Present and future of hemodialysis

P. Zucchelli and A. Santoro
Department of Nephrology and Dialysis Malpighi, Policlinico S. Orsola-Malpighi, Bologna, Italy.

Introduction

Renal replacement therapy (RRT) of end-stage renal disease (ESRD) is nearly 30 years old. Notwithstanding the many successes obtained during this period, it cannot be claimed that hemodialysis and other related techniques should be considered asymptomatic or ideal treatments for ESRD. The absence of an in-depth knowledge of the pathogenesis of the uremic syndrome does not make it possible to accurately predict the future path of RRT; as things stand today, only serendipity can open a new era in this field.

During this meeting we shall try to reflect upon the treatment modalities of the Nineties on the basis of what we have learnt in the Eighties. The first aspect that should be discussed is what goals RRT can actually achieve, without taking into account renal transplantation as this would go beyond the scope of this session. The key guideline objectives of RRT[1] are listed in table I. In our opinion, the fundamental factors that ought to be taken into consideration in order to achieve those goals are: i) the age of the patient, ii) cardiovascular problems of uremic patients treated by dialysis, and iii) the adequacy of renal replacement treatment.

Table I. Goals of ESRD treatment

- Long-term survival.
- Low rate of long-term morbidity with low hospitalization.
- Absence of treatment-induced complications.
- Physical and psychological «independence» of the patient.

Age of the patient treated by dialysis

Over the past decade numerous Reports from various Registries[2-4] have documented that a progressively growing proportion of aged patients with ESRD has been submitted to RRT in most of the economically developede countries. This is because elderly people are particularly prone to renal insufficiency, and because older patients have easier access to life-saving treatments. On the other hand, in younger people preventive care and therapeutic measures seem to have significantly reduced the incidence of ESRD. Although older patients do have a higher mortality rate, high-performance blood purification techniques have brought about a significant improvement in their overall survival over the last few years. Increased survival rates and high acceptance rates have together determined a progressive increase in the median age of RRT patients.

Moreover, recent Reports[4-6] have described higher gross RRT patient mortality in the USA than in other industrialized countries. The lower survival of RRT patients in the USA compared with the EDTA Registry and Japan can partly be explained by the higher median age of US patients and by the higher incidence of co-morbid conditions such as atherosclerotic heart disease, cerebrovascular disease, diabetes mellitus and non-skin malignancies. The tendency to prescribe shorter dialysis is also an important factor in increased patient mortality. Wether this is due to the intrinsic problems of short dialysis, or to inadequate understanding of the elements of the dialysis process (other than time) remains uncertain. What is certain is that the trend towards shorter dialysis times (less than 3 hours) may lead to underdialysis and thus to adverse clinical outcomes.

Co-morbid conditions, in particular cardio-vascular problems, are frequently associated with age. Moreover, cardiovascular diseases are the major causes of morbidity and mortality in aged uremic patients.

Cardiovascular problems in dialysis patients

Despite considerable progress in the treatment of ESRD, cardiovascular complications are still the major cause of high morbidity and mortality in these patients. These complications may be put into two major groups: a) dialysis-associated cardiomyopathy, and b) dialysis-induced hypotension. Both complications are definitely more frequent in aged patients than in younger ones[7-10].

Correspondencia: Prof. Pietro Zucchelli.
Department of Nephrology and Dialysis Malpighi.
Policlinico S. Orsola-Malpighi.
Via P. Palagi, 9.
40138 Bologna, Italy.

a) *Dialysis-associated cardiomyopathy*

The presence of myocardial dysfunction is frequently encountered in patients on maintenance hemodialysis.

Left-ventricular dilatation appears in 10-20 % of dialysis patients and is frequently associated to congestive heart-failure.

Left-ventricular hypertrophy is the predominant finding that can occur in over 50 % of ESRD patients. This abnormality, which is the result of a chronically increased cardiac workload seems to be linked to the age of the patient, his/her total length of time on dialysis and, in some cases, to severe secondary hyperparathyroidism. L.V. hypertrophy may progress towards an asymmetric septum hypertrophy and may result in L.V. diastolic dysfunction, ie. a reduced diastolic compliance of the left venticle. It is thus reasonable to assume that impaired L.V. filling subsequent to altered diastolic mechanical properties may increase susceptibility to intradialytic hypotension. Doppler sonography in patients with recurrent dialysis hypotension shows a marked reduction in proto-diastolic ventricular filling, while the ventricular chamber is only filled by atrial contraction[10]. Moreover, patients with L.V. hypertrophy are susceptible to volume overload and pulmonary vascular congestion.

L.V. diastolic dysfunction is associated with increased mortality from congestive heart failure, coronary artery disease and sudden death.

b) *Intradialytic hypotension*

This remains a serious problem since it occurs in about 20-25 % of patients undergoing maintenance hemodialysis[10-12]. Dialysis-related hypotension is clearly a complex, multifactorial phenomenon in which factors related to the dialytic modalities and to the patient's characteristics are involved.

