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A mechanistic analysis of the National Cooperative Dialysis Study (NCDS)

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A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). The purpose of the NCDS was to determine the probability of clinical failure (PF) as a function of the level of dialysis and protein catabolic rate (pcr, g/kg/day). The level of dialysis prescribed in the NCDS was mechanistically defined as Kt/V (product of dialyzer urea clearance and treatment time divided by body urea volume), which exponentially determines decrease in BUN during dialysis and is also a mathematical analogue of pcr, BUN. Mechanistic analysis (MA) showed that PF was a discontinuous function of Kt/V as it was prescribed in the NCDS and that a dependence of PF on pcr could not be assessed because of the study design. The MA results were compared to those reported with statistical analysis (SA) that used BUN and pcr. The SA predicts PF is strongly dependent on pcr with nutrition-dependent high PF for pcr $\leq$ 0.8 and low PF with high pcr and intensive dialysis. The MA suggests SA results may not be valid because a continuous outcome function is assumed and, due to study design, Kt/V was a dependent variable of pcr and these two variables cannot be clearly separated by analysis of BUN and pcr alone.

Une analyse mécaniste de la National Cooperative Dialysis Study (NCDS). Le but de la NCDS a été de déterminer la probabilité d'un échec clinique (PF) en fonction des niveaux de dialyse et de la vitesse de catabolisme des protéines (pcr, g/kg/jour). Le niveau de dialyse prescrit lors de la NCDS était défini de façon mécaniste comme Kt/V (produit de la clairance de l'urée du dialyseur et du temps du traitement divisé par le volume corporel de l'urée), lequel détermine de façon exponentielle la diminution de BUN au cours de la dialyse et est également un analogue mathématique de pcr, BUN. L'analyse mécaniste (MA) a montré que PF était une fonction discontinue de Kt/V, tel qu'il était prescrit lors de la NCDS, et qu'une dépendance de PF sur pcr ne pouvait être précisée en raison du schéma de l'étude. Les résultats de MA ont été comparés à ceux rapportés par analyse statistique (SA) lesquels utilisaient BUN et pcr. SA prédit que PF dépend fortement de pcr, avec un PF élevé, dépendant de l'alimentation, pour pcr $\leq$ 0.8, et un PF bas avec un pcr élevé et une dialyse intense. La MA suggère que les résultats de SA pourraient n'être pas valables car elle suppose le devenir comme une fonction continue, et en raison du schéma de l'étude, Kt/V était une variable dépendante de pcr. Ces deux variables ne peuvent être clairement séparées par l'analyse de BUN et de pcr individuellement.

The concept of a National Cooperative Dialysis Study (NCDS) arose from the National Institutes of Health-sponsored conference on Adequacy of Dialysis held in 1975 [1]. The persisting pathophysiology of multiple organ systems in dialyzed patients was reviewed in depth at that conference, and it was concluded that a carefully controlled multicenter cooperative study was required to determine if quantitative relationships between residual morbidity and the magnitude of dialysis prescribed could be established.

The NCDS undertaken subsequently was a large-scale, carefully controlled study with comprehensive monitoring of multiple treatment and outcome variables [2]. The probability of clinical outcome failure in dialyzed patients as a function of multiple treatment variables has been determined by stepwise logistic regression, which is similar to ordinary multiple linear regression [3]. The statistical model predicts that failure is very high with protein intake less than .8 g/kg/day due to inadequate protein nutrition and that minimal failure is associated with high levels of protein intake (1.1 to 1.6 g/kg/day) and intensive dialysis [4] when quantitatively interpreted.

Consideration of the mechanisms of uremia, nutritional requirements, and rates of hydrogen ion, potassium, and phosphate loading at high levels of protein intake results in some skepticism with regard to these statistically derived results. A reasonable approach would suggest that if the statistical results are correct, it should be possible to reach the same conclusions by mechanistic analysis of the nutritional and dialytic parameters. The following is the result of such a mechanistic analysis.

Design of the study

It is necessary to review the design of the NCDS to elucidate the mechanistic interrelationships between the dialysis treatment and nutritional variables. The variable volume urea kinetic model [5, 6] was used to design and control the NCDS. The clinical rationale for this model was based on two concepts: *1)* Both inadequate and excessive protein intake are common and undesirable in dialysis patients and, therefore, dietary protein intake, as measured by the kinetically determined normalized protein catabolic rate (see Eq(9) Appendix, pcr, g/kg/day), should be documented to be within the usually accepted normal range of 1.1 $\pm$ .3; and *2)* the magnitude of dialysis required for adequate therapy is dependent on the pcr and should be sufficient to result in a relatively fixed midweek predialysis BUN (CO_2, mg/dl) at the prevailing pcr for individual patients. Thus, the urea model was used to determine pcr

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and the level of dialysis required to achieve specified BUN levels with thrice weekly treatments.

The study was designed initially to compare outcome with two nominal CO_2 levels of 70 and 120 mg/dl over the targeted pcr range 1.1 ± .3 g/kg/day. However, at the extremes of pcr, it was apparent that achieving these fixed CO_2 levels would be very difficult technically. At low pcr, extremely low dialyzer clearances would be required to achieve CO_2 of 120 while at high pcr, very high clearances would be required to achieve CO_2 of 70 mg/dl. Consequently, the time averaged concentration (TAC) of BUN was used and targeted at 50 and 100 mg/dl. This resulted in targeting BUN at the middle of the sawtoothed concentration profile rather than the maximum CO_2 values, was a little less sensitive to the extremes of pcr and more feasible technically. However, there was clear separation of both CO_2 and TAC between the low and high BUN therapies and the CO_2 values (averaging ~ 70 and 110) will be used primarily in this analysis because they are clinically more familiar and mathematically can be related more directly to the level of prescribed dialysis. As will be shown quantitatively below, this study design resulted in a linear dependence on pcr of the amount of dialysis prescribed so that the treatment and nutritional variables cannot be treated as independent variables.

