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Measurement of residual glomerular filtration rate in the patient receiving repetitive hemodialysis

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Measurement of residual glomerular filtration rate in the patient receiving repetitive hemodialysis. The objective of the current study was to determine the best index of residual glomerular filtration rate (GFR) by comparing simultaneously measured clearances of inulin, ^{125}I-iothalamate, endogenous creatinine, urea and ^{169}ytterbium diethylenetriaminepentaacetic acid (^{169}YB-DTPA) in patients receiving repetitive hemodialysis. In patients with GFR <5 ml/min but >1 ml/min, ^{125}I-iothalamate clearance showed the best correlation with inulin clearance. However, creatinine clearance correlated better with inulin clearance than urea clearance and as well as urea + creatinine/2. In the patients with measured GFR <1 ml/min, the correlation of ^{125}I-iothalamate, creatinine, urea and urea + creatinine/two clearances with inulin clearance was satisfactory. Similarly, satisfactory correlations were obtained when the relationships were examined across the entire range of measured clearances <5 ml/min. A simple, practical method is described for the accurate serial measurement of residual GFR in patients receiving repetitive dialysis.

Mesure de la filtration glomérulaire résiduelle chez les malades en hémodialyse chronique. L'objectif de ce travail est de déterminer le meilleur indicateur de filtration glomérulaire (GFR) par la comparaison des clearances simultanées de l'inuline, du ^{125}I-iothalamate, de la créatinine endogène, de l'urée, et de l'acide diethylènetriaminepentaacétique marqué par l'ytterbium 169 (^{169}YB-DTPA) chez les malades en hémodialyse chronique. Pour les GFR compris entre 1 et 5 ml/min, la clearance de ^{125}I-iothalamate est la mieux corrélée avec celle de l'inuline. La clearance de la créatinine est mieux corrélée avec celle de l'inuline que ne l'est la clearance de l'urée ou la moitié de la somme des clearances de l'urée et de la créatinine. Pour les GFR inférieurs à 1 ml/min la corrélation des clearances de ^{125}I-iothalamate, creatinine, urée, et urée + créatinine/deux avec celle de l'inuline est satisfaisante. De la même façon, une corrélation satisfaisante est obtenue quand la relation est étudiée pour l'ensemble des valeurs inférieures à 5 ml/min. Une méthode simple et pratique de mesure précise et répétitive de GFR chez les malades en hémodialyse chronique est décrite.

Preliminary clinical support now has been provided [1] for an earlier theoretical prediction [2] that a residual glomerular filtration rate (GFR) may have an important influence on the amount of dialysis required by patients with end-stage kidney disease. As a consequence, it has become important to investigate methods for accurately measuring the small amount of residual GFR in patients receiving maintenance hemodialysis. Although there have been reported studies of GFR measurement in patients with significantly reduced GFR [3, 4], there have been none to date in patients receiving hemodialysis. This study presents the results of 38 simultaneous clearance measurements in a group of patients receiving intermittent dialysis, all of whom had GFR's <5.0 ml/min.

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Methods

Simultaneous renal clearance of inulin, endogenous creatinine, urea nitrogen, ^{125}I-iothalamate and ^{169}YB-DTPA were performed in stable, uremic adult patients in the age range from 20 to 65 yr, treated with repetitive hemodialysis from two months to 7 yr, with thrice-weekly dialysis schedule (24 to 30 hr/week). Hemodialysis was performed on Kiil-type dialyzers (D_1, 1 m^2; and D_3, 0.63 m^2) using a cuprophan membrane (PT 150, 17.5 μ), dialysate flow of 500 ml/min and blood flow of 200 ml/min. All the patients were dialyzed with glucose-free dialysate and had a blood glucose concentration below 200 mg/100 ml. Creatinine and urea nitrogen determinations were done by standard autoanalyzer methodology. No pretreatment of the serum was done to remove the creatinine chromogen since the interference is minimal with high plasma creatinine concentrations. Inulin concentration was determined by the method of Steele [5]. ^{125}I-iothalamate and ^{169}YB-DTPA were counted in a deep well gamma counter (Nuclear Chicago). All the patients had a residual GFR below 5 ml/min. The residual GFR was measured by clearances of inulin, endogenous creatinine and urea in 38 patient studies, ^{125}I-iothalamate in 21 patient

studies and ^{169}YB-DTPA in 12 patient studies. In five patients no isotope clearance studies were performed (Tables 1 and 2).

