

## Mathematical Modeling of Artificial Kidney Function By Using Blood Samples In Patients With Renal Diseases

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### Abstract

In Hemodialysis ,blood is pumped from the body to special filter (dialyzer ) made of tiny plastic capillaries . the blood is purified when the waste products diffuse from the blood across the membrane of these tiny capillaries to the dialysate purified “clean”blood is then returned to the body and spent dialysate is drained.

The purpose of this study is demonstrate the effect of increase nominal dialysate flow rate from 500-800 ml/min on the amount of the small solute (urea) removed from the blood and examine its effect on the amount of dialysis deliverd.

Hemodialysis (HD) is a technique of removing or clearing solutes from the blood and removal of extra fluid from the body, by using dialyzing machine. The principle of hemodialysis is primarily, the diffusion of solutes and ultrafiltration for removal of extra fluid. Kinetic modeling is a widely used analytic process that describes a system from its mass balance the clinical goals of modeling in dialysis therapy are to improve clinical understanding of the uremic syndrome and quantified doses of dialysis . In this study, we are interested for new model emerges form generalization of signal-pool urea kinetic model (variable volume single pool VVSP) which able to yield an accurate estimate of urea kinetic model such as urea nitrogen generation rate, urea removal during dialysis and dialyzer urea clearance for quantifying and prescribing dialysis. The mathematical development of the variable volume single pool ( VVSP) model for application is based primarily on the three blood samples. This development provides a method to combine all of the treatment parameters ( $V_t, PCR, G$ ),urea is unique among the possible markers in providing information regarding a patients nitrogen balance . Urea concentration is directly related to the protein catabolic rate blood urea concentrations reflected the balance between protein catabolism and clearance. We present the results obtained form a clinical study carried out on a group of 12 end stage renal disease (ESRD) patients for blood flow rate less than 200ml/min and greater than 200ml/min, 6 patients with dialysate flow rate (DFR) 500 ml/min and 6 patients with DFR 800 ml/min to show the different in variable volume single pool (VVSP ) models for both groups (500 & 800 ml/min) this method done typically in patients treated with HD twice-weekly so a standard modeling techniques include a standard blood urea nitrogen (BUN) samples which are drawn before the beginning of HD, after the end of HD, and before the beginning of the next HD and considering that volume changes occurring over the

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dialysis cycle this is the key idea that underlies the variable volume single-pool (VVSP) model.

**Keywords:** hemodialysis (HD), urea kinetic modeling, Variable Volume single-pool (VVSP)

## النموذج الحسابي او الصيغه الحسابية لعمل الكلية الصناعية باستخدام عينات دم لمرضى الاعتلالات الكلوية

### الخلاصة

عند الغسل الكلوي الدموي (الديلزة) يضخ الدم من الجسم إلى المرشح الخاص (dialyzer) مكون من أنابيب شعرية بلاستيكية صغيرة جدا يتم تنقيته الدم عند انتشار المكونات المهمة من الدم عبر غشاء الأنابيب الشعرية إلى سائل الديلزة ويعاد الدم المنقى ثانياً إلى الجسم والسائل المستهلك يتم صرفه. تهدف الدراسة لبيان تأثير زيادة المعدل التدفق سائل الديلزة من 500 ملم/دقيقة إلى 800 ملم/دقيقة على مقدار المواد الذائبة الصغيرة التي أزيلت من الدم وفحص ودراسة هذا التأثير على كمية الغسل الكلوي (الديلزة) الموفرة للمريض. الديلزة هي إحدى التقنيات لأزاله أو تنظيف المواد المذابة في الدم, وأيضا أزاله السوائل الزائدة من الجسم, باستخدام جهاز التحليل أو المحلل والذي يعرف بالكلية الصناعية؛ إن مبدأ الديلزة يعتمد في الأساس على انتشار المواد المذابة والترشيح الفائق لأزاله السوائل الزائدة. في العملية التحليلية التي تصف النظام على أنه كتلة متوازنة, و الأهداف السريرية من هذه الطريقة العلاجية هي تطوير الفهم السريري للأعراض المتزامنة أو المصاحبة لليوريا الدموية و لتحديد كمية جرعات الديلزة هذا النموذج تستخدم بشكل واسع. في هذه الدراسة تم الاهتمام بالنموذج الجديد (variable volume single pool VVSP) الذي له القابلية على إعطاء تقديرات مضبوطة لإنتاج اليوريا الحركية مثل نسبة النتروجين الموجودة و اليوريا المزالة خلال عملية الديلزة و نقاء أو صفاء اليوريا التي تمت عليها عملية الديلزة التي من خلالها سيتم تحديد الديلزة التي ينصح باستعمالها و إعطاء وصف كمي صحيح لها.