Control of middle molecules was also partially addressed in the study design. The low and high BUN groups were each divided into long and short treatment time groups so that the effect of middle molecule removal could be evaluated, middle molecule flux being more time dependent. The four experimental groups thus established were: Group 1 = TAC of 50 (CO_2 ~ 70) and treatment time 4.5 to 5.0 hr; Group 2 = TAC of 100 (CO_2 ~ 110) and treatment time 4.5 to 5.0 hr; Group 3 = TAC of 50 (CO_2 ~ 70) and treatment time 3 ± 0.5 hr; Group 4 = TAC of 100 (CO_2 ~ 110) and treatment time 3 ± 0.5 hr.

Mathematic interrelationships between dialysis and nutritional variables

The urea model was used to measure pcr in each patient and to prescribe two levels of dialysis corresponding to CO_2 values of ~ 70 or ~ 110 mg/dl. The study results show this was fairly well achieved with an average difference in CO_2 of 38 mg/dl between the low and high BUN target levels over a pcr range of 0.6 to 1.4 g/kg/day (see Fig. 3). Thus, the study provided two clearly separated levels of therapy, as defined by BUN, over a wide pcr range and statistical analysis of outcome was based primarily on the BUN and pcr variables.

The physiologic mechanisms by which dialysis controls uremic morbidity remain unknown. The BUN has not been shown to have concentration-dependent toxicity in the range studied, but is traditionally considered to be a marker molecule to indicate the level of dialysis prescribed. The mechanism by which dialysis controls BUN in an individual patient can be quantified from the total urea clearance prescribed, which is given by the product of the dialyzer urea clearance (K, ml/min) and the treatment time (t, min). This parameter can be generalized by normalization to the urea distribution volume (V, ml) as Kt/V, a dimensionless parameter that describes the prescribed fractional clearance of total body water. The mathematical meaning of Kt/V is shown in Eq(1) of the Appendix where it can be seen to exponentially determine the total decrease in BUN during a dialysis treatment.

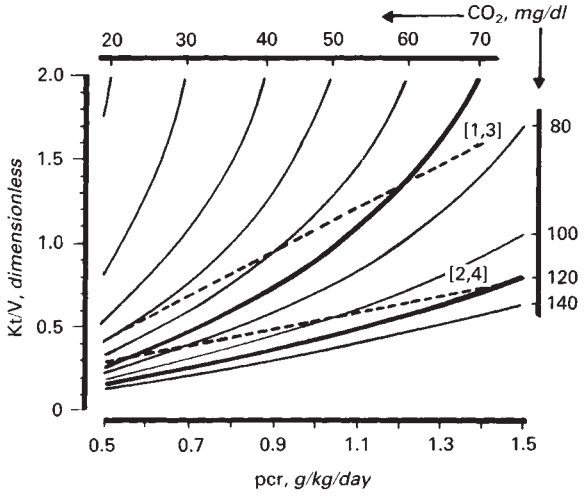

Fig. 1. *The relationship of Kt/V to pcr for constant CO_2.*

Although Kt/V in this analysis refers specifically to the fractional urea clearance, it also provides an index to proportionate fractional clearances provided by the dialyzer of all low molecular weight toxic substances that may be accumulating in uremic plasma. In this sense, Kt/V can be considered to be a more fundamental mechanistic parameter of the level of dialysis prescribed compared to BUN which represents the concentration of a single relatively non-toxic solute. Thus, Kt/V is a basic, generalizable dialysis parameter and serves as the basis of the mechanistic analysis reported here.

If Kt/V and CO_2 were similarly related to the nutritional pcr parameter, these conceptual differences would be of no significance and Kt/V and CO_2 could be considered to be interchangeable dialysis parameters. However, it can be shown that mathematically Kt/V and CO_2 have quite different functional relationships to pcr. Although the rigorous variable volume urea model was used to control the study, these differing functional relationships can be illustrated using a truncated version of the model. The key relationships are listed below, while formal development can be found in the Appendix.

$$(1) \qquad -\frac{Kt}{V} \simeq \ln\left[1 - \frac{.49\,(pcr - .16)}{CO_2}\right]$$

$$(2) \qquad CO_2 \simeq .49\left[1/\left(1 - e^{\frac{-Kt}{V}}\right)\right](pcr - .16)$$

Sensitivity of BUN to pcr and magnitude of dialysis, Kt/V

Equation (1) demonstrates how Kt/V was prescribed as a function of pcr with CO_2 held relatively constant at levels of ~ 70 and ~ 110 mg/dl. Numerical solution of this approximation expression for constant CO_2 values over a wide range is shown in Figure 1. The loci of these curves is of considerable interest and demonstrate the complex relationships of CO_2, Kt/V, and pcr.

Consider first the lower bound of pcr shown, .5 g/kg/day. It is apparent that, due to a low urea generation rate, CO_2 is very sensitive to slight changes in Kt/V in the target CO_2 range of 70 to 120 mg/dl. Although the CO_2 values are substantially separated, there is trivial