Intradialytic hypotension is particularly frequent and debilitating in elderly dialysis subjects. Among these patients autonomic dysfunction and a lower cardiac reserve limit the response to volume removal during dialysis. In fact, as a result of ageing, a variety of structural and functional changes may occur in the cardio-vascular system and these may add to uremic cardiovascular dysfunctions. These changes invólve i) structural alterations of the arterial wall, ii) impairment of the autonomic nervous control of the circulation, and iii) impairment of cardiac performance. These changes may explain the greater susceptibility of elderly patients to circulating volume changes (fig. 1). Furthermore, poor nutritional status, as recently published, may play an additional role[13,14].

The adequacy of renal replacement treatment

This problem may regard: a) the correction of acid-base status, b) a good nutritional status, and c) an adequate dialysis prescription.

a) *The correction of acid-base status*

As the kidney has a fundamental role in maintaining acid-base homeostasis, it is quite clear why ESRD is associated with metabolic acidosis. Experimental studies in animals and clinical observations suggest that acidosis *per se* may lead to various detrimental effects in uremic patients, such as an increased protein turnover, the enhancement of renal bone lesions, and myocardial dysfunction. Moreover, it is now clear that acetate may have numerous untoward effect, especially with the use of high-flux and high-efficiency dialyzers (table II)[15-20]. It is therefore mandatory to use bicarbonate as a buffer base in hemodialysis with high-flow treatments using large surface area filters.

b) *Good nutritional status*

A common problem in RRT patients is protein malnutrition which is an important factor underlying the morbidity and mortality of such patients. In a sample of more than 12,000 hemodialysis patients, low serum albumin levels were highly associated with the mortality suffered by hemodialysis patients[6]. In addition, there is now evidence that the hemodialysis procedure *per se* is a strong catabolic stimulus, partly owing to the interaction between blood and cellulose membranes.

Many nutritional abnormalities are mitigated or can disappear completely provided that dialysis patients are adequately dialyzed with biocompatible membranes, that metabolic acidosis is corrected and that protein intake is sufficient[21,22].

c) *An adequate dialytic prescription*

Even after studying treatment schedules for 20 years no clear definition of the optimal dialysis prescription has been achieved. The US National Cooperative Dialysis Study has provided the most comprehensive analysis at

Table II. Possible untoward effects of acetate

- *Hypoventilation related hypoxemia:*
  - Respiratory symptoms in patients with compromised cardiopulmonary function.
  - Fatigue and nausea due to a reduction in transcutaneous oxygen tension.
- *Intracellular acidemia:*
  - Appearance of some EEG abnormalities.
- *Insufficient correction of metabolic acidosis:*
  - Increased protein turnover.
  - Enhancement of renal bone lesions.
- *Long-term metabolic and «toxic» effects:*
  - Cytokine production.
  - Perturbation in intermediate metabolism.
- *Increased frequency of symptomatic hypotension in critically ill patients.*

