Single-Sample Method for the Estimation of Glomerular Filtration Rate in Children

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A method for the determination of the glomerular filtration rate (GFR) in children which involves the use of a single-plasma sample (SPS) after the injection of a radioactive indicator such as radioiodine labeled diatrizoate (Hypaque) has been developed. This is analogous to previously published SPS techniques of effective renal plasma flow (ERPF) in adults and children and GFR SPS techniques in adults. As a reference standard, GFR has been calculated from compartment analysis of injected radiopharmaceuticals (Sapirstein Method). Theoretical volumes of distribution were calculated at various times after injection (V_t) by dividing the total injected counts (I) by the plasma concentration (C_t) expressed in liters, determined by counting an aliquot of plasma in a well type scintillation counter. Errors of predicting GFR from the various V_t values were determined as the standard error of estimate (Sy.x) in ml/min. They were found to be relatively high early after injection and to fall to a nadir of 3.9 ml/min at 91 min. The Sy.x V_t relationship was examined in linear, quadratic, and exponential form, but the simpler linear relationship was found to yield the lowest error. Other data calculated from the compartment analysis of the reference plasma disappearance curves are presented, but at this time have apparently little clinical relevance.

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Single-plasma sample methods for the estimation of effective renal plasma flow (ERPF) have been presented in both adults (*1–3*) and children (*4*), and for the estimation of glomerular filtration rates in milliliters per minute (GFR) in adults (*5,6*). Since, in adults, single-plasma sample methods have proven to be superior to conventional inulin clearances in terms of patient acceptance, economy, and simplicity, and in terms of accuracy compared to other single injection methods (*7*), we have developed a similar method to determine GFR for use in pediatric practice and research.

MATERIALS AND METHODS

Selection of Subjects

Twelve male pediatric patients aged 8 to 15 yr and 18 female patients aged 4 to 15 yr were chosen for study. Diagnostic categories, sexes, ages, heights, and weights are presented in Table 1. Iodine-131 diatrizoate ([^{131}I]DTZ) was the indicator substance used in dosages from 10 to 50 μCi based on age.

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Techniques

Reference standard production. GFR was first calculated by the method of Farmer (*8*) using formulae presented by Sapirstein (*9*) based on the assumption of a two-compartment mammillary model:

$$GFR = \frac{I \cdot \lambda_a \cdot \lambda_b}{A \cdot \lambda_b + B \cdot \lambda_a}, \quad (1)$$

where I represents the total counts per second of the radiopharmaceutical injected, λ_a the slope of the slower of the two exponents that result from a semilogarithmic plot of the plasma disappearance curve, and A the slower component's intercept on the y-axis. Similarly, λ_b represents the slope of the faster of the two components and B its intercept on the y-axis. GFR determined by this method was used as a reference standard. Plasmas were sampled at 10-min intervals up to 90 min after injection.

The model assumes that the dose is injected into a first volume of distribution (V_1), which includes and exceeds the plasma volume. It leaves this volume by two pathways, one into a second closed volume (V_2) (the exchange volume) and another into an open ended volume (V_3) corresponding to urinary excretion. The flow ($F_{1\text{-}3}$) from V_1 to V_3 is the GFR.

The injected or sampling volume (ml), which includes (and exceeds) the plasma volume is represented by the formula:

$$V_1 = \frac{I}{A + B}. \quad (2)$$

TABLE 1
Basic Demographic Data

Case no.	Sex	Age (yr)	Wt (lb)	Height (in.)	Final diagnosis
1	M	14	227	72	Urethritis
2	M	16	145	65	Urethritis
3	F	15	103	62	Urethritis
4	F	9	67	54	Conversion reaction
5	F	13	87	58	Chr. glomerulonephritis
6	F	9	54	50	Chr. glomerulonephritis
7	M	12	75	54	Nephrotic syndrome
8	F	9	67	62	Chr. glomerulonephritis
9	F	11	49	50	Chr. glomerulonephritis
10	M	13	87	60	Chr. glomerulonephritis
11	M	14	165	73	Chr. glomerulonephritis
12	F	8	49	48	Urinary tract infection
13	F	10	65	53	Urinary tract infection
14	F	12	59	51	Chr. urinary tract infection
15	M	12	72	53	Bilat. familial dwarf kidney
16	F	12	75	60	Bilat. familial dwarf kindey
17	M	10	84	57	Bilat. familial dwarf kidney
18	M	10	68	50	Bilateral hydronephrosis
19	F	12	80	56	Hydronephrosis
20	M	8	60	50	Renal failure, hydronephrosis
21	M	6	42	45	Acute glomerulonephritis
22	M	11	59	63	Acute glomerulonephritis
23	F	4	38	41	Acute glomerulonephritis
24	F	9	47	48	Lupus erythematosus, membr. glomerulo
25	F	15	104	62	Lupus erythematosus
26	F	14	104	56	Lupus erythematosus
27	F	15	131	73	Membr. glomerulonephritis
28	F	9	63	53	Membr. glomerulonephritis
29	M	15	153	70	Chronic renal failure
30	F	12	96	60	Renal artery stenosis

The intercompartmental flow (ml/min), V_1 to V_2 ($F_{1\text{-}2}$) is assumed to be equal in magnitude to the flow from V_2 to V_1, $F_{2\text{-}1}$, i.e., a steady state between those two compartments.

$$F_{1-2} = \frac{V_1(A \cdot \lambda_a + B \cdot \lambda_b)}{A + B} - F_{1-3} \text{ ml/min.} \quad (3)$$

The exchange volume (V_2) ml is represented by the formula:

$$V_2 = \frac{F_{1-3} \cdot F_{1-2}}{V_1 \cdot \lambda_a \cdot \lambda_b}. \quad (4)$$

The rate constants $k_{1\text{-}2}$, $k_{2\text{-}1}$, $k_{1\text{-}3}$, represent the fractional flow from one compartment (or volume) to another. For example, $k_{1\text{-}2}$ represents that fraction of V_1 flowing into V_2 per unit time, subscripts indicating beginning and end-volumes.

$$k_{1-3} = \frac{F_{1-3}}{V_1} \quad (5)$$

$$k_{1-2} = \frac{F_{1-2}}{V_1} \quad (6)$$

$$k_{2-1} = \frac{F_{2-1}}{V_2}. \quad (7)$$

Body surface areas (SA) were calculated by the formulae of Dubois and Boyd (*10,11*).

Data processing. The counting rate of the plasma at any time expressed as counts per second per liter of plasma (C_t) was divided into I at each sampling time, resulting in a theoretical volume of distribution (V_t) expressed in liters. For each sampling time, all the V_t obtained from the 30 patients were plotted against their reference GFRs. Correlations were tried in linear, quadratic, and exponential algorithms, the latter by the Gauss-Newton method which seeks coefficients interatively for the equation

$$GFR = G_{max}\,[1 - e^{-\alpha}\,(V_t - V_{lag})], \quad (8)$$

where G_{max} is the asymptotic maximum value of GFR, e the base of the natural logarithm, α is the rate constant (slope), V_t as above and V_{lag} the intercept of the best fitting line on the x-axis. Errors at each sampling time were expressed as standard errors of estimate (Sy.x).

RESULTS

Values of I, A, B, λ_a, and λ_b are presented in Table 2 for each of the 30 patients. Individual patient values for V_1, V_2, $F_{1\text{-}3}$ (GFR), $F_{1\text{-}2}$, $k_{1\text{-}2}$, $k_{2\text{-}1}$, and $k_{1\text{-}3}$ are given in Table 3. Except for the rate constants, they are all appropriately lower than the values shown in adults (*5*). Table 4 presents the mean values found in children and adults.