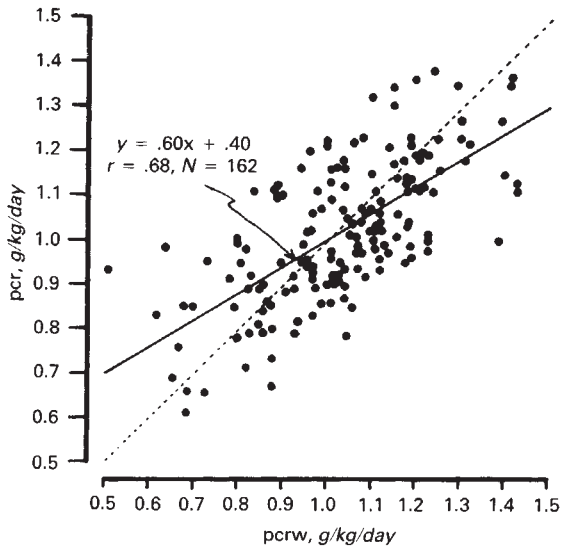

Fig. 2. *Comparison of pcr to pcrw.*

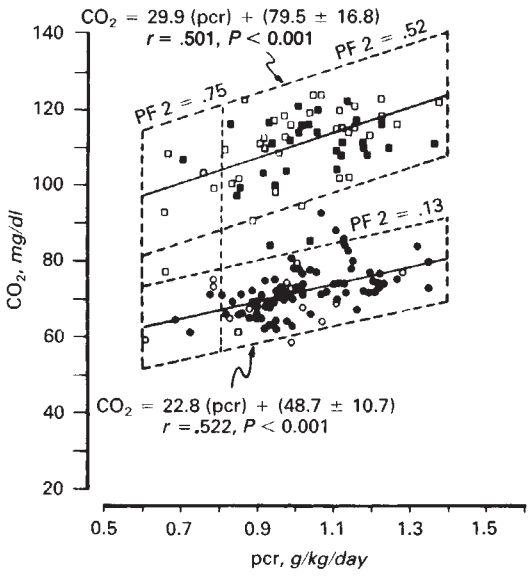

Fig. 3. *The domains of groups 1,3 and 2,4 patients as a function of pcr and CO_2.* Symbols are: ●, group 1,3 success; ■, group 2,4 success; ○, group 1,3 failure; □, group 2,4 failure.

separation of Kt/V with values of .27 and .15 shown for the low and high BUN target values, respectively.

At the upper bound of pcr, the constant BUN lines become widely separated with a much larger increase in Kt/V for a given decrease in BUN. This is due to the high interdialytic urea generation rate and the need to reduce BUN to very low end-dialysis levels so that the interdialytic rise will not exceed the pre-dialysis target level. Since removal is first order (that is, proportional to BUN), it becomes progressively less efficient as BUN falls so that therapy represented by Kt/V increases sharply as BUN decreases. This effect can be seen in Figure 1 where Kt/V increases from .71 to 2.02 as CO_2 is reduced from 120 to 70 mg/dl at pcr = 1.4 g/kg/day.

The actual regression of Kt/V on pcr found in the NCDS for the groups 1,3 and 2,4 patients are also depicted as dotted lines on Figure 1. The slopes are linear and somewhat shallower than the curves of constant BUN at 70 and 120 mg/dl. As noted earlier, this reflects the decision to hold TAC rather than CO_2 constant at two levels that somewhat flattened and linearized the dependence of prescribed Kt/V on pcr. However, the general relationship of reduced Kt/V at low pcr, irrespective of the BUN target, and marked separation of Kt/V between low and high BUN groups at high pcr is still readily apparent. At pcr = .6, the Kt/V are .34 and .55 for the high and low BUN groups, respectively, while at pcr = 1.4, these values are .74 and 1.59.

The actual Kt/V vs pcr lines, as depicted in Figure 1, are linear and yield regressions of:

Kt/V = 1.29(pcr) − (.22 ± .26), r = .813, $P < 0.001$ (groups 1,3)

Kt/V = .51(pcr) + (.03 ± .14), r = .758, $P < 0.001$ (groups 2,4)

The slopes of these regressions are constants defining the level of treatment (Kt/V) prescribed relative to pcr (Kt/V /pcr, kg · day · g^{-1}) and, as such, are fundamental Treatment/Nutrition (T/N) constants for the low and high BUN groups. The value of T/N for groups 1,3 was two and a half times that for groups 2,4, indicating that to maintain a patient in group 1,3, treatment had to increase 2.5 times more in response to increased pcr compared to a patient in groups 2,4. However, the absolute level of treatment prescribed differs very little between groups 1,3 and 2,4 at low pcr values.

The determining factors of BUN are nutrition (in the form of protein and its catabolism) and treatment related. In fact, the BUN level will reflect the level of protein catabolism relative to the treatment provided:

$$\text{BUN} = \frac{\text{Nutrition}}{\text{Treatment}} = f\left(\frac{\text{pcr}}{\text{Kt/V}}\right)$$

The BUN provides no insight into how treatment varies relative to nutrition since the two variables are not separated. The level of treatment, when expressed as the mechanistic parameter Kt/V, is clearly separated from the nutritional variable and provides a non-ambiguous parameter of treatment.

Clinical consideration of treatment separation at low and high pcr

The relationship of Kt/V to pcr shown in Figure 1 for the groups 1,3 and 2,4 patients can be better appreciated in a clinical context by examination of the actual treatment prescribed for a patient of average size at low and high pcr. At pcr = .6, the $\overline{\text{Kt/V}}$ values are .55 and .34 for the low and high BUN groups. Assuming an average V = 37,000 ml and t = 234 min (3.9 hr), it can be readily calculated that dialyzer clearances of 84 and 51 ml/min would be prescribed. These clearances are minimally separated and typical of the low efficiency parallel ridge support Kiil dialyzers widely used 20 years ago with treatment times of 8 to 12 hr, which results in Kt/V values of ~ 1.0. Thus, in both groups 1,3 and 2,4 patients with low pcr, the average treatment consisted of dialysis for ~ 4 hrs with dialyzer efficiency about one-half to one-third of modern dialyzers. The marked reduction in treatment at low pcr for both high and low BUN groups in the NCDS is more clinically apparent when viewed in this historical perspective.

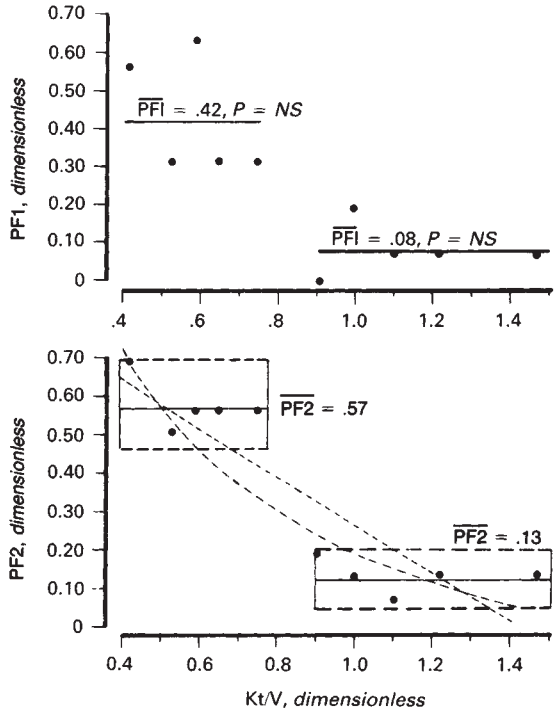

Fig. 4. *The relationships between probability of failure 1 (PF1) and probability of failure 2 (PF2) to the level of dialysis, Kt/V.*

At pcr = 1.4, similar calculations show that the average patient in the low BUN groups would require dialyzer clearance of 245 ml/min, while in the high BUN groups a clearance of 108 ml/min would be prescribed. Thus, prescribed clearance ranged from 84 to 245 ml/min as a function of pcr in groups 1,3, but covered a much smaller range in groups 2,4, from 51 to 108 ml/min.