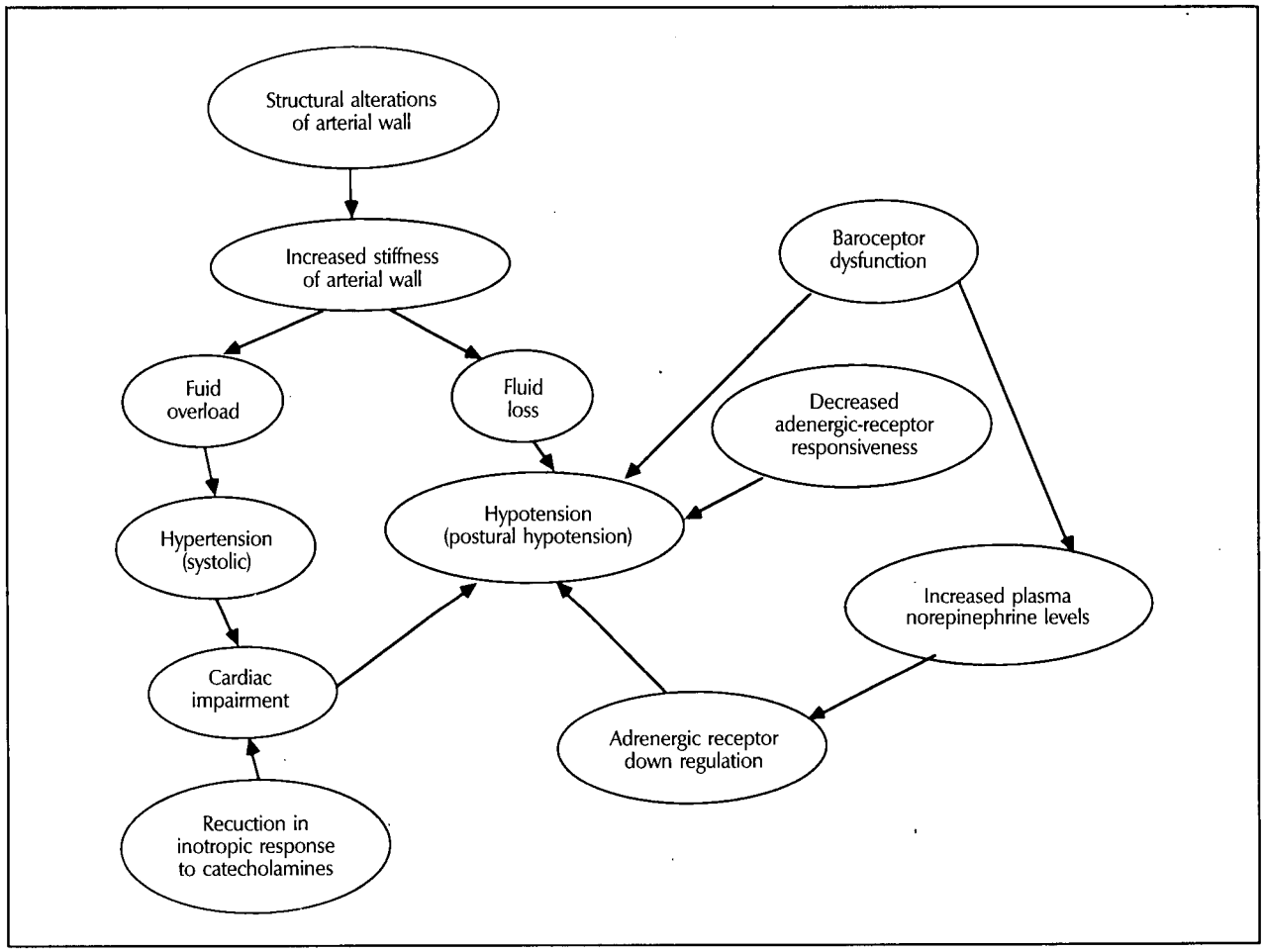


Fig. 1.—Various alterations present in uremic aged patients that can induce systemic hemodynamic modifications.

the adequacy of dialysis with the choice of urea as the principal marker of uremic toxicity. According to these results, nutrition (or PCR), mid-week pre-dialysis BUN and Kt/V index are mathematically interrelated. The three parameters BUN, PCR, and Kt/V are all required to describe the domain of adequate dialysis, clearly indicating that the best nutritional status and the lowest urea concentration induce low morbidity and mortality[23-26].

It is beyond the scope of this work to discuss the numerous problems connected to the use of various models in evaluating an adequate dialysis prescription. We only wish to stress how important is to obtain a direct, routine quantitative measurement of various markers, like urea, during the hemodialysis session as a tool towards achieving an optimum dialysis prescription. It is our personal belief that in the near future these different biochemical markers will be determined utilizing the ultrafiltrate fluid. We could speculate that if an accurate sensor for urea concentration could be developed, frequent and immediate determinations of the urea concentration, in connection to a computer, would enables the continuous calculation of Kt/V; dialysis could thus be stopped once the pre-set efficiency level was reached.

Technological progress

The natural consequences of what we have reported above and of the results of numerous papers published over the last decade are the «ingredients» for optimal dialysis, as listed in table III. Moreover, hemodiafiltration, and

Table III. «Ingredients» for optimal dialysis treatment

- Bicarbonate as buffer.
- Dialysis system with precise volumetric control of ultrafiltration and infusion rates.
- Sterile dialysis fluids.
- Biocompatibility of the whole extracorporeal circuit.
- Urea, bicarbonate, sodium and potassium modeling.
- Continuous cardiovascular monitoring.

its possible modifications, with the use of high flux dialyzers and more biocompatible membranes would be the best way of treating ESRD patients. In fact, hemodiafiltration can achieve higher removal both of small molecules as well as low molecular weight proteins i.e. beta-2-microglobulin. In addition, the higher utilization of convective solute transport may enhance cardiovascular stability during treatment. Indeed, convective transport is able to decrease left ventricular end-diastolic pressure and pulmonary wedge pressure.

Finally, pyrogen-free dialysate will definitely utilize backfiltration positively to increase depurative capacity, while preventing cytokine release which can alter blood pressure control. Needless to say, the technological progress in blood purification treatment only represents a part of the complex problem of treating ESRD. The undoubted importance of a good nutritional status and anemia have been stressed earlier. Anemia and nutritional deficiencies actually represent important co-factors in the regulation of blood pressure and they both represent important therapeutic manoeuvres in ESRD.

One of the first steps that should be taken in preventing blood pressure instability during the hemodialysis session is the monitoring of the determinats of arterial pressure: cardiac output, blood volume and total peripheral resistances.

During dialysis the hypotensive event is often sudden and unexpected, and only continuous monitoring can highlight negative trends or negative associations among hemodynamic variable changes that may favour the onset of sharp reductions in blood pressure.

