Kt/V: finding the tree within the woods

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**Keywords:** dialysis efficacy; Kt/V determination

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**Introduction**

Dialysis efficacy is one of the predominant factors determining survival in haemodialysis patients. The index Kt/V_urea_, which is a function of dialyser urea clearance, treatment time, and urea distribution volume, is by far the most commonly used marker for dialysis adequacy and was found to be related to morbidity and mortality in various studies [1,2]. Therefore, Kt/V_urea_ or more commonly called Kt/V, is generally proposed as the predominant treatment parameter in influential guidelines and multi-centre studies [3,4]. Nevertheless, despite the fact that the concept of Kt/V has been introduced more than 15 years ago [1], there is still ample discussion about the best method to assess this parameter. The main problem is that the so-called single-pool methods assume that urea is present in one homogeneous distribution volume. This is actually not the case, as is evident from the significant increase in blood urea nitrogen (BUN) after the termination of dialysis (rebound). In addition, the fact that large intra- and inter-individual differences exist in post-dialytic urea rebound may lead to significant errors in the estimation of dialysis dose, if solely calculated by the single-pool methods [5,6]. Therefore, a refinement of the methods to assess Kt/V appears to be mandatory.

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**Which types of rebound can be distinguished?**

There are three main causes of rebound after dialysis. The first type of rebound, occurring within 15–20 s after the end of dialysis is a result of access recirculation, if present. Still, using ultrasound dilution techniques, it appears that access recirculation is far less frequent than earlier believed and will occur predominantly when access flow is less than blood flow [7]. The second type of rebound is a result of cardiopulmonary recirculation, which takes place until 1–2 min after the end of dialysis. Cardiopulmonary recirculation, which is a result of the fact that a part of the purified blood which enters the venous circulation and the heart is directed immediately by the arterial system to the fistula without passing the tissues. This type of recirculation, which is partly dependent upon the efficacy of dialysis, is inherently present in every haemodialysis treatment, except in patients with central venous catheter [8].

The third type of rebound, which appears to be a result of a disequilibrium of urea distribution within different body pools, is not finished until 30–60 min after the end of dialysis, depending on the intensity of dialysis. It was shown that 99% of the post-dialytic urea rebound was complete at 48 min and 94% at 30 min [9]. The cause of this phenomenon is still subject of debate. A first hypothesis assumes that during dialysis, a concentration gradient exists between the intracellular and extracellular spaces, because of resistance of the cell membrane to urea transport.
which leads to rebound of urea from the intracellular space after the end of dialysis. A second hypothesis (regional flow model) assumes that this phenomenon is because of differences in perfusion of various tissues, which may lead to rebound of urea from the less well perfused regions of the body [10].

How to compensate for urea rebound

The best way to compensate for rebound is to measure blood urea 30–60 min after the end of dialysis. Despite the fact that rebound may not be entirely complete, the Kr/V, which takes the 30-min post-dialytic sample into account is often used in the literature as the reference method [4]. However, this approach is cumbersome in clinical practice both for hospital staff and patients. Therefore, several formulae have been developed in order to compensate for urea disequilibrium. One of the most frequently used formulae is the empirically derived Daugirdas–Schnedt formula, which corrects the single-pool Kr/V for treatment time [11]. The thus derived values were found to be well related to the actual equilibrated Kr/V, and to be as reliable as values based on dialysate collection techniques [4]. One factor that remains of concern is the post-dialytic blood urea sample in case of access recirculation. Therefore, two techniques have been proposed to eliminate the influence of recirculation by gradually reducing the speed of the blood pump just before the termination of dialysis (‘slow-flow’ and ‘stop-flow’ techniques), as immediate stopping of the blood pump may lead to ‘freezing’ of the blood sample and, thus, to under-estimation of the actual BUN in case of access recirculation. It should be pointed out that the most commonly used ‘slow-flow’ technique, which reduces blood pump speed to a low rate at the end of the haemodialysis session before blood sampling after approximately 15 s, only appears to compensate for access, but not for cardiopulmonary recirculation [12].

Another approach to compensate for urea disequilibrium is the use of additional blood samples during dialysis, from which the post-dialytic equilibrated BUN is estimated. The first description of such a method was performed by Smye et al. who proposed the use of an additional BUN sample 80 min after the start of dialysis. The theoretical basis for this approach lies in the fact that the urea disequilibrium can be predicted by the deviation from the linear curve of an intra-dialytic BUN sample [13].

There remains discussion in the literature about the agreement between the approach by Smye et al. and reference methods [4–6]. Other authors have proposed the use of an additional BUN sample 30 min before the end of dialysis [14,15]. Nevertheless, as shown by Castro et al. in this issue of the journal, this approach also appears to yield largely discordant results compared with the ‘gold standard’ technique of equilibrated post-dialytic BUN [16]. One of the problems with the intra-dialytic methods is the fact that small errors in the intra-dialytic sample may give large errors in the estimation of the equilibrated post-dialytic BUN [17]. Therefore, apart from the additional burden of taking three blood samples, there appears, in our opinion, to be little advantage in using additional intra-dialytic samples for the determination of Kt/V.