The relationship of BUN to pcr at constant level of dialysis, Kt/V

Equation *(2)* above demonstrates the approximate relationship of CO_2 to pcr as a function of Kt/V. The expression indicates that when Kt/V is held constant, CO_2 will increase linearly with pcr, and the slope will approximately equal .49 $[1/(1 - e^{-\frac{Kt}{V}})]$. Examination of the slope term shows that it will decrease as Kt/V increases and approach a limit of .49 when Kt/V is very large and $e^{-\frac{Kt}{V}} \rightarrow 0$. Thus, if lines of constant treatment (Kt/V) are plotted on pcr, CO_2 coordinates there will be marked separation at low Kt/V values with lines merging to approach CO_2 = .49(pcr − .16) as Kt/V increases. This will provide a graphic portrayal of the simultaneous relationships between pcr, CO_2 and Kt/V as the level of dialysis (Kt/V) is incresed over the entire pcr, CO_2 domain and will be used in the course of discussion of pcr, CO_2 mapping of NCDS data (Fig. 6). In this figure, the rigorous urea model was solved for CO_2 for the case of V = 37,000 ml, residual renal urea clearance (Kr)=0, interdialytic weight gain = .75 kg/day and with typical asymmetric thrice weekly treatment over a wide range of pcr and Kt/V values. The original data points for groups 1,3 and 2,4 patients are also depicted to portray visually the relationship of these to the level of dialyssis prescribed. The loci of these curves again demonstrate that CO_2 is a complex function of both Kt/V and pcr and does not provide a clear separation of dialysis and nutritional variables.

Analysis of outcome with BUN and pcr vs. analysis with Kt/V, BUN, and pcr

Equations *(1)* and *(2)* show that there are three mathematically and mechanistically related kinetic parameters describing the levels of protein nutrition and dialysis in this study. The statistical analysis was based on two kinetic varibles, BUN and pcr standing alone [3], while the mechanistic analysis reported here is based on all three of the interrelated variables Kt/V, BUN, and pcr clearly separated. Further simplification and rearrangements of Eq*(1)* are helpful to clarify the significance of these differences between the statistical and mechanistic analyses. Simplification of the functional relationships between Kt/V, BUN, and pcr in Eq*(1)* can be expressed as

$$\frac{Kt}{V} = f1\left[\frac{pcr}{BUN}\right] \tag{3}$$

$$BUN = f2\left[\frac{pcr}{Kt/V}\right] \tag{4}$$

$$pcr = f3\,[(Kt/V) \cdot BUN] \tag{5}$$

Equation *(3)* shows that analysis of outcome dependence on Kt/V can also be considered mathematically to be equal to analysis of outcome as a function of $\frac{pcr}{BUN}$. To analyze outcome as a simultaneous function of all three variables it is necessary to clearly separate each variable. This was accomplished in two steps in the mechanistic analysis by first analyzing outcome as a function of Kt/V and then as a function of Kt/V, BUN, and pcr using the graphic relationships between the three variables in Figure 6.

In the statistical analysis, only BUN and pcr are included in outcome analysis and thus only two of the three interrelated nutritional and treatment variables are included. Although it would appear that BUN and pcr are discrete, separated treatment and nutritional variables, Eqs *(4)* and *(5)* show that BUN is a function of pcr/(Kt/V) while pcr is a function of (Kt/V)(BUN). This can be perceived more clearly from consideration of the logistic regression equation used for statistical analysis [3]:

$$\ln [F/(1 - F)] = \beta 0 + \beta 1 BUN + \beta 2 pcr \ldots + \beta k \chi ki \tag{6}$$

The difficulty with considering BUN and pcr as discrete independent variables can be best visualized by substituting Eqs *(4)* and *(5)* into *(6)*, which results in

$$\ln [F/(1 - F)] = \beta 0 + \beta 1\,[f2(pcr/(Kt/V))] + \beta 2\,[f3\,[(Kt/V)(BUN)]] \ldots + \beta k \chi ki \tag{7}$$

It is apparent from Eq*(7)* that because of the kinetic relationships BUN and pcr cannot be considered to be separated independent variables in the logistic regression, although they appear to be. Each of these variables is dependent on the other variable as a function of Kt/V and, as discussed earlier, Kt/V

was a dependent variable of pcr and BUN due to the study design. We believe it is particularly troublesome in the statistical analysis to consider pcr as a discrete variable having specific nutritional significance with respect to outcome of therapy in the context of this study. This will be considered more fully later.

Methods

The mechanistic analysis of outcome is based on the mean values of Kt/V, pcr, and CO_2 for each patient throughout the experimental phase of the study.[1] Clinical outcome was comprehensively monitored and detailed reports on the many organ systems describing the magnitude of residual morbidity for individual organ systems provide a wealth of detailed pathophysiologic information [2]. However, to systematically analyze the four therapy groups, an overall description of morbidity was required and developed [3] based on two quantifiable criteria, medical drop out (MDO) and hospitalization (H), which could be used to categorize the overall outcome for each patient. The MDO criterion was based on the appearance of de novo clinical abnormalities or worsening of residual morbidity in any organ system. The clinical abnormalities resulting in MDO were largely gastrointestinal (anorexia, nausea, vomiting, and GI bleeding), cardiac (pericarditis, pleuritis, sudden death, and congestive heart failure) and hematologic (increased anemia and transfusion requirements). Patients withdrawn from the study due only to MDO were categorized as falling into failure mode 1 (F1). A second failure mode (F2) was defined comprised of H and/or MDO so that if a patient experienced either H or MDO the outcome was categorized as F2. The success/failure modes 1 and 2 classification for each patient used for the mechanistic analysis was obtained from NCDS staff and therefore identical to that used in the statistical analysis of the data.