This presupposes that the sensors and the measurement systems used are indeed able to provide both continuous and in real-time measures, of the various parameters to be monitored. The traditional instruments which are still used to measure arterial pressure, the heart's electrical activity and stroke volume are unsuitable for intradialytic monitoring. In fact, the physiologic sensor used has to meet certain characteristics: it must be non-invasive, safe, relatively simple to apply and not bothersome to the patient. It must also be interfaceable with a recorder and hence with a personal computer to supply the trends of the parameters being examined. We have developed a non-invasive continuous recording system for hemodynamic intradialytic monitoring[27]. The set-up consists of an automatic arterial pressure recorder, a trans-thoracic biolectrical impedance monitor and an optical system to measure the intradialytic blood volume changes by optical absorbance. The instruments are connected to a computer to obtain on-line recordings, graphic displays and filtering of several parameters: heart rate, blood pressure, total peripheral resistance, cardiac output, blood volume changes.

On-line continuous recording systems of the intradialytic changes of blood volume provide new openings both in the study and the prevention of sudden intradialysis blood pressure reductions.

On the basis of the continuous recording of hemodynamic parameters it is possible to obtain alarm signals of hemodynamically critical situations. By making a statistical analysis of the temporal trends of volemia and heart rate one might identify discriminatory mathematical functions with which to predict the apperarance of intradialytic hypotensive episodes a few minutes in advance. An actual on-line alarm system can be developed, which makes it possible to signal pre-collapse states ahead of time, so that therapeutic measures can be enforced (infusion of normo-hypertonic solutions, plasma expanders, etc.) which prevent the onset of actual collapse episodes (fig. 2). The best way, however, to prevent intradialytic hypotension could be to develop automatic control systems that make it possible to pilot the hemodynamic variables trends along pre-set trajectories, using a series of interactions between controlled parameters and control parameters.

The system, developed by us to predict and to control the intradialytic blood volume changes[27] consists of 3 units: i) an optical sensor of blood volume changes, ii) dialysis machine, with volumetric control of ultrafiltration, interfaced with a personal computer with which the machine communicates on several parameters (ultrafiltration rate, conductivity and temperature of the dialysate, etc.) and iii) a specially-designed software package that integrates three different modules: the acquisition, estimation and control module.

The system keeps up pre-determined blood volume changes during dialysis treatments and ensures that by the end of the treatment the desired patient weight loss is achieved (fig. 3). The core of the system is made up of an adaptive controller which, on the grounds of continuous volemia and ultrafiltration rate measurements estimates the coefficients that link the two variables and makes it possible to pilot the volemia trends by means of ultrafiltration modulation.

The application of automatic dialysis for patients with blood pressure instability can bring about some advantages in regard to intradialytic blood pressure behaviour.

Of course, in a single-input/single-output control system, pre-set trends of volemia may at time seem incompatible with the weight reductions or the dialysis duration and this may jeopardize pressure stability inducing or even encouraging the appearance of collapse episodes. In light of this, the need to add other control variables to the model, such as dialysate sodium concentration, can have beneficial effects both upon the volemia trend as well as on the behaviour of arterial pressure. Apart from the increased technical complexity of the system, it will of course be necessary to investigate how much will actually be gained through improving both the management and the control of the symptoms of the dialysis session. Moreover, a concrete advantage in terms of cardiovascular stability could be achieved in critical vascular patients who present hypotensive episodes during their routine treatments.

AK 100

EL FUTURO

SU SEGURIDAD

gambro s.a.