TABLE 2
Infected Dose (I), Intercepts (A, B), and Slopes (λ_a, λ_b) of Curves Following Injection of DTZ*

Case no.	I	A	B	λ_a	λ_b
1	1,598,250	73	77	0.0107	0.1460
2	1,581,060	105	150	0.0099	0.1540
3	1,422,496	138	172	0.0119	0.1270
4	1,722,528	245	310	0.0128	0.1066
5	1,585,776	151	108	0.0061	0.0792
6	1,057,638	151	198	0.0119	0.1066
7	1,629,834	184	138	0.0146	0.0645
8	1,062,637	123	109	0.0080	0.0666
9	1,130,160	240	67	0.0030	0.0815
10	1,605,606	168	57	0.0121	0.1155
11	1,722,528	112	65	0.0077	0.0792
12	742,812	168	114	0.0103	0.1109
13	647,047	75	68	0.0126	0.0770
14	753,720	80	135	0.0092	0.0792
15	1,211,280	271	137	0.0038	0.0963
16	1,642,267	215	171	0.0070	0.0924
17	1,642,278	172	169	0.0097	0.0894
18	1,446,220	175	245	0.0124	0.1070
19	1,572,078	175	171	0.0104	0.0866
20	1,527,540	258	166	0.0037	0.0815
21	558,415	89	161	0.0068	0.0894
22	1,126,940	194	97	0.0140	0.0529
23	657,264	116	90	0.0119	0.0956
24	997,800	199	222	0.0132	0.1730
25	1,113,276	115	106	0.0121	0.2100
26	1,053,237	95	132	0.0080	0.1733
27	1,382,430	116	83	0.0049	0.0924
28	1,542,090	230	242	0.0099	0.1027
29	1,009,185	60	40	0.0082	0.1118
30	1,626,354	145	165	0.0087	0.1210

*I is in cps; A, B in cps/ml plasma.

TABLE 3
Individual Volumes of Distribution (V_1, V_2), Flow Rates (F) and Fractional Clearing Constants (k)

Case no.	V_1 (l)	V_2 (l)	F_{1-3} (ml/min)	F_{1-2} (ml/min)	k_{1-2}	k_{2-1}	k_{1-3}
1	10.66	8.32	217	637	0.060	0.077	0.020
2	6.20	6.51	136	450	0.073	0.069	0.022
3	4.59	3.77	110	238	0.052	0.063	0.024
4	3.10	2.29	78	124	0.040	0.054	0.025
5	6.12	3.36	60	164	0.027	0.049	0.010
6	3.03	2.38	73	126	0.042	0.053	0.024
7	5.06	1.66	110	71	0.014	0.043	0.022
8	4.58	2.56	63	100	0.022	0.039	0.014
9	3.68	0.93	14	60	0.016	0.064	0.004
10	7.14	1.81	111	162	0.023	0.089	0.016
11	9.73	4.12	112	218	0.022	0.053	0.011
12	2.63	1.30	43	91	0.035	0.070	0.016
13	4.52	2.18	95	101	0.022	0.046	0.021
14	3.51	3.22	73	114	0.032	0.035	0.021
15	2.97	1.33	16	87	0.029	0.065	0.005
16	4.25	2.57	50	140	0.033	0.055	0.012
17	4.82	3.07	84	153	0.032	0.050	0.017
18	3.44	2.79	88	144	0.042	0.052	0.026
19	4.54	2.75	84	135	0.030	0.049	0.018
20	3.60	1.99	21	102	0.028	0.051	0.006
21	2.23	2.67	37	96	0.043	0.036	0.017
22	3.87	0.81	72	32	0.008	0.040	0.019
23	3.19	1.58	61	93	0.029	0.059	0.019
24	2.37	1.92	61	170	0.072	0.089	0.026
25	5.04	3.72	111	428	0.085	0.115	0.022
26	4.64	5.19	83	400	0.086	0.077	0.018
27	6.95	4.14	56	232	0.033	0.056	0.008
28	3.27	2.31	60	127	0.039	0.055	0.018
29	10.09	5.25	132	369	0.037	0.070	0.013
30	5.25	4.40	90	269	0.051	0.061	0.017

As shown in Figure 1, the error of GFR prediction from single-plasma samples falls from 12.0 ml/min 70 min after injection to a nadir of 3.9 ml/min at 91 min increasing to 5.5 ml/min at 110 min. The error at earlier and later sampling times is significantly higher than these. The magnitude of the lowest error is the same for both quadratic and linear equations; the equations are also similar at this time since the coefficients for the first two elements of the equation are essentially identical and the third coefficient −0.00004 is negligible.