All clearance measurements were carried out during a 24-hr interdialytic period between two dialyses. Bladder catheterizations were not performed in order to avoid the risk of infection. In order to increase the accuracy of the urine collections, patients were instructed not to void for up to 12 hr prior to the beginning and the end of each 24-hr clearance period. All clearance measurements were performed on the same blood and urine samples.

At the beginning of the clearance measurement period after spontaneous bladder emptying, a single dose of inulin (50 mg/kg) and 0.3 μCi/kg of either ^{125}I-iothalamate or ^{169}YB-DTPA was injected in a 50 ml solution of normal saline over a period of ten minutes.

In a pilot study involving ten 24-hr clearance periods, hourly venous blood samples were drawn during the first six hours and analyzed for urea, creatinine and inulin. The results of this study revealed that during the six-hour interval, plasma urea and creatinine rose very slowly as expected. More important was the observation that the fall in plasma inulin concentration was linear and not exponential. On the basis of these results, in the next nine studies hourly sampling was omitted, and the following protocol was continued: Four venous blood samples were drawn: first, at the beginning of the period immediately after the bladder was emptied and before injection of the material; second, one hour after injections, to allow injected material to equilibrate; third, 12 hr after injection; and fourth, at the end of the 24-hr measurement period. As shown in Table 3, concentrations of urea, creatinine and inulin as measured directly on the 12-hr sample did not differ significantly from values calculated as the mean of the initial and final samples. On the basis of these results, the 12-hr sample was omitted on the remaining 19 studies, and clearance calculations for all studies reported in Tables 1 and 2 were based on the average of the initial and final plasma concentrations. Thus, the values for plasma urea and creatinine were obtained by calculating the means ($\bar{X}$) of the zero time and the 24-hr values. ^{125}I-iothalamate and ^{169}YB-DTPA clearances were calculated from the means of the 1-hr and 24-hr plasma values. The plasma inulin values were calculated by using the means of the 1-hr and 24-hr samples from which the zero values were subtracted.

Statistical methods. The correlation between inulin and each test substance was analyzed by the method of linear regression, and the correlation coefficient was calculated. The *P* values of the correlation coefficient were calculated by Fisher's transformation test.

Results

The patients were divided into two groups: those with GFR's more than 1.0 (Table 1) and those with GFR's less than 1.0 (Table 2). In group I, inulin clearance values ranged from 1.08 to 3.99 ml/min, with the mean value for the group of 1.94 ml/min

Table 1. Comparative GFR values in patients receiving dialysis: Group I, clearance >1 ml/min, <5 ml/min[a]

Patient No.	Sex	Diagnosis	Time on dialysis	urine *ml/24 hr*	Inulin *ml/min*	Creatinine *ml/min*	Urea *ml/min*	^{125}I-Ioth	^{169}TB-DTPA
1	M	GN	5 yr	604	1.86	2.36	1.40	1.61	
2	M	GN	3 yr	499	1.55	1.81	1.22	1.58	
3	M	PKD	2 mo	797	2.32	2.80	1.68	2.20	
4	F	PKD	4 yr	1340	1.24	1.13	1.54		2.13
5	M	GN	6 yr	962	1.43	1.78	1.33		
6	F	PN	2 yr	1357	2.87	4.01	2.30	2.72	
7	M	GN	4 yr	1482	2.12	3.11	1.85	2.08	
8	F	GN	3 yr	1120	1.47	1.60	1.28		1.49
9	M	GN	5 yr	744	1.95	2.08	1.41		1.58
10	M	GN	5 yr	1193	3.12	3.61	3.25		4.04
11	F	GN	5 yr	610	1.05	0.86	1.09		0.75
12	M	GN	5 yr	590	1.78	2.12	1.36	1.68	
13	M	PKD	4 mo	545	3.99	2.18	1.17		
14	F	PKD	4 yr	915	1.83	1.17	1.42		1.35
15	F	PN	2 yr	742	2.60	3.34	1.57	2.39	
16	M	GN	4 yr	1020	1.85	2.24	1.44	1.72	
17	F	GN	3 yr	767	1.28	1.48	1.07		1.32
18	M	GN	6 yr	510	1.48	1.63	1.04		1.34
19	M	GN	5 yr	590	2.08	2.14	1.86		1.81
20	F	GN	5 yr	389	1.57	0.77	0.94		0.50
21	F	PKD	6 yr	750	1.60	1.10	0.55	1.62	