إن التطبيقات للتطورات الحسابية للموديل (VVSP) يعتمد بشكل رئيسي على العينات الثلاثة للدم. هذا التطور امكنا من الحصول على طريقه لمزج المعاملات الثلاثة  $V_t, PCR, G$ , و تعتبر اليوريا من العلامات المميزه التي يمكن الحصول عليها و بغض النظر عن توازن النتروجين للمريض. تركيز اليوريا يتعلق بشكل مباشر مع نسبة الايض للبروتين, تراكيز اليوريا بالدم تعطينا معلومات عن نسبة التوازن بين عمليتي التصفيه والايض للبروتين.

نحن قدمنا النتائج الماخوذه من دراسة سريرية حيث تتضمن مجموعه من 12 مريضا مصابا بالاعتلال الكلوي وكان معدل جريان الدم لهم اكبر او اقل من 200 ملم/ثانيه, ستة منهم معدل التدفق 500ملم/ثانيه و ستة مرضى معدل تدفقهم 800ملم/ثانيه لنرى الفرق في الحالتين 500 و 800 ملم /ثانيه في هذا الموديل ينفذ نضريا معالجه المرضى بالديلزة مرتين في الاسبوع وكذلك التقنية القياسية تتضمن (BUN) القياسي, ترسم أعينه قبل بداية الديلزة وبعد نهايتها وقبل بداية الديلزة القادمة وتعد تغييرات الحجم تحدث فوق دوره التصفيه وهذا هو مفتاح الفكرة تحت VVSP موديل.

### Introduction

When kidney fail, dialysis is necessary to remove waste products such as urea from the blood. [2]

To see whether dialysis is removing enough urea the clinic should periodically (normally once a month) test a patient's blood to measure dialysis adequacy.

Several patient-specific factors that determine how much dialysis is needed, these include the patient's size (Body water volume), fluid gain between dialysis and the rate of protein catabolism.

Patient's with high rates of urea appearance required more dialysis. Similarly, weight gain between dialysis, although it increases the requirement for fluid removal during each treatment. Urea modeling provides an independent measure of patient's protein intake (PCR) that can serve as a guide for physician's prescription [11].

Urea kinetic modeling determines the important parameters of dialysis effectiveness and provides an estimate of dialysis efficiency through the use of three BUN.

Urea kinetic models are in interrelationships and of great importance in clinical applications of urea kinetic modeling, the single-compartment, variable-volume model is the most commonly applied clinical tool for quantitating hemodialysis [3]

The VVSP model can be solved to develop a relationships among  $Co_1, Co_2, nPCR$  and  $G$ , the mathematical development of the

VVSP model for clonical application is based primarily on these variables.

This model, is considerably more realistic than the (Fixed Volume) FVSP model because it includes the volume changes occurring over the dialysis cycle.

Formal urea kinetic model in its single-pool, variable-volume formulation, allows the iterative, computer-based estimate of urea distribution volume  $V$ , urea generation rate  $G$ , and the nutritional status of the patient, the normalized protein catabolic rate (nPCR) may be derived from the kinetic estimates of  $(Q, V)$  according to reference [3].