The error nadir of the exponential equation also occurs at 91 min and is insignificantly higher at 3.90 ml/min. However, it is lower than the linear equation error at earlier sampling times. At 87 min after injection the errors for the two methods were identical at 3.98 ml/min.

Table 5 presents coefficients and estimation errors at 10-min intervals for equations of linear, quadratic, and exponential nature.

Because blood samplings at some specific time are often frustrated, especially in children, coefficients for other (linear equation) sampling times on a minute by minute basis around the ideal time have been calculated from interpolated C_t values (Table 6).

Differences between GFR estimated from the 91-min plasma sample method and that of the reference standard did not differ at the 0.01 level by the paired t-test.

Correlation coefficients for the volumes V_1 and V_2, height, weight, age, and surface area are presented in Table 7. The highest correlation among these parameters occurred between the theoretical volumes of distribution and body weight. The coefficients are significantly higher than those observed in the adult. Correlations were slightly higher with surface areas calculated from the Boyd equation in children (Table 8). They were slightly higher using the Dubois equation in adults.

TABLE 4
Mean and s.d. Values from DTZ Studies in Children

	Children		Adults	
	Mean	s.d.	Mean	s.d.
V_1 liters	4.84	2.20	8.40	2.17
V_2 liters	3.03	1.67	4.51	1.62
F_{1-3} ml/min	80.	41.	79.	34.
F_{1-2} ml/min	188.	139.	225.	99.
k_{1-2}	0.039	0.020	0.028	0.014
k_{2-1}	0.060	0.017	0.051	0.015
k_{1-3}	0.017	0.006	0.010	0.005

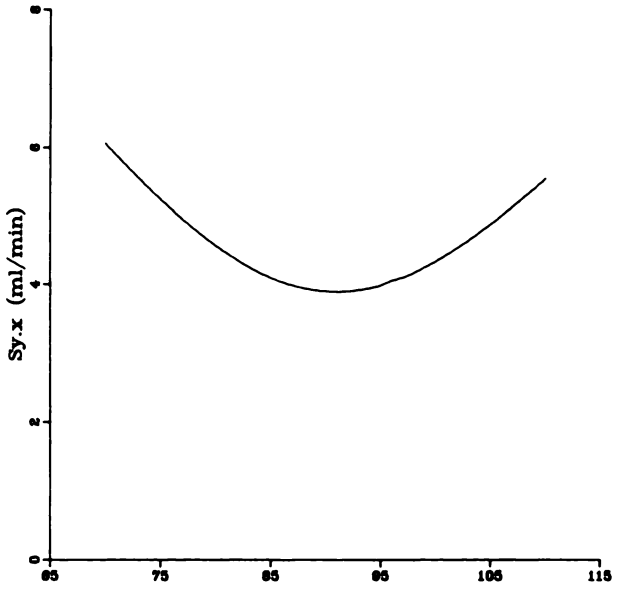

FIGURE 1
Standard error of estimates of GFR (linear equations) by calculated (interpolated) plasma concentration reciprocals at various times after injecton of the radiopharmaceutical. The smallest error was observed at 91 min after injection.

The GFR estimated from a calculated theoretical volume of distribution at 91 min, the sampling time associated with the lowest prediction error, are plotted against the reference standard GFRs in Figure 2. The line shown was calculated through the data is based on a least squares line or fit.

DISCUSSION

As we have shown in adults, it was found that making use of a regression equation, GFR can be estimated in children within acceptable error from a single sample drawn at 91 min after injection. This time interval is significantly less than the intervals of 120, 150, or 220 min in adults (depending on level of GFR), which were determined to be optimum but is higher than the interval of 53 min used in the estimation of ERPF in children. The method is useful in the determination of renal function in children with minimal invasion, minimal risk, and great accuracy.

