

## CHAPTER IV

### RESULTS AND DISCUSSION

#### Characteristics of the patients and dosage regimen

The patients with heart failure taking digoxin who met the criteria of this study were evaluated. Eighty three patients who were admitted in the hospital or were the out patients of the cardiology clinic were analyzed. Table III showed the characteristics of the patients, table IV showed the dosage regimen administered to each patients. Maintenance dose of digoxin was administered to the patients in three different patterns to maintain digoxin blood level, the dosage regimen usually prescribed by physician were 0.25 mg per day, 0.125 mg per day and 0.25 mg per day alternately with 0.125 mg per day. The percentage of patients taking various dosages of digoxin were concluded in table V. The eighty-three patients studied could be divided into two groups. One group of patients used only digoxin to control the abnormalities of the heart and another group of patients used digoxin along with other drugs. In this study, 18% of patients (15 out of 83) took digoxin without other drugs. 82% (n=63) of patients took digoxin without other drugs, (showed in Table VI and Figure 3). Physicians in Chulalongkorn Hospital tended to use conventional dosage regimen and have not applied pharmacokinetics to the digoxin dosage regimen calculation.

Patients with heart failure or other abnormalities of the function of the heart usually use many groups of drug for the best clinical improvement. Diuretics, Vasodilators, ACEI or other groups of drug are always used

**Table III** Characteristics of patients

Patient Number	Sex	Age (year)	TBW <sup>1</sup> (kg)	IBW <sup>2</sup> (kg)	Height (cm)
1	M	62	50.0	62.88	164
2	M	38	53.0	59.20	160
3	M	70	58.0	68.40	170
4	M	68	60.0	66.56	168
5	M	66	52.0	61.04	162
6	M	73	54.0	73.92	176
7	M	44	58.0	52.76	153
8	M	36	83.0	73.00	175
9	M	36	53.0	64.72	166
10	M	49	86.0	73.00	175
11	M	35	48.4	68.40	170
12	M	33	60.0	61.04	162
13	M	56	80.0	63.80	165
14	M	76	50.0	66.56	168
15	M	36	48.0	66.56	168
16	M	68	63.0	68.40	170
17	F	38	50.0	46.42	151
18	F	44	57.0	48.26	153
19	F	42	44.0	51.48	156.5
20	F	71	50.0	51.94	157
21	F	21	45.5	49.18	154
22	F	48	39.0	45.50	150



Table III (Continuing)

Patient Number	Sex	Age (year)	TBW <sup>1</sup> (kg)	IBW <sup>2</sup> (kg)	Height (cm)
23	F	81	47.0	45.50	150
24	F	54	54.0	54.70	160
25	F	39	45.0	49.18	154
26	F	44	86.4	59.30	165
27	F	63	58.4	51.94	157
28	F	46	54.5	45.50	150
29	F	48	50.0	48.26	153
30	F	63	47.0	49.18	154
31	F	35	49.0	45.50	150
32	F	73	46.0	54.70	160
33	F	46	57.0	61.14	167
34	F	53	57.6	58.38	164
35	F	69	68.2	48.26	153
36	F	41	51.2	51.94	157
37	F	48	53.4	49.18	154
38	F	53	46.0	49.18	154
39	M	44	52.7	66.52	168
40	M	28	46.0	61.04	162
41	M	39	45.5	61.96	163
42	M	36	48.0	58.28	159
43	M	19	43.5	70.24	172
44	F	28	47.0	50.10	155



Table III (Continuing)

Patient Number	Sex	Age (year)	TBW <sup>1</sup> (kg)	IBW <sup>2</sup> (kg)	Height (cm)
45	F	50	39.0	51.02	156
46	F	43	41.3	48.26	153
47	F	34	63.0	63.80	165
48	F	23	47.7	61.14	167
49	F	60	59.5	48.26	153
50	F	37	54.0	46.42	151
51	F	70	48.0	49.18	154
52	F	48	42.0	51.94	157
53	F	37	43.0	47.80	152.5
54	F	21	38.0	45.50	150
55	M	58	58.0	63.80	165
56	F	36	50.0	52.86	158
57	M	36	48.0	50.46	150.5
58	M	68	63.0	53.49	153.8
59	M	50	60.0	63.80	165
60	F	58	62.0	47.34	152
61	F	67	54.1	53.50	158.7
62	F	56	80.0	45.50	150
63	F	34	51.0	56.54	162
64	M	47	73.2	68.40	170
65	F	19	48.2	48.26	153
66	F	23	39.0	47.34	152