[a] ^{125}I-ioth, ^{125}I-iothalamate; GN, glomerulonephritis; PKD, polycystic kidney disease; PN, pyelonephritis.

Table 2. Comparative GFR Values in Patients receiving dialysis: Group II, clearance <1 ml/min

Patient No.	Sex	Diagnosis	Time on dialysis	Urine *ml/24 hr*	Inulin *ml/min*	Creatinine *ml/min*	*Urea ml/min*	^{125}I-Ioth	^{169}TB-DTPA
22	F	PKD	6 yr	657	0.74	0.97	0.77	0.75	
23	F	GN	4 yr	468	0.30	0.59	0.55	0.57	
24	F	GN	3 yr	58	0.06	0.19	0.12	0.15	
25	F	PKD	5 yr	162	0.19	0.24	0.17		
26	M	GN	5 yr	328	0.48	0.54	0.46	0.42	
27	M	PKD	5 yr	204	0.15	0.27	0.18	0.19	
28	F	PKD	2 yr	195	0.21	0.30	0.22	0.19	
29	M	GN	6 yr	10	0.009	0.02	0.009	0.007	
30	F	PKD	5 yr	223	0.28	0.28	0.24		0.25
31	M	GN	6 yr	240	0.48	0.56	0.28		
32	F	GN	4 yr	578	0.73	0.79	0.72	1.03	
33	F	GN	3 yr	19	0.01	0.09	0.05	0.09	
34	F	PKD	5 yr	145	0.22	0.24	0.16		
35	M	GN	5 yr	197	0.38	0.40	0.37	0.34	
36	M	PKD	5 yr	119	0.15	0.18	0.11	0.18	
37	F	PKD	2 yr	134	0.31	0.23	0.09	0.32	
38	F	PKD	5 yr	150	0.27	0.16	0.14		0.15

(Table 1). The correlation coefficients for the four regressions were all highly significant at a P value of <0.001. The best correlation existed between ^{125}I-iothalamate (r = 0.98) and inulin clearance, but creatinine clearance (r = 0.90) showed a better correlation than urea clearance (r = 0.81), and the averaged combined creatinine and urea clearances $(C_{CR} + C_{UR})/2$ were similar to creatinine clearance alone (r = 0.92).

In group II (GFR <1 ml/min) there were 17 clearance measurements for inulin, creatinine and urea; and 12 measurements of ^{125}I-iothalamate (Table 2). Inulin clearances ranged from 0.009 to 0.74 ml/min with the mean value for the group of 0.32 ml/min. In this group the ^{125}I-iothalamate (r = 0.93), creatinine (r = 0.93), urea (r = 0.89) and $(C_{CR} + C_{UR})/2$ (r = 0.92) clearances correlated well with the inulin clearance and were all significant, $P < 0.001$.

When the relationships were examined across the entire range of measured clearances, <5 ml/min (Fig. 1), the correlation of creatinine clearances with inulin clearances (r = 0.95) was the same as those for urea (r = 0.94) and $C_{CR} + C_{UR}/2$ (r = 0.94) and only slightly below those of ^{125}I-iothalamate (r = 0.99). All were different from $r = 0$, $P < 0.001$.