We favor the linear equation for routine clinical use because of greater ease of handling and greater accuracy. Just why a linear relationship exists between GFR and the V_ts in patients from 4 to 16 yr of age at 91 min and an exponential relationship exists at the optimum sampling time in adults is not clear, but similar findings were obtained when estimating ERPF. Why a single sampling time seems to be ideal for all levels of GFR in children but a function of the magnitude of GFR in adults is also unclear, however, a similar situation also obtained when estimating ERPF (unpublished data).

TABLE 5
Coefficients and Constants of Different GFR Estimation Functions and Their Standard Errors

	Linear*		
Time	A	B	Sy.x
10	5.26	9.94	20.0
20	1.44	8.05	17.1
30	−3.12	7.20	1.47
40	−6.54	6.58	12.4
50	−8.52	6.01	10.1
60	−9.33	5.45	8.0
70	−9.26	4.91	6.1
80	−8.53	4.39	4.6
90	−7.32	3.91	3.9
100	−5.68	3.46	4.3
110	−3.75	3.05	5.5
120	−1.56	2.68	7.1
130	0.80	2.35	8.7
140	3.31	2.04	10.3
150	5.92	1.78	11.9

	Quadratic†			
	A	B	C	Sy.x
10	12.48	8.19	0.08567	20.0
20	0.25	8.27	−0.00827	17.1
30	−7.61	7.90	−0.02276	14.7
40	−11.69	7.29	−0.02064	12.3
50	−13.25	6.60	−0.01551	10.1
60	−13.19	5.89	−0.01041	7.9
70	−11.99	5.19	−0.00612	6.0
80	−10.04	4.54	−0.00280	4.5
90	−7.60	3.94	−0.00043	3.9
100	−4.81	3.39	−0.00112	4.9
110	−1.86	2.92	−0.00201	7.6
120	1.15	2.50	0.00240	7.0
130	4.10	2.15	0.00242	8.6
140	6.94	1.84	0.00219	10.2
150	9.60	1.59	0.00184	11.8

	Exponential‡			
	F_{max}	α	V_{lag}	Sy.x
10	6,965	0.00145	−0.46	20.0
20	3,096	0.00270	0.02	17.1
30	1,037	0.00775	1.09	14.7
40	1,022	0.00720	1.70	12.3
50	1,171	0.00564	2.08	10.1
60	1,455	0.00404	2.28	7.9
70	2,011	0.00258	2.33	6.0
80	3,493	0.00130	2.22	4.5
90	4,023	0.00100	2.14	3.9
100	4,130	0.00086	1.92	4.4
110	3,993	0.00078	1.55	5.6
120	3,860	0.00071	0.95	7.1
130	4,182	0.00057	0.04	8.7
140	3,977	0.00053	−1.17	10.3
150	4,065	0.00045	−2.83	11.9

* $GFR = A + BV_t$.
† $GFR = A + BV_t + CV_t^2$.
‡ $GFR = F_{max}[1 - e^{-\alpha}(V_t - V_{lag})]$.

All GFRs in ml/min.

TABLE 6
Coefficients for Linear Prediction of GFR*

Time	A	B	Sy.x
80	−8.53	4.39	4.56
81	−8.43	4.34	4.45
82	−8.33	4.29	4.35
83	−8.22	4.25	4.25
84	−8.10	4.20	4.17
85	−7.99	4.15	4.09
86	−7.86	4.10	4.03
87	−7.73	4.05	3.98
88	−7.60	4.00	3.94
89	−7.46	3.96	3.91
90	−7.32	3.91	3.90
91	−7.17	3.86	3.89
92	−7.02	3.82	3.90
93	−6.86	3.77	3.92
94	−6.71	3.73	3.95
95	−6.55	3.68	3.99
96	−6.74	3.64	4.06
97	−6.22	3.59	4.10
98	−6.04	3.55	4.17
99	−5.86	3.51	4.25
100	−5.68	3.46	4.34

*GFR = A + B (V_t) ml/min.

Quadratic equations gave a better estimate of GFR at early sampling times. The error values crossed at 78 min. In adults exponential equations were used to estimate GFR and exponential curves were found to be associated with the least error.

The Sy.x values apparently are not a function of age. Differences between calculated and observed values compared to age yield a correlation coefficient of 0.00.