Marshall MR. et al, stated that solute removal indices (SRIs) were determined from net urea removal and urea distribution volume supplied from direct dialysis quantification (DDQ) and by mass balance using variables supplied from blood based formal variable –volume single-pool (VVSP) urea kinetic modeling. Equivalent renal urea clearances (EKRs) were calculated from urea generation rates and time averaged concentration (TAC). [10]

HJ Kemp et al demonstrated the gold standard method for determining  $Kt/V$  and Normalized Protein Catabolic Rate (nPCR) in hemodialysis by urea kinetic modeling. It was based on Gotch and Sargent's variable volume single pool model used in the National Cooperative Dialysis Study (NCDS). In this model two mathematical expressions are derived to describe the fall in urea concentration during

dialysis and the rise of urea concentration in the interdialysis period. [5]

Manael Prado et al are interested in a single pool model able to yield an accurate estimate of urea nitrogen generation rate, urea removal and dialyzer urea clearance, from standard BUN samples which are drawn before the beginning of HD, between 30 second and 2 minute after the end of HD, and 30-60 minute afterwards. Then generalized single-pool urea kinetic model can be solved to provide two parameters: urea distribution volume ( $V_t$ ) and urea generation rate( $G$ ), they conclude that this new model emerges from a generalization of the standard single pool urea kinetic model joins the simplicity of signal-pool models to accuracy of double pool models .[9]

The aim of this study is to demonstrate the mathematical analysis of dialysis with VVSP kinetic which can be done by a numerical solution of serial values for urea Generation rate and time averaged urea concentration (TAC) urea distribution volume at the end of dialysis ( $V_t$ ) and to demonstrate the calculation of PCR which is an important parameter of dialysis therapy. Then PCR can be accurately calculated with applied urea kinetics and has required measurement of ( $C_{01}, C_{02}, C_{t1}$ )urea concentration during the first and second dialysis of the week and iteration of equal to determine  $V_t$  and  $G$ .

#### Experimental work

This study involved 12 patients with end stage renal

disease(ESRD),the patients divided into two groups for each part ,6 patient  $Q_d=500$  ml/min and other group  $Q_d=800$  ml/min and the procedure Patients were treated with HD as followed :-

- 1- Dialysis session time ( $t$ ) of (3houre) and the time interval between dialysis session (69hr).
- 2- The blood flow rate less or equal to 200 ml/min and greater than 200 ml/min
- 3- The dialysate flow rate either 500ml/min or 800ml/min.
- 4- A blood samples have been drawn from the patients at the beginning of dialysis for the first session of the week (pre-dialysis ) from the arterial line ( $C_{01}$ ), at the end of dialysis (post-dialysis  $C_{t1}$ ) and at the begging of dialysis for the second session of the week (pre-next dialysis  $C_{02}$ ).
- 5- The blood samples used measuring: blood urea concentration mg/dl. While other data obtained either from the patients or from the machine such as patients weight before and after dialysis (kg) and Ultra-filtration UF goal (ml) (amount of body water drainage).[4]

In this study, the urea kinetic modeling used is Variable-Volume Single-Pool (VVSP) Urea Model [1].

This model is considerably more realistic than the FVSP model because

it includes the volume changes occurring over the dialysis cycle.  $V$  is considered a single pool coextensive with total body water but with expansion during the interdialytic interval from fluid retention and contraction during dialysis by ultra-filtration. The rate of interdialytic expansion is represented by constant term,  $\alpha$  and is calculated as the total interdialytic weight gain divided by the length of the interval  $\Theta$ . The rate of contraction during dialysis is represented by the constant term,  $Q_F$ , which is calculated from total weight loss during dialysis divided by the time of dialysis,  $t$ . The totally urea clearance has been calculated for patients treated with HD at a given blood flow rate multiply by the urea difference as below:-

$$K = [Q_b * (C_{o1} - C_{t1})] / C_{o1}$$

It is necessary to determine the end dialysis volume  $V_t$  in the patient is for monitoring the technical quality of delivered dialysis therapy it is calculate by [4] :-

$$V_t = Q_F \cdot t \left[ \left[ 1 - \frac{G - C_t (K - Q_F) \frac{Q_F}{K - Q_F}}{G - C_o (K - Q_F)} \right]^{-1} - 1 \right]$$

The urea generation term ( $G$ ) during the inter dialytic interval. clinically applied urea kinetics have generally been based on measurement of  $C_{o1}, C_{t1}$  and  $C_{o2}$  during the first and

second dialysis of the week and estimated by :- [1]

$$G = \alpha [C_o - C_t ((V_i + \alpha \Theta) / V_i)^{-1}] / [1 - ((V_i + \alpha \Theta) / V_i)^{-1}]$$