Table III (Continuing)

Patient Number	Sex	Age (year)	TBW <sup>1</sup> (kg)	IBW <sup>2</sup> (kg)	Height (cm)
67	F	21	59.1	54.70	160
68	M	43	60.0	58.28	159
69	F	63	49.0	47.34	152
70	M	17	51.0	52.30	152.5
71	M	45	53.0	59.20	160
72	M	66	50.5	59.38	160.2
73	F	55	60.5	28.02	131
74	M	27	63.0	73.00	175
75	F	36	55.0	50.10	155
76	F	25	48.2	55.64	161
77	F	46	48.0	51.02	156
78	M	47	53.0	59.20	160
79	F	35	47.0	45.50	150
80	F	40	48.0	45.50	150
81	F	56	55.5	50.56	155.5
82	M	21	58.8	59.20	160
83	F	46	46.2	45.50	150
mean $\pm$ SD	F = 49	46.07229 $\pm$ 15.66321	53.7729 $\pm$ 10.10826	55.3264 $\pm$ 8.718039	158.6771 $\pm$ 7.774352
(Range)	M = 34	(19-73)	(38-86.40)	(28.02-73.92)	(131-176)

1. TBW = Total Body Weight

2. IBW = Ideal Body Weight

**Table IV**      **Dose of digoxin**

Patient Number	Dose (mg/day)	Patient Number	Dose (mg/day)
1	0.25	43	0.25
2	0.25	44	0.25
3	0.125	45	0.125
4	0.125	46	0.125
5	0.125	47	0.25
6	0.125 / 0.25	48	0.125
7	0.125	49	0.25
8	0.25	50	0.125
9	0.25	51	0.125
10	0.25	52	0.25
11	0.25	53	0.25
12	0.25	*54	0.125
13	0.25	55	0.125
14	0.25	56	0.125
15	0.25	57	0.25
16	0.125	58	0.25
17	0.25	59	0.25
18	0.125 / 0.25	60	0.125
19	0.25	61	0.125 / 0.25
20	0.25	62	0.25
21	0.25	63	0.25
22	0.25	64	0.125
23	0.125	65	0.25
24	0.125	66	0.125
25	0.25	67	0.25
26	0.25	68	0.25
27	0.25	69	0.25
28	0.25	70	0.25
29	0.125	71	0.125
30	0.25	72	0.125
31	0.125	73	0.125
32	0.25	74	0.25
33	0.25	75	0.125
34	0.25	76	0.25
35	0.125 / 0.25	*77	0.25
36	0.125	78	0.125
37	0.25	79	0.125
38	0.25	80	0.125
39	0.25	*81	0.25
40	0.25	*82	0.125
41	0.25	*83	0.125
42	0.25		