Since the ^{169}YB-DTPA clearance measurements were performed only 12 times, they were not subdivided in the groups. The correlation between ^{169}YB-DTPA and inulin clearances were the least satisfactory (r = 0.72, $P < 0.006$). However, inadequate numbers of performed measurements in this study may be a factor which prevents the definitive conclusion regarding the usefulness of this substance in residual GFR measurements.

Discussion

Although the endogenous creatinine clearance is the most commonly used test of renal function in clinical practice, clearance of inulin remains the accepted standard and the most valid technique for GFR measurement. However, its determination is procedurally and analytically too complex for daily clinical application. Many other methods have been used for the evaluation of GFR, including particularly in recent years different isotope techniques.

The common advantage of all of these isotopes is the quantitative exactness and simplicity with which they can be measured in the blood and urine. However, considerable difference of opinion has been expressed concerning these methods. Nelp, Wagner and Reba [6] in 1964 developed a method for measur-

Table 3. Comparison of mean value used for calculations and 12-hr (midpoint) value for all tests[a]

Test	N[b]	Plasma mean	Plasma, 12-hr	$\bar{x}_{diff}$	SD_{diff}	P
Creatinine, *mg/100 ml*	19	11.23	11.39	−0.16	0.40	>0.1
Urea nitrogen, *mg/100 ml*	18	60.21	61.27	−1.06	4.32	>0.3
Inulin, *mg/100 ml*	18	25.02	24.18	+0.84	2.07	>0.1
^{125}I-Ioth, *counts*	12	13.965×10^3	12.86×10^3			
^{169}YB-DTPA, *counts*	6	2024	1896			

[a]Mean values of all plasma values.
[b]N = number of specimens.

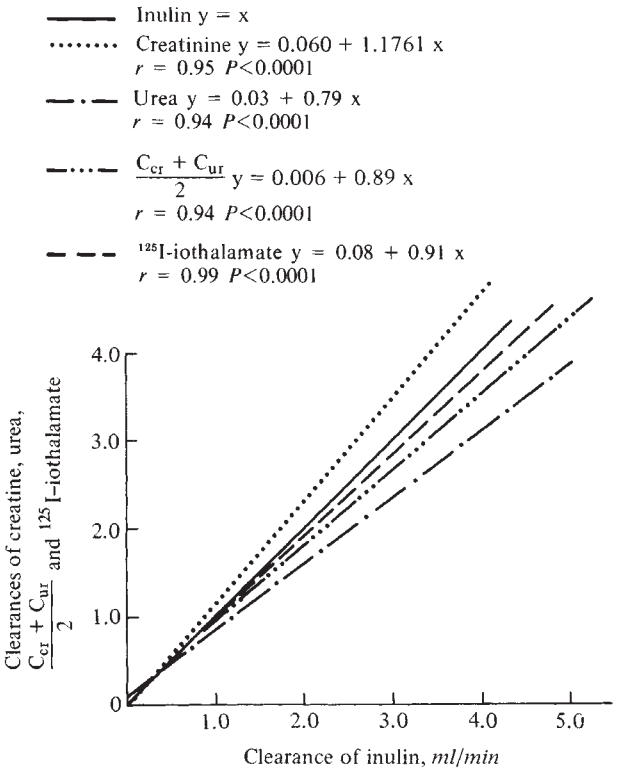

Fig. 1. Simultaneous clearances of creatinine, urea, averaged combined creatinine and urea (C_{CR} + C_{UR})/2 and ^{125}I-iothalamate plotted as a function of inulin clearance across the whole range of measured clearances <5 ml/min.

ing GFR using radioactive B-12 and found a close correlation between ^{57}Cr-cyanocobalmin and inulin clearance. The problem was that even with massive vitamin B-12 preloading, a still significant amount of radioactive cyanocobalmin was bound to plasma protein [7]. The clearance of ^{51}Cr-EDTA has been claimed to approximate the inulin clearance [8–11], but there are data suggestive of ^{51}Cr-EDTA tubular reabsorption [12, 13]. The ^{125}I-iothalamate clearance is 90 to 100% of simultaneous inulin clearance [14] only when not corrected for plasma binding (8 to 27%), and is a satisfactory substitute for inulin clearance in man [8]. Similarly, a high degree of agreement existed between the clearances of ^{169}YB-DTPA and 113m In-DTPA, and with 113m In-DTPA and ^{14}C-inulin, but not with ^{169}YB-DTPA and endogenous creatinine [15, 16].