Clinical outcome as a function of Kt/V

The entire experimental data base was ordered by increasing values of mean Kt/V for individual patients and outcome for each patient recorded as success, failure 1, or failure 2. The ordered data was divided into ten equal groups of 16 patients and then the mean Kt/V and fraction of patients exhibiting F1 or F2 were calculated for each group. These data were then used to analyze the dependence of outcome failure on Kt/V.

Comparison of PCR/wt and PCR/(V/.58)

The final data analysis with the statistical model [3] was based on pcrw, PCR divided by body wt, while the therapeutic recommendations resulting from the statistical model [4] were based on pcr, PCR divided by V/.58. The mechanistic model analysis and therapeutic recommendations are based entirely on pcr. Since two definitions of normalized net protein catabolic rate (considered equivalent to dietary protein intake under these conditions) are used for analysis and therapy, it is important to examine how they relate to each other.

The term pcrw is calculated from

$$\text{pcrw} = \frac{\text{PCR}}{\text{wt}} = \frac{k \cdot \Delta\text{BUN} \cdot V}{\text{wt}} \tag{8}$$

where ΔBUN is the interdialytic rate of increase in BUN, V is urea distribution volume and k is an appropriate proportionality constant (see Appendix for more detail.

The pcr term is calculated from

$$\text{pcr} = \frac{\text{PCR}}{V/.58} = \frac{k \cdot \Delta\text{BUN} \cdot V}{V/.58} = .58k \cdot \Delta\text{BUN} \tag{9}$$

The definitions of pcrw and pcr are not identical. In the case of pcrw, the k · ΔBUN term is multiplied by V/wt while in the case of pcr, the k · ΔBUN term is normalized to V/.58 and V cancels out of the expression. Although both definitions include ΔBUN in the calculation, they differ with respect to V/wt.

The overall relationship between pcr and pcrw can be seen by dividing Eq(7) by Eq(6) resulting in

$$\frac{\text{pcr}}{\text{pcrw}} = \frac{\text{Wt}}{(V/.58)} \tag{10}$$

When pcr/pcrw is unity, wt must be equal to (V/.58). The ratio of pccr/pcrw for all NCDS experimental phase data was 1.00 ± .15, M ± SD, $N = 162$ and reflects the mean ratio of V/wt = .59 ± .08 in the data base. Thus, overall, pcr, and pcrw agree well, since the normalization term V/.58 closely approximates the actual mean value of .59 for V/wt in the data base.

Linear regression of pcr on pcrw in the data base is shown in Figure 2 and given by

$$\text{pcr} = .60\text{pcrw} + (.40 \pm .23),\ N = 162,\ r = .68 \tag{11}$$

The regression of pcr on pcrw is compared in Figure 2 to a slope 1.0 regression through the origin. The actual regression line intersects the slope 1.0 regression at the point where pcr = pcrw = 1.0 and is rotated clockwise around this point. The regression difference of (pcr − pcrw), g/kg/day, is + .2 when pcrw = .5, zero when pcrw = 1.0, and − .2 when pcrw = 1.5 g/kg/day. Thus, there is a small, predictable difference between pcr and pcrw at the lower and upper bounds of their values. However, as will be shown later (Fig. 5), both the mechanistic and statistical models show a similar dependence of outcome on either BUN and pcr or BUN and pcrw if outcome is assumed to be continuous function of either of these parameters.

There is no disagreement with NCDS staff conclusions that pcr is clearly preferable to pcrw for prescription of protein

[1]These values were computed from the kinetic data contained in the final raw data files of the NCDS at the close of the study and obtained from the Harvard Health Sciences Computer Facility. The quality of kinetic data was monitored throughout the study on each patient by interactive modeling sessions between the participating center and the kinetic control facility, Quantitative Medical Systems. Additionally, the Harvard Health Sciences Computing Facility performed kinetic error detection evaluations throughout the study. Consequently, the incidence of kinetic data entry and coding errors in the final raw data base was very low at .26 and .98%, respectively [7]. The pcr and CO_2 were each measured 20 to 30 times over the six-month experimental period and Kt/V reported 70 to 80 times for each patient. The data base used for this mechanistic analysis underwent subsequent additional data processing at Harvard, during which additional data entry and coding errors were corrected for creation of the final data base used for analyses by the NCDS. Although the kinetic data base used for the mechanistic analysis is not quite identical with the final clean data base, it is not reasonble to think that significant differences would result in the mean kinetic parameters calculated here in view of the large number of measurements comprising each mean value and the demonstrated low incidence of kinetic entry and coding errors. We assume responsibility for the quality of these data and for our analysis and interpretation, which may not reflect the opinion of the NCDS staff.

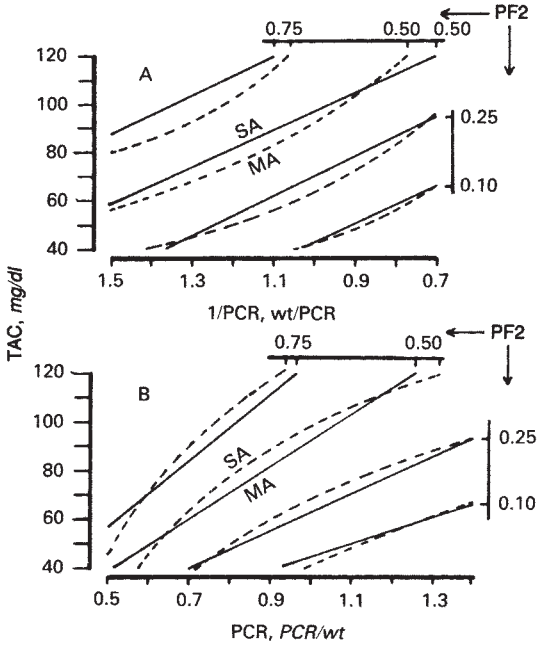

Fig. 5. *Prediction of failure by statistical analysis (SA) compared to mechanistic analysis (MA) with continuous function assumed.*