\* Patients with adjustment of the dosage regimen  
/ alternate with

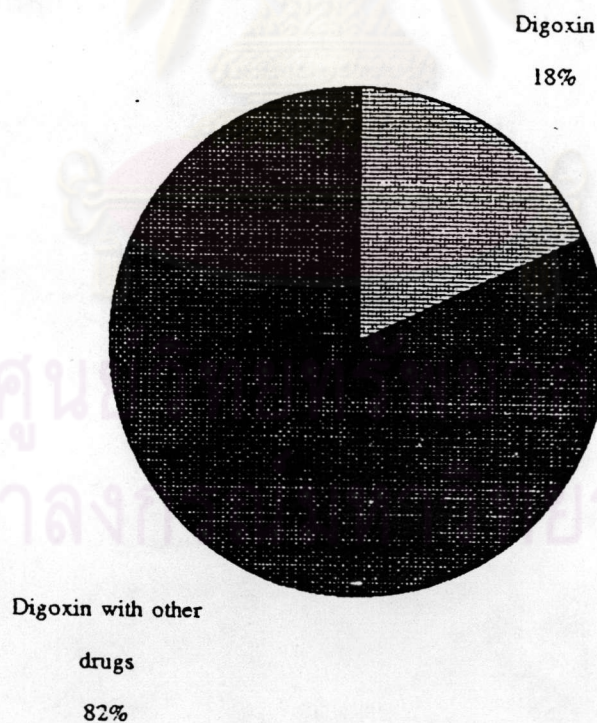


**Table V** Percentage of patients taking various doses of digoxin

Dosage of digoxin	Total number of patients (percent)
0.125 mg/day	49 (59.04)
0.25 mg/day	30 (36.14)
0.125 alternate 0.25 mg/day	4 (4.82)

**Table VI** Percentage of patients taking digoxin with or without other drug

Drug	Number of patients (percent)
digoxin	15 (18)
digoxin with other drugs	68 (82)

**Figure 3** Percentage of patients taking digoxin alone and digoxin with other drugs.

Diuretics, Vasodilators, ACEI or other groups of drug are always used concomitantly with digoxin. In this study, 55 out of 83 patients took digoxin with diuretics, 14 out of 83 patients took digoxin with diuretics and ACEI, 8 out of 83 patients took vasodilators and digoxin. In this study, diuretics which were commonly prescribed by physicians composed of two groups, i.e., loop diuretics and potassium sparing diuretics. Loop diuretics were prescribed to 22 patients while potassium sparing diuretics were prescribed to 24 patients. (Drugs used concomitantly with digoxin were shown in Appendix B) Table VII and figure 4 showed the various groups of drug, total number of patients in each group and the percentage for each groups.

### 1. Serum digoxin levels and the therapeutic range

The serum concentrations which were required for treatment to attain therapeutic levels were 0.8 to 2.0 ng/ml. (Brodie, 1986) When the data was analyzed. Many patients' digoxin levels were within the desired range. Among the 83 patients included in this study, 54 patients (65.06%) had measured serum concentration within the therapeutic range, 28 patients (33.73%) had serum level with in the subtherapeutic range and only 1 patient (1.20%) had serum level with overtherapeutic range. 54 patients' serum digoxin levels were classified into various groups of different concentration ranges which were showed in table VIII.

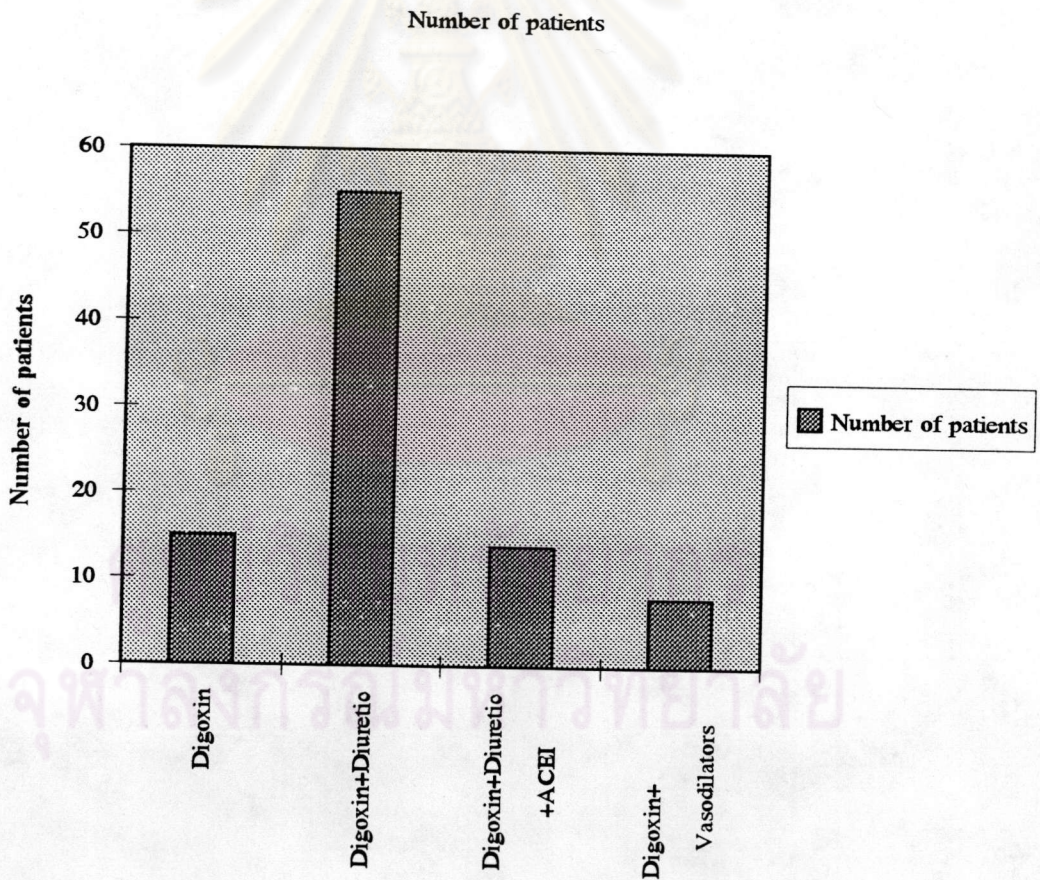
All of the 83 patients were followed up for their clinical results. The patient was indicated as showing improvement if he or she had not shown the side effects or the undesired symptom of the present disease. Seventy-seven patients showed sign of improvement, four patients showed negative improvement and two patients had the undesired effect from the drug and symptom of the present disease.