Formal urea kinetic model in its single –pool variable volume formation allows the iterative computer-based estimate of urea distribution volume ( $V_t$ ) and urea generation rate ( $G$ )

A parameters that closely parallel fractional urea removal is the fractional fall in BUN during a single dialysis often expressed as the urea reduction ratio (URR) [7], which determined by the change of urea concentration from  $C_{o1}$  and  $C_{t1}$ .

$$URR = [100 * (C_{o1} - C_{t1})] / C_{o1}$$

The change from  $C_{t1}$  to  $C_{o2}$  is determined by the rate of urea generation  $G$  and Volume of distribution of urea. Urea is the bulk waste product of protein catabolism constituting about 90% of waste nitrogen accumulating in body water between dialysis the net rate of urea nitrogen generation ( $G$  mg/min) is linearly dependent on the net rate of protein catabolism and because  $G$  can be measured by urea kinetic analysis, [7] this technique provides a price measure of the net protein catabolic rate.

$$PCR = 9.35 * G + 0.29 * Vt$$

The protein catabolic rate is more difficult to approximate with simple formulas because the dialysis schedule, residual clearance, and fluid gain play significant roles, so we need a third BUN measurement.

A statistical analysis of the NCDS data showed that the patient outcome concentrated best with time averaged blood urea concentration (TAC) and strongly correlated with normalized with normalized protein catabolic rate NPCR, the time – averaged concentration is the mean blood urea during a full dialysis cycle ,in this case twice weekly Schedule .

the TAC equation is:-

$$TAC_{urea} = \frac{\{(C_{o1}+C_{t1}) + (C_{t1}+C_{o2})\}}{2(t+\Theta)}$$

$$NPCR = PCR / Vt / 0.58$$

### Results and Discussions

The gold standard method for determining TAC in haemodialysis is by urea kinetic modeling based on variable-volume single-pool model used by Gotch and sargent NCDS study.[5]

In this model two mathematical expressions are derived to describe the fall in urea concentration during dialysis and the rise of urea concentration in the interdialysis period.

The equations are expressed in term of the dialyser clearance residual renal function duration of dialysis intradialytic weight loss , urea generation G and the volume of distribution of urea G, three blood urea measurements are required one after the dialysis and then one before and one after the next dialysis session. The two equations .are solved iteratively to derive modeled values for G and V which are

used calculate NPCR A number of computer programs are available which will perform urea kinetic modeling.

This study was initially designed to look at the effects of protein in take a secondary analysis of the date showed that low protein in take reflected by low PCR was a better predictor of morbidity than was TAC<sub>urea</sub> treatment failure was excessive in both high flow TAC<sub>urea</sub> group if the PCR was less than 0.89g/kg/day in our study the effect of increasing dialysate flow rate 500-800 with increasing PCR show an increasing in urea generation rate (G) with little decrease in time average concentration ,in general all the result appropriate by using the VVSP model which three blood urea measurement.[6]

During the dialytic procedure a sharp decrease in the concentration of urea occurs which determined by the urea reduction ratio (URR). Followed by a gradual increase during the interdialytic period which determined by the amount of urea generated during dialysis (urea generation rate) which depends on the dietary protein intake and distribution volume of urea, the results are shown in the Tables 1 and 2 .

Our results are determined by mass balance using variables supplied from blood based formal variable-volume single pool (VVSP) urea kinetic modeling which is based on three points kinetic modeling that mean three blood samples used in our mathematical calculations to establish patient parameters from clinical data

and predict the effect of therapy changes and prescribe dialysis treatment to achieve clinical goals .

The patients randomized in to four treatment groups, the groups were based on combinations of blood flow rate  $\leq 200$  ml/min or greater 200 ml/min and dialysate flow rate 500 and 800 ml/min (see tables 1 and 2).

The results above is used to determine the effect of normal and elevated in dialysate blood flow on the use of the variable volume-signal pool urea model, modeling attempts simplification by viewing the body as a system that acts as a single pool.

