. 1964). The catheter was made of silicon rubber, the intraperitoneal end was coiled and had numerous perforations extending 23 centimeters from the tip; a long subcutaneous tunnel was supposed to hinder periluminal infection. To impede further infection and leakage, a tri-flanged step was created for securing the catheter in the deep abdominal fascia.

In 1965, Henry Tenckhoff, at the University of Washington, was beginning to treat patients with chronic intermittent peritoneal dialysis (Tenckhoff et al. 1965). After initial few dialyses in the hospital, the patients would be trained for home dialysis. On the weekends, Tenckhoff would go to patient's home, insert the catheter and begin dialysis. After the appropriate time on dialysis, the patient would remove the catheter and cover the exit wound with a dressing. Although the method was successful, the technique was cumbersome, and Tenckhoff recognized its limitations. Tenckhoff developed an improved version of the Palmer catheter (Tenckhoff and Schechter 1968). He shortened the catheter and suggested two designs, straight and curled. In addition, he added Dacron felt cuffs to help seal the openings through the skin and abdominal fascia. He also developed a trocar (insertion tool) to provide easy placement of the catheter. The Tenckhoff catheter has become the gold standard of peritoneal access. Even today, forty years later, the Tenckhoff catheter in its original form is the most widely used catheter type. Some of the original recommendations for catheter insertion such as an arcuate subcutaneous tunnel with downward directions of both intraperitoneal and external exits are still considered very important elements of catheter implantation.

### 26.1.3 Development of Continuous Ambulatory Peritoneal Dialysis

Intermittent peritoneal dialysis provided inadequate control of uremia in many patients but was associated with a high rate of infectious complications when used for chronic dialysis (Ahmad et al. 1979). In 1978, Robert Popovich and colleagues described their experience with a new technique, called "portable/wearable equilibrium peritoneal dialysis technique" which subsequently was renamed continuous ambulatory peritoneal dialysis (CAPD). CAPD caused a rejuvenation of interest in peritoneal dialysis since it improved hypertension and biochemical control of uremia as well as improved hemoglobin and quality of life. Despite these encouraging results, patients had a high peritonitis rate (1 episode every 3–4 patient months) mainly because they were using dialysis solutions in glass containers—the only containers that were available in the United States at that time. This meant they had to connect and disconnect the tubing to the glass containers via a spike five times a day, contributing to the high rate of peritonitis (Nolph et al. 1980; Popovich et al. 1976, 1978).

The introduction of plastic bags for peritoneal fluid made dialysis simpler and safer. The dialysate was instilled using the standard Y-set with one arm of the Y closed. After instillation, the bag was retained and used to collect the spent dialysate. The next advancement came with the development of spike connectology, which reduced the incidence of peritonitis markedly (Oreopoulos 1998; Oreopoulos et al. 1978). Plastic bags were introduced in the United States in 1978.

Umberto Buoncristiani introduced the "flush before fill" technique using a Y-set which further decreased the incidence of peritonitis (Buoncristiani 1996). During an exchange, the peritoneal dialysate is first drained from the peritoneal cavity into an empty bag. Before introducing the fresh dialysis solution into the peritoneal cavity the Y-connecting system is flushed with fresh dialysis solution and drained into the drainage bag. This allows any bacteria to be flushed into the spent fluid. The fresh fluid is then introduced into the peritoneal cavity and the Y-connector is disconnected from the CAPD catheter. The early Y-set technique, in addition, flushed the system with a disinfectant, hypochlorite, during each exchange (Buoncristiani 1989).

A further modification of the Y-set is the twin bag system in which the dialysate bag and the drainage bag come already attached to the Y shaped tubing. This eliminates the need for spiking and all that is required is to connect and disconnect the tubing to the catheter. Even though Buzzato *et al* introduced the twin bag system as early as 1980, for years the system

was not successful chiefly because the only commercial model available at that time employed a needle and a rubber cap as connectors at the bag and the catheter side respectively (Bazzato et al. 1980). This made the system less effective in preventing peritonitis because the flush was not complete due to the cul-de-sac formed between the needle and rubber cap. Now that the needle and rubber cap have been replaced by Luer-lock connectors, peritonitis rates have declined considerably.

### 26.1.4 Development of Automated Peritoneal Dialysis

Fred Boen is credited with developing the first peritoneal dialysis cycler in the early 1960s (Boen et al. 1962, 1964). This device used sterile dialysate prepared in the hospital and delivered to the bedside in 40-L carboys. Therapy consisted of multiple 2-L exchanges delivered over a 10-h period. An automatic solenoid device controlled delivery of the dialysate into the peritoneal cavity. Intermittent dialysis was performed once a week and access was obtained by repeated punctures. Noting difficulties with delivery and handling of the carboys, Tenckhoff designed an automated system that mixed dialysate concentrate with distilled water processed by a 'miniature still' (Tenckhoff et al. 1969). This system proved to be expensive, bulky, and time-consuming to use, and was soon abandoned. After the development of reverse-osmosis water, Tenckhoff adapted the technology to develop a new cycler. This cycler used reverse-osmosis water and a proportioning system to mix treated water with dialysate concentrate (Tenckhoff et al. 1972). Large amounts of dialysate could be easily prepared at a relatively lower cost. Higher glucose concentrations were achieved by adding hypertonic glucose to the mixture.

Norman Lasker developed a mechanical system for peritoneal dialysis or in the other words a peritoneal cycler (Lasker et al. 1966). The system used 2-liter bottles and flexible plastic reservoir bags and delivered the dialysate into the abdomen using gravity. The cycler was capable of warming the dialysate and regulating the quantity of fluid instilled into the abdomen. In 1970, the first patients received home dialysis with this cycler. In 1981, Diaz-Buxo and coworkers proposed continuous cyclic peritoneal dialysis (CCPD) to reduce the high incidence of peritonitis and eliminate the multiple interruptions created by dialysate exchanges during the day needed for CAPD, while maintaining the quality of dialysis (Diaz-Buxo et al. 1981). An automated cycler was used to provide three nocturnal cycles with 2 liters of dialysate lasting 3 hours each. Two liters were left in the abdomen in the morning.

### 26.1.5 Peritoneal Dialysis Solutions

During the early days of PD, parenteral solutions including 0.9% N-saline, 5% dextrose, and Ringer's solution were used as dialysate. Soon it was realized that the composition of the PD fluid must be similar to interstitial fluids to prevent electrolyte disturbances and that the fluid must be hypertonic relative to blood to achieve adequate fluid removal. Bicarbonate was tried as a buffer and dextrose was used as an osmotic agent. This led to two main problems: 1) during the sterilization procedure, carrmelization of the glucose had to be avoided, and 2) solutions containing both bicarbonate and calcium could not be stored together because of precipitation of calcium carbonate. In 1938, Jonathan Rhoads started adding lactate to the solution to correct metabolic acidosis (Rhoads 1938). Carmelization of glucose was prevented by formulating PD fluids at a pH of 5.0–5.5. The composition of commonly used PD solutions and the modifications over time are discussed in a following section.

## 26.2 TYPES OF PERITONEAL DIALYSIS

There are several different ways in which PD can be used for the treatment of uremia and allows the therapy to be tailored to the patients' needs. Thus, in most patients, the selection of the PD modality largely depends upon which therapy suits the patients' lifestyle. The therapy can either be continuous or intermittent – however, unlike the early days of PD, intermittent use of the therapy generally implies that treatment is undertaken on at least a daily basis. In patients with no significant residual renal function, it is always desirable to use a continuous therapy.

### 26.2.1 Peritoneal Dialysis Techniques: Continuous Therapies

#### 26.2.1.1 Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD is a therapy that is performed manually by the patient. A typical prescription requires the patient to perform four exchanges of dialysate over a 24-hour period using a fill volume ranging from 1.5 to 3.0 L. In many Asian countries, however, patients perform only three exchanges and probably because of the smaller body size, have comparable or better outcomes (Lam et al. 2006). Since its original description, there have been few changes in the basic therapy, although there have been many changes in the connection devices or "connectology" used to perform the exchanges.

#### 26.2.1.2 Continuous Cycling Peritoneal Dialysis (CCPD)

CCPD is the most widely practiced form of automated peritoneal dialysis (APD) (USRDS 2006). In its most common form, the patients use an automated cycler to perform 3-5 exchanges while they sleep with a subsequent daytime dwell. Since this modality entails the presence of dialysate in the peritoneal cavity for 24 hours, patients continually undergo dialysis and qualify it as a continuous therapy. Some patients also need a day-time "manual" exchange, either to maximize solute clearances or to enhance fluid removal. The modern-day cyclers are substantially smaller in size, portable and more versatile than the early-generation machines – contemporary cyclers manufactured by Baxter Healthcare and Fresenius Medical Care are depicted in Fig. 26.1 and 26.2 respectively.

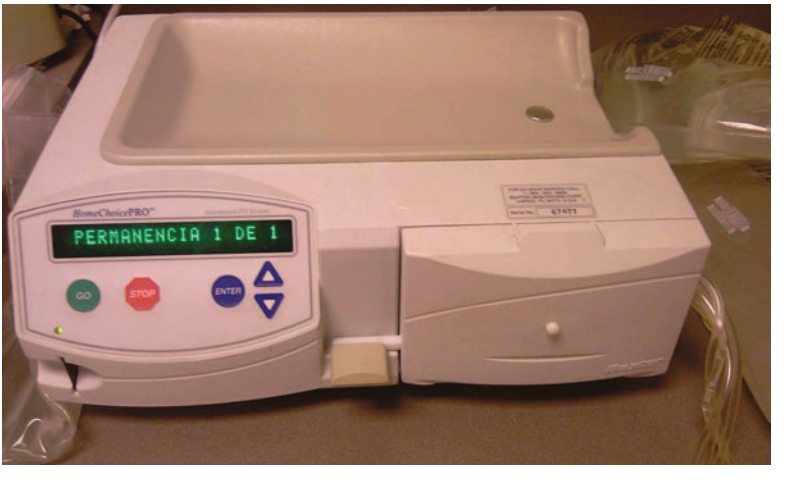


**Fig. 26.1** Home Choice Pro (®Baxter Healthcare) cycler for peritoneal dialysis. The scooped surface on the top is to place the dialysate bag and the machine warms the fluid to room temperature prior to instillation in the abdominal cavity. The knob on the right hand opens a compartment to place the cassette where all the tubings are organized. The display screen on the left provides easy-to-follow instructions to patients in a variety of languages. The slit on the bottom left holds a card that records treatment data for up to 90 days and the information can either be downloaded via a modem or directly from the card onto a computer in the dialysis unit for the staff to review and advise the patient.


**Fig. 26.2** Liberty cycler (®Fresenius Medical Care) for peritoneal dialysis. The scooped surface on the top is to place the dialysate bag and the machine warms the fluid to room temperature prior to instillation in the abdominal cavity. The knob on the right hand opens a compartment to place the cassette where all the tubings are organized. The touch-screen on the left provides easy-to-follow instructions to patients in a variety of languages.

#### 26.2.1.3 Tidal Peritoneal Dialysis (TPD)

TPD is best performed nightly by the use of an automated cycler. It involves the maintenance of an intrapertioneal reservoir of dialysate – this is achieved by an incomplete drainage of the fluid at the end of each dwell. Additional amounts of fluid are instilled with each exchange to maintain an optimal intraperitoneal volume. The hypothesis that TPD will enhance solute clearances has not been borne by recent studies (Aasarod et al. 1997; Juergensen et al. 2000; Vychytil et al. 1999a). It, can however, be used for patients who have infusion pain – the reservoir of dialysate minimizes pain upon instillation of fresh dialysate (Juergensen et al. 1999).

### 26.2.2 Peritoneal Dialysis Techniques: Intermittent Therapies

Because intermittent therapies typically use multiple short dwells, they tend to be automated but can be done manually. As indicated above, they should rarely be used in patients without significant residual renal function.

#### 26.2.2.1 Intermittent Peritoneal Dialysis (IPD)

By definition, IPD implies that therapy periods alternate with times when the peritoneum has been drained ("dry abdomen"). Typically the patient uses multiple short dwell exchanges three or four times a week either in a hospital or a dialysis unit. In recognition of the inadequate metabolic control of uremia in many patients, IPD is now rarely used.

#### 26.2.2.2 Nightly Intermittent Peritoneal Dialysis (NIPD)

NIPD, by definition, is a form of IPD that is done every night generally with the use of a cycler. It is best utilized by patients with significant residual renal function. Daytime ambulatory peritoneal dialysis (DAPD) is based on the same concept as NIPD, but DAPD is usually a manual technique, and the patient typically has a "dry time" during the night. In addition to its use in patients with significant residual renal function, NIPD can also be used for management of patients with heart failure, or patients treated with CAPD or CCPD, who have developed hernias or leaks (Bilora et al. 2002).

### 26.2.3 Selection of PD Modality

The rate of transfer of solutes across the peritoneal membrane is determined by the number of blood vessels per unit surface area – the effective peritoneal surface area (Mateijsen et al. 1999). There is considerable variability in the effective peritoneal surface area between individuals (Twardowski et al. 1987). Greater the peritoneal transport rate, faster is the rate of glucose absorption across the peritoneal membrane – under these circumstances, the osmotic gradient for fluid removal is dissipated more rapidly. Thus, individuals with fast solute transport rate may have insufficient fluid removal with longer dwell times as in the case of CAPD and are better treated with at least some short dwells as a part of the prescription as is often the case with automated PD. In contrast, patients with low solute transfer

rate require longer dwell times to maximize solute removal and may best with treated with CAPD. Consistent with these arguments, slow transporters have a lower risk of death when treated with CAPD and fast transporters have a lower risk of death when treated with APD (Johnson et al. 2010b).

However, the considerations above don't apply to the overwhelming majority of PD patients for three reasons. First, over 70% of patients have "average" transport type and in these patients, PD prescriptions can be adjusted to maximize solute and fluid removal. Second, fast transporters are considerably more common than slow transporters. Peritoneal transport rate, while useful to design appropriate PD prescriptions, explains only 15% of the variability in fluid removal with PD (Davies 2001). Hence, to choose a PD modality based upon peritoneal transport rate alone is inappropriate. Finally, these considerations are less important in patients with at least some residual kidney function. Thus, patient choice dictates which PD modality they are treated with.

In 2008, over 60% of PD patients in the United States were treated with automated PD (CCPD or NIPD) (USRDS 2010). Some studies have shown that short, night-time exchanges with automated PD are insufficient to ensure adequate salt and water removal even in individuals with average transport type (Rodriguez-Carmona et al. 2004). This has raised concern that automated PD patients may be volume overloaded, compared to those treated with CAPD. However, two studies have now shown that careful management of automated PD prescription – limiting the number of night-time exchanges to 3-5, liberal use of icodextrin for the long day dwell and a day-exchange – is effective in obviating volume overload (Boudville et al. 2007; Davison et al. 2009). Consistent with these observations, the risk for death or transfer to HD for patients treated with either continuous ambulatory PD (n=42,942) or automated PD (n=23,439) from 1996-2004 in the United States were virtually identical (Mehrotra et al. 2009, 2011). These data are consistent with studies from Australia, New Zealand, and Netherlands (Badve et al. 2008; Michels et al. 2009). These data are highly reassuring that with current practice patterns, outcomes with both CAPD and automated PD are identical. It appears likely that patient choice will continue to drive the expansion of the use of automated PD in many developed countries, including the United States. On the other hand, financial considerations are likely to continue to limit the use of automated PD in many developing countries.

## 26.3 PERITONEAL DIALYSIS ACCESS

### 26.3.1 Preoperative Assessment for Catheter Selection

Evaluation of the patient in advance of the peritoneal dialysis access procedure permits selection of the most appropriate catheter device and exit-site location (Crabtree et al. 2005). The patient must be evaluated fully dressed and in the upright and recumbent positions to assess location of belt line and skin folds. In addition, conditions such as urinary or fecal incontinence, chronic intertrigo, and presence of intestinal or urinary stomas will affect the choice of catheter type. The patient's bathing habits and occupation may influence the preference for exit-site location. Examination should include a search for abdominal wall hernias that will require repair at the time of the catheter placement procedure.

The selected catheter device must be able to produce deep pelvic position of the catheter tip for good hydraulic function, an exit-site easily visible to the patient that is free of contamination or mechanical irritation, and minimal resiliency forces from tubing shape memory in its passage through the abdominal wall to prevent catheter tip migration and superficial cuff extrusion (Dombros et al. 2005; Gokal et al. 1998). Three variations of the Tenckhoff catheter are available that offer maximum flexibility in exit-site location according to the patient's body habitus and special needs while affording good hydraulic function with minimal tubing stress (see Fig. 26.3) (Crabtree 2006c). Catheters with a preformed bend in the intercuff segment are best suited for providing an exit-site below the level of the belt line. Patients with low lying belt lines or lower abdominal skin folds may be better suited with a catheter with a straight intercuff segment that is bent to produce a laterally directed exit-site that emerges above the level of the belt line in the mid-abdominal region (Crabtree et al. 2005). Individuals with significant obesity, floppy skin folds, intertrigo, presence of stomas, or who desire deep tub baths are candidates for a two-piece extended catheter system that can remotely locate the exit-site to the upper abdomen or chest (see Fig. 26.4) (Crabtree 2004; Crabtree and Fishman 2003a; Twardowski et al. 1998).

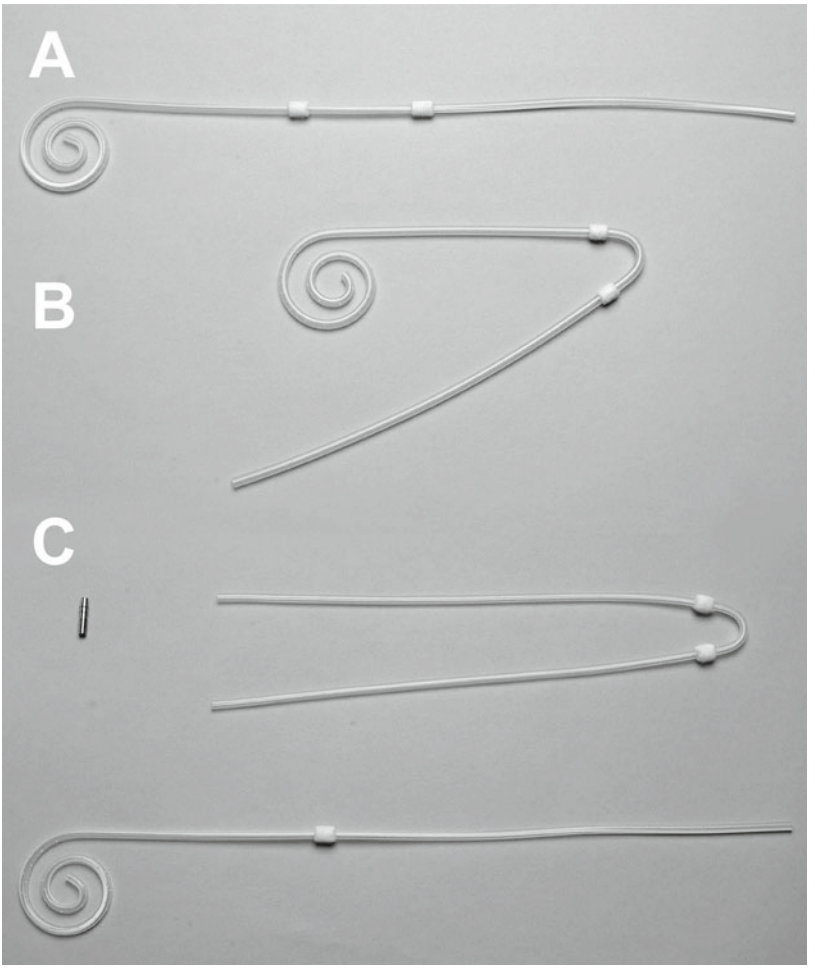


**Fig. 26.3** Peritoneal dialysis catheters. A: Two-cuff, straight intercuff segment, coiled-tip Tenckhoff catheter. B: Two-cuff, preformed intercuff arcuate bend, coiled-tip Tenckhoff catheter. C: Extended Tenckhoff catheter system. (left) titanium connector; (right) two-cuff, preformed intercuff arcuate bend extension tube; (bottom) one-cuff, coiled tip abdominal catheter.

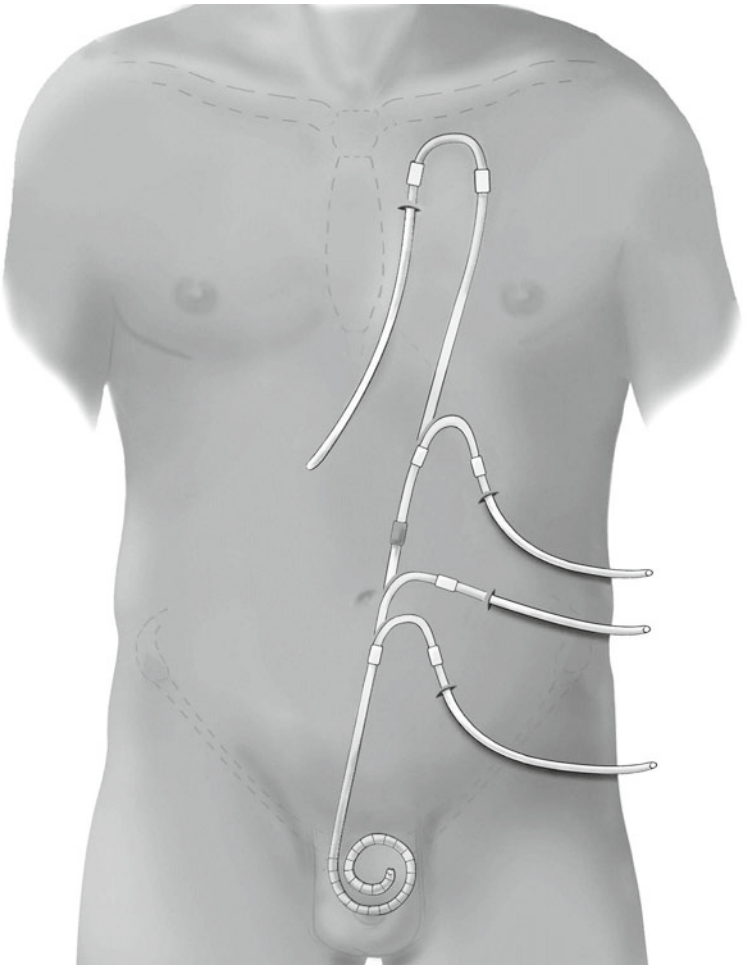

**Fig. 26.4** Tenckhoff catheter modifications that provide for a variety of exit-site locations based upon patient-specific characteristics.

### 26.3.2 Preoperative Preparation

Prevention of constipation is an important concern to avoid postoperative colon distention that can affect catheter flow function by external tubing compression or catheter tip displacement from the pelvis (Brook et al. 2004; Gokal et al. 1998). Moreover, constipation has been associated with translocation of bacteria through the bowel wall with peritonitis (Singharetnam and Holley 1996; Suh et al. 1996). Narcotic analgesics, ileus, reduced physical activity, and incisional soreness during bearing down predispose the patient

to postoperative stool retention. An enema or a stimulant suppository is administered the evening before surgery to evacuate the lower colon. More aggressive therapy starting well in advance of the procedure is required for patients with severe chronic constipation. Perioperative use of stool softeners and osmotic laxatives (sorbitol 70%, lactulose, or polyethylene glycol) are recommended for prevention and treatment of constipation.

To reduce the skin bacterial count, the patient should shower on the day of surgery with a chlorhexidine soap wash of the operative site. Removal of body hair should be performed in the preoperative holding area, preferably with electric clippers to reduce the risk of skin nicks and abrasions that could subsequently harbor bacteria. Patients are instructed to empty the bladder prior to the implantation procedure; otherwise, a Foley catheter should be inserted. A single dose of a prophylactic antibiotic to provide antistaphylococcal coverage is administered prior to the procedure. A first-generation cephalosporin is recommended. Vancomycin is substituted in the event of cephalosporin allergy (Dombros et al. 2005; Gokal et al. 1998).

### 26.3.3 Best Demonstrated Practices in Access Placement

Regardless of the technique utilized to implant the peritoneal dialysis catheter, there are best demonstrated practices that should be followed in every case. Adherence to these recognized practices can reduce the risk of catheter tip migration, pericatheter leaks and hernias, superficial cuff extrusion, and catheter-related infections.

The dialysis catheter should be inserted off of the midline in a paramedian location through the body of the rectus muscle with the deep cuff placed within the rectus sheath to provide for good tissue ingrowth and fixation of the catheter, thus reducing the risks of pericatheter leak and hernia (Helfrich et al. 1983; Spence et al. 1985). Oblique passage of the catheter through the muscle further immobilizes the intramural tubing segment and maintains the catheter tip in pelvic orientation (Comert et al. 2005; Crabtree and Fishman 2005; Helfrich et al. 1983; Ogunc 2005; Poole and Tervit 2000). Historically, midline implantation of dialysis catheters was preferred because of less dissection required to reach the peritoneal cavity and lower risk of bleeding. However, the relative thinness of the fascia and peritoneum in the midline infraumbilical region makes it difficult to achieve a good seal around the catheter resulting in an unacceptable rate of pericatheter leaks. Due to the limited fascial attachments and compromised tissue ingrowth of the deep catheter cuff, there is a higher incidence of external catheter displacement resulting in late pericatheter

leaks, hernias, and extrusion of the superficial cuff through the exit wound (Spence et al. 1985).

Subcutaneous tunneling of the catheter to the exit-site should be performed with a trocar or stylet device that does not exceed the diameter of the tubing and results in a tight skin hole around the catheter. The risk of early catheter-related infections can be reduced by avoiding patulous tunnel tracks and exit wounds (Crabtree et al. 1999). The direction of the tunnel tracks should precisely follow the design pattern of catheters possessing a preformed bend that produces a downward facing exit-site. Devices with a straight intercuff segment should use a laterally directed tunnel track in which the skin exit-site is cephalad to the level of the muscle insertion site of the catheter. This tunnel track configuration creates a gentle arch with minimal tubing stress to provide a mid-abdominal exit-site. The superficial cuff should be positioned 2-3 cm from the skin exit wound with catheters equipped with a preformed bend and 4 cm for catheters having a straight intercuff segment. Proper positioning of the superficial cuff relative to the exit wound leaves it less prone to extrusion and to infection spreading from the exit-site (Crabtree 2003; Favazza et al. 1995; Helfrich and Winchester 1982).

The catheter adapter and transfer set should be connected to the catheter at the time of the implantation procedure. Performing these catheter attachments in the sterile environment of the operating room eliminates potential contamination that may accompany disturbing the dressing and opening the catheter system to make these necessary connections in the immediate postoperative period.

Immobilization of the catheter to prevent motion at the exit wound and accidental displacement is required during the first several weeks following implantation until sufficient time has been allowed for exit-site healing and catheter cuff fixation by tissue ingrowth. The catheter is secured to the skin adjacent to the exit wound with medical adhesive tincture and sterile adhesive strips (Crabtree and Fishman 2005; Helfrich et al. 1983). A suture should never be used to anchor the catheter. Sutures left in for several weeks commonly produce stitch pustules or abscesses that risks early exit-site and tunnel track infection. Further immobilization of the catheter is obtained with a dressing that covers the entire device.

Unless soiled or loosened, dressings are changed at weekly intervals for the first 2 weeks or until such time that the patient undergoes training in daily exit-site care. Dressing changes should be under the exclusive purview of peritoneal dialysis nursing staff using masks and sterile technique (Dombros et al. 2005; Gokal et al. 1998). Catheter irrigation by the dialysis

staff is performed within 72 hrs of the implantation procedure and weekly to demonstrate patency and to clear any blood and fibrin that may be present from the postoperative period.

### 26.3.4 Peritoneal Catheter Placement Techniques

Methods for peritoneal dialysis catheter insertion include placement by percutaneous guidewire technique (performed blindly or with fluoroscopic guidance), open surgical dissection, and laparoscopic implantation. While the majority of catheters are inserted by surgeons using an open dissection technique, an increasing proportion of catheter placement procedures are now being done laparoscopically. Optionally, the implantation technique may include embedding the external limb of the catheter tubing under the skin with delayed exteriorization when initiation of dialysis is needed. An overview of each of the implantation approaches is presented below.

#### 26.3.4.1 Percutaneous Guidewire Technique

Placement of catheters by blind percutaneous puncture is performed using a modification of the Seldinger technique (Mellotte et al. 1993; Ozener et al. 2001; Zappacosta et al. 1991). The convenience of this approach is that it can be performed at the bedside under local anesthesia using prepackaged self-contained kits that include the dialysis catheter. The abdomen is usually prefilled with dialysis solution instilled with a needle inserted through either a midline infraumbilical incision or lateral to the rectus sheath. A guidewire is passed through the needle into the peritoneal cavity. The needle is withdrawn. A dilator with overlying peel-away sheath is advanced through the fascia over the guidewire. The guidewire and dilator are removed. Stiffened over a stylet, the dialysis catheter is directed through the sheath toward the pelvis. As the deep catheter cuff advances, the sheath is peeled away. When the deep cuff stops at the level of the fascia, the remainder of the sheath is removed from around the catheter. The addition of fluoroscopy to the procedure permits confirmation of needle entry into the peritoneal cavity by observing the flow of injected contrast solution around loops of bowel (Georgiades and Geschwind 2002; Savader et al. 2000). The guidewire is advanced into the pelvis under fluoroscopic control. The remainder of the procedure proceeds as described for blind placement. Although the radiopaque tubing stripe permits fluoroscopic imaging of the final catheter configuration, the proximity of adhesions or omentum cannot be assessed. Percutaneous guidewire placement techniques leave the deep catheter cuff external to the fascia. Subcutaneous

tunneling of the catheter to the selected exit-site is performed as described in the section on best practices.

#### 26.3.4.2 Open Dissection Placement

A paramedian incision is made through the skin, subcutaneous tissues, and anterior rectus sheath. The underlying muscle fibers are split to expose the posterior rectus sheath. A small hole is made through the posterior sheath and peritoneum to enter the peritoneal cavity. A purse-string suture is placed around the opening. The catheter, usually straightened over an internal stylet, is advanced through the peritoneal incision toward the pelvis. Despite being an open procedure, the catheter is advanced mostly by feel, therefore, blindly, into the peritoneal cavity. The stylet is partially withdrawn as the catheter is advanced until the deep cuff abuts the posterior fascia. After satisfactory placement has been achieved, the stylet is completely withdrawn and the purse-string suture is tied. Encouraging the catheter tip to remain oriented toward the pelvis is achieved by oblique passage of the catheter through the rectus sheath in a craniocaudal direction (Helfrich et al. 1983; Spence et al. 1985). The catheter tubing is exited through the anterior rectus sheath at least 2.5-cm cranial to the level of the purse-string suture and deep cuff location. Attention to detail in placement of the purse-string suture and repair of the anterior fascia is imperative to prevent pericatheter leak and hernia. Subcutaneous tunneling of the catheter to the selected exit-site is performed as described in the section on best practices.

#### 26.3.4.3 Laparoscopic Implantation

Laparoscopy provides a minimally invasive approach with complete visualization of the peritoneal cavity during the catheter implantation procedure. The advantage of laparoscopic catheter placement over other approaches is the ability to proactively employ adjunctive procedures that significantly improve catheter outcomes. Laparoscopically guided rectus sheath tunneling places the catheter in a long musculofascial tunnel oriented toward the pelvis and eliminates catheter tip migration (Comert et al. 2005; Crabtree and Fishman 2005; Ogunc 2005; Poole and Tervit 2000). Observed redundant omentum that lies in juxtaposition of the catheter tip can be displaced from the pelvis into the upper abdomen and fixed to the abdominal wall (omentopexy) (Crabtree and Fishman 2003b; Ogunc 2005). Compartmentalizing adhesions that may affect completeness of dialysate drainage can be divided. Intraperitoneal structures that siphon up to the catheter tip during the intraoperative irrigation test can be laparoscopically resected,

including epiploic appendices of the sigmoid colon and uterine tubes. Previously unsuspected abdominal wall hernias can be identified and repaired at the time of the catheter implantation procedure (Crabtree 2006c).

Through a lateral abdominal wall puncture site remote from the point of intended catheter placement, the abdomen is insufflated with gas through a pneumoperitoneum needle to create an intraperitoneal working space. A laparoscopic port and laparoscope are inserted. Under laparoscopic guidance, the catheter is introduced at a second puncture site and placed in a musculofascial tunnel oriented towards the pelvis, usually through the use of a port device that creates the rectus sheath tunnel (Crabtree and Fishman 2005). Some variations of the technique use a third laparoscopic port site to introduce laparoscopic forceps to assist in the catheter tunneling process (Comert et al. 2005; Ogunc 2005; Poole and Tervit 2000). The catheter tip is directed into the true pelvis under visual control. The deep cuff of the catheter is positioned in the rectus muscle just below the anterior fascial sheath. A purse string fascial suture is placed around the catheter at the level of the anterior sheath. The laparoscope is left in place until a test irrigation of the catheter demonstrates successful flow function. After any indicated adjunctive procedures are completed, subcutaneous tunneling of the catheter to the selected exit-site is performed as described in the section on best practices.

#### 26.3.4.4 Catheter Embedding Procedure

Catheter embedding has been characterized as the 'AV fistula of peritoneal dialysis' (Dasgupta 2002). The catheter is implanted in advance of intended use and allowed to 'mature' in the subcutaneous bed until the start of dialysis. One benefit may be that the catheter is allowed to heal in a sterile environment without the potential contamination posed by the presence of an exit wound (Moncrief et al. 1993). Firm tissue ingrowth of the cuffs and absence of biofilm formation have been speculated to reduce catheter infection-related peritonitis. Another important attribute of catheter embedding is greater patient acceptance for earlier commitment to peritoneal dialysis by catheter placement ahead of time. The patient is not burdened with catheter maintenance until dialysis is needed. The need for insertion of vascular catheters and temporary hemodialysis can be averted in patients previously implanted with an embedded catheter. When needed, the catheter is simply exteriorized and the patient begins full dose dialysis without the necessity of a break-in period. The embedding technique permits more efficient surgical scheduling of catheter implantation as a non-urgent procedure (McCormick et al. 2006).

Catheter embedding can be incorporated into any of the implantation approaches using any catheter device (Crabtree 2006c). After flow function of the catheter is confirmed, the tubing is flushed with heparin, plugged, and buried in the subcutaneous tissue. Embedding should not be performed if anticipated need for dialysis is less than 4 weeks. Catheters have been embedded for months to years with a 93% function rate after exteriorization (McCormick et al. 2006).

### 26.3.5 Complications of the Dialysis Catheter

Non-infectious complications specifically related to the peritoneal catheter include flow dysfunction of the intraperitoneal end, leaks and hernias around the transmural segment, and displacement of the outer portion with superficial cuff extrusion.

#### 26.3.5.1 Flow Dysfunction

Disturbances in hydraulic performance of the catheter can result from catheter tip migration to a position of poor drainage function by inherent resiliency forces of the rubber tubing or blockage of the side drainage holes by adherent intraperitoneal structures (Brook et al. 2004; Crabtree 2006b; Gokal et al. 1998). These conditions must be differentiated from catheter displacement or compression resulting from distended bowel or bladder. Migration of the catheter tip is caused by excessive bending of a straight catheter with creation of tubing stress, poor immobilization of the intramural catheter segment, and weak fixation of the deep cuff. An attempt can be made to reposition the catheter; however, recurrent migration indicates the need for new catheter placement using recognized best practices.

Intraabdominal structures may siphon up to the catheter and become adherent to the side drainage holes resulting in outflow or 2-way flow obstruction. Most commonly, these tissues include the omentum, epiploic appendices of the colon, and uterine tubes (Crabtree 2006b). Infrequently, the catheter may become blocked by intestinal adhesions despite absence of apparent antecedent infection. The inflammatory effect of residual intraperitoneal blood leftover from the catheter placement procedure has been observed to cause local adhesions and catheter blockage (Gadallah et al. 2001).

Adopting laparoscopic implantation techniques that employ selective prophylactic omentopexy effectively eliminates the occurrence of omental entrapment (Crabtree and Fishman 2003b). Transluminal guidewire

(Davis et al. 1982; Dobrashian et al. 1999; Simons et al. 1999) or Fogarty catheter manipulation (Gadallah et al. 2000a) is associated with high failure and recurrence rates in approximately 27-55% of cases, especially since there is no definitive treatment of the intraperitoneal structure causing the obstruction. In contrast, laparoscopy permits expedient diagnosis and treatment of catheter flow dysfunction through procedures such as omentopexy, resection of epiploic appendices and uterine tubes, and adhesiolysis (Crabtree 2006b). Laparoscopic rescue of obstructed catheters is often considered the primary intervention after diagnoses of constipation, fibrin plug, and urinary retention have been excluded.

#### 26.3.5.2 Pericatheter Leaks and Hernias

Leaks and hernias around the abdominal wall segment of the catheter can be avoided by following the previously discussed best practices in placement. Leaks from early catheter use are managed by reducing dialysate volume, recumbent dialysis, or temporary catheter rest (Leblanc et al. 2001; Tzamaloukas et al. 1990; Winchester and Kriger 1994). Dramatic early leaks require surgical exploration for technical error. Pericatheter hernias and late leaks are best dealt with by removal of the catheter, repair of the defect, and reinsertion of the catheter at a new abdominal wall location (Crabtree 2006a).

## 26.4 PERITONEAL DIALYSIS SOLUTIONS

The success of modern-day dialysis therapy is based upon its ability to remove uremic toxins (solute transfer), correct metabolic acidosis, and remove salt and water (ultrafiltration). The composition of conventional PD solutions, summarized in Table 26.1, allows the therapy to best achieve each of these three goals. In addition to movement of uremic toxins along their concentration gradient, the dialysate concentrations of sodium, potassium, and magnesium are lower than in uremic plasma and allows for their diffusive removal. Lactate is used as a buffer to correct metabolic acidosis – during the course of dwell, bicarbonate enters the dialysate and is removed from the body but lactate is absorbed and converted in the liver to bicarbonate. The low-lactate solution (35 meq/L; PD-1) is generally insufficient to correct uremic metabolic acidosis and hence, is no longer commercially available in the United States. Finally, high concentrations of dextrose are used to exert an osmotic force across the peritoneal membrane to remove excess salt and water. Conventional PD solutions are available in three different strengths – 1.5%, 2.5%, and 4.25% dextrose (or 1.36%, 2.25%, and 3.86% glucose) and patients are trained to change the dialysate

concentrations based upon the amount of fluid that needs to be removed on any given day. Unlike the dialysate used for hemodialysis, PD solutions are sterile. In order to minimize the generation of toxic glucose degradation products during heat sterilization, the pH of the solution is substantially below the physiologic pH (5.5).

**Table 26.1** Composition of various glucose-based peritoneal dialysis solutions

| | **PD-1** | **PD-2** | **PD-4** |
|---|---|---|---|
| **Na, mEq/L** | 132 | 132 | 132 |
| **K, mEq/L** | 0 | 0 | 0 |
| **Ca, meq/L** | 3.5 | 3.5 | 2.5 |
| **Mg, mEq/L** | 0.75 | 0.75 | 0.75 |
| **Cl, mEq/L** | 102 | 96 | 96 |
| **Lactate, Eq/L** | 35 | 40 | 40 |
| **pH** | 5.2 | 5.2 | 5.2 |
| **Dextrose** | 1.5%, 2.5%, 4.25% | 1.5%, 2.5%, 4.25% | 1.5%, 2.5%, 4.25% |
| **Note:** PD-1 is not commercially available in the United States; over 85% of glucose-based dialysate sold in the United States now is PD-4 | | | |

As is evident, conventional PD solutions are unphysiologic (hyperosmolar, low pH, presence of glucose degradation products) and have been implicated in damaging the peritoneal membrane after long-term PD. There has been a rapid expansion of our knowledge of the pathways whereby conventional PD solutions damage the peritoneum (see Fig. 26.5) (Chin and Yeun 2006). Accumulating evidence suggests the primacy of the role of advanced glycosylation end-products (AGE), formed from the high glucose concentrations in PD fluids. AGE formation is amplified by glucose degradation products, which themselves are also directly cytotoxic (Hirahara et al. 2006; Leung et al. 2005). The AGE and glucose degradation products stimulate the release of a lot of mediators, the most important of which is the transforming growth factor β (TGF β) - a 'master molecule' in the processes that induce peritoneal sclerosis (Selgas et al. 2006). Glucose, AGEs, glucose degradation products, and interleukin-1 induce the synthesis and release of TGF β from peritoneal mesothelial cells. Glucose in the PD fluid can induce the synthesis and release of leptin from peritoneal adipocytes and angiotensin II from mesothelial cells (Kyuden et al. 2005; Teta et al. 2005). Both leptin and angiotensin II, in turn, also stimulate TGF β release (Kyuden et al. 2005;

Leung et al. 2006). Growth factors like vascular endothelial growth factor, fibroblast growth factor, and connective tissue growth factor are additional key players in the pathways leading to peritoneal sclerosis (Selgas et al. 2006). Oxidative stress and endothelin-1 may also contribute to inducing the functional and structural changes in the peritoneal membrane (Noh et al. 2006; Shimizu et al. 2006). These mediators induce mesothelial cell injury and there is increasing evidence that mesothelial cells transdifferentiate to fibroblasts (Selgas et al. 2006). The myofibroblasts thus formed from epithelial-mesenchymal transformation, along with the resident fibroblasts in the submesothelial matrix, lead to increased deposition of collagen and extracellular matrix (Selgas et al. 2006). This submesothelial thickening is a key component of peritoneal sclerosis seen in some long-term PD patients. The increased peritoneal vascular density results in an increased effective peritoneal surface. This, in turn, may lead to problems with ultrafiltration with the use of CAPD.

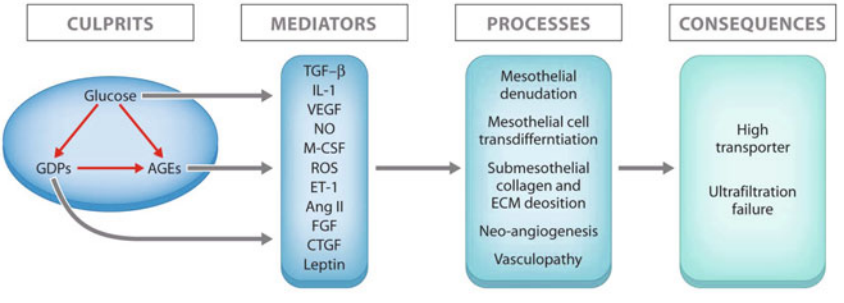


**Fig. 26.5** A clinician's view of the long-term effects of bioincompatible peritoneal dialysis solutions on peritoneal membrane. AGE, advanced glycosylation end products; AngII, angiotensin II; CTGF, connective tissue growth factor; ECM, extracellular matrix; ET1, endothelin-1; FGF, fibroblast growth factor; GDP, glucose degradation products; M-CSF, macrophage colony-stimulating factor; NO, nitric oxide; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. (Reproduced with permission from Agarwal R, Mehrotra R. NepSAP 2006; 6 (3): 117-189))

Given the desire to maintain the long-term integrity of the peritoneal membrane as a dialyzer, numerous modifications of the conventional PD solutions have been tested and several are now commercially available (see Table 26.2). A detailed description of each solution is beyond the scope of this chapter; a brief description of three of these solutions is provided herein.

**Table 26.2** Advanced peritoneal dialysis solutions manufactured by the two largest suppliers commercially available in different parts of the world

| Manufacturer | Solution | FDA Approved? | Compartments | Buffer Concentration | | Osmotic Agent | pH |
|---|---|---|---|---|---|---|---|
| | | | | Lactate | Bicarbonate | | |
| Baxter HealthCare | Extraneal | Yes | One | 40 | 0 | 7.5% Icodextrin | 5.2 |
| | Nutrineal | No | One | 40 | 0 | 1.1% amino acids | 6.4 |
| | Physioneal | No | Two | 10 or 15 | 25 | Glucose | 7.4 |
| Fresenius Medical Care | Balance | Yes | Two | 35 | 2.5 | Glucose | 7.0 |
| | BicaVera | No | Two | 0 | 34 | Glucose | 7.4 |

### 26.4.1 Glucose/Lactate/Low GDP Solutions

A solution with very low concentrations of glucose degradation products – with the same composition as conventional PD solutions – is produced when the components of the solution are separated into two compartments at the time of heat sterilization. One compartment contains the osmotic agent (glucose) at a very low pH and the second contains the electrolytes. Patients break the seal between the two compartments just prior to intraperitoneal instillation to yield a solution at physiologic pH. The generation of glucose degradation products appears to be the least at a high glucose concentration (50-60%) and a low pH (2.2-2.6) (Erixon et al. 2006). However, there is only limited evidence for tangible clinical benefits. An early, short-term crossover study suggested that patients had a higher urine volume during the period they were treated with solutions with low concentrations of glucose degradation products (Williams et al. 2004). However, three subsequent randomized controlled trials with longer periods of follow-up have been unable to confirm any beneficial effect of these solutions on preserving residual renal function (Fan et al. 2008; Kim et al. 2009; Szeto et al. 2007). Despite our understanding of the role of glucose degradation products in causing peritoneal membrane damage, there are no studies that have demonstrated that the solutions with low concentrations of glucose degradation products are superior in preserving the integrity of the peritoneal membrane over conventional solutions. Finally, an observational study from Korea has shown a lower risk for death among patients treated with the solutions with low glucose degradation products (Lee et al. 2005, 2006). The data while encouraging, are limited by the study design and cannot be considered conclusive. Given the paucity of data demonstrating clinical benefit, the role of these solutions in the practice of peritoneal dialysis remains uncertain.

### 26.4.2 Bicarbonate or Bicarbonate/Lactate Solutions

Concerns regarding the unphysiologic nature of the buffer (lactate) and acidic pH of the traditional solutions led to the development of bicarbonate based solutions (with/without lactate). These solutions necessarily have at least two compartments, yield a solution with a physiologic pH, and are more biocompatible in *in vitro* cell culture systems (Fusshoeller et al. 2005). The improved biocompatibility is not entirely explained by a higher pH and may, in part, be related to lower concentrations of glucose degradation products (Zareie et al. 2006). The higher pH and reduced concentration of lactate in some of these solutions reduces the initial vasodilatation induced by the conventional solutions; this, in turn, enhances ultrafiltration with bicarbonate/lactate buffered solutions (Simonsen et al. 2006). In contrast, pure bicarbonate solutions are associated with lower ultrafiltration and higher urine volume (Montenegro et al. 2006). Furthermore, solutions with bicarbonate buffers have now been repeatedly shown to be more efficient in correcting metabolic acidosis associated with ESRD (Montenegro et al. 2006). There is no evidence that bicarbonate based PD solutions are superior in preserving the long-term peritoneal membrane as a dialyzer, over the conventional PD solutions. Finally, in an observational study of more than 2000 patients from Korea, those treated with bicarbonate/lactate PD solutions had a 30% lower risk for death – this finding was confirmed in a variety of analyses including sophisticated approaches that adjusted for propensity of being treated with a particular solution (Han et al. 2009). However, observational studies only generate hypotheses – only randomized, controlled clinical trials can provide conclusive evidence for benefit. It is unclear if such clinical trials would be undertaken in the near future. Hence, there is limited evidence to support the widespread use of these solutions in the clinical practice of peritoneal dialysis.

### 26.4.3 Icodextrin/Polyglucose

In addition to the limitations imposed by their biocompatibility, conventional PD solutions are also limited by the use of glucose as an osmotic agent. Since glucose is readily absorbed when the dialysate is left in the peritoneal cavity for prolonged periods of time – the osmotic gradient for fluid removal dissipates over time (Mujais and Vonesh 2002). This leads to inadequate fluid removal during the long dwells and can lead to clinically manifest volume overload. Icodextrin or polyglucose, available as a 7.5% solution, is a glucose polymer with a molecular weight of about

16,800 (Mistry and Gokal 1996). This exerts an oncotic pressure and generates slow but sustained ultrafiltration. Since icodextrin is absorbed slowly, it stays in the peritoneal cavity for longer period of time to generate greater ultrafiltration than glucose in the long dwells of either CAPD or APD (Davies et al. 2003; Finkelstein et al. 2005; Konings et al. 2003; Lin et al. 2009; Wolfson et al. 2002). In randomized, controlled clinical trials, this higher ultrafiltration volume has been shown to result in tangible improvements in the volume status of PD patients – a reduction in extracellular water, and regression of left ventricular hypertrophy (Davies et al. 2003; Konings et al. 2003). However, in clinical trials, no consistent benefit on blood pressure control has been demonstrated (Paniagua et al. 2009).

Icodextrin solution has significantly lower concentration of glucose degradation products than conventional PD solutions and an observational study has demonstrated its superiority in maintaining the long-term function of the peritoneal membrane over conventional glucose-based solutions (Davies et al. 2005). Furthermore, the higher ultrafiltration with icodextrin during the long dwell can allow for a reduction in the use of hypertonic solutions for other exchanges. This, in turn, has been shown to have a salutary effect on glycemic control (Marshall et al. 2003; Paniagua et al. 2009). Furthermore, reduction in glucose exposure has been shown to mitigate the hypercholesterolemia seen in PD patients (Bredie et al. 2001; Lin et al. 2009). Finally, an observational cohort study has demonstrated a lower risk for death in patients treated with icodextrin (Han et al. 2009). However, there is no randomized, controlled clinical trial to substantiate that benefit.

In summary, over the last decade, a large body of data has accumulated on the benefits associated with the use of icodextrin. It is particularly advantageous for the long dwell for patients with high-average or high peritoneal transport with inadequate ultrafiltration or as a glucose-sparing strategy.

## 26.5 COMPLICATIONS OF PERITONEAL DIALYSIS

### 26.5.1 Non-Infectious Complications of Peritoneal Dialysis

#### 26.5.1.1 Mechanical Complications

##### 26.5.1.1.1 Hernias and Leaks

The most common anatomic complication of peritoneal dialysis is hernias. The usual sites for these are sites of previous abdominal incisions

and the umbilical, inguinal and pericatheter regions (Van Dijk et al. 2005). The incidence of hernias on CAPD ranges between 10% and 25%, while for automated peritoneal dialysis the incidence is approximately 9% (Bargman 1993; Rocco and Stone 1985). The higher pressures in sitting and standing as against in the supine position may be partly responsible for this difference (Twardowski et al. 1983). However, even though intraperitoneal pressure (IPP) rises proportional to the infused volume, there is no consensus between studies whether higher fill volumes increase the incidence of hernias and leaks (Del Peso et al. 2003; Hussain et al. 1998; Van Dijk et al. 2005). It may be possible that the IPP required to cause hernias are much higher than achieved under usual clinical conditions, and patients who develop hernias have structural weakness of the abdominal wall. Susceptible patients include older multiparous females, patients with autosomal dominant polycystic kidney disease, those with prior hernias or dialysate leaks, and prolonged corticosteroid treatment (Del Peso et al. 2003; O'Connor et al. 1986; Van Dijk et al. 2005). Smaller diurnal fill volumes may be considered for susceptible patients. Surgery is recommended for most hernias because of the risk of bowel or omental incarceration and strangulation.

Dialysate leaks are another frequent complication and occur more often in CAPD than APD. Risk factors for development of leaks are the insertion of the peritoneal dialysis catheter in the midline, increased IPP, and a weak abdominal wall. Early leaks are usually external while late leaks infiltrate the abdominal wall. These may present as abdominal wall or genital edema, pericatheter pseudohernias, and rarely as a vaginal leak of dialysate. Leaks may cause ultrafiltration failure and weight gain. Fluid leaks may be detected by radionucleotide imaging, magnetic resonance peritoneography, or by computerized tomography scans with contrast in the dialysate (Leblanc et al. 2001; Scanziani et al. 2006).

Early leaks are managed by reducing dialysate volume, recumbent dialysis, or temporary catheter rest (Leblanc et al. 2001; Tzamaloukas et al. 1990; Winchester and Kriger 1994). Dramatic early leaks require surgical exploration for technical error. Late leaks are best dealt with by removal of the catheter, repair of the defect, and reinsertion of the catheter at a new abdominal wall location (Crabtree 2006a).

#### 26.5.1.1.2 Superficial Cuff Extrusion

The cuff should be implanted approximately 2–3 cm beneath the skin as a compromise between the need of a short sinus tract to prevent infections but

not so short as to favor cuff extrusions (Flanigan and Gokal 2005). Poor fixation of the transmural segment of the catheter, such as accompany midline placement with weak fascial attachment to the deep cuff or guidewire insertion techniques that position the deep cuff external to the fascia, may predispose to outward displacement of the device with superficial cuff extrusion through the exit-site (Spence et al. 1985). Another cause of cuff extrusion is excessive bending of a catheter with a straight intercuff segment in the subcutaneous track. Resilience or memory forces eventually lead to catheter straightening with migration of the cuff towards the exit-site (Twardowski et al. 1985). Shaving of the extruded cuff is usually recommended as a toilet procedure to eliminate absorbent material that harbors bacteria in the vicinity of the exit-site (Helfrich and Winchester 1982).

#### 26.5.1.1.3 Hydrothorax

Hydrothorax usually develops on the right side due to fluid traversing the diaphragm through defects in the diaphragm (Leblanc et al. 2001). Patients may range from being asymptomatic to having severe respiratory compromise. Many patients developing hydrothorax are females; multiparity confers an additional risk. Treatment options include low-volume supine dialysis, pleurodesis, or surgical repair, including video-assisted thoracoscopy (Szeto and Chow 2004).

#### 26.5.1.1.4 Back Pain

Back pain is another complication related to increased IPP. The increased IPP can pull lumbar vertebrae into a more lordotic position and increase the stress on the spine. Poor muscle tone, osteoporosis and degenerative joint disease can worsen the process. The treatment is aimed at reducing IPP by switching to APD, preferably with dry days (Bargman 1993).

#### 26.5.1.1.5 Encapsulating Peritoneal Sclerosis (EPS)

EPS is an infrequent but very severe complication in patients on long-term PD. Diagnosis comprises the fulfillment of two key criteria: firstly, symptoms that might indicate an obstructive ileus, which may range from mild symptoms such as anorexia to marked weight loss and bowel obstruction, and secondly the demonstration, either at laparotomy or from imaging techniques, that this ileus is due to peritoneal membrane thickening resulting in encapsulation and cocooning of the bowel (Augustine et al. 2009).

EPS is rare before 3 years on peritoneal dialysis. Published data have shown that the incidence of EPS at 5 and 8 years varies from 2.1% and 5.9% in Japan (Kawanishi et al. 2004). In the Scottish Renal Registry, the 8-year cumulative incidence of EPS between 2000 and 2007 was 8.1% and in Australia and New Zealand, between 1995 and 2007 was 3.9% (Brown et al. 2009b; Johnson et al. 2010a). It often manifests after discontinuation of PD in patients who have received a kidney transplant or transferred to hemodialysis. The only consistent risk factor is the duration of PD; association with episodes of peritonitis is less consistent (Brown et al. 2009a).

Patients present with abdominal pain, low grade fever, nausea, vomiting and features of intermittent intestinal obstruction. Patients develop progressive protein-energy wasting and loss of ultrafiltration. Hemoperitoneum or sterile non-resolving or recurrent peritonitis may be seen (Augustine et al. 2009). Plain radiographs show thickening and calcification of the bowel walls and calcification of the peritoneum but are rarely, if ever, diagnostic. Computerized tomographic scan findings include peritoneal thickening and calcification, and bowel tethering, thickening, dilatation, calcification, and septation (Tarzi et al. 2008; Vlijm et al. 2009). Histological findings of the sclerotic tissue demonstrate dense fibrous tissue permeated with a chronic inflammatory infiltrate.

Treatment options center around bowel rest, parenteral nutrition, and surgical lysis of adhesions when obstruction is present (Kawanishi et al. 2006). Immunosuppression, generally a short course of treatment with corticosteroids, may be useful during the inflammatory phase of the disease (Brown et al. 2009a). Case-series suggest that a trial of tamoxifen may be warranted (Korte et al. 2011).

#### 26.5.1.1.6 Hemoperitoneum

Hemoperitoneum is not an infrequent complication of peritoneal dialysis (Lew 2007). The presence of even minimal amounts of blood can color the peritoneal fluid pink or red. Performance of the dialysis procedure by PD patients often brings cases to light, which would have been otherwise clinically silent.

The commonest cause of hemoperitoneum is related to the gynecological conditions such as retrograde menstruation, ovulation, cyst rupture and endometriosis. Peritonitis and encapsulating peritoneal sclerosis can cause

hemoperitoneum but is extremely uncommon. In a number of patients, no definite etiology can be determined; it has been suggested that hemoperitoneum may have been a result of minor tears of the omental vessels. Occasionally, peritoneal catheter has been reported to have eroded into the major mesenteric vessels leading to hemoperitoneum. The management of hemoperitoneum is often expectant and if necessary, directed at the primary cause. If flushing the peritoneal cavity two or three times does not result in a clear effluent, addition of 500-1000 units of heparin to each bag of dialysate is often recommended to prevent catheter clotting. Desmopressin and unconjugated estrogens can ameliorate uremic bleeding but are generally unnecessary.

### 26.5.2 Infectious Complications of Peritoneal Dialysis

Peritoneal dialysis related infections include infection of the catheter exit site, subcutaneous track (tunnel), and the peritoneal cavity. These infections are a major cause of hospitalizations, technique failure, catheter loss and mortality but are preventable.