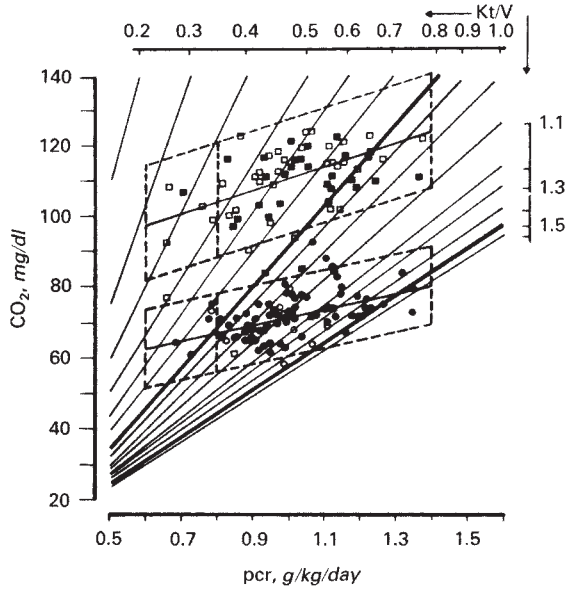

Fig. 6. *The distribution of groups 1,3 and 2,4 patients with respect to pcr, CO_2, and Kt/V.* Symbols same as Fig. 3.

intake and dialysis. Lowrie and Teehan recommend use of pcr [4], as do we because of the rigorous mathematical relationships between CO_2 (and TAC), pcr, and Kt/V as depicted in Figure 6. For example, if pcr is known and a specific CO_2 targeted, it is possible to read directly from Figure 6 the Kt/V required. When pcrw is used, there is a similar approximate relationship between these variables, but it may vary considerably in individual patients depending on body water content.

Results of mechanistic analysis

The simplest portrayal of outcome might be that shown in Figure 3 where the groups 1,3 and 2,4 domains are shown on pcr, CO_2 coordinates, and definition 2 success and failure are coded. It is apparent that probability of failure 2 (PF2, dimensionless) was much higher for groups 2,4 than 1,3 patients with pcr > .80 with PF2 values of .52 and .13, respectively. It is also apparent that PF2 was high (PF2 = .75) in both high and low BUN groups when pcr < .80. This is quite puzzling conceptually in that it suggests that PF2 might be BUN dependent for pcr > .80 and BUN independent for pcr < .80. A possible interpretation is that two mechanisms of failure are involved: *1)* With low pcr there is failure due to inadequate protein nutrition; *2)* with adequate pcr, failure is dialysis dependent.

The results of analysis of PF1 and PF2 as functions of Kt/V are shown in Figure 4. The relationships are similar for PF1 and PF2 so only the more inclusive PF2 will be discussed in detail. What is clear from Figure 4 is that there was persistent high PF2 (57% failure) at Kt/V values from .4 to .8, which dropped abruptly to low levels (13% failure) when Kt/V values exceeded .9 (from .9 to 1.5). Within these two Kt/V ranges there was no significant relationship between morbidity and Kt/V (regression analysis shows zero slope in each range). Consequently, Figure 4 indicates a step function relating morbidity to normalized treatment and thus shows that the relation of morbidity to the level of treatment cannot be considered to be a continuous function.

The data depicted in Figure 4 can be mathematically analyzed in a variety of ways, yielding highly significant statistical relationships. If a linear dependence of PF2 on Kt/V is assumed the resulting regression equation is

$$PF2 = .904 - .641(Kt/V),\ r = .883,\ P < 0.001$$

If PF2 is assumed to exponentially approach zero, the resultant function is

$$PF2 = 1.797e^{-2.239(Kt/V)},\ r = .858,\ P = 0.002$$

These two regression curves are shown on Figure 4 and obviously fit the data to continuous functions reasonably well. Inspection of the data, however, shows that they conform to a discontinuous step function with sharp decrease in PF1 and PF2 in the region of Kt/V = .80. It is apparent that highly significant continuous functions can be found to describe the relationship because the data distribution conforms to essentially two clusters of points, which are widely separated on both the ordinate and abscissa.

Equation *(3)* shows that analysis of outcomes as a function of Kt/V is mathematically equal to analysis of outcome as a function of pcr and BUN. Therefore, it would be expected that if outcome is assumed to be a continuous function of Kt/V and outcome predicted by this analysis is transformed to pcr, TAC coordinates, the resulting outcome plot should be very similar to that resulting from the logistic statistical analysis based on TAC, pcrw. In other words, both analyses should give very similar results when continuous functions are assumed to describe the relationships since both analyses are based on pcr or pcrw and BUN or their mechanistic analogue, Kt/V.

Figure 5 demonstrates the similarity in mechanistic and statistical prediction of outcome based on Kt/V or PCR/Wt, TAC assuming a continuous function. The exponential expres-

sion above was taken to be the regression of PF2 on Kt/V, solved for constant levels of failure ranging from .75 to .10, and then Kt/V was transformed to pcr, TAC coordinates. The resultant constant outcome curves are plotted in Figure 5 along with constant outcome curves calculated from the logistic statistical model regression coefficients [3] for t = 3.9 hr and no prehospitalization. In Figure 5A the abscissa is expressed as 1/pcr for the mechanistic Kt/V regression and wt/PCR for the logistic statistical analysis (SA). The statistical outcome curves are linear since the data was actually fit to the linear statistical model as Wt/PCR [3], while the MA outcome curves are nonlinear since Kt/V relates directly, not reciprocally, to pcr. In Figure 5B where the abscissa is expressed as pcr and PCR/wt, the MA curves are linear while the statistical curves are nonlinear, the inverse of Figure 5A.

It is apparent from the curves in Figures 5A and B that mechanistic analysis with Kt/V alone gives results very similar to logistic statistical analysis with Wt/PCR and TAC alone when continuous functions are assumed for both analyses. The location of the constant outcome curves on pcr, TAC coordinates are nearly identical but curvilinear or linear depending on whether or not pcr and pcrw are expressed reciprocally. As noted above, the analyses agree well because pcr and BUN are an analogue of Kt/V. However, mechanistic analysis of outcome as a function of the Kt/V analogue, which can be readily visualized graphically in Figure 4, shows outcome is a discontinuous function of Kt/V and hence of pcr and BUN.

