Chapter (16)

Ionic Dialysance and Conductivity Modeling

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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 (α) 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 α 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 ΔC 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 (ΔC) 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).

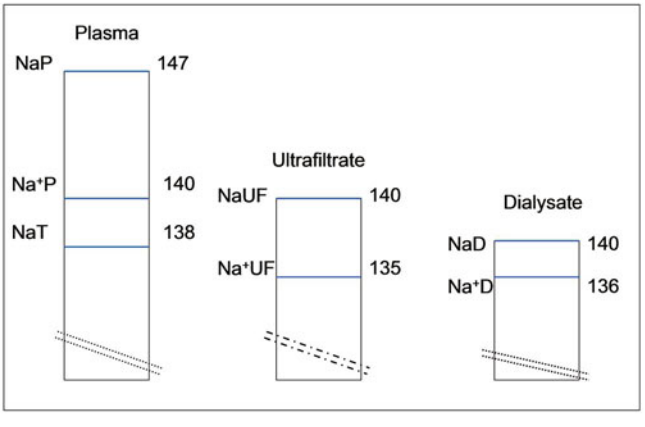

Fig. 16.1 Relationship between total plasma sodium concentration (NaT), Plasma Water Sodium Concentration (NaP) and Ionized Sodium Concentration (Na+P) in blood; between Total (NaUF) and Ionized Sodium (Na_{UF}^+) in the Ultrafiltrate; between Total (NaD) and Ionized Sodium (Na_D^+) in Dialysate.

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).

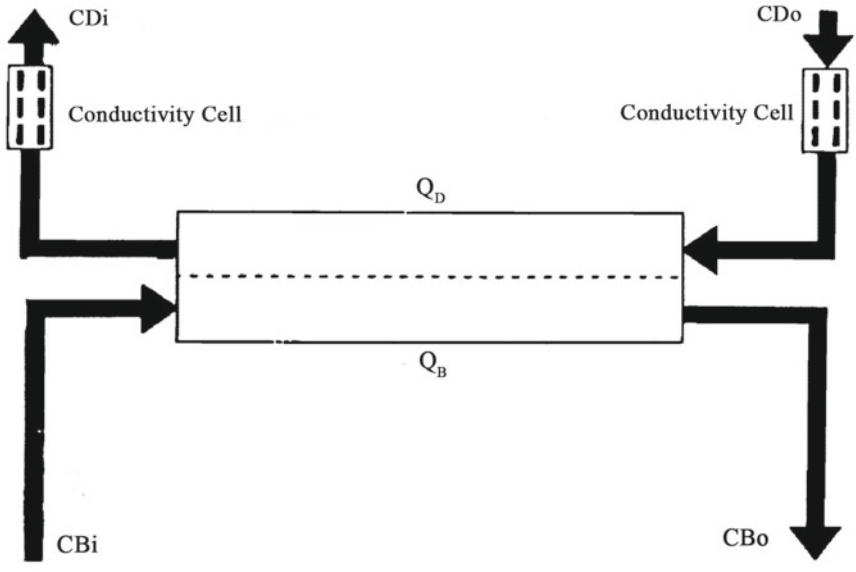

Fig. 16.2 Setup for dialysance measurement. C_{Bi} (C_{Bo}): blood inlet (outlet) concentration. C_{Di} (C_{Do}): dialysate inlet (outlet) concentration. Q_B (Q_D) blood (dialysate) flow. [Adapted from Lindsay RM, Sternby J (2005) Future directions in dialysis quantification. Semin Dial.; 14(4):300-7,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

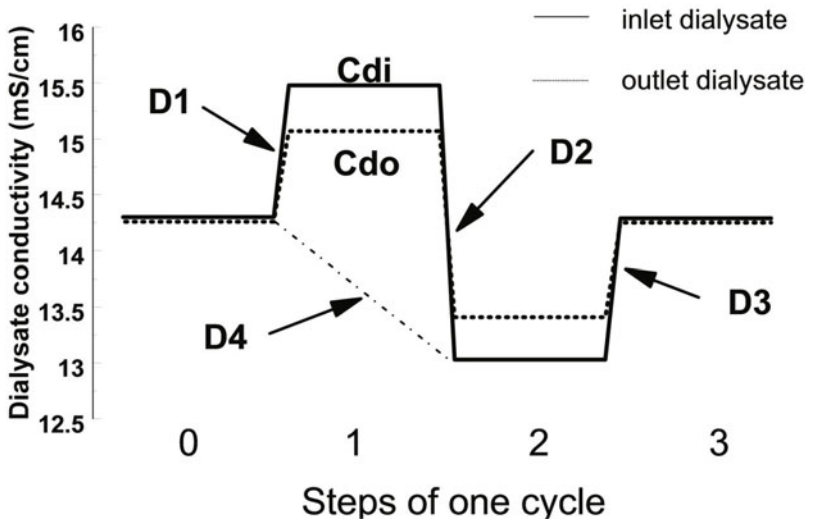

Fig. 16.3 Pattern of variation of inlet (solid line) and outlet (dashed line) dialysate conductivities. Starting at baseline conductivity (Step 0), the inlet dialysate conductivity (C_{di}) increased by 8% (Step1). After the target value was reached, C_{di} decreased to 8% below baseline (Step 2). When 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 (ΔC_{di}-ΔC_{do}) and the diffusive gradient (ΔC_{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 ΔC_{ns}) induced during the measurement. Recirculation of the acute $\Delta C_s Na$ or ΔC_{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}).