V_1 was again found to be larger than the expected plasma volume and nothing in our present data suggests an anatomic location for V_1 or V_2. V_1 seems to approximate the sum of the two volumes (V_1 and V_2) of human serum albumin using the same compartment model (*12*). The albumin molecule may be stopped initially at the endothelial wall, thus delineating its V_1, (the plasma volume) then more slowly penetrate the next contiguous space thus bounding its V_2. The DTZ molecule probably penetrates immediately all the way to this last limit, thus forming its V_1. Similar data were obtained in adults when estimating GFR (*5*) and in adults (*1*) and children (*4*) when estimating ERPF using orthoiodohippurate.

It should be stressed that V_t is a theoretical value.

TABLE 7
Correlation Coefficients Between Volumes and Body Parameters in Children

	Age	Wt	Ht	BuBois	Boyd
V_1	0.67	0.91	0.85	0.92	0.92
V_2	0.62	0.88	0.65	0.82	0.85
$V_1 + V_2$	0.70	0.97	0.82	0.95	0.96

TABLE 8
Correlation Coefficients Between Volumes and Body Parameters in Adults

	Age	Wt	Ht	BuBois	Boyd
V_1	0.02	0.55	0.48	0.58	0.57
V_2	0.16	0.46	0.41	0.48	0.47
$V_1 + V_2$	0.10	0.65	0.56	0.67	0.66

This is due to the fact that I/C_t at a specific time does not represent the total intracorporeal volume of distribution since some of the dose has been concentrated and excreted. It rather represents the volume that would contain the total injected amount of the indicator assuming a uniform concentration (C_t) equal to that of the plasma sampled at any time t.

We have described an accurate noninvasive and cost-effective method for the estimation of GFR in children. Probably the chief source of error is estravasation of the injected dose. Therefore, it is desirable to employ a three-way stopcock for injecting. The injection site may be examined with the scintillation camera if the study is accompanied by scintigraphy. In our experience, it is important to use the formula appropriate to the sampling time even though it was not the "ideal" 91 min; errors are usually considerably less.

In the usual clinical situation, after injecting the patient, a carefully measured identical volume is injected into a 1-liter volumetric flask for dilution. A 1:1000 aliquot (1-2 ml) of the injected dose is counted along with an equal volume of the 91-min plasma. If more than one patient is being studied, a single standard

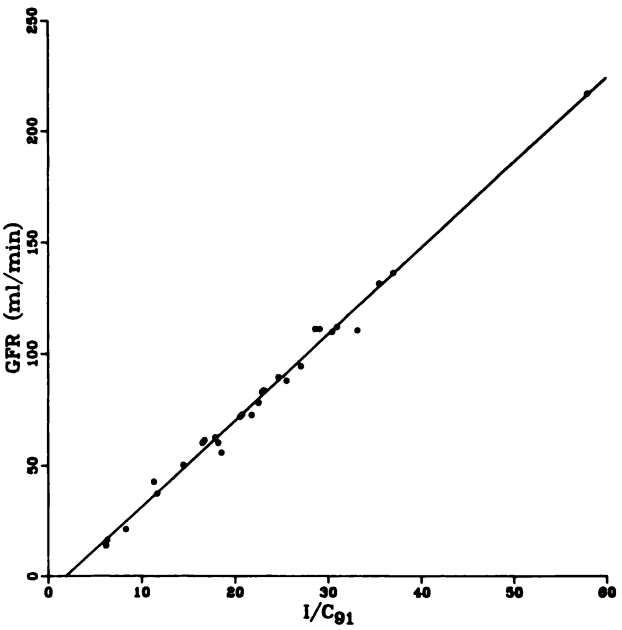

FIGURE 2
Plot of GFR calculated from the whole plasma DTZ disappearance curve in children versus the apparent DTZ distribution at 91 min.

may be used, with total injected counts (I) being calculated, adjusting for dose differences among patients.

In addition to accuracy, noninvasiveness, and cost effectiveness the test has the advantage of being suitable for studying several patients at one sitting and can also be combined with scintigraphy.

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