#### 26.5.2.1 Prevention of Infectious Complications

The strategies demonstrated to reduce infectious complications are summarized in Table 26.3. Introduction of infections through the lumen of the catheter, or intraluminal infections generally occur through touch contamination at the time of performing an exchange. Advances in connection and disconnection of PD catheters (connectology) have led to dramatic reductions in intraluminal infections (Daly et al. 2001; Szeto et al. 2005). Thus, “flush-before-fill”, use of double-bags and luer-locks are probably the most important contributors to reduction in peritonitis rates over the last two decades. The use of these disconnect systems has to be complemented with training and retraining of patients in aseptic technique. Careful washing and drying of hands and use of masks during exchanges is critical. Alcohol-based gels may be used to disinfect hands if hand washing is not possible. Patients should be trained in recognizing and reporting all episodes of accidental contamination during a PD exchange; appropriate administration of prophylactic antibiotics in such cases is another key strategy for reduction of infection risk (Bender et al. 2006).

**Table 26.3** Practices demonstrated to reduce the risk for infectious complications after the immediate post-operative period in patients undergoing peritoneal dialysis

| |
|---|
| **Intraluminal Infections** |
| ▸ Disconnect Systems and Twin Bags |
| ▸ Patient Training and Retraining |
| **Periluminal Infections** |
| ▸ Reduce nasal carriage of Staphylococcus aureus |
| ▸ Intranasal mupirocin |
| ▸ Rifampicin |
| ▸ Exit Site Application of antibiotics |
| ▸ Mupirocin |
| ▸ Gentamicin cream |
| ▸ Ciprofloxacin otologic solution |
| **Others** |
| ▸ Prophylactic antibiotics before invasive procedures |
| ▸ Anti-fungal prophylaxis with prolonged antibiotics |

Peri-luminal infections typically involve either the colonization or infection of the exit-site and are associated with the risk of infection tracking along the catheter tunnel track into the peritoneal cavity. The prevention of periluminal infections starts at the time of catheter insertion. The use of a single dose of prophylactic antibiotic in the immediate pre-operative period, atrauamtic surgery, good hemostasis, avoidance of sutures at the exit site, and immobilization of the external segment to facilitate healing all minimize the risks of infections in the immediate post-operative period (Crabtree and Burchette 2006; Flanigan and Gokal 2005; Gadallah et al. 2000b; Li et al. 2010; Twardowski 2004). Meticulous, daily exit-site care of healed exit-sites minimizes the risk of peri-luminal infections. Crusts should be softened and then removed rather than forced off. Healed exit-sites should be cleaned daily with antimicrobial soap or chlorhexidine and patted dry. Over the last decade, compelling evidence has accumulated to indicate that prophylactic antibiotics reduce the risk for both exit site infection as well as peritonitis. Since *Staphylococcus aureus* accounts for the vast majority of cases of exit-site infections, initial efforts to reduce periluminal infections were targeted at this organism. Early studies indicated that the nasal carriage of *Staphylococcus aureus* is a risk factor for peritoneal dialysis related infections (Crabtree et al. 2000; Luzar et al. 1990; Nouwen et al. 2006). Reducing nasal carriage by using intranasal mupirocin for 5 to 7 days decreases the incidence of *Staphylococcus aureus* exit-site infections, peritonitis and catheter loss (Crabtree et al. 2000; Perez-Fontan et al. 1992). Alternatively, oral

rifampin (600 mg/day for 5 days every 3 months) reduces *Staphylococcus aureus* exit-site infections, is as effective as intranasal mupirocin but is often poorly tolerated (Bernardini et al. 1996; Zimmerman et al. 1991). A meta-analysis reported up to 18% of the isolates were resistant to rifampin and the drug had to be discontinued in 7% of patients due to toxicities (Falagas et al. 2006). Moreover, periodic re-treatment of nasal carriers is frequently necessary because of a high recolonization rate (Mupirocin Study Group 1996; Crabtree et al. 2000; Perez-Fontan et al. 1992).

Given these limitations, daily application of antibiotics at the exit site as a part of daily care, has gained support. Thus, daily application of mupirocin at the exit site reduces infections, including peritonitis (Mehrotra et al. 2003; Thodis et al. 2000). Intermittent usage has been associated with an increasing prevalence of resistance to mupirocin and, thus, needs to be avoided (Perez-Fontan et al. 2002b). *Pseudomonas aeruginosa* is the second most frequent cause of exit site infection and periluminal infections. While mupircoin reduces gram positive infections, it has no effect on rates of Pseudmonas infections. Recent trials demonstrate the benefits of substituting mupirocin with either gentamicin cream or ciprofloxacin otologic solution (Bernardini et al. 2005; Mahaldar et al. 2009; Montenegro et al. 2000). Irrespective of the antibiotic used, daily prophylactic application at the exit site should be the standard of care.

Several case series have demonstrated an association between invasive procedures like colonoscopy, gynecologic procedures and dental work with episodes of peritonitis (Fried et al. 2000). It has been opined that antibiotic prophylaxis may be indicated prior to such procedures (Bender et al. 2006). Finally, episodes of fungal peritonitis are often preceded by courses of antibiotics. Some studies have demonstrated that the use of anti-fungal prophylaxis with either nystatin or fluconazole may reduce the incidence of fungal peritonitis (Lo et al. 1996; Robitaille et al. 1995; Wadhwa et al. 1996). Others have been unable to confirm these benefits (Thodis et al. 1998; Williams et al. 2000). Given the conflicting results, it is recommended that prophylaxis, preferably with nystatin swish and swallow, be used in centers with high rates of fungal peritonitis.

#### 26.5.2.2 Exit Site and Tunnel Infections

The presence of purulent drainage at the exit site generally implies the presence of infection, while erythema may indicate infection, a reaction to

the catheter, or trauma (Twardowski and Prowant 1996). On the other hand, the presence of scabs and crust do not indicate infection. Tunnel infections present with pain, erythema and swelling over the subcutaneous pathway. Exit site inflammation may be present or it may look completely normal. Often, tunnel infections are occult and can be diagnosed only by ultrasonography (Holley et al. 1989; Vychytil et al. 1999b).

As discussed above, *Staphylococcus aureus* and *Pseduomonas aeruginosa* are the most common organisms that lead to exit site or tunnel infections (Bunke et al. 1995; Gupta et al. 1996; Piraino et al. 1986). An attempt may be made to treat early infections with erythema and no drainage with topical mupirocin or gentamicin cream or ciprofloxacin drops. Application of soaks of hypertonic saline or sodium hypochlorite one to four times a day may be effective and may be used as primary therapy for mild infections or adjuvant therapy for severe infections (Piraino et al. 2005; Twardowski 2004).

In the presence of frank infection, empiric antibiotic therapy may be initiated immediately or delayed until the results of the culture are available. Gram-positive organisms are treated with an oral penicillinase-resistant penicillin, cephalexin, or sulfamethoxazole trimethoprim. In slowly resolving or particularly severe-appearing *Staphylococcal aureus* exit site infection, rifampin 600 mg daily may be added for synergy. Oral antibiotics are generally as effective as intraperitoneal antibiotics for most exit site infections with the exception of methicillin-resistant *Staphylococcus aureus*. Gram-negative organisms may be treated with oral quinolones such as ciprofloxacin. The presence of *Pseudomonas aeruginosa* should prompt the use of an additional antibiotic like ceftazidime, imipenem-cilastin, meropenem or an aminoglycoside. These infections are often refractory to treatment, have frequent relapses and may require catheter removal (Li et al. 2010). Antibiotic therapy should be continued until the exit site appears entirely normal, with a minimum of 2 weeks of therapy.

Chronic exit site infections are harder to treat and may require prolonged courses of antibiotics, shaving of the external cuff or partial reimplantation of the external segment of the catheter (Clouatre et al. 2000; Suh et al. 1995). Deroofing of the catheter track with shaving of the external cuff and allowing the wound to heal by secondary intention has been reported to successfully salvage the peritoneal dialysis catheter (Crabtree and Burchette 2005).

Patients with exit site or tunnel infection may require catheter removal if they are associated with intercurrent peritonitis with the same organism, with the possible exception for coagulase-negative Staphylococcus (Piraino et al. 2005). Other indications for catheter removal with an exit site infection include the failure of medical therapy, or abscess formation.

#### 26.5.2.3 Peritonitis

Peritonitis is a major cause of morbidity of PD patients. Several large case series have reported that peritonitis is associated with a 3-6% short-term mortality rate (Mujais 2006; Perez-Fontan et al. 2005). It is often unrecognized that cardiovascular events, possibly precipitated by acute infection, and not systemic sepsis, is the major cause of early mortality in patients with peritonitis (Perez-Fontan et al. 2005). Peritonitis is also a major cause of technique failure and transfer to hemodialysis (Guo and Mujais 2003; Mujais 2006). Furthermore, severe or repeated episodes of peritonitis can lead to peritoneal membrane failure (Del Peso et al. 2005).

##### 26.5.2.3.1 Incidence and Risk Factors

The initial reports on CAPD peritonitis describe an episode every other month or greater (Rubin et al. 1980). However, the improvements described above have substantially reduced the risk for peritonitis. The International Society of Peritoneal Dialysis recommends a minimum standard of one episode in 18 patient-months (Li et al. 2010). Linking Medicare claims with the United States Renal Data System, for patients enrolled between 4 and 9 months after start of PD (1994-'97), the average time to first episode of peritonitis was 16.1-17.1 months (Oo et al. 2005). A more contemporary industry survey involving up to 10% of the US PD patient population reported a much lower incidence of 1 episode every 33 patient-months compared to 1 episode every 28 months in Canada (Mujais 2006). The Australian Peritonitis Registry and Scottish Renal registry recently reported peritonitis rates of 1 every 19 to 20 patient months (Kavanagh et al. 2004; Negoi et al. 2006). Single centers have reported incidence of infections as low as one episode every 60 months (Kim et al. 2004). Earlier reports found the incidence of peritonitis in APD to be significantly lower than CAPD (Diaz-Buxo et al. 1985; Levy et al. 1990; Price and Suki 1981; Walls et al. 1981). With the introduction of disconnect systems, the incidence of peritonitis has markedly decreased with CAPD and is comparable between the two modalities (Oo et al. 2005; Troidle et al. 1998; Yishak et al. 2001).

Risk factors for peritonitis include younger age, diabetes mellitus, hypoalbuminemia, higher co-morbidity and lower residual kidney function in some but not all studies (Chow et al. 2005a; Perez-Fontan et al. 2005; Prasad et al. 2007). As discussed above, an exit site infection may be a precursor for the development of peritonitis (Troidle and Finkelstein 2006). HIV positive patients suffer from peritonitis more frequently (Tebben et al. 1993). Prior bacterial peritonitis especially due to gram-negative or polymicrobial pathogens is a risk factor for fungal peritonitis (Chou et al. 2006). There is an increasing recognition of the association between psychosocial factors and peritonitis - recent studies suggest that if one accounts for the presence of depression, poverty or illiteracy, medical factors may lose their value in predicting risk for peritonitis (Brown 2005; Chow et al. 2005b). Identifying risk factors allows us to intensify efforts to prevent infectious complications in these sub-groups of patients.

#### 26.5.2.3.2 Microbiology and Pathophysiology of Peritonitis

Table 26.4 summarizes the common etiological organisms. As can be seen, gram positive infections constitute the majority of episodes of peritonitis. Organisms like diptheroids and *Corynebacterium*, often dismissed as contaminants in other clinical settings, constitute an important minority of gram-positive peritonitis. Cultures are reported to be negative in up to 20% of episodes (Kim et al. 2004; Mujais 2006; Szeto et al. 2005). Anaerobic organisms and polymicrobial peritonitis are rare and there are only a handful of cases reports of viral peritonitis (Liesker et al. 2006; Rotellar et al. 1992).

Touch contamination remains the most frequent source of infection leading to peritonitis by skin organisms such as coagulase-negative Staphylococcus, Corynebacterium, diptheroids and some gram-negative organisms (Gokal 2000; Holley et al. 1994; Perez-Fontan et al. 2002a). Exit site and tunnel infections are associated with a pericatheter spread of infection and usually involve *Staphylococus aureus* or *Pseudomonas aeruginosa* (Bunke et al. 1995; Gupta et al. 1996; Piraino et al. 1986; Read et al. 1989). Infections may also be introduced into the peritoneum by hematogenous seeding, transmigration across the bowel wall or secondary to a bowel perforation and ascending through the gynecologic tract.

**Table 26.4** Organisms commonly associated with infectious complications of peritoneal dialysis

| |
|---|
| **Gram Positive Bacteria** (~60%)[1]<br>▸ Coagulase-Negative Staphylococcus<br>▸ Staphylococcus aureus<br>▸ Streptococcus sp<br>▸ Enterococcus sp<br>▸ Corynebacterium<br>▸ Others (e.g., diphtheroids) |
| **Gram Negative Bacteria** (~20%)[1]<br>▸ Escherichia coli<br>▸ Pseudomonas aeruginosa<br>▸ Klebsiella sp<br>▸ Enterobacter sp<br>▸ Acinetobacter sp<br>▸ Serratia sp<br>▸ Citrobacter sp<br>▸ Proteus sp |
| **Others** (<5%)[1]<br>▸ Fungi like Candida sp.<br>▸ Mycobacteria |
| [1]Prevalence estimates based on survey of a large cohort of PD patients in the United States and Canada (Mujais 2006) |

#### 26.5.2.3.3 Clinical Presentation and Diagnosis

Patients with peritonitis usually present with abdominal pain and cloudy fluid which may be accompanied by fever, nausea, diarrhea and other constitutional symptoms. A diagnosis of peritonitis usually requires the presence of two out of the following three: abdominal pain, increased peritoneal dialysis fluid cell count (white blood cell count > 100/mm$^3$, > 50% polymorphonuclear cells) and a positive gram stain and/or culture (Piraino et al. 2005). The number of cells in the effluent depends in part on the duration of the dwell. In patients on automated peritoneal dialysis, the initial dialysate cell counts may be less than 100 WBC/ mm$^3$, and may never reach typical levels required for the diagnosis. With short dwells, the percentage of polymorphonuclear cells is more important than the absolute number of white cells. Patients undergoing NIPD may have abdominal pain while the peritoneum is "dry". Under such circumstances, 1 L of dialysate should be instilled and allowed to dwell for at least 1 hour, and then drained and analyzed.

Some of the causes of cloudy dialysate among PD patients are listed in Table 26.5. On occasions, the initial drain of stagnant fluid present in the abdomen all day in patients with only partial daytime exchanges or dry days may appear cloudy even in the absence of peritonitis. In such circumstances, even if the white blood cell count exceeds 100/mm$^3$, mononuclear cells will predominate and the dialysate rapidly clears with the initiation of regular exchanges. The dialysate should be cultured promptly. The optimal culture technique is to centrifuge the dialysate at 3000*g* for 15 minutes, suspending the sediment in 5-10 ml effluent and inoculating this suspension into two blood culture bottles.

**Table 26.5** Differential Diagnosis of Cloudy Dialysate in PD patients

| |
|---|
| **Generally Associated with Abdominal Pain** |
| ▸ Infectious Peritonitis |
| ▸ Intraperitoneal and Juxtaperitoneal visceral inflammation |
| ▸ Chemical peritonitis |
| ▸ Pancreatitis |
| ▸ Malignant Ascites (peritoneal carcinomatosis) |
| ▸ Sclerosing Encapsulating Peritonitis |
| **Generally Not Associated with Abdominal Pain** |
| ▸ Eosinophilic peritonitis |
| ▸ Chylous ascites |
| ▸ Specimen taken from dry abdomen |

#### 26.5.2.3.4 Initial Treatment of Peritonitis

The initial selection of antibiotics for the treatment of peritonitis should generally be dictated by the nature and sensitivities of the isolates at the institution as well as prior isolates from the patient (Li et al. 2010). However, some key principles should be kept in mind. Empiric antibiotic coverage should be effective against both gram positive and gram negative organisms. Antibiotics should preferably be administered intraperitoneally – either with every exchange (continuous dosing) or with a single exchange once daily (intermittent dosing). An excellent resource is the article entitled "Peritoneal Dialysis-Related Infections Recommendations: 2010 Update" available at the International Society of Peritoneal Dialysis website (www.ispd.org) (Li et al. 2010).

To provide adequate coverage for both gram-positive and gram-negative organisms, typically two antibiotics are administered. Generally, empiric therapy consists of either a first generation cephalosporin or vancomycin

(if high prevalence of methicillin-resistant organisms) for coverage of gram positive organisms and ceftazidime, cefipime, aztreonam or aminoglycosides for gram negative organisms. The concern that use of aminoglycosides will lead to a more rapid loss of residual kidney function has not been substantiated in subsequent observational or randomized, controlled clinical trials (Lui et al. 2005; Schaefer et al. 1999). However, repeated or prolonged courses of aminoglycosides must be avoided to prevent vestibular and ototoxicity. Quinolones may be used for coverage of gram negative organisms if local sensitivities support such use. Both cefipime and impinem/cilastatin have the potential to be used as monotherapy for empiric treatment of infection (Elwell et al. 2005; Leung et al. 2004). Cefipime appears to provide equivalent cure rates to that obtained with vancomycin and netilmicin (Wong et al. 2001).

In selecting antibiotics for empiric coverage, the changing spectrum of organisms and their antibiotic sensitivities need to be taken into account. Methicillin-resistant *Staphylococcus aureus* has become more frequent, and the problem appears to have worsened with the isolation of VISA (Vancomycin Intermediate resistant *Staphylococcus aureus*) and VRSA (Vancomycin Resistant *Staphylococcus aureus*) organisms (Salzer 2005). Additionally, some centers have reported an increasing incidence of gram negative organisms that produce extended spectrum beta lactamases (ESBL)int (Szeto et al. 2006; Yip et al. 2006). The importance of correctly identifying these organisms cannot be over-emphasized since cephalosporins, widely used as empiric therapy, are ineffective in ESBL infections even if the organism appears sensitive *in vitro* (Perez-Fontan and Lueiro 2006).

Some antibiotics require administration only once a day (viz., aminoglycosides) or once every few days (viz., vancomycin). Cephalosporins, however, may be administered either with each peritoneal dialysis exchange (continuous dosing) or a large dose may be administered in a single exchange during a 24-hour period (intermittent dosing). For successful intermittent intraperitoneal therapy, high concentrations of the drug must be achieved in the systemic circulation that enough drug will diffuse back into the dialysate in subsequent drug-free exchanges (Manley and Bailie 2002). Furthermore, the exchange performed with dialysate containing the antibiotic must dwell in abdominal cavity for at least 6 hours. It should be remembered that clearance of the antibiotics is enhanced in the presence of peritonitis. The clearance is also higher and is directly related to the residual kidney function (Manley and Bailie 2002).

The data on the dosing of antibiotics for patients undergoing APD are more limited. If intermittent dosing is chosen, the clearance of the

antibiotics are higher with more frequent night time exchanges. For the drugs on whom data are available, when cefazolin, cefipime or ceftazidime given in a single exchange, the concentrations of the drug may not be adequate during shot nighttime cycles for most organisms (Elwell et al. 2005, 2002; Low et al. 2000).

Oral ciprofloxacin in a dose of 750 mg twice a day provides dialysate concentrations that exceed the MIC for *Escherichia Coli* and Klebsiella sp, but below those needed for *Pseudomonas aeruginosa* (Yeung et al. 2004). In spite of these pharmacokinetic data, intermittent dosing of antibiotics for APD patients provides cure rates between 73-88%, catheter removal rates of 7.5-17.5%, and peritonitis-related deaths of 2-10% - outcomes not significantly different than seen among patients undergoing CAPD (Troidle and Finkelstein 2005). An attractive and effective alternative is to add antibiotics to every dialysate bag (day and night) used by patients undergoing APD.

#### 26.5.2.3.5 Subsequent Antibiotic Therapy

Antibiotics should be modified, if necessary, once the etiologic organism is isolated and sensitivities are reported. Most patients experience symptomatic improvement and clearing of the dialysate in 48 hours. A failure to respond should lead the physician to recheck cell counts and cultures.

**Gram Positive Bacteria Peritonitis:** Coagulase negative Staphyloccus infections generally requires two weeks of treatment with either cefazolin or vancomycin. Episodes of peritonitis with organisms that are methicillin resistant *in vitro*, may demonstrate clinical improvement with cefazolin due to high intraperitoneal levels. However, switching to vancomycin provides superior cure rates and reduces the incidence of relapse (Vas et al. 1997). Relapsing peritonitis due to biofilm is often seen with coagulase-negative Staphylococcal peritonitis and requires catheter replacement (Williams et al. 1989). *Corynebacterium* is a skin commensal associated with peritonitis and exit-site infections. Treatment with two weeks of antibiotics provides a cure rate of 67%; hence prolonged treatment should be considered for such infections (Barraclough et al. 2009).

The incidence of peritonitis secondary to *Staphyloccus aureus* has considerably declined over the previous decade. Intraperitoneal *Staphyloccus aureus* infections require treatment with vancomycin, teicoplanin or cefazolin for 3 weeks. Oral rifampin for the first week can be added for synergy (Piraino et al. 2005). Antibiotics effective against VISA or VRSA infection are quinupristin/dalfopristin, linezolid and daptomycin. The first

two have been successfully used intraperitoneally in PD patients (Salzer 2005). *Stapylococcus aureus* peritonitis may be associated with a concomitant exit-site or tunnel infection and if this be the case, the catheter needs to be removed (Bayston et al. 1999; Gupta et al. 1996).

Streptococcal and enterococcal infections generally respond best to intraperitoneal ampicillin (O'Shea et al. 2009). Once-daily, low-dose intraperitoneal aminoglycosides can provide synergy to ampicillin for enterococcal peritonitis. In cases of ampicillin resistance or allergy, vancomycin or clindamycin may be used. Linezolid, daptomycin and quinupristin/dalfopristin are indicated for vancomycin resistant enterococcus (Salzer 2005). Streptococcal infections usually need therapy for 14 days while enterococcal infection needs treatment for 21 days (Li et al. 2010).

**Gram-Negative Bacteria Peritonitis:** *Pseudomonas aeruginosa* infections should treated for three weeks with a combination of antibiotics with different mechanisms of action. The choice of antibiotics can be an oral quinolone with an anti-pseudomonal beta-lactam or an aminoglycoside (Siva et al. 2009; Szeto et al. 2001). These infections are often associated with a catheter tunnel infection in which case the catheter must be removed. Antibiotics should be continued for 2 weeks after transfer to hemodialysis (Li et al. 2010). Pseudomonas infections may lead to permanent membrane failure. Strenotrophomonas infections generally need prolonged treatment, preferably with two antibiotics (Szeto et al. 1997; Tzanetou et al. 2004). Recommended antibiotics include trimethoprim/sulfametoxazole, minocycline and ticarcillin/clavulanate (Hussain et al. 1998).

Other single gram-negative infections are often treated with a single antibiotic based on sensitivity and convenience (Li et al. 2010). However, a study from Hong Kong suggests that a significant proportion of peritonitis from gram negative organisms may require combination therapy despite *in-vitro* sensitivity to the single agent used initially (Szeto et al. 2006). If ESBL-producing enterobacteriaceae are isolated, a switch to carbapenems is indicated (Perez-Fontan and Lueiro 2006).

**Polymicrobial and Anaerobic Bacteria Peritonitis:** A detailed discussion of polymicrobial peritonitis is outside the scope of this Chapter. With multiple enteric organisms or mixed gram-negative/gram-positive organisms, one must consider intra-abdominal disease, such as ischemic bowel or diverticular disease. However, the overwhelming majority of patients with polymicrobial peritonitis do not have a surgically treatable cause and the vast majority of patients with any primary intra-abdominal process do not have

polymicrobial peritonitis (Szeto et al. 2002). The treatment should depend upon the mixture of organisms isolated. Initial coverage should include metronidazole combined with ampicillin and ceftazidime or an aminoglycoside (Kern et al. 2002; Steiner and Halasz 1990; Szeto et al. 2002).

**Culture Negative Infections:** In about 20% of episodes, the dialysate cultures are negative. Studies have demonstrated equivalence of outcomes when culture negative peritonitis is treated with either vancomycin and ceftazidime or teicoplanin and ceftazidime; others have found no differences between a cefepime monotherapy compared to vancomycin plus netlimycin (Schaefer et al. 1999; Wong et al. 2001). It is generally agreed to treat these episodes with a single agent for a period of two weeks (Piraino et al. 2005).

**Fungal Peritonitis:** Not withstanding some case reports of successful treatment of fungal peritonitis with medical therapy, anti-fungal medications should be used only as adjuncts to the prompt removal of the peritoneal dialysis catheter. In a large case series, failure to remove the catheter was associated with an 8-fold higher risk for death (Wang et al. 2000). Optimal initial coverage of fungal peritonitis therapy is amphotericin B or fluconazole with/without flucytosine (Li et al. 2010). Treatment needs to be adjusted after the organism is identified and the minimal inhibitory concentration (MIC) known. Candida albicans, C. parapsilosis, and C. tropicalis are generally susceptible to fluconazole while C. krusei and C. glabrata need therapy with amphotericin or an echinocandin (capsofungin, micafungin, anidulafungin) (Wang et al. 2000). In patients in whom peritoneal dialysis catheter is removed, treatment duration should be two weeks. Amphotericin B or oral voriconazole for 5 weeks are indicated for filamentous fungi (Ghebremedhin et al. 2009). After completion of anti-fungal therapy, some patients may be able to successfully re-start PD. In many others, the high incidence and severity of peritoneal adhesions preclude further treatment with peritoneal dialysis (Wang et al. 2000).

#### 26.5.2.3.6 Indications for Removal of the Dialysis Catheter

The peritoneal dialysis catheter should be removed for relapsing peritonitis (recurrence with the same organism within 4 weeks of completing antibiotics), refractory peritonitis (failure of response in 5 days), and fungal peritonitis (Li et al. 2010). Catheter-related infections (generally *Staphylococcus aureus* (Gupta et al. 1996) or *Pseudomonas aerugionsa* (Siva et al. 2009; Szeto et al. 2001), particularly when associated with exit-site or

tunnel infection usually require catheter removal. Consideration for catheter removal should also be given in patients with mycobacterial peritonitis and multiple enteric infections. Reinsertion should be considered 3 to 4 weeks after removal of the catheter.

Simultaneous removal and replacement of the dialysis catheter may be considered in patients with relapsing peritonitis, bacterial peritonitis with an exit-site infection with the same organism, and suspected catheter contamination (i.e. persistent positive dialysate cultures without clinical signs of peritonitis and a dialysate leukocyte count <100 $m^3$) (Majkowski and Mendley 1997; Posthuma et al. 1998). Evidence suggests that the peritoneal WBC count should be less than 100/μl and antibiotics continued for 10 days after the WBC normalized or 7 days after surgery (Posthuma et al. 1998). Even though the simultaneous exchange of catheters is reported in refractory and fungal peritonitis, it is not recommended (Swartz and Messana 1999).

## 26.6 CONCLUSION

In summary, peritoneal dialysis is a viable and cost-effective renal replacement therapy for long-term treatment of uremia. Over the last three decades, a large number of different peritoneal dialysis solutions have been developed in order to mitigate the limitations of the initial formulations. There has occurred a progressive and substantial decline in infectious complications of the therapy and a better understanding of how best to manage non-infectious complications leading to increased success with the therapy.

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## ESSAY QUESTIONS

1. What are the changes in how peritoneal dialysis therapy is performed today that has led to significant reductions in infectious risk of patients?
2. What are the key considerations in selecting the peritoneal dialysis modality for an individual patient?
3. What are the best demonstrated practices in the placement of peritoneal dialysis access?
4. What are the advantages of laparasocopic placement of peritoneal dialysis catheters over other traditional techniques?
5. What is our current understanding of how conventional peritoneal dialysis solutions produce damage to the peritoneum limiting its use as a long-term dialyzer membrane?
6. What are the demonstrated benefits of the use of icodextrin and what is its optimal place in the current practice of peritoneal dialysis?
7. What is the clinical presentation and how is the diagnosis of encapsulating peritoneal sclerosis established?
8. What are the principles in selecting an empiric regimen for the treatment of PD-related peritonitis?
9. What are the indications for the removal of peritoneal dialysis catheter in patients with PD-related peritonitis and when should it be replaced?
10. What are the causes of cloudy dialysate in a patient treated with peritoneal dialysis?

## MULTIPLE CHOICE QUESTIONS

### Choose the best answer

1. Which one of the following best summarizes the contemporary comparisons of survival of patients treated with in-center hemodialysis and peritoneal dialysis:

A. Similar five-year survival, but lower 10-year survival for patients treated with peritoneal dialysis
B. Similar five-year survival, but lower 10-year survival for patients treated with in-center hemodialysis
C. Similar five- and ten-year survival for patients treated with either dialysis modality
D. Lower five- and ten-year survival for patients treated with peritoneal dialysis
E. Lower five- and ten-year survival for patients treated with in-center hemodialysis

2. Patients can do peritoneal dialysis either by performing manual exchanges (continuous ambulatory peritoneal dialysis, CAPD) or by using a cycler (automated peritoneal dialysis, APD). In a patient with an average rate of peritoneal solute, which one of the following best summarizes how best to select a peritoneal dialysis modality?

A. Patients with high-average transport are best treated with APD and low-average transport with CAPD
B. Patients should choose which peritoneal dialysis modality works best for them based upon their life-style
C. CAPD is associated with a lower death risk compared to APD for patients with average peritoneal transport rate
D. APD is associated with a lower risk for transfer to hemodialysis in patients with average peritoneal transport rate

3. Under which of the following circumstances is it best to choose tidal peritoneal dialysis?

A. Infusion pain
B. Enhance solute clearances
C. Enhance fluid removal
D. Limit long-term damage to the peritoneal membrane

4. Which of the following components of the peritoneal dialysis solution has been primarily implicated in causing long-term damage to the peritoneal membrane?

A. Low pH
B. High glucose concentration

C. Absence of potassium
D. Use of lactate as buffer
E. Low sodium concentration

5. Which of the following best summarizes the demonstrated benefit of icodextrin as an alternative to conventional glucose-based peritoneal dialysis solution?
A. Improvement in appetite
B. Decrease in peritoneal albumin loss
C. Preservation of residual renal function
D. Regression of left ventricular hypertrophy

6. Which of the following best describes the benefit of embedding the external limb of the peritoneal dialysis catheter in the subcutaneous tissue at the time of placement?
A. Allows for an elective start of peritoneal dialysis
B. Reduction in risk for infectious complications of peritoneal dialysis
C. Reduction in risk for non-infectious complications of peritoneal dialysis
D. Reduction in need for patients to transfer to hemodialysis

7. Which of the following is the best approach to reduce the risk of extrusion of the superficial cuff?
A. Use of a single-cuff catheter
B. Daily application of antibiotics at the exit-site
C. Creating the exit site at least one inch from the superficial cuff
D. Rectus sheath tunneling of the PD catheter

8. Which of the following best describes the rationale for a low pH for conventional glucose-based PD solutions?
A. Use of lactate as buffer
B. Minimize the formation of glucose degradation products
C. Prevent the precipitation of calcium lactate or magnesium lactate
D. The intraperitoneal pH is 5.2

9. Which one of the following best summarizes the benefits that have been consistently been demonstrated in randomized controlled trials of peritoneal dialysis solutions with low concentrations of glucose degradation products?

A. Preservation of residual renal function
B. Long-term preservation of peritoneal solute transport rate
C. Reduction in all-cause and cardiovascular mortality
D. None of the above

10 Which one of the following is the most widely used peritoneal dialysis solution:

A. Dextrose-based PD solution with lactate buffer and 2.5 meq/l calcium
B. Dextrose-based PD solution with bicarbonate/lactate buffer and 2.5 meq/l calcium
C. Dextrose-based PD solution with lactate buffer and 3.5 meq/l calcium
D. Dextrose-based PD solution with bicarbonate/lactate buffer and 3.5 meq/l calcium

11. Who is credited with the introduction of the modern-day continuous ambulatory peritoneal dialysis for the treatment of end-stage renal disease?

A. Maxwell and Boen
B. Moncrief and Popovich
C. Ganter and Grollman
D. Buoncristiani and Buzzato

12. A 55-year old white male with end-stage-renal disease from diabetic nephropathy is being treated with continuous ambulatory peritoneal dialysis. He was treated for 2 weeks with intraperitoneal vancomycin for *Staphylococcus epidermidis* peritonitis 1 month ago. He is symptomatic once again with abdominal pain and a cloudy bag. Cell count in the PD fluid is 822 WBC/$mm^3$ with 60% neutrophils and 40% lymphocytes. Yeast is seen on the spun sample.

The appropriate initial therapy is:

A. Start intraperitoneal vancomycin and ceftazidime
B. Start intraperitoneal vancomycin and amphotericin B
C. Start iv amphotericin B
D. Prompt removal of PD catheter and iv amphotericin B

13. A 42-year old female with ESRD due to IgA nephropathy has been treated with APD for the past 5 years. She has had an episode of peritonitis every year. She has been symptomatic with abdominal pain, distension, and nausea and vomiting. A CT scan shows non-specific air fluid levels and fecal retention. She is treated conservatively with laxatives and symptoms resolve. Every few weeks, she starts having recurrence of the above symptoms but with worsening abdominal pain. The dialysate shows between 50-80 WBC/$mm^3$ on multiple occasions and bacterial cultures are repeatedly negative. A laparoscopy is performed and reveals peritoneal membrane thickening with multiple adhesions. Histological findings of the sclerotic tissue demonstrate dense fibrous tissue permeated with a chronic inflammatory infiltrate. She should now be treated with:

A. Antitubercular drugs for a mycobacterial peritonitis
B. Amphotericin B for a fungal peritonitis
C. Bowel rest and total parenteral nutrition

14. A patient on automated peritoneal dialysis is being treated with 4 exchanges of 2L each overnight in an 8 hour period and a last bag fill of icodextrin. He develops a cloudy pain but has no abdominal pain. He does not recall any "break" in a technique. A peritoneal cell count is 1022/$mm^3$. The differential is 50% neutrophils, 20% eosinophils, 30% monocytes. The appropriate initial treatment is:

A. Discontinue icodextrin
B. Start treatment with cefazolin and ceftazidime
C. Obtain a flat plate abdomen to look for intraperitoneal air
D. Start oral steroids

15. A 28 year old female with end stage renal disease from lupus nephritis is initiated on peritoneal dialysis. Three months after initiating dialysis, the patient calls the dialysis unit complaining of a blood tinged bag. She has some lower abdominal pain but no fever, nausea or vomiting. Her last menstrual period was 2 weeks ago. She is hemodynamically stable and her abdomen is soft. The dialysate bag looks grossly bloody and dialysate cell counts are WBC of 48/ $mm^3$ and over 80,000 RBC/ $mm^3$. The cause of her hemoperitoneum is likely:

A. Retrograde menstruation
B. Rupture of an ovarian cyst
C. Pancreatitis
D. Peritonitis

16. A 58-year old male has been on CAPD for the past year. He notices a progressive scrotal swelling which is diagnosed as an inguinal hernia. The appropriate recommendation for the hernia is:

A. Reduce fill volumes and convert the patient to automated peritoneal dialysis
B. Use a hernia support garment
C. Prompt surgery

17. The use of mupirocin has been shown to reduce the incidence of exit site infections and peritonitis from gram positive organisms. It is appropriate to use mupirocin intermittently to save on medication costs.

A. True
B. False

18. Tunnel infections are caused most often by:

A. Pseudomonas aeruginosa and Staphylococcus epidermidis
B. Pseudomonas oryzihabitans and Staphylococcus epidermidis
C. Pseudomonas aeruginosa and Staphylococcus aureus
D. Pseudomonas oryzihabitan and Staphylococcus epidermidis
E. Stenotrophomonas maltophilia and Staphylococcus aureus

19. A patient on automated peritoneal dialysis with a "dry day" develops abdominal pain. The pain is localized in the epigastrium and is described as dull with radiation to the back. He is nauseated and throws up twice. He is examined in the peritoneal dialysis unit and noted to have a low grade fever of 100.2$^{o}$ F and mild diffuse abdominal tenderness. Fluid is drained from the dialysis catheter and appears turbid. The analysis finds 180 WBC/ mm$^{3}$ with 50% lymphocytes, 20% monocytes and 30% neutrophils. Serum amylase is 160 IU/ml. The patient is suffering from:

A. Peritoneal dialysis peritonitis
B. Gastritis
C. Pancreatitis

20. A 35 year old patient has been treated with CAPD for the past 6 months. She was able to drain her dialysate in 10 minutes and instill fluid 2 L in 6 minutes. She recently started taking diltiazem sustained release for supraventricular tachycardia. Now, it takes over 30 minutes for her to drain her abdomen while there has been no change in the fill time. A KUB reveals the catheter tip to be lying in the left upper quadrant of the abdomen. She states that her bowel movements have been regular. The next step is:

A. Introduce a guide wire and try to reposition the catheter
B. Introduce a fogarty catheter to reposition the catheter
C. Obtain a surgical consultation to reposition the catheter
D. Use laxatives
E. Switch to automated peritoneal dialysis so the patient is supine for most of the exchanges

Chapter (27)

# Peritoneal Dialysis Solutions

Leonard Ebah and Declan de Freitas

**CHAPTER OUTLINES**

- Introduction
- Electrolytes
- Osmotic Agents
- High molecular weight osmotic Agents
- Buffers
- The quest for biocomptatible PD fluids
- Conclusion

**CHAPTER OBJECTIVES**

After completing this chapter, the reader is expected to:

- Understand the mechanisms for exchange of solutes through the peritoneum.
- Know the components of current PD solutions and their concentrations.
- Understand the advantages and shortcomings of the various PD solution constituents.
- Understand the mechanisms for fluid removal in PD.
- Appreciate the importance of biocompatibility

**KEY TERMS**

- Peritoneal dialysis solutions
- Electrolytes
- Icodextrin
- Lactate
- Bicarbonate
- End Stage Renal Disease
- Dialysis

**ABSTRACT**

Peritoneal dialysis (PD) solutions contribute to homeostasis in patients with end stage renal disease (ESRD) by removing accumulated electrolytes and toxins, maintaining acid-base balance, and removing excess fluid through ultrafiltration. To achieve these functions, current PD solutions are an electrolyte solution of sodium, calcium and magnesium to which an osmotic agent and a buffer are added. Glucose remains the most used osmolyte, although icodextrin and amino acid solutions are also available. Icodextrin is a glucose polymer that confers the advantage of sustained ultrafiltration and minimal metabolite absorption. Amino acid solutions are used in patients as a form of nutritional supplementation. Older PD solutions used lactate as the buffer, but lactate/bicarbonate and bicarbonate

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only buffered solutions are more physiological and increasingly used. Accumulated evidence of local and systemic effects of PD fluids due to low pH and glucose degradation products (GDPs) has led to a drive towards more biocompatible solutions. Thus, the wide variety of PD solutions can be tailored for a patient specific management approach.

## 27.1 INTRODUCTION

The role of the peritoneal dialysis (PD) is to enable the removal of toxins, specific electrolytes and fluid from the body, in addition to providing a source of bicarbonate and in some cases, amino acids. This is achieved by varying the type of dialysis solution and using the peritoneal membrane as an endogenous semi-permeable barrier for this two-way exchange. Solute removal is achieved by diffusion of toxins and electrolytes down their concentration gradient, and to some degree by convection through ultrafiltration. The composition of PD solutions can also be altered to administer electrolytes or amino acids as part of the treatment. Fluid balance is controlled by the addition of osmotic agents to PD solutions to enable net fluid removal. Thus PD solutions play a key role in achieving electrolyte homeostasis, acid-base neutrality, euvolaemia and a non-uraemic state.

The first description of the use of PD fluid was by Ganter in 1923 (Gokal 2000a). He demonstrated that repeated instillation and draining of physiological sodium chloride solution into the peritoneum of ureter-ligated animals improved symptoms of uraemia and blood urea levels. He also applied the technique in a woman with renal failure but this did not save her, an outcome similar to that of several other investigators in the field in the following two decades. It was in 1946 that Fine et al. successfully treated a patient with severe uraemia by peritoneal irrigation using Ringer's solution with dextrose (Fine et al. 1946). PD fluids as they exist today first appeared in the 1950s when the Don Baxter company produced a dialysis solution in a sterile 1L bottle (Maxwell et al. 1959).

The general composition of PD solutions varies little between manufacturers. They are made up of three essential components as shown in Table 27.1:

- Electrolytes
- Osmotic agents
- Acid-base buffers

**Table 27.1** Components of a peritoneal dialysis solution

| Component | Concentration | Comments |
|---|---|---|
| Na | 132-135 mmol/L | |
| K | 0-2 mmol/L | |
| Ca | 1.25 and 1.75 mmol/L | |
| Mg | 0.25 and 0.75 mmol/L | |
| Glucose anhydrous | 1.36%, 2.27% and 3.86% | Corresponding to 1.5%, 2.5% and 4.25% glucose monohydrate respectively |
| Lactate | 35-40 mmol/L | pH 6.3-7.0 |
| Bicarbonate | 34 mmol/L | pH 7.4. Bicarbonate 25/lactate 15 mmol/L solutions also exist (pH 7.4) |
| Icodextrin | 7.5% | In replacement of glucose |
| Amino Acid | 1.1% | In replacement of glucose |

## 27.2 ELECTROLYTES

The major cations involved in achieving and maintaining homeostasis during peritoneal dialysis are sodium, potassium, calcium and magnesium. Electrical neutrality is maintained through the addition of chloride and bicarbonate (or lactate).

### 27.2.1 Sodium

The average dietary sodium intake in the UK and other western countries is between 150 and 200 mmol/day, much higher than the recommended allowance of 70-100 mmol per day for adults (SACN 2003). High dietary sodium intake has been convincingly linked to hypertension, cardiovascular diseases and increased mortality (Strazzullo et al. 2009). The kidneys are responsible for excreting excess sodium and water, thereby serving as a key organ in the regulation of extracellular fluid volume with sodium being one of the key extracellular osmolytes. Loss of kidney function and the resultant sodium accumulation leads to hypervolaemia and hypertension. In PD patients, some sodium is excreted in urine in those with residual renal function, but a larger proportion is achieved via the dialysate. Current PD fluids contain sodium in concentrations of 132-135 mmol/L, which is usually slightly lower than plasma sodium concentrations (normal range 135-145 mmol/L). Initially, when a PD solution is instilled into the peritoneal cavity, water is exchanged more rapidly than sodium, a phenomenon referred to as sodium

sieving (Nolph et al. 1969). As the dwell continues, sodium diffuses down its concentration gradient, resulting in a net loss of sodium. Convective transport of sodium also occurs via ultrafiltration, the extent of which will depend on the glucose concentration of the PD fluid. Wang et al. analysed peritoneal sodium removal in 68 CAPD patients using three different dialysate glucose concentrations (Wang et al. 1997). They found that the convective sodium loss was twice as much as the diffusive losses; sodium removal therefore increased with increasing ultrafiltration and hence with "stronger" glucose dialysates. Diffusive sodium loss is very time-dependent and therefore much greater in CAPD (up to 210 mmol per day ) than in APD (averaging 90 mmol per day) where the duel times are shorter (Ortega et al. 2001; Rodriguez-Carmona et al. 2004).

Lower concentrations of dialysate sodium (102-126 mmol/L) have been used to manage hypervolaemia (Davies et al. 2009; Raja et al. 1973), with the intended benefit of increased diffusive sodium removal and its accompanying fluid loss. Raja et al. successfully used a 120 mmol/L sodium dialysate with 7% glucose to achieve equivalent fluid removal (3-4 L per day) as a 4.5% dextrose/130 mmol Na solution in 18 oedematous patients using 2 hour dwells without complications (Raja et al. 1973). Such high concentrations of glucose have now been abandoned, but this demonstrated the principle of diffusive sodium removal using low sodium PD fluids. More recently, Nakayama et al. achieved greater net sodium removal (27.8±5.1 mmol) in a 240 minute dwell with an ultralow sodium solution (Na 98 mmol/L, glucose 2.48%), compared to standard sodium PD fluids (Na 132 mmol/L, Glucose 1.36% and 2.26%). At the end of the study, there was a significant reduction in body weight and blood pressure in the ultralow sodium group, compared to the standard sodium patients (Nakayama et al. 1996). Similarly, Davies et al. achieved net sodium removal, improvement in nocturnal BP and reduction in thirst in a short term controlled trial of a 102 and 115 mol/L sodium dialysate (Davies et al. 2009). Other authors (Ates et al. 2001; Imholz et al. 1994a; Khandelwal and Oreopoulos 2004; Leypoldt et al. 1995; Vande Walle et al. 1997, 2005) have replicated the advantages of low sodium dialysate on improving sodium balance and the ensuing cardiovascular benefits, especially in fluid overloaded patients but this has yet to be incorporated into routine clinical practice. The above low sodium studies have established the safety of hyponatric PD fluids, with little difference between plasma sodium concentration in patients using these and those using higher sodium dialysates. Some authors have advocated for these low sodium solutions to be used in patients with volume overload and resistant hypertension (Khandelwal and Oreopoulos 2004; Van Biesen et al. 2005). Although this

is yet to be incorporated into routine clinical practice, there is a case for tailoring dialysate sodium to the individual patient's needs, with perhaps careful prescription of low sodium dialysate for patients with marked hypervolaemia. There are logistical and financial limitations to such an approach as these fluids are not readily commercially available.

### 27.2.2 Potassium

An average adult ingests about 80 to 100 mmol of potassium per day. The kidney is responsible for excreting approximately 80 %, with sweat and GI losses accounting for the remainder. Potassium accumulation in end stage renal failure can be associated with weakness and life threatening cardiac arrhythmias. As such, extracellular potassium needs to be kept within very tight boundaries (3.5-5.5 mmol/L). PD contributes to potassium homeostasis through the removal of excess potassium, the correction of acidosis and maintenance of residual renal function.

Commercially available PD solutions generally contain no potassium. Potassium removal in PD is mainly by diffusion, although there may be some convective loss when large ulrafiltrate volumes are achieved. However, as with sodium, there is potassium sieving across peritoneal aquaporins, so net effluent potassium concentration tends to be lower than extracellular concentrations (Brown et al. 1973b). Typically, patients will lose about 35 mmol of potassium per day via the dialysate, an amount that is much smaller than the average ingested quantity of potassium (Nolph et al. 1979). There is some potassium loss via the kidneys in patients with residual renal function, but most importantly, there is evidence of enhanced intestinal excretion of potassium in ESRD, with reported daily digestive losses of up to 20 mmol (Blumenkrantz et al. 1982).

Up to a third of PD patients develop hypokalaemia (Szeto et al. 2005; Tziviskou et al. 2003). Jung et al. (2009) found the annual incidence rate of *de novo* hypokalaemia to be 7.1% in a cohort of 82 normokalaemic PD patients. As commercial PD fluid solutions do not come with potassium, and intravenous and oral routes have certain limitations, addition of potassium to the dialysate has been recommended to correct hypokalaemia. Spital and Sterns successfully increased serum potassium by 0.44±0.11 mmol/L in hypokalaemic CAPD patients by adding 20 mmol/L of potassium to the dialysate bag (Spital and Sterns 1985). About 75% of the potassium load was absorbed within 2 hours. Higher concentrations (40 mmol/L) resulted in symptoms such as abdominal pain. Addition of 20 mmol/L of potassium chloride to PD fluid is now an accepted method of correcting hypokalaemia

that is resistant to relaxation of dietary restrictions or oral potassium supplementation.

### 27.2.3 Calcium

In kidney failure, calcium homeostasis is related to dietary calcium intake, phosphate levels, parathyroid levels, vitamin D prescription and dialysate levels. Normal serum ionised calcium concentrations vary between 1.15 mmol/L and 1.29 mmol/L. Hypocalcaemia and hypercalcaemia commonly occur leading to bone disease and vascular calcification.

In peritoneal dialysis, calcium exchange is by ultrafiltration and diffusion down both a concentration and an electrochemical gradient (Andersen 1981; Bender et al. 1992; Eddington et al. 2009; Parker and Nolph 1980; Simonsen et al. 2003; Stoltz et al. 1971). PD solutions can therefore remove calcium from extracellular fluid, or result in net calcium gain depending on concentration and electrochemical gradient, and ultrafiltration. The ionised calcium content of PD fluid can be varied depending on the individual patient's calcium requirements, with a range of 1.25 to 1.75 mmol/L in commercial solutions. Previously, PD fluids with a high calcium content (1.75 mmol/L) were used in an attempt to correct hypocalcaemia. This resulted in hypercalcaemia and metastatic calcification, especially when calcium salts replaced aluminium as the main oral phosphate binders used in patients with kidney failure. As a result, dialysis fluids with lower (1.15 to 1.25 mmol/L) calcium concentrations have been developed and are in routine use today. Several observational and randomised controlled studies have confirmed their superiority to the higher calcium solutions in maintaining normal serum calcium levels and control of renal osteodystrophy (Cheng et al. 1993; de Fijter et al. 1996; Hutchison and Gokal 1992; Hutchison et al. 1993, 1992; Piraino et al. 1992). In a randomised controlled trial of 103 patients, Weinreich et al (1995) described fewer episodes of hypercalcaemia in the low calcium (1.25 mmol/L) group and an increase of the tolerated dose of calcium-based phosphate binders. However, in several patients, low calcium dialysate resulted in a net loss of calcium, with the development or worsening of hyperparathyroidism, and in several cases a tendency to develop alkalosis and hypomagnesaemia (Rotellar et al. 1993; Sanchez et al. 2004). Conversely, Sanchez et al (2004) found that although patients randomized to low calcium dialysate had a tendency to hyperparathyroidism, bone biopsies did not discriminate between low and standard dialysate calcium patient groups. There is some evidence that low calcium development or progression of hyperparathyroidism with such

lower calcium fluids can be prevented by administration of vitamin D (Banalagay et al. 1993). Bender et al (1992) found net calcium loss in CAPD exchanges using 1.25 mmol/L calcium solutions as opposed to net calcium gain with 1.75 mmol/L calcium solutions. The loss increased with increasing glucose concentration: -0.1±0.3 mmol loss with 1.25 calcium/1.5% dextrose; -0.7±0.25 mmol with 4.25% dextrose. In routine clinical practice, low calcium dialysates tend to be most frequently used. However, dialysate calcium prescription should be tailored to the individual patient circumstances, depending on their calcium balance and parathyroid status. There is a potential role for solutions containing 1.75 mmol/L of calcium in hypocalcaemic patients or those in whom non-adherence to vitamin D or calcium supplementation is a problem. With many patients now using non-calcium based phosphate binders, there is a need for clinicians to monitor their bone biochemistry frequently and revise the dialysate calcium prescription as indicated.

### 27.2.4 Phopshate

PD solutions do not contain phosphate and phosphate removal through PD is negligible.

### 27.2.5 Magnesium

The normal serum magnesium level ranges from 0.65-1 mmol/L. Hypomagnesaemia is associated with cardiac arrhythmias and muscle weakness, while the significance of hypermagnesaemia is uncertain and subject to considerable debate (Cisari et al. 1989; Gonella et al. 1981; Meema et al. 1987).

Magnesium concentration in PD patients depends on nutritional intake and dialysate concentrations. Exchange across the peritoneum is mainly by diffusion, but some convective transport may occur when the ultrafiltration volume is high (Parker and Nolph 1980). Previously, dialysate magnesium concentrations were in the middle physiological range (0.75 mmol/L). However, this tended to result in magnesium accumulation (Parker and Nolph 1980). Although the effects of these higher magnesium levels remain unclear, magnesium concentrations in PD fluids were reduced, with current solutions containing 0.25 mmol/L of magnesium. Use of this concentration has been shown to result in hypomagnesaemia, and patients with previously high magnesium levels have seen these normalized (Hutchison et al. 1993; Merchant et al. 1992). In a retrospective analysis, Ejaz et al found that 64% of patients developed hypomagnesaemia after a

median of 8 months when converted from a 0.5-0.6 mmol/L magnesium dialysate to a 0.25 mmol/L solution (Ejaz et al. 1995) and 13 of the 21 hypomagnesaemic patients required oral magnesium supplementation. The effects of hypomagnesaemia in these patients are not clear. A few studies have shown that low dialysate magnesium negatively correlates with parathyroid hormone levels (Cho et al. 2002; Wei et al. 2006).

## 27.3 OSMOTIC AGENTS

Osmotic agents are introduced into PD fluids to achieve fluid removal. Such agents result in a PD solution that is hyperosmolar in relation to extracellular fluid, thereby resulting in fluid removal through ultrafiltration. The ideal osmotic agent should be cheap, non-toxic, biocompatible, small enough to alter the PD fluid viscosity, but large enough not to be absorbed into the circulation. Potential osmotic agents trialled include glucose, glycerol, xylitol, sorbitol, fructose, mannitol, gelatine, glucose polymers, polypeptides and dextrans. Most of these proved unsuccessful due to their side effects. There has been relative success in this endeavour with the use of glycerol, amino acid and glucose polymers as osmolytes, but only glucose, glucose polymers and amino acids are in routine clinical use.

### 27.3.1 Glucose

Excess fluid removal in PD is mainly achieved by osmosis. Glucose was the first successful osmotic agent used in PD solutions and has since remained the cornerstone of standard PD solutions (Gault 1973). Three main strengths of glucose are used: weak (1.36% dextrose anhydrous), intermediate (2.27% dextrose anhydrous) and strong (3.36% dextrose anhydrous) (Feriani et al. 2000). These correspond to 1.5%, 2.5% and 4.25% dextrose monohydrate respectively.

When a glucose solution is instilled into the peritoneum, the osmotic gradient and hence the ultrafiltration rate is maximal at the beginning. However, since glucose is continuously absorbed into the circulation down its concentration gradient, the osmotic gradient diminishes progressively, with equilibrium reached after a few hours. There may even be reversal of the osmotic process, resulting in net fluid gain into extracellular fluid (Krediet et al. 1987; Mactier et al. 1987; Maher et al. 1985; Nolph et al. 1979; Rubin et al. 1979; Twardowski et al. 1986; Waniewski et al. 1995). Stronger glucose solutions achieve more rapid ultrafiltration and a greater fluid volume removal but also result in enhanced glucose absorption. Glucose concentrations stronger than the

current strong bags (e.g. 7% dextrose) have since been abandoned due to concerns with local and systemic toxic effects (Gault 1973). Equilibrium glucose concentration is achieved more rapidly with weak (1.27%) PD fluid, resulting in cessation of ultrafiltration within 3-6 hours. The rate of fluid absorption from and into the PD fluid depends on the lymphatic flux, and this is different from one patient to another (Mactier et al. 1987; Nolph et al. 1987). Patients with a so-called high transporter status absorb glucose very rapidly and reach the equilibration point earlier. In such patients, shorter PD fluid dwells are needed to achieve net fluid removal.

The main shortcoming of glucose as an osmotic agent is its rapid absorption. Up to 80 % of the instilled glucose is absorbed into the circulation, leading to an extra 60 to 240g uptake of glucose per day from the PD fluid, contributing up to 20% of a patient's daily caloric intake (Andersson et al. 1971; Bodnar et al. 1993; Bouma and Dwyer 1984; Brown et al. 1973a; Grodstein et al. 1981; Krediet et al. 1987; Pajek et al. 2008; Podel et al. 2000). Thus hyperglycaemia, hyperlipidaemia, hypertriglyceridaemia, obesity, and hyperinsulinaemia have all been reported in patients undergoing PD with glucose based solutions (Antikainen 1993; Breborowicz et al. 2004; Heaton et al. 1983; Jiang et al. 2008; Selby et al. 2007; Turgan et al. 1981). Although it is unclear whether the chronic exposure to hyperglycaemia may lead to manifestations of *de novo* diabetes, the above metabolic effects have been clearly linked to increased cardiovascular risk in these patients (Babazono et al. 1996; Bartens et al. 1996; Garcia-Lopez et al. 2007; Selby et al. 2007).

In order to avoid caramelization when the glucose-containing bags of PD fluid are sterilized, the solution is maintained at a non-physiological, acidic pH of 5-5.5. Several *in vitro* and *in vivo* studies have documented the deleterious effects of this non-physiological pH on peritoneal cells (Ikehara et al. 2005; Kim et al. 2007; Musi et al. 1998; Szeto et al. 2007). Also, during storage, the glucose in the bag partly breaks down, forming glucose degradation products (GDPs) such as 5-hydroxymethylfurfural (5-HMF) (Wieslander et al. 1996; Wieslander and Linden 1996). GDPs have been linked to increased inflammation, impaired host defence, impaired peritoneal membrane preservation, vascular alterations, a more rapid decline in residual renal function and increased exit site infections and peritonitis rates (Ikehara et al. 2005; Krishnan et al. 2005; Linden et al. 2001; Mortier et al. 2002; Musi et al. 1998; Okabe et al. 2004; Puig-Kroger et al. 2003; Witowski et al. 2003). It has also been suggested that some of the untoward effects of GDPs are due to increased, irreversible formation of advanced glycation end products (AGEs) which have been shown to promote atherosclerosis, inflammation, increased oxidation and

alteration of peritoneal membrane structures (Honda et al. 1999; Lamb et al. 1995; Mahiout et al. 1996; Rashid et al. 2006; Schmitt et al. 2007). All these shortcomings of the glucose based acidic PD fluids led, in the past two decades, to a drive to develop newer more so called biocompatible fluids with less GDPs and a more physiologic pH.