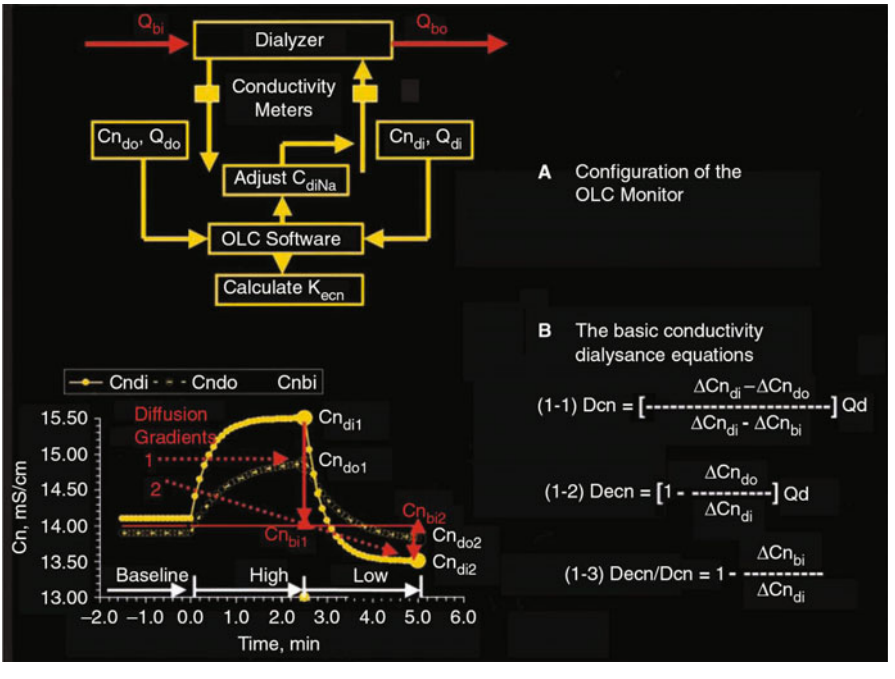

Fig. 16.4 (A) A schematic depiction of the on-line clearance monitor. (B) Typical dialysate inlet and outlet conductivity profiles and a stable blood inlet profile. The three basic conductivity dialysance equations are shown. [Adapted from Gotch FA, Panlilio FM, Buyaki RA (2004) Mechanisms determining 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 (ΔC_{ndi}, ΔC_{ndo}) and any change in ΔC_{nbi}. ΔC_{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).

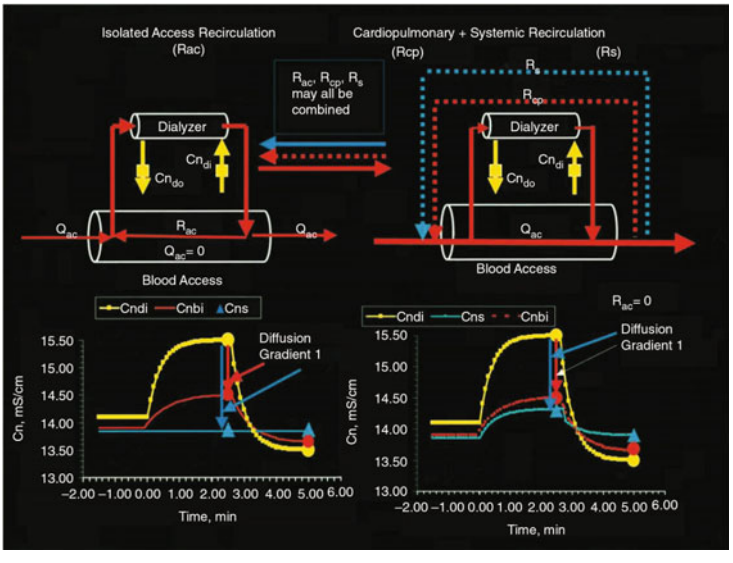

Fig. 16.5 The left upper and lower panels depict the effect of isolated access recirculation on effective conductivity dialysance. The right panels illustrate the effects of cardiopulmonary and salt loading with systemic recirculation on effective conductivity dialysance. Note that in each instance the 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 ΔNa_{pwi} and inversely proportional to ΔNa_{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 ΔNa_{pwi} and ΔNa_{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 ± 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