PRINCIPE DE VERGARA, 43 - 2º A
Tels. 431 91 05 - 431 62 71
28001 MADRID

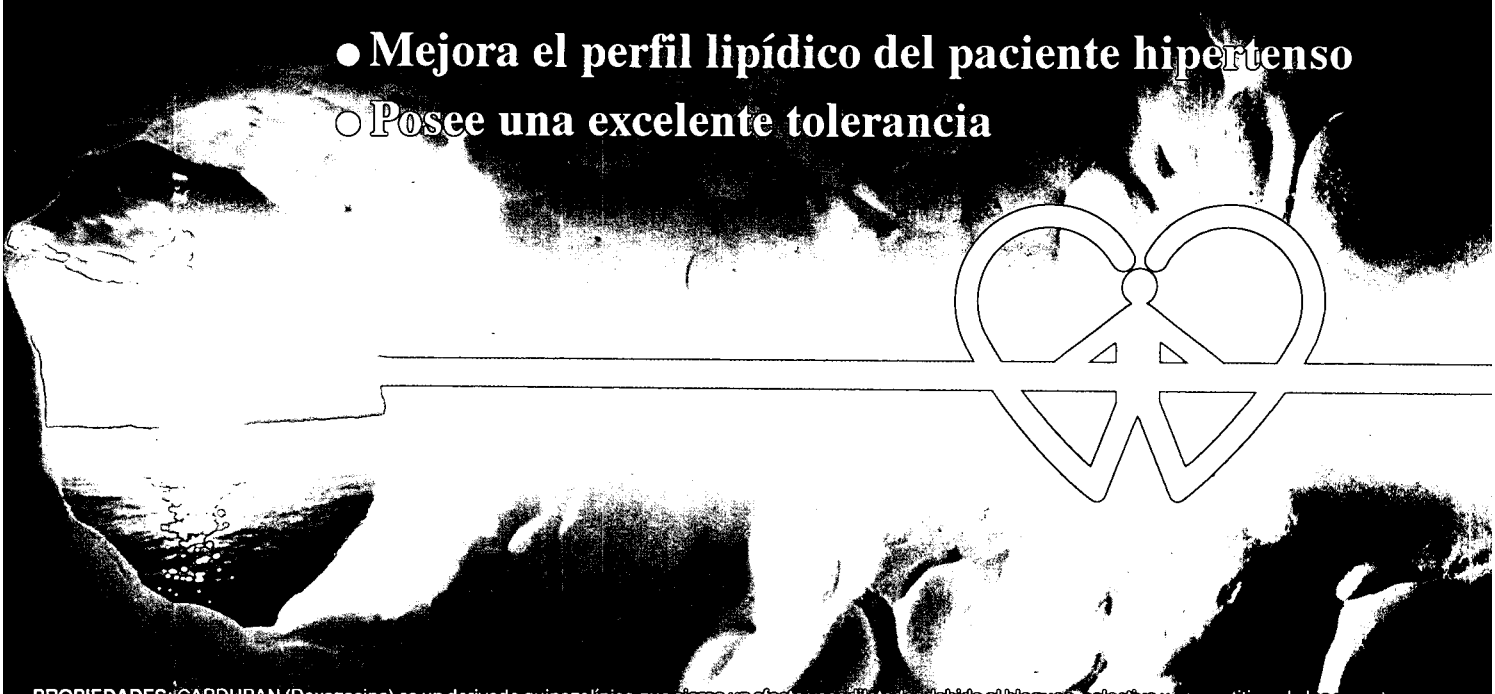
Una sola dosis diaria

CARDURAN®

(doxazosina)

EL PRIMER ANTIHIPERTENSIVO DE DOSIS UNICA DIARIA QUE MODIFICA FAVORABLEMENTE EL RIESGO CORONARIO

- Controla eficazmente la presión arterial
- Proporciona 24 horas de eficacia con una dosis única diaria
- Mejora el perfil lipídico del paciente hipertenso
- Posee una excelente tolerancia



PROPIEDADES: CARDURAN (Doxazosina) es un derivado quinazolínico que ejerce un efecto vasodilatador debido al bloqueo, selectivo y competitivo, de los receptores adrenérgicos, post-sinápticos alfa$_1$. La administración de CARDURAN pruduce una disminución de la presión arterial clínicamente significativa, como consecuencia de la reducción de las resistencias vasculares sistémicas. Una única dosis diaria proporciona una reducción clínicamente significativa de la presión arterial a lo largo de todo el día y hasta 24 horas después de la toma de la medicación. Tras su administración, tiene lugar una reducción gradual de la presión arterial, los efectos de variación ortostática de la presión arterial se pueden comparar con los que producen otros tratamientos con fármacos activos. La reducción máxima de la presión arterial se alcanza normalmente a las 6 horas de la administración. Se ha comprobado en pacientes con hipertensión arterial tratados con doxazosina que las presiones arteriales en posición supina son simllares a las observadas en posición erecta. Doxazosina produce efectos favorables sobre los lípidos sanguíneos: un aumento significativo de la fracción colesterol unido a lipoproteínas de alta densidad/colesterol total y una tendencia hacia la reducción favorable de los triglicéridos totales. Basándose en la asociación establecida entre hipertensión y lípidos sanguíneos con la enfermedad cardíaca por coronariopatía, los efectos favorables del tratamiento con doxazosina sobre ambos, presión arterial y lípidos, suponen una reducción del riesgo de desarrollar enfermedad cardíaca por coronariopatía. **INDICACIONES**: Tratamiento de la hipertensión arterial leve o moderada. **DOSIFICACION:** La dosis inicial de doxazosina es de 1 mg una vez al día. Según la respuesta de cada paciente, la dosis puede aumentarse a 2 mg tras 1 ó 2 semanas de tratamiento. Con posterioridad, la dosis puede seguir siendo aumentada, a intervalos de tiempo similares, a 4mg, 8mg ó 16 mg hasta conseguir la reducción deseada de la presión arterial del paciente. **CONTRAINDICACIONES:** CARDURAN está contraindicado en los pacientes con conocida sensibilidad a quinazolinas. **ADVERTENCIAS Y PRECAUCIONES: Advertencia :** Esta especialidad contiene lactosa. Se han descrito casos de intolerancia a este componente en niños y adolescentes. Aunque la cantidad presente en el preparado no es, probablemente, suficiente para desencadenar los síntomas de intolerancia, en caso de que aparecieran diarreas debe consultar a su Médico. **Embarazo y Lactancia:** Aunque en los estudios en animales no se han observado efectos teratogénicos, la seguridad de doxazosina durante el embarazo o lactancia no ha sido todavía establecida. Por ello doxazosina solamente debe ser empleado en estas circunstancias cuando, en opinión del médico, los posibles beneficios de la medicación superen sus riesgos potenciales.**Niños**: Se carece de experiencia en la utilización de doxazosina en niños. **INCOMPATIBILIDADES**: En experiencias clínicas realizadas hasta la fecha, CARDURAN (Doxazosina) ha sido administrado sin presentar interacción medicamentosa adversa con los siguientes fármacos: diuréticos tiazídicos, furosemida, Beta-bloqueantes, antiinflamatorios no esteroideos, antibióticos, agentes hipoglucemiantes, uricosúricos y anticoagulantes. Datos procedentes de estudios "in vitro" con plasma humano indican que doxazosina carece de efectos sobre la ligazón proteica de los distintos fármacos estudiados: digoxina, warfarina e indometacina. **EFECTOS SECUNDARIOS:** Durante los ensayos clínicos realizados en pacientes con hipertensión arterial, las reacciones más frecuentes asociadas al tratamiento con doxazosina fueron hipotensión postural (rara vez asociada con desmayo), mareo cefalea, fatiga, mareo postural, vértigo, edema y astenia. **INTOXICACION Y SU TRATAMIENTO**: En caso de que una sobredosificación diera lugar a hipotensión arterial, el paciente debe ser colocado en posición supina con la cabeza hacia abajo. En caso de que se consideren apropiadas, se llevarán a cabo otras medidas de mantenimiento en casos individuales. La diálisis sanguínea no está indicada ya que doxazosina está unido en alto grado a las proteinas plasmáticas. **PRESENTACIONES:** CARDURAN TABLETAS 2 mg: Envase con 28 tabletas P.V.P. IVA 2.782 Ptas. CARDURAN TABLETAS 4 mg: Envase con 28 tabletas P.V.P. IVA 3.576 Ptas.