### 27.3.2 Glycerol

Glycerol is a low molecular weight alcohol with a higher osmotic strength than glucose (Daniels et al. 1984; Lindholm et al. 1987). It can be sterilized at a more physiological pH and as such can be used to produce PD fluid that is theoretically more biocompatible than glucose based fluids (Daniels et al. 1984). As it does not require insulin to be metabolized, the effects of hyperinsulinaemia as seen with glucose based fluids can be avoided. The main drawbacks of glycerol based PD fluids are the accumulation of glycerol (which has been occasionally associated with hyperosmolar symptoms), the need for high concentrations to achieve reasonable ultrafiltration (owing to the fact that it is very rapidly absorbed) and hypertriglyceridaemia (Heaton et al. 1986; Heaton et al. 1984; Lindholm et al. 1987; Smit et al. 2000). Furthermore, the beneficial effect of reduced insulin requirements have been shown to be unsustained (Heaton et al. 1986). However, glycerol based PD solutions have been shown to be safe when glycerol levels are carefully monitored, and it is postulated that they may have a role in diabetic patients (Drouin et al. 1984; Heaton et al. 1984). A combination of glycerol and amino acid based solutions has been proposed to alleviate some of the shortcomings of glycerol only solutions (Faict et al. 1991; Lameire and Faict 1994; Van Biesen et al. 2004, 1997).

### 27.3.3 Amino Acids

During peritoneal dialysis, there is an unavoidable loss of proteins and amino acids in the effluent, contributing to the frequently observed malnutrition in these patients (Lindholm and Bergstrom 1988; Young et al. 1991). The proposal by Gjessing in 1968 (Gjessing 1968), and a decade later by Oreopoulos et al. (Feriani et al. 2000) to use amino acids in PD fluids, both to avoid the unwanted metabolic consequences of glucose and to provide nutritional supplementation therefore seemed very logical. Amino acid based PD solutions have been trialled at various concentrations ranging between 0.6% and 2.76% (Lindholm et al. 1988; Van Biesen et al. 2004). Ultrafiltration volumes and small solute removal over a six hour dwell time were similar between a 2% amino acid solution

and a 4.25% glucose monohydrate solution (Williams et al. 1982). A 1% amino acid solution was also shown to achieve similar ultrafiltration and dialysis efficacy as 1.5% dextrose monohydrate (Goodship et al. 1987). Young et al. found that for longer dwell times (8 hours), a 1% amino acid solution tended to achieve slightly less net fluid removal than 1.5% dextrose monohydrate solution (Young et al. 1989). An increase in peritoneal permeability due to amino acid-mediated vasodilatation has been implicated in this ultrafiltration loss in longer dwells (Vychytil et al. 2003). In practice, 1.1% commercial amino acid solutions are considered to deliver equivalent ultrafiltration and solute removal as weak (1.5%) dextrose monohydrate solutions, with the added benefit of providing nutritional supplementation (Lindholm et al. 1993).

The nutritional benefits of amino acid based PD solutions have been extensively studied. Older studies have provided conflicting data, partly due the varying composition and concentrations in amino acid solutions used (Dombros et al. 1990; Feriani et al. 2000). More recently, Asola et al. found increased muscle amino acid uptake in patients using a 1.1% amino acid PD fluid (Asola et al. 2008). Tjiong et al. found improved nitrogen balance in six out of eight patients treated with an amino acid/glucose dialysate in a randomised crossover trial (Tjiong et al. 2005). Taylor et al. (2002) found improved normalized protein catabolic rates with the use of 1.1% amino acid dialysate in a retrospective analysis of 22 patients over a 30 month period. Similar beneficial effects, including improved appetite have been reported in both adult and paediatric patients (Jones et al. 1998a, b; Qamar et al. 1999).

Increased urea levels and a tendency to acidosis remain the main concerns with amino acid based PD fluids. Attempts to resolve the latter have involved the elimination of acidogenic amino acids in the formulation, and the preference of a high bicarbonate content (34-40 mmol/L) buffer (Bender et al. 2008; Jones et al. 1997). In all, there seems to be a place for amino acid dialysate, especially in malnourished PD patients. The possibility to use bicarbonate-buffered solutions with a more physiological pH offers an added advantage in terms of biocompatibility.

## 27.4 HIGH MOLECULAR WEIGHT OSMOTIC AGENTS

The main shortcoming of the small osmotic agents is their rapid absorption, resulting in ultrafiltration loss and metabolic derangements. Larger, less well absorbed osmotic agents possess the theoretical benefits of maintaining ultrafiltration for longer periods. The force pulling the fluid

in this case is the colloid osmotic pressure which is determined more by the number of osmotically active macromolecules than by the osmotic gradient (Starling 1896). This means that an osmotic pull can be sustained even with PD fluids of similar osmolality to extracellular fluid.

Polypeptide PD fluids were first trialled by Klein et al. in the 1980s (Klein et al. 1986), and later by a few other investigators (Imholz et al. 1994b; Martis et al. 1993; Wang and Lindholm 1997). Although they showed some promise in terms of sustained ultrafiltration (up to 14 hours) and minimal absorption, peptide use never gained acceptance, partly due to the fact that another high molecular weight agent, icodextrin, was being tested about the same time, with significant promise (Mistry et al. 1994). Apart from icodextrin, other high molecular weight substances tested so far *in vitro* and in animal studies have been abandoned for various reasons. These include the synthetic polymers polyacrylate, dextran, polyethyleneamine (bleeding, toxicity), plasma expanders like gelatine (high viscosity) and hydroxyethyl starch (accumulation) and albumin (expensive) (Feriani et al. 2000; Gjessing 1969; Nolph et al. 1978; Twardowski et al. 1978). The glucose polymer icodextrin is the only high molecular weight osmotic agent that has shown adequate efficacy and safety profile to be incorporated in currently commercialized PD solutions.

### 27.4.1 Icodextrin

Dextrin is a glucose polymer obtained from hydrolysis of corn starch, with predominantly α 1-4 glucose to glucose linkages. Studies using a dextrin preparation with a biomodal distribution (67% 1-12 glucose units and 33% >12 glucose units) showed improved ultrafiltration profiles and small molecule clearance compared to corresponding glucose (5% dextrin versus 1.5% dextrose monohydrate, and 10 % dextrin versus 4.25% dextrose monohydrate) solutions but resulted in net higher glucose absorption (Mistry et al. 1987).

Recognising that transperitoneal glucose polymer absorption for chain lengths of up to 12 monomers was similar to that of glucose, Mistry and Gokal prepared a polymer made of on average of 20 glucose monomers, namely icodextrin. A 5% solution of icodextrin with an average molecular weight of 16800 Da and osmolality of 332 mOsm/kg was produced for clinical testing against various glucose concentrations (Mistry and Gokal 1989; Mistry et al. 1987). A subsequent 3 month clinical study confirmed the sustained ultrafiltration up to 12 hours using 7.5% icodextrin, when compared to 1.5% dextrose monohydrate, with less glucose absorption than the glucose solution and the only noticeable untoward effect being an

accumulation of maltose (Mistry and Gokal 1993). The findings of this study were later confirmed by a randomised controlled multicentre longer term (6 months) trial with 209 patients (The MIDAS study). A 7.5% icodextrin solution achieved similar small molecule clearances as 4.25% dextrose monohydrate over a 12 hour dwell, and 3.5 times higher ultrafiltration than 1.5% dextrose monohydrate after 8 hours (Mistry et al. 1994). The ultrafiltration volume increased steadily, and peaked between 12 and 14 hours, demonstrating the key advantage of icodextrin over glucose solutions, namely sustained ultrafiltration. Again, maltose levels were higher in the icodextrin group although overall carbohydrate absorption was significantly lower. The maltose accumulation has not been shown to produce any deleterious effects, apart from interfering with some commercial finger prick glucose readings. Davies found that after stopping icodextrin use, maltose levels returned to pre-treatment levels within 7-10 days (Davies 1994).

Subsequent clinical trials have identified other uses for icodextrin. Wilkie et al. found that icodextrin use restored clinically relevant ultrafiltration in patients with ultrafiltration failure, thereby extending CAPD technique survival by a median of 22 months (Wilkie et al. 1997). In a randomised controlled trial, Davies et al. found improved fluid status in patients using 7.5% icodextrin compared to those on 2.27% anhydrous dextrose, with no worsening of residual renal function (Davies et al. 2008, 2003). Woodrow et al. (1999), and Wolfson et al. (2002) obtained similar findings in separate randomised controlled trials.

Icodextrin benefits from good long term safety data, apart from a few concerns about exfoliative skin conditions, some of which were later attributed to staphylococcal infections (Lam-Po-Tang et al. 1997; Wilkie et al. 1997) and sterile peritonitis, which was limited to a very small proportion of patients and symptoms tend to improve upon cessation of icodextrin use (Basile et al. 2003; Gokal 2002). Its clinical use has been extended to most peritoneal dialysis patients as either a long daytime dwell in those on overnight APD or a night time dwell in those on daytime CAPD. It is also recommended for use in diabetic patients in order to reduce glucose load (Gokal 2000b). As icodextrin interferes with some finger prick glucose estimation tests and some serum amylase determinations, this should be borne in mind by clinicians when these tests are carried out.

## 27.5 Buffers

One of the key roles of the kidneys is to correct the metabolic acidosis generated mainly by protein metabolism in the cells. This is achieved by

enhancing the elimination of $H^+$ ions and the generation of bicarbonate to buffer excess protons in the circulation (Pitts and Lotspeich 1946). As renal function deteriorates, this function is gradually lost. The ensuing acidosis leads to catabolism and poor nutritional status (Bergstrom 1995; Lofberg et al. 1997; Szeto and Chow 2004), which has been associated with worsened survival in observational studies (Bommer et al. 2004; Kovesdy et al. 2009). One of the aims of dialysis is to correct this acidosis, which in PD, is achieved by adding a buffer to the dialysate. The buffer traverses the peritoneal membrane down its concentration gradient into extracellular fluid to neutralise $H^+$ ions and maintain a bicarbonate level of around 22-28 mmol/L. Lactate and bicarbonate are the two buffers in routine use today.

### 27.5.1 Lactate

Lactate occurs in two isomers, D and L- lactate, with the L-isomer being the most preponderant in biological fluids. Commercially available PD fluids tend to contain a racemic mixture of both isomers in concentrations of 35-40 mmol/L. L-lactate is easily metabolized to pyruvate by lactic dehydrogenase. The lactate load from peritoneal dialysis is about 0.19 mmol/kg/h, only representing about one quarter of the endogenous L-lactate turnover (Fabris et al. 1982; Searle and Cavalieri 1972). This implies that lactate infusion from PD can be easily handled by the body's metabolism.

When a lactate-containing dialysate is instilled, there is rapid transfer of lactate into the circulation, with the majority absorbed within 2 hours, and almost all by the end of a 6 hour dwell (La Greca et al. 1981; Rubin et al. 1982). As acidosis is corrected and extracellular fluid bicarbonate levels increase, bicarbonate may be lost back into the dialysate, especially in longer dwells and high ultrafiltration exchanges (Feriani et al. 1996; Richardson and Roscoe 1986). Thus, the rapid absorption confers a particular advantage in short dwell systems. Suggestions to increase dialysate lactate concentration to 40 mmol/L have been supported by studies showing a reduction in the proportion of patients with acidosis, albeit with an increase in the prevalence of alkalosis, which may in itself have deleterious consequences (Nolph et al. 1983). There have been several reports of lactate accumulation, especially the D-lactate form, which is metabolized at a slower rate and has been associated with encephalopathy (Thurn et al. 1985). The main concern with the use of lactate-buffered PD fluids is their unphysiological pH (pH 5-7). Several studies have shown the detrimental effects of these bioincompatible solutions to the peritoneal membrane structure and function, in addition to

host defence systems (Bajo et al. 2001; Buoncristiani et al. 1996; Cooker et al. 2001; Han et al. 2009; Ing et al. 1997; Ito and Yorioka 2008; Jorres et al. 1997; Jorres et al. 1991; Mortier et al. 2005; Plum et al. 1998; Puig-Kroger et al. 2003; Rogachev et al. 1997; Topley et al. 1996; Wieczorowska-Tobis et al. 2001; Wu et al. 2005; Zheng et al. 2001). This has engendered a drive to develop more biocompatible, bicarbonate based PD fluids with a more physiological pH.

### 27.5.2 Bicarbonate

The early use of bicarbonate based PD fluids was prevented by its precipitation with divalent ions to form carbonates and caramelization with glucose during sterilization, resulting in acidic fluids (Boen 1961). Problems with precipitation and caramelization have been circumvented by the use of a dual chamber bag with extemporaneous mixing of the two solutions just prior to use, and the addition of glyglycine or acetate (Feriani et al. 1993; Yatzidis 1991, 1993; Yatzidis et al. 1996). A lactate/bicarbonate mixture (25 mmol/L bicarbonate, 10 or 15 mmol/L lactate) has been shown to be as effective as a lactate based solution in correcting acidosis (Feriani et al. 1996). A patient-tailored, individualized approach with these fluids has been proposed; hence the dialysate buffer concentration chosen will depend on the patient's acid-base status (Dratwa et al. 2003). A patient with a tendency to alkalosis will use the solution with a lower concentration of buffer mixture (35 mmol/L), whilst those who tend to be acidotic will use the 40 mmol/L bags.

Bicarbonate-only buffered PD fluids are commercially available at a concentration of 34 mmol/L. This has been shown in randomised controlled trials to achieve similar levels of serum bicarbonate correction as the standard 35 mmol/L lactate solutions (Feriani et al. 1998). Comparative trials of 34 mmol/L and 39 mmol/L bicarbonate dialysates resulted in the increase of the proportion of patients with normal acid-base balance (Feriani et al. 1997; Feriani et al. 2004). Feriani et al (2004) proposed that the existence of the two solutions allows for individualised therapy, based on the patient's initial acid-base status. Also, long term studies with the use of these solutions have shown that they are very well tolerated. Mactier et al. found that bicarbonate based PD fluids reduced the incidence of infusion pain (Mactier et al. 1998). Concerns regarding lower ultrafiltration and their effect on residual renal function have been conflicting (Krediet et al. 2008; Pajek et al. 2009).

## 27.6 THE QUEST FOR BIOCOMPATIBLE PD SOLUTIONS

Exposure of the peritoneal cavity to PD solutions produces local and systemic effects with the potential for deleterious long term consequences. Standard lactate-containing PD solutions have an "unphysiological" pH of 5-7. In an *in vitro* experiment, Topley et al. showed that a lactate-buffered solution at a pH of 5.2 had detrimental effects on human peritoneal mesothelial cells and polymorphonuclear leucocytes. (Topley et al. 1996). These effects were absent when the same cells were exposed to a lactate or bicarbonate solution at a more physiological pH of 6.8 and 7.4 respectively. Mortier et al. demonstrated that low pH lactate solutions caused a localised sustained vasodilatation and postulated this may contribute to long term peritoneal vessel sclerosis (Mortier et al. 2002). Several other *in vitro* and animal studies have confirmed the detrimental effects of these solutions on leucocyte activation and cytokine production (Duwe et al. 1981; MacKenzie et al. 1998; Mortier et al. 2004; Plum et al. 1998), and to the mesothelial integrity and vasculature (Breborowicz et al. 1997; Hekking et al. 2001; Jorres et al. 1998; Yang et al. 1997). There has been some debate whether these *ex vivo* mainly short term observations translate into long term effects *in vivo*. In a randomised controlled trial over 12 weeks comparing standard acidic lactate-buffered PD solutions with a pH-neutral lactate-buffered solution (The Euro-Balance Trial), indicators of peritoneal membrane integrity (effluent VEGF, TNFα and hyaluronic acid) were more favourable with the neutral solution (Williams et al. 2004). This study also showed a favourable effect of neutral pH solutions on the preservation of residual renal function, as has another randomised controlled study (Kim et al. 2008; Williams et al. 2004). Szeto et al (2007) found the use of a pH-neutral lactate containing solution to result in better peritoneal membrane function and lower C-reactive protein levels after 1 year. In a paediatric trial on 28 children, lactate-buffered acid pH solutions were less effective in correcting acidosis at three months, and resulted in lower effluent CA 125 levels (higher levels being associated with peritoneal membrane integrity) (Haas et al. 2003; Krediet 2001). Infusion pain has been associated with low pH PD fluids. This has been shown to resolve on switching to neutral pH fluids (Mactier et al. 1998; Rippe et al. 1997; Yamamoto et al. 1992). One retrospective analysis has shown worse survival with the standard low pH lactate buffered fluids compared to neutral pH fluids (Lee et al. 2005). This is yet to be confirmed by controlled trials.

Whilst a low pH has been associated with detrimental effects, some authors have argued that these observed effects of older PD solutions are mainly due their high content in GDPs (Musi et al. 2004; Wieslander et al. 2000). GDPs are produced during heat sterilization of PD fluids and occur in higher concentrations in the older lactate-buffered acidic pH fluids (Cooker et al. 1997). GDPs have been shown to produce several detrimental effects both locally and systemically and to increase the levels of advanced glycation end products (AGEs) (Linden et al. 1998, 2001; Wieslander et al. 1996; Wieslander and Linden 1996; Wieslander et al. 2000; Witowski et al. 2004; Zeier et al. 2003). Even in the absence of data from long term controlled studies, there is a theoretical benefit to using PD solutions with a PH closer to extracellular pH, a similar osmolality to plasma, buffered with the physiological buffer in extracellular fluid, i.e. bicarbonate, with lower absorption of proven toxic substances like GDPs. Current so-called biocompatible solutions largely answer these criteria. It remains to be seen whether their widespread use will translate into longer term clinical and survival benefits.

## 27.7 CONCLUSION

PD solutions have remained essentially unchanged in the past half century, with the main advances being the advent of icodextrin and more physiological bicarbonate buffered solutions. There are significant challenges for the future, with the objective being to invent solutions that achieve effective dialysis and ultrafiltration without causing any deleterious short or long term effects both locally and systemically.

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## ESSAY QUESTIONS

1. List the various constituents of a modern PD solution and their concentration ranges.
2. Explain the mechanisms of sodium transport through the peritoneum and the putative benefits of low sodium solutions.
3. Discuss why there has been a shift from higher or physiological calcium levels in PD fluids to lower levels.
4. Discuss how ESRD patients on PD handle potassium load and why some patients may need potassium added to their dialysates.
5. What are the glucose solutions available and what are the advantages of each over the others?
6. What is icodextrin and what are its advantages over glucose-containing PD solutions.
7. Discuss amino acid PD solutions, the evidence for them and their main clinical uses
8. What is the role of a buffer in the PD fluid? Explain the evolution of the buffers used.
9. Name the characteristics of an ideal PD solution.
10. What is a biocompatible PD solution? Discuss the evidence for the bio-incompatibility of PD solution.

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. Peritoneal dialysis aims to…
   A. Provide excess sodium lost by the failing kidneys
   B. Provide supplemental bicarbonate
   C. Provide glucose as a form of nutritional supplementation
   D. Remove excess fluid by diffusion

2. The following electrolytes are found in standard PD solutions…
   A. Sodium bicarbonate
   B. Calcium gluconate
   C. Magnesium phosphate
   D. Potassium chloride

3. In PD patients, sodium removal is achieved by…
   A. Diffusion into the dialysate
   B. The residual renal function
   C. Ultrafiltration
   D. All of the above

4. Regarding sodium sieving in PD…
   A. Sodium diffuses more rapidly than chloride
   B. Water movement is more rapid than sodium movement
   C. May contribute to hyponatraemia with certain PD solutions
   D. Is how peritoneal dialysis removes sodium

5. Low sodium PD solutions have been shown to…
   A. Achieve similar diffusive sodium removal to standard sodium solutions
   B. Achieve similar ultrafiltration to standard sodium solutions
   C. Increase cardiovascular risk
   D. Result in hypernatraemia when in hypertonic glucose solution

6. Potassium balance and renal failure…
   A. Potassium loss is greater with dialysis than with gut and sweat gland loss combined
   B. Peritoneal dialysis can be used to remove up to a third of ingested potassium
   C. Hypokalaemia is occurs in up to 50% of cases
   D. 40 mmol of KCL is added to each PD bag to prevent hypokalaemia

7. Regarding calcium in PD solutions…
   A. Accumulation leads to metastatic calcification
   B. Only one of the divalent ions calcium or magnesium can be used
   C. Calcium can only be used with lactate solutions
   D. Has no effect on parathyroid function

8. Studies of magnesium in peritoneal dialysis have shown…
   A. A relationship between high PTH and hypomagnesaemia
   B. Hypermagnesameia is a frequent complication of currently available PD solutions
   C. That hypomagnesaemia may occur with 0.75 mmol/L fluids
   D. Mortality is increased when high magnesium dialysate is employed

9. Fluid removal in PD…
   A. Occurs by diffusion
   B. Depends solely on dialysate glucose concentration
   C. Is better at night as transport is more efficient then
   D. Is higher with more concentrated glucose solutions

10. Ultrafiltration…
   A. Is higher with 1.36% glucose than with 4.25% dextrose monohydrate
   B. Is higher in the last few hours of dialysis as the efficiency increases with time
   C. Stops when plasma and dialysate glucose concentrations become equal
   D. Only occurs with low sodium dialysates

11. Weak glucose bags…
   A. Achieve smaller but more sustained fluid removal
   B. Are reserved for diabetic patients only
   C. Are only used in paediatric patients
   D. Achieve similar levels of ultrafiltration to amino acid based solutions

12. Amino acid solutions…
    A. Can result in a metabolic acidosis
    B. Achieve the same ultrafiltration as 2.5% dextrose monohydrate
    C. Prevent protein loss but are not a source of amino acids
    D. Can only be used in short dwells

13. Amino acid solutions…
    A. Can increase appetite
    B. Improve nitrogen balance
    C. Are a source of nutritional supplementation
    D. All of the above

14. Regarding high molecular weight osmotic agents…
    A. Icodextrin and mannitol are the main ones in commercial use
    B. They are more rapidly absorbed aiding ultrafiltration
    C. Less of the osmotic agent is absorbed, leading to less ultrafiltration
    D. Icodextrin sustains ultrafiltration for up to 12 hours

15. Icodextrin…
    A. Is a glucose polymer with 10 monomers on average
    B. Is ideal for long dwells in APD patients
    C. Achieves similar ultrafiltration levels to 1.5% dextrose over 8 hours
    D. Patients with diabetes need their glucose levels checked more regularly

16. Regarding icodextrin safety…
    A. Dermatitis is a frequent complication
    B. Lactose accumulation is a concern
    C. It may worsen diabetes control
    D. It may interfere with bedside glucose tests

17. Buffers are added to PD fluids…
    A. To dissolve the sodium and calcium salts
    B. In order to correct the acidosis that occurs in renal failure
    C. Because patients in renal failure are deficient in lactate
    D. But cannot cross the peritoneal membrane

18. Lactate containing PD fluids…
    A. Do not alter peritoneal membrane function
    B. May be associated with infusion pain
    C. Lead to lactic acidosis
    D. Are biocompatible

19. Bicarbonate based PD solutions…
    A. Have a pH of 5.5
    B. Have been shown to reduce infusion pain
    C. Dual chamber systems have been invented to avoid precipitation with sodium
    D. Sterilization can lead to caramelization with glucose

20. Which of the following statements about PD solutions containing bicarbonate is incorrect…
    A. Cannot be used in fluid overloaded patients as they result in less ultrafiltration
    B. Have shown to be less detrimental to the peritoneal membrane, compared to lactate solutions
    C. May be associated with a survival advantage
    D. May help preserve residual renal function

Chapter (28)

# Kinetic Modeling of Peritoneal Dialysis

Michael F. Flessner

**CHAPTER OUTLINES**

- Introduction to Trans-peritoneal Transport.
- Mathematical Models of Trans-peritoneal Transport.
- Applications
- Conclusion

**CHAPTER OBJECTIVES**

- Introduce the complexity of the peritoneal transport system
- Describe anatomical Considerations of peritoneal dialysis
- Discuss physiology of Transport:
  - Diffusion
  - Convection through tissue
  - Transcapillary transport.
  - Blood flow
  - Lipid Solubility
- Describe the mathematical Models of Transperitoneal Transport:
  - Simple Membrane Models
  - Capillary (Three-Pore) Models.
  - Multi-Compartmental Models.
  - Distributed Model
- Introduce some applications for:
  - Peritoneal Dialysis
  - Intraperitoneal Chemotherapy
  - Macromolecular
  - Transport through tissue

**KEY TERMS**

- Peritoneum
- Peritoneal Cavity
- Compartmental Models
- Membrane Models
- Capillary Models
- Distributed Models.

**ABSTRACT**

This chapter presents the anatomy and physiology of the peritoneal barrier as background for understanding the complex process of the transperitoneal transport system. Kinetic models are presented in three general forms: membrane models, compartmental models, and distributed models. Applications of each of these are offered to illustrate the use of each model scheme.

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springerlink.com 

## 28.1 INTRODUCTION

### 28.1.1 Therapeutic Uses of the Peritoneal Cavity and Early Model Approaches

From the early days of peritoneal dialysis, clinical nephrologists have considered the transport between blood and the solution in the peritoneal cavity as a transfer across a membrane barrier. The first mathematical models (Babb et al. 1973; Pyle et al. 1981) were some variation of the concept displayed in Fig. 28.1. Bidirectional transport is assumed to be symmetric between the plasma and the peritoneal cavity across a structure termed the "peritoneal membrane". The rate of mass transfer from the plasma to the peritoneal cavity is equal to the time-averaged clearance term ( $\overline{K}$ ) multiplied by the source concentration (plasma concentration or $C_P$):

$$\text{Rate of mass transfer} = \overline{K} \times C_P \tag{28.1}$$

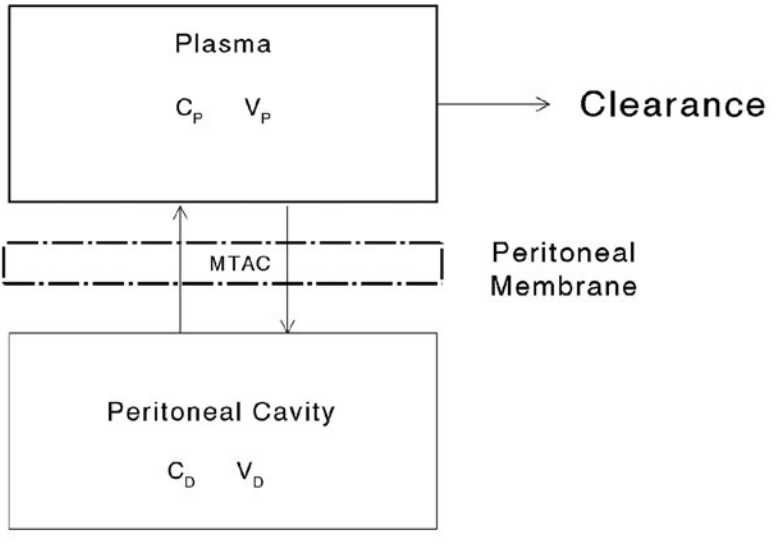


**Fig. 28.1** Two-Compartment model of peritoneal dialysis. C = concentration, V = volume. Subscripts P = plasma or distribution compartment, D = dialysis fluid in peritoneal cavity. MTAC = mass transfer-area coefficient (see text)

While the plasma concentration is relatively constant versus time, the peritoneal dialysis solution concentration does increase with time, and therefore early modelers used the engineering concept of a mass transfer coefficient (MTC, sometimes termed "permeability or P") multiplied by the active surface area ($A_D$) times the difference between the source concentration and the time-varying dialysate concentration ($C_D(t)$):

$$\text{Rate of mass transfer} = \text{MTC} \times A_D \times [C_P - C_D(t)] \qquad (28.2)$$

This simple model concept still is used today to quantitate peritoneal transport in patients (see below for further details). Since it is rare that the active surface area of peritoneal transport is measured, the $\text{MTC} \times A_D$ is lumped together in the mass transfer-area coefficient (MTAC) that is shown in Fig. 28.1. The parameter MTAC lumps together several different processes, and mathematical modelers have introduced modifications to this simple equation in order to simplify a complex biological system that is not analogous to the artificial kidney of hemodialysis.

Since transport of small substances across the proposed peritoneal membrane is relatively symmetric (Flessner 1996b), drugs can be delivered from the peritoneal cavity into the plasma. Indeed, intraperitoneal chemotherapy and immunotherapy have been tested in humans (Alberts et al. 1996; Markman et al. 1992; Markman and Walker 2006) and found to be effective in the treatment of ovarian and colorectal carcinoma that is metastatic within the peritoneal cavity (Barakat et al. 2002; Markman 1999). In contrast to dialysis that focuses on removal of marker molecules (i.e., urea and creatinine) from the plasma, these processes often require a much more detailed model description to simulate drug levels in the targeted tumor tissue. The "Distributed Model" of peritoneal transport attempts to simulate these processes and involves significantly more complexity.

This chapter will introduce different types of models and their application to specific clinical uses of the peritoneal cavity as a portal of drug administration or metabolic waste removal. The next section will describe the system of the peritoneal cavity and the elements that must be taken into account in attempting to describe the system quantitatively. As we will see the peritoneal barrier is much more than a simple membrane. Because this is living tissue, forces that would not necessarily affect transport across a blood capillary can significantly change transport across the peritoneum.

## 28.1.2 Anatomy and Physiology of the Peritoneal Cavity

### 28.1.2.1 Anatomical Considerations

Part of the difficulty in understanding physiologic transport in the peritoneal cavity is due to the convoluted anatomy. The peritoneal cavity is one of the two coelomic chambers in the embryo; as the embryo develops, the simple cavity transitions to a type of "collapsed balloon" folded in on itself by the growth of the gastro-intestinal tract and the genitourinary tract. These organs push the cavity from the outside and eventually collapse it to a potential space that normally contains ~150 ml of serous fluid (McGowan et al. 1968). No attempt will be made to fully describe peritoneal anatomy, but a brief summary of pertinent aspects will be provided below. The reader is referred to textbooks of anatomy such as Hollinshead (Hollinshead 1962) or diZerga (2000).

Peritoneal terminology divides the lining of the cavity into two parts, depending on whether it is adherent to organs or skeletal muscle. The visceral portion of the peritoneum adheres to all of the abdominal organs, including the stomach, pancreas, the liver, the small and large intestines, the bladder, fallopian tubes and uterus in the female. The parietal peritoneum is continuous with the visceral peritoneum but overlies the diaphragm, abdominal muscle, and retroperitoneal muscle and kidneys (these are termed retroperitoneal). The normal peritoneum that adheres to the abdominal wall of the rat is depicted in Fig. 28.2. It is made up of a single layer of mesothelial cells plus the underlying connective tissue; in the rat, the mean thickness is 15-25 μm (Flessner et al. 2010) while the human peritoneum is on the order of 80-100 μm (Baron 1941). If we consider transport between the peritoneal cavity and the blood contained within the blood vessel (see arrow), we observe that there are three major barriers: the peritoneum, the cell-interstitial matrix, and the blood capillary endothelium. There may also be a stagnant fluid layer that overlies the mesothelial cells (Nolph et al 1980). In addition, there is lymph drainage from tissue planes of muscle and subcutaneous space of the abdominal wall and from the parenchyma of the abdominal organs, and a specialized diaphragmatic lymph system (see below) (Allen 1956; Courtice and Steinbeck 1950). Lymph flow is important for the return to the central circulation of protein that leaks to the cavity.

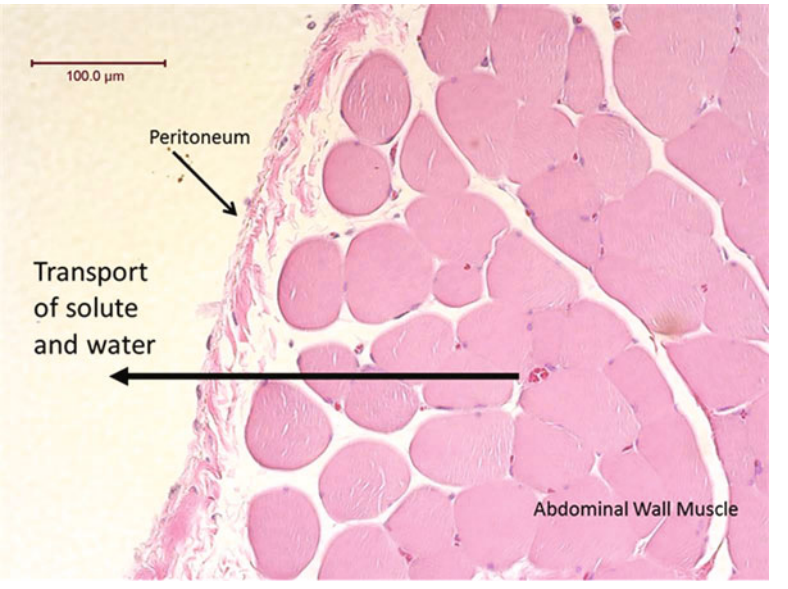


**Fig. 28.2** H&E stain of rat abdominal wall, illustrating the pathways for solute and water transport from the blood to the peritoneal cavity

#### 28.1.2.2 Compartmental Model Concept

Figure 28.3 is a more complicated compartmental model of peritoneal transport. This incorporates the peritoneal cavity, peritoneal tissue, plasma and drug distribution compartment (may include extracellular and intracellular space, depending on properties of the drug (Flessner et al. 1984). In addition, excretion of the drug as well as lymph flow from the cavity to the plasma is modeled. One or more body exchange compartments can be added to the distribution compartment in order to model complicated plasma pharmacokinetics (highly bound substances such as vancomycin) (Flessner et al. 1984). With unbound, small molecular weight substances such as glucose, creatinine, or gentamicin, this compartment is typically not needed. Drugs transported from the peritoneal cavity pass across the peritoneum through the tissue and are taken up by the blood capillaries. Substances in the plasma follow the typical pharmacokinetics of their molecular size and properties. Upon comparison of Fig. 28.1 and Fig. 28.3, one will note the interposition of the peritoneal tissue and also the lymph flow from the peritoneal cavity into the plasma.

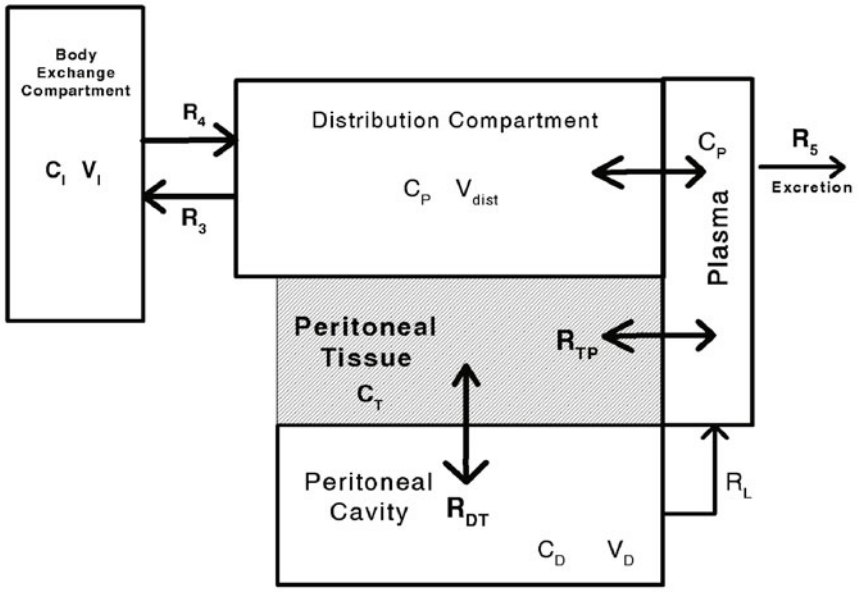


**Fig. 28.3** Compartmental model incorporating the peritoneal tissue as a separate compartment and a body exchange compartment to allow for complex pharmacokinetics. Nomenclature: C = concentration, V = volume, R = rate of solute and water transport; Subscripts: I = body exchange compartment, P = plasma, D = dialysis fluid, T = tissue, Dist = distribution volume for drug or substance.

### 28.1.2.2 Water Transport, Lymphatics, Osmosis, and Hydrostatic Pressure-Driven Convection

In order to remove fluid from patients in kidney failure, peritoneal dialysis solutions are made hypertonic by the addition of glucose in concentrations of 1.5 - 4.25% to an isotonic salt solution. The solution also increases intra-abdominal hydrostatic pressure that depends on patient position and characteristics. As it turns out, water flow from the blood compartment into the peritoneal cavity is a complicated phenomenon, often termed "net ultrafiltration":

$$\text{Net Ultrafiltration} = \frac{\text{volume out} - \text{volume in}}{\text{duration of dwell}} = F_{\pi} - (F_P + F_L) \quad (28.3)$$

where $F_{\pi}$ = osmotic filtration from the blood space to cavity via the tissue space, $F_P$ = hydrostatic pressure-driven convection from the cavity to the tissue space, and $F_L$ = lymph flow from the cavity.

Figure 28.4 depicts the two major lymphatic systems that drain the peritoneal cavity. The primary system is drainage through the stomata in the diaphragm and takes up 70-80% of peritoneal lymph flow (Flessner et al. 1983; Yoffey and Courtice 1970). These open and close depending on whether the diaphragm is relaxed (open position) or descended (closed position) (Allen and Weatherford 1959; Bettendorf 1978). These stomata drain to collecting lymphatics in the upper part of the diaphragm and subsequently to the parasternal lymphatics and the right lymph duct that joins the venous circulation in the neck. These stomata have been shown to readily take up red blood cells and 25 μ diameter beads (Allen 1956; Bettendorf 1979) in the early days of medicine, blood transfusion in neonates was carried out via injection into the peritoneal cavity (Rusznyak et al. 1967). Blood was absorbed primarily through these sub-diaphragmatic lymphatics, where the rate of flow depends on the rate of breathing and pumping action of the diaphragm (Elk et al. 1990; Schad and Brechtelsbauer 1977). A second lymphatic system drains much of the viscera, including the intestines and stomach. The visceral lymphatics drain to the Cisterna Chyli, a chamber that forms the base of the thoracic duct. The thoracic duct drains to the left venous system in the neck.

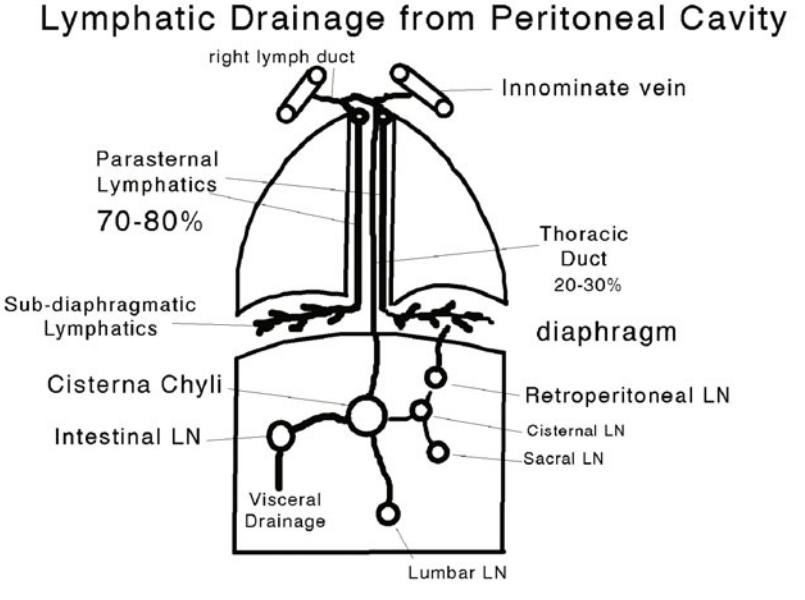


**Fig. 28.4** Lymphatic pathways from the peritoneal cavity

Measured lymph flow rates in normal peritoneal dialysis patients vary from 7 to 20 mL per hour (Flessner 1992). In patients with severe ascites due to liver failure, rates of transport can rise to 60 mL per hour, while occlusion from metastatic cancer such as testicular or ovarian carcinoma will lower the rate to near zero (Dykes and Jones 1968). The flow rates are measured by determining the transfer of radiolabeled protein from a 2 liter, 1.5% dextrose solution placed in the cavity to the plasma. The lymph flow, however, accounts for only 10-20% of the total fluid loss rate of labeled protein from the cavity of normal dialysis patients (60-90 ml/hr) (Daugirdas et al. 1980; Mactier et al. 1987b; Rippe and Haraldsson 1987; Rippe et al. 1986; Zhu et al. 1998). While some clinicians assumed that disappearance from the cavity equals lymph delivery to the blood (Krediet et al. 1994; Mactier et al. 1987a), others have demonstrated that there are two different phenomena: direct lymph uptake as discussed above (Joffe and Henriksen 1995) and direct convection into the local tissue that depends on hydrostatic pressure (Flessner et al. 1989; Flessner and Schwab 1996).

Intraperitoneal pressure is dependent on the volume of fluid placed in the peritoneal cavity and the position of the patient (Gotloib et al. 1981; Twardowski et al. 1983). In adult patients, the pressure is greatest in the sitting position and least in the supine position (Twardowski et al. 1983). Measurements in animals have demonstrated nearly constant rates of lymph flow from the peritoneal cavity above IP pressure of 2 cm $H_2O$, while the convective flow from the cavity is directly proportional to the IP pressure (Flessner and Schwab 1996).

Figure 28.5 illustrates a cross-section of the abdominal cavity below the transverse colon and shows how the fluid exerts pressure against the tissue of the abdominal wall. This relatively small pressure force (2 to 10 mmHg) causes convection of fluid from the cavity into the tissue because the typical tissue pressure is -1 to -2 mmHg (Reed 1981; Zakaria et al. 1999b) and because the peritoneum does not act as a barrier (Flessner et al. 1985b, c). Therefore, this positive pressure gradient of ~4-14 mmHg causes water (and solute) movement of in the amount of 1.5-2 L per day in the wrong direction, i.e., back into the body (Flessner 1992). Treatment of an anephric patient can therefore be compromised by the lack of net fluid removal.

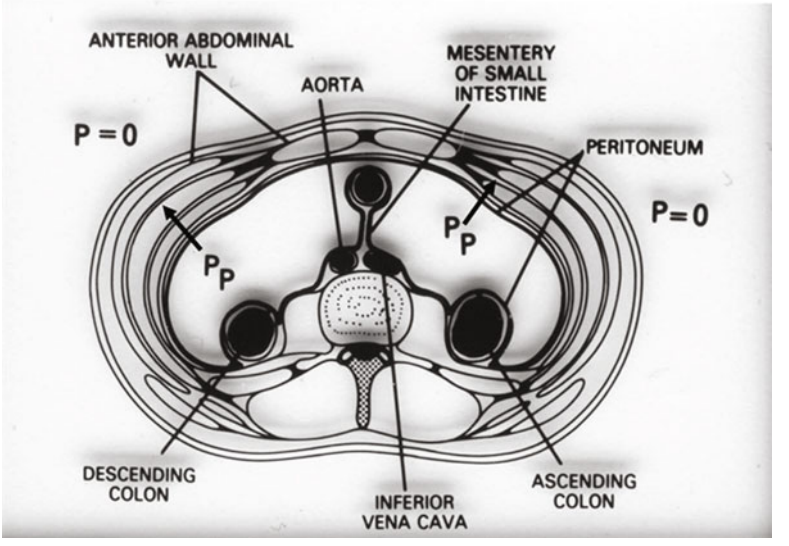


**Fig. 28.5** Cross-section of the abdomen below the transverse colon. When 2-3 liters of dialysis fluid are infused into the peritoneal cavity, hydrostatic pressure increases within the cavity ($P_P$) and drives fluid and solutes back into the body via structures such as the abdominal wall.

Clinicians typically use the middle term of Eq. (28.3) to calculate net fluid removal, but as discussed above, this term does not detail the individual contributions of osmotic ultrafiltration (clinical solutions vary from ~332 to 485 osm/kg) into the cavity minus the lymph flow and the hydrostatic pressure-driven flow from the cavity into the tissue. To increase mass transfer of waste metabolites out of the body, the clinician typically attempts to maximize the volume in the peritoneal cavity to increase peritoneal surface area and the solute "sink", but this has had the detrimental effect of increasing intra-abdominal pressure and potentially reversing the net gains of fluid removal from patients who have no kidneys. Therefore the representation of lymph and convection in Figure 28.3 is important to the mathematical modeler because of the potentially large solute and fluid transfer via this pathway. Subsequent paragraphs will demonstrate how this property of the cavity can be used to deliver drugs to metastatic tumors.

#### 28.1.2.3 Is the Anatomic Peritoneum a Barrier?

Data from experiments in animals clearly shows that the peritoneum is not a significant barrier to either small solutes or large proteins (Flessner and

Dedrick 1994; Flessner et al. 2003). The mesothelial cells are covered with glycocalyx, which can adsorb charged proteins (Flessner et al. 1997). However, once those sites are saturated, transport of proteins from the cavity through the peritoneum into the tissue or from the blood via the tissue to the cavity occurs readily (Flessner and Dedrick 1994; Flessner et al. 1992a), while small solutes transport very rapidly (Flessner et al. 1985a, d). The barrier properties of the anatomic peritoneum can therefore be represented by an additional layer of tissue overlying the parenchyma (muscle cells or cellular tissue structure) but has no intrinsic membrane qualities. It should be noted however that an intact peritoneum is extremely important for protection of the transport system and the total barrier. When mesothelial cells are damaged or removed, interstitial fibroblasts and myofibroblasts undergo changes and cause a scar to develop over the normal parenchymal tissue and significant disruptions in the peritoneal transport (Aroeira et al. 2007; Dobbie et al. 1994; Yanez-Mo et al. 2003).

#### 28.1.2.4 The Interstitium and Its Effects on Transport

While conceptual and mathematical models of the peritoneal barrier neglect the interstitial part of the barrier, transport between blood and the cavity is significantly altered by its presence (Flessner 1996a). Indeed with pathological changes in the peritoneum and the underlying tissue, alterations in transport can only be understood if the interstitium is taken into account. The importance of the interstitium is elegantly illustrated by studies of inert gas absorption from the peritoneal cavity of pigs (Collins 1981). These gases are often used in invasive procedures, such as peritoneoscopy or laparoscopy, to separate the parietal from the visceral tissues and make their surfaces visible to examining surgeon. Gases are also often used to study blood perfusion because their transport across the endothelium can be equated quantitatively with the flow in a single capillary or bed of microvessels. Since gas is transported across the endothelium very rapidly, the absorption rates of different gases should be the same if each was equivalent to the blood flow rate in the surrounding tissue if the interstitium was not a barrier. However six inert gases, administered simultaneously to the peritoneal cavity, demonstrated a hundredfold range of peritoneal clearance that correlated with the log of the diffusivity of the gas in water (Collins 1981). These results imply that the cell-interstitial matrix limits the transport of inert gases and further indicates that all larger solutes are limited in their transfer by the tissue space that separates the dialysis solution in the cavity from the blood vessels in the sub-peritoneum tissue space (Flessner 1996a, 1991, 2005).

The interstitial matrix that occupies the space between cells has been recently found to be a very ordered structure (Laurent et al. 1995; Rubin et al. 1995). Collagen fibers are bound to interstitial cells and possibly to pericytes surrounding vessels, as well as parenchymal cells, via beta-1 integrins (Rubin et al. 1995). The collagen fibers form a structure or skeleton around which wrap very large molecular weight hyaluronan molecules (1 to 40 x $10^6$ daltons) to which are bound proteoglycans that interact with the surrounding cells. Hyaluronan molecules are typically negatively charged and therefore present significant barriers to large negatively charged proteins and can sequester small positively charged substances if in high enough density (Flessner 2001a; Laurent et al. 1995). Proteins are typically restricted to about 50% of the extracellular space (ECF), which means that for muscle that has a normal ECF of 12 to 20%, only about 6% of the total tissue space will be available for transport of large molecular weight proteins (Flessner 2001b).

### 28.1.2.5 Interstitial Diffusion

Transport coefficients in the interstitial space depend on the properties of that space. The process of diffusion is governed by a effective diffusivity for substance "i" ($D_{eff,i}$):

$$D_{eff,i} = \frac{D_i \theta_i}{\tau_i} \tag{28.4}$$

where $D_i$ = diffusivity in the tissue void or space available to the solute "i"; $\theta_i$ = fraction of the tissue space that is available to the solute; $\tau_i$ = tortuosity for solute "i" through the tissue space (a tortuosity of 2 means the solute must travel twice the diffusion distance in water because of intervening structures). If the solute is water soluble and the extracellular space expands due to influx of water, $\theta_i$ and therefore $D_{eff,i}$ become variables of time, interstitial pressure gradients driving the water flow, properties of tissue, and position within the tissue (Zakaria et al. 1999a, b, 2000).

### 28.1.2.6 Interstitial Convection

Convection or the movement of fluid and solute due to solvent drag through tissue is governed by properties of the tissue, the solvent, the substance, and the local pressure forces that may vary with time (Flessner 2001b). Darcy's Law for steady fluid flow through tissue is as follows:

$$Q = -KA\frac{dP_T}{dx} \tag{28.5}$$

where Q = flow rate, K = hydraulic conductivity, A = cross-sectional area of transport, and $dP_T/dx$ = the pressure gradient within the tissue. The rate of solute convection is the product of the local tissue concentration within its tissue void ($C_{T,i}$), the local flow rate, the ratio of the solute void space ($\theta_i$) to the space available to water ($\theta_w$), and a solute retardation factor ($f_i$, ratio of solute to solvent velocity):

$$\text{Solute Convection} = Qf_iC_{T,i}\frac{\theta_i}{\theta_w} = -C_{T,i}f_iKA\frac{\theta_i}{\theta_w}\frac{dP_T}{dx} \qquad (28.6)$$

where all entities in Eq. (28.6) are potentially variable with respect to time and location within the system. This equation assumes that the influence of osmotic pressure gradients on convection is negligible. From equations (28.4) and (28.6), it can be observed that changes in the interstitial space will affect the diffusivity and the hydraulic conductivity through that space. In addition, inflammation can increase or decrease the concentrations of the interstitial components of collagen and may significantly influence the rate of transport of large proteins (> 70 kda) to the peritoneal cavity through the tissue. Increases in intraperitoneal pressure resulted in flow of water into the local tissue, in particular the abdominal wall (Stachowska-Pietka et al. 2007; Zakaria et al. 1999a, b).

#### 28.1.2.7 Transcapillary Transport: Pore Theory, Aquaporin, and the Inter-Endothelial Glycocalyx

Many modelers have utilized "Pore Theory", which has existed for nearly 60 years as an explanation for transcapillary transport (Pappenheimer et al. 1951). This theory hypothesizes that there are three types of pores in blood capillary endothelium. The water-only poor was actually verified by Agre and colleagues (Agre et al. 1993). This has subsequently been demonstrated in animals to be responsible for approximately one half of the osmotic filtration from the blood into the peritoneal cavity (Ni et al. 2006; Yang et al. 1999). These investigators showed in aquaporin-1 knockout mice that when animals were dialyzed with a hypertonic solution, the filtration was about 40 to 50% of the flow in normal mice. The absorption of isotonic fluid was unchanged by the removal of Aquaporin 1, demonstrating the separate pathways for hydrostatic pressure-driven fluid flow in the tissue. The other two pores are so-called "large pores" for proteins or macromolecules (> 70 kda) and the "small pores" for smaller solutes. These pores are thought to represent a large or small inter-cellular gap, respectively (Rippe and Haraldsson 1994).

Developments in the microcirculation literature over the last decade have focused on the endothelial glycocalyx, a 0.42-0.50 μm thick layer that lines the space between the cells and helps determine permeability for larger molecular weight solutes (Klitzman and Duling 1979; Vink and Duling 1996). This layer may also alter Starling Forces (Adamson et al. 2004; Levick 2004). Hyaluronan, a major component in the interstitium, has been found to make up a major part of the endothelial glycocalyx barrier. Treatment with an enzyme that breaks down the hyaluronan increases the permeability to 70 kda and 45 kda dextrans labeled with fluorescein-isothiocyanate (FITC) (Henry and Duling 1999; VanTeeffelen et al. 2005). Inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) cause modification of the glycocalyx and result in increased permeability of macromolecules, even when TNFα- enhanced white cell adhesion was inhibited (Henry and Duling 2000). Many other insults and processes such as angiogenesis result in decreased amounts of glycocalyx and increased permeability of the microvasculature (Platts and Duling 2004; Platts et al. 2003; Rubio-Gayosso et al. 2006). In terms of mathematics, pore theory is simpler than pore-matrix theory that includes the glycocalyx (see Fig. 28.6 and discussion below). Significantly more data is required by the modeler to justify the incorporation of pore-matrix properties into the endothelium in any sophisticated mathematical model.

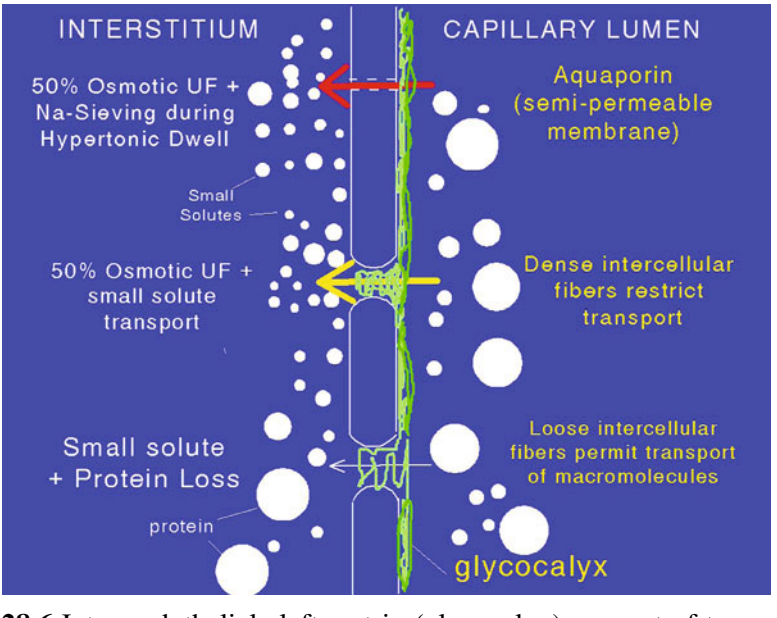


**Fig. 28.6** Inter-endothelial cleft-matrix (glycocalyx) concept of transcapillary transport

### 28.1.2.8 Treatment of Metastatic Cancer in the Peritoneal Cavity

Treatment of intraperitoneal ovarian or colorectal metastatic cancer presents special problems inherent to the tumor tissue. Although after surgical debulking of the larger tumors, these metastatic implants are relatively small (0.5-1 cm diameter), their interstitial properties and the interstitial pressure are significantly different from normal tissue. Pressures up to 40 mmHg have been recorded in some carcinomas (Boucher et al. 1990; Flessner et al. 2005; Flessner et al. 2004). As you will recall, the typical pressure within a tissue is -1 to -2 mmHg. This increased interstitial pressure presents a significant barrier to the penetration of agents from the peritoneal cavity into the tumor tissue, particularly for large immunotherapeutic substances dependent on convection. This would be discussed in more detail in the application section.

Another concern in treating tumors is the loss of intraperitoneal surface area due to peritoneal adhesions that limit access to the tumor nidus. Adhesions form between damaged parts of the peritoneum prior to debulking surgery or in the weeks after surgery and restrict flow of fluid and contact of fluid with the target tissue. If the therapeutic solution does not touch the surface, then no solute exchange occurs across the surface nor does drug transport from the cavity into the tissue. If this does occur either in dialysis or in intraperitoneal chemotherapy, the therapy can be compromised.

### 28.1.2.9 Lipid Solubility

Torres and colleagues (Torres et al. 1978) demonstrated that increasing lipid solubility of an agent will increase the rate of transfer from the cavity into the surrounding tissue and blood. They tested the absorption of model compounds dissolved in 50 mL of saline in the rat and found that as the heptane-water partition coefficient ($K_{hep}$) increased above 0.001, the absorption rate increased significantly. Barbital with a $K_{hep}$ of 0.001 was found to have an absorption of 57% at the end of one hour. On the other hand, thiopental with a $K_{hep}$ of 3.3 had a total absorption of 96% at the end of one hour. Studies with drugs which are lipid soluble such as hexamethylmelamine in the mouse (Wikes and Howell 1985) and thioTEPA in human subjects (Lewis et al. 1990) have shown peritoneal clearances of an order of magnitude greater than would be expected for similar molecular weight drugs that are purely hydrophilic. Capillary permeability and tissue diffusivities are not available for these drugs at this time.

#### 28.1.2.10 Effective Blood Flow

Because of the interference of the tissue with the transfer of gases between the peritoneal cavity in the blood, there is a problem in the estimation of actual blood flow and blood perfusion. Gas clearances of hydrogen and $CO_2$ have been determined to be approximately 4 to 7% of the cardiac output. However these probably underestimate the true blood flow because of resistance of the interstitium. Experiments were carried out in animals in which a diffusion chamber was placed directly on the liver, stomach, abdominal wall, and cecum (Demissachew et al. 1999; Kim et al. 1997a, b). In these experiments the mass transfer rate of urea across the surface was determined under conditions of control blood flow and blood flow reduced by 50 to 80%, followed by no blood flow (after the animal was euthanized). Blood flow was monitored simultaneously with laser Doppler flowmetry. All four tissues demonstrated significant decreases in urea transport after blood flow ceased. However, only the liver displayed a significant decrease in the rate of transfer during periods of reduced blood flow. With regard to extraction of water with a hypertonic solution, the same chambers were utilized and demonstrated statistically non-significant decreases in water flow in the cecum, stomach, and abdominal wall (Demissachew et al. 1999). The liver however did demonstrate a large drop in water transfer with reduced blood flow. Thus the transfer of solutes and water across the surface of the liver can be altered by changes in blood flow. However the total surface area of the liver as a percentage of the total peritoneal area is likely less than 5% of the active peritoneal transfer area in the human and only about 7% in the rat. Therefore, blood flow limitations appear to be insignificant with regard to the transfer of solutes and water across the peritoneum. This is of particular importance to intensive care patients who are in shock and who may have poor perfusion in their tissues compared to normal dialysis patients. While more cumbersome than continuous renal replacement therapies via hemodialysis or human filtration, peritoneal dialysis in capable hands is a distinct alternative to these techniques that require more technology.