Urea and endogenous creatinine clearances have been used most extensively for the clinical estimation of GFR because of their simplicity of analysis in the body fluids and because there is no need for continuous infusion. However, the overestimation of GFR measured by endogenous creatinine (and underestimation by urea) was a long-known disadvantage of these procedures, documented by many investigators in the patient with less advanced renal failure [3, 17, 18]. Skov [4] found increased creatinine/inulin clearance ratios (1.27) in 22 patients with inulin clearance between 1.6 and 4.7 ml/min. Thus, it was suggested that averaged combined creatinine and urea clearance (C_{CR} + C_{UR})/2 would be the best replacement for inulin clearance. Indeed, in this study the combined value is numerically closer to inulin than creatinine alone. However, since the correlation coefficient is the same for creatinine vs. inulin (0.95) as it is for creatinine + urea/2 vs. inulin (0.94), it is simpler to multiply the clearance value obtained for creatinine by 0.95 to get the true GFR than it is to measure and calculate creatinine and urea/2. For practical purposes, even this correction may be superfluous, since as shown in Fig. 1, all the clearances approach zero, and therefore, the numerical differences are very small in the range under consideration.

Limiting factors of this study (in terms of the accuracy of the evaluation of the absolute level of residual GFR) include the inaccuracy of urine collection performed without bladder catheterization, especially in the patients with very low urinary outputs. However, the risk of introducing urinary tract infection, especially in the patient with a low GFR, was too great to undertake such a procedure. The errors from this source cancel when one clearance method is compared with another, and do not detract from the conclusions reached in this study.

Appendix

A practical method for the measurement of GFR in dialysis patients. The amount of residual GFR in dialysis patients has emerged as a crucial variable which can effect impressive amounts of solute removal of substances in the mol wt range 500 to 5,000 [19, 1]. Consequently, it now becomes important to devise a simple, practical method of accurately measuring the serial changes in residual GFR over time in patients receiving repetitive dialysis. Since the prime requirements of the method are reproducibility of results and simplicity rather than measurement of the absolute level of GFR, creatinine clearance is employed.

Method. A major factor which adversely affects accuracy is the very small daily volume of urine characteristic of most dialysis patients. In order to minimize the error from this source, the clearance period for this method has been set at 2½ to 3 days, as over a weekend in patients on a Monday, Wednesday, Friday dialysis schedule. If a given patient has a urine volume in excess of 500 ml/24 hr, the clearance period could be shortened to 24 to 36 hr.

The patient begins urine collection by voiding as

Table 4. Creatinine clearances and urinary outputs measured on three successive weekend periods

Patient No.	Sex	Age *yr*	Diagnosis	Time on dialysis	1st weekend measurements		2nd weekend measurements		3rd weekend measurements	
					Urinary output *ml/24 hr*	C_{cr} *ml/min*	Urinary output *ml/24 hr*	C_{cr} *ml/min*	Urinary output *ml/24 hr*	C_{cr} *ml/min*
9	F	51	GN	3 yr	1007	1.6	1056	1.7	1043	1.8
8	F	43	GN	4 yr	570	1.1	547	1.1	690	1.2
39	M	41	PKD	1 yr	1031	5.9	780	4.4	952	5.0
27	M	62	PKD	6 yr	49	0.09	47	0.09	61	0.1
25	F	61	PKD	6 yr	101	0.13	115	0.15	72	0.11
40	F	53	PN	2 yr	1283	4.4	1193	4.8	1209	4.6
41	M	65	GN	5 mo	542	3.7	728	3.5		

soon after dialysis as possible (no later than one hour) and discarding the specimen. All urine is collected, and the final voiding is planned as close to the beginning of the next dialysis as possible. In patients with very small urine volumes, it is best to plan for the initial and final voiding, by not voiding for 12 to 14 hr prior to these points.