The assessed HD regimens shown in the Table (1) are of two regimens with dialysate flow rate 500 ml/min, regimen A served as a control to which the alternative regimens were compared. Regimen B used the same dialysate flow rate as in regimen A but with a blood flow rate  $> 200$  ml/min regimens shown in table (2) has a relatively high  $Q_d=800$  ml/min, regimen C with  $Q_b \leq 200$  ml/min and regimen D with  $Q_b > 200$  ml/min .

The two regimens with higher  $Q_d=800$  ml/min were associated with increased in urea reduction ratio than regimens A and B, because a low  $Q_d$  resulted in nearly complete saturation of the effluent dialysate with respect to urea. That will result in approximately low in pre-urea concentration of the second dialysis and in a low time-averaged urea concentration ( $TAC_{urea}$ ). Elevated BUN reflects the net rate of generation relative clearance consequently high BUN may reflect a higher rate of catabolism or intake. And regimen D

with  $Q_b > 200$  ml/min and higher dialysate flow rate from 500 to 800 ml/min can be expected to increase the urea clearance rate on the order of 10% to 15%. This effect is most pronounced at higher blood flow rates because increased flow rates help maximized the urea concentration gradient along the entire length of the dialysis membrane Figure 1 and Figure 2. To analyze dialytic process inter-dialytic intervals assuming zero-order kinetics, rather than as a first -order process .this simplification allows a simple averaging of urea concentration ( $TAC_{urea}$ ) Figure 3 and 4 shows a net urea generation is determined by protein catabolic rate and is a linear function as protein Catabolic rate increased the rate urea generation increases linearly . According to our modeling regimen D with urea generation rate slightly high than the others also associated with low TAC, to assess quantitatively the effect of clearance on the kinetic parameters TAC and increase in urea EKR.

The NCDS (national cooperative dialysis study) was published in 1981 and was the first and largest prospective study to show correlation between the amount of hemodialysis prescribed and morbidity.[8]

The groups were based on combinations of low and high time-averaged urea concentration ( $TAC_{urea}$ ) and short and long dialysis time protein in take has relationship with TAC urea was achieved by altering dialysis parameters and not through dietary manipulation, has two regimens with the high and low TAC

urea (for time 3h -4.5h) were associated with increased morbidity group with high TAC and time 3h their morbidity was much increased than in group with low TAC and time long dialysis time 4.5hr .

In our study 500 to 800 ml/min the  $TAC_{urea}$  was low in the second group dialysate flow rate 800 ml/min so there morbidity was less than in first group dialysate flow rate 500 ml/min. William R .CLARK et al demonstrate of the primary importance of flow rates in determine diffusive small solute clearance accomparism between EKR which quantifies effective urea removal by in corporating TAC, and weekly single-pool (kt/v) for the high flow regimens ,in which the dialysate flow rate is 600/ml/min and blood flow rate 350 ml/min, EKR value for urea are approximately low than those for low flow regimens in which the dialysate flow rate is only 100 ml/min in comparison to our research we found that as there is increase in dialysate flow rate from 500 to 800 ml/min there is a clearly decrease in EKR from 0.1073 to 0.0158 for same group of blood flow rate less or equal to 200 ml/min.[12]

### Conclusions

Urea kinetic modeling is a remarkable conceptual a advance and useful tool for understanding the physiology and quantification of dialysis. the primary goal in developing the HD model was to compare effective solute clearances achieved with different treat regimens of varying flow rates.

In this study the mathematical development of the VVSP models for clinical application is based primarily on the three blood samples. This development provides a method to combine all of the treatment parameters ( $V_t$  ,G ,PCR , $Q_b$  , $Q_d$  and URR) into a single quantified dialysis dosage parameter. in the VVSP model the more rigorous kinetics of the double-pool model are simplified by assuming urea is removed from a single compartment and that concentration equilibrium prevails throughout this volume of distribution during and after dialysis. The compartment is assumed to expand and contact uniformly with fluid retention between dialyses and ultra-filtration during dialysis. The FVSP model is further simplified with the assumption that volume is fixed throughout the treatment cycle.