## 28.2 MATHEMATICAL MODELS OF TRANSPERITONEAL TRANSPORT

### 28.2.1 Simple Membrane Models

The simple membrane model is illustrated in Fig. 28.1. In this model there is a volume in the peritoneal cavity, which is assumed to be a well-mixed system. In other words, the concentration at any one time in the

peritoneal cavity is the same. This is obviously a gross simplification if one considers the complexity of peritoneal anatomy (Hollinshead 1962); Fig. 28.5 is simplified with many of the internal structures removed for illustration. Although some pooling of the solution does occur in the peritoneal cavity, most of it is distributed in and around the viscera, and therefore parts of the volume could be significantly different depending on the transport characteristics of the tissue that the fluid is in contact (Leypoldt 2002). In its simplest form, the model is similar to the original Pyle-Popovich (Pyle et al. 1981) model and Eq. (28.2):

$$\text{Rate of mass transfer} = \frac{d(C_D V_D)}{dt} = MTAC\,[C_P - C_D(t)] + QSC_P \qquad (28.7)$$

$$\text{Rate of mass transfer} = \frac{d(C_P V_{Dist})}{dt} = -MTAC\,[C_P - C_D(t)] - QSC_P - K_E C_P \qquad (28.8)$$

where: $V_D$ = dialysate volume, $V_{Dist}$ = volume of the body compartment (the volume of distribution in the body for the solute in question), Q = mean net flow rate from the plasma to the peritoneal cavity, S = sieving coefficient = fraction of solute that transports with the net flow, $K_E$ = excretion rate coefficient that varies depending on the substance and the residual renal function of the patient on dialysis. While the $V_{Dist}$ is thought to be relatively constant, $V_D$ is often a function of time and is fitted to a simple polynomial equation (Rippe and Stelin 1989):

$$V_D(t) = a_0 + a_1 t + a_2 t^2 \cong V_{D,0} + Qt \qquad (28.9)$$

where $a_i$ = empiric coefficients from the fitting process, $V_{D,0}$ = volume of dialysis fluid instilled into the cavity at time $t = 0$ . Versions of this simple set of equations have been incorporated into computerized clinical applications such as ADEQUEST (Baxter Healthcare) or PACK-PD (Fresenius, Inc); the membrane model used in the Peritoneal Dialysis Capacity (PDC, Gambro, Inc) is discussed below in the section on the capillary model. The ordinary differential equations can be solved simultaneously as long as the MTAC and Q or their equivalents are known. By measuring the changes in concentration of glucose and creatinine and volume in the peritoneal cavity with respect to time in a Peritoneal Equilibration Test, which is a 4-hour prescribed dwell with periodic sampling (Twardowski et al. 1987), estimations of the MTAC can be made for individual patients and then used for predictions.

Figure 28.7A shows the MTAC for various substances versus the molecular weight from two different sources (Bomar et al. 1974; Flessner et al. 2000; Lasrich et al. 1979; Popovich et al. 1979). Figure 28.7B was derived from data for substances transporting from the peritoneal cavity into the blood (Dulaney and Hatch 1984; Flessner et al. 2000; Popovich et al. 1979) and in the opposite direction (Lasrich et al. 1979). The curves are similar, and it was subsequently observed in rodents that the rates of transfer across the peritoneum are symmetrical for substances of 5000 daltons or less (Flessner 1996b). Substances with molecular weight less than or equal to inulin will transport at the same rate from the blood to the peritoneal cavity or from the cavity to the blood. However substances which are large such as albumin or immunoglobulin have an asymmetrical transport because of their ability to be absorbed into the tissue but not into the blood except through lymphatic flow (Dedrick and Flessner 1989). Protein does leak out into the peritoneal cavity and often amounts to 8 to 20 g per day depending on the individual patient (Dulaney and Hatch 1984).

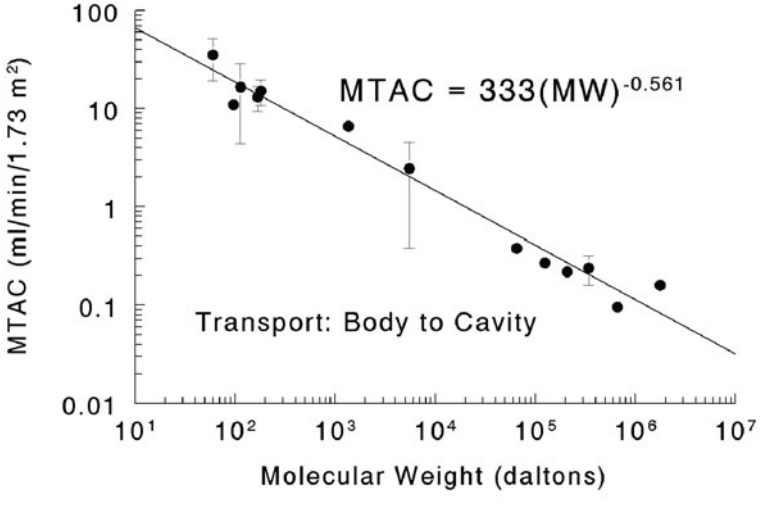


**Fig. 28.7A** MTAC for transport from the body (plasma) to the peritoneal dialysis fluid (data from Popovich et al. 1979).

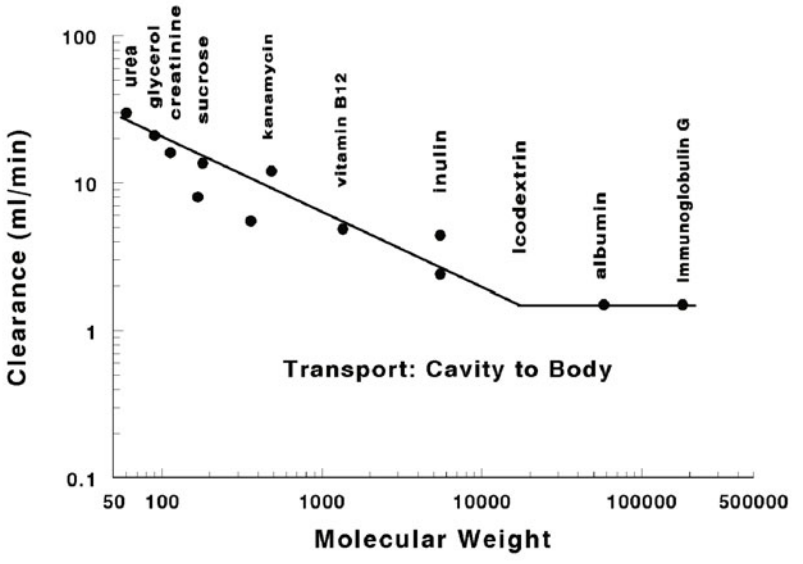


**Fig. 28.7B** Clearance rates of substances from the peritoneal cavity to the body (redrawn from Flessner and Dedrick 1994)

The simplicity of the "membrane" model makes it quite robust. A Peritoneal Equilibration Test (PET) can be carried out (Nolph et al. 1989; Twardowski et al. 1987), and values for the appearance rate of urea and creatinine as well as the disappearance of glucose from the cavity can be calculated by measuring the changes in volume and concentration of these substances within the cavity and relating these to their concentrations in the blood. Concentrations in the blood tend to be relatively stable for the four hour period of the PET.

### 28.2.2 Capillary (Three-Pore) Model

A variation on the membrane model is the capillary model or Three Pore theory of Rippe and colleagues (Rippe 1993), that replaces “membrane” in Figure 28.1 with the capillary endothelium. The theory incorporates pores similar to the Figure 28.6 except that there is no glycocalyx and the capillary is directly bathed by the dialysis solution. This theory is equivalent to a capillary floating in the peritoneal dialysis solution, neglects the cell-interstitial matrix, and assumes that the entire peritoneal barrier is the endothelium (see Fig. 28.8 and compare to Fig. 28.2). The

resulting solution of this is a simple set of equations to solve, and the model has been shown to be mathematically equivalent to a simple membrane model (Vonesh and Rippe 1992). Waniewski has reviewed extensively the differences and the likenesses in these two approaches (Waniewski et al. 1996). Parameters that are utilized in the pore theory are markedly different when they are used within a tissue (Waniewski et al. 2009). In recent years, Rippe and colleagues (Rippe and Venturoli 2007) have put additional barriers in series with the blood capillary in order to take into account properties of the tissue. However, this does not simulate the distributed nature of the blood capillaries (see Fig. 28.2), nor can it properly simulate fluid loss to the local tissues or to the lymphatics. This model is of very little use to chemotherapy where the penetration of normal and tumor tissue is desirable to simulate.

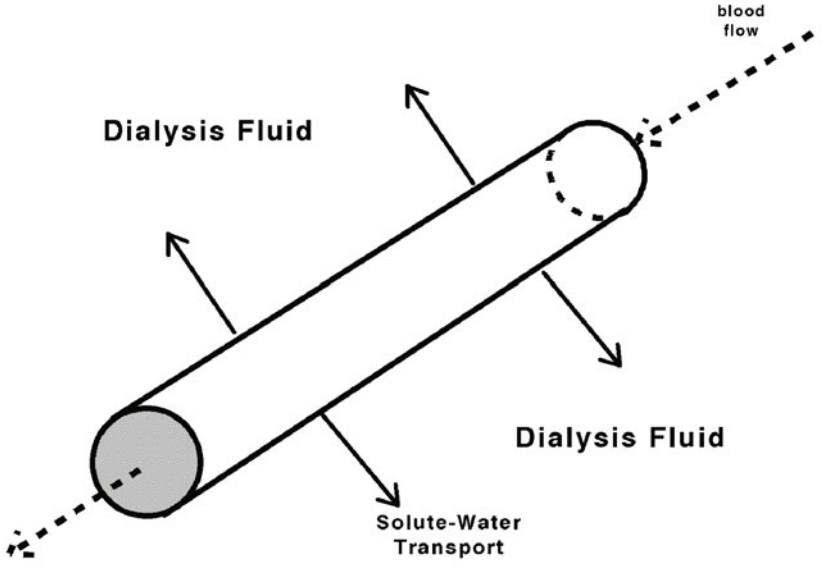


**Fig. 28.8** Capillary model of peritoneal dialysis removes the surrounding tissue and reduces the complexities of Figures 28.2-28.3 to that of a capillary within the dialysis solution in the cavity.

### 28.2.3 Multi-Compartmental Models

Compartmental models can be more sophisticated than the simple 2-compartmental model of Fig. 28.1. As illustrated in Fig. 28.3, models can

incorporate tissue as well as secondary compartments in order to simulate the tissue as well as the distribution in the body of drugs with complex pharmacokinetics. Dedrick and colleagues (Dedrick et al. 1978) have utilized this in a whole body model for treatment of intracavitary carcinoma with intravenous (IV) or intraperitoneal (IP) methotrexate. This is illustrated in Fig. 28.9. In this model, plasma circulates to multiple tissues including the liver, the G.I. tract, the kidney, skin, muscle, and bone marrow. Note that drugs put into the peritoneal cavity are in part absorbed across the gut wall and enter the portal system and subsequently into the liver, where metabolism and concentration in the biliary circulation may occur. After simplifications and assuming the 2-compartment model of Fig. 28.1, the following equations can be solved simultaneously (Dedrick et al. 1978):

$$V_{Dist}\frac{dC_P}{dt} = MTAC\left[C_D - RC_P\right] - K_eC_P \tag{28.10}$$

and

$$V_D\frac{dC_D}{dt} = MTAC(RC_P - C_D) \tag{28.11}$$

where R is the equilibrium dialysate to plasma concentration ratio (to account for protein binding of the drug); $K_e$ = whole body clearance by all processes. If the peritoneal concentration, $C_D$, is held constant and the parameters are constant, then Eq. (28.10) and Eq. (28.11) can be solved for the following equation:

$$\frac{C_P}{C_D} = \frac{MTAC}{R(MTAC) + K_e}\left[1 - e^{\frac{R(MTAC)+K_e}{V_{Dist}}t}\right] \tag{28.12}$$

The authors provide further solutions to the problem of intermittent dialysis and a declining concentration in the peritoneal cavity (Dedrick et al. 1978). Use of more complex compartmental model is justified when the pharmacokinetics of the drug indicates a need or there are safety issues with a toxic chemotherapeutic agent. In most dialysis applications, small, unbound marker molecules are simulated and a single body compartment is sufficient.

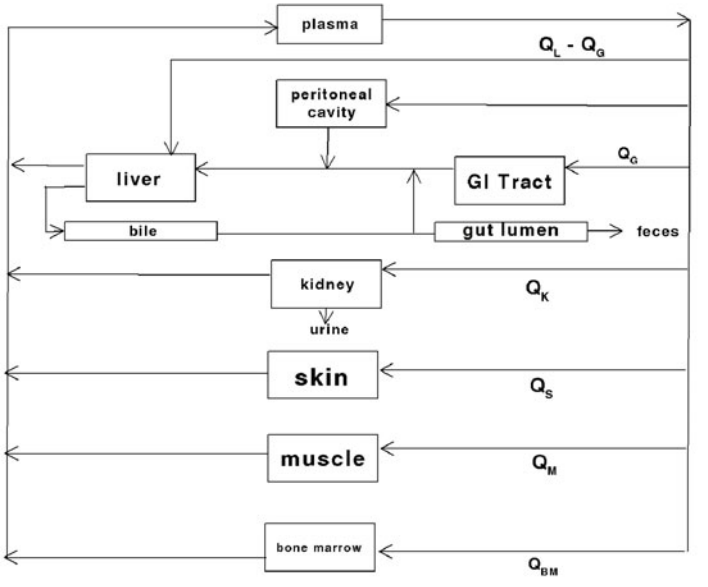


**Fig. 28.9** Multi-compartmental model for administration of chemotherapy intravenously or intraperitoneally. $Q_i$ = flow through compartment "i". Redrawn from Dedrick et al. 1978.

### 28.2.4 Distributed Model of Peritoneal Transport

To simulate transport phenomena within a specific tissue space with a distributed model, the circulation and distribution in the body can be modeled as a series of compartments. This simplifies the overall model and allows emphasis to be placed on the tissue space of interest. Figure 28.3 uses this concept to simplify transperitoneal transport for most substances of interest in dialysis. The model details are as follows:

*Mass Balances:* A mass balance on dialysis fluid in the peritoneal cavity in Fig. 28.3 gives the following equation:

$$\frac{dC_D V_D)}{dt} = -\left(R_L + R_{DT}\right) \tag{28.13}$$

where $R_L$ = lymph flow and $R_{DT}$ = the net rate of mass transfer between peritoneal cavity and tissue.

A mass balance on the distribution compartment of Fig. 28.3 gives the following equation:

$$\frac{d(C_P V_{Dist})}{dt} = R_{TP} + R_L + R_4 - (R_3 + R_5) \tag{28.14}$$

where $R_{TD}$ = mass transfer between the peritoneal tissue and the plasma compartment, and $R_3$ and $R_4$ are rates of mass transfer between the body exchange and distribution compartments; $R_5$ = rate of excretion. A mass balance on the body-exchange compartment yields:

$$\frac{d(C_I V_I)}{dt} = R_3 - R_4 \tag{28.15}$$

where $C_I$, $V_I$ are the concentration, volume of the body-exchange compartment, respectively.

The mass conservation equation for unidirectional transport in the peritoneal tissue is as follows:

$$\frac{\partial(\theta_i C_{T,i})}{\partial t} = D_{eff,i}\frac{\partial^2 C_{T,i}}{\partial x^2} - \frac{\partial(f\frac{\theta_i}{\theta_w} J_V C_{T,i})}{\partial x} - J_{s,i} a \tag{28.16}$$

where $J_s$= the local transcapillary solute flux ($g \cdot cm^{-2} \cdot s^{-1}$), a = capillary area density, $C_T = C_T(x,t)$.

*Volume Balances*: A balance on the volume of the peritoneal cavity gives the following:

$$\frac{dV_D}{dt} = -(F_L + F_{DT}) \tag{28.17}$$

where $F_L$ = lymphatic flow from the peritoneal cavity and $F_{DT}$ = net flow from the peritoneal cavity to the tissue space.

Analogous volume balances can be written for the distribution and body-exchange compartments. Typically, these compartments are assumed to be constant in volume, but can be modeled as variable if sufficient data are available.

*Rate Laws:* The rate of mass flow via lymphatics is:

$$R_L = F_L C_D \tag{28.18}$$

The rates equation for that portion of the transport from the cavity via tissue and blood capillaries is found by expanding Eq. (28.13):

$$V_D \frac{dC_D}{dt} = F_{DT} C_D - R_{DT} \tag{28.19}$$

The rate of mass transfer from the peritoneal cavity to the tissue can be expressed as a boundary condition to Eq. (28.16) at the peritoneum (x = 0):

$$R_{DT} = \left\{ -D_{eff,i} A \frac{\partial C_{T,i}}{\partial x} + f_i \frac{\theta_i}{\theta_w} J_V A C_{T,i} \right\}_{x=0} \tag{28.20}$$

The local volume flux in the tissue is defined by the following rate equations to find transport across the blood capillary between the tissue and blood capillary. If the transcapillary convective flux, $J_c$, is assumed to be constant, integration over the total thickness (x = 0 to $x_1$):

$$J_V(x) = (J_c a)x_1 - (J_c a)x \tag{28.21}$$

If evaluated at x = 0:

$$F_{PT} = J_v(0)A = (J_c a)Ax_1 \tag{28.22}$$

The expression for $J_c$ can be taken from Chang (Chang 1980):

$$J_c = L_P \left[ P_T - P_P - \sum_j \sigma_j (\pi_{T,j} - \pi_{P,j}) \right] \tag{28.23}$$

where $L_P$ = filtration coefficient; $P_T$ and $P_P$ are the hydrostatic pressures in the tissue and plasma, respectively; $\pi_{T,j}$ *and* $\pi_{P,j}$ are the osmotic pressures of component "j" in the tissue and plasma respectively, and $\sigma_j$ = reflection coefficient for osmotic solute "j".

$$J_{s,i} = \sum_j \chi_{i,j} J_c \left[ C_{T,i,j} - C_{P,i,j} \frac{\exp(-\gamma_{i,j})}{1-\exp(-\gamma_{i,j})} \right] \tag{28.24}$$

Where $\chi_{i,j}$ = sieving coefficient of the "j" portion of the capillary barrier for solute "i"; $\gamma_{i,j}$ = ratio of the convective flux through the "j" portion of the capillary barrier to the rate of diffusive flux for the solute "i". See references for details (Chang et al. 1975; Flessner et al. 1984; Fu et al. 1995; Hu and Weinbaum 1999; Weinbaum et al. 2003; Zhang et al. 2006).

Other rate equations between the different compartments are defined in the following equations:

$$R_{TP} = \int_0^{x_1} (J_s a) A dx$$

$$R_3 = K_3 C_P V_{dist}; \quad R_4 = K_4 C_I V_I; \quad R_5 = K_5 C_P V_{dist} \tag{28.25}$$

*Boundary conditions: Concentrations and initial volumes of compartments should be specified at time zero (t = 0):*

$C_P = C_P(0)$; $V_{Dist} = V_{Dist}(0)$; $V_D = V_D(0)$; $C_D(0) = 0$ for dialysis or some initial concentration if dialysis fluid contains chemotherapy; $C_T = C_T(0)$ if tissue concentration is constant or $C_T = g(x)$ if tissue concentrations are a steady-state initial concentration; the boundary condition at the end of the tissue space (opposite to peritoneal edge): $C(x_1) = C_P(t)$ or $dC(x_1)/dx = 0$, depending on the direction of transport.

These conditions then make up a set of equations which can be solved with various numerical techniques (Carnahan et al. 1969). What is absolutely necessary are to have the various coefficients. The diffusivity of various substances in water and in tissue is plotted in Fig. 28.10 (Seames et al. 1990; Venturoli and Rippe 2001). The hydraulic conductivity of tissue for substances is plotted in Fig. 28.11. Compartmental parameters are typically estimated from pharmacokinetic data and modeling. The most difficult parameters are those for the tissue compartment; this requires specialized experimental techniques such as quantitative autoradiography or fluorescence. These must be carefully put together and the data from tissue penetration experiments utilized in order to fit this model to the true phenomenon.

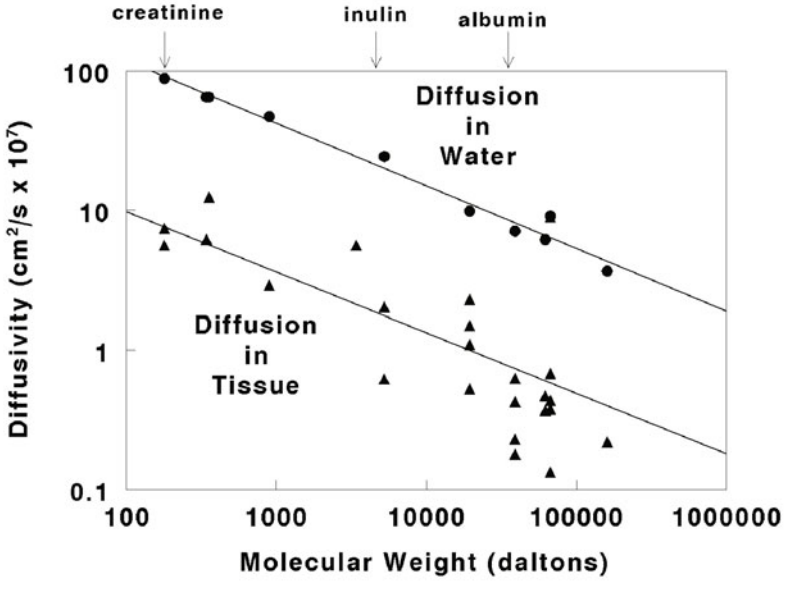


**Fig. 28.10** Diffusivity in water and tissue (redrawn from Dedrick 1986)

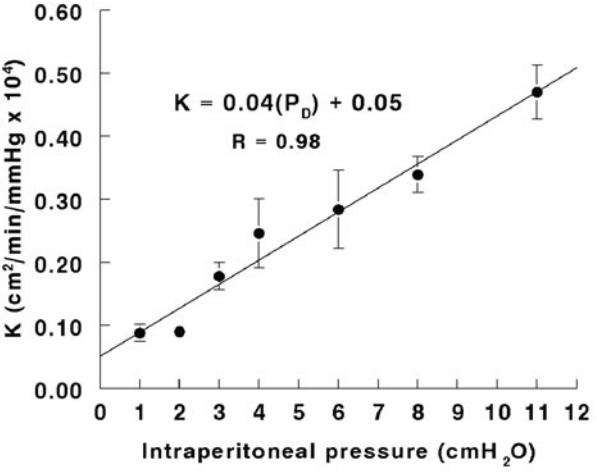


**Fig. 28.11** Hydraulic conductivity in abdominal wall tissue under various conditions of intraperitoneal pressure (redrawn from Zakaria et al. 1997)

## 28.3 APPLICATIONS

### 28.3.1 Peritoneal Dialysis Applications

Applications of membrane models have been made by many investigators (Flessner et al. 1985d; Rippe and Stelin 1989; Vonesh and Rippe 1992; Waniewski et al. 1992; Waniewski et al. 1993). These papers contain many examples of using simple models in clinical situations in order to predict from initial data (such as a Peritoneal Equilibration Test (Twardowski et al. 1987)) what might happen under different dialysis conditions. In this way the clinical treatment of an individual patient can be optimized. This type of model is the basis of the three different computer programs that are available: Adequest 2.0 (Baxter Corp), PACK-PD (Fresenius Corporation), and Peritoneal Dialysis Adequacy (Gambro, Inc).

*Example 28.1*

Patient MP progresses to renal failure (estimated glomerular filtration rate $\leq$ 10 ml/min. He has a peritoneal dialysis catheter placed, and two weeks later begins treatment. He is 55 years old, weighs 80 kg, and is 1.7 m tall. He does have residual kidney function as measured by the average of creatinine and urea clearances (calculated as urine concentration x urine volume/(plasma concentration x collection time) as 9.5 mL per minute. He will be started on a regimen of four 2-liter exchanges per day of continuous ambulatory peritoneal dialysis (the fluid is infused into the abdomen

over 10-15 min, allowed to remain 4-6 hours and then drained over 20-30 min with the cycle repeated a total of 4 times/day).

One month later he performs a four-hour peritoneal equilibration test (PET), during which a 2.5% glucose dialysis solution (2.26 g/dl in an isotonic salt solution produces a total osmotic pressure of 397 mosm/kg) is placed into the peritoneal cavity in the volume of two liters. At four hours the volume is drained and determined to be 2.4 L. His urea concentration in the dialysate is 50 mg per deciliter while the plasma BUN is 60 mg/dl. The dialysate creatinine concentration is 6 mg per deciliter with a serum creatinine of 10 mg/dl. The glucose concentration was determined both at the beginning of the four-hour dwell as 2260 mg/dl and at the end of the four-hour dwell is 960 mg/dl. The plasma glucose concentration is normal at 95. Calculate the MTAC for creatinine.

## Solution

***Solution 1*: Assumption of constant peritoneal volume**

From Eq. (28.2)

$$\bar{V}_D \frac{d[C_D(t)]}{dt} = MTAC\left[C_P - C(t)\right] \tag{28.26}$$

Where $\bar{V}_D$ = mean volume = 2200 ml and $C_P$ = 10 mg/dl.

After integration of Eq. (28.26) and rearranging:

$$MTAC = \frac{\bar{V}_D}{\Delta t} \ln\left[\frac{C_P - C(0)}{C_P - C(240)}\right] \tag{28.27}$$

After inserting values into Eq. (28.27), the MTAC = 15.23 ml/min for MP. This value is well within the range for a normal patient (see Fig. 28.7).

***Solution 2*: Calculate the MTAC from this data using the Pyle-Popovich approach with a variable $V_D$.**

First, assume that the net volume increase is a constant rate over the four hours:

$$\frac{dV_D}{dt} = Q = \frac{400\ ml}{4 \times 60\ min} = 1.67\ ml/min \tag{28.28}$$

After integration, Eq. (28.28) becomes:

$$V_D = 2000 + 1.67 \times t \tag{28.29}$$

From Eq. (28.7), we obtain:

$$C_D \frac{dV_D}{dt} + V_D \frac{dC_D}{dt} = MTAC\left[C_P - C_D(t)\right] + QSC_P \qquad (28.30)$$

After substitution of Eq. (28.29), rearranging and assuming S = 1.0 (if S=0, the equation reverts to Solution 1):

$$\frac{dC_D}{dt} = \left\{\frac{MTAC + Q}{V_0 + Qt}\right\}[C_P - C_D(t)] \qquad (28.31)$$

After integration and substitution of the values for C and V:

$$MTAC = Q\left\{\frac{\ln\dfrac{C_P}{C_P - C_D(t=240)}}{\ln\dfrac{V_0 + Q\times 240}{V_0}}\right\} = 6.3 \text{ ml/min} \qquad (28.32)$$

This demonstrates a large effect on the mass transfer rate with S = 1, but if S is ~0.3-0.6, this will significantly diminish the effect of the convective transport.

***Solution 3*: Use the 3-Pore theory to estimate rates of mass transfer**

With three pores, the model is a more complicated membrane with several more parameters to define such as the pore diameter and the relative pore density (Rippe 1993; Stelin and Rippe 1990). In order to delineate the properties of the aquaporin, the “small pore”, and the “large pore”, the dialysis prescription has to be altered for 24 hours to separate the effect of these different entities. For the “water-only” or aquaporin, very short dialysis (1-2 hours) with a high concentration of glucose must be carried out in order to observe the major effects of influx of water devoid of the solute sodium; the amount of "sodium sieving" determines the aquaporin effect. For the "large pore", a longer period of low glucose, dialysate dwell (> 6 hours) insures that the effects of the slower protein loss can be observed. The so-called "small pore" requires a combination of short and longer dwells with several different exchanges, typically using 2.5% glucose solutions.

These procedures do provide more physiologic data to fit the model, but the procedure has to be balanced with the practical problem of obtaining patient cooperation. Patients are not equivalent to laboratory animals and cannot be always forced or trained to do exactly what the investigator-physician needs. Therefore the there are practical limitations in the implementation of this particular mathematical theory. For examples of application of the theory, please consult reference: (Rippe et al. 1991).

### 28.3.2 Compartmental Models for Intraperitoneal Chemotherapy

An illustration of a complex compartmental model used to predict the transfer of drug from the peritoneal cavity into various tissues and ultimately into the plasma is shown in Fig. 28.12 (Flessner et al. 2000). Solute and water balances are required around each compartment, and some of the information required for implementing the model is contained in Table 1 of reference (Flessner et al. 2000). As it turns out the permeability term "P" from Eq. (28.1) is approximately the same for each abdominal tissue (Flessner 1996b), and therefore solute transfer rates can be found by multiplying the P for the molecule by the surface area of exposure:

$$S_{i,j} = P_i A_j \left[ C_{D,i}(t) - C_{P,i} \right] \tag{28.33}$$

where $S_{i,j}$ = rate of solute transfer of substance "i" across surface "j"; $A_j$ = surface area of "j" that is in contact with the dialysis fluid. The total solute transfer rate across the peritoneum would equal the sum of all of the "$S_{i,j}$" and can be approximated by Eq. (28.2).

The area term should not be equated to the actual peritoneal area of each tissue; experiments in humans (Chagnac et al. 2002, 1999) and in animals (Flessner et al. 2001a, b) have demonstrated that the maximal area in contact with 2 to 3 L of peritoneal fluid is on the order of 30 to 40% of the total area. And it appears as though even with movement of fluid from one place in the peritoneum to the other the relative surface area is about the same. In fact, it has been shown that the PA or MTAC can be scaled from small animal to man by ~ surface area or (body weight)$^{0.67}$ (Dedrick 1986).

Small substances (MW < 500 d) are typically diffusion-dominated, and the solution could be simplified by assuming that the effect of convection is insignificant. The $P_i$ can be related to intrinsic tissue parameters of diffusivity and capillary permeability ($p_i$) times the capillary area density for tissue "j" ($a_j$) (Dedrick 1986) through the following relationship:

$$P_i = \sqrt{D_i \times (p_i a_j)} \tag{28.34}$$

Steady-state conditions are typically approached within 30 min (Flessner et al. 1985a), and the concentration in the tissue ($C_T$):

$$\frac{C_T - C_P}{C_D - C_P} = \exp\left\{ -\sqrt{\frac{p_i a_j}{D_i}} x \right\} \tag{28.35}$$

This equation can provide estimates of the steady-state concentration in the tissue surrounding the cavity.

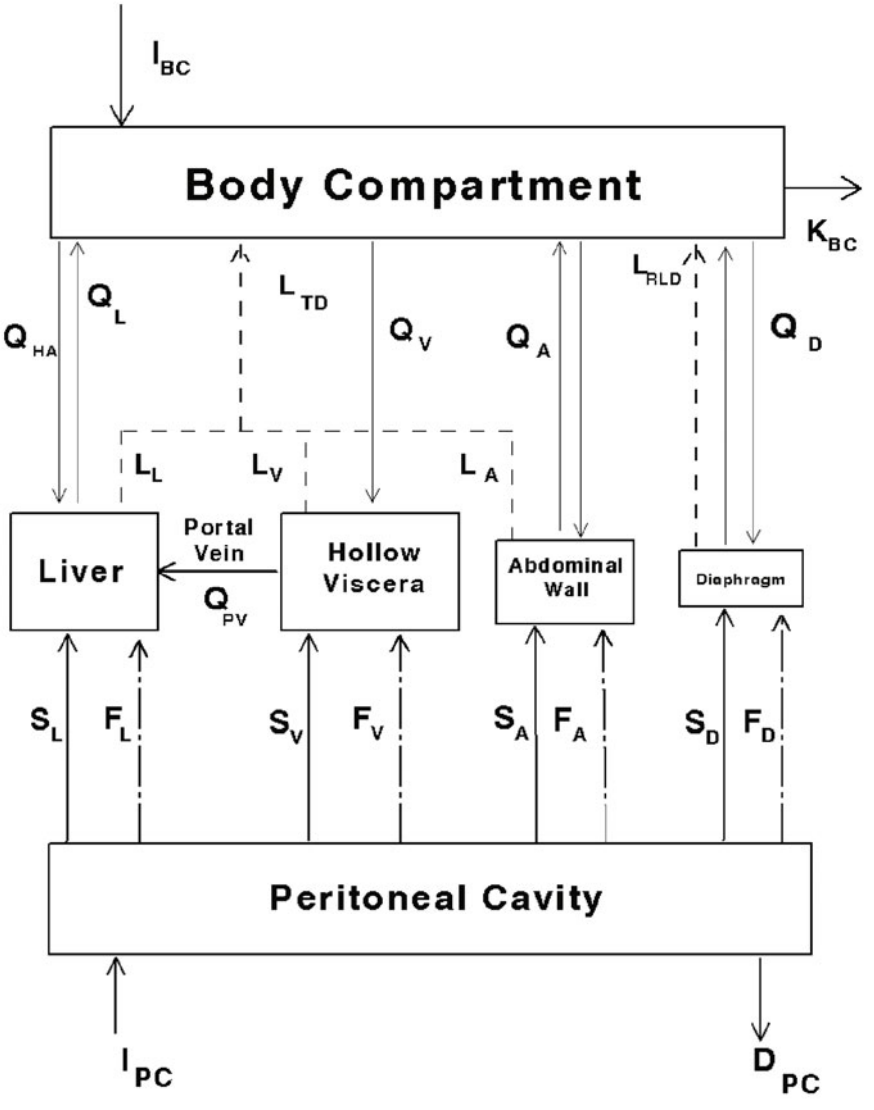


**Fig. 28.12** Multi-compartmental model of peritoneal transport that emphasizes various tissue compartments. $I_{BC}$ = input; $K_{BC}$ = excretion; L = lymph flow; Q = blood flow; S = solute transport; F = volume flow; D = volume removal rate. Subscripts: HA = hepatic artery; L = liver, TD = thoracic duct; RLD = right lymph duct; V = viscera; A = abdominal wall; D = diaphragm; PV = portal vein; PC = peritoneal cavity. Redrawn from (Flessner et al. 2000).

### 28.3.2.1 Pharmacokinetic Advantage Theory

If the drug is infused into the peritoneal cavity and a constant rate then the pharmacokinetic advantage of the IP administration ($R_{IP}$) is equal to (Flessner et al. 2000):

$$R_{IP} = \left( \frac{C_D}{C_P} \right)_{IP} \tag{28.36}$$

If the drug is infused at a constant rate intravenously, then the pharmacokinetic advantage of the intravenous administration with regard to the peritoneal cavity ($R_{IV}$) is (Flessner et al. 2000):

$$R_{IV} = \left( \frac{C_D}{C_P} \right)_{IV} \tag{28.37}$$

The overall pharmacokinetic advantage ($R_d$) of intraperitoneal therapy to intravenous therapy is the ratio of Eq. (28.36) to Eq. (28.37):

$$R_d = \frac{R_{IP}}{R_{IV}} \tag{28.38}$$

This number expresses the relative advantage that can be achieved by administration of the drug directly into the peritoneal cavity when compared to the intravenous route. If there is no elimination of drug in the peritoneum, it can be shown that the pharmacokinetic advantage may be expressed by the following (Dedrick 1986):

$$R_d = 1 + \frac{K_e}{MTAC} \tag{28.39}$$

As will be seen in the examples below, there is a large pharmacokinetic advantage for hydrophilic drugs. If a typical antibiotic would be given would be expected to have an MTAC of 10 mL/min (see Fig. 28.7) and if the drug is cleared by the kidney at 100 ml/min, $R_d$ = 11. If the drug is eliminated by tissues within the peritoneal cavity such as the liver, there is a first pass effect that has the effect of increasing the natural pharmacokinetic advantage given by the equation:

$$R_{ip} = \frac{1 + \dfrac{K_e}{MTAC}}{1 - f_{liver} E} \tag{28.40}$$

where $f_{liver}$ = fraction of absorbed drug that enters the liver via the portal system and E = the fraction of a drug removed by the liver in the first pass (Dedrick 1986).

### 28.3.2.2 Application of the Pharmacokinetic Advantage to Cisplatin Therapy for Peritoneal Metastatic Disease

*Example 28.2*

**Calculate the pharmacokinetic advantage of IP versus IV for metastatic ovarian carcinoma**

*Solution*

First we assume that there is no local metabolism, and therefore Eq. (28.39) applies. To estimate the MTC, we can use Eq. (28.34) with a diffusivity of $1.9 \times 10^{-6}$ $cm^2/s$ based on transport in the brain (Morrison and Dedrick 1986 ) and a "pa" of $1.4 \times 10^{-3}$ $s^{-1}$ (based on hexose in the jejunum (King et al. 1986), we obtain MTC = $(1.4 \times 1.9 \times 10^{-9})^{0.5} = 5.158 \times 10^{-5}$ cm/s. Assuming an area of 30% of 10000 $cm^2$ (Flessner et al. 2001b; Rubin et al. 1988), the MTAC = 0.206 cc/s or 12.4 cc/min. Estimates of $K_e$ from the literature (Goel et al. 1989) provides a measurement of 329 ml/min. Therefore,

$$R_d = 1 + \frac{K_e}{MTAC} = 1 + \frac{329}{12.4} = 27.5$$

*Example 28.3*

**Calculate the pharmacokinetic advantage of treating peritonitis with vancomycin ip versus iv.**

*Solution*

Intraperitoneal vancomycin is utilized frequently by clinicians to treat peritonitis from staphylococcal species or gram-positive organisms. Vancomycin has a molecular weight of approximately 1500 da. Nearly 55% of the drug is bound to serum protein. The volume of distribution is quite variable over a range of 0.64 L per kilogram in normal young humans (Cutler et al. 1984) to 0.93 L per kilogram in the elderly (Moellering 1984). Patients with renal failure have volumes of distribution of 0.9 L per kilogram (Moellering 1984). The serum half-life of vancomycin is typically six hours, but in renal failure patients, the normal half-life becomes markedly prolonged. Clearance of the drug in the normal patient is 100-140 mL/min (Rotschafer et al. 1982). If the clearance is correlated with an iothalamate-measured glomerular filtration rate (GFR), the clearance rate is less is

approximately 5 mL/min for patients whose GFR ≤ 10 ml/min (Cunha and Ristuccia 1983; Matzke et al. 1984). From Fig. 28.7, the MTAC is approximately 4 mL/min. Let us assume that the clearance from the body of our patient is about 5 ml/min per minute and that the drug is given by continuous infusion. The $R_d$ would therefore be estimated by:

$$R_d = 1 + \frac{K_e}{MTAC} = 1 + \frac{5}{(4 \times 0.45)} = 3.8 \qquad (28.41)$$

The MTAC is modified by the protein binding (unbound fraction = 1 - 0.55).

Because of toxicity from the drug it is typically not given as continuous infusion but it is given as a single IP administration over 6 to 8 hours once or twice per week, depending on the residual renal function and clearance of the drug from the body. Bunke and colleagues (Bunke et al. 1983) demonstrated a regional IP advantage of 3.9 and an IV advantage of 0.26. Therefore, the pharmacokinetic advantage of the 3.9 divided by 2.6 = 15. This provides a strong theoretical and experimental argument for intraperitoneal vancomycin and other antibiotics for the treatment of peritonitis.

### 28.3.3 Application of the Distributed Model to Tissue Transport of Macromolecules

Transport of substances such as proteins or macromolecules requires the introduction of the tissue space to the model in order to appropriately predict what is happening in the transport process. As shown in Fig. 28.13, diffusion and convection of a substance are dependent not only on the size of the molecule but also on the pressure profile and the hydraulic conductivity in the tissue. With a positive pressure in the peritoneal cavity, the initial cell layers and extracellular space will be expanded depending on the degree of pressure in the cavity. This has actually been determined in animal experiments (Zakaria et al. 2000). It is also seen in human beings when dialysis patients have malformations in their abdominal wall tissue, and the pressure pushes fluid through the tissue and into the subcutaneous space. While there have been no measurements of gradients of pressure within the abdominal wall or tissue extracellular space in human beings, there is data in animals (Zakaria et al. 1997). Osmotic forces have little to do with the extracellular space, but they can draw fluid from the vasculature into the extracellular space (Zakaria et al. 1999a).

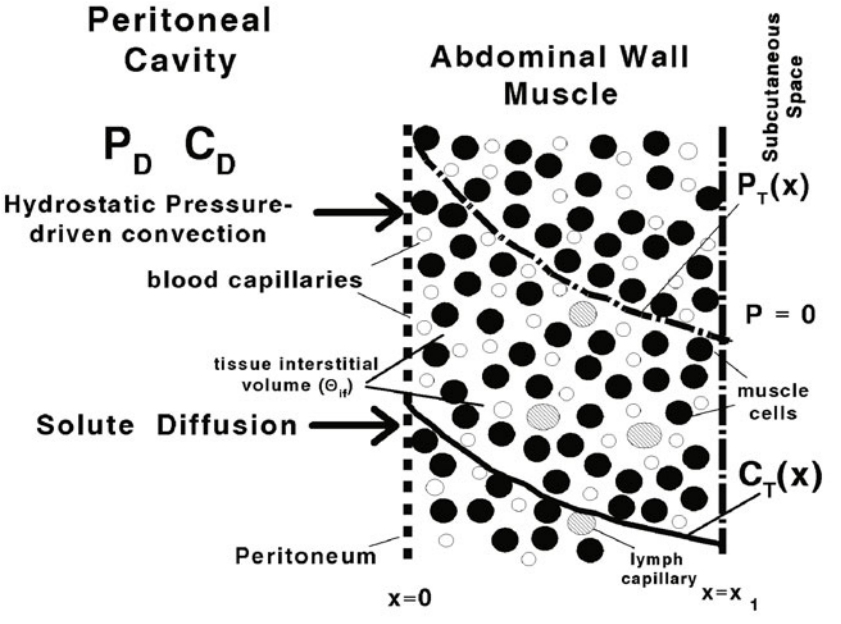


**Fig. 28.13** Distributed model of peritoneal transport from the cavity into the abdominal wall. Solute diffusion and convection occurs from the cavity into the tissue, driven by the respective gradients of concentration ($C_T$) and pressure ($P_T$). The tissue space is filled with blood and lymph capillaries that are distributed in a cell-interstitial network.

Proteins are sensitive to expansion of the interstitial space, and interstitial compliance ($\Omega$) is determined by the change in interstitial space divided by the change in pressure in the tissue (Flessner 2001b):

$$\Omega_j(P_T) = \frac{d\theta_w}{dP_T} \tag{28.42}$$

The equations for solute and water balances are given in equations (28.11) - (28.17) above. If this interstitial compliance is significant in the physiologic range of IP pressures (0-10 mmHg), the parameters K and $D_{eff}$ become variable functions of $P_T$. These parameters and the various rate

equations have to be defined by experimentation. A volume balance on the interstitial water space is as follows:

$$\frac{\partial \theta_w}{\partial t} = \frac{\partial}{\partial x}\left[ K \frac{\partial P_T}{\partial t} \right] + F_{capillary} - F_{lymph} \tag{28.43}$$

Where: $F_{capillary}$ = flow from blood capillaries to the interstitial space and $F_{lymph}$ = lymph flow from the space. If there is tissue binding of the protein, the unbound or free ($C_{free}$) must be used in the calculations:

$$C_{tissue} = C_{free} + C_{bound} \tag{28.44}$$

Rate equations for binding, capillary permeability, and lymph flow must be derived from experiment or from the literature. To solve this series of equations, one must define initial and boundary conditions, the parameters $D_{eff}$ and K as functions of $P_T$ and $\theta_{if}$ and $\theta_w$ as functions of $\Omega(P_T)$. For a detailed discussion of this approach, please refer to (Flessner 2001b).

By manipulating the various coefficients, we attempted a model fit of profile data from rodent experiments. In these experiments we examined immunoglobulin G (IgG) penetration from an isotonic solution in the peritoneal cavity into the tissues of rats. The intraperitoneal volumes resulted in pressures of 2.2 to 3 mmHg in the cavity throughout the 180 minute experiment. Concentrations in the cavity were nearly constant, and after the animals were sacrificed the tissue was rapidly collected and frozen, and quantitative autoradiography was carried out to measure the labeled IgG in the tissue (Flessner and Dedrick 1994; Flessner et al. 1992b). The model intraperitoneal pressure was sent to 3 mmHg and previously derived parameters were utilized to predict the tissue void, hydraulic conductivity, the interstitial volume. Three parameters were required to improve the model fit: the minimum tissue void volume was set to 0.07, with variation of the high-pressure side to the low-pressure side of 0.10 to 0.07. The solute retardation factor (f) was set to 0.3 to produce a better fit to the curve. Since we did not have any binding data from these experiments we found that setting the coefficient to $8.66 \times 10^{-4}$ improved the fit considerably. The final fitted curve is as in Fig. 28.14.

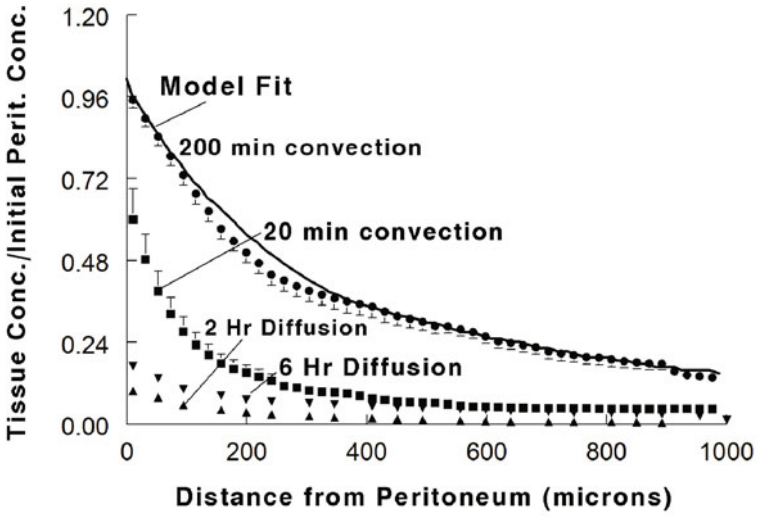


**Fig. 28.14** Normalized Immunoglobulin G profiles (Flessner et al. 1992) in abdominal wall of rats demonstrating the increase in transport with hydrostatic pressure-driven convection ($P_D$ = 3 mmHg) over diffusion ($P_D$ = 0 mmHg). A fit (solid line) of the distributed model is plotted (derived from (Flessner 2001b)).

Because of the complexity of this model and the number of parameters that need to be fitted, there is a family of curves which can be found or can be fitted to these data. As more data is gathered, the model then can be refined. However this does give one the impression of how macromolecular drugs given in this body cavity will penetrate normal tissue. While the available data was limited to just three hours of transport, the model can be utilized to predict tissue concentrations at various times after administration under various conditions. Waniewski and Stachowska-Pietka (Stachowska-Pietka et al. 2007; Waniewski et al. 2009) have recently implemented variations of this particular model in order to include osmotic changes in the tissue from hypertonic solutions place in the cavity and have calculated variations in the interstitial space. Reference to these papers should be made for further explanations.

## 28.4 CONCLUSION

Kinetic models of peritoneal transport take three general forms: membrane models, compartmental models, and distributed models. Since each of these requires a variety of data inputs, each should be selected for the

intended use. Membrane models and compartmental models neglect the anatomy and lump several physiologic phenomena and are therefore simpler to use. However, these models are perfectly adequate for dialysis simulation, since the desired output includes only concentrations in the blood and the peritoneal cavity. Prediction of penetration of drugs into tumors or other tissue targets generally requires more detailed, data-driven parameters in the simulation of tissue concentration profiles. Hence, there is still a great need for tissue-level data to understand how chemotherapeutic and macromolecular agents and uremic poisons move across the peritoneum.

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## ESSAY QUESTIONS

1. Define the difference between membrane models and distributed models.
2. Describe the data necessary for the fitting of a compartmental model.
3. Describe the data necessary for the fitting of a distributed model.
4. Describe the peritoneal barrier.
5. Why are hypertonic solutions used in peritoneal dialysis?

6. How does lymph flow from the peritoneal cavity affect dialysis?
7. Describe how lipid solubility affects tissue transport.
8. Two liters of a solution of 1.5% dextrose are instilled into the cavity of a peritoneal dialysis patient and at the end of 4 hours, two liters are drained and the concentration of creatinine in the dialysis fluid = 7 mg/dl while the serum creatinine has remained stable at 10 mg/dl. Estimate the MTAC. Why is the serum creatinine stable during the dialysis?
9. The same patient in question 8 comes into the dialysis center 6 months later and needs to use a higher glucose solution to remove fluid from his body. You know from previous measurements that he will remove a net of 500 ml over 4 hours with a 4.25% dextrose solution. What will be the difference in the total mass of creatinine removed, if the initial volume = 2 liters, the serum concentration = 10 mg/dl, and the sieving coefficient (S) for creatinine ~ 0.3?
10. A new drug is developed for use in treating metastatic ovarian carcinoma. When the drug is given in 2 liters of dialysis fluid, the approximate steady state concentration in the cavity = 100 mg/L, while the concentration in the plasma = 10 mg/L. When given intravenously, the steady-state concentration in the plasma = 10 mg/L with a concentration in the cavity = 1 mg/L. He asks you to help him decide which is the best route to use for cancer that is restricted to the peritoneal cavity.

## SELF-TEST QUESTIONS

### A. Mark the following statement as either True (T) or False (F)

1. Peritoneal dialysis depends solely on the biophysical properties of the peritoneal membrane or peritoneum, which is made up of a single layer of mesothelial cells and several layers of connective tissue.
2. The peritoneal cavity is normally a small space in the abdomen with a surface area that is a fraction of the body surface area.
3. Net ultrafiltration, as determined from a patient dialysis test (i.e., Peritoneal Equilibration Test), is equal to the net volume difference divided by test duration. This calculation can distinguish between the osmotic filtration and the different flows out of the cavity.

4. During dialysis with an intraperitoneal volume of 2-3 liters, the fluid loss to the body is chiefly due to lymphatic flow through the diaphragm.
5. The rate of a solute's diffusion through tissue is typically an order of magnitude less than its diffusive rate through water and proportional to the ratio of the fractional tissue space available to the solute divided by the degree of tortuosity in the diffusion path.

6. Convection, the rate of solute flow through a tissue bed, is proportional to slope of the concentration profile of the solute within the tissue.

7. Inert gas absorption from the peritoneal cavity has demonstrated that normally there are no blood flow limitations of transport across the peritoneal barrier and that the tissue cell-interstitial matrix is a significant transport barrier.

8. Compartmental models of trans-peritoneal transport are an accurate representation of the tissue-level mechanisms governing the physiologic process.

9. The size-discriminating portion of the peritoneal barrier is the blood capillary endothelium.

10. Intraperitoneal delivery of therapy is the ideal method for metastatic carcinoma in the brain and lungs.

## B. MULTIPLE CHOICE QUESTIONS

**Choose the Best Answer**

11. The structures of the peritoneal barrier that provide the physiologic resistance to transport include:

A. Peritoneum
B. Mesothelial cells
C. Fibroblasts
D. All of the above
E. None of the above

12. The inter-endothelial cleft, lined by a glycocalyx, provides:

A. Lubrication of peritoneal cells
B. Secretion of cytokines
C. Inflammatory response
D. Size-selective barrier
E. All of the above

13. The cell-interstitial matrix:

A. Is not a barrier to solutes and water flow
B. Is a non-selective barrier to solutes and water flow
C. Is a size-selective barrier to solutes
D. Brings blood capillaries into close approximation
E. Is the major barrier to lipid soluble substances

14. Hydrostatic pressure from the dialysate solution in the cavity:
A. Is chiefly responsible for fluid flow from the dialysis solution to the body
B. Is responsible for fluid removal from the body
C. Decreases transport of drugs from the cavity into the tissue
D. Does not affect solute transport across the peritoneum
E. Does not affect water transport across the peritoneum

15. Convection across a tissue space:
A. Arises from solute gradients
B. Arises from hydrostatic pressure gradients
C. Arises from osmotic pressure gradients
D. A and C
E. B and C

16. Inert gas absorption from the peritoneal cavity:

A. Occurs at the same rate no matter what the gas
B. Does not occur
C. Is proportional to the diffusivity in the tissue
D. Is totally metabolized in the mesothelial cells
E. None of the above

17. Drugs are administered in the peritoneal cavity because of:

A. Pharmcokinetic advantage of route
B. Less systemic exposure
C. Demonstrated effectiveness in treatment of intra-abdominal malignancies
D. A, B, C
E. none of the above

18. Compartmental models are useful because:

A. Simplified mathematics
B. Lumped parameters require less detailed data
C. They simulate tissue-level mechanisms
D. A and B
E. None of the above

19. Membrane models of peritoneal transport:

A. Collapse the peritoneal barrier to a single membrane
B. Do not include the interstitium
C. Include transcellular transport
D. None of the above
E. A and B

20. Clinicians can directly measure which of the following in peritoneal dialysis:

A. Peritoneal volume
B. Osmotic ultrafiltration
C. Solute concentrations
D. A and C
E. None of the above

Chapter (29)

# Factors Affecting Peritoneal Dialysis Dose

Karen CY To and K. Scott Brimble

**CHAPTER OUTLINES**

- Concept of Dose and Adequacy in Peritoneal Dialysis (PD)
- Patient-Specific Factors Affecting Chronic PD Dose
- Prescription-Specific Factors Affecting Chronic PD Dose
- Factors Affecting PD Dose in the Treatment of Acute Kidney Injury
- Conclusion

**CHAPTER OBJECTIVES**

- To review the concept of and evidence for dose and adequacy in PD
- To understand the various physiological and sociological patient-specific factors affecting achieved PD dose
- To understand the various PD modalities, prescription-specific factors affecting dose
- To review the various factors and PD technique considerations in the treatment of acute kidney injury

**KEY TERMS**

- dialysis dose
- adequacy
- effective peritoneal surface area
- membrane transport characteristics
- residual urine function
- body surface area and weight
- compliance
- PD modality
- exchange frequency
- fill volume
- ultrafiltration
- middle molecule clearance
- acute kidney injury

**ABSTRACT**

Dose of dialysis has traditionally been measured as small solute clearance (i.e. urea or creatinine). Treatment of acid-base, electrolyte, and volume disturbances should also be recognized as important functions of peritoneal dialysis (PD) that are not specifically measured when measuring urea clearance. There are a myriad of patient- and prescription-specific factors that affect the delivered dose of PD. Although patients with significant residual renal function (RRF) can likely initiate on virtually any

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standard PD therapy, with loss of RRF, one may need to tailor the PD prescription to the patient's membrane transport characteristics. High transporters as measured by the PET are better suited to automated peritoneal dialysis (APD) with more frequent exchanges, and the use of icodextrin as a long dwell, whereas patients with lower transport status will tend to do well on CAPD where exchanges are longer. Larger patients may tolerate increased volumes as a means of increasing the dose of PD. More frequent exchanges can be used in either CAPD or APD but one must recognize there is a limit due to loss of dialysate contact time from frequent filling and draining. Understanding the patient's physiological characteristics, personal preferences and social circumstances coupled with a sound comprehension of the principles of PD and the prescription-factors that affect dose will lead to the best care for that patient.

## 29.1 CONCEPT OF DOSE AND ADEQUACY IN PERITONEAL DIALYSIS

This chapter will review the factors that influence dose of peritoneal dialysis (PD). Those in the dialysis community routinely use the terms *prescription* and *dose* when speaking of dialysis and more specifically, PD. This brings to mind the analogy of prescribing a medication such as an ace inhibitor. One provides a prescription to a patient that outlines the medication name, how many tablets are to be included, how often the patient is to take it, and the *dose* of the medication. The *dose* is usually measured by mass and/or number of pills (i.e. one 5 mg tablet). The efficacy of achieving the desired effect – i.e. lowering of blood pressure – will vary between patients for a given dose.

The term *dose* in peritoneal dialysis is not as straightforward. One of the earliest references to *dose* of dialysis in PD was by Twardowski in 1989 in the context of the clinical value of the peritoneal equilibration test (PET) in patients (Twardowski 1989). He suggested that patients with low transport status may need “high-dose PD prescriptions”. Later Blake and colleagues evaluated the effects of *dose* of PD on clinical outcomes: dose was measured by the dialysis index (a now seldom used measure determined using urea kinetic modeling) and the more well-known $Kt/V_{urea}$ (Blake et al. 1991). Still others have simply defined the *dose* of dialysis as the drain volume – i.e. the total amount of fluid removed from the patient which is the sum of instilled dialysate plus ultrafiltrate (Tzamaloukas et al. 2007). This would seem reasonable in continuous ambulatory PD (CAPD). The weekly measured peritoneal Kt/V for urea ($pKt/V_{urea}$) is defined as:

$$pKt / V_{urea} = \frac{7 \times (D / P_{urea}) \times V_D}{V} \quad (29.1)$$

where K is solute clearance, $D/P_{urea}$ is the ratio of dialysate to plasma concentration of urea in 24-hours of collected dialysate, $V_D$ the drain volume, and V is total body water.