Pfizer

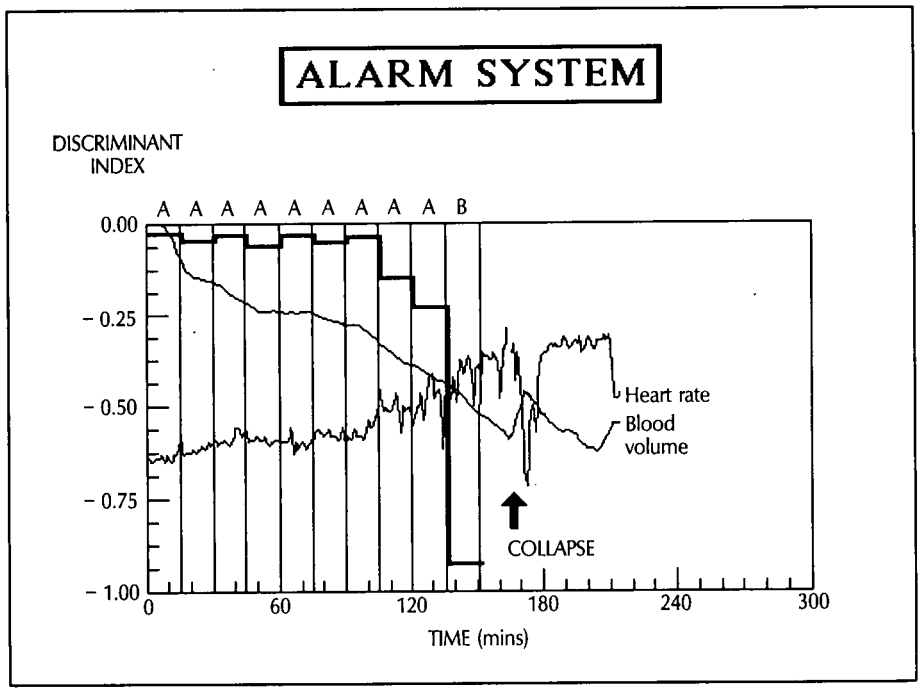


Fig. 2.—Continuous recording of heart rate, blood volume and a discriminatory index (obtained by statistical analysis) signalling the appearance of a collapse episode during a hemodialysis session.