Direct urea monitoring

Although, if the correct approach is used, the assessment of Kt/V by pre- and post-dialytic blood sampling may give an adequate estimation of dialysis dose, the use of mathematical calculations may sometimes be a restriction for busy doctors. Although the use of calculators, which are also available on the Internet, partly offsets this problem, there appears to be a need for other methods to assess dialysis adequacy. An interesting approach is the estimation of urea removal via the dialysate, which can practically be calculated with the use of on-line urea monitors attached to the dialysate side of the module. The principle of these monitors is to measure urea in a portion of spent dialysate or ultrafiltrate, which is sampled frequently during the dialysis session. Urea is measured by changes in conductivity resulting from conversion of urea into ammonium and bicarbonate by the enzyme urease. Kt/V can be assessed with the urea monitor by measuring changes in dialysate urea concentration dialysate, which are proportional to changes of blood urea, or by total urea mass removal in relation to the estimated total urea body mass [18,19]. Urea removal is measured by the monitor by means of integration of the time-concentration profile of the urea appearing in the dialysate, which is necessary because urea removal progressively declines along the dialysis session, whereas total urea body mass is derived mathematically from the urea mass removal rate and the slope of the dialysate urea concentration curve [18,19]. When urea removal is used for determination of Kt/V, rebound needs not be considered because there is no rebound in the total urea mass of the body [19]. In contrast, when changes in dialysate urea concentration are used to assess Kt/V, a correction factor for rebound is necessary, which has been taken into consideration by the manufacturers.

Despite the fact that Kt/V assessed by dialysate and blood-sampling techniques, respectively, may differ to some degree in individual patients [20], in general, results between the two techniques appear to be comparable provided an adequate curve fit calculation for the dialysate side methods is used [4,18,19,21]. Moreover, on-line urea monitoring may also provide other relevant data, such as protein catabolic rate and urea distribution volume. Nevertheless, drawbacks of the use of direct urea monitoring are the costs and additional handling procedures for the dialysis staff.
Methods based on ionic dialysance

Another recently introduced approach estimates Kt/V from ionic dialysance. Ionic dialysance can be assessed during the dialysis session by temporarily increasing dialysate conductivity (equivalent to the dialysate sodium concentration) in the inlet port and measuring the change in conductivity at the dialysate outlet. The underlying assumption is that plasma conductivity does not change during temporary changes in dialysate conductivity because of the large sodium distribution pool [22]. Urea clearance can be assessed from ionic dialysance because sodium and urea have comparable molecular weights. This technique has already been integrated on some commercially available dialysis modules. Its great advantage would be the presence of an inexpensive, readily available on-line estimation of dialysis adequacy and sodium removal, which can be assessed at every dialysis treatment. Some theoretical and practical considerations, however, deserve attention. It has recently been pointed out that plasma conductivity may change to some degree during an increase in dialysate conductivity because of cardio-pulmonary recirculation [22]. Moreover, also the dialyser clearance and the charge of the dialysate membrane may influence the relation between ionic dialysance and urea clearance [23]. It should also be pointed out that by the ionic dialysance methods only clearance and treatment time are estimated, whereas the V component has to be derived from anthropometric formulae or kinetic modelling. Nevertheless, in preliminary studies, ‘Dt/V’ assessed by ionic dialysance appeared to be well related to Kt/V determined by urea kinetic modelling [24], so that in our opinion this method certainly deserves further consideration and study.

Conclusion

Calculation of Kt/V by single-pool models has the theoretical disadvantage of overestimating dialysis dose as a result of post-dialytic urea rebound. Therefore, newer formulae, which are certainly more correct from a theoretical point of view, have been developed to account for the post-dialytic urea disequilibrium. It is to be expected that these formulae will replace the older mathematical models in the future. In the meantime, it should not be forgotten that in the large studies relating outcome to mortality, single-pool calculations were actually applied and that the DOQI guidelines propose the use of an adjusted single-pool calculation for the determination of Kt/V [1–3]. In our opinion, newer methods, based on dialysate urea monitoring or ionic dialysance will probably gain wider popularity and deserve further study in larger trials.

We should not forget the obvious fact that, important as this parameter may be, Kt/V as a clearance marker of small molecular weight substances focuses only on one part of dialysis treatment. Good dialysis means more than an adequate Kt/V. Consideration of the best way to calculate Kt/V should go hand in hand with improvement of all the other aspects of dialysis therapy.

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Editor’s note

Please see also original article by Castro et al., pp. 1814–1817.