With the longer dwells used in CAPD (as opposed to automated PD [APD]) one can assume that $D/P_{urea}$ approaches unity so that Eq. (29.1) can be simplified to (Heimburger 2009):

$$pKt / V_{urea} = \frac{7 \times V_D}{V} \quad (29.2)$$

Assuming V is equal to 58% of weight (Wt) in kilograms one can then expresses Kt/V as a function of body weight and drain volume:

$$pKt / V_{urea} = \frac{12 \times V_D}{Wt} \quad (29.3)$$

The relationship between drain volume, body size, and estimated $pKt/V_{urea}$ is shown for a number of scenarios in Table 29.1 below.

**Table 29.1** Relationship between drain volume, body size, and estimated $pKt/V_{urea}$

| Weight (kg) | Fill volume (L) | Number of exchanges | Drain Volume (L) | $pKt/V_{urea}$ |
|---|---|---|---|---|
| 50 | 2.0 | 4 | 8.0 | 1.92 |
| 50 | 2.0 | 3 | 6.0 | 1.44 |
| 75 | 2.0 | 4 | 8.0 | 1.28 |
| 75 | 2.5 | 4 | 10.0 | 1.60 |
| 65.4 | 2.0 | 4 | 8.0 | 1.47 |

The latter example represents the average weight for patients in the control group of the ADEMEX study (Paniagua et al. 2002) (described in more detail later), all patients were on 2.0-L x 4 exchanges. Measured $pKt/V_{urea}$ was actually about 7.5% higher at 1.58, the difference presumably due to a combination of errors in assumptions about equilibration of urea, total body water estimation, and collection and measurement errors. Nevertheless, it does illustrate the point that for patients on CAPD with four or fewer exchanges, the drain volume is a useful tool to estimate the

dose of dialysis when taking into account the patient's weight. It should be noted that while one could increase the number of exchanges to increase the $pKt/V_{urea}$, the assumption that the urea concentration will equalize between dialysate and plasma becomes increasingly inaccurate as exchanges become shorter.

The assumption that urea will equilibrate between dialysate and plasma during an exchange (and therefore one can predict $pKt/V_{urea}$ based on drain volume and body weight) is particularly problematic with patients on APD. One can craft a number of different scenarios where the total dose (i.e. drain volume) received is the same yet what is achieved in terms of the various functions of dialysis – small solute removal including phosphate, volume removal, middle molecule removal – will actually differ. Three examples for APD are shown in Table 29.2. Total therapy ranges between 9-hours and 24-hours and ultrafiltration volume from 1.0-L to 1.5-L in the examples. Nevertheless drain volumes in each of the scenarios is 15.5-L. Small solute clearance may well be similar in these scenarios, depending on membrane transport properties etc., other aspects of adequacy such as fluid removal and middle molecule clearance will not be.

**Table 29.2** Three different APD prescriptions with the same drain volume

| | **Patient 1** | **Patient 2** | **Patient 3** |
|---|---|---|---|
| Modality | APD | APD | APD |
| Night-time therapy, hours | 9 | 9 | 10 |
| Night-time fill volume, L | 2.0 | 2.5 | 2.0 |
| Number of cycles | 7 | 5 | 5 |
| Day-time therapy, hours | 0 | 4 | 14 |
| Day-time volume, L | 0 | 2.0 | 4.0 (manual exchange) |
| Ultrafiltration volume, L | 1.5 | 1.0 | 1.5 |
| Total drain volume, L | 15.5 | 15.5 | 15.5 |

For these and other reasons, the fact that *dose* in PD is usually defined by small solute clearance such as urea, is not completely satisfactory. The nephrologist and PD nurse must recognize that this viewpoint largely ignores other functions of dialysis and consider these issues when prescribing PD therapy. The most recent Canadian Society of Nephrology guidelines on hemodialysis (HD) have noted this fact.

> "Urea clearance as assessed by Kt/V or PRU is a surrogate for dialysis dose. Although practice guidelines have traditionally emphasized the role of urea clearance, this parameter is only one component of dialysis adequacy. In addition to considering urea clearance and volume status, the clinician must consider many other measures and indicators in assessing a patient's health and prescribing treatment, including control of extracellular volume and BP, uremic symptoms, quality of life, control of hyperphosphatemia, adequate nutritional status, and treatment of anemia."(Jindal et al. 2006)

The term 'adequacy' is perhaps more familiar to most dialysis providers and was described in the context of PD as early as 1976 by Lindsay and colleagues (Lindsay et al. 1976). Platelet adhesion was noted to be markedly impaired in uremia and it was suggested that platelet adhesion could be used as a measure of dialysis adequacy. A number of studies in the late 1970s and early 1980s characterized neurological abnormalities in uremia including changes in memory and characteristic electroencephalographic changes that improved to a greater extent with more intensive dialysis (Shinaberger 2001; Teschan 1975; Teschan et al. 1981). These objective measures are no longer used clinically in the day-to-day management of patients and adequacy becomes more of a subjective concept. Many nephrologists would define adequacy to represent that amount of delivered dialysis that alleviates uremic symptoms (nausea, anorexia, fatigue etc.), restores acid-base balance, achieves fluid homeostasis, and alleviates malnutrition. Such a definition would seem equally appropriate for hemodialysis (HD) and PD patients. Other aspects of adequate treatment of ESRD might include correction of hyperphosphatemia, hypocalcemia, vitamin D deficiency and anemia; however, these complications are less responsive to dialysis with some exceptions (Ifudu et al. 1996; Ifudu et al. 2000; Movilli et al. 2001; Walsh et al. 2010).

As time has gone on, it has become increasingly apparent that when one considers adequacy one must consider all aspects of the PD prescription (i.e. mode of PD, total time, exchanges, fill volume etc.) in order to achieve the desired results in a given patient based on their individual characteristics, particularly transport status and residual renal function (RRF). Ultimately, it stands to reason that one should evaluate the delivery of dialysis as *adequate* when increasing the dialysis dose does not lower the mortality risk and/or further improve quality of life (Golper et al. 1997). No single measurement can truly measure the adequacy of dialysis. Published guidelines recognize this yet based on the best evidence and/or

opinion generally advises a lower limit for small solute removal (i.e. $Kt/V_{urea}$) in patients to achieve adequacy.

Numerous observational studies suggested that greater clearances of small solutes were associated with improved survival on PD (Bhaskaran et al. 2000; Churchill et al. 1998; Jager et al. 1999; Jansen et al. 2005; Lam et al. 2006; Lo et al. 2005; Maiorca et al. 1995; Rumpsfeld et al. 2009, 2006), although others have not (Brown et al. 2003; Diaz-Buxo et al. 1999). The CANUSA study (Churchill et al. 1998) in particular led to the recommendation of a target total $Kt/V_{urea}$ of 2.0 (peritoneal plus renal) in guidelines although this was based on inferences from modeling of data that assumed RRF and peritoneal clearance were equivalent. Since then these findings have subsequently been shown to be largely explained by the presence or absence of RRF (Bargman et al. 2001). However, two important randomized controlled trials have since shown that increased small solute clearance was not associated with improved survival (Lo et al. 2003; Paniagua et al. 2002). ADEMEX in particular was very telling – 965 CAPD patients were randomized to 2.0-L x 4 exchanges or an increased volume of dialysate (Paniagua et al. 2002). There was no benefit in either group studied despite good separation in clearance values ($pKt/V_{urea}$ 1.62 vs. 2.13). Approximately 55% of patients were anuric.

Despite all the concerns in limiting the view of adequate PD therapy as simply sufficient small solute removal, it remains important to consider the factors that affect dialysis dose in PD. It is clear that some amount of PD therapy is clinically important, recent guidelines have suggested a minimum $Kt/V_{urea}$ of 1.7 (Blake et al. 2011). Although peritoneal clearance does not appear to predict clinical outcomes in patients with RRF, clearance does seem to be important in patients who are anuric based on the majority of observational studies (Bhaskaran et al. 2000; Jansen et al. 2005; Lo et al. 2005).

It is worth reminding the reader that there are two main PD modalities available to patients – CAPD and APD. CAPD is the simpler of the two, involves manual exchanges of fluid using gravity, and it is performed over 24 hours. Although the timing of the exchanges could be varied to achieve different desired effects; usually only the fill volume (standard is 2.0-L) and the number of exchanges (standard is 4 although 3 is used in some countries) (Lo et al. 1996) are varied to achieve different doses of dialysis. APD on the other hand is amenable to greater variation in prescription. The therapy can be continuous or discontinuous (i.e. part or all of the daytime is dry), the number of exchanges overnight and the duration of the cycles manipulated as can be the volume. In either the case of CAPD or

APD, one can vary the prescription by altering the dialysate used to achieve differing ultrafiltration rates.

In the subsequent sections, the various factors that affect dose in PD will be reviewed. These are broken down into patient-specific and prescription-specific factors. The special case of clearance of middle molecules and PD in the treatment of AKI will also be considered.

## 29.2 PATIENT-SPECIFIC FACTORS AFFECTING CHRONIC PD DOSE

### 29.2.1 Peritoneal Membrane

The abdominal peritoneum is divided into the visceral peritoneum, which lines the visceral organs and accounts for approximately 80% of the total surface area; and the parietal peritoneum which lines the remainder of the abdominal cavity (Albanese et al. 2009; Bouchet 1989; Fischbach et al. 2003; Pawlaczyk et al. 1996; Rubin et al. 1988). Functionally in PD, the parietal peritoneum appears to be more important than the visceral peritoneum (Flessner 1991). The peritoneal membrane consists of three anatomical components: a single mesothelial cell layer, the interstitium which is composed of mucopolysaccharide matrix and bundles of collagen fibers, and the capillary wall (Flessner 1996b, 1991). The peritoneal microvasculature is comprised of true capillaries and post capillary venules, while most of the lymphatic drainage is through stomata located in the diaphragmatic peritoneum. For a more in-depth discussion on the topic of peritoneal anatomy, functional structure, or physiology, please refer to previous chapters.

Peritoneal transport comprises three simultaneous processes: diffusion, ultrafiltration, and fluid absorption (Burkart 2000). There is now cumulative evidence supporting the view that the major site of resistance to peritoneal transport is provided by the peritoneal capillary and is likely the key determinant of transport capacity (Flessner 1996b; Krediet 2000a). The mesothelium is no longer considered an important transport barrier (Flessner et al. 2003; Krediet et al. 1993). Furthermore, the barrier function of the interstitial tissue is not well known (Flessner 1996b).

The three-pore model of peritoneal transport is a simple simulated computer model that for the most part, adequately describes peritoneal permeability and selectivity (Rippe et al. 1991; Rippe et al. 2004). Using this model, the capillary endothelium contains three distinct types of pores. The major exchange route for water and solute is through a large number of “small pores” (radius 40-50 Angstroms), corresponding to paracellular clefts in the endothelium (Bundgaard 1984). Small pores account for 95%

of the hydraulic conductance and functionally for approximately 50% of the effective ultrafiltration (Fusshoeller 2008). A second very small population of "large pores" (radius 250 Angstroms), likely representing interendothelial clefts serve as the transcapillary pathway for albumin and other large proteins (Rippe et al. 2004). The third population consists of the abundant "ultra-small pores" (radius 3-5 Angstroms) that are responsible for the transport of solute-free water across the capillary wall. Ultra-small pores have been predicted to mediate 40 to 50% of the ultrafiltration and the "sodium sieving" observed during a dwell with hypertonic dextrose. Aquaporin-1 (AQP1), a protein belonging to a family of integral plasma membrane proteins has been found to be the molecular counterpart of the ultra-small pores (Devuyst 2010; Devuyst and Ni 2006).

#### 29.2.1.1 Effective Peritoneal Surface Area

In adults, the anatomic surface area is approximately equal to the body surface area, ranging from 1.0 to 2.0 $m^2$ (Albanese et al. 2009; Nagy 1996). However, during a session of PD, the entire peritoneum is not in contact with dialysate to partake in solute and water transport. Moreover, the peritoneal surface area that is in contact with dialysate participates to varying degrees, determined primarily by the peritoneal vascularity (Krediet et al. 1994). This has led to the term, "effective peritoneal surface area" which emphasizes the importance of peritoneal membrane vascularity over its anatomic surface area. The effective peritoneal surface area is the product of the vascular peritoneal surface area and the permeability (also referred to as size selectivity). In turn, the vascular peritoneal surface area is dependent on the peritoneal surface area in contact with dialysate (PSA-CD) and on the density of perfused capillaries (Chagnac et al. 1999). Using stereologic methods applied to CT scans of the peritoneal membrane, the PSA-CD was estimated to be 0.55 $m^2$ (25 to 30% of the anatomic surface area) in adult PD patients (Chagnac et al. 1999). An increase from a 2.0 to 3.0-L dwell volume was associated with an 18 % increase in the PSA-CD from a mean value of 0.57 to 0.67 $m^2$, and in a 28% increase in the mass transfer area coefficient (MTAC) for creatinine from 10.6 to 13.6 ml/min. The MTAC is also known as the permeability-surface area product and is equal to the theoretical clearance of a solute that would be achieved if the concentration gradient was always infinitely high. The MTAC is typically calculated with the aid of a computer program,

$$\mathrm{MTAC} = \frac{V_D}{t} \times \ln\left(\frac{P - D_0}{P - D_t}\right) \tag{29.4}$$

where $V_D$ is the drain volume, t is the dwell time (240 minutes), P is the plasma concentration, $D_0$ is the dialysate concentration before inflow, $D_t$ is the dialysate concentration at the end of the dwell (Krediet et al. 2000a). Although the effective surface area cannot be measured directly, it can be characterized by the MTAC of creatinine, expressed as ml/min (Krediet et al. 1993).

The transport of macromolecules such as serum proteins are size-selectively restricted, and thus determined by both the effective surface area and permeability (size-selectivity) of the peritoneum. On the contrary, the transport of low-molecular-weight solutes is not hindered by the intrinsic permeability of the peritoneum and is therefore mainly dependent on the effective surface area ( Krediet et al. 1994). Consequently, changes in the D/P ratios of small solutes and in the MTAC reflect changes in the effective surface area (Krediet et al. 1993). The effective surface area can increase markedly in certain situations, such as, peritonitis, ultrafiltration failure following chronic PD, and following intraperitoneal administration of nitroprusside, a vasodilator (Douma et al. 1997; Krediet et al. 1987, 2000a).

### 29.2.2 Peritoneal Blood Flow

The visceral peritoneum receives its blood supply from the superior mesenteric artery and drains into the portal system while the parietal peritoneum receives its blood supply from the lumbar, intercostal, and epigastric arteries and its venous drainage is through the inferior vena cava (Bouchet 1989). The number of perfused peritoneal capillaries is dynamic and varies with changes in splanchnic blood flow, although a direct relationship is unlikely (Aune 1970).

Under physiological conditions, peritoneal blood flow (estimated between 50 and 100 ml/min) does not limit the transfer of solutes, as the MTAC for urea and creatinine are 17 and 10ml/min, respectively (Flessner and Lofthouse 1999; Heimburger et al. 1992; Rosengren and Rippe 2003; Waniewski et al. 1992). This is demonstrated by the finding that a reduction in blood flow by hemorrhagic hypotension resulted only in a marginal decrease in urea and creatinine clearance (Erbe et al. 1967; Greene Jr et al. 1970). It is important to note that the "effective blood flow" available is only a fraction of the total blood flow through the tissues surrounding the peritoneal cavity because some capillaries are too far from the mesothelium to be active in the exchange process or they are in a part of the peritoneum not in contact with dialysate (Flessner 1996a, b). Moreover, there is evidence indicating that perhaps peritoneal blood volume rather than blood flow *per se*, determines the degree of peritoneal mass transfer (Pietrzak et al. 1989).

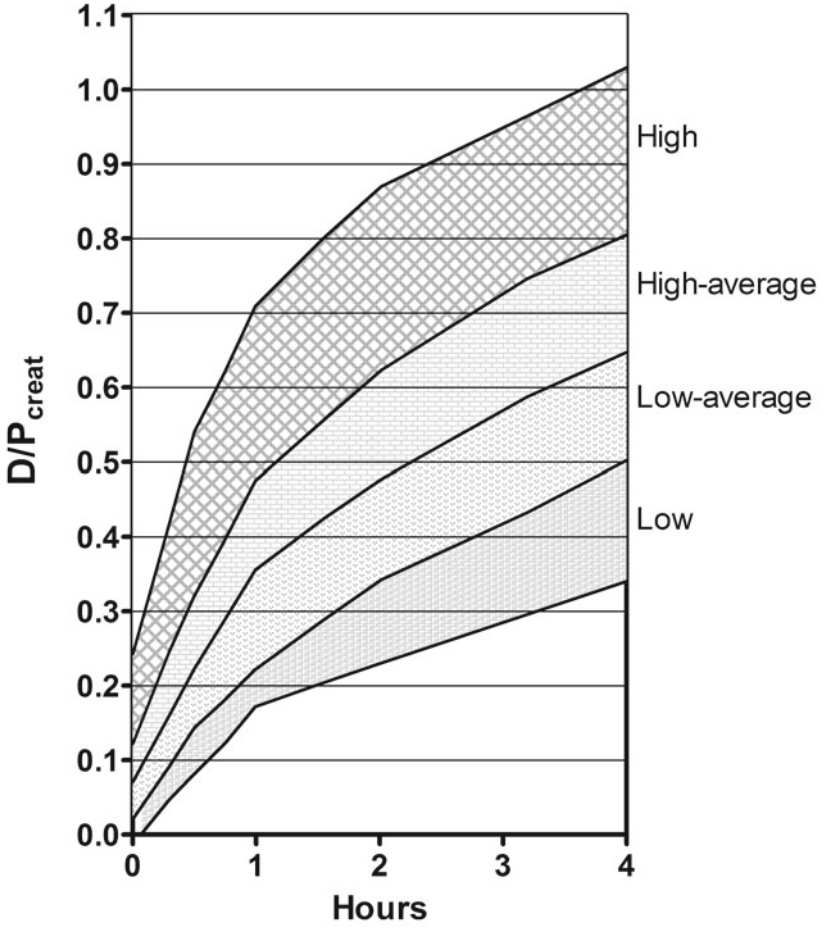
Therefore, in PD, the clearance of small solutes is not limited by peritoneal blood flow, but rather, dialysate flow (Flessner and Lofthouse 1999).

### 29.2.3 Peritoneal Equilibrium Test

First described in 1987 by Twardowski, the peritoneal equilibration test (PET) is the most widely used standard test for evaluation of peritoneal transport characteristics, specifically solute transport and ultrafiltration capacity, which are fundamental in guiding the PD prescription (Twardowski et al. 1987). There is considerable variability in membrane transport properties between-patients and within-patients over time. The goals (van Biesen et al. 2010) of evaluating peritoneal membrane transport are: 1) To optimize the PD prescription with respect to small solute clearance, volume management, and treatment of uremia; 2) To evaluate peritoneal membrane function over time; 3) To assess other membrane characteristics, such as, osmotic conductance of glucose, aquaporins, lymphatic reabsorption, hydraulic conductance (in patients with ultrafiltration failure).

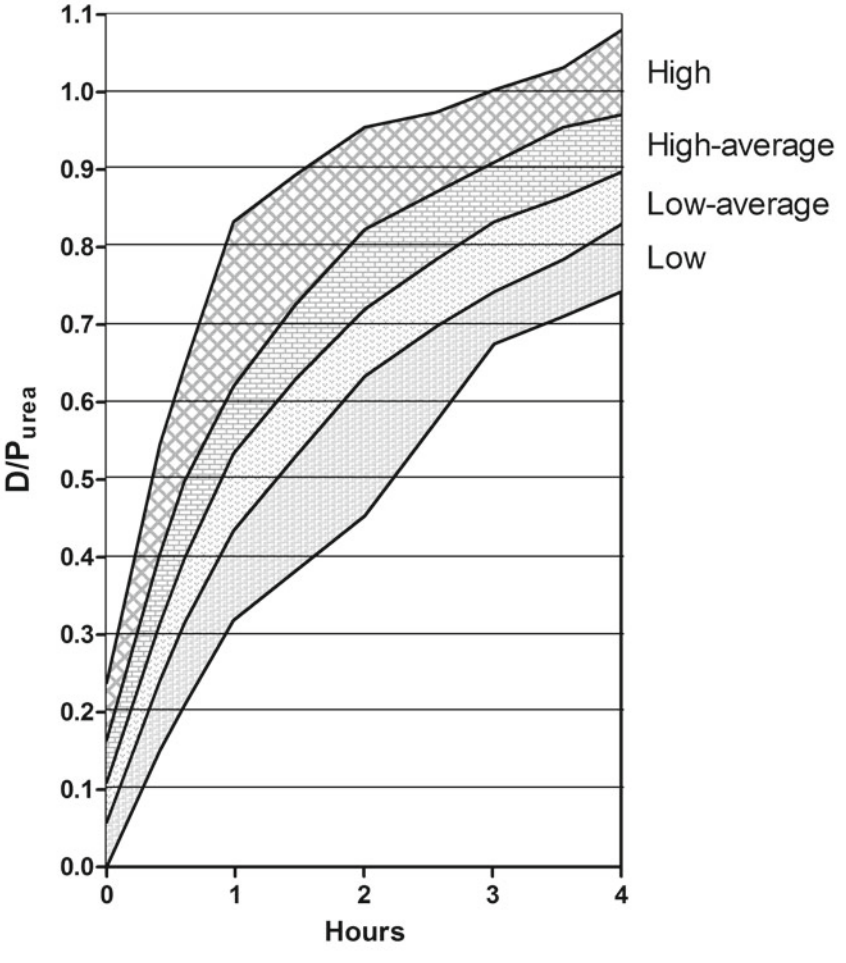
This semi-quantitative assessment is influenced by the molecular weight of the solute of interest, membrane permeability, and the peritoneal effective surface area. There is far less between-patient variability in the peritoneal clearance of urea due to its more rapid equilibration between dialysate and plasma than with creatinine at 4-hours as illustrated in Fig. 29.1 (more narrow distribution of the $D/P_{urea}$-time curve). As such, the 4-hour peritoneal clearance of creatinine is used to characterize the small-solute transport characteristics of the membrane. Conventionally, the PET test is performed with 2.0-L of 2.5% dextrose solution for a 4-hour dwell. The technical aspects of the test are outlined elsewhere (Twardowski et al. 1987). Equilibrium ratios (D/P) between dialysate and plasma for urea (D/P urea), and creatinine (D/P creatinine) are calculated at 4-hours. For glucose, $D/D_0$ glucose is calculated to determine the fraction of absorbed glucose from the dialysate at 4-hours to the initial dialysate glucose concentration ($D_0$). Peritoneal transport status is then classified into one of four membrane categories based on the 4-hour D/P creatinine: High, High-average, Low-average, and Low. High transporters (defined as a D/P creatinine greater than +1 standard deviation [SD] from the mean) have the highest D/P creatinine and the lowest $D/D_0$ glucose (< -1 SD from the mean). Conversely, low transporters (defined as a D/P creatinine less than -1 SD from the mean) have the lowest D/P creatinine and the highest $D/D_0$ glucose (> +1 SD from the mean). In 90% of properly conducted PETs this inverse relationship between $D/D_0$ glucose and D/P creatinine is observed (Prowant et al. 2010). The PET is also used to measure the net ultrafiltration. Ultrafiltration volumes correlate positively with the 4-hour $D/D_0$ glucose and negatively with D/P creatinine. A baseline PET

study is performed shortly after a patient has been established on PD and can be repeated routinely (i.e. yearly) based on local practice patterns or when there is clinical suspicion of change in membrane transport characteristics (i.e. hypervolemia, malnutrition, metabolic disturbances). Consideration of individual patient-specific peritoneal membrane characteristics (small solute clearance and ultrafiltration capacity) will allow nephrologists to tailor a PD prescription to meet the needs of the patient.



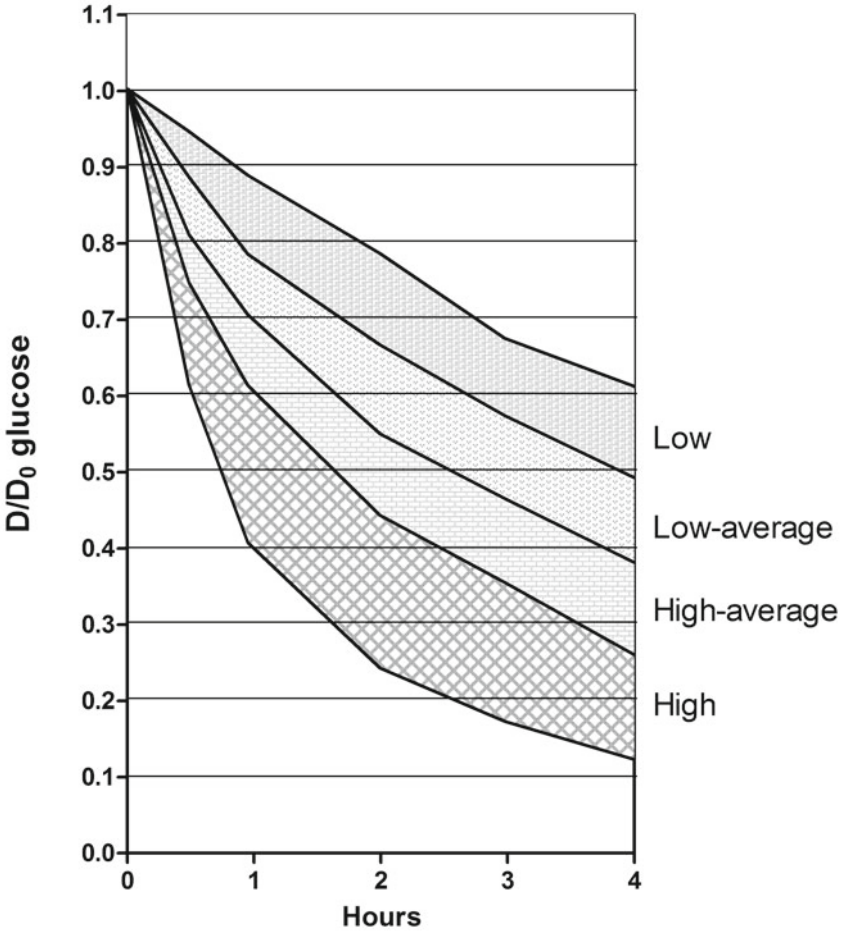

(a)

**Fig. 29.1** Standard peritoneal equilibration curves for (a) creatinine, (b) urea, and (c) glucose absorption showing ranges for High, High-average, Low-average, and Low transporters. (Adapted from Twardowski ZJ, et al. Peritoneal equilibration test. Perit Dial Bull 1987:7:138)




(b)

**Fig. 29.1** (Continued)




(c)

**Fig. 29.1** (Continued)

#### 29.2.3.1 Peritoneal Membrane Transport Status

As originally described by Twardowski (Twardowski et al. 1987), peritoneal membrane transport status is classified into one of four transport categories. However, it has been proposed that the classification should be changed to three categories that may be more intuitively related to the dwell time (van Biesen 2010): Fast, Average, and Slow transporter status. In the discussion that will follow, the classification as it was originally

described by Twardowski was used but the reader should be aware of this alternative classification used in the literature.

#### 29.2.3.1.1 High Transporters

High transporters have a relatively larger effective peritoneal surface area or higher intrinsic membrane permeability and achieve the most rapid diffusive transport, resulting in the highest D/P creatinine values (Li and Chow 2007). This also explains the observation of higher dialysate protein losses and lower serum albumin values. However, high transporters have the lowest $D/D_0$ with reduced ultrafiltration capacity owing to more rapid dissipation of the glucose osmotic gradient and resultant negative ultrafiltration in dwells with 1.5% dextrose for longer than 3 hours (Perl et al. 2009; Mujais et al. 2000). High transporters dialyze well with respect to small solute clearance but ultrafiltration poorly and are best suited for PD prescriptions with short dwells, preferably less than 3-hours. The convenience of APD in performing frequent exchanges with short dwell times makes this modality the ideal choice for High transporters. For High transporters who choose to do CAPD due to lifestyle preferences, such as, sleep disturbance from the cycler, consideration for the use of icodextrin for the long night dwell should be given, especially when there is loss of RRF.

Amongst the four transporter types, High transporters have been associated with the highest mortality (Rumpsfield et al. 2006; Brimble et al. 2006; Churchill et al. 1998; Fried 1997). This was best demonstrated in a meta-analysis by Brimble et al (Brimble et al. 2006) that included 19 studies (9 prospective) in PD patients with PET data and mortality and/or technique failure outcomes. Compared to patients with low transport status, High transporters had a 77% increased mortality risk (RR 1.15 for every 0.1 increase in D/P creatinine, $P<0.001$); a finding that was present in studies from diverse geographic regions and in patients with a variety of comorbidities. There was a trend towards death-censored technique failure in those with higher transport status (D/P creatinine) that did not meet statistical significance ($P=0.12$). Furthermore, studies that enrolled patients on APD demonstrated a lower mortality risk for a given increase in peritoneal membrane solute transport rate compared with those that did not, suggesting APD may be more appropriate for High transporters. Possible mechanisms for the adverse outcome seen in High transporters include: protein losses leading to malnutrition, volume overload, inflammation, and greater systemic exposure to glucose.

An observational study by Johnson et al (Johnson et al. 2010) using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA)

registry also suggested that the higher mortality associated with High transporters can be abrogated by the use of APD.

The ANZDATA registry included data from 4128 incident PD patients who started PD between 1999 and 2004, of which 628 were High transporters. There were 486 patients in the CAPD and 142 in the APD group. Compared to High transporters treated with CAPD, APD-treated High transporters were more likely to be Caucasian (P=0.006), younger (P=0.003), and less likely to have diabetes (P=0.03). Mean baseline PET $D/P_{4hr}$ creatinine was comparable between the APD and CAPD groups (0.88 vs. 0.87, P=0.15). On multivariate intention-to-treat analysis, treatment with APD was associated with superior survival (adjusted HR 0.56, P=0.01) and comparable death-censored technique survival (HR 0.88, P=0.4). There were no statistically significant differences in patient survival or death-censored technique survival between APD and CAPD for High-average and Low-average transporters. Conversely, Low transporters treated with APD compared to CAPD had a higher mortality rate (HR 2.19, P=0.04). One of the main limitations of this study was the lack of adjustment for RRF due to incomplete data collection.

Randomized controlled trials supporting the use of APD to improve clinical outcomes in High transporters are lacking. A randomized open-label trial (Bro et al. 1999) comparing APD and CAPD in 25 prevalent PD patients with High or High-average transporters showed statistical difference in net ultrafiltration, $Kt/V_{urea}$ and creatinine clearance, but was not powered to evaluate patient or technique survival. A meta-analysis by Rabindranath included 3 randomized controlled studies of APD versus CAPD involving 139 patients with different transport status, including the study above (Bro et al. 1999) and found no difference in patient or technique survival. However, the meta-analysis lacked statistical power and subgroup analysis was not undertaken in High transporters (Rabindranath et al. 2007).

#### 29.2.3.1.2 Low Transporters

Low transporters have low membrane permeability or a small effective peritoneal surface area, resulting in a lower D/P creatinine that is semilinearly correlated with the dwell duration. Serum albumin values tend to be higher since dialysate protein losses are lower. The $D/D_0$ glucose values are higher resulting in excellent net ultrafiltration that peak late in a long dwell. There is sustained ultrafiltration even in dwells longer than 4 hours. Low transporters benefit from higher volumes (see section on Fill Volumes in CAPD and APD) and continuous regimens, such as CAPD

(Burkart et al. 1996). Low transporters are more difficult to treat with APD unless they have significant RRF.

#### 29.2.3.1.3 High-Average and Low-Average Transporters

The equilibration of creatinine for "Average" transporters is moderately fast, with a steeper equilibration slope in the beginning than at the end of a dwell. Ultrafiltration capacity is also intermediate. Dwell times less than 2 hours and longer than 7.5 hours should be avoided except for one exchange per day (the "long dwell") (van Biesen et al. 2010).

In clinical practice however, patient lifestyle and preferences are the main driving force for choice of PD modality rather than peritoneal transport characteristics. Most patients, irrespective of their membrane transport status can be managed successfully the majority of the time with APD or CAPD, especially when they have RRF. However, when RRF is lost over time, the PD prescription (dwell time) should be chosen to match the peritoneal transport characteristics if targets for solute clearance and/or ultrafiltration are not achieved (see Table 29.3).

**Table 29.3** Peritoneal equilibration test results, ultrafiltration, and preferred PD modality (Twardowski et al. 1987; Birkart et al. 1996)

| Transport Status | 4-hr D/P creatinine | Ultrafiltration | Preferred PD Modality |
|---|---|---|---|
| High | > 0.81 | Poor | APD |
| High-average | 0.65 to 0.81 | Adequate | APD/CAPD |
| Low-average | 0.50 to 0.64 | Good | APD/CAPD |
| Low | < 0.50 | Excellent | CAPD |

Membrane transport characteristics can change over time. Some patients develop histomorphological and functional changes of the peritoneal membrane during long-term PD and following recurrent episodes of peritonitis (Davies et al. 2011). Typical morphological changes during PD include the loss of mesothelium, sub-mesothelial fibrosis, angiogenesis, vasculopathy, and basement membrane duplication (Fusshoeller 2008). Chronic exposure to glucose based PD solutions, glucose degradation products, and resulting advanced glycation end-products are the most important factors contributing to the development of fibrosis and a large effective surface area (Krediet et al. 2000b; Fusshoeller 2008). Based on biopsy registry data, high-volume APD patients tended to have more

peritoneal fibrosis after less time on PD, pointing to a cumulative dose exposure effect (Fusshoeller 2008).

The functional peritoneal alterations include impaired transport of water and solute. Ultrafiltration failure is defined clinically as net ultrafiltration < 400 ml over a 4-hour dwell with 3.86% dextrose and affects approximately 35% of all PD patients after 4 years of treatment (Smit et al. 2004). Ultrafiltration failure is classified into four types (which can overlap) based on the underlying pathophysiology (Fusshoeller 2008): type 1 - large effective peritoneal surface area; type 2 - low osmotic conductance to glucose; type 3 - low effective peritoneal surface area; and type 4 – high effective lymphatic absorption rate.

The most frequent cause of ultrafiltration failure is a large effective peritoneal surface area with resultant hyperpermeability of the membrane (type 1) (Fusshoeller 2008). There is rapid dissipation of the osmotic gradient (from rapid glucose absorption) leading to less fluid removal and/or fluid absorption. The use of icodextrin and shorter dwell times with APD may help to maintain adequate ultrafiltration. Strategies for the prevention of ultrafiltration failure include: the avoidance of excessive glucose exposure, preservation of RRF, and prevention of peritonitis (Davies et al. 2011).

### 29.2.4 Residual Renal Function

Randomized trials of dialysis adequacy and observational studies in adult patients have confirmed that RRF is a stronger predictor of patient survival than PD dose (Bargman et al. 2001; Lo et al. 2003; Paniagua et al. 2005). In the CANUSA study, a prospective observational study of incident peritoneal dialysis patients, each 5 L/week of RRF was associated with a 12% reduction in the relative risk of death (Bargman et al. 2001). Subsequent studies have shown a consistent association between RRF and lower rates of adverse cardiac outcomes, including left ventricular hypertrophy and congestive heart failure (Wang et al. 2002; Wang et al. 2004). RRF has also been postulated as the main reason for the early survival advantage seen in PD patients compared to HD patients, especially in non-diabetics (van den Wall Bake et al. 2006).

The minimum recommended delivered small solute clearance, as measured by the total (peritoneal and renal) $Kt/V_{urea}$ is $\geq$ 1.7/week (NKF-K/DOQI 2006; Blake et al. 2011). Therefore, the more RRF a patient has, the less important the dialysis dose is in contributing to clearance targets. The RRF contribution to urea clearance can be estimated from a 24-hour

urine collection. Take the example of a 70-kg male patient with residual renal urea clearance of 4 ml/min. The total weekly residual $Kt/V_{urea}$ is 0.96 units/week [urea clearance of 40-L (4 ml/min x 1-L/1000 ml x 60 min/hr x 24-hr/d × 7d/wk) divided by total body water ($V_{urea}$) of 42-L (70-L × 0.6)], and thus contributes 56% of the total target $Kt/V_{urea}$ (0.96/1.7). As a guide, for each 1 ml/min of residual renal clearance, 0.25 is added to the total $Kt/V_{urea}$ for a 70-kg man (van Biesen et al. 2010). Similarly, each 1ml/min of residual renal creatinine clearance adds 10 L/week/1.73$m^2$ to the total weekly creatinine clearance. Patients with substantial RRF that reach the weekly target for creatinine clearance (≥ 50 – 60 L/week/1.73 $m^2$) are at risk of $Kt/V_{urea}$ values below the target (Tzamaloukas 1998; NKF K/DOQI 2006). This is due to the differential renal tubular handling of creatinine and urea in advanced renal failure, secreted in the former and reabsorbed in the latter. Therefore, residual renal creatinine clearance overestimates the glomerular filtration rate, while residual renal $Kt/V_{urea}$ underestimates it. As such, RRF should be evaluated by a 24-hour collection and calculation of the mean urea and creatinine clearance should be used.

Observational data from a recent large study of 583 PD patients found that APD was associated with a higher risk of complete RRF loss in the first year of dialysis compared to CAPD (Michels et al. 2011). However, in a 2007 Cochrane Systematic Review, there was no associated difference between PD modality and preservation of RRF (Rabindranath et al. 2007). The PD prescription should aim to preserve RRF by gradually increasing the dialysis dose, accurately targeting ultrafiltration to avoid dehydration, and using the lowest possible dialysate dextrose concentration required to achieve ultrafiltration (Davies 2009). Two randomized clinical trials have suggested that the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II blockers (ARB) preserve RRF independent of their effects on blood pressure (Li et al. 2003; Suzuki et al. 2004). Prevention of RRF loss also involves the avoidance of potential nephrotoxins (Bargman et al. 2001). National guidelines (Blake et al. 2011; NKF-K/DOQI 2006) recommend the use of ACEI or ARBS in PD patients to preserve RRF, and the use of diuretics to increase urine volume (in patients with ≥ 100 ml urine/day).

### 29.2.5 Body Surface Area (BSA) and Body Weight

BSA and body weight affect the prescribed PD dose. Weekly creatinine clearance is normalized to 1.73 $m^2$ of BSA, while urea clearance is normalized to V, total body water or urea distribution space. V is calculated by Watson's formula and expressed in liters (Watson et al. 1980). BSA is

calculated using Du Bois' formula (Du Bois and Du Bois 1916). The relationship between V and BSA is not linear and is affected by the degree of change of body weight and by gender (Tzamaloukas et al. 1998). Comparing these formulas, an increase in body weight in a given patient will produce an increase in V that is disproportionately greater than the increase in the BSA. That is because body weight is weighted more in the Watson formula than the Du Bois formula. The result is that weight gain causes a relatively smaller decrease in normalized creatinine clearance than in $Kt/V_{urea}$. Achieving clearance and volume targets in larger patients may require higher fill volumes, such as 2.5 or 3-L fills, especially when RRF is lost but may be limited by discomfort. The effect of increasing fill volumes on clearance and patient tolerability will be discussed later in the chapter.

Technique survival in CAPD has been shown to depend mostly on clearances in relation to body size and RRF (Twardowski et al. 2009). In a prospective observational study of 277 CAPD patients, none of the large patients (BSA > 1.9 $m^2$, weight > 75 kg, BMI > 25 $kg/m^2$) remained on CAPD for more than 80 months once RRF was lost, mostly because of inadequate clearances or difficulties with volume control (Twardowski et al. 2009). There were no associations between PET D/P creatinine and BSA, PET $D/D_0$ glucose and BSA, or PET drain volume and body weight. In a retrospective study of 93 PD (CAPD and APD) patients, there was no association between BMI and long-term technique survival (Barone et al. 2010).

### 29.2.6 Peritonitis

During an acute episode of infectious peritonitis, vasoactive substances cause enhanced perfusion of blood flow and vasodilation of peritoneal capillaries to increase the effective peritoneal surface area. This results in a transient increase in small solute clearance and a reduction in ultrafiltration (i.e. conversion to High transporter status) that is usually reversible within 1 or 2 weeks of starting appropriate antibiotic therapy (Krediet et al. 1987). In order to preserve ultrafiltration in this setting, adjustment to the PD prescription may be needed by using shorter dwell times and/or non-dextrose dialysate solutions, such as icodextrin. Recurrent peritonitis may result in hyperpermeability of the peritoneal membrane and morphological changes, such as, submesothelial fibrosis and angiogenesis (Fusshoeller 2008).

### 29.2.7 Patient Compliance

The achieved or delivered PD dose may be significantly lower than the prescribed dose due to poor compliance, commonly through omission of

exchanges or shortening of dwell times. The reported prevalence of non-compliant CAPD patients varies between 10 and 40% and in APD patients between 15 and 20% (Rivetti et al. 2002). In a large questionnaire-based study (Blake et al. 2000) of 656 CAPD patients from Canada and the US, the overall noncompliance rate was 13% (defined as missing more than one exchange per week or more than two exchanges per month). The rate of noncompliance was likely underestimated as the survey measured admitted rather than actual noncompliance. On multiple regression analysis, the following characteristics were independent predictors of noncompliance: greater than 4 exchanges per day, black race, being employed, younger age, and the absence of diabetes (Blake et al. 2000). The results of this study highlight the importance of patient lifestyle considerations when considering CAPD prescriptions and avoidance of more than four exchanges per day. Patient compliance with PD has been evaluated by the administration of questionnaires, home visits, teledialysis, or the use of removable memory cards from cycler machines (Juergensen et al. 2004).

In an attempt to minimize the dialysis burden for patients new to PD, one approach would be to incrementally increase the dialysis component of solute clearance as RRF declines. However, this approach requires diligent monitoring of RRF every 2 month as previously suggested (NKF-K/DOQI 2006). In a study using urea kinetic modeling targeting a weekly $Kt/V_{urea}$ of 2.0, an average sized patient with High-average transport characteristics and RRF can be initiated and maintained for approximately 8-months with a single 2.5-L nocturnal exchange and for 8 to 17 months with two nocturnal exchanges of 2.5 L each (Keshaviah et al. 1994). Another alternative to improving compliance is the use of larger volume exchanges instead of increasing the number of exchanges per day to increase clearance (discussed in the next section). In parts of the world where the cost of dialysis is incurred by patients, this may also affect PD compliance and hence achievable dose of PD.

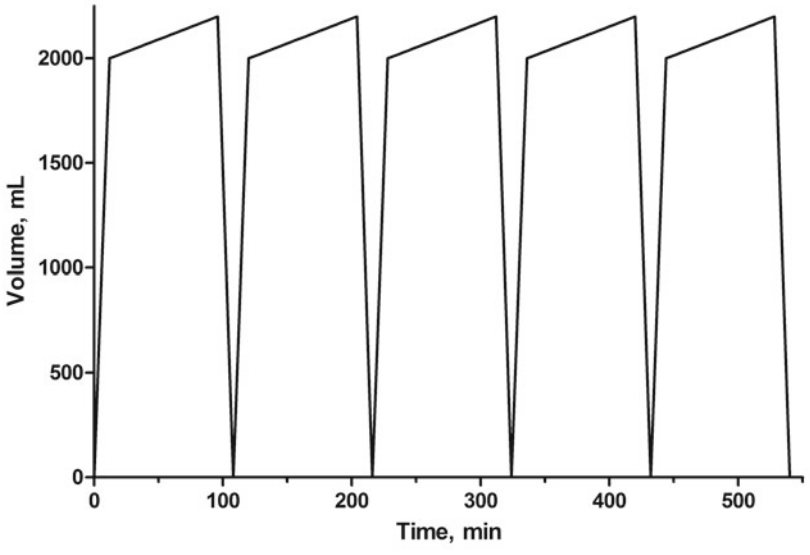
## 29.3 PRESCRIPTION SPECIFIC FACTORS AFFECTING CHRONIC PD DOSE

### 29.3.1 APD and Cycle Frequency

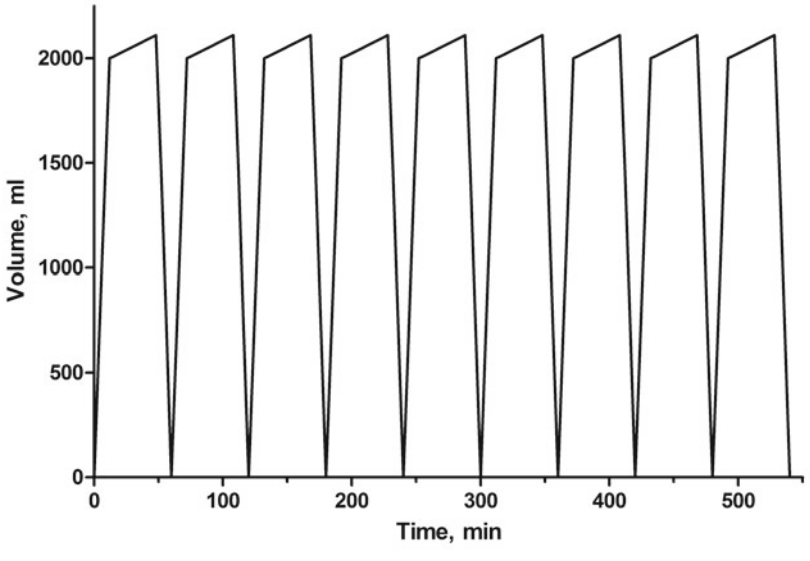
Overnight cycles using an automated device have been used now for decades (Diaz-Buxo et al. 1981; Diaz-Buxo et al. 1984). APD refers to any

type of PD therapy involving an automated device (Kathuria and Twardowski 2009). APD therefore includes: intermittent PD (IPD) whereby patients received 12-24-hours of therapy several times (but not every day) a week, continuous cyclic PD (CCPD) whereby patients perform cycles at night and a long daytime exchange during the daytime, nocturnal intermittent PD (NIPD) which is essentially CCPD without a daytime exchange, and tidal (TPD) which is discussed in more detail below. All of these involve a number of cycles, generally through the night for patient convenience. Another form of APD is continuous flow PD, which has been evaluated as a method to increase solute clearance through the continuous flow of dialysate in and out of the peritoneal space (Diaz-Buxo 2004). It is discussed in more detail later in the setting of acute kidney injury (AKI).

A number of studies have attempted to determine what the optimum number of cycles are in a given time period. Recognizing that with each cycle, time is required to drain and fill, it stands to reason that at some point there is a trade-off where increasing the number of cycles in a given period of time will lead to diminished solute clearance as the drain and fill times becomes an ever-increasing proportion of each cycle and the total dialysis time. Figure 29.2 illustrates this point. A simple analysis of the volume × time product in the different scenarios demonstrates that with increasing frequencies of exchanges, longer fill/drain times have an increasingly negative effect on the total dialysate volume available to the peritoneal membrane (see Fig. 29.3). These examples assume a total therapy time of 9.0-hours, an overall ultrafiltration of 1.2-L for all scenarios, fill volumes of 2.0-L, and varying combined fill and drain time. With increasing number of cycles, the detrimental effect of increasing the drain and fill time is more pronounced. This of course ignores the fact that small solute clearance is not linear and will decrease over the length of an exchange as the concentration gradient dissipates, depending on a number of factors (i.e. fill volume, gradient, solute properties, peritoneal membrane transport properties etc.), but nevertheless illustrates the point and is likely very relevant when considering middle molecule clearance, as is discussed later.

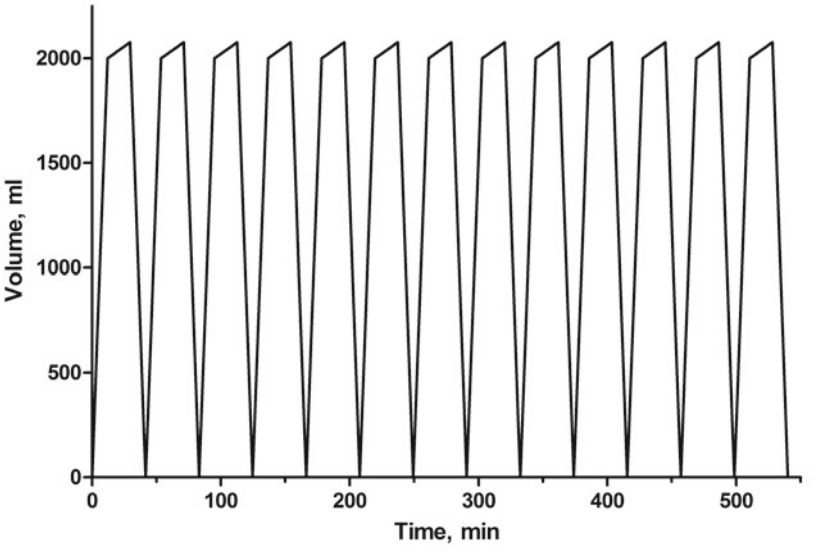



(a)




(b)

**Fig. 29.2** Nightly intermittent PD over 9 hours showing three scenarios with 2.0-L fill volumes: (a) 5 exchanges; (b) 9 exchanges; and (c) 13 exchanges.




(c)

**Fig. 29.2** (Continued)

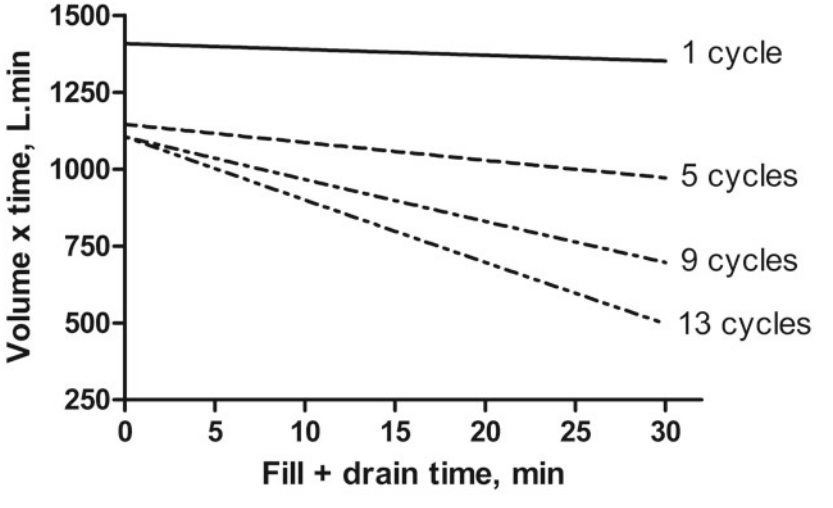



**Fig. 29.3** The calculated product of *volume x time* in 9 hours of nightly intermittent PD based on varying number of exchanges (1, 5, 9, and 13) of 2.0-L and fill and drain times for each exchange. The calculations assumed a net ultrafiltration for all scenarios of 1.2-L.

How long does the fill and drain phases take? Brandes et al found that fill rate was faster for a greater fill height and for patients in the supine position (Brandes et al. 1995). Larger bore catheters did not influence the findings. The average fill rate was 290 ml/min and was completed after 7.9 minutes. The drain phase was characterized by an initial rapid and linear rate of 350 ml/min achieving 83% of the fluid removal after about 5 minutes. This was followed by a transition phase and a subsequent much slower drain rate (36 ml/min), presumably due to the viscera collapsing on the catheter at the transition point. Not surprisingly, the time to the transition point was shortened by an increased drain height. These results suggest that the drain time could be shortened without leaving much fluid behind and thereby increasing clearances by lengthening the dwell times.

Baczynski and colleagues conducted a study in 17 PD patients to determine the impact of drain and fill periods of a cycle on solute removal (Baczyski et al. 2010). Briefly, they carried out an infusion of dialysate followed immediately by drainage; the time taken was noted and a sample drawn to determine the solute mass removal (concentration × volume) during the first experiment. In the second experiment, an exchange with the same dialysate volume was then performed for the same duration as in the first dwell. The fluid was then again removed and a sample drawn. This is shown schematically in Fig. 29.4. The PD efficacy of the infusion and drainage period was calculated as the ratio of the solute removal in the first experiment to that of the second experiment, less correction made to subtract the additional impact of an infusion and drainage period in the second experiment. The authors took into account the residual volume present in each experiment, which was assumed to be 222-ml based on previous experiments by the research group. This value is likely to vary between patients in reality and may introduce some error in the calculations. They also adjusted for the time-dependency of solute removal – i.e. there will be less solute removal during the drain phase in the second experiment because of the preceding dwell, lessening the concentration gradient across the peritoneal membrane. This 'correction factor' was based on previously determined isotope experiments and estimated to be 0.89 for urea and 0.90 for creatinine. Thus for determination of the efficacy of urea removal during the inflow and drain phases, the final equation would be:

$$k = \frac{C_1 V_1}{C_2 \left( V_2 + 222 \right) - 222 C_1 - 0.89 C_1 V_1} \tag{29.5}$$

where $C_1$ and $C_2$ represent the solute concentrations (urea or creatinine) of the drawn samples in the two experiments and $V_1$ and $V_2$ the respective volumes of dialysate upon drainage. The overall estimate of k was 0.87 for urea and 0.68 for creatinine, however several patients had values greater than unity, bringing into question the validity of such a method. An alternative, more pragmatic approach is to use a value of 0.5, assuming that on average half of the dialysate volume is available to the peritoneal membrane during the inflow or drain period (Amici 1998).

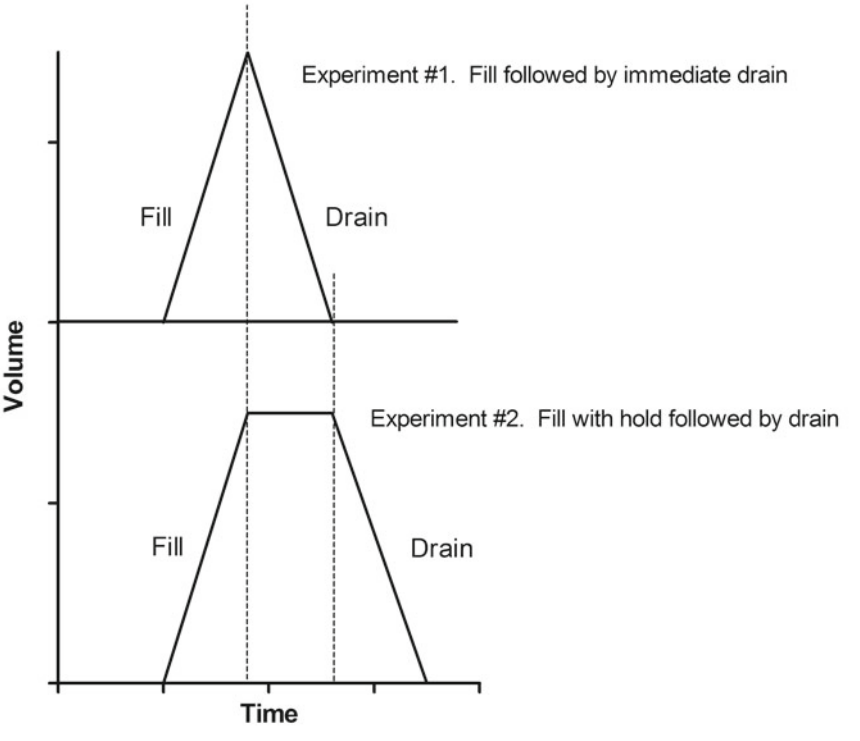



**Fig. 29.4** An illustration of the experiment conducted by Baczyski et al. 2010 designed to determine solute clearance restricted to the fill and drain phases of an exchange. The upper panel shows fluid is infused followed immediately by drainage of the fluid. In the lower panel fluid is held after the initial infusion for the same period of time as the drain phase determined from the first experiment. Fluid is then drained out.

Juergensen and colleagues (Juergensen et al. 2002) examined the effects of increasing the exchange frequency (and therefore total volume) in 11 APD patients over a fixed time period of 9-hours. Patients had fill volumes of 2.5-L during the cycles with a final volume of 2.0-L to hold during the

day. They used convenient total volumes of 9.5-L (3 cycles), 14.5-L (5 cycles), and 19.5-L (7 cycles) to make use of 2, 3, or 4 × 5-L dialysate bags. Each participant performed each of the schedules one week apart. The authors found, not unexpectedly, that peritoneal clearance, as measured by either $pKt/V_{urea}$ or peritoneal creatinine clearance, increased with increasing cycle frequency (to a maximum of seven). The $pKt/V_{urea}$ increased from 1.68 in the 9.5-L trial to 2.06 in the 14.5-L and 2.29 in the 19.5L trials, respectively. This increase of 23% and 36% in the 14.5-L and 19.5-L trials was greater than the 16% and 21% increases observed for the creatinine clearance. The increase in clearances observed was accompanied by increases in ultrafiltration, more so in the Low-Average transporters compared to the High-Average and High transporters.

### 29.3.2 CAPD and Exchange Frequency

Similarly to APD, one would expect that an increase in exchange frequency in CAPD would lead to increased clearance of small solutes. This is at the expense of increased costs and possible decreased quality of life due to the increased time involved in performing the exchanges during the daytime. Szeto and colleagues evaluated 100 anuric CAPD patients who were stable but required an increased intensity of dialysis using a non-randomized design (Szeto et al., 2002). Fifty agreeable participants added an additional 2.0-L exchange (baseline 3 or 4 exchanges) while an additional 50 participants who did not agree to the increase represented the control group. A significant increase in $Kt/V_{urea}$ of 21% was observed in the intervention group (1.58 to 1.91); no change was seen in the control group. A similar increase was observed with creatinine clearance. Ultrafiltration volume increased 210 ml with the increase in the number of exchanges.