**Table VII** Percentage of patients taking digoxin with various groups of drug.

Drug	Number of patients (percent)
digoxin	15 (18.07)
digoxin + diuretic	55 (66.26)
digoxin + diuretic + ACEI	14 (16.87)
digoxin + Vasodilator	8 (9.64)



**Figure 4** Number of patients taking various drug group with digoxin

The clinical result as related to the therapeutic range was also presented in Table IX.

**Table VIII** Number of patients with measured digoxin level within various sub ranges

Measured Digoxin Level (ng/ml)	Number of patients
0.80 - 0.90	9
0.91 - 1.01	9
1.02 - 1.12	10
1.13 - 1.23	7
1.24 - 1.34	7
1.35 - 1.45	7
1.46 - 1.56	3
1.57 - 1.67	1
1.68 - 1.78	-
1.79 - 1.89	1
1.90 - 2.00	-
<b>Total</b>	<b>54</b>



**Table IX** Percentage of patients showing clinical improvement in each group of digoxin serum concentration ranges

Serum digoxin levels (ng/ml)	Number of patients	Percentage	Number of patients showed improvement	Percentage of improvement
within therapeutic levels	54	65.06	50	92.60
subtherapeutic levels	28	33.73	26	92.85
overtherapeutic levels	1	1.20	1	100

All of the sign of showing improvement of patients were analyzed. Most of them were the out patients that taking digoxin with or without other drugs to control their heart function as prescribed with the traditional dosage regimen by the physician. During this study, the serum digoxin levels were drawn at the time and the control of the compliances for the patients as described before. Furthermore, the side effects were monitored. The patients had taken the drugs for some period of time before they were scheduled to meet the physician in the cardiology clinic. When the patients stayed at home, they were instructed to go immediately to the hospital if they had any sign and/or symptom of the undesired effects. The out patient of cardiology clinic normally showed sign of good clinical improvement after some period of time while the negative improvement was found among patients admitted in the cardiology ward, four patients were male and two were female. One female was admitted in the hospital for mild mitral stenosis, aortic regurgitation and tricuspid regurgitation. The other female patient was twenty-one years old, had anemia



as her underlying disease and the undesired outcomes came from her disease. Four patients were admitted with various abnormalities of the heart. During this study they were suffered from other diseases, unrelated to the heart. One patient developed influenza, two of them got diarrhea from the amoebic and the last one was infected by the virus. The side effect of digoxin was observed in one female patient, she was forty-six years old, developing rheumatic heart disease. She had severe tricuspid regurgitation with mitral regurgitation and showed negative improvement.

## **2. Serum digoxin concentration in patient using various group of drugs concomitantly with digoxin.**

Serum digoxin concentrations were influenced by other drugs, the serum concentrations could be increased or decreased causing change in clinical effect in the patient.