These conflicting reports are amenable to rational explanation through mathematical analysis of the interactions among the models. Only the VVSP model interaction s will be analyzed mathematically the FVSP model is an over simplification and not suitable for clinical use.

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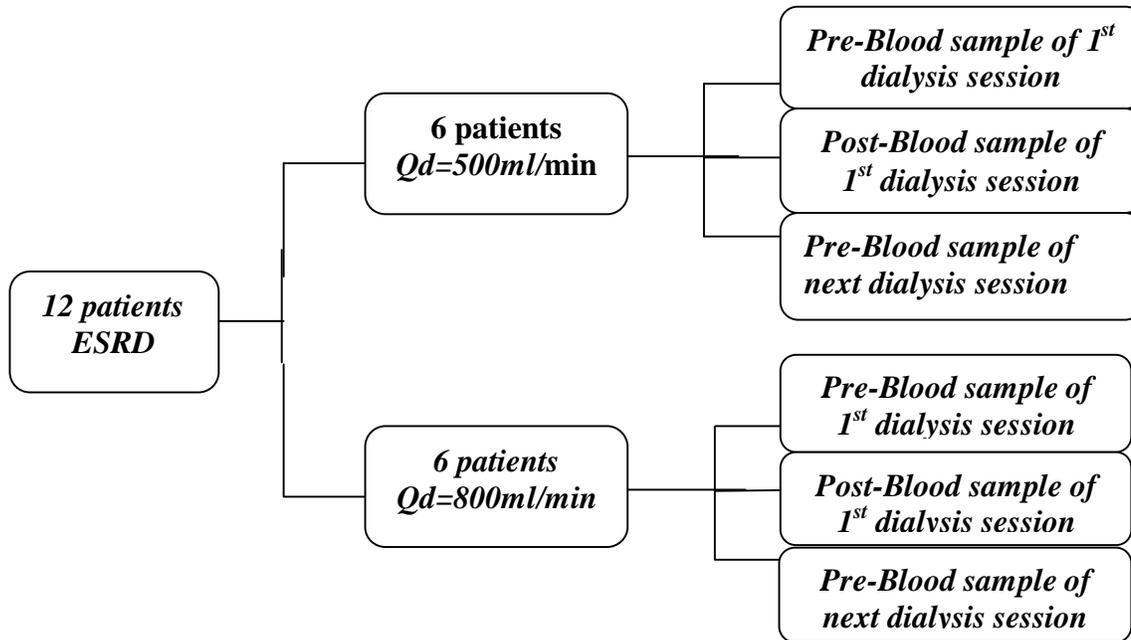
Table (1) Dialysis Parameters for patients with dialysat flow rate 500ml/min

Qd	Regimen	Qb	URR	Vt	G	PCR	EKR	TAC
500	A	≤200	28.459	0.0713	1.2507	11.72	0.1073	235.62
	B	>200	32.302	0.0121	8.7583	81.89	0.0297	280.1

Table (2) Dialysis Parameters for patients with dialysat flow rate 800ml/min

Qd	Regimen	Qb	URR	Vt	G	PCR	EKR	TAC
800	C	≤200	32.606	0.0052	3.768	35.23	0.0158	234.48
	D	>200	39.686	0.0167	11.577	108.2	0.0428	278.52

Chart (1) Distribution of patients according to dialysate flow rate and Blood samples time.



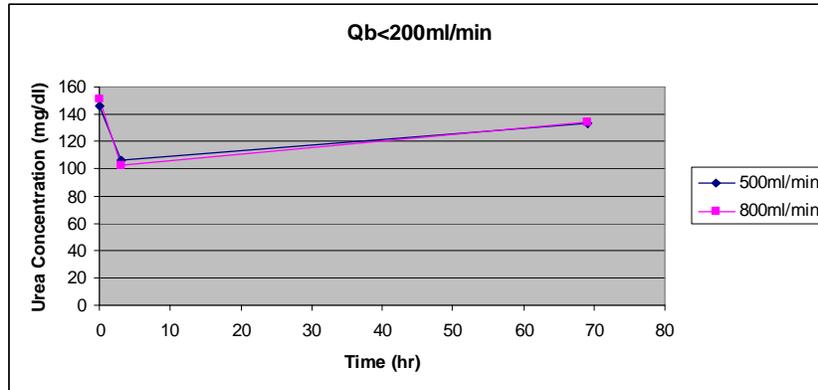


Figure (1) Changes in urea concentration during hemodialysis and between dialyses treatment for patient with blood flow rate  $< 200$ ml/min