### 29.3.3 Fill Volumes in CAPD and APD

As has been previously pointed out, peritoneal clearance of small solutes such as urea are determined solely by dialysate flow rate once equilibrium has been achieved between the plasma and dialysate. To enhance dialysate flow rate, i.e. drain volume, the options include increasing the fill volumes, increasing the number of exchanges, or enhancing ultrafiltration by increasing the osmotic strength of the dialysate (Krediet et al. 1998). From a patient's perspective it would seem likely that an increase in the fill volume, if not associated with adverse symptoms, would be preferable to an additional exchange which is time-consuming and may impact on quality of life.

The traditional peritoneal dialysate volume (fill volume) used in patients is 2.0-L. Increasing the fill volumes with each exchange should increase solute removal by increasing dialysate flow rate, but as already mentioned, at the expense of additional fluid used and potential side-effects including patient discomfort, the development of hernias etc. Keshaviah and colleagues carried out a study to determine the relationship between BSA, fill volume and solute removal in PD patients (Keshaviah et al. 1994). They found that the $K_oA$ (overall membrane permeability × surface area) increased in a linear fashion between 0.5 and 2.0-L fill volumes with a near-doubling over this range. Diminishing returns were observed however as the fill volume was increased to 3-L with less than a 10% further increase in the $K_oA$. However, the peak $K_oA$ increased with BSA, suggesting that fill volumes can be increased with larger patients. The explanation for the effect of fill volume on $K_oA$ is that it recruits a greater amount of the peritoneal membrane surface area. Even higher volumes appeared to decrease the $K_oA$, suggesting that at these volumes complete mixing of the dialysate does not occur.

A more recent study further clarified the effects of increased fill volume as previously mentioned. Ten PD patients underwent two separate studies of a 2.0-L and 3.0-L dwell. Each 1.0-L of solution contained 790-ml of 1.36% glucose-based solution, 160-ml of 0.45% NaCl, 50-ml of CT-contrast, and radio-labeled albumin to estimate peritoneal volume (Chagnac et al. 2002). CT-imaging of the peritoneal space was undertaken to estimate peritoneal surface area in contact with the PD solution. The authors found that increasing the dialysate volume from 2-L to 3-L (resulting increased volume 46%) led to an 18% increase in effective peritoneal surface area (0.57 to 0.67 $m^2$).

Previous modeling studies suggest that for the typical CAPD on 2.0-L × 4 exchanges, in the absence of RRF, a significant proportion of patients would not be able to achieve a total weekly $Kt/V_{urea}$ of 1.7 (Nolph et al. 1994). Low/Low-average transports more than 67 kg would likely have weekly $Kt/V_{urea}$ values less than this while High-average and High transporters above 63- and 61-kg respectively, would also be receiving insufficient dialysis based on this criterion. In the absence of peritoneal function testing, another study suggested that 90% of CAPD patients receiving a drain volume:total body volume ratio of at least 0.304 would have a $pKt/V_{urea}$ of at least 1.7 (Tzamaloukas et al. 2007). As an example, a 70-kg patient with an estimated volume of 40.6-L would need to have a drain volume of 12.3-L, an improbable value in CAPD patients. Such a drain volume would be difficult to achieve without some combination of 3.0-L fill volumes, increased number of exchanges, and/or high ultrafiltration rates.

The average weight in the validation cohort was 69.3-kg and the average drain volume 9.0-L as a point of comparison. This would confirm the suggestion that standard CAPD 2.0-L × 4 exchanges in insufficient in the majority of CAPD patients based on clinical practice guidelines, particularly in the absence of significant RRF.

While there is no question that increasing fill volumes will increase small solute clearance, tolerability must be assessed. This question has been addressed in several studies. A small study of 11 patients sought to determine whether 2.5-L exchanges could be tolerated in a CAPD regimen (George et al. 1989). Eight of the patients substituted all 4 of their 2.0-L exchanges while the remaining 3 patients substituted 1 exchange. In the 8 patients who substituted all exchanges for the larger volume, the daily urea clearance increased 14.6% and the creatinine clearance 9.5%. No change in the ultrafiltration was observed although a trend to increased ultrafiltration in the 2.5-L fill volume group was observed. More modest changes were seen in the remaining three patients. Importantly, the vast majority of patients tolerated the increased volumes without worsening symptoms – 10 of the 11 patients would continue the 2.5-L fill volumes.

Harty et al. conducted a randomized controlled trial in CAPD patients in which patients already on a 2.0-L × 4 exchange prescription were randomized in a 2:1 fashion to receive an increase in fill volume of 0.5-L or to maintain the same prescription (Harty et al. 1997). The primary outcome was urea and creatinine clearance at 1-year. As a result, 42 patients were randomized to the increased volume and 26 patients to maintain current volumes. Unfortunately, 28 patients failed to complete the 1-year follow-up (transplant, transfer to HD, medical illness, and death) and 7 patients in the increased fill volumes group were intolerant to the change in regimen (29%). Not surprisingly, patients who were intolerant had lower body weight and BSA and were more likely to be women, reflecting the smaller size of the female patients. Of the remaining 17 patients who tolerated the increased volumes, daily drain volume increased from 8.9-L to 10.7-L at 1-year ($P< 0.0001$) and $pKt/V_{urea}$ increased from 1.59 to 1.78 (12% increase, $P=0.0005$). RRF declined at a similar rate in those who were tolerant to the prescription change and the control group. While these findings suggest that increasing fill volumes can increase drain volume and small solute clearance, they also point to the fact that larger volumes are often poorly tolerated.

Harris and colleagues randomized 12 CAPD patients in a double-blind cross-over design to either 2.0, 2.5, or 3.0-L exchanges (Harris et al. 2001). Intra-peritoneal pressure was measured and the McGill pain questionnaire

administered to assess tolerability. With the larger volumes there was a tendency to increased discomfort based on only one of the sub-domains. Intra-peritoneal pressure increased with the larger volumes immediately post infusion but tended to drift back towards baseline after 3-hours into the exchange. It should be noted that only a 1.36% glucose-based fluid was used. Presumably higher strength dialysate would lead to greater ultrafiltration and drain volume and a greater potential for discomfort due to increased intra-peritoneal pressures.

A multi-centered study of 81 CAPD participants was carried out to determine the resulting intra-peritoneal pressure and subjective discomfort of increasing fill volume from 2.0 to 2.5 and 3-L (M de Jesus et al. 2000). Participants were blinded to the fill volumes to prevent bias. Not surprisingly there was an increase in intra-peritoneal pressure with increasing fill volumes; this was associated with a small but statistically significant increase in diastolic blood pressure. More importantly, subjective discomfort was higher for the larger volumes, however, 44% of participants had a low discomfort score with 3.0-L fill volumes compared to 86% of participants with 2.0-L and 64% of participants with 2.5-L volumes. The authors did not find any relationship between intra-peritoneal pressure and subjective discomfort. Intra-peritoneal pressure may be a more useful measure in children. In one small study of five children, initial fill volume of 940 $ml/m^2$ was titrated upwards based on intraperitoneal pressure measurements (Fischbach et al. 1997). As a result of this, the fill volume was increased to 1230 $ml/m^2$ and weekly $Kt/V_{urea}$ increased from 1.61 to 2.03.

Twardowski and colleagues have shown that increasing fill volume to 3.0-L is tolerated in about 50% of patients – those who did not tolerate this increase had dramatic decreases in forced vital capacity and forced expiratory volume particularly in the supine position (Twardowski et al. 1983).

A different approach was taken in a recent study to assess the impact of higher fill volumes on patient tolerance (Davis et al. 2011). The authors searched the Manufacturer and User Facility Device Experience (MAUDE) database to investigate events reported related to “overfilling”. Overfill, as the authors point out, was a term historically used by manufacturers to describe an event when an excessive amount of fluid infusion takes place, either due to machine malfunction or user error, leading to an increase in intraperitoneal volume. Overfill can also occur as a result of excessive ultrafiltration or because of inadequate drainage of intraperitoneal fluid prior to the next fill. The authors identified such complaints and related the severity of the event (minor, moderate, major, or death) to the ratio of the drain volume to fill volume (DV/FV). A significant

relationship was observed with higher ratios observed in the more serious cases. There were ten reports of major complaints with an associated DV/FV ratio of 2.14, as compared to 1.63 for minor cases. Insufficient drain associated with subsequent infusion was the presumed cause of 88% of cases.

Patient discomfort may not be the only drawback to increased fill volumes. One study has demonstrated that there is a significant decrease in cardiac output, measured non-invasively, with an accompanying decrease in stroke volume and increase in total peripheral resistance as the dialysate volume was increased from 2.0-L to 3.0-L (Ivarsen et al. 2007). This was hypothesized to be due to decreased venous return from the increased intra-abdominal pressure. Additionally, there has been evidence to suggest that increased fill volumes (i.e. 3.0-L) are associated with increased appearance of inflammatory markers such as TNF-α without increased removal of middle molecules such as ß2-microglobulin (Paniagua et al. 2004).

A small study of 8 CAPD patients with inadequate solute removal or ultrafiltration using a standard 2.0-L × 4 exchange regimen underwent two separate experiments of a 4-hour dwell with either 2.0-L or 3.0-L of dialysate. The mass transfer of small solutes such as urea and creatinine increased about 40% without a similar increase in the MTAC, suggesting that the higher volumes increased solute removal primarily by increasing the dialysate flow rate and therefore the transperitoneal concentration gradient rather than by increasing the effective surface area (Krediet et al. 1988). These results are not necessarily different from that of Keshaviah's group who observed minimal increases in the $K_oA$ beyond 2.0-L (but substantial increases up to 2.0-L). The increased volume did not affect ß2-microglobulin removal, consistent with previous observations that middle molecule clearance is more a function of total contact time with the peritoneal membrane surface as is discussed later. The study was limited by the small sample size and multiple comparisons. Of some concern, the ultrafiltration volume decreased in the 3.0-L versus 2.0-L fills, presumably due to increased lymphatic absorption from the higher intra-abdominal pressures. As the authors point out in a subsequent review, higher glucose strength solutions may offset the increased lymphatic absorption by the increased transcapillary ultrafiltration.

The largest study to address the issue of increased fill volumes was the ADEMEX study (Paniagua et al. 2002). CAPD patients were randomized to continue 2.0-L × 4 exchanges or to an intensified PD regimen to achieve a target peritoneal creatinine clearance of 60 L/week/1.73 $m^2$. This enhanced clearance was achieved as follows. Patients with a BSA of ≤ 1.78 $m^2$

received a prescription of 2.5-L × 4 exchanges while those patients with a BSA > than 1.78 $m^2$ received 3.0-L × 4 exchanges. Patients who failed to reach the clearance target but tolerated the increased volume received a fifth exchange through the night. Patients who achieved the peritoneal creatinine clearance but were intolerant of the increased fill volumes underwent a combination of 2.5 (daytime) and 3.0-L (overnight) exchanges. Ultimately, only 85 patients required a fifth exchange indicating that this study was primarily an intervention of increased fill volumes. Total daily dialysate volume was 10.0-L for 37% of patients, ranging up to 15.0-L for 14% of patients. The peritoneal creatinine clearance increased from 44.5 to 57.0-L/week/1.73 $m^2$ and the $pKt/V_{urea}$ from 1.59 to 2.13 (Paniagua et al. 2005). It is difficult to know however, specifically what the relationship was between increased fill volumes and enhanced clearances due to the lack of information about patient-specific interventions and associated increased clearances. A 100-ml/day increase in ultrafiltration was also observed with the increased fill volumes.

### 29.3.4 Increasing Ultrafiltration

A number of studies have examined the impact of ultrafiltration on clinical outcomes. The data comes primarily from observational studies, which demonstrate at least a trend to increased mortality with smaller ultrafiltration volumes (Ates et al. 2001; Brown et al. 2001; Jansen et al. 2005). This type of data can be confounded by RRF (although NECOSAD was a study of anuric patients), membrane transport status, salt and fluid intake, and middle molecule clearance. Increasing ultrafiltration, through the use of dialysis fluid with higher strength of glucose or the use of an icodextrin-based solution, should increase the removal of solutes of varying sizes via convective clearance. Most studies have evaluated the role of these solutions as a means to increase ultrafiltration rather than clearance however. A recent meta-analysis and systematic review identified five randomized controlled trials comparing urea and creatinine clearance using icodextrin or a glucose-based solution for an overnight dwell (Qi et al. 2011). Peritoneal creatinine clearance ranged between 2.59 and 4.4 with a weight mean difference of 0.51 compared to glucose. Similar results were seen with urea. Results were highly significant for both solutes and heterogeneity in the studies was not observed. This meta-analysis confirms the clinical impression that enhanced ultrafiltration with icodextrin will increase small solute clearance, presumably through increased convective clearance. While increasing the glucose strength of dialysis solutions will presumably also increase clearance through increased convective clearance, the increased glucose exposure may have long-term detrimental effects on the

patient and is therefore not a recommended strategy to increase solute clearance (Blake et al. 2011).

### 29.3.5 Tidal PD

TPD is a method that has been around for decades (Steinhauer et al. 1991). The basic concept is that rather than exchanging the entire drain volume only a portion of it is removed with a similar amount re-infused in order to maintain dialysate contact with the peritoneal membrane. While advantageous in patients who have pain with outflow of the dialysate where typically a small portion of the fluid is left in with each exchange, its role to enhance clearances has not been shown to be as useful. Additional, as discussed below, TPD may also have a role in patients who have prolonged drain profiles.

One of the earliest studies to promote the usefulness of TPD was that of Flanigan et al (Flanigan et al. 1992). Using an automated device, 30 to 50 ml/kg of dialysate was infused and left to dwell. Subsequently, a tidal drain volume was removed (tidal inflow + weight gain/number of exchanges), the remaining volume is called the reserved volume. Fresh dialysate was then infused (typically 10 to 25 ml/kg) and the process is repeated for the required number of cycles. The hope is that the trade-off between decreased solute clearance because of equilibration of the reserve volume would offset the decreased clearance that occurs during the fill and drain phases of the cycle. In this particular study, APD consisted of 10-hours of overnight therapy (4-5 x 40-mL/kg exchanges) plus a daytime dwell of 20 mL/kg. Patients were then converted to TPD using 8-hours overnight with an initial fill volume of 40 mL/kg and tidal exchanges of 10 to 20 mL/kg to provide hourly dialysate flows of 25 to 70 mL/kg/hr. Hourly dialysate flows were increased incrementally to achieve urea removal equal to that observed with APD. Although TPD delivered enhanced urea removal, 16.0-L vs. 9.5-L used in APD was required.

Another study took CAPD patients through a series of prescription changes to evaluate solute clearance (Rodriguez et al. 1998). Patients went from CAPD to APD (average overnight volume 14.3-L, exchange volume 2.4-L, daytime volume 1.9-L), 50% TPD (matched to the APD regimen but exchanges reduced from 59.3-minutes to 37.8-minutes), and 25% TPD (exchange 19-minutes). $Kt/V_{urea}$ increased in APD compared to CAPD (2.03 vs. 1.51) while TPD was intermediate (1.88 with 50% TPD and 1.80 with 25% TPD. Another smaller study found similar clearances of urea and creatinine between intermittent PD and 50% TPD when dialysate flow rates were matched (Piraino et al. 1994).

Juergensen and colleagues carefully studied varying TPD prescriptions compared to conventional APD (Juergensen et al. 2000). One group of patients received a total of 15.0-L dialysate over 9.5-hours with the tidal volume varied between 10%, 25%, and 50%. A second group of patients received 24.0-L of dialysate over the same time period using 25% and 50% tidal volumes. In the 15.0-L group, the 10% and 25% tidal volumes achieved significantly less $Kt/V_{urea}$ than the 50% TPD and APD regimens. No differences in peritoneal creatinine clearance were observed. No differences were observed in the 24.0-L group although there was a trend to increased creatinine clearance in the 50% tidal volume and APD regimens.

Finally, one study compared APD to TPD in 30 patients using both one APD and one TPD treatment session using the same overnight duration (9 hours), total treatment volume (15.0-L), and fill volume (2.5-L) (Vychytil et al. 1999). A tidal volume of 50% was used. The authors found that urea clearance was modestly higher during APD than TPD (0.52 vs 0.49). When patients were sub-divided into Low/Low-average and High/High-average groups, only the lower transport group demonstrated enhanced clearance in the APD group.

Finally, Gotch using mathematical modeling examined the impact of varying drain/fill times on the efficiency of APD compared to TPD. His analyses suggested that patients with prolonged fill/drain periods would receive enhanced clearance with TPD whereas patients with typical fill/drain profiles would be better served continuing with traditional APD unless the dialysis flow rate exceeds 2 L/hr (Gotch 2002).

### 29.3.6 Miscellaneous Scenarios in APD

A number of options could be considered in APD patients when the dose is to be increased in order to achieve target. Two different scenarios are considered below. Demetriou and colleagues carried out a study that asked whether the addition of a manual exchange versus increasing the nightly dialysate flow volume was the best strategy to increase clearance in APD patients (Demetriou et al. 2006). The study design was a randomized crossover of 22 Low-average or High-average patients comparing 1 week of each of the following 2 strategies. In the manual daytime exchange intervention, patients performed 5 exchanges of 2.0-3.0-L (based on BSA) overnight over 9 hours with a 10-hour last fill of 2.0-L icodextrin, followed by a subsequent manual exchange of 2.0-2.5-L for the last 5-hours before the next cycle. Somewhat unusually, 75% tidal volumes were used rather than standard APD exchanges overnight. In the high-flow arm, patients again performed APD over 9 hours using variable volumes and 75%

tidal volumes, this time however with 13 exchanges. Participants then had a last fill of 2.0-L icodextrin until the next evening (15-hours). Eighteen patients completed the study and were included in the analyses. High-flow treatment was associated with a modest but significant increase in urea clearance (12.83 vs. 11.68-L) and creatinine clearance (12.83 vs. 11.68-L), however no difference was observed with phosphate clearance, ultrafiltration, and ß2-microglobulin clearance. Of concern, sodium removal was decreased in the high flow group (128.0 mmol/day vs. 176.4 mmol/day). This finding was almost certainly due to the sodium sieving that takes place with such short dwell times. Also a major concern was the estimation of a 34.3%-59.4% increased cost associated with the high-flow strategy. The rationale for using a 75% tidal volume was not clearly identified and the possibility that use of standard APD may have modified these results must be acknowledged.

Another important, albeit small study, measured urea and creatinine clearance in 8 patients using the following four APD prescriptions: 5 × 2.0-L, 7 × 2.0-L, 9 × 2.0-L, and 50% TPD, 14.0-L (Perez et al. 2000). All prescriptions occurred over 9-hours. Urea clearance increased from 7.5 to 8.6 and 9.1-L/night with the increasing number of exchanges. Creatinine clearance increased in a similar fashion. The TPD strategy was only superior in clearance to the 5-exchange prescription with a urea clearance of 8.3-L/night. Unlike the aforementioned study by Demetriou (Demetriou et al. 2006), sodium removal was enhanced with the increasing number of exchanges (114.9 mmol/night with 5 exchanges and 194.2 mmol/night with 9 exchanges). Patients with Low or Low-average transport status tended to have more modest benefits from the increased exchanges.

### 29.3.7 Middle Molecule Clearance

A large body of knowledge exists on the relationship between so-called middle molecules and their role as uremic toxins. A detailed discussion of this role is beyond the scope of this chapter. What is relevant, however, is the impact of different PD treatment strategies on middle molecule clearance. Clearance of middle molecules does not appear to simply follow from that of the smaller solutes such as urea.

It has been previously suggested that PD was associated with greater middle molecule clearance than with HD due to the high peritoneal membrane permeability, continuous mode of therapy, and better preservation of RRF (Keshaviah 1993). The latter is not only associated with enhanced clearance of middle molecules through convective clearance, but tubular metabolism and secretion as well (Evenepoel et al. 2006). A more recent

study compared high-flux HD to CAPD and APD found that HD was associated with greater clearance of ß2-microglobulin and p-cresol, a protein-bound toxin (Evenepoel et al. 2006). However, clearance of both of these molecules was greater in CAPD than APD, although the differences did not reach statistical significance due to the small sample size. An older study demonstrated that removal of ß2-microglobulin in CAPD patients was linear for up to 400 minutes, consistent with the notion that increasing the number of exchanges is not beneficial but rather duration of contact with the peritoneal membrane (Lysaght et al. 1989). This is further supported by the observation that CAPD patients tended to have higher clearances of ß2-microglobulin with two exchanges compared to three or four exchanges per day over twenty-four hours (Kim et al. 2001).

Finally, the use of icodextrin to enhance ultrafiltration has also been shown to be associated with enhanced clearance of middle molecules as compared to either 1.36% or 3.86% glucose-based dialysate (Ho-dac-Pannekeet et al. 1996). These and other studies suggest that middle molecule removal in PD is achieved through prolonged contact with the peritoneal membrane and amount of ultrafiltration achieved. Whether this is clinically important is less clear and requires further study.

## 29.4 FACTORS AFFECTING PERITONEAL DIALYSIS DOSE FOR THE TREATMENT OF ACUTE KIDNEY INJURY

The use of PD and factors affecting dosing in the treatment of AKI warrants special consideration. There is no consensus on the best dialysis method or dose in AKI and both hemodialysis (HD) and PD are used (Gabriel et al. 2008; Burdmann and Chakravarthi 2011). In the 1970s, PD gained widespread popularity in the treatment of AKI (Ash and Bever 1995; Steiner 1989). The only prerequisite for performing PD was an intact peritoneal cavity and access could be established promptly and safely by the insertion of a semi-rigid catheter at the bedside. With the availability of a flexible single cuff Tenckhoff catheter and automated cycler in the 1980s, studies reported positive results compared to intermittent HD in electrolyte and metabolic control (Sipkins and Kjellstrand 1981). However, with the increasing popularity of continuous (extracorporeal) renal replacement therapy (CRRT) since the late 1990s, PD has fallen out of favor (Hyman and Mendelssohn 2002; Rao et al. 2003). In a large international prospective observational study (Uchino et al. 2005) of AKI patients in the intensive care units at 54 centers in 23 countries, 73% of the 1738 enrolled patients were treated with dialysis. CRRT was used most often (80%), followed by intermittent HD (17%), compared to approximately 3%

treated with PD. Nonetheless, acute PD remains the mainstay of dialysis therapy in pediatrics and in adults in developing countries due to its ease of administration, availability, technical simplicity, large volume removal with hemodynamic tolerability, gradual correction of acid-base and electrolyte imbalance, and lack of need for anticoagulation (Ansari 2011; Alarabi et al. 1994; Gabriel et al. 2006; Reznik et al. 1991).

### 29.4.1 PD Dose and Adequacy Considerations in AKI

The adequacy of dialysis dose in AKI is the subject of controversy as there are no satisfactory markers of adequacy or consensus on what rate of urea solute removal is adequate or optimal (Claure-Del Granado and Mehta 2011; Paganini 1998). Urea kinetic modeling has been applied to patients with AKI, although, it has not been validated for use in the critically ill population (Schiffl 2007; Claure-Del Granado and Mehta 2011). There are several limitations to the extrapolation of the clearance-based dialysis dosage, such as $Kt/V_{urea}$ and creatinine clearance from the chronic dialysis population for use in AKI. Firstly, patients with AKI are often in a hypercatabolic state. Urea generation can vary on a hourly basis requiring a dynamic urea kinetic model (Chitalia et al. 2002). Secondly, the calculation of the volume of distribution of urea ($V_{urea}$) using derivative formulae has been shown to consistently underestimate the true $V_{urea}$ due to excessive production of endogenous water in AKI (Himmelfarb et al. 2002). Furthermore, there are neither randomized studies comparing various doses of PD and its effect on clinical outcomes in AKI; nor are there clinical guidelines on a minimum target dose of PD in AKI (Evanson et al. 1998; Paganini 1998; Claure-Del Granado and Mehta 2011). Extrapolating data from HD studies in AKI, a minimum weekly dose of standard $Kt/V_{urea}$ of 2.1 has been suggested with even higher small solute targets in highly catabolic patients (Chionh et al. 2010).

The clearance of MMW molecules, such as, pro-inflammatory cytokines, with the goal to attenuate the inflammatory response has been a treatment target in sepsis-associated AKI but currently there are no established method and clinical evidence for dosing PD based on MMW clearance (Ronco et al. 2008; Chionh et al. 2010). Clearance of small urea and MMW molecules in AKI, however, may not be the major determinants of short-term outcomes, but rather the adequate removal of “very small waste” (i.e. potassium, hydrogen ions, etc.) and fluid overload (Claure-Del Granado and Mehta 2011). However, these parameters have not been the target of dialysis adequacy measurements in randomized dialysis dose studies. Persistent hypervolemia in critically ill patients have been associated

with adverse clinical outcomes, including, mortality, prolonged ventilation, AKI and increased length of intensive care stay (Bagshaw et al. 2008; Cerda et al. 2010; Yerram et al. 2010). The use of PD in AKI adequately accomplishes volume removal and is well tolerated in hemodynamically unstable patients (Chitalia et al. 2002; Gabriel et al. 2007). One limiting factor with the use of PD in AKI is the control of ultrafiltration volume due to a combination of inability to accurately monitor intraperitoneal volumes and variability in ultrafiltration with fixed dextrose exchanges (Chionh et al. 2010). Although the same situation applies in patients on chronic PD, the requirement in the intensive care setting for higher fluid intakes coupled with more rapid changes in clinical status makes the use of PD a challenge in AKI requiring experienced staff.

Hypercatabolism is often found in patients with rhabdomyolysis, multiorgan failure, and sepsis. Given the slow continuous solute removal with PD, the efficiency of PD to treat uremia in hypercatabolic patients has been the subject of controversy (Mehta and Letteri 1999; Steiner 1989; Phu et al. 2002). Several studies have reported positive outcomes associated with PD in hypercatabolic patients (Bohorques et al. 1990; Chitalia et al. 2002; Gabriel et al. 2006, 2007; Gastaldi et al. 1981; Indraprasit et al. 1988). However, these studies are limited by small sample size, inconsistent definition of hypercatabolism, inappropriate or lack of measurements for catabolic state, and variable definitions of PD success (Ansari 2011).

### 29.4.2 PD Prescription Factors Affecting Dose

Similar to in chronic PD, the key determinants of solute clearance in AKI are dialysate flow rate, effective peritoneal surface area, BSA/body weight, and RRF (Chitalia et al. 2002; Gabriel et al. 2008). The acute PD dialysis session length can vary significantly (12 to 72 hours) depending on the etiology and duration of AKI, the amount of solute and fluid removal required, and the need for ongoing nutritional support (Passadakis and Oreopoulos 2007). Acute PD prescriptions should be reassessed every 24 hours in acutely ill patients to see if changes need to be made to meet catabolic demands, solute and fluid targets. Dextrose based solutions play a key role in acute PD; other solutions such as amino acid and icodextrin have little utility in this setting. With a standard regimen, using 2.0-L hourly exchanges with 1.5% dextrose results in an ultrafiltration rate of 50 -150 ml/hour (1200 – 3600 ml/24 hour). The use of higher tonicity dextrose solutions, 2.5% – 4.25% can result in large volume fluid removal of 200 – 400 ml/hour (Passadakis and Oreopoulos 2003).

### 29.4.3 PD Techniques in AKI

#### 29.4.3.1 Intermittent PD

Classical Intermittent PD (IPD) is the oldest PD modality and has been used widely in the treatment of AKI (Cameron et al. 1967; Tzamaloukas et al. 1973). A typical acute IPD session is 16-24 hours long, with each session comprising 20-30 exchanges of 1- 3-L of dialysate every hour (Passadakis and Oreopoulos 2007; Burdmann and Chakravarthi 2011). The delivered doses with IPD typically vary from 40 to 60-L per session (urea clearance 8 – 12 ml/min). In a randomized trial (n = 70) comparing acute intermittent PD (IPD) and hemofiltration in a Vietnamese population, in which malaria (69%) was the leading cause of AKI, treatment with IPD was associated with higher mortality, slower decline in creatinine and worse acid-base control (Phu et al. 2002). However, this study has been criticized as the IPD group used rigid catheters, an open system with manual exchanges, and too short a fill time that may have contributed to the poorer outcomes observed (Daugirdas 2002). Adequate small solute clearance may be difficult to achieve with IPD in hypercatabolic patients (Burdmann and Chakravarthi 2011).

#### 29.4.3.2 High-Volume PD

High-volume continuous PD (HVPD) is a modality developed to increase higher small solute clearance. A 24-hour treatment using HVPD (36-44 L/session) can produce as much small solute removal as a 4-hour session of HD (Gabriel et al. 2007). This was demonstrated in a prospective cohort study of 30 AKI patients that used high volume PD (targeting $pKt/V_{urea}$ 0.65 per session), the achieved normalized creatinine clearance and $pKt/V_{urea}$ values were 110 L/week/1.73 $m^2$ and 3.8 respectively. The same group (Gabriel et al. 2008) followed up with a randomized control trial in 120 patients with AKI secondary to acute tubular necrosis comparing high volume PD with daily HD. The high volume PD session was defined as 24-hours of dialysis with sessions performed 7 days per week using a cycler through a flexible Tenckhoff catheter. Two-liter exchanges were performed with 35 to 50 minute dwell times for a total of 36 to 44-L/day and 18 to 22 exchanges/day. In the daily HD group, a session lasted at least 3-hours and was performed 6 times/week. Baseline characteristics were similar for age, gender, severity of AKI, and APACHE II score, predialysis urea and creatinine. Patients that were highly catabolic, as defined by Schrier's criteria (Schrier 1979) were excluded. Metabolic control, mortality, and renal function recovery were similar in both groups. However,

the reported 30-day mortality was high in both groups (HVPD 58% versus daily HD 53%, P=0.49). The weekly delivered $Kt/V_{urea}$ was lower in the HVPD group (3.6 versus 4.7, P<0.01).

#### 29.4.3.3 Continuous Equilibrated PD

Continuous equilibrated PD (CEPD) is similar to CAPD but more intensive and can be performed manually or with a cycler. Compared to IPD, the dwell times are longer. Dialysate is continuously instilled and drained every 2-6 hours to provide 4 to 8 dwells daily (Bohorques et al. 1990). This technique provides low-flow continuous dialysis that may not be adequate for highly catabolic patients (Ansari 2011). Compared to IPD, CEPD achieves lower solute clearance due to the lower dialysate flow rates (urea clearance 5 – 7 ml/min) (Amerling et al. 2003; Nolph 1988).

#### 29.4.3.4 Tidal PD

TPD is performed with a cycler using rapid exchanges and a constant tidal volume in the peritoneal cavity that is not drained, typically 50% of the initial fill volume (2 to 3-L) (Chitalia et al. 2002; Passadakis and Oreopoulos 2003; Ansari 2011). Sessions vary from 8 to 12 hours, during which 26 to 30-L of dialysate are exchanged. TPD increases solute clearances by increasing the peritoneal contact time for constant clearance while maintaining high dialysate flow rates. One randomized crossover study of 87 patients compared CEPD to TPD in AKI reported higher small solute clearance with TPD (creatinine clearances in ml/min of 9.94 in TPD vs. 6.74 in CEPD, P=0.001; and urea clearance in ml/min of 19.85 in TPD vs. 10.63 in CEPD, P=0.001); ultrafiltration volumes (2.8 L/session TPD vs. 2.0 L/session CEPD, P=0.03), even though the total volume of dialysate per session was the same (26 L) (Chitalia et al. 2002). In the same study, TPD was superior to CEPD in the removal of potassium and phosphate.

#### 29.4.3.5 Continuous Flow PD

Continuous flow PD (CFPD) has regained popularity in recent years and has long been considered to have the highest solute clearance and ultrafiltration of any PD modality (Dell'Aquila et al. 2007; Ronco and Amerling 2006). This technique maintains a certain intraperitoneal volume (2-3L) with a continuous influx and outflow of dialysate without interruptions through the use of double lumen catheters (Ronco and Amerling 2006). This eliminates wasted time during inflow and drain and there is a

continuous concentration gradient for solute clearance. Continuous dialysate flows of 100 to 300 ml/min can be achieved with urea clearances in the range of 30 to 50 ml/min (Amerling et al. 2003). An 8 hour session with CFPD in a 70 kg patient can yield a $Kt/V_{urea}$ 0.58/session or a weekly standardized $Kt/V_{urea}$ 4.0 assuming daily treatments (Cruz et al. 2001). Mean ultrafiltration rates using 1.5% dextrose solution have been reported as 13.4 ml/min in a single pass dialysate system (Cruz et al. 2001). The main limitation for widespread use of this technique is the cost associated with use of commercially available dialysate due to the high dialysate flow rates. The dialysate can be used in a single pass or in a recirculation loop with a regeneration system to lower costs (Dell'Aquila et al. 2007).

## 29.5 CONCLUSION

PD offers patients a home-based therapy to carry out their dialysis in a variety of different ways, including APD and CAPD. Dose of dialysis has traditionally been measured as small solute clearance (i.e. urea or creatinine) although one may also measure the clearance of middle molecules or protein-bound molecules such as β2-microglobulin or p-cresol. Treatment of acid-base disturbances, electrolyte disorders, and volume disturbances should also be recognized as important functions of PD that are not specifically measured when measuring urea clearance.

Earlier studies suggested the need for a higher level of small solute clearance than was achievable in many patients – these results have been since shown to be a function of RRF. Randomized trials have shown that increasing the dose of PD beyond a peritoneal $Kt/V_{urea}$ of 1.7 (or alternatively increasing the CAPD prescription beyond 2.0-L x 4 exchanges) is not associated with improved quality of life or survival. Nevertheless, some dose of dialysis is important for patients and some data exists that suggests there is a threshold effect of small solute clearance on outcomes in anuric patients.

There are a myriad of patient- and prescription-specific factors that affect the delivered dose of PD (see Fig. 29.5). Although patients with significant RRF can likely initiate on virtually any standard PD therapy, with loss of RRF one may need to tailor the PD prescription to the individual patient. Larger patients may tolerate increased volumes as a means of increasing the dose of PD to patients. More frequent exchanges can be used in either CAPD or APD, one must recognize however that there is a limit to this after which time lost with filling and draining of dialysate becomes an ever-increasing proportion of the total dialysis time. Patients with higher transport status as measured by the PET are better suited to APD with more frequent exchanges and the use of icodextrin as a long dwell,

whereas, patients with lower transport status will tend to do well on CAPD where exchanges are longer, allowing more time for equilibration of solutes. A properly functioning PD catheter is vital to the delivery of PD and hence the achievable PD dose. Understanding the patient's physiological characteristics, personal preferences and social circumstances coupled with a sound comprehension of the principles of PD and the prescription-factors that affect dose will lead to the best care for that patient.

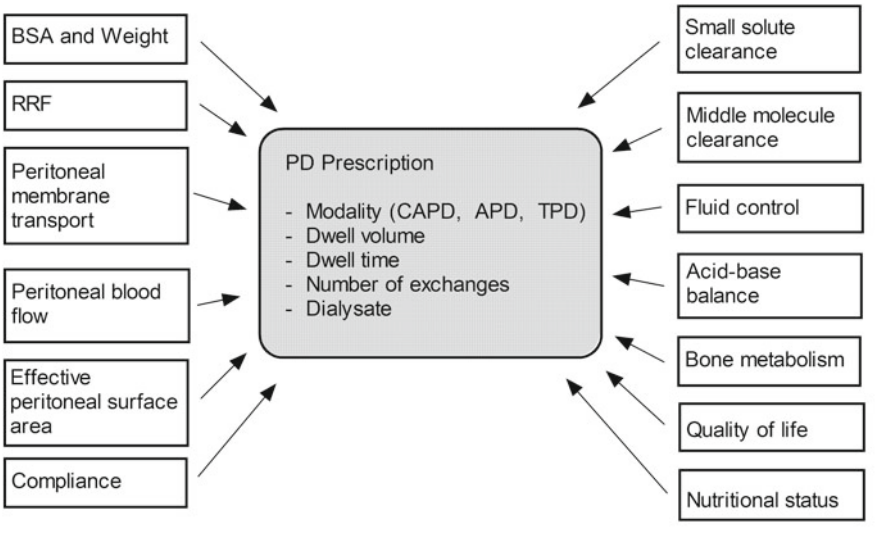



**Fig. 29.5** Factors affecting peritoneal dialysis delivered and achieved dose. RRF = residual renal function; BSA = body surface area; SA = surface area

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## ESSAY QUESTIONS

1. Discuss some of the patient and prescription factors that would violate the assumption that dialysate and plasma urea concentrations are equivalent at the completion of an exchange.
2. Discuss the advantages and disadvantages of increasing fill volume from 2.0-L to 2.5-L in an APD patient on a 9-hour overnight schedule as opposed to increasing the number of exchanges from 5 to 7.
3. Discuss the advantages and disadvantages of using tidal PD as opposed to standard APD.
4. Compare and contrast the factors that influence small solute clearance such as urea from that of a middle molecule such as β2-microglobulin in PD.
5. A patient known to have Low-average transport status on CAPD presents with peritonitis. Three days later the patient now presents with fluid overload. Discuss what has likely happened and suggest a prescription modification to manage the problem.
6. Compare and contrast the four peritoneal membrane transport categories with respect to small solute clearance and ultrafiltration. What is the preferred PD modality for each transport type?
7. A 50 year-old man with diabetes as the cause of his renal failure has been on CAPD for 5 years. He has progressive leg swelling and shortness of breath over the last 2 weeks. Work-up for cardiac disease is non-contributory. His last PET done 1-year ago indicates a High-average transport status. Thinking in terms of patient and prescription-specific factors, what are potential causes?
8. Discuss how residual renal function (RRF) affects the PD dose and ways to preserve it in patients on PD?
9. A patient with known Low membrane transport status has been on NIPD for 5 years and has lost his RRF. His PD prescription consists of 12-L over 8 hours (2-L volumes, 6 exchanges with 1.5% dextrose solution). His last adequacy test showed that he is not meeting targets for small solute removal. He is adamant to stay on APD due to lifestyle factors. What modifications would you make to his PD prescription to improve small solute clearance?
10. What are the advantages and disadvantages of using Continuous Flow PD in the treatment of AKI?

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. A 70-kg patient with high-average transport status is prescribed 2.0-L x 4 exchanges. His UF is 1.0-L. His estimated peritoneal $Kt/V_{urea}$ is:
   A. 1.70
   B. 1.55
   C. 1.62
   D. 1.83

2. A CCPD patient performs 5 exchanges x 2.0-L over 9 hours and holds 1.8-L during the daytime. His UF overnight is 0.8-L and his UF when he comes on to the cycler machine the next evening is 0.5-L. What is his total drain volume?
   A. 11.8-L
   B. 11.1-L
   C. 12.3-L
   D. 13.1-L

3. A patient on NIPD performs 6 exchanges over 9-hours each night. It takes 8 minutes to fill and 9 minutes to drain each cycle. What is his dwell time for each cycle?
   A. 54 min
   B. 90 min
   C. 73 min
   D. 17 min

4. Which of these factors is a potential drawback to increasing fill volumes in PD patients?
   A. decreased cardiac output
   B. decreased vital capacity
   C. increased patient discomfort
   D. all of the above

5. A patient performs TPD using 2.0-L fill volumes, 50% tidal volumes, and receives 14-L over 8-hours. How many exchanges were performed?
   A. 13
   B. 7
   C. 14
   D. 16

6. You have a CAPD patient on 2.0-L x 3 exchanges a day and you decide to modify the prescription to maximize middle molecule clearance. Which scenario would increase the clearance of middle molecules?

A. increase to 4 exchanges a day
B. convert to NIPD, 7 exchanges over 9-hours
C. convert to TPD using 50% tidal volumes, total volume 14.0-L over 9 hours
D. None of the above

7. Which of the following does not affect drain time in a CAPD patient?

A. malpositioned catheter
B. bore size of catheter
C. drain height
D. none of the above

8. A patient with some RRF whose PET study demonstrated him to have low transport status is initiated on CAPD 4 exchanges with 2.0-L volumes using 1.5% dextrose bags. His initial Kt/Vurea is only 1.5. Which of the following modifications to his prescription would not improve his clearance?

A. conversion of overnight dwell to icodextrin
B. addition of furosemide
C. increase in overnight fill to 2.5-L
D. none of the above

9. TPD is useful in which of the following circumstances?

A. Abdominal pain associated with drainage of the dialysate
B. As a general method to increase small solute clearance
C. Extremely prolonged drain time
D. A and C
E. all of the above

10. Which of the following has been shown to be associated with improved survival in PD patients?

A. increased number of exchanges in CAPD
B. increased number of cycles in APD
C. greater middle molecule clearance
D. residual renal function

11. In a patient with no RRF, the use of APD is most ideal for which membrane transport status?

a) Low
b) Low-average
c) High-average
d) High

12. Which anatomical component of the peritoneal membrane is the major determinant of transport?

A. mesothelium
B. interstitium
C. peritoneal capillary
D. lymphatic

13. According to the three-pore model, which pores transport solute-free water?

A. ultra-small pores
B. small pores
C. large pores
D. ultra-large pores

14. Effective peritoneal surface area is the product of which of the following?

A. permeability x peritoneal size selectivity
B. density of capillaries x anatomic peritoneal surface area
C. vascular peritoneal surface area x peritoneal size selectivity
D. density of capillaries x vascular peritoneal surface are

15. Which PD technique used is AKI can achieve the highest small solute clearance?

A. Continuous Equilibrated PD (CEPD)
B. Continuous Flow PD (CFPD)
C. Intermittent PD (IPD)
D. High-volume PD (HVPD)

16. The weekly residual renal $Kt/V_{urea}$ for an 80 kg man with residual renal urea clearance of 4 ml/min is approximately:

A. 1.04
B. 0.84
C. 0.52
D. 1.22

17. During an episode of acute peritonitis, what transient changes in peritoneal membrane characteristics can be seen?

A. increase in small solute clearance and increase in ultrafiltration
B. decrease in small solute clearance and decrease in ultrafiltration
C. increase in small solute clearance and decrease in ultrafiltration
D. decrease in small solute clearance and increase in ultrafiltration

18. Patient compliance with PD can be assessed with which of the following methods?

A. home visit
B. teledialysis
C. memory cards from cycler machine
D. all of the above

19. What morphological peritoneal membrane changes are typical in long-term PD patients?

A. loss of mesothelium
B. sub-mesothelial fibrosis
C. angiogenesis
D. all of the above

20. In AKI, why may the use of clearance-based dialysis dosage, i.e. $Kt/V_{urea}$ and creatinine clearance be inaccurate?

A. $V_{urea}$ is consistently overestimated
B. urea generation is stable
C. $V_{urea}$ is consistently underestimated
D. none of the above

Chapter (30)

# Future Directions and New Technology in Peritoneal Dialysis

Michael Francis Flessner

**CHAPTER OUTLINE**

- Inflammatory change in the peritoneal barrier.
- Rethinking dialysis solutions.
- Additives to solutions to decrease inflammation.
- New polymer materials for dialysis catheters
- Personalized Medicine: use of genetic testing to optimize therapy
- The "Wearable Dialyzer"
- Conclusion

**CHAPTER OBJECTIVES**

- To explore the sources of peritoneal inflammation.
- To explain the need for new catheter materials to minimize the foreign body reaction.
- To explore the biocompatibility of new solutions and technology.
- To propose the possibility of personalized peritoneal dialysis.

**KEY TERMS**

- inflammation
- polymer catheter
- foreign body reaction
- biocompatibility
- wearable dialyzer
- genomics
- Personalized medicine.
- glucose degradation products

**ABSTRACT**

Although peritoneal dialysis was first developed in the early 20th century, there are still many challenges that need to be addressed by bioengineers working with nephrologists. The peritoneal dialysis catheter sets up a foreign body reaction in the cavity and often becomes infected; new polymers are needed to minimize the resulting inflammation. New osmotic agents are needed to substitute for glucose that sets up a "diabetic state" in

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the cavity that leads to peritoneal sclerosis. New technology that can be worn by the mobile patient and that provides continuous dialysis is an exciting development that presents significant challenges to the design engineer. Computational biology attempts to quantitatively integrate the findings in clinical studies, genomics, proteomics, metabolomics to move health care toward "personalized medicine" in order to predict outcomes and to improve care of the individual patient.

## 30.1 INFLAMMATORY CHANGE IN THE PERITONEAL BARRIER

With infection, insertion of a dialysis catheter, or initiation of dialysis, both the innate and the adaptive immune systems are involved in an inflammatory response that is heavily influenced by the uremic condition of the patient. Uremia alters the human immune response and produces changes in the peritoneum (see Fig. 30.1) (Williams et al. 2002). Progressive kidney failure results in the decreased excretion of organic compounds, peptides and other products of metabolism (Hauser et al. 2008). These substances bind to antigen presenting cells that subsequently upregulate dendritic cells, leading to increases in B cells and T cells, which ultimately produce inflammation (Hauser et al. 2008). The most immediate response comes from the antigen presenting cell binding to toll-like receptors (TLR) on macrophages, which leads to increased production of chemokines and cytokines such as TNFα (Hauser et al. 2008). However, among the effects of uremia are the impairment of monocyte and monocyte-derived dendritic cell function in hemodialysis patients (Lim et al. 2007). Disturbances in acquired immunity in dialysis patients is evidenced clinically by increased mortality due to sepsis, high failure rates for vaccination, less resistance to mycobacterium tuberculosis, and alteration in systemic lupus erythematosis (Eleftheriadis et al. 2007). Others have found that serum resistin, a 12-kilodalton protein expressed in inflammatory cells, is elevated in uremia and inhibits polymorphonuclear cells in their chemotaxis and oxidative burst (Cohen et al. 2008).

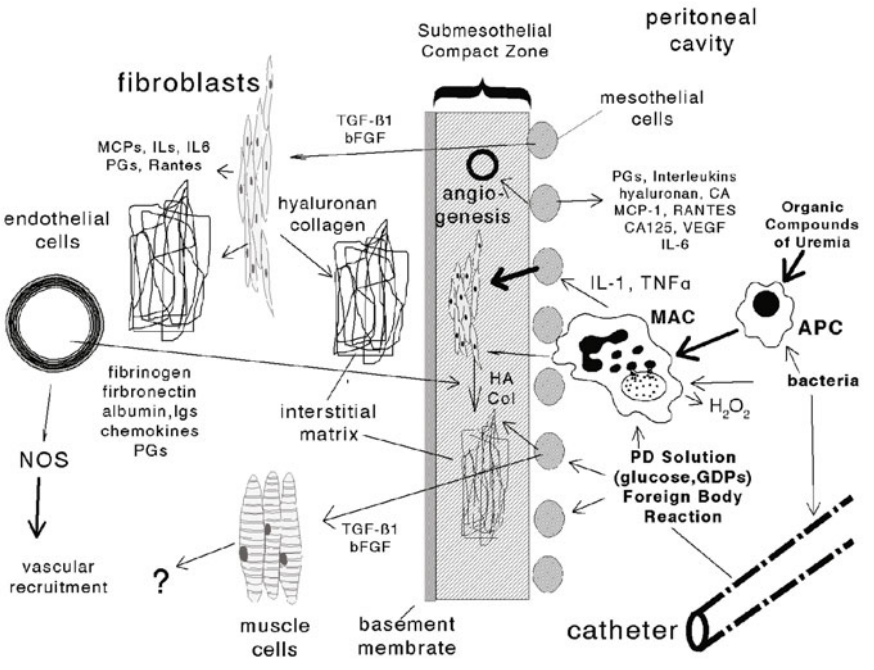


**Fig. 30.1 Inflammatory cascade that alters the peritoneal barrier**. Uremic compounds increase in the serum and bind to antigen presenting cells (APC) that activate, in turn, macrophages (MAC). MAC secrete IL-1 and TNFα that stimulate mesothelial cells to secrete a host of cytokines and chemokines, which result in an inflammatory cascade and an increase in the width of the submesothelial compact zone and angiogenesis. Insertion of a catheter and subsequent use of high concentrations of glucose solutions that also contain glucose degradation products (GDP) enhance the inflammation and cause ongoing damage to the tissue. To prevent these changes in the peritoneum, research is needed on new solutions, new catheter materials, and reagents that retard the inflammatory response.

Cytokine dysregulation has been observed in uremia and results in chronic imbalances in the immune system (Carrero et al. 2008). Peritoneal mesothelial cells are a target of a local aldosterone system that upregulates connective tissue growth factor (CTGF), a profibrotic cytokine

(Okazaki et al. 2009). CTGF in the peritoneal dialysate correlates with the creatinine dialysate to plasma concentration ratio (D/P) and is increased 11.4-fold above pre-peritoneal dialysis effluent in PD patients with rapid transport and ultrafiltration failure (Mizutani et al. 2010). Williams and colleagues (Williams et al. 2002) showed that there are inflammatory changes in the peritoneum with uremia prior to any dialysis or in hemodialysis patients who had never been exposed to peritoneal dialysis or abdominal surgery. The thickness of the peritoneum was significantly greater in both cases, and 28% of the peritoneal biopsies showed significant vasculopathy prior to any dialysis.

At the beginning of peritoneal dialysis, the initial insult to the cavity is the placement of peritoneal dialysis catheter. Typically made of polymer (silicone, polyurethane), the catheter is tunneled through the abdominal wall near the umbilicus and inserted into the lower pelvis. While there has been limited human research on the inflammation due to catheters (Fijen et al. 1988), there is now strong evidence from animal models that polymer catheters result in significant changes in the peritoneum and the overall transport system (see Fig. 30.2) (Flessner et al. 2007; Flessner et al. 2010). Even short exposures of less than one week will produce accumulation of white cells on the catheter and alterations in thickness and number of blood vessels in the peritoneum. Over time, however, the acute inflammation decreases and the amount of scarring and vascular changes subside substantially. However, after introduction of dialysis solutions, inflammatory changes persist and are significantly greater than in animals that are daily-injected intraperitoneally with the same solution via a needle instead of a catheter (Flessner et al. 2010). Bacterial peritonitis or infection of the peritoneum will greatly increase the inflammation and result in more changes than those induced by the catheter.

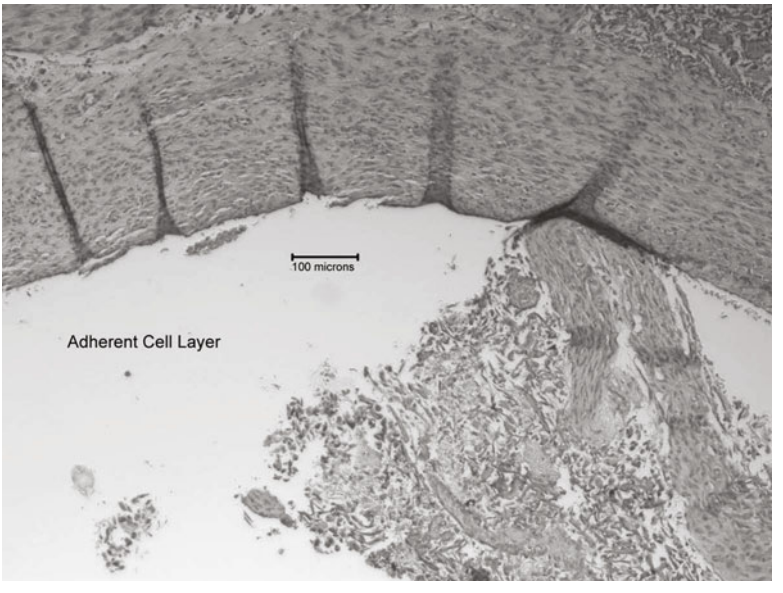


**Fig. 30.2** Adherent cell layer resulting from 2 weeks of peritoneal implantation of a sterile polyethylene catheter (catheter position would be in within the open area in the figure) in a rat. The multiple layers of cells resemble a tissue and illustrate a foreign body reaction to a sterile polymer. Research is needed to discover biomaterials that do not cause acute inflammation.

Peritoneal dialysis solutions vary in their pro-inflammatory properties. Lactate-buffered solutions are typically heat-sterilized, resulting in the production of glucose degradation products (GDP). It is hypothesized that GDP lead to advanced glycation end products (AGE) that damage the peritoneal barrier (Booth et al. 1997). While the development of bicarbonate-based solutions that have significantly less glucose degradation products should provide benefit, there have been no long-term trials of these solutions (Bargman 2006). The solutions still suffer from the use of high concentrations of glucose that are required to raise the osmotic pressure in order to withdraw fluid from the body. These glucose concentrations are significantly higher than clinical plasma concentrations that would qualify as severe diabetes. For example a 2.5% glucose solution contains approximately 2.3 g per hundred milliliters or 23 g per liter of solution (23,000 mg per liter or 2300 mg percent). Normal glucose in the plasma is on the order of 70 to 110 mg percent. Therefore this solution causes the cells of the peritoneum and those within approximately 1 mm

of the peritoneum to be bathed in an extremely high concentration of glucose. *There is a great need to develop an osmotic agent that is more benign than glucose and is still capable of inducing fluid removal from the body.*

Aside from alternative osmotic agents or catheter materials for the peritoneal catheter, there are potential additives to solutions that may decrease the ongoing inflammation induced by the dialysis procedure (Krediet et al. 2009; Schilte et al. 2010). However, there is a real need for an integrative approach (Barabasi et al. 2011) to eliminating or combating these pro-inflammatory processes. Some of these agents are biologicals that are hazardous and extremely expensive. Simpler solutions are needed in order to decrease overall inflammation and contain costs. *There are many aspects of this complex problem that require a more quantitative approach to this dilemma.*

There have been a spate of papers in the last 10 years concerned with genetic testing and the correlation of single nucleotide polymorphisms (SNPs) with the transport status and the outcome of patients on PD (Axelsson et al. 2006). Most of these investigations have been performed in Northern European or Asian countries. However, genome wide association studies or examination of individual SNPs have rarely produced definitive markers for patient outcomes. It is clear now that genetic determination of a particular patient phenotype is much more complicated (Barabasi et al. 2011). Epigenetics involving micro-RNA that do not code proteins likely have significant influence over the outcomes in patients. *While the era of personalized medicine (see Fig. 30.3) is potentially very exciting, the realization of definitive prognostic criteria is still challenging; quantitative tools such as computational or systems biology will continue to be opportunities for engineers and quantitative scientists* (Barabasi et al. 2011).

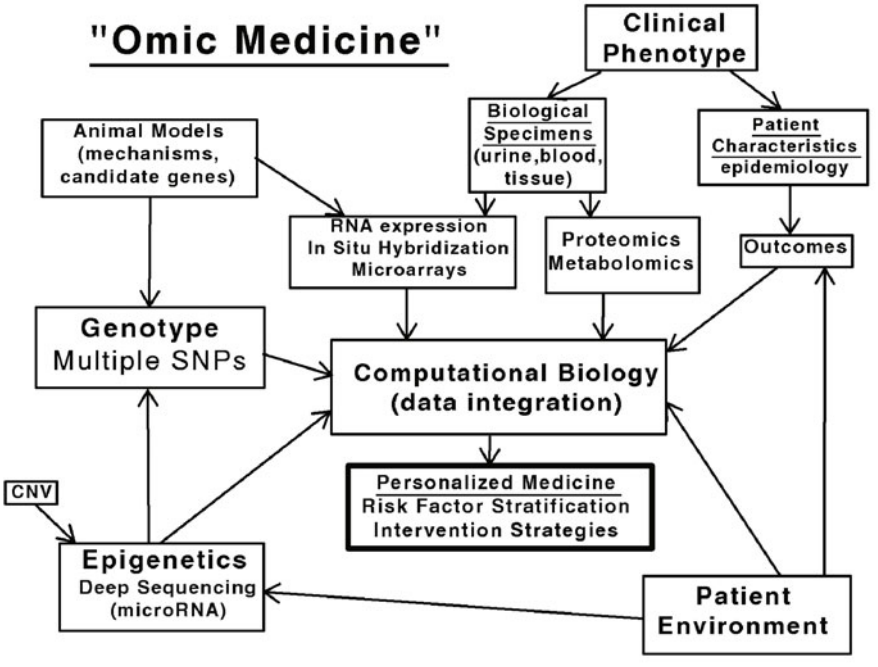


**Fig. 30.3** Omic Medicine" requires the quantitative discipline of computational biology to integrate the multiple and complex parts that include epigenetics, genomics, proteomics, metabolomics, and epidemiology. It is the field of the future bioengineer.

Along with attempts at prediction of outcomes, the entire procedure of peritoneal dialysis is being examined for improvements of technical convenience. Indeed both hemodialysis and peritoneal dialysis are undergoing changes in the engineering approaches. Each of these techniques is being streamlined and compartmentalized into a “wearable apparatus”, weighing 1-1.5 kg. While the miniaturization of dialysis apparatus is technically feasible and will likely be available to patients in the next few years, the interface of the biomaterials that act as foreign bodies and the solutions that are utilized present the same inflammatory stimuli as in the standard technique. *Therefore, the biomaterial problems and challenges of the solution will need to be solved in order to truly optimize dialysis with a wearable device.*

The use of peritoneal dialysis solution as a delivery device to introduce intraperitoneal chemotherapy is now well established. There are modified solutions and delivery techniques that can be used in order to maximize the

effect of the solutions. This involves the use of hyperthermic mixtures of solution. In addition, the maintenance of the volume in the peritoneal cavity over periods of greater than 12 to 18 hours is potentially possible with solutions that contain a starch instead of glucose. *Because the goal is delivery of the chemotherapeutic agent into the tumor tissue, these procedures will continue to require mathematical modeling for delivery optimization and outcome prediction.*

A new area which is undergoing basic and translational research to humans is the use of peritoneal dialysis for resuscitation of septic patients or for optimization of organ recovery from potential organ donors (Matheson et al. 2009). In animal models this is been shown to increase blood flow to the visceral organs of the peritoneum and to decrease overall inflammation with the potential for improved outcomes in either organ transplantation or in survival of the patients.