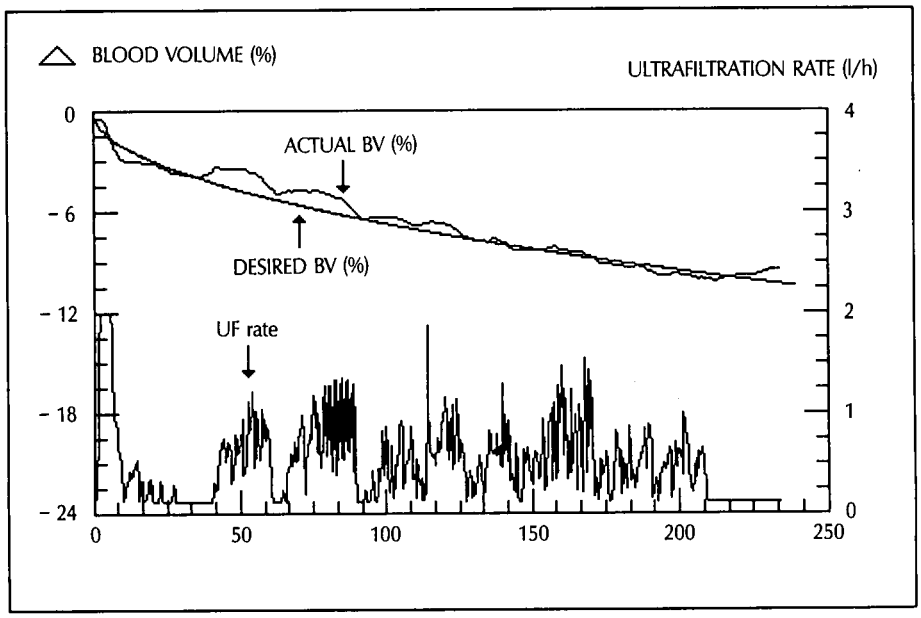


Fig. 3.—An example of a dialysis session with automatic blood volume (BV) control. The ultrafiltration (UF) rate is continuously adjusted by an adaptive controller to obtain the desidered BV trends.

Concluding remarks

Over the last few years there has been an increasing prevalence of chronically ill patients in the dialysis population. Hence, in order to improve dialysis tolerance, update dialysis procedures and additional devices have to be introduced in patient monitoring to better personalize the treatment.

Closed-loop dialysis, as depicted in figure 4, can be envisaged in the up-coming future. A system with different sensors will provide a continuous set of physical and biochemical measures regarding the patient. The continuous presence of an expert retroactive system will be able to adjust the setpoints of the dialysis machine on the basis of real-time informations automatically coming from the patient. Unfortunately, this type of dialysis will increase

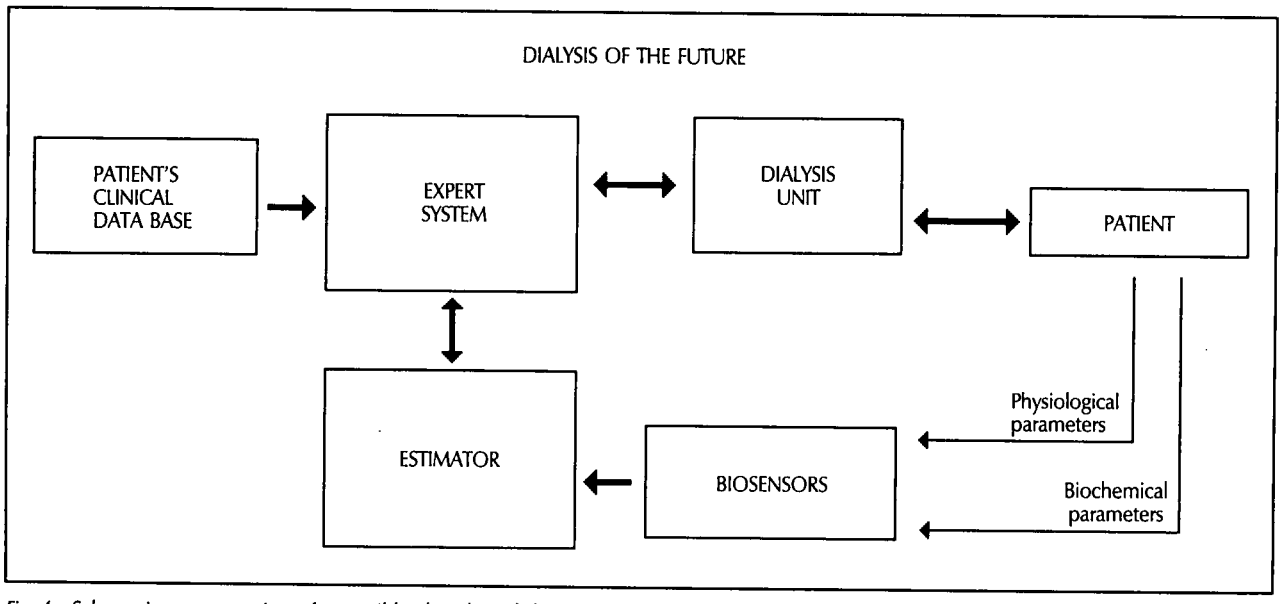


Fig. 4.—Schematic representation of a possible closed-up dialysis in the up-coming future.

treatment costs which are already very high. Can society afford such extra costs? If not, it is not hard to envisage a return to a primitive-like dialysis therapy, more straightforward and basic but definitely more prone to distressing, recurrent and persistent side-effects.