It does not follow that Kt/V is the sole parameter determining the clinical outcome of dialysis therapy. The kinetics and study design resulted in a strong relationship between prescribed Kt/V to pcr and CO_2 so that outcome dependence on Kt/V must also be analyzed with respect to pcr and CO_2. The distribution of all patients (with success/failure coded) is depicted in Figure 6 on pcr, CO_2 coordinates, with Kt/V identity lines depicted as well. This plot reveals the graphic interrelationships of these three variables clearly separated. Inspection of these data shows that both pcr and CO_2 distribute over a wide range for Kt/V < .80. The mechanistic reasons are that, due to the kinetic relationships and the study design, all of the groups 2,4 patients with high BUN have low Kt/V values at all levels of pcr and the groups 1,3 patients with low pcr have low BUN and Kt/V values. Thus, it can reasonably be concluded that levels of prescribed Kt/V < .80 provide inadequate dialysis with high probability of failure irrespective of pcr (and hence BUN). This provides a simple, unified explanation for the puzzling outcome results depicted in Figure 3 with high failure rates in all groups 2,4 patients and in groups 1,3 patients with low pcr.

In contrast to the case for Kt/V < .80, inspection of Figure 6 reveals that when Kt/V > .80, the data base is comprised almost entirely of groups 1,3 patients with pcr > .80 and CO_2 tightly constrained to < 90 mg/dl at maximal pcr. There were no patients treated with high Kt/V who had high BUN. The mechanistic reason for the constraint on BUN was that the study design required that Kt/V increase linearly with pcr (Fig 1) to hold TAC constant which resulted in a minimal positive slope on CO_2 as a function of pcr. In view of the study design and resultant data distribution, clinical outcome results are unknown for patients treated with Kt/V > .80 and CO_2 values higher than those studied in the groups 1,3 patients. The NCDS should be considered silent in this domain of high BUN which

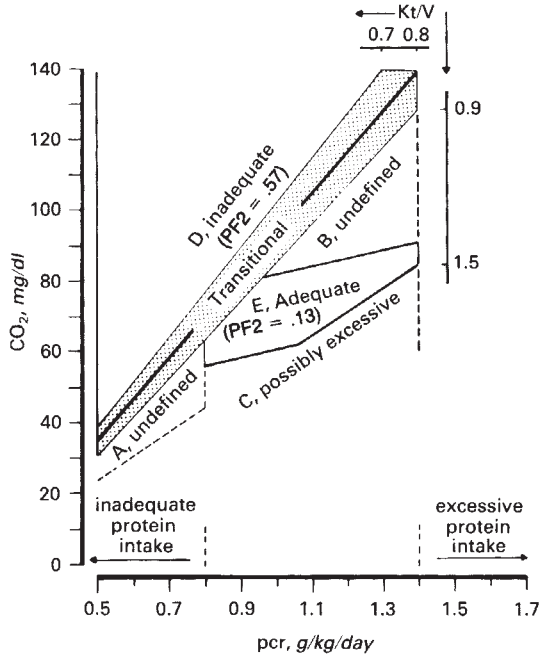

Fig. 7. *Probability of failure 2 (PF2) domains defined by mechanistic analysis of the NCDS.*

mechanistically would be comprised of therapy with low levels of (Kt/V)/pcr which were rigorously excluded by the study design when Kt/V exceeded .80.

It should also be noted in Figure 6 that no patients with pcr < 80 were treated with prescribed Kt/V > .80. Again, because of a study design that resulted in low prescribed Kt/V for all patients at low pcr, the NCDS must be considered silent in the domain of pcr < .80 and Kt/V > .80.

Finally, it can be noted in Figure 6 that the maximal Kt/V prescribed was ~ 1.5. Since $\overline{PF2}$ was constant at .13 over the Kt/V range 0.8 to 1.5 (with CO_2 constrained as described above), it can be tentatively concluded that levels of Kt/V > 1.5 may be excessive dialysis and not likely to effect a decrease in $\overline{PF2}$ below the .13 level.

Mechanistic outcome failure probability map

The concept of an outcome failure probability map on pcr, CO_2 coordinates has considerable clinical value. The coordinates for individual patients provide ready visualization of the risk of treatment failure in terms of the nutritional parameter and the BUN, which is a familar traditional parameter of treatment and which, under well-defined conditions with respect to Kt/V, can serve as a rigorous surrogate for the level of dialysis prescribed.

A probability of failure 2 map was constructed from the data in Figures 4 and 6 and is depicted in Figure 7. Domains A and B were not included in the NCDS by design and are therefore considered to be undefined by the study. Domain C is considered to be possibly an area of excessive dialysis bounded by .8 < pcr < 1.4 and Kt/V > 1.5. Domain D with Kt/V < .70 represents inadequate dialysis with constant PF2 = .52 ± .13, M ± 2 SD, as seen in Figure 4. A transitional zone is depicted corresponding to Kt/V = .8 ± .1 and represents the disconti-

nuity region of the PF2 function in Figure 4. Finally, Domain E is the area of adequate dialysis defined by the NCDS with constant PF2 of .13 ± .07, M ± 2 SD. The domain is bounded by .9 < Kt/V < 1.5 with CO_2 = 22.8pcr + (48.7 ± 10.7) as shown in Figure 3.

Discussion

It is apparent that mechanistic and statistical analyses lead to very different conclusions regarding the functional relationship of outcome failure to the level of dialysis and protein intake prescribed. A mechanistic analysis leads to the conclusion that outcome was not a continuous function of protein nutrition and the level of dialysis as they were prescribed in the study, although highly significant continuous statistical functions could be derived. When outcome is analyzed as a function of the Kt/V analogue of pcr and BUN, it can be seen that the apparent continuous function derives from the data distributing essentially as two point clusters widely separated on both ordinate and abscissa. The statistical model is based on the assumption of a continuous function of outcome on the pcr, CO_2 analogue of Kt/V.