## 30.2 RETHINKING DIALYSIS SOLUTIONS

The following characteristics would be ideal for an alternative replacement for glucose. The agent should not produce GDP and should not add to the metabolic burden of the patient. It should either decrease or not increase uremia. The solution should not inflame or alter the peritoneal barrier. The substance should produce an effective osmotic pressure for adequate fluid removal over a minimum of 4 to 6 hours. It should be relatively inexpensive and not increase the cost of the solutions from the present level. Amino-acids, with similar molecular size as glucose, were thought to be ideal replacements for glucose, increasing nutrition while eliminating the carbohydrate effect. However, the problems of amino acids include increased uremia if given in the overnight dwell and significantly increased solution expense.

In recent years, the single advance in an alternative solution has been the use of icodextrin in patients (Krediet et al. 1997). Icodextrin is a polymer of an average molecular weight of 20,000 daltons. It is rapidly broken down in the peritoneal cavity of rodents, due to the high concentrations of tissue amylase. The corresponding enzyme concentration in humans is low, and the starch is slowly metabolized to maltose. The icodextrin produces a slow but continuous movement of fluid from the body into the peritoneal cavity over time periods up to 8 to 12 hours (Krediet et al. 1997). Indeed it has been utilized for intraperitoneal drug delivery in higher concentrations that will maintain the volume and a maximal surface contact area for up to 48 to 96 hours (Gilbert et al. 1999). A recent study (Freida et al. 2009) utilized mixtures of glucose at 2.6% and icodextrin at 6.8% in

dialysis patients to optimize the long dwell ultrafiltration and to decrease the glucose exposure. Long-term studies have not have yet to be carried out with this type of solution. While in general most clinical studies over the last 15 years have shown that icodextrin is relatively safe to use, its use in all dwells throughout the day has not been recommended and may be detrimental to the patient. Typically its use has been limited to just a single dwell during the night or day, but there have been recent efforts to use it in two exchanges per day (Dousdampanis et al. 2011). That the non-metabolized maltose does increase in the plasma may be the limiting factor for the use of icodextrin around-the-clock. This will likely be a problem of any substance that it is not endogenous to the body and that is metabolized to products which cannot be further metabolized by human cells and removed from the body. Therefore, while the use of icodextrin has been an advance, it clearly does not replace glucose.

Amino acids have been substituted for glucose and have been utilized in many different studies (Nishimura et al. 2009; Zareie et al. 2005). PD taurine (Nishimura et al. 2009) is an effective osmotic agent and more biocompatible than glucose in rats. It is not clear what long-term benefits or problems could appear after utilizing a single amino acid over months to years, but most studies utilizing amino acids or mixtures of amino acids and glucose have been shown to help patients who are poorly nourished. However their effect on long-term peritoneal dialysis and the peritoneum itself requires much larger clinical trials to evaluate the progression of nutritional and inflammatory markers and peritoneal changes (Tjiong et al. 2009). *The design of a compound that meets the ideal characteristics but does not present side effects continues to be a challenge for the biochemist and bioengineer.*

## 30.3 ADDITIVES TO DIALYSIS SOLUTIONS TO DECREASE INFLAMMATION

There have been a number of small (n = 36 to106) clinical trials comparing biocompatible with conventional solutions. Fan (2009) and Davies (2009) in their reviews demonstrated that results were variable with some studies showing improvement of residual renal function but also an increase in transport, while others showed no change. Several showed increases in CA-125 (a marker of the mesothelium) but no significant changes in IL-6, TGF-β or TNF-α. In some cases high sensitivity CRP decreased, but in other cases, there was no change. Most of these studies had a duration of less than one year; this has limited the results because of the slow changes in the peritoneum. So despite the emphasis on solution

biocompatibility, there is no convincing evidence that new solutions will affect mortality or technique failure. Longer term prospective studies with low GDP solutions are needed. While the search for the ideal osmotic agent goes on, additives that decrease inflammation may represent "bridging solutions".

Most studies with solution additives have been performed in animals. Addition of heparin to PD fluid does not prevent adverse changes in the rat peritoneum (Schilte et al. 2009b). Substituting citrate for lactate in rat peritoneal dialysis solutions induced more ultrafiltration but decreased serum calcium to an extent that there could be danger to humans. Bicarbonate-buffered PD solutions result in less angiogenesis and fibrosis than lactate-buffered peritoneal dialysis fluid in rats (van Westrhenen et al. 2008), but there are no human studies with which to correlate.

Since uremia, the presence of a catheter and the dialysis solution all upregulate the cellular immune system made up of mast cells, peritoneal macrophages, mesothelial cells, interstitial fibroblasts and myofibroblasts, agents that directly manipulate the immune system are now being advocated (Schilte et al. 2009a). Suppression of the innate immune system with cromoclycate (mast cell stabilizer) or corticosteroids (blocks macrophage function) are possibilities. Chemokine or cytokine receptor blockers could prevent biochemical signals that are critical to the inflammatory cascade. Examples of substances to directly combat the mediators are humanized anti-TNF-α, prostaglandin receptor blockers, BMP-7, or any of the inhibitors of the renin-angiotensin-aldosterone system. Other signaling pathways can be blocked with oral Cox-2 inhibitors, oral MAP kinase inhibitors, oral growth factor receptor blockers, anti-RAGE antibodies or oral AGE breakers, and PKC inhibitors (Schilte et al. 2009a).

Attempts to modify the complex immune system (see Fig. 30.1) are often empiric and focus on a single pathway. Early attempts to block TNF-α in support of patients with acute kidney injury failed. A systems biology approach toward the peritoneal immune response may provide integrative solutions to the vexing changes that often result in technique failure. *This is a new area of research for engineers and scientists with a mathematical background* (see Fig. 30.3).

In treatment of metastatic carcinoma that is restricted to the peritoneal cavity, the optimal method of therapy is to administer agents in dialysate fluid in order maximize concentrations at the site of the tumor. The trade-off of any of these substances which act systemically would be the effects on the whole body. This is why intraperitoneal therapy might be the best

way to localize the inhibition to the peritoneum. Relatively high concentrations of the agent can be obtained in the cavity with an excellent pharmacokinetic advantage (Dedrick et al. 1978). The penetration of small (~glucose) and large (immunoglobulins) can be modeled (see Chapter 30), and predictions of concentration versus time versus location from the source solution can now be made (Flessner 2001; Flessner et al. 1984; Stachowska et al. 2007; Waniewski et al. 2009). The trade-offs, advantages, and economics of these approaches are prime areas for quantitative assessments by teams of researchers, including biomedical engineers.

## 30.4 NEW POLYMER MATERIALS FOR DIALYSIS CATHETERS

By definition a silicone or polyurethane catheter in the peritoneal cavity is a foreign body. Its presence induces an immune response in the cavity, depicted in Fig. 30.1, an integrated cellular system making up the peritoneal barrier. While the physical barrier to solutes and water transport resides primarily in the capillary wall and the surrounding interstitial-cell matrix, resident macrophages, mesothelial cells, muscle cells, and fibroblasts play major roles in the maintenance of the barrier and its alteration after inflammatory response from a catheter material, GDP-containing dialysis solution, bacteria, or a combination of these factors. These stimuli set off a chain reaction that causes the secretion of cytokines and chemokines into the peritoneal fluid and into the surrounding tissue (Flessner 2007). It causes an apparent epithelial-to- mesenchymal transition of the mesothelial cells (Yanez-Mo et al. 2003) as well as the production of myofibroblasts and the recruitment of polymorphonuclear cells, mast cells, T-lymphocytes, dendritic cells into the peritoneal cavity (Tang and Eaton 1995). Recent evidence in animals has shown that after 1 to 7 days of placement in the peritoneal cavity of a rat, there are significant changes in thickness and angiogenesis of the sub-mesothelium (unpublished data, M.Flessner). This sets up an immediate inflammatory state that does not start subsiding until after eight weeks and is still present after five months. In the typical patient initiated on peritoneal dialysis, the catheter is placed 2 to 3 weeks prior to beginning dialysis therapy, and the insult of the catheter is added to the effects of uremia. These inflammatory stimuli are followed closely by introduction of solutions containing high concentrations of glucose and GDP. The hypertonic nature of the dialysis fluid and the fact that it is drained out along with millions of macrophages cause significant perturbations in the cellular immune system (Jorres et al. 1993). Studies in humans support the findings in animals (Mackenzie et al. 2003). Recent studies in rodents with different polymer catheters demonstrate that

different materials provide a variable reaction, typically less with silicone and more severe with polyethylene (Hu et al. 2001).

Figure 30.2 portrays an adherent cell layer on a polyethylene catheter after two weeks in the peritoneal cavity of a rat. Its appearance is not unlike an artificial tissue with multiple cell layers but no blood vessels. Since the initial steps of sterile intraperitoneal biofilm formation include the irreversible adsorption and denaturation of fibrinogen on the implant (Tang and Eaton 1993), followed by binding of white cells and the whole cascade of cytokines, one of the measures to deter the cascade might be to decrease this initial protein binding (Tang and Eaton 1999). The molecular determinants of biocompatibility have been investigated by Tang and colleagues (Hu et al. 2001; Tang and Eaton 1999) by altering conformations of sites for cell binding. They hypothesized that exposure of the P1/P2 epitopes of fibrinogen to biopolymers may be critical for binding of inflammatory cells, and blockade of the protein sites would alter the cell binding. Utilizing a scrambled P1 epitope or scrambled P2 epitope, they demonstrated a markedly decreased binding of macrophages and polymorphonuclear cells. An antibody to epitope P1 markedly retarded white cell binding, and different materials resulted in significantly different epitope exposure. Dacron, polyethylene, and polyvinyl chloride were among the worst in terms of large amounts of fibrinogen and inflammatory cell binding. Polyurethane and poly-dimethyl ciloxane had far less protein binding and significantly suppressed surface enzyme marker for macrophages.

The question is: can the surface of implanted polymeric foreign bodies be altered to retard or prevent adsorption of plasma protein and the formation of inflammatory biofilm without other side effects? To modulate the foreign body response, Tang and colleagues (Kamath et al. 2008; Tang and Eaton 1993) modified the surface of micron-sized particles of polypropylene with four functional groups: -OH, $NH_2$,-CF(x), COOH, using radiofrequency glow discharge plasma polymerization. They found that the -OH and $–NH_2$ induced the thickest fibrous capsule, while the –CF(x) and -COOH demonstrated the least inflammatory fibrotic response and cellular infiltration. *These advances in biomaterial research have the potential for decreasing the foreign body response and therefore the inflammation in the peritoneal cavity.*

Some of the most detrimental changes in the peritoneum occur after bacterial peritonitis, and the adherence of white cells and bacteria to the catheter can develop into a continuous biofilm that enhances peritoneal inflammation. These bacteria secrete a protective gel that makes their eradication difficult even with intraperitoneal antibiotics (Dasgupta et al. 1986).

That an infected catheter can re-infect the patient multiple times until it is actually removed is a well-known phenomenon that has been studied by several investigators (Costerton 1984; Dasgupta et al. 1987, 1989; Reed et al. 1986). Unfortunately, attempts to introduce an anti-bacterial substance into the catheter (such as silver) have not been effective in preventing infection, and infected catheters often have to be removed and replaced (Crabtree et al. 2003; Fung et al. 1996; Walboomers et al. 2001).

## 30.5 PERSONALIZED MEDICINE AND PERITONEAL DIALYSIS

Some patients who progressed to end-stage renal disease may have the genetic makeup that results in significantly greater inflammation from uremia and from the insults of a peritoneal catheter and daily exposure to dialysis solution. In a subset of the EAPOS study cohort of 233, 13 of 22 patients displayed steady-state volume and solute transport over five years, while the other 9 had progressive increase in solute transport (Davies et al. 2001, 2005). The latter group had earlier loss of residual renal function and required the use of more hypertonic solution to maintain sufficient fluid removal. There were no differences in rates of peritonitis between these groups. While we do not know the outcomes for these specific patients, the decrease of residual renal function and the requirements for higher glucose solutions typically results in an earlier failure of the peritoneal barrier and the requirement to switch to hemodialysis. Indeed this was one of the results of the EAPOS study (Davies 2001).

So the question is: can we genotype candidate patients for peritoneal dialysis and predict how they will fare with the technique? If they were predicted to have early complications, then nephrologists could take added precautions in care of the patient on peritoneal dialysis or advise them to choose hemodialysis. On the other hand, if they were a low responder to the various immunologic insults of the dialysis procedure, they might do quite well. There have been many attempts at correlation of single nucleotide polymorphisms (SNPs) with the patient's phenotypic transport status. Rapid transporters have clinically been shown to progress to ultrafiltration failure and to lose their ability to do peritoneal dialysis. Gillerot and colleagues (Gillerot et al. 2005) investigated the association of SNPs of VEGF, eNOS, and IL-6 with baseline peritoneal equilibration test in 152 Caucasian patients, and they determined metabolites in plasma and dialysate fluid. They performed RT-PCR of IL-6 mRNA in 8 peritoneal biopsies and showed that the 174G/C polymorphism of IL-6 correlated with higher permeability parameters and inflammation. On the other hand, VEGF and eNOS polymorphisms showed no effect. The CC and GC

polymorphisms demonstrated higher levels of IL-6 in the plasma and dialysate, and the mass transfer-area coefficient (MTAC) was significantly greater than that of the GG variant. While this finding is encouraging, it is rare that the correlation of a single SNP or several SNPs may result in a definitive genetic marker of a disease or hard outcome (McKnight et al. 2010)

Figure 30.3 illustrates the complexity of the new "Omic" approaches to medicine and the need for integration of a large amount of data. Instead of just looking at single SNPs or multiple genes within genome-wide association studies (GWAS), it is apparent that the patient (physiologic/social) environment has an effect on micro-RNA, non-coding regions that exert control over protein-coding regions of the genome and that likely impact the function of the immune system (Bartel 2009). Deep sequencing of the genome is performed to examine the entire genome instead of just the coding regions. Micro-RNA are likely correlated with the patient's environment, which in peritoneal dialysis includes the factors of uremia, foreign body reaction to the catheter, patient adherence factors, dialysis solutions used, and episodes of peritonitis; these combine to regulate the expression of protective or destructive SNPs. mRNA expression in the mesothelium and underlying tissue will reflect the control of these epigenetic factors and will help determine the inflammatory response and alterations in the peritoneal barrier. Unfortunately, there is a lack of peritoneal biopsy specimens for study, even from available animal models.

Proteomics, the study of protein products expressed by the genome, is just beginning to be applied to peritoneal dialysis (Brewis and Topley 2010; Wang et al. 2010) and may have eventual impact in the search for a replacement for glucose as the osmotic agent in the dialysis solution (Cuccurullo et al. 2011; Lechner et al. 2010) and in the correlation of dialysate protein with transport status (Sritippayawan et al. 2007). Metabolomics, the study of small molecules (MW < 1500 daltons) in a physiological system (Griffiths et al. 2010), is being used to develop urine biomarkers of disease (Ryan et al. 2011) and drug-induced renal injury (Boudonck et al. 2009a, b). However, these studies will not progress until more comprehensive techniques of bioinformatics and computational biology (Chuang et al. 2010; Kohl et al. 2010) are used to study how the genome and environment influence molecular and cellular systems in the body. These are new areas of opportunity for engineers and other quantitative scientists (Barabasi et al. 2011; Loscalzo et al. 2007).

## 30.6 THE "WEARABLE DIALYZER"

An exciting area of medical research is the development of a "wearable dialyzer" that provides continuous dialysis to the patient in a convenient, easy-to-wear size. Most advances have been in hemodialysis with a gradual, step-by-step technological evolution. Groups have miniaturized and manufactured wearable ultrafiltration systems or wearable artificial kidneys that are convenient and very effective for the patient (Gura et al. 2005; Nissenson et al. 2005a; Ronco and Fecondini 2007). Different publications (Kliger 2007a, b) have demonstrated that more frequent hemodialysis treatments are beneficial to patients, and a recent NIH-funded clinical trial showed significant improvement in morbidity and mortality (Chertow et al. 2010; Rocco et al. 2011; Suri et al. 2007). In patients with normal kidneys, the blood is filtered for 168 hours a week. The advantage of a wearable system is that one could mimic the action of the continuous treatment of blood by the kidneys and gently filter the blood for waste solutes and water rather than compress this treatment into three hours, three times per week.

The requirements for such a device have been discussed by Ronco et al (2008) are: (1) that the device must be wearable and have its own power pack, (2) that the amount of dialysate required has to be minimal with online processing (sorbent system or small purification process that can be done by the patient, (3) that the patient should be able to wear the device and carry out all of his activities of daily life. Another application includes wearable ultrafiltration device that can treat patients with low cardiac output who suffer from congestive heart failure. In the initial experiments, a standard commercially available high flux polysulfone human filter was strapped to a belt and worn around the waist, with the total weight of 2.5 pounds (Davenport et al. 2007; Nissenson et al. 2005b). Blood flow was maintained at over 100 mL per minute and with an ultrafiltration rate ranging from 122-288 mL per hour (average 151 mmol of sodium remove during the treatment). In standard hemodialysis, rapid removal of fluid over just a few hours often results in severe hypotension and therefore and limits the capability of removing the fluid (Ronco et al. 2009; Ronco and Fecondini 2007). Because the wearable device is continuous over many hours and has a much lower rate of fluid removal, these devices work well with patients with cardiac failure.

There has recently been interest in a wearable artificial kidney using the peritoneal cavity (Ronco 2009). The dialysis process is begun with an infusion into the peritoneal cavity so that diffusion of blood toxins into the dialysate occurs. After this initial infusion of fluid, the device processes

the used dialysate through a sorbent cartridge. During reprocessing, the osmotic agent needs to be added back, and this is a technical challenge that has not been solved. The functional prototype at this time is only 1 kg, and this would appear to be a very reasonable size that could easily be worn by the patient, who is carrying around 2-3 liters in his abdomen at any one time. Technical problems and the cost of these devices will determine whether they are successful. There still remain major problems: the use of glucose as a osmotic agent, the possibilities that there are other substances such as plasma proteins that are needed to keep the peritoneum healthy, and the use of catheter in the peritoneal cavity. *These are however fertile areas for bioengineers to bring about innovations and improve patient lives.*

## 30.7 CONCLUSION

Inflammation from uremia, foreign body reaction to the dialysis catheter, and the use of bio-incompatible solutions cause peritoneal barrier alterations that result in dysfunction of the dialysis system. Engineers are developing new polymer materials to decrease protein adsorption and inflammatory cell binding to polymer materials; catheters of all types are an ongoing problem in acute and chronic care of patients. Research and development on additives that can be mixed with dialysis solutions to decrease inflammation may help to preserve the barrier. Inexpensive alternative osmotic agents that permit sufficient fluid removal but that are not toxic to the patient have yet to be developed. Continuous reclamation of dialysis fluid with a wearable peritoneal dialysis apparatus may preserve the barrier and provide dialysis that is closer to an "artificial kidney". This is a significant opportunity for bioengineers to assist clinicians in patient care that is minimally invasive on lifestyles. Finally, in the era of "personalized medicine", new findings in genomic medicine must be combined with phenotypic data and metabolic and proteomic studies with the discipline of computational biology to promote optimization of medical therapies, including peritoneal dialysis.

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## ESSAY QUESTIONS

1. What are the main factors affect the occurrence if inflammatory change in the peritoneum?
2. For what purpose Dextrose is used in peritoneal dialysis solutions? Comment on metabolic effects of glucose.
3. What are the major steps in a foreign body response?
4. Describe the time period and specify the material in the foreign body response to polymer catheters
5. Why does a replacement need to be found for glucose in the peritoneal dialysis fluid?
6. What is the most severe, acute inflammation of the peritoneum that sometimes requires removal and replacement of the catheter?
7. What are the major drawbacks to use of alternative osmotic agents that are not of endogenous origin?
8. How does a continuous, wearable, hemodialyzer reprocess the dialysis fluid?
9. Define Computational ("Systems") Biology.
10. What are the shortcomings of the wearable peritoneal dialyzer devices?

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. Inflammation in the peritoneum first begins:
   A. As the patient progresses in uremia
   B. At the placement of the catheter
   C. At the initiation of dialysis
   D. 1 year after dialysis initiation

2. Polymer biomaterials that set up a foreign body reaction are…
   A. Polymer tubing that drains the peritoneal cavity from the dialysis catheter
   B. Polymer bags containing the dialysis solution
   C. Polymer dialysis catheters
   D. Polymer drain bags

3. Polymer catheters induce inflammatory change in the rodent peritoneum within…
   A. 1 minute
   B. 1 day
   C. 1 month
   D. 1 year

4. Glucose is used in peritoneal dialysis solutions…
   A. To nourish the patient
   B. To produce an iso-osmotic solution
   C. To produce a hypertonic solution
   D. To produce a bio-compatible solution

5. Glucose degradation products…
   A. Help with the dialysis procedure
   B. Are necessary intermediates in dialysis
   C. Result from heat sterilization
   D. Interact with the polymer catheter

6. Newer, so-called, "biocompatible solutions" produced without GDP have been demonstrated to…
   A. Unequivocally improve dialysis in humans
   B. Markedly improve inflammation
   C. Improve nutrition
   D. None of the above

7. Foreign body reactions to catheters are thought to begin with…
   A. Binding of fibrinogen to the polymer
   B. Binding of macrophages to the polymer
   C. Release of cytokines from macrophages
   D. Release of chemokines from macrophages

8. The following does not contribute to inflammatory change in the peritoneum…
   A. Polymer catheter
   B. GDP in dialysis solution
   C. High salt concentration in solution
   D. Glucose in solution

9. The peritoneal cavity cannot be used as a…
   A. Stimulant for the lungs
   B. Delivery portal for chemotherapy
   C. Dialysis device
   D. Nutrition device

10. Wearable dialyzers have not been developed for which of the following…
   A. Peritoneal dialysis
   B. Hemodialysis
   C. To deliver nutrition to the patient
   D. To insure mobility of the patient

11. The challenge of the current wearable peritoneal dialyzer is…
   A. To reduce its weight
   B. To reduce its size
   C. To replace the glucose in the dialysis solution
   D. To replace the protein that is lost in the system

12. Correlating genetics with the patient outcomes in peritoneal dialysis is important…
   A. To predict how well the patient will do with a kidney transplant
   B. To predict the diseases that the patient will not have
   C. To predict the patient's nutritional need
   D. To predict how the patient will do on dialysis

13. Patient SNPs have been correlated with…
   A. Peritoneal transport
   B. Levels of cytokines in the blood and dialysate
   C. A and B
   D. None of the above

14. Personalized medicine would…
   A. Be predictive of the patient outcome
   B. Assist the physician in caring for the patient
   C. Allow the patient to choose alternative therapies
   D. All of the above

15. Amino acids in dialysis solutions…
    A. Help nourish the patient
    B. Substitute for glucose
    C. A and B
    D. None of the above

16. Which substance can substitute for glucose and produces a more sustained rate of fluid removal?
    A. glycerol
    B. icodextrin
    C. maltose
    D. albumin

17. To better simulate the kidney…
    A. Dialysis should be continuous
    B. Dialysis should be three times/week
    C. Dialysis should exchange with the urine
    D. Dialysis should remove protein from the blood

18. Single additives to dialysis solution to block an inflammatory pathway typically do not work well because of all but one of the following…
    A. Of the expense
    B. Of complex, multiple signaling pathways
    C. Of the innate immune system
    D. Of the adaptive immune system

19. Systems or Computational Biology is…
    A. Computerized biology of the immune system
    B. Genetic analysis of the patient
    C. Systems analysis of dialysis
    D. An integrative discipline

20. Potential areas for the bioengineer may involve…
    A. Computational biology
    B. Design of wearable dialysis apparatus
    C. Development of new dialysis catheters
    D. All of the above

# Part V

# Challenges and General Guidelines

Chapter (31)

# Present and Future Dialysis Challenges

Nestor Velasco, MD, FRCP

**CHAPTER OUTLINES**

- Historical Perspective
- Alternatives To Dialysis
- Dialysis Challenges
- Current Best Practice
- Addressing Main Challenges
- Research Challenges
- Conclusion

**CHAPTER OBJECTIVES**

- Give overview of renal replacement therapy goals
- Define scope of dialysis strengths and limitations
- Describe areas of clinical need priority
- Describe desirable future developments.

**KEY TERMS**

- Haemodialysis
- Peritoneal dialysis
- Haemodiafiltration
- Transplantation
- Dialysis frequency
- Experimental alternatives
- Wearable artificial kidney


## ABSTRACT

A brief historical review of the successful development of dialysis as treatment for replacing lost renal function is given here. A discussion on the short-comings of different dialysis treatments is followed by references to the merits and limitations of kidney transplantation, xeno-transplantation, of newer biological systems and of novel ideas and devices. A discussion on current unmet dialysis challenges includes the design of services suitable for an aging and frail population, quality of life and acceptability of treatments taking into account cultural social and individual diversity. A general review of current dialysis Best Practice includes references to national and international guidelines with the need for technical improvements in different modalities and variations of different therapies aimed at solving individual patient problems. The need for more attention


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and for better solutions to the problem of chronic fluid overload is presented with the place for new dialysis technology in addressing it.

## 31.1 HISTORICAL PERSPECTIVE

The original description of dialysis was made by Thomas Graham of Glasgow University in 1854 when he demonstrated the passage of urea and sodium from urine to the other side of a membrane made of an ox bladder. He coined the term dialysis and predicted that it would be used for treating renal failure (Graham 1854). Experiments with animal dialysis since 1889 (Richardson 1889) were helped by the development of collodion membranes and tubing in 1907 (Bigelow 1907) culminating in the first successful animal dialysis using collodion and anticoagulation with Hirudin derived from leeches by Abel et al published in 1914 at John Hopkins University School of Medicine (Abel et al. 1914). The first human hemodialysis was performed by Haas from the University of Giessen, Germany in 1924 (Haas 1925), but the first human haemodialysis that survived acute renal failure was treated by Kolff in 1943 (Kolff and Berk 1943) who introduced the rotating drum and used cellophane membranes (Kolff and Berk 1944).

Alwall modified the dialyzer and applied hydrostatic pressure to produce ultrafiltration, publishing his ideas in 1947 (Alwall 1947) and 1963 (Alwall 1963). The coil dialyzer was developed by Kolff in the mid 1950's (Kolff and Watschinger 1956) and by 1960 Kiil developed a low resistance flat dialyzer that did not require blood pump and could be re-assembled repeatedly (Kiil 1960). All these developments were rapidly adopted by different hospitals in America and Europe interested in the urgent need to improve the appalling survival of patients in acute kidney failure.

Since vascular access for dialysis was found to be increasingly difficult as patients arteries and veins were damaged by the procedures the development of dialysis for chronic kidney failure had to wait until 1960 when Quinton and Scribner developed their external arterio-venous shunt made of silastic allowing continuous circulation while not in use (Quinton et al. 1960) and thereafter Brescia and Cimmino developed their internal arterio-venous fistula (Brescia et al. 1966).

The dialysis industry was born and was responsible for much of the subsequent improvements and developments, including the design of disposable dialyzers and lines that would be proven safer, preventing transmission of viral diseases. Also the development of progressively sophisticated dialysis machines capable of preventing air embolism, facilitating and

minimizing anticoagulation needs, having volumetric controls that facilitate accurate fluid removal, computerized memory allowing access to individual patient history, as well as of auditing treatment standards of groups of patients, etc. The development of newer dialysis membranes capable of better clearances of uraemic toxins and more biocompatible also contributed to the current success of chronic dialysis programmes in operation in most countries in the world today.

## 31.2 ALTERNATIVES TO DIALYSIS

Patients reaching end stage renal failure (Chronic Kidney Disease CKD-5) can no longer maintain the various essential kidney functions like fluid balance, acid-base balance, removal of toxins, endocrine function, etc. with the immediate threat to their survival that the lack of those functions entails. If this failure happens rapidly like in Acute Kidney Injury (AKI) the survival is poorer even if treatment is instituted (Uchino et al. 2005). Frequently the reasons for having acute renal failure are also reasons for other systems and organs failing simultaneously and renal replacement therapy is only part of the solution to a wider problem that requires holistic management. Equally, chronic renal impairment is frequently complicated by intercurrent illness that can make critical demands to the failing kidneys that have lost their spare capacity to deal with this. These situations can bring the need for urgent and appropriate replacement of renal function to be established earlier than in the previously accepted plan. The management of situations like fluid overload treated with parenteral diuretics or like hyperkalaemia treated with cationic exchange resins is usually temporarily useful. Strict fluid and dietary restrictions although needed are not a substitute for dialysis in the long term.

Patients presenting early in their CKD-4 where there is enough time for planning and choosing the type of renal replacement could also receive pre-emptive renal transplantation avoiding the need for dialysis while having a better outcome (Meier-Kriesche and Schold 2005). Nevertheless most patients do require dialysis treatment for a period before renal transplantation, as the arrangements for transplantation are time-consuming and the patient has to be in optimal condition to stand this major surgical procedure. In the long-term successful renal transplantation remains the best current treatment to improve survival and quality of life (Schnuelle et al. 1998; Wolfe et al. 1999) and as such is likely to continue to be the obvious alternative to regular dialysis.

Renal transplantation has improved patients quality and possibly length of life, but is only partially available and suitable for no more than 40% of

advanced renal failure patients due to both limited kidney supply and unsuitable characteristics of potential recipients. The dangers of viral infections transmission across species have dampened the hopes for xeno-transplantation, and other biological processes of creating or harvesting suitable kidneys are still far from being available (Cascalho and Platt 2001)

Novel ideas for the treatment of acute kidney injury have included animal studies giving intravenous injections of modified cells producing SAA serum amyloid A protein. The recovery of kidney function was remarkable and those cells were found to be integrated into the architecture of healing tubules (Kelly et al. 2010). It is possible to contemplate future therapies involving administration of human cultured tubular cells or similar that might stop or retard the progression of renal disease significantly. Nevertheless unintended harmful results of therapies with cell injections can happen (Thirabanjasak et al. 2010) and this approach is still experimental.

### 31.2.1 Other New Experimental Technologies

As cultured human proximal renal tubular cells can now be produced in sufficient quantities they can be arranged on hollow fibre scaffolds and a renal tubule cell assist device (RAD) created. This was successfully tried in acute renal failure patients treated with veno-venous haemofiltration, improving metabolic and acid base balance. The use of this RAD for the treatment of acute kidney injury proved to be promising as it appeared to improve patient survival when compared with conventional renal replacement therapy alone (Tiranathanagul et al. 2005; Tumlin et al. 2008) Another new concept for renal replacement technology is the construction of very specialised membranes using nanotechnology with engineered pores capable of recognising and allowing passage to individual molecules only (Nissenson et al. 2005). These membranes with pores for all useful molecules can ensure that they are re-infused while others are discarded in the ultrafiltrate. There is no need for dialysate and there is hope that this continuous convective and portable treatment can also be small and wearable.

Recently a new prototype for a portable and wearable artificial kidney utilizing an adsorption cartridge was developed (Gura et al. 2006; Davenport et al. 2007; Gura et al. 2009a, b). It uses a hollow fibre dialyzer with continuously regenerated dialysate using cartridges with sorbents. The device is operated with batteries, weighs less than five pounds and is worn as a belt. It was successfully tried for several hours in eight patients and, although there were some problems with clotting and dislodging of a fistula

needle, it showed promise and future technical breakthroughs might make similar devices practical.

## 31.3 DIALYSIS CHALLENGES

Dialysis is the main form of renal replacement treatment for an increasingly older population of patients who depend on it for their survival but who also hope to enjoy good quality of life with as little interference from the treatment as is possible. Quality of Life (QoL) could be good in different groups of patients with end stage renal disease. Concerns for patients perception of the burden of disease and on overall patient satisfaction should be explored when new interventions are planned (Gayle et al. 2009). Chronic kidney disease patients, not yet on dialysis, already have impaired QoL when compared with healthy controls but still better than those on dialysis (Perlman et al. 2005). This health-related QoL can be an indicator of the effectiveness of the medical care, but is also dependent on the disease itself. There are physical, psychological and social factors determining QoL that require to be specifically addressed. Many studies have shown that treatment of anaemia and of depression can improve QoL independent of effects on hospitalisation or survival. Renal transplantation appears to have the best QoL when compared to haemodialysis or with peritoneal dialysis (Valderrábano et al. 2001). The challenge for the next decade will be to continue to devise interventions that meaningfully increase the QoL of patients with CKD at all stages (Kimmel and Patel 2006). The impact of well-meaning and well indicated interventions like over-prescription of phosphate binders on QOL has to be taken into account (Chiu et al. 2009). Encouraging behavioural changes to lifestyle could have a positive impact to QOL (van Vilsteren et al. 2005).

Although much progress has been achieved making dialysis safer and more acceptable to these patients, there are major challenges that continue to exist in this field including the relatively poor long-term patient survival. Although these renal patients constitute a heterogeneous population of people with different co-morbidities (some of which are associated with poor survival independent of the renal failure) there are reasons to believe that by improving dialysis quality it is possible to improve the outlook of many of these patients. Another challenge to finding a universally suitable form of treatment for chronic kidney disease is the diversity of cultural, social and individual situations that patients have and that affect the type of treatment available. For every one of the young independent and capable individuals that would flourish with self-delivered home dialysis there are many others that require assisted and supervised treatments. Different

configurations of health service providers try to respond to these needs minimising the ensuing personal and family problems like adequate transport, home care, etc. For these reasons it is unlikely that improved home systems of renal replacement therapy will alone be able to solve all these problems. A growing population of renal patients will remain dependent on intermittent dialysis for the foreseeable future.

## 31.4 CURRENT BEST PRACTICE

The success of dialysis therapy depends on multiple factors that require individual attention. National and international organizations like K/DOQI and European Best Practice have been created to define and obtain acceptable standards of renal replacement treatments. A continuous effort by leading researchers and acknowledged clinical experts is necessary to update these guidelines or recommendations. This set of standards has been made relevant and available to clinical workers (doctors, nurses, dietitians, etc) and its implementation has been aided by the presence of national and international renal registries. Although the epidemiology of renal disease is not easily separated from the epidemiology of the prevalent co-morbid conditions, this recording of treatments and outcomes has been helpful in improving the prognosis of patients receiving renal replacement therapy. Another function of organizations like the British Renal Registry is the annual publication of comparative results from different renal units in the country. As they are usually provided with similar resources it is possible to encourage healthy competition to achieve improvements in outcomes and accepted surrogate markers of health.

The National Cooperative Dialysis Study (NCDS) showed that for hemodialysis patients the timed urea concentration and protein catabolic rate (PCR) were associated to patient outcomes (Lowrie et al. 1981; Harter 1993). Emphasis was made in differentiating low pre-dialysis urea levels produced by good dialysis from those produced by insufficient protein intake and malnutrition.

Individualization of treatments was possible by urea kinetic modeling (Kt/V) that was introduced as a way of quantifying treatment prescribed and delivered. In this model the clearance of the dialyzer (K) is multiplied by the treatment time (t) and divided by the volume of urea distribution (V) of the individual patient. Another way of quantifying dialysis treatment is by calculating the Urea Reduction Ratio (URR) that although less accurate correlates with the Kt/V and is easier to calculate requiring only pre and post dialysis blood urea levels. This was accepted and integrated on the guidelines for treatment in most countries as a way to guarantee

minimal treatment levels (NKF-K/DOQI 2006; EBPG for hemodialysis 2002; Jindal et al. 2006) although under-treatment was also found to be heavily dependent on shorter times (Held et al. 1996).

HEMO was the largest prospective study designed to find the optimal dose of dialysis, but it had disappointing results, as not all those with higher Kt/V had better outcomes (Eknoyan et al. 2002; Depner et al. 2004; Port et al. 2004). There is no universal agreement about urea kinetics being the only way to measure adequacy of dialysis and the better outcomes of more prolonged or/and more frequent treatments despite equivalent Kt/V are an indicator of the need for continuing the search for better ways of prescribing individualised dialysis treatments (Kooistra et al. 1998; Keshaviah 1995; Cheng et al. 1998). Increasing dialysis time is probably more important than increasing the efficiency of dialysis per se but arrangements to allow the patients to have a non-over-medicalised existence are essential for their quality of life. This early concern leads to the establishing of daily home dialysis by Shaldon in the 1960's (Shaldon 1968). The better patient survival observed in the well-known dialysis French centre in Tassin (Charra et al. 1992) was associated with increasing dialysis times and frequency and this beneficial effect on survival has been observed in many centres advocating daily dialysis and nocturnal dialysis programmes (Udall et al. 1994; Saran et al. 2006). The challenges that some of these programmes present include the avoidance of over-treatment and depletion of nutrients and blood components like calcium and phosphate. Solutions to this problem have included both the supplementation of the deficiency (ies) (Ing et al. 1992; Al-Hejaili et al. 2003) and the reduction of the intensity of dialysis. As blood and dialysate flows are lower than in conventional dialysis there is less concern about under-treatment and systems like single-needle and central venous catheters are sufficient and recommended. All major manufacturers of dialysis machines have produced models suitable for daily home dialysis (Kjellstrand et al. 2004; Ledebo and Fredin 2004; Trewin 2004; Schlaeper and Diaz-Buxo 2004; Ash 2004; Kelly 2004) including the user friendly Nxstage system (see Fig. 30.1 and Fig. 30.2) that is truly portable incorporating disposable cartridges and a small water treatment (Clark and Turk 2004). An important challenge is providing safe systems for use at home by patients with only minimal supervision. The risks of major bleeding through accidental equipment or lines disconnection appears to have been minimised with the use of connection boxes, moisture sensors and enuresis pads triggering an alarm to the patient or by remote monitoring via internet or phone line (Pierratos 1999; Hoy 2001; Heidenheim et al. 2003) frequently while these patients are asleep.

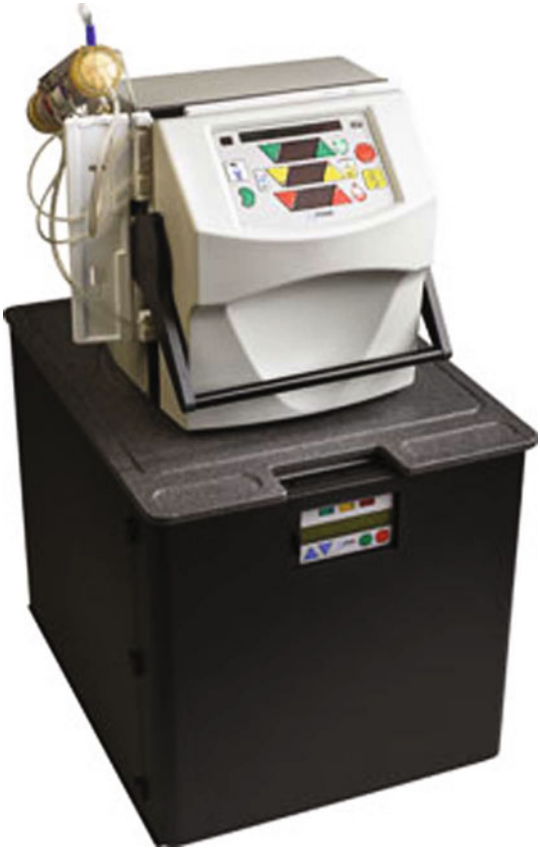

**Fig 31.1** "NxStage System One" a compact FDA approved home dialysis system shown over "Pureflow SL" system for production of high purity dialysate from tap water. [Adapted from NxStage Medical, Inc with permission].

**Fig 31.2** Patient working in his boat while dialyzing simultaneously. [Adapted from NxStage Medical, Inc with permission].

For peritoneal dialysis the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines recommend a weekly total solute removal in terms of $Kt/V_{urea}$ for CAPD of greater than 2.1 per week (Chatoth et al. 1999), but lower clearances have not necessarily worse outcomes as shown by the ADEMEX randomised prospective trial (Paniagua et al. 2002) that lead to lowering the recommended targets to more achievable weekly Kt/Vurea levels of 1.7 and 1.8 (Moran and Correa-Rotter 2006). Different modalities of delivering peritoneal dialysis either continuously or intermittently have been successfully and widely used. The automated nocturnal systems are an improvement facilitating treatment for many patients (Rabindranath et al. 2007; Michels et al. 2009; Mehrotra et al. 2009) and different variations with shorter dwelling times, such as tidal peritoneal dialysis (TPD) and continuous flow peritoneal dialysis (CFPD) are limited by the increasing cost of using more dialysate fluid (Dombros et al. 2005). The obvious advantage of APD over CAPD is the freeing of time for the patient to have more social activities or work.

While there is a clear need for expansion of these home hemodialysis programmes that have been proven successful in improving patient survival their cost-effectiveness has not been their only barrier to their expansion. The real or perceived difficulties in applying them to an increasingly older and frequently frail patient population has brought the growth of other intermittent forms of dialysis supervised or actually delivered by dialysis nurses and other suitably trained staff . The highest relative cost of in-hospital dialysis should not be paid for potentially independent patients or for others with low levels of dependence and there is a continuous

challenge to find alternative ways of delivering high-quality and low-cost treatments.

For many patients the use of intermittent haemodiafiltration (HDF) where the value of convective treatments is added to that of conventional haemodialysis has proven to be a convenient way of maximising therapy within the constraints of time. Although continuous or daily treatments, such as with normal kidneys, do not allow for the accumulation of fluid and toxins and are superior, they have the inconvenience of occupying large amounts of a patient's time. Unless treatments are done at home or during the night this could adversely affect their quality of life: "live in order to dialyze instead of dialyze in order to live". Any arrangements for in-centre delivered treatment have to take into account the considerable time wasted by the patients on the transport and waiting for transport before and after each dialysis frequent the reason for lack of satisfaction. This can limit the acceptable number of dialysis sessions to three times per week. Since time is precious for this group of patients there is some sense in trying to maximise the efficiency of each session while maintaining enough time to allow the safe removal of fluid , the normalisation of blood pressure and the achievement of validated metabolic and nutritional targets like phosphate levels (Velasco 2006). HDF has been favourably compared with conventional haemodialysis and the observational DOPPS study suggested a substantial improvement in survival of 35% when compared to HD (Canaud et al. 2006). Further prospective studies like the Convective Transport Study (CONTRAST) comparing HDF and low flux HD recently completed appeared to show better survival only to patients receiving more than 20 litres convection (Grooteman et al. 2011) while the Turkish HDF Study, comparing HDF and high-flux HD, also showed better outcomes for HDF only when substitution volume fluid were above 17.4 litres (Ok et al 2011) both studies were presented at ERA-EDTA XLVIII Prague June 24, 2011). Our own experience of converting all conventional HD patients to HDF in our centre has been associated to a marked improvement in 5 year patient survival and lower standardized mortality rate than comparative Scottish dialysis populations (Scottish Renal Registry Report 2009).

Not all dialysis systems or modalities would be suitable for all patients and through the life of a single patient different renal replacement systems are usually required. Combination of systems could also be used and variations or adaptations of those systems can make them suitable for individual patient needs. For instance developing home haemodialysis and peritoneal dialysis programmes where these treatments are delivered or supervised by a trained health worker rather than the patient or relatives have been successful (Assisted Peritoneal Dialysis APD) (Brown et al. 2007).

A North American prospective study on patient suitability for different treatment modalities showed that 98% of chronic kidney disease III and IV (CKD3-4) patients were considered medically eligible for haemodialysis (HD), 87% of patients were assessed as medically eligible for peritoneal dialysis (PD) and 54% of patients were judged medically eligible for transplant. Age was the leading cause of non-eligibility for both PD and transplantation (Mendelssohn et al. 2009). Although intermittent three times per week HDF is probably suitable for most if not all hemodialysis patients and it is also clear that other more frequent modalities should be considered for patients for whom this is acceptable and affordable. It is possible to envisage future technological breakthroughs that could make home treatments more widely used. There is a need for innovations that lower the complexity of the treatment from the patient point of view with user-friendly equipment and safer fool-proof procedures due to be developed.

## 31.5 ADDRESSING MAIN CHALLENGES

Successful haemodialysis requires continuous existence of suitable access to the circulation and this is not always possible to maintain throughout every patients life. Developing new surgical techniques and better materials remains a challenge for the foreseeable future. Equally, peritoneal dialysis requires a healthy peritoneum acting as a suitable membrane and there is a need for developing more bio-compatible dialysis solutions that preserve its function. Any developments that can reduce or abolish infection related to dialysis access would produce immediate clinical benefits and better patient survival.

The short-comings of dialysis are related to the failure to adequately replace the function of the normal kidneys. While understandably a lot of attention has been paid over the years to the replacement of the lost metabolic and endocrine functions of the diseased kidneys, comparatively less research has been done on the optimal ways to replace the lost ability to regulate fluid balance appropriately. Dialysis patients frequently die of cardiovascular diseases associated to hypertension, left ventricular hypertrophy, vascular calcification and accelerated atherosclerosis, all of which are produced or aggravated by chronic fluid overload. Robust dialysis systems that continuously address this recurrent problem are required in order to prevent the worsening of these disease processes and perhaps even inducing their regression. We have just completed a prospective study on the clinical benefits of using a novel semi-automated system for diagnosis and correction of subtle chronic fluid overload with very promising results

(Velasco et al. 2011a, b) although this field is ripe for further creative bio-engineering technical solutions.

The individualisation of treatments is more than likely the best solution for improving the quality of current treatments and improving patient survival. This would take into account regular data generated by the machines involved in dialysis, as well as by the individual patient responses with adjustments to the treatment. Online technology allows HDF, monitoring adequacy, etc, but future developments can expand the safety of dialysis systems to monitor and maintain adequate fluid balance as well. General improvements to treatment are possible like our adoption of a programme of Haemodiafiltration for All that has been responsible for lower rates of hypotension episodes and for improved pre-dialysis blood pressures (Spalding and Velasco 2008) obviating the need for the use of lower dialysate temperatures for patients with recurrent intra-dialytic hypotension. Semi-automation of fluid removal with computerised memory of previous treatments and records of patient tolerability coupled with regular measures of bioimpedance generated body composition can form the basis for delivering a more physiological dialysis treatment trying to replicate the role of the native kidneys. Short-term future improvements are based on current technology and therefore more realistic of being implemented. Other long-term developments to this individualisation are also required to make life for renal failure patients better and hopefully with comparable survival to the general population.

## 31.6 RESEARCH CHALLENGES

From the above discussions it is possible to see that there is a need for improving survival of the dialysis patients with new strategies that decrease the main causes of premature death like cardiovascular disease and infection. Some factors intrinsic to the dialysis process itself may contribute to this higher risk, examples are the failure of normalization of fluid overload and the increasing risk of acquiring infection via dialysis access. Research includes the development of technological answers to better patient monitoring and treatment strategies that go beyond the single dialysis session tolerability to the attaining of healthier mid and long term goals. The design and manufacturing of safer and simpler dialysis machines for home use remains a continuous challenge that when resolved would make home dialysis possible for many more patients with its decreased cost to society. There is obvious need for continuous research for the development of new surgical techniques and strategies to improve dialysis access and new materials to minimize and abolish thrombosis and infection. The

continuous support for exploring more experimental models above mentioned is required while maintaining the search for better and more available biological treatments like transplantation. Perhaps more importantly there is a pressing need for finding new ways to slow or stop the deterioration of renal function of CKD patients to limit the number of future dialysis patients.

## 31.7 CONCLUSION

This research into developing new forms of treatment discussed in this chapter should be centred on the solution to real patients' needs rather than be limited to the development of commercially viable modifications to current treatments. In a progressively better informed public and with a better worldwide communication among health care workers in this field of renal replacement therapy it is also possible to obtain rapid commercial success when a solution to a real and perceived need is demonstrated. While biological treatments like successful renal transplantation continue to appear superior it should not be forgotten that most end stage renal disease patients today are being kept alive by technological means like dialysis and that survival of those patients is comparatively better today than even a few years ago. As most general populations are now living longer and patients now can survive diseases that were once lethal, the population requiring renal replacement therapy is increasing in numbers and presents new challenges for improving their QoL and length of life.

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## ESSAY QUESTIONS

1. List four essential technical inventions necessary for the development of hemodialysis
2. List four systems that have replaced dialysis or have this potential.
3. List four reasons for one single dialysis system not being suitable for treating all patients?
4. Name two recognised organisations publishing consensus on dialysis standards.
5. What are the main factors in the prescription of dialysis affect clinical outcomes?
6. Name a method of quantifying dose of dialysis treatment
7. Name a way of controlling the cost of increasing dialysis duration and frequency?
8. Name a way of improving current in-centre dialysis
9. Describe a technological way to diagnose dialysis patients fluid overload
10. Name two areas of development to improve outcomes of dialysis patients.

## SELF-TEST QUESTIONS

**Mark the following statement as either True (T) or False (F)**

1. First dialysis treatments were developed first for chronic renal failure.
2. Human dialysis was tried before animal dialysis.
3. Dialysis procedures success was dependent on the development of anticoagulation.
4. Survival of acute renal failure patients is better than chronic renal failure.
5. Dialysis should be commenced as early as possible e.g. CKD3.
6. Successful kidney transplant has better survival than dialysis.

7. The transplantation of modified organs from animals could be immediately available.

8. Nanotechnology on hollow fibre scaffolds is required for Renal Tubule Assist Device (RAD).

9. Portable and wearable artificial kidney will be on sale in 2012.

10. Specially designed membranes could be permeable to selected blood proteins.

11. Wearable artificial kidney does not require anticoagulation.

12. Quality of Life of dialysis patients is superior to QoL of CKD 4-5 patients.

13. QoL of dialysis patients is not dependent on anaemia.

14. All dialysis patients should expect similar QoL and survival.

15. All dialysis patients should be treated at home.

16. Guidelines from K/DOQI and European Best Practice do not need updating.

17. All world dialysis units should have similar outcomes.

18. Shorter dialysis times are ideal if Kt/V is kept to a minimum.

19. High Kt/V does improve patient's outcomes.

20. HEMO Study showed conclusively Kt/V is not useful.

21. It is more important to increase the dialyzer efficiency than the time.

22. Poor patient survival with prolonged dialysis times was shown in Tassin (France).

23. Daily dialysis has better survival than thrice weekly.

24. Danger of over-treatment is present in daily dialysis.

25. Nocturnal daily dialysis requires higher blood flows.

26. Alarm systems are required for nocturnal home dialysis.

27. If Kt/V is less than 2.1 per week Continuous Peritoneal Dialysis (CAPD) should be abandoned.

28. Automated Peritoneal Dialysis (APD) demands more patient time than CAPD

29. Haemodiafiltration (HDF) can improve In-centre dialysis.

30. Transport to dialysis centres is a major cost concern.

31. High-volume HDF can have better patient survival compared to conventional HD.

32. All dialysis patients should be on HDF.

33. All dialysis patients should be suitable for transplantation.

34. Patient can use more than one modality of dialysis through time.

35. Thrice weekly HDF is superior to daily dialysis.

36. Adequate vascular access lasts for life for most patients.

37. Peritoneal dialysis fluids can damage the peritoneum.

38. Chronic fluid overload is not always easy to detect and can produce cardiovascular disease.

39. Bioimpedance body composition monitoring can be useful to detect fluid excess.

Chapter (32)

# Clinical Practice Guidelines in Nephrology

Thomas M. Kitzler and Nathan W. Levin

**CHAPTER OUTLINES**

- From randomized controlled trials to evidence-based medicine
- The development of clinical practice guidelines in nephrology
- From recommendation to implementation
- Conclusion

**CHAPTER OBJECTIVES**

- To outline the methods of evidence-based medicine
- To describe the development process of clinical practice guidelines
- To define what is quality of evidence and strength of recommendation
- To highlight the importance of clinical practice guidelines in clinical practice
- To describe the role and scope of clinical practice guidelines in nephrology
- To give an overview about the currently available standards to assure quality of dialysis therapy
- To describe the challenges to guideline implementation in nephrology

**KEY TERMS**

- Evidence-based medicine
- Clinical practice guidelines
- Quality of evidence
- Strength of recommendation
- Nephrology guidelines
- Dialysis standards

**ABSTRACT**

The pursuit of evidence for the effectiveness of medical interventions was an early characteristic of western medicine. The development of scientific methods to identify the most effective treatment modalities culminated in the concepts and paradigms of evidence-based medicine (EBM) in the second half of the 20th century. The premise of Archie Cochrane, a founder of EBM, that "all treatment must be proved to be effective" is still valid today. Meanwhile, the increasing awareness that many patients do

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not receive the best standard of care as determined by scientific evidence raised questions on how to better assist physicians in their clinical decision making. This brought the attention to clinical practice guidelines (CPGs), which include graded recommendations developed by experts based on the quality of the available scientific evidence. CPGs are considered one of the most potential tools in helping to improve patient outcomes by providing doctors and patients with information on best-practice standards. While previous approaches for guideline development were often based on tradition or authority, the recommendations found in modern best-practice guidelines are based on standardized methods for grading quality of evidence and strength of recommendation.

In Nephrology this has inspired the development of guidelines by different organizations. While this has certainly led to some improvement in patient care, the uncoordinated approach to guideline development has led to redundancy in some areas of kidney disease management. Therefore, a new initiative, Kidney Disease: Improving Global Outcomes (KDIGO), was founded in 2003 in order to globally coordinate and promote the development of CPGs in nephrology. However, despite the improvement in the development process, there still remain obstacles to the implementation of CPG recommendations.

## 32.1 FROM RANDOMIZED CONTROLLED TRIALS TO EVIDENCE-BASED MEDICINE AND CLINICAL PRACTICE GUIDELINES

*"Believe that with your feelings and your work you are taking part in the greatest; the more strongly you cultivate this belief, the more will reality and the world go forth from it."* – Rainer Maria Rilke

Medicine is defined as the science and art of healing. It is also the amalgamation of these two different avocations into one craft to which it owes much of its reputation as an imperfect science.

It has been reported that the first traces of evidence-based medicine (EBM) date as far back as to ancient Greece, however, it was the advent of decision theory in the mid-20$^{th}$ century, which stated for the first time that a formal statistical approach to clinical judgments could lead to the possibility of improved clinical decision making (Elstein 2004; Lusted 1968; Meehl 1954). It took another forty years, until the 1990s, before EBM was introduced to the medical community. EBM was initially defined in opposition to clinical experience, but later definitions have emphasized its complementary character, aiming to improve clinical experience with better

evidence (Timmermans and Mauck 2005). Based on sound scientific evidence, EBM sets itself to establish the most effective algorithms of clinical practice. One important tool of EBM in order to apply and implement these algorithms involves the use of clinical practice guidelines (CPGs).

### 32.1.1 An Overview of How It All Got Started

One of the first historical accounts of a primitive example of a controlled study is found in the bible in the book of Daniel on the comparison of rich vs plain diet: "*Daniel then said to the guard whom the chief official had appointed over Daniel, Hananiah, Mishael and Azariah, "Please test your servants for ten days: Give us nothing but vegetables to eat and water to drink. Then compare our appearance with that of the young men who eat the royal food, and treat your servants in accordance with what you see." So he agreed to this and tested them for ten days. At the end of the ten days they looked healthier and better nourished than any of the young men who ate the royal food."* From there it was still a long way until the development of the methodological framework defining a clinical randomized controlled trial (RCT) as we think of it nowadays.

The pursuit of evidence for the effectiveness of therapeutic interventions by making comparisons was an early hallmark of western medicine. Francesco Petrarca (1304 – 1374) an Italian scholar and one of the earliest humanists wrote in 1364 in his "Letter to Bocaccio" the following visionary words: "*I solemnly affirm and believe, if a hundred or a thousand men of the same age, same temperament and habits, together with the same surroundings, were attacked at the same time by the same disease, that if one half followed the prescriptions of the doctors of the variety of those practising at the present day, and the other half took no medicine but relied on Nature's instincts, I have no doubt as to which half would escape.*" (Harrison 2009). The foreseeing brilliance of his statement is underlined by his consideration of matching study groups based on their demographics and characteristics. But also within-patient comparison was an early method to assess effectiveness of different therapies. In 1575, the French surgeon, Ambrose Paré, noted the following observation: "*A German guard was very drunk and his flask caught fire and caused great damage to his hands and face, and I was called to dress him. I applied onions to one half of his face and the usual remedies to the other. At the second dressing I found the side where I had applied the onions to have no blisters nor scarring and the other side to be all blistered."* (Harrison 2009). Nevertheless, the method of choice was to compare in-between patients, and in 1662, JB Van Helmont was presumably the first to make a

suggestion for patient randomization by stressing the use of lotteries in order to make fair comparisons (Harrison 2009). The first prospective, controlled clinical trial was undertaken by the naval surgeon James Lind in 1747 and assessed the usefulness of citrus fruit as a treatment for scurvy. Another famous example is the methodical evaluation of the effectiveness of bloodletting, which was first challenged by the observations and reports from the surgeon John Clark.

Despite the advent of group comparison there was still a great deal of uncertainty regarding the design, conduct, and analysis of clinical studies. Further enlightenment came with the recognition that much illness was self-limiting and the appreciation of the influential effect of the patient's psychology on treatment outcomes. In the late 18th century this led to the introduction of "patient blinding", and in 1772, William Cullen, the renowned Edinburgh physician and lecturer, referred in his lectures to the use of placebos in medicine (Harrison 2009).