References

1. Simon P: Evolution of dialysis therapy. *Contr Nephrol* (Karger, Basel) 71:10-16, 1989.
2. Brunner FP and Selwood NH: Results of renal replacement therapy in Europe, 1980 to 1987. *Am J Kidney Dis* 15:384-396, 1990.
3. Combined Report on regular dialysis and Transplantation in Europe, XIX, 1989. Presented at the XXIIth Congress of the European Dialysis and Transplant Association. European Renal Association. Vienna, 5-8 Sept 1990.
4. Hull AR and Parker TF III: Proceedings from the morbidity, mortality and prescription of dialysis. Symposium, Dallas, Tx, September 15 to 17, 1989. *Am J Kidney Dis* 15:373-383, 1990.
5. Held PJ, Brunner F, Odaka M, García JR, Port FK and Gaylin DS: Five year survival for end-stage renal disease patients in the United States, Europe, and Japan, 1982 to 1987. *Am J Kidney Dis* 15:451-457, 1990.
6. Lawrie EG and Lem NL: Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15:458-482, 1990.
7. Kramer W, Wizemann V, Thormann J, Kindler M, Mueller K and Schlepper M: Cardiac dysfunction in patients on maintenance hemodialysis. *Contr Nephrol* (Karger, Basel) 52:97-107, 1986.
8. Huting J, Kramer W, Schutterle G and Wizemann V: Analysis of left ventricular changes associated with chronic hemodialysis. A non invasive follow up study. *Nephron* 49:284-290, 1988.
9. London JM, Guerin AP, Marchais SJ and Metivier F: Cardiomyopathy in end stage renal failaure. *Seminars in Dialysis* 2:102-107, 1989.
10. Santoro S, Mancini E, Spongano M and Zucchelli P: The heart and cardiovascular instability during hemodialysis. *Rev Portug Nephrol Hypert* 1:15-27, 1991.
11. Degoulet P, Reach I, Di Giulio S, DeVries C, Rouby JJ, Aimè F and Vonlanthen M: Epidemiology of dialysis-induced hypotension. *Proc Eur Dial Transplant Ass* 18:133-138, 1981.
12. Zuccheli P: Hemodialysis-induced symptomatic hypotension. A review of pathophysiological mechanisms. *J Artif Organs* 10:139-144, 1987.
13. Zucchelli P, Sturani A, Zuccalà A, Santoro A, Degli Esposti E and Chiarini C: Dysfunction of the autonomic nervous system in patients with end-stage renal failure. *Contr Nephrol* (Karger, Basel) 45:69-81, 1985.
14. Zucchelli P, Zuccalà A and Santoro A: Hemodynamic alteration in aged patients during hemodialysis, other dialysis procedures and transplantation. In *Hypertension and renal Disease in the Elderly.* Martinez-Maldonado (ed.). Blackwell Scientific Publ. Boston. (In press.)
15. De Broe M: Acid Base Balance and ventilation in dialysis patients. *Contr Nephrol* (Karger, Basel) 71:40-51, 1989.
16. Mansell MA, Morgan SH, Moore R, King CH, Laker MF and Wing AJ: Cardiovascular and acid-base effects of acetate and bicarbonate haemodialysis. *Nephrol Dial Transplant* 1:229-232, 1987.
17. Veech RL: The untoward effects of the anions of dialysis fluid. *Kidney Int* 34:587-597, 1988.
18. Danielson A, Gutiérrez A, Hultman E and Bergstrom J: Patient-related factors influencing the plasma acetate concentration during haemodialysis. *Nephrol Dial Transplant* 2:526-530. 1987.
19. Monti JP, Gallice P, Baz M, Murisasco A, Crevet A and Elson R: Intraerythrocytic pH variations during hemodialysis: A 31 P-NMP Study. *Kidney Int* 35:871-874, 1989.
20. Vinay P, Prud'homme M, Vinct B, Cournoyer G, Degoulet P, Leville M, Gougoux A, St-Louis G, Lapierre L and Piette J: Acetate metabolism and bicarbonate generation during hemodialysis: 10 years of observation. *Kidney Int* 31:1194-1204, 1987.
21. Gutiérrez A, Alvestrand A, Wehren J and Bergstrom J: Effect of in vivo contact between blood and dialysis membranes on protein catabolism in humans. *Kidney Int* 38:487-494, 1990.
22. Bergstrom J, Alvestrand A and Furst P: Plasma and muscle free aminoacids in maintenance hemodialysis patients without protein malnutrition. *Kidney Int* 38:108-114, 1990.
23. Hakim RM: Assessing the adequacy of dialysis. *Kidney Int* 37:822-832, 1990.

24. Lindsay RM and Henderson LW: Adequacy of dialysis. *Kidney Int* 33 (Suppl. 24):S92-S104, 1988.
25. Gotch FA: Dialysis of the future. *Kidney Int* 33 (Suppl. 24):S100-S104, 1988.
26. Zucchelli P and Santoro A: Il modello di cinetica dell'urea rivisitato. In: *Nefrologia Dialisi Trapianto*. Atti XXIX Congresso Nazionale Società Italiana di Nefrologia, Giardini Naxos 8-11 Giugno 1988. Wichtig Editore Milano, 235-240, 1989.
27. Santoro A, Spongano M, Mancini E, Rossi M, Paolini F and Zucchelli P: L'instabilità cardiovascolare intradialitica ed il monitoraggio emodinamico. In: *Attualità Nefrologiche e Dialitiche*. Wichtig Editore, 31-43, 1990.