Diuretics are commonly administered together with digoxin in the treatment of congestive cardiac failure. Digoxin is excreted principally by the kidney, largely in an unchanged form, and a direct relation between glomerular filtration rate measured by creatinine clearance and tubular mechanisms also appear to play a significant role. Alteration of tubular mechanisms by the diuretics spironolactone, possibly inhibited distal tubular secretion of digoxin. Steiness (1974) showed that in nine digitalized patients with "congestive heart disease" placed on 100 mg spironolactone daily for 10 days showed significant increase in plasma digoxin concentrations. Since the renal digoxin clearance approached the glomerular filtration rate of the free unbound fraction in plasma, inhibition of tubular digoxin secretion was supposed.



In this study, measured serum digoxin concentrations with or without other drugs were analyzed. The mean serum digoxin concentration in the group of patients administered with digoxin alone was  $1.136 \pm 0.2932$  ng/ml (means  $\pm$  SD) (n=15) while the mean serum concentrations of the patients administered with the loop diuretics and the potassium sparing diuretics equal to  $0.8759 \pm 0.2695$  ng/ml (n=23) and  $1.0795 \pm 0.4104$  ng/ml (n=24) respectively. Using analysis of variance, comparison between the digoxin alone group and the digoxin concomitantly with the loop diuretic group showed significant difference while significant difference could not be observed at 95% level of confidence between the concomitantly with potassium sparing diuretic group and the digoxin alone as shown in table X and table XI respectively.

Our data suggested that it should be more practical to use potassium sparing diuretics in patients with heart failure to maintain the good clinical outcome and prevent the undesired effect from the increased or decreased serum digoxin concentrations causing from the loop diuretics for a long time treatment. However, Brown et al. (1976) concluded from their study that the effect of furosemide on the renal excretion of digoxin did not significantly affect the excretion of digoxin in their subjects (4 patients with heart disease and 2 volunteers without heart disease). Malcolm et al. (1976) also presented that no need to alter loading or maintenance dose of digoxin when furosemide is also given. Since the mechanism and the pharmacologic properties of furosemide, the interplay of the several mechanisms and the consequent effects on renal handling of digoxin cannot be predicted for a long term, monitoring of the clinical outcome and the electrolyte balance would be the useful method for the patients care.





Vasodilators and the ACEI were the two drug groups which often used in combination with digoxin to benefit the better controlling of the heart disease. The drugs may influence serum digoxin concentrations. In this study, there was no significant difference between measured serum digoxin concentration of the digoxin alone group and the digoxin with vasodilator group. The ACEI and diuretics together with digoxin showed significant difference of serum level with the digoxin alone group. Table XII and Table XIII showed the results of these comparisons respectively. Nevertheless, further collection in a larger number of patients should be done before any definite conclusion could be made.

### **3. The serum concentration versus the age and the dosage regimen**

The typical patient with adverse drug reactions is usually elderly patients with advanced heart disease and atrial fibrillation, often associated with pulmonary disease and abnormal renal function. So, the titrating dose to the elderly must be concentratly considered. From this study, the dosage regimens were classified into three patterns. The patients' age and the measured serum digoxin concentration were analyzed under the dose administered. The result and the analysis of variance in patients aged 20-60 years and above 60 years were shown for the dose 0.125 mg per day in table XIV , XV, XVI. Table XVII, XVIII, XIX, XX were the results of the dose 0.25 mg per day in patients aged <20 years, 20-60 years and aged above 60 years and table XXI, XXII were for the dose 0.125 alternate with 0.25 mg per day in patients aged 20-60 years and above 60 years respectively. Significant difference were found in patients' age and the measured serum digoxin level among the dose 0.125 mg per day at 95% level of confidence.