The next notable advancement in study analysis arrived in the 19th century with Pierre Louis, a Parisian physician, who is regarded as the founder of modern epidemiology. To him in order to evaluate facts it was necessary to enumerate them. This led him to apply "la methode numérique" to assess the clinical effectiveness of bloodletting, one of the first retrospective statistical approaches in evaluating the effectiveness of a medical therapy (Claridge and Fabian 2005; Rangachari 1997). From there it took less than a hundred years until the statistician Karl Pearson published in 1904 what is believed to be the first meta-analysis (the current mainstay of evaluating evidence), by reviewing seven studies on the effectiveness of a heat inactivated typhoid vaccine routinely used in the British army (Engels et al. 1998). The implementation of statistical methods in the evaluation of medical therapies eventually led to the study design, which is currently considered the gold standard in medical evidence: the double-blinded RCT. The first double-blinded RCT was conducted in 1946 and investigated the effectiveness of streptomycin treatment on pulmonary tuberculosis (Medical Research Council 1948). Later, it was Archie Cochrane's well-known "Effectiveness and efficiency" (1972) promoting the widespread use of RCTs. His maxim that "all treatment must be proved to be effective" has not lost any of its relevance in the twenty-first century.

Over the next decades, many decisive events like the development of decision theory in the 50s, the advent of new means of data collection in the 70s, and the concepts of peer review and quality assurance in the 80s, led to the development of the standards and methods of EBM. Eventually, it was a group of investigators around David Sackett from McMaster

University who first coined the term EBM, and who stated in 1996 the afterwards commonly cited definition that EBM is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al. 1996).

### 32.1.2 The Methods of Evidence-Based Medicine

The online Oxford dictionary defines evidence as "the available body of facts or information indicating whether a belief or proposition is true or valid". Evidence is called for when we are dealing with questions like "When is a theory true?" or "When is a theory acceptable?" However, it was Sir Karl Popper, the Austro-British philosopher, who was one of the first to question an approach solely based on these two questions. He recognized that many of the contemporary theories of his time (e.g. psychoanalysis of Freud or individual psychology of Adler) had one unifying characteristic when confronted by these questions, their *explanatory power*. He noted *"These theories appear to be able to explain practically everything that happened within the fields to which they referred.....you saw confirmed instances everywhere: the world was full of verifications of the theory. Whatever happened always confirmed it."* In other words, it was an easy task to filter out the evidence needed in order to support the belief system one belonged to. Karl Popper recognized that it was the way these theories were formulated that made them inaccessible to rigid scientific testing. Hence, he introduced a new school of thought and set out the cornerstones for how we develop and test scientific theories nowadays. In the 1930s Popper made falsifiability, the possibility that an assertion can be contradicted by an observation or the outcome of a physical experiment, a criterion of empirical statements in science. Consequently, he concluded that it is neither the theory nor the evidence that enables us to '*distinguish between science and pseudo-science*.', but rather the way a theory is formulated in order to make it accessible to scientific testing. (Stanford Encyclopedia of Philosophy). In light of this, EBM can be seen as an attempt to elevate medicine from the level of a pseudo-science to the level of a science; by adhering to the rigor of accepted scientific methods in order to produce sound scientific evidence, which can then be used by physicians to guide and justify their decision-making process.

#### 32.1.2.1 Randomized Controlled Trials vs. Observational Studies

RCTs are a form of clinical trial used to assess the safety and efficacy of a health care service (e.g. medicine or nursing) or of health technologies (e.g. medical interventions, surgeries, or diagnostic tests). In RCTs patients

are prospectively followed after random assignment to either the treatment group or the control group; thereby eliminating the bias of patient selection. Additional measures such as double-blinding (i.e. neither the investigator nor the patient is aware of who belongs to the treatment or to the control group) allow for a higher scientific rigor by reducing the influence of unconscious bias on therapy outcomes, such as placebo effect or observer bias. In comparison, an observational study draws inferences about the possible effect of a therapy on subjects based on historical data. The assignment of subjects to the treatment group and control group is outside of the investigators control. Moreover, the bias in patient selection for control groups has been reported to be responsible for the observed overestimation of treatment effects when compared with RCTs (Sacks et al. 1982). The belief in the scientific preponderance of RCTs has led some experts in their criticism of observational studies to say that 'If you find that a study was not randomized, we'd suggest that you stop reading it and go on to the next article" (Benson and Hartz 2000). Thus, RCTs are currently considered the gold standard for assessing the effectiveness of therapeutic agents (Abel and Koch 1999; Byar et al. 1976; Feinstein 1984). This is reflected in the development of CPGs where the available evidence is graded according to study design. The highest grade is reserved for "evidence obtained from at least one properly randomized controlled trial."

Notably, there is some recent literature reporting no significant difference in the estimation of treatment effects between well-designed observational trials and RCTs (Benson and Hartz 2000; Concato et al. 2000). Another study indicates good correlation between randomized and nonrandomized studies, however, differences in the estimation of the magnitude of treatment effects were found to be common (Ioannidis et al. 2001). Despite the notion that observational studies commonly produce results that are similar to those found in RCTs, this is not always the case (Atkins et al. 2004). A well known example is results from observational studies that suggested hormone replacement therapy decreased the risk of coronary heart disease in post-menopausal women, while subsequent RCTs found that there was no risk reduction and even an increase of risk (Hulley et al. 1998; Rossouw et al. 2002).

However, it must be mentioned that observational studies are a necessary and useful epidemiological tool to identify risk factors and prognostic indicators, and they can be conducted in situations where RCTs are either impossible or unethical (Naylor and Guyatt 1996). Sometimes, observational studies may provide even better evidence, as is generally the case for adverse effects, due to the high number of patients. Furthermore, their low costs make them an attractive means for independent investigators, even

more so in times where RCTs, due to their high costs, remain in the hands of research driven by pharmaceutical companies.

Lately, it has been recognized that RCTs may also give biased results if they lack methodological rigor (Juni et al. 2001; Schulz et al. 2010). Moreover, it has been shown that many reports of RCTs lack the necessary information and transparency in order for their readers to assess a trial accurately. This has inspired the development of the CONSORT (Consolidated Standards of Reporting Trials, http://www.consort-statement.org/) statement in 1996 (Begg et al. 1996). However, systematic reviews of the literature in the following years yielded that many trial reports remain incomplete in reporting transparent information on its methodology and findings (Begg et al. 1996; Chan and Altman 2005; Glasziou et al. 2008). The CONSORT 2010 statement includes a 25 item checklist and flow diagram, and provides guidance on how to report RCTs (Schulz et al. 2010). Notably, it does not contain any information on how to design, conduct, and analyze a randomized trial. The idea is to allow informed readers to assess the accuracy of an RCT by providing them, through a standardized reporting system, with all the necessary information.

#### 32.1.2.2 Systematic Reviews and Meta-analyses

The current mainstay in EBM in evaluating the available evidence is by the use of systematic reviews. It is important to distinguish systematic reviews from narrative reviews, which are also often published in medical journals, but since they only include a portion of the relevant studies in their evaluation they can potentially introduce bias (PLoS Medicine Editors 2007). A commonly used definition of a systematic review is found on the Web site of the Cochrane Collaboration (http://www.cochrane.org/resources/glossary.htm), which is named after Archie Cochrane the British medical researcher who was one of the first avid promoters of RCTs and a founder of EBM. Their definition is stated as follows: "A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies." A well performed systematic review is considered the highest level of evidence for medical decision making.

A meta-analysis is a statistical approach where the findings of several studies (e.g. from several RCTs) addressing a set of similar questions are combined into one analysis in order to assess the clinical effectiveness of a

healthcare intervention. This has the advantage of conferring greater statistical power since individual studies are often too small to demonstrate a statistical significant difference between two treatments. Furthermore, there is concern that in a narrative review studies demonstrating no significant difference between two treatments are more likely to be left out, whereas a meta-analysis that is carried out in a rigorous systematic review offers the advantage of an unbiased synthesis of empirical data, by also including studies that did not demonstrate any significant difference between treatments.

### 32.1.3 Why Do We Need Guidelines in Medicine?

Half a century ago the common belief was that "medical decisions were doing very well on their own" (Eddy 2005). It was well accepted "that through the rigors of medical education, followed by continuing education, journals, individual experiences, and exposure to colleagues, each physician always thought the right thoughts and did the right things. The idea was that when a physician faced a patient, by some fundamentally human process called the "art of medicine" or "clinical judgment", the physician would synthesize all of the important information about the patient, relevant research, and experiences with previous patients to determine the best course of action" (Eddy 2005). This assumption came into question in the early 70s when John Wennberg and his colleagues documented for the first time wide variations in health care practice patterns (Eddy 2005; Wennberg and Gittelsohn 1973). The implications of these findings were fundamental: "When different physicians are recommending different things for essentially the same patients, it is impossible to claim that they are all doing the right thing" (Eddy 2005). Further trials revealed that a large proportion of procedures performed by physicians were considered inappropriate by the standards of their own experts (Chassin et al. 1987). Only 15 percent of medical practices were based on solid clinical trials, and it is estimated that it takes on average 17 years for only 14% of new scientific evidence to enter day-to-day medical practice (Eddy 2005; Westfall et al. 2007).

This inspired the design of studies investigating the complexity of medical decision making. Soon it became evident that it is impossible for anyone to accurately process all of the needed and available information (Eddy 2005; Eddy 1984). Atul Gawande, the American physician and journalist, noted that "The ninth edition of the World of Health Organization's international classification of disease has grown to distinguish more than thirty thousand different diseases, syndromes, and types of injury – more than thirteen thousand different ways, in other words, that the body

can fail." This is also reflected in the increased amount of available scientific data on different treatment modalities. A recent report in 2007 estimated that the annual number of published systematic reviews is somewhere around 2,500 (Moher et al. 2007). It is simply impossible for any practicing physician to find the time to screen and analyze all the relevant studies and literature in order to identify for his patients the best available treatment options based on the most solid scientific evidence. Moreover, there is actually no indication that the passive dissemination of scientific evidence, in the form of meta-analyses and systematic reviews in medical journals, without accompanying practical recommendations, leads to any significant changes in clinical practice patterns (Weingarten 1999). This notion drew attention to the role and development of CPGs and the way they could help to influence and guide physician-patient decisions.

The Institute of Medicine defines CPGs as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Sackett et al. 1996). Thus, practice guidelines based on the methods and scientific rigor of EBM intend to provide strong scientific evidence to achieve consistency, effectiveness, and safety in medical care. This can be applied to virtually any aspect of clinical practice: from when and how to order diagnostic tests, to when to provide a certain medical service.

It is important to mention at this point the impact of EBM and CPGs on the ever changing character of the physician-patient relationship. From its early beginnings this relationship was characterized by its static patriarchal nature, where the "unknowing" patient had to cooperate with the "all-knowing" doctor and follow his instructions. The realization of physicians' limitations in medical decision making and the subsequent development of CPGs have helped to define a more modern emancipated version of this relationship. The nowadays easily accessible information of CPGs enables patients to assume a more active role in the medical decision making process. This concept is sometimes referred to as patient empowerment, and aims at providing patients with the information needed to actively engage them in their health management.

Identifying unnecessary/ineffective procedures, interventions, and diagnostic tests, and making this information available to physicians and patients, will not only allow us to cut down on unnecessary health-care spending in a time of limited resources; but even more important, it will help to protect our patients from unnecessary suffering. With an increasing number of studies demonstrating that patients receive inappropriate or in some cases even detrimental care, mostly due to the "overuse",

"underuse", or "misuse" of care, evidence-based CPGs are considered as one of the most promising and effective tools for improving the quality of patient care (Bodenheimer 1999; Grol 2001; Schuster et al. 1998).

In conclusion, the promotion of CPGs can help to:

- Reduce the variation in accepted clinical practices (e.g. underutilization of treatments of demonstrated efficacy, overutilization of ineffective treatments).
- Help to reduce the currently escalating health care costs, and to improve the use of limited resources.
- To reduce the inequality in health care access.
- Help physicians to oversee and judge the usefulness of the rapidly increasing number of diagnostic and therapeutic options.
- Identify gaps in clinical knowledge. This is based on the increased awareness of the cognitive limitations of experts, who are facing an increasing body of conflicting information.
- Improve health care quality and accountability.
- To improve patient-physician relationships through patient autonomy and empowerment.

## 32.2 THE DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES IN NEPHROLOGY

Nephrology is facing the same challenges as other medical specialties. The ever increasing number of available treatments and diagnostic techniques, combined with an exponential increase in the number of publications, make it difficult for busy practitioners to keep an overview of the best scientific evidence available to assist them in their clinical decisions. This has inspired the formation of several organizations dedicated to develop CPGs with recommendations for specific areas of kidney disease management.

### 32.2.1 Guideline Organizations in the Field of Nephrology

The first set of evidence-based CPGs in nephrology was developed in 1993 in the United States by the Renal Physicians Association and stated how to deliver the minimum dose of hemodialysis and how the delivered dose should be measured (Hornberger 1993). In 1995 the National Kidney Foundation (NKF, http://www.kidney.org/) launched its Dialysis Outcome Quality Initiative (DOQI), which led to the publication of the first broadly accepted CPGs in nephrology in 1997. The first guidelines covered four

areas of kidney disease management: hemodialysis adequacy, peritoneal dialysis adequacy, vascular access, and management of anemia (Eckardt and Kasiske 2009). The development of these initial guidelines by the NKF had been enabled through an educational grant from Amgen. In 1996, the pharmaceutical company approached Dr. Nathan Levin, later with Dr. Garabed Eknoyan, who both became the first two co-chairs of the initiative, in conjunction with the US National Kidney Foundation and asked them to initiate and direct the development of CPGs for kidney disease management. At first, the circumstance that the guideline development was supported by funding from the industry created some uneasiness among other experts. However, soon it was recognized that the DOQI program represented the first attempt to give evidence-based guidance to clinical care teams and to reduce variability in practice patterns in the over 3,100 dialysis facilities in the United States. Moreover, the implementation of concrete standardized plans with a measurable impact on quality of life of dialysis patients also allowed assessing their effectiveness in clinical practice. The favorable impact of these guidelines on the quality of care delivered to dialysis patients in the United States has been well studied and documented (Collins et al. 2002). Later, guideline development was extended to the care of patients with non-dialysis-dependent kidney disease (i.e. chronic kidney disease), which led to the start of a new program named Kidney Disease Outcomes Quality Initiative (KDOQI) in 1999. The first set of new guidelines was published in 2002 (K/DOQI Workgroup 2002). To this day, KDOQI has published guidelines in 13 areas of kidney disease management and they have been translated into at least 10 languages.

In 1999, the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA, http://www.era-edta.org/) introduced the initiative for the European Best Practice Guidelines (EBPG). In January 2008 the name of the initiative was changed to European Renal Best Practice (ERBP). The mission statement found on their website is "to help to increase the visibility and implementation of European Nephrology recommendations and guidance and to enhance the quality of European and worldwide nephrology practice." Their guidelines are divided into the areas of clinical nephrology, hemodialysis, peritoneal dialysis, and transplantation. Around the same time the Council of the Australian and New Zealand Society of Nephrology (ANZSN) and the Board of Kidney Health Australia (KHA) launched their project named Caring for Australians with Renal Impairment (CARI, http://www.cari.org.au/), which led to the formulation of the CARI guidelines. The CARI guidelines cover areas of chronic kidney disease, hemodialysis, and transplantation. Guidelines for

kidney disease management are also found in Canada from the Canadian Society of Nephrology (CSN, http://www.csnscn.ca/), and from the United Kingdom Renal Association (UK-RA, http://www.renal.org/). Additional English language guidelines were developed, and in several other countries, clinical practice guidelines were developed in local languages (Eckardt and Kasiske 2009).

Soon it became apparent that there was need for a more uniform and global approach to the whole process. The uncoordinated development of guidelines by various organizations has resulted in redundancy of CPGs in some areas of kidney disease management. For example, it has been reported that between 1998 and 2000 more than 10 CPGs on the management of anemia in patients with chronic kidney disease were published in the English language; in areas that are less attractive from a commercial perspective, but are equally or even more important from a clinical point of view, fewer guidelines were developed (Eckardt and Kasiske 2009). Moreover, the association of some work group members with the industry has created some concern regarding the objectivity of guideline development. All of this, together with the sometimes limited available evidence, on which guideline recommendations are based on, raised considerable concerns about the process of guideline development. Nevertheless, the mounting data mapping the epidemic proportions that kidney disease reaches throughout the world highlight the importance of a global initiative for CPG development in kidney disease management. These circumstances have led in 2003 to the foundation of Kidney Disease: Improving Global Outcomes (KDIGO, http://www.kdigo.org/).

KDIGO is a non-profit organization incorporated under Belgium law and independent of established professional medical associations. The independent organization has the explicit mission "To improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines", with the aim to develop more CPGs and to coordinate the development of CPGs by different international organizations in kidney disease management (Eckardt and Kasiske 2009).

### 32.2.2 A Global Approach to Develop Clinical Practice Guidelines

#### 32.2.2.1 International Work Groups on the Search for Evidence

KDIGO is led by an international board of directors with approximately 50 board members. Most are practicing nephrologists, but there are also participating patient representatives and clinical experts from overlapping

disciplines (Eckardt and Kasiske 2009). The board of directors elects an executive committee, which is co-chaired by two elected board members, which are responsible for planning and overseeing all of KDIGO's activities. All positions are rotated and a nominating committee proposes new members for the board of directors, the executive committee, and the co-chairs.

The KDIGO guidelines are developed by independent, international, multidisciplinary work groups comprising 15-20 voluntary members, led by two co-chairs. The executive committee appoints and oversees the composition of these work groups. They usually include practicing nephrologists, experts in pediatric nephrology and representatives of relevant non-nephrology disciplines (e.g. cardiology). Since the search for relevant publications and data extraction is a time-consuming process, requiring specific training and expertise, KDIGO decided to contract the Evidence-based Practice Center (EPC) of the Tufts New England Medical Center in Boston, MA, USA (Eckardt and Kasiske 2009). The EPC "produces evidence reports based on systematic reviews and other analyses such as decision/cost-effectiveness analyses. The analyses critically appraise, summarize, and synthesize the results of all studies that have addressed a similar clinical research question" (http://www.ahrq.gov/clinic/epc/nemcepc.htm). The Tufts Medical Center EPC consists of a broad range of clinical and methodology experts which collaborate with other organizations. The qualifications and experience of EPC members are listed on their website as follows:

- Meta-analysis
- Biostatistics
- Decision analysis
- Cost-effectiveness analysis
- Predictive modeling
- Consumer education
- Managed care decision-making

The evidence review team interacts and collaborates with each work group throughout the whole development process. Furthermore, it teaches the work groups, including their chairs, about the methods of evidence-based guideline development. An integral part of KDIGO's guideline development process, and a clear distinction from other guideline organizations, is an open, public review. After the evidence review team extracted the data from the relevant literature, the KDIGO work groups review the evidence they are provided with and develop an advanced draft of a guideline, which is then discussed by the KDIGO board of directors.

The questions and comments derived from this review are integrated into the next draft guidelines and are submitted for external review. KDIGO invites individual experts for review, but any interested individual can volunteer to participate after registration through the KDIGO website. The comments derived from the external review process are forwarded to each work group member for guideline completion. Usually, the work groups develop a guideline within a minimum period of 1.5 years, during which the members meet at least three times in person and communicate on a regular basis through teleconferences and email (Eckardt and Kasiske 2009).

Ideally, recommendations should be free of bias, but recent evidence suggests that they are not (Hirsh and Guyatt 2009). Since the introduction of CPGs, much concern has been raised regarding the ties to the pharmaceutical industry by some of the participating work group members. In fact, most contributing authors declare some sort of potential conflict of interest, due to some form of involvement with the industry, such as honoraria for consultation, speaking engagements, or research support (K/DOQI Workgroup 1997). Thus far, no commonly accepted solution has been found on how to assure that potential conflict of interest of some work group members does not sway the guideline development process. KDIGO decided to tackle this problem by applying stringent rules of openness and transparency, requiring all work group members to declare their industry relationships (Eckardt and Kasiske 2009). The declarations are stored at the KDIGO offices and are available at all KDIGO meetings. They are also summarized in each guideline document.

#### 32.2.2.2 The Quality of Evidence and Strength of Recommendation

The grading of quality of scientific evidence represents a cornerstone in CPG development. Quality of scientific evidence has been described as the extent to which "one can be confident that an estimate of effect or association can be correct." This is based on the likelihood that further targeted research would not change confidence in the estimate (Uhlig et al. 2006). Unfortunately, expert clinicians as well as organisations giving out recommendations to the medical community have often erred as a result of not taking sufficient account of the quality of evidence (Guyatt et al. 2008). For example, based on the recommendations made by their professional organizations, clinicians encouraged postmenopausal women for more than a decade to use hormone replacement therapy (American College of Physicians 1992; Guyatt et al. 2008). These recommendations were based on data from observational studies which suggested that such therapy substantially decreases postmenopausal women's cardiovascular risk.

However, it has been shown that if the development process of these practice guidelines would have included an approach taking into account the quality of the available evidence, the low quality of data coming from these observational studies would have most likely hampered the development of such recommendations (Guyatt et al. 2008; Humphrey et al. 2002). Eventually, several well designed RCTs demonstrated that hormone replacement therapy not only fails to reduce cardiovascular risk, it even increases it (Guyatt et al. 2008; Hulley et al. 1998; Rossouw et al. 2002).

A similar problem occurred when the US Food and Drug Administration licensed the two antiarrhythmic drugs, encainide and flecainide, based on data demonstrating their ability to reduce asymptomatic ventricular arrhythmias associated with sudden death. However, Guyatt et al. noted correctly that "This decision failed to acknowledge that because arrhythmia reduction reflected only indirectly on the outcome of sudden death the quality of the evidence for the drugs' benefit was of low quality" (Guyatt et al. 2008). Later, a RCT demonstrated that the two licensed drugs increase the risk of sudden death, which led Guyatt et al. to conclude that "Appropriate attention to the low quality of the evidence would have saved thousands of lives" (Echt et al. 1991; Guyatt et al. 2008). But history has shown that it is not only inattention to the low quality of evidence that may prevent patients from unnecessary suffering, it is also the "failure to recognize high quality evidence", which may prevent patients from receiving a higher standard of care (Guyatt et al. 2008). A good example was the failure of experts to recognize the high quality evidence, available through the combined analysis of several well conducted RCTs, showing effectiveness of thrombolytic therapy for the prevention of myocardial infarction (Antman et al. 1992). Many of the individual trials failed to show a statistically significant difference between the standard of care and the use of thrombolytic therapy, however, when the results of these trials were analyzed in a combined approach (i.e. meta-analysis), a significant benefit of the treatment in form of a reduction in mortality could be shown (Antman et al. 1992). Had a meta-analysis been conducted at an earlier stage, patients would have profited much earlier from the benefits of thrombolytic therapy. These examples highlight the importance for a guideline development process based on an approach grading the quality of the available scientific evidence.

The quality of evidence (e.g. RCTs vs. observational studies) in combination with other effects (e.g. appreciable harms, burdens, or costs) entails the graded strength of recommendation regarding a specific healthcare intervention. In other words the strength of recommendation indicates "the extent of the grader's confidence that adherence to the recommendation

will do more good than harm." This should give assistance to clinicians, when offering their treatments, to weigh up the desirable and undesirable effects according to the patients values and preferences.

Therefore, CPGs and recommendations must not only be based on, but also clearly indicate if (Guyatt et al. 2008):

1. the evidence is of high quality,
2. the desirable effects clearly outweigh the undesirable effects, or if
3. there is a close or uncertain balance between desirable effects and undesirable effects.

Limitations to this approach are "that quality of evidence and the balance of desirable and undesirable effects are a continuum and any discrete categorisation involves some degree of arbitrariness" (Guyatt et al. 2008). However, most organizations producing guidelines have agreed upon that the benefits of an explicit and transparent grade of recommendation outweigh the disadvantages.

#### 32.2.2.3 KDIGO Guideline Development Process: Implementation of the GRADE Methodology

*"Clinical guidelines are only as good as the evidence and judgments they are based on" – GRADE Working Group*

A systematic and explicit approach on grading evidence and making judgments can help to reduce errors, facilitate their critical appraisal, and can help to improve communication (Atkins et al. 2004). Since the 1970s an increasing number of systems for grading the quality of evidence and strength of recommendation have been developed and employed (Atkins et al. 2004; Briss et al. 2000; Eccles et al. 1996; Greer et al. 2000; Guyatt et al. 1995; West et al. 2002). Hence, there is great inconsistency in how guideline developers worldwide grade quality of evidence and strength of recommendation. For example, the grading systems used in the development of nephrology guidelines demonstrate considerable variation (Uhlig et al. 2006). Therefore, the KDIGO Board of Directors commissioned in 2004 an evidence-rating group composed of individuals with expertise in nephrology, CPG development, and systematic review of literature to develop a uniform grading system for use in developing guidelines for patients with kidney disease (Uhlig et al. 2006). The evidence-rating group identified the specifications for an ideal system for grading quality of evidence and strength of recommendation related to nephrology (see Table 32.1).

**Table 32.1** Specifications for an ideal system for grading evidence and recommendations related to nephrology (Uhlig et al. 2006).

| |
|---|
| *Supports the user in making well-informed decisions* |
| Simple and easily understood |
| Explicit and transparent system of grading |
| Comprehensive evaluation of quality of evidence, not only study design |
| Incorporates evaluation of all important clinical outcomes |
| Explicit consideration of balance between benefits and harms |
| Applicable when grading evidence in the nephrology domain |
| Consistent with grading systems in other specialities |
| Applicable to a range in clinical questions and types of evidence |

Next, the evidence-rating group reviewed several grading systems and decided that KDIGO would adopt the grading system developed by the GRADE (Grades of Recommendation Assessment, Development and Evaluation) working group (Atkins et al. 2004). The GRADE working group started out in 2000 and its mission statement found on the official website (http://www.gradeworkinggroup.org/) is to "develop a common, sensible approach to grading of quality of evidence and strength of recommendation." The idea is to have one single system that "should avoid shortcomings of other systems and include their strengths." The advantages of the GRADE system over other systems have been summarized as follows (Guyatt et al. 2008):

- Developed by a widely representative group of international guideline developers.
- Clear separation between quality of evidence and strength of recommendation.
- Explicit evaluation of the importance of outcomes of alternative management strategies.
- Explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings.
- Transparent process of moving from evidence to recommendations
- Explicit acknowledgement of values and preferences.
- Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers.
- Useful for systematic reviews and health technology assessments, as well as guidelines.

The GRADE system assists guideline developers by clearly outlining the most crucial steps for developing CPGs (see Table 32.2).

**Table 32.2** Sequential steps of developing CPGs according to GRADE (Atkins et al. 2004; Uhlig et al. 2006).

| | |
|---|---|
| **Step 1:** | *Establishing the process* – Prioritization of problems and definition of key questions to be addressed. Selection of guideline group, agreement of group processes. |
| **Step 2:** | *Systematic review* – Prepare systematic reviews of the best available evidence for all important outcomes. Formulation of good questions, identification of important clinical outcomes including harms. |
| **Step 3:** | *Prepare evidence profile for important outcomes* – Preparation of evidence profiles: for each patient subgroup, profiles are prepared based on the results of systematic reviews which tabulate the summary of findings for each relevant outcome and appraise design and methodological quality of studies, consistency, and directness of the evidence as well as other modifying factors. |
| **Step 4:** | *Quality of evidence for each outcome* – Grading the quality of evidence for each clinically important outcome. Based on criteria in Table 32.3 |
| **Step 5:** | *Relative importance of outcomes* – Weighting relative importance of each outcome: ranking of importance of outcomes as 'critical', or 'important, but not critical'. |
| **Step 6:** | *Overall quality of* evidence – Grading the overall quality of evidence across all important outcomes. Consideration of the quality of the evidence for each important outcome in view of the relative importance of each outcome. |
| **Step 7:** | *Balance of benefits and harms* – Assessment of the net health benefit across all important clinical outcomes. |
| **Step 8:** | *Balance of net benefits and costs* – Review of other considerations, including costs, in addition to net health benefit and quality of the evidence. |
| **Step 9:** | *Strength of recommendation* – Formulation of a guideline recommendation and grading the strength of the recommendation based on the level of confidence, that adherence will do more good than harm. See Table 32.4 |
| **Step 10:** | *Implementation and evaluation* – Using effective implementation strategies that address the barriers to change, evaluation of implementation, and keeping up to date |

GRADE, Grades of Recommendation Assessment, Development, and Evaluation.

#### 32.2.2.3.1 Grading Quality of Evidence and Strength of Recommendation According to the GRADE Approach

One more advantage of the GRADE system is the clear separation of grading the quality of evidence from the strength of recommendation. The quality of evidence for each important clinical outcome is graded according to the steps outlined in Table 32.3.

When performing a systematic review of the available evidence the reviewers should consider four key elements in their evaluation: (1) study design, (2) study quality, (3) consistency, and (4) directness (Atkins et al. 2004):

1. Study design refers to the basic study design, which is broadly categorized as observational studies and RCTs.
2. The study quality refers to the detailed study methods (e.g. for a meta-analysis the adequacy of blinding and follow up).
3. Consistency refers to the similarity of estimates of effect across studies. Important unexplained inconsistency decreases the confidence in the estimate of effect.
4. Directness is described as the extent to which the people, interventions, and outcome measures are similar to those of interest.

By combining the above four elements the quality of evidence is determined for each main outcome. The levels for the quality of the evidence are (Atkins et al. 2004):

- **High** = Further research is very unlikely to change confidence in the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- **Very low** = Any estimate of effect is very uncertain.

For example, the quality grade for an aggregate of RCTs starts at the entry level of ‘high’, whereas the evidence derived from several observational studies starts at the entry level of ‘low’. Evidence from studies of other designs, such as case-control studies, is ranked at the entrance level ‘very low’. In the next steps of evaluating the quality of evidence for a particular outcome, the level of quality can either be *downgraded* (in case there are limitations to the methodological quality of the studies, inconsistencies between studies, imprecise or sparse data, or a high probability of reporting

bias) or *upgraded* (in case there is evidence of a strong or very strong association between the intervention and the outcome, a dose-dependent gradient, or if unmeasured confounders would have reduced the effectiveness of an intervention) (Uhlig et al. 2006).

**Table 32.3** GRADE system for grading the quality of evidence (Atkins et al. 2004; Uhlig et al. 2006).

| **Step 1: Starting grade quality of evidence based on study design** | **Step 2: Reduce grade** | **Step 3: Raise grade** | **Final grade for quality of evidence and definition** |
|---|---|---|---|
| Randomized trials=high<br><br>Observational study=low<br><br>Any other evidence=very low | *Study quality*<br>-1 level if serious limitations<br>-2 levels if very serious limitations<br>*Consistency*<br>-1 level if important inconsistency<br><br>*Directness*<br>-1 level if some uncertainty<br>-2 levels if major uncertainty<br>-1 level if sparse or imprecise data<br>-1 level if high probability of reporting bias | *Strength of association*<br>+1 level if strong*, no plausible confounders<br>+2 level if very strong**, no major threats to validity<br>+1 level if evidence of a dose-response gradient<br><br>+1 level if all residual plausible confounders would have reduced the observed effect | High=Further research is unlikely to change confidence in the estimate of the effect<br><br>Moderate=Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate<br><br>Low=Further research is very likely to have an important impact on confidence in the estimate and may change the estimate<br><br>Very low= Any estimate of effect is very uncertain |

GRADE, Grades of Recommendation Assessment, Development, and Evaluation.

* Strong evidence of association is defined as 'significant relative risk of > 2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.

** Very strong evidence of association is defined as 'a significant relative risk of > 5 (<0.2)' based on direct evidence with no major threats to validity.

Eventually, the consideration of factors, such as the baseline risk of the population, features of particular practice settings, availability of the service, the accessibility to care, and the costs of an intervention, in combination with the quality of evidence entails the strength of a recommendation (Table 32.4) (Uhlig et al. 2006). This process involves an evaluation of the trade-off between benefits and harms. The GRADE Working Group suggests the following definitions to categorize the trade-offs:

- **Net benefits** = the intervention clearly does more good than harm.
- **Trade-offs** = there are important trade-offs between the benefits and harms.
- **Uncertain trade-offs** = it is not clear whether the intervention does more good than harm.
- **No net benefits** = the intervention clearly does not do more good than harm.

Eventually, the following four factors should be considered before making a recommendation: (1) the trade-offs, (2) the quality of the evidence, (3) the translation of the evidence into practice in a specific setting, and (4) the uncertainty about the baseline risk of the population of interest. The strength of recommendation can range from 'strong' (i.e. 'We recommend you do it.' for a positive recommendation or 'We recommend you do not do it.' for a negative recommendation) to 'weak' ('We suggest you do it' or 'We suggest you do not do it') (Guyatt et al. 2006). Also, according to the GRADE approach a guideline development group can reach the conclusion that a recommendation cannot be issued in case the net health effect is unclear, or if the potential benefits are outweighed by the costs.

#### 32.2.2.4 The Scope of Guidelines in Kidney Disease Management

KDIGO has built up on the previously developed guidelines by other organizations (e.g. CARI, CSN, UK-RA, EBPG, and KDOQI). As mentioned before, due to the initially uncoordinated approach of guideline development there is currently a redundancy of guidelines in some specific areas of kidney disease management (e.g. anemia management), while in other areas there is a lack of good practice recommendations (e.g. acute kidney injury). The goal of KDIGO is to coordinate the overall process by continuously updating existing guidelines and promoting the development of guidelines in new areas, but also by inhibiting the development of guidelines in areas where there is currently not enough new quality

**Table 32.4** Strength of guideline recommendations, consensus-based statements, and linkage to quality of evidence (Atkins et al. 2004; Uhlig et al. 2006).

| Recommendation or statement | Description in GRADE approach | Prerequisite | Assumption | Implication |
|---|---|---|---|---|
| Strong guideline recommendation | We recommend (should) | The quality of the evidence is 'high' and other considerations support a strong recommendation | Most well-informed individuals will make the same choice (Atkins et al. 2004) | The expectation is that the recommendation will be followed, unless there are compelling reasons to deviate from the recommendation in an individual |
| Weak guideline recommendation | We suggest (might) | The quality of evidence is 'high' or 'moderate', and other considerations support a 'weak' recommendation | A majority of well-informed individuals will make this choice, but a substantial minority may not (Atkins et al. 2004) | The expectation is that consideration should be given to follow the recommendation |
| Consensus-based statement | Not applicable | The quality of the evidence is 'low', 'very low', or absent. This is a consensus based on expert opinion, supported in the public review of the statement | | The expectation is that consideration should be given to follow the statement |

GRADE, Grades of Recommendation Assessment, Development, and Evaluation

evidence available to improve existing practice recommendations. The current scope of guidelines covers 18 areas of kidney disease management (see Table 32.5).

**Table 32.5** Scope of guideline topics in the field of kidney disease (Eckardt and Kasiske 2009).

| Guideline topics | Publication year | | |
|---|---|---|---|
| | DOQI/KDOQI* | EBPG* | KDIGO |
| ***Syndromes*** | | | |
| CKD evaluation, classification and stratification | 2002 | - | 2012 |
| Acute kidney injury | - | - | 2011 |
| ***Specific disease*** | | | |
| Chronic glomerulonephritis | - | - | 2011 |
| ***Renal Replacement therapy*** | | | |
| Hemodialysis | 1997, 2006 | 2002, 2007 | - |
| Vascular access | 1997, 2006 | 2007 | - |
| Peritoneal disease | 1997, 2006 | 2005 | - |
| Care of the kidney transplant recipient | - | 2000, 2002 | 2009 |
| ***Comorbidities, specific treatment aspects*** | | | |
| Anemia | 1997, 2001, 2006, 2007 | 1999, 2004 | 2012 |
| Bone and mineral metabolism | 2003 | - | 2009 |
| Bone and mineral metabolism in children | 2005 | - | - |
| Hypertensive and antihypertensive agents | 2004 | - | 2012 |
| Cardiovascular disease | 2005 | - | - |
| Hemodynamic instability on hemodialysis | - | 2007 | - |
| Dyslipidemia | 2003 | - | 2013 |
| Nutrition | 2000 | 2007 | - |
| Nutrition in children | 2008 | - | - |
| Diabetes | 2007, 2011 | 2012 | - |
| Hepatitis C | - | - | 2008 |

* For simplification only previous guidelines by DOQI and/or KDOQI in the US and EBPG in Europe are included in addition to KDIGO guidelines. Table has been adapted from the original.

### 32.2.3 Quality Assurance in Dialysis

One important aspect of assuring safety and good quality of care in chronic kidney disease management is by providing practitioners with CPGs to assist them in their clinical decision making. However, the main therapeutic modality for patients with end stage renal disease is hemodialysis, which involves an elaborate ultra-pure water preparation system, and the highly complex daily routine of dialysis machine handling and maintenance. The standards of care and essential elements of good practice regarding delivery of hemodialysis are specified by the Association for the Advancement of Medical Instrumentation (AAMI, http://www.aami.org/). AAMI is a nonprofit organization founded in 1967. It is an alliance of over 6,000 members from around the world dedicated to increase the understanding, safety, and efficacy of medical instrumentation through effective standards, educational programs, and publications. Its members include health care institutions, research and teaching facilities, government agencies, manufacturers, test houses, trade associations and individual health care professionals. It is the primary resource for the industry, the professions, and government for national and international standards for safety in medical technology. The AAMI standards program comprises 100 technical committees and working groups that produce standards, recommended practices, and technical information reports for medical devices. The developed standards and recommended practices represent a national consensus and many of them have been approved by the American National Standards Institute (ANSI) as American National Standards. The AAMI also collaborates with the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), as well as U.S. Technical Advisory Groups (TAGs). The current AAMI standards and best practice recommendations regarding dialysis are summarized in Table 32.6.

**Table 32.6** Hemodialysis standards and practice recommendations by the AAMI

| |
|---|
| **ANSI/AAMI RD47, Reprocessing of hemodialyzers:** Addressed to physicians and other health care facility personnel, this recommended practice describes the essential elements of good practices for reprocessing hemodialyzers in order to help ensure device safety and effectiveness. |
| **ANSI/AAMI/IEC 60601-2-16, Medical electrical equipment – Part 2-16: Particular requirements for basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment:** Specifies the minimum safety requirements for single-patient hemodialysis, hemodiafiltration and hemofiltration equipment. These devices are intended for use either by medical staff or under the supervision of medical expertise. |

**Table 32.6** (Continued)

| |
|---|
| **ANSI/AAMI/ISO 11663, Quality of dialysis fluid for hemodialysis and related therapies:** Specifies minimum requirements for dialysis fluids used for haemodialysis and haemodiafiltration, including substitution solution for haemodiafiltration and haemofiltration. This standard does not address the requirements for the water and concentrates used to prepare dialysis fluid or the equipment used in its preparation. |
| **ANSI/AAMI/ISO 13958, Concentrates for hemodialysis and related therapies:** Specifies minimum requirements for concentrates used for hemodialysis and related therapies. For the purpose of this International Standard, "concentrates" are a mixture of chemicals and water, or a mixture of chemicals in the form of dry powder or other highly concentrated media, that are delivered to the end user to make dialysis fluid used to perform hemodialysis and related therapies. This standard is addressed to the manufacturer of such concentrates. |
| **ANSI/AAMI/ISO 13959, Water for hemodialysis and related therapies:** Specifies minimum requirements for water to be used in the preparation of concentrates, dialysis fluids for hemodialysis, hemodiafiltration and hemofiltration and for the reprocessing of hemodialysers. Does not address the operation of water treatment equipment nor the final mixing of treated water with concentrates to produce the dialysis fluids used in such therapies. That operation is the sole responsibility of dialysis professionals. Does not apply to dialysis fluid regenerating systems. |
| **ANSI/AAMI/ISO 23500, Guidance for the preparation and quality management of fluids for hemodialysis and related therapies:** This recommended practice covers the appropriate prescription of dialysate, handling of concentrates, operation of water treatment equipment and handling of its product water, monitoring of systems and the dialysate produced, and risks and hazards of dialysate preparation failure. It presents a systems diagram and explanation for the production, monitoring, and use of dialysate for hemodialysis in the facility. |
| **ANSI/AAMI/ISO 26722, Water treatment equipment for hemodialysis applications and related therapies:** ISO 26722 is addressed to the manufacturer and/or provider of water treatment systems and/or devices used for the express purpose of providing water for haemodialysis or related therapies. The standard covers devices used to treat water intended for use in the delivery of haemodialysis and related therapies, including water used for: (1) the preparation of concentrates from powder or other highly concentrated media at a dialysis facility; (2) the preparation of dialysis fluid that may be used for the preparation of substitution fluid; (3) the reprocessing of dialysers for multiple uses. The scope includes all devices, piping and fittings between the point at which potable water is delivered to the water treatment system and the point of use of the dialysis water, e.g., water purification devices, online water quality monitors (such as conductivity monitors), and piping systems for the distribution of dialysis water. |

**Table 32.6** (Continued)

| |
|---|
| **ANSI/AAMI/ISO 8637, Cardiovascular implants and extracorporeal systems - Hemodilayzers, hemodiafilters, hemofilters and hemoconcentrators:** This lnternational Standard specifies requirements for haemodialysers, haemodiafilters, haemofilters and haemoconcentrators, hereinafter collectively referred to as "the device," for use in humans. |
| **ANSI/AAMI/ISO 8638, Cardiovascular implants and extracorporeal systems - Extracorporeal blood circuit for hemodialyzers, hemodiafilters and hemofilters** |

## 32.3 FROM RECOMMENDATION TO IMPLEMENTATION

Evidence from recent years suggests that implementation of best practice guideline strategies is associated with better patient care and improved patient outcomes. Also, guidelines have been proposed as an important tool to improve health care rationing by eliminating ineffective/useless diagnostic tests and interventions and by making more efficient use of health care resources. However, effective and timely transfer of guidelines into clinical practice remains fragmented and inconsistent (Grol 2001; Ploeg et al. 2007). Identifying these barriers remains of paramount importance in order to ensure patients' safety.

### 32.3.1 Challenges and Limitations to the Implementation of Clinical Practice Guidelines

Clinical practice guidelines "are designed to improve the quality of healthcare, to reduce the use of unnecessary, ineffective or harmful interventions, and to facilitate the treatment of patients with maximum chance of benefit, with minimum risk of harm, and at an acceptable cost." (National Health & Medical Research Council, 1999) Moreover, their implementation should improve quality of care by reducing inappropriate variation of health care services and by expediting the use of new effective advances to everyday practice (Audet et al. 1990; Cabana et al. 1999; Chassin et al. 1987). However, one major health care conundrum is the consistent gap between what is currently considered the best practice as determined by scientific evidence and the actual delivered clinical care. Studies from countries such as the United States and the Netherlands suggest that 30-40% of patients do not receive the current standard of care as suggested by scientific evidence, and 20% of the provided care can at best be considered unnecessary, but in fact may potentially harm the patients (Grol and Grimshaw 2003; Grol and Wensing 2004). Studies confirm that

implementation of CPGs and adherence to clinical practice recommendations improves health care and patient outcomes in terms of mortality (Collins et al. 2002; Dharmarajan et al. 2011; Lesho et al. 2005; Oh et al. 2011). The Dialysis Outcomes and Practice Patterns Study (DOPPS, http://www.dopps.org/) is a prospective, longitudinal, observational study of hemodialysis patients and facilities in twelve countries. The goal is to identify which hemodialysis practice patterns are associated with the best patient outcomes. DOPPS has developed a series of country reports giving information on the attainment of guideline goals and their impact on patient outcomes. For example, a DOPPS study performed in Germany found that the highest relative risk of mortality was found in patients with albumin levels outside the target range recommended by guidelines (http://www.dopps.org/d_cdArchive/DoppsCD2009/CountryReports.htm). A DOPPS study in Sweden estimated that adherence to nephrology guideline target levels for albumin and vascular access could save as many as 441 and 409 life-years, respectively (Wikstrom et al. 2010). Another DOPPS study performed in United States calculated that if half of all patients lying outside target values, for four hemodialysis guidelines and two other modifiable factors, are brought within them, this could potentially lead to a saving of 69,367 life years (Port et al. 2004). Yet, despite this knowledge the overall adherence rate to guideline recommendations remains unsatisfactory (Oh et al. 2011). These findings highlight the importance of pointing out major obstacles and barriers as well as facilitators to implementation of guideline strategies. This will hopefully allow us to develop more effective means to successfully implement best practice recommendations.

#### 32.3.1.1 Obstacles and Barriers to the Implementation of Guideline Recommendations

More than a decade ago the main barriers to following clinical practice recommendations were thought to be mostly due to the unawareness and unfamiliarity of physicians with CPGs. Some of the identified reasons were a lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, the inertia of previous practice, and external barriers (Cabana et al. 1999). While many of these barriers might still be in place, it is nowadays widely accepted that implementation of guideline recommendations faces a variety of complex challenges on many different organizational levels. They can be summarized as follows (Grol and Wensing 2004; Ploeg et al. 2007):

- Negative staff attitudes and beliefs (e.g. guideline too rigid, use of guideline costs too much time, dislike of imposed activities).
- Limited integration of guideline recommendations into organizational structures and processes (e.g. no support by management, inadequate staffing for implementation activities such as educational sessions, and lack of integration of the guideline into policy, procedures, and documentation).
- Time and resource constraints (e.g. heavy workloads, being short staffed, high patient to staff ratios, no financial compensation, and high patient acuity).
- Organizational and system level changes (e.g. changes in nursing roles and models of care, staff turnover, staff rotation, and structural renovations on units).

#### 32.3.1.2 Facilitators of Guideline Recommendations Implementation

As much as it is important to point out hurdles that prevent successful CPG implementation, it is important to identify facilitators and incentives that enable successful implementation of CPG recommendations into every day clinical practice. Many factors have been found to improve the implementation of guideline recommendations (Grol and Wensing 2004; Ploeg et al. 2007):

- Learning about the guideline through group interaction (e.g. through small group educational sessions for staff, through social interaction with peers).
- Positive staff attitudes and beliefs. CPGs were perceived positively when implementation was believed to improve patient outcomes, when there is congruence of guideline with current knowledge, when there is active involvement in the process, and when changes through guideline were incremental, rather than radical.
- Leadership support (e.g. support from nurse managers and administrators at all levels of the organization), was closely linked with positive staff attitudes and beliefs.
- Unit-based champions (e.g. nurse educators, nurse practitioners, clinical experts, and CRNs taking on leadership roles).
- Teamwork and collaboration (e.g. participants share common goal of improving patient care through successfully implementing the guideline).
- Professional Association Support (e.g. financial support to hire CRNs, free up staff time to attend educational sessions related to the best-practice guideline).
- Inter-organizational collaboration and networks (to promote integration, coordination, and continuity of client care).

Although many challenges and facilitators have been identified, one must remain cautious when considering their value for the development of CPG implementation strategies. Currently, we still lack sufficient in-depth knowledge as to which factor is the most valuable and promising one to prove useful in the field.

### 32.3.2 Specific Challenges to the Development of Clinical Practice Guidelines in Nephrology

The users of practice guidelines need to know how much confidence they can place in the evidence behind their recommendations. Grading the quality of evidence and the strength of recommendation helps nephrologists to judge the clinical usefulness of such recommendations. However, nephrologists are confronted with a situation, which sets their field clearly apart from other specialties of internal medicine: the currently low number of adequately designed RCTs. The number of RCTs (2779) published in nephrology from 1996 to 2002 is fewer than in all other specialties of internal medicine (Strippoli et al. 2004). The typical struggles that the medical community is facing as a whole when trying to bridge the gap between basic science and human studies are well described (Strippoli et al. 2004; Sung et al. 2003; Taylor et al. 2003):

- the lack of willing participants,
- the regulatory burden,
- the fragmented infrastructure,
- the existence of incompatible databases,
- the lack of qualified investigators,
- the career disincentives,
- the practice limitations,
- the high research costs, and
- the lack of funding.

However, there seem to be some factors specific to the field of nephrology, which aggravate the whole situation. For example, some of the diseases encountered by nephrologists are very rare (e.g. many glomerular diseases). This makes it difficult to achieve a sufficiently big enough sample size for an RCT. Another factor is the multitude of causes leading to kidney injury. In other words, many different diseases/injuries can cause one common outcome (i.e. kidney injury). Therefore, it is more complex to study the effectiveness of an intervention in a population combined by one common outcome, yet multifaceted by its underlying ailments. Also, the great burden of end stage renal disease on patients' quality-of-life, with mortality rates comparable to those found in oncology populations, makes

the design of RCTs in many instances seem unethical; since the design of a randomized trial often entails withholding of a specific therapy that could potentially improve patients quality of life.

Of great concern is also the fact that the overall quality of the RCT reporting process in nephrology was found to be low and has not shown improvement in over 30 years. The reported problems were (Strippoli et al. 2004):

- Unclear allocation concealment, with the majority of trials not reporting the methods by which patients were allocated to the randomization intervention.
- Lack of reported blinding of outcome assessors.
- Failure to perform "intention-to-treat" analysis.

As a result, the lack of quality evidence entails a lower graded strength of the recommendations (i.e. consensus statements based on expert opinions) made by CPGs to guide nephrologists in their clinical decision making.

In the future, adherence to the recently developed CONSORT statement in the development of RCT reports will hopefully lead to an increase in their quality. Furthermore, the establishment of multicenter networks such as the Frequent Hemodialysis Network (FHN) can help to achieve higher patient numbers for the performance of adequately powered RCTs. Recent examples of well-designed RCTs (e.g. HEMO, ADEMEX, FHN study) have given hope in the field of nephrology, by yielding new evidence on therapy modalities by applying highest scientific standards (K/DOQI Workgroup 2005; Chertow et al. 2010; Eknoyan et al. 2002; Paniagua et al. 2002). This will hopefully drive the development of high graded best-practice guideline recommendations and lead to an improvement in patient outcomes.

## 32.4 CONCLUSION

The advent of EBM has helped to recognize the limitations in physicians' ability to identify and implement optimal care strategies for their patients. The development of clinical practice guidelines, including graded recommendations based on the strength of the currently available evidence, is aimed at assisting physicians by facilitating their decisions about optimal care. However, the field of Nephrology is facing special circumstances hindering the developmental process of clinical practice guidelines. A lack of RCTs is lowering the strength of recommendations found in the currently available guidelines. The foundation of multicenter networks,

such as the FHN, will hopefully lead to an improvement in the quality of RCTs in nephrology.

Furthermore, the acceptance and implementation of nephrology guidelines is complicated by a complex situation, where personal beliefs and administrative shortcomings hinder the optimal implementation of the best available knowledge. This is even more disappointing in view of the fact that it has been shown that adherence to clinical practice guidelines has the potential to reduce unnecessary health care costs and, more importantly, improve patient outcomes. Therefore, identifying the most relevant obstacles to guideline implementation and designing effective strategies to overcome those remains of paramount importance.

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## ESSAY QUESTIONS

1. Given that doctors think to know best, what kind of evidence is needed to convince the skeptical doctor about what treatment to use?

2. What is your definition of evidence in a medical context? What is the basis for knowing that it is the current best evidence?

3. Trace the development of guidelines in nephrology in the United States.

4. What criteria should be used to report the structure of a well-designed clinical trial?

5. Compare randomized trials (RCTs) with observational studies; are there advantages for the latter?

6. What kinds of standards and guidelines are required for machines, dialyzer, or water used in dialysis? How are they derived?

7. Compare narrative reviews, meta-analysis and systematic reviews of the medical literature.

8. How do you define the term "evidence-based practice"?

9. What are the essential factors of the GRADE system in regard to 1) Quality of evidence 2) strength of recommendation?

10. On which facilitators would you focus on in the organization of a program to implement a set of guidelines on the treatment of high blood pressure in the general population?
How can those facilitators benefit guideline acceptance?

11. Much money and time are spent on preparing guidelines; why are only a fraction ever implemented?

## MULTIPLE CHOICE QUESTIONS

**Choose the best answer**

1. All the following will aid the health care worker in providing best management and care to end stage renal disease patients except:

A. Best-practice guidelines based on the methods of evidence based medicine.
B. Good clinical acumen in diagnosis and management.
C. Decisions based solely on physicians' clinical judgement due to their long term experience.
D. Updated and dedicated health care workers.

2. Science is distinguished from pseudo-science by…

A. The explanatory power of its theory.
B. The amount of evidence.
C. The use of a formal scientific approach to test the developed theory.
D. By the plausibility of its theory.

3. A double-blinded study is a form of a RCT where neither the investigator nor the patient is aware of who belongs to the treatment or to the control group? This measure prevents…

A. Patients from opting out of the study in case they are assigned to the control group.
B. The occurrence of adverse events.
C. Unconscious bias on therapy outcomes (e.g. placebo effect or observer bias).
D. Patients from opting out of the study in case they are assigned to the treatment group.

4. In CPGs the available evidence is graded according to study design. The current gold standard yielding the highest quality evidence is derived from…

A. large observational studies.
B. RCTs.
C. Narrative reviews.
D. Double-blinded RCTs.

5. The CONSORT statement was developed to…

A. Improve the study design of RCTs.
B. Provide guidance on how to properly report RCTs.
C. Help register RCTs.
D. Make RCTs available for public review.

6. A meta-analysis based on a rigorous systematic review is considered less biased than a narrative review, because…

A. It uses a statistical approach.
B. It combines the results of several RCTs.
C. It can demonstrate the clinical effectiveness of a healthcare intervention.
D. It also includes studies that did not demonstrate a significant difference between treatments.

7. Studies estimated that the average time that it takes for only 14% of new scientific evidence to enter day-to-day medical practice is…

A. 17 years.
B. 17 months.
C. 7 years.
D. 7 months.

8. Passive dissemination of scientific evidence in medical journals…

A. Has been shown to be sufficient in guiding physicians in their clinical decision making.
B. Leads to significant changes in practice patterns.
C. Has not been shown to lead to any significant changes in clinical practice patterns.
D. Is considered superior than the use of CPGs.

9. The main aim of CPGs is to…

A. Achieve consistency, effectiveness, and safety in medical care.
B. Control physicians' behaviour.
C. Create jobs for guideline developers.
D. Eliminate clinical judgement.

10. In CPGs the graded strength of recommendation is based…

A. On the opinion of many experts in the field.
B. Solely on the quality of evidence derived from clinical trials.
C. On the quality of evidence derived from clinical trials in combination with other factors (e.g. appreciable harms, burdens , or costs)
D. On the opinion derived from several work groups.

11. Obstacles to the implementation of guideline recommendations are…

A. Hard to identify.
B. Well recognized and manifold, however, at the current moment we do not know which one has the most value in order to be addressed.
C. Not very common.

12. All of the listed factors are well known struggles hampering the realization of clinical trials, except:

A. The lack of willing participants.
B. The regulatory burden associated with their execution.
C. The lack of scientific relevance.
D. The lack of funding.

13. The field of nephrology is confronted with a special situation when compared with other specialities of internal medicine. The lack of properly designed RCTs has been ascribed to many facts. The following proposals may help to increase the number of well-performed RCTs in the future except:

A. The establishment of multicenter networks in order to achieve a bigger population size.
B. Adherence to the CONSORT checklist when reporting the trial.
C. Development of more trials investigating the effect of an intervention.
D. Performing more studies sponsored by the industry.

14. According to the GRADE approach, which of the following statements regarding the development of guideline recommendations is not true?

A. The working group must always issue a recommendation (i.e. recommended or not recommended) regarding a certain intervention.
B. Four factors should be considered before making a recommendation: (1) the trade-offs, (2) the quality of the evidence, (3) the translation of the evidence into practice in a specific setting, (4) the uncertainty about the baseline risk of the population of interest.

C. A guideline development group can reach the conclusion that a recommendation cannot be issued in case the net health effect is unclear, or if the potential benefits are outweighed by the costs.
D. The consideration of factors, such as the baseline risk of the population, features of particular practice settings, availability of the service, the accessibility to care, and the costs of an intervention, in combination with the quality of evidence entails the strength of a recommendation

15. In the grading system developed by the GRADE working group, the level *low* for the quality of evidence is defined as:

A. No further research is required.
B. Further research is highly unlikely.
C. Any estimate of effect is very uncertain.
D. Further research is likely to change the estimate.

16. Clinical practice guidelines must clearly indicate all of the following except:

A. If the desirable effects clearly outweigh the undesirable effects.
B. If there is a close or uncertain balance between desirable effects and undesirable effects.
C. The personal beliefs of working group members contradict current evidence.
D. The evidence is of high quality.

17. Which of the following is not a major reason why physicians and patients may benefit from the development of clinical practice guidelines?

A. Reduction of variation in accepted clinical practices.
B. Identification of gaps in clinical knowledge.
C. Improvement of health care quality.
D. Reduction of physicians' accountability.

18. The advantage of the GRADE system over other systems are all of the following except:

A. Clear separation between quality of evidence and strength of recommendation.
B. Developed by a small group of methodologists.
C. Developed by a widely representative group of international guideline developers.
D. Explicit acknowledgement of values and preferences.

19. Following statement regarding the development of guidelines in Nephrology is not correct:

A. The favorable impact of these guidelines on the quality of care delivered to dialysis patients in the United States has been well studied and documented.
B. It represented the first attempt to give evidence-based guidance to clinical care teams and to reduce variability in practice patterns in the over 3,100 dialysis facilities in the United States.
C. Globally the development of best practice guidelines in the field of nephrology was a well coordinated venture from the beginning.
D. The uncoordinated development of guidelines by various organizations has resulted in redundancy of CPGs in some areas of kidney disease management.

20. Which of the following statements is not a characteristic of an observational study?

A. They are more time-consuming than RCTs.
B. They are a useful epidemiologic tool to identify risk factors and prognostic indicators.
C. They can be conducted in situations where RCTs are impossible or unethical.
D. They may provide better evidence for adverse effects.

# Erratum: Biofeedback Systems and Their Application in the Hemodialysis Therapy

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In the original version, the third author name is misspelt. It should be read as "Ahmad Taher Azar''.

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