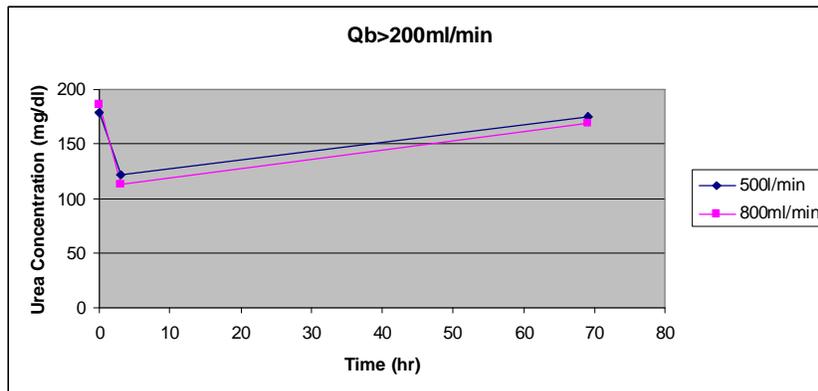


Figure (2) Changes in urea concentration during hemodialysis and between dialyses treatment for patient with blood flow rate  $> 200$ ml/min

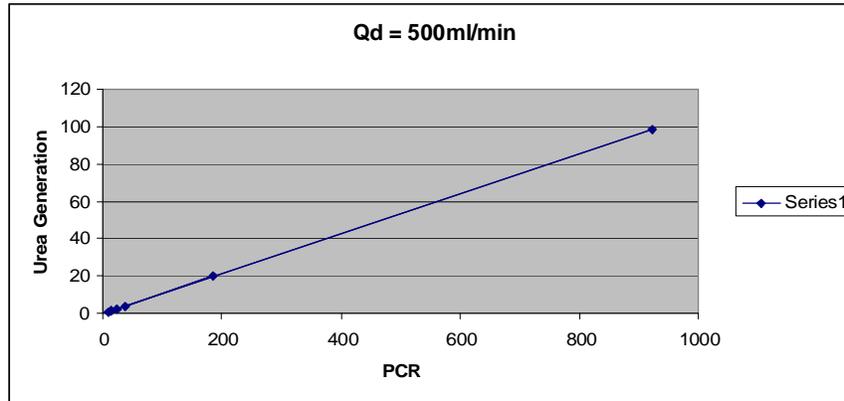


Figure (3) Relationship between protein catabolic rate (g/day) and urea generation (g/day) in uremic patients with dialysate flow rate = 500ml/min

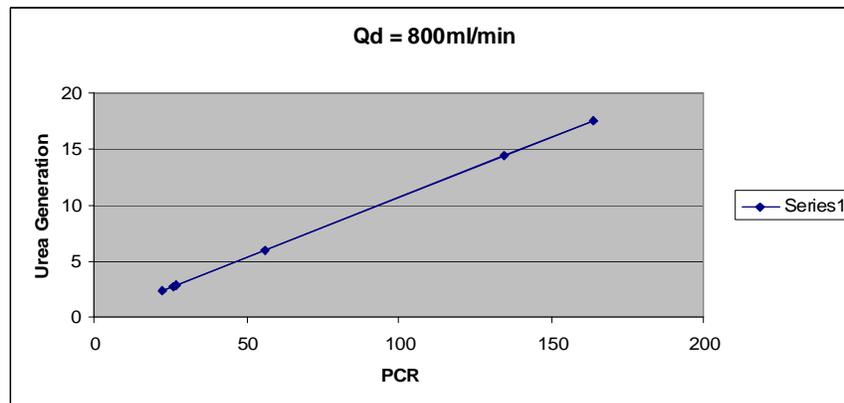


Figure (4) Relationship between protein catabolic rate (g/day) and urea generation (g/day) in uremic patients with dialysate flow rate = 800ml/min