There are significant clinical implications of these differing analytic results. The statistical model leads to the conclusions that in patients with pcr < .80, there is a high incidence of poor clinical results due to inadequate protein nutrition and that these patients will not be benefitted by increasing dialysis. The mechanistic analysis shows that all patients in the study with pcr < .80 received greatly reduced dialysis (Kt/V < .70) and leads to the conclusion that there is a high probability of failure with Kt/V < .70 at all levels of pcr. Since no patients with pcr < .80 were treated with higher Kt/V values, it is concluded mechanistically that the relative importance of dialysis and nutrition in low pcr patients cannot be judged from this study. It is therefore not possible to provide clear recommendations for management of low pcr patients. It can be recommended that Kt/V should not be reduced below 0.9 (which would result in quite low BUNs of 30 to 40 mg/dl at pcr = .6). It would be desirable to increase dietary protein intake if possible and move the therapy coordinates into the adequate zone of Figure 7, but, in our experience, ~ 15% of patients have persistently low pcr values and are very resistant to dietary manipulation. In these patients, it would seem reasonable to provide a level of dialysis sufficient to maintain the coordinates of therapy in Domain A of Figure 7. Further research would appear to be necessary to determine the dependence of outcome on the levels of dialysis and protein intake in this undefined therapeutic domain.

The two models also differ with regard to prediction of an adequate dialysis prescription. The authors caution against quantitative use of the statistical model to estimate the probability of treatment failure in an individual patient and recommend only that an adequate protein intake be prescribed and TAC held in the range common to the group 1,3 patients [4]. However, the statistical model does clearly predict that, all else being constant, the mean probability of failure continuously diminishes as therapy coordinates move to the lower right-hand corner of Figure 5B, a domain of high protein intake and intensive dialysis. Thus, the conceptual implication of the statistical model is that the optimal therapy prescription would be comprised of high protein intake and intensive dialysis.

The mechanistic model indicates the probabiilty of therapy failure does not decrease as Kt/V increases from 0.9 to 1.5 in proportion to pcr, increasing from 0.8 to 1.4 (Figs 4 and 7). Consequently, it is concluded that a fully adequate dialysis prescription is provided with pcr = 1.0 and Kt/V = 1.0 (a level of treatment that is 25% greater than the step function value in Fig. 4) and that prescribing higher levels of these nutritional and dialysis parameters are of no apparent clinical value with the cellulosic dialyzers in current use on a thrice weekly treatment schedule.

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Appendix

The rigorous variable volume urea model was used to design and control the NCDS [5]. However, some important generalized relationships between treatment variables can be shown from a truncated version of the model assuming fixed volume, no urea generation during dialysis, and a symmetric thrice weekly treatment schedule. The concentration relationships during dialysis with these assumptions is given by

$$(1) \qquad Ct \simeq CO\, \bar{e}\, \frac{Kt}{V}$$

where CO = predialysis BUN,mg/ml;
CT = post dialysis BUN; K = clearance, ml/min;
t = length of dialysis, min;
V = urea distribution volume, ml.

Rearrangements of Eq(*1*) and subtraction of CO from both sides results in

$$(2) \qquad CO - Ct \simeq CO\left(1 - \bar{e}\, \frac{Kt}{V}\right)$$

The term CO-Ct describes the change in BUN during dialysis (ΔC) and in steady-state therapy must be equal to the interdialytic rise in BUN. Thus, Eq(*2*) can also be written as

$$(3) \qquad \Delta C \simeq CO\left(1 - \bar{e}\, \frac{Kt}{V}\right)$$

Equation (*3*) can now be developed to examine some interrelations between treatment variables. The assumption of a symmetrical schedule will result in constant CO if urea generation (ΔC) and the magnitude of dialysis (Kt/V) remain constant so that CO can be considered to be the target mid-week predialysis BUN or CO_2. Solution of Eq(*3*) for Kt and Kt/V results in

$$(4) \qquad -Kt \simeq V \cdot \ln\left(1 - \frac{\Delta C}{CO}\right)$$

$$(5) \qquad -\frac{Kt}{V} \simeq \ln\left(1 - \frac{\Delta C}{CO}\right)$$

The total magnitude of therapy prescribed is Kt while the normalized value is Kt/V. To examine the interactions between Kt/V, CO, and pcr, it is necessary to incorporate pcr in Eq(*5*).

The total protein catabolic rate (PCR, g/day) is calculated directly from the net urea generation rate (G, mg/min), and G is calculated from the product of ΔC and V divided by the interdialytic time interval (θ). An average value for θ can be calculated to be 2646 minutes, assuming symmetrical thrice weekly dialysis with mean t = 3.9 hr. Therefore, the expression for G is

$$G \simeq \frac{\Delta C \cdot V}{2646} \tag{6}$$

The PCR is calculated from the relationship

$$PCR = 9.35G + .00028V \tag{7}$$

Combining Eqs (6) and (7) results in

$$PCR \simeq .0035\Delta CV + .00028V \tag{8}$$

The relationship between PCR and normalized value pcr, g/kg/day is

$$pcr \simeq \frac{PCR}{V/.58} = .58\left(\frac{PCR}{V}\right) \tag{9}$$

where V is expressed in liters and the body is considered to be 58% water or .58 liter/kg.

Combination of Eqs (8) and (9) and reconciliation of units results in

$$pcr \simeq 2.03\Delta C + .16 \tag{10}$$

Equation (10) shows that pcr is related to ΔC by numerical constants and Eq(5) can be written as

$$-\frac{Kt}{V} \simeq \ln\left(1 - \frac{.49pcr - .16}{CO}\right) \tag{11}$$

Equation (11) shows how Kt/V was prescribed in the NCDS as a function of pcr and CO. The implications of this relationship are discussed in the paper.

It is also useful to solve Eq(11) for CO_2 which results in

$$CO_2 \simeq .49\left[1/\left(1 - \bar{e}\frac{Kt}{V}\right)\right](pcr - .16) \tag{12}$$

Equation (12) indicates that whenn Kt/V is held constant, CO will increase linearly with pcr. The significance of this relationship is discussed in the paper.

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