Arterial blood samples for the creatinine clearance are obtained as "off dialysis" samples at the end of the dialysis preceding the clearance measurement and an "on dialysis" sample at the dialysis which terminates the clearance measurement. Using the "off dialysis" sample does introduce an error due to a muscle to extracellular fluid dysequilibrium which accounts for much of the rise in plasma concentration in the first hour following dialysis [20]. However, the convenience of using an "off" sample in our view makes this error acceptable. Actually, this error is very small since the serum creatinine concentration rises a large amount during the clearance period. The average of the "on" and "off" sample is used in calculating the clearance.

Results. The data in Table 4 demonstrate the reproducibility of results with this clearance method when a patient measures his clearances on three successive weekend periods. That this degree of accuracy of clearance measurement is adequate to monitor this variable in dialysis patients is suggested by the data in Table 5. Note that the clearance values do not jump up and down when measured over a period of months. Most tend to decrease with time, which is the usual course of events.

Discussion. Even though the method presented here may not accurately measure the true GFR, it will reflect serial changes in GFR over long periods of time, which is the information one needs to correlate changes in GFR with changes in dialysis requirements. The method is designed to permit the patient

Table 5. Change in urine volume and creatinine clearance with time in a group of typical repetive dialysis patients

Patient No.												
39	Time, *mo*	0	2	3	8	11	14	17				
	UV, *ml/24 hr*	1007	1062	1043	895	885	836	535				
	C_{cr}, *ml/min*	1.62	1.75	1.82	1.32	1.13	1.28	1.02				
17	Time, *mo*	0	1/4	3/4	5	10	12	13	15	16	17	18
	UV, *ml/24 hr*	570	547	690	576	482	297	332	266	255	278	266
	C_{cr}, *ml/min*	1.11	1.07	1.21	1.03	0.76	0.47	0.46	0.47	0.46	0.44	0.46
42	Time, *mo*	0	1	2	6	10	11	12	13			
	UV, *ml/24 hr*	535	496	587	559	134	65	82	60			
	C_{cr}, *ml/min*	2.25	1.68	1.83	1.39	0.38	0.28	0.32	0.24			
32	Time, *mo*	0	1	3	6	12	13	15	17	18		
	UV, *ml/24 hr*	212	123	121	106	34	47	21	26	25		
	C_{cr}, *ml/min*	0.29	0.14	0.16	0.13	0.05	0.06	0.04	0.03	0.02		
25	Time, *mo*	0	11	12	12.5	17	22	25	28			
	UV, *ml/24 hr*	110	101	115	72	62	66	35	33			
	C_{cr}, *ml/min*	0.25	0.13	0.15	0.11	0.10	0.10	0.07	0.07			
43	Time, *mo*	0	3	9	10	11						
	UV, *ml/24 hr*	302	328	135	76	109						
	C_{cr}, *ml/min*	1.50	1.41	0.74	0.34	0.56						
27	Time, *mo*	0	11	12	12.5							
	UV, *ml/24 hr*	155	49	47	61							
	C_{cr}, *ml/min*	0.26	0.09	0.09	0.10							
44	Time, *mo*	0	1	1.5	4	6	8	10	12			
	UV, *ml/24 hr*	1283	1193	1209	1158	1261	1342	1151	1221			
	C_{cr}, *ml/min*	4.42	4.81	4.57	3.66	3.65	3.65	3.39	3.44			

receiving home dialysis to collect for himself the necessary blood and urine specimens. It can be used equally well on in-center dialysis patients.

One further simplification of the method is possible. If one plots urine volume vs. creatinine clearance using the data in Table 5, the correlation is extremely good for each individual patient. In other words, once the relationship between urine volume and creatinine clearance is accurately determined, changes in 24-hr urine volume can be used for approximate calculation of clearances as they both decrease with time.

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