**Table X** Comparison of the measured serum digoxin level in digoxin alone group and digoxin with loop diuretic group.

Digoxin alone		Digoxin with loop diuretic				
Patient Number	Measured digoxin level (ng/ml)	Patient Number	Measured digoxin level (ng/ml)			
7	0.47	4	0.84			
9	1.32	5	0.80			
10	1.00	12	1.10			
11	1.30	13	0.77			
14	1.10	17	1.12			
19	1.30	39	1.03			
20	1.49	40	0.72			
21	1.31	41	1.17			
23	1.31	42	0.94			
29	0.67	47	0.80			
30	1.35	48	0.51			
37	0.85	50	0.41			
57	0.98	52	1.31			
58	1.45	54	0.36			
59	1.12	61	1.05			
mean ± SD	1.136 ± 0.2932	65	0.66			
(Range)	(0.47 - 1.49)	70	1.03			
		72	1.21			
		73	1.19			
		75	0.99			
		76	0.67			
		79	0.59			
		mean ± SD	0.8759 ± 0.2695			
		(Range)	(0.36 - 1.21)			
ANOVA						
Source	df	SS	MS	F	Prob	Fcrit
Between	1	0.5971	0.5971	7.65	0.0089	4.17
Within	35	2.7309	0.0780			
Total	36	3.3280				

**Table XI** Comparison of the measured serum digoxin level in digoxin alone group and digoxin with potassium sparing diuretic group.

Digoxin alone		Digoxin with potassium sparing diuretic				
Patient Number	Measured digoxin level (ng/ml)	Patient Number	Measured digoxin level (ng/ml)			
7	0.47	2	1.32			
9	1.32	18	0.90			
10	1.00	24	0.79			
11	1.30	25	1.52			
14	1.10	26	1.52			
19	1.30	28	1.04			
20	1.49	31	0.70			
21	1.31	32	1.41			
23	1.31	33	0.97			
29	0.67	34	1.80			
30	1.35	35	0.86			
37	0.85	36	0.94			
57	0.98	38	0.86			
58	1.45	43	0.72			
59	1.12	45	0.73			
mean $\pm$ SD	1.136 $\pm$ 0.2932	46	0.50			
(Range)	(0.47 - 1.49)	53	2.11			
		63	1.61			
		64	1.37			
		66	1.00			
		67	1.37			
		69	1.08			
		78	0.53			
		81	1.14			
		mean $\pm$ SD	1.0795 $\pm$ 0.4104			
		(Range)	(0.50 - 2.11)			
ANOVA						
Source	df	SS	MS	F	Prob	Fcrit
Between	1	00280	0.0280	0.20	0.06584	4.17
Within	37	5.0788	0.1372			
Total	38	5.1068				



**Table XII** Comparison of the measured serum digoxin level in digoxin alone group and digoxin with vasodilator group.

Digoxin alone		Digoxin with vasodilator				
Patient Number	Measured digoxin level (ng/ml)	Patient Number	Measured digoxin level (ng/ml)			
7	0.47	1	0.88			
9	1.32	3	0.74			
10	1.00	6	1.21			
11	1.30	8	0.63			
14	1.10	15	0.98			
19	1.30	16	1.45			
20	1.49	44	1.16			
21	1.31	74	1.23			
23	1.31	mean $\pm$ SD	1.0350 $\pm$ 0.2763			
29	0.67	(Range)	(0.63 - 1.45)			
30	1.35					
37	0.85					
57	0.98					
58	1.45					
59	1.12					
mean $\pm$ SD (Range)	1.136 $\pm$ 0.2932 (0.47 - 1.49)					
ANOVA						
Source	df	SS	MS	F	Prob	Fcrit
Between	1	0.2387	0.2387	3.23	0.0828	4.28
Within	21	1.6257	7.3898E-02			
Total	22	1.8644				

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**Table XIII** Comparison of the measured serum digoxin level in digoxin alone group and digoxin with diuretic and ACEI.

Digoxin alone		Digoxin with diuretic and ACEI				
Patient Number	Measured digoxin level (ng/ml)	Patient Number	Measured digoxin level (ng/ml)			
7	0.47	22	0.91			
9	1.32	27	1.55			
10	1.00	49	1.36			
11	1.30	51	0.75			
14	1.10	55	0.66			
19	1.30	56	0.65			
20	1.49	60	0.62			
21	1.31	62	0.77			
23	1.31	68	1.10			
29	0.67	71	0.73			
30	1.35	77	0.83			
37	0.85	80	0.45			
57	0.98	82	0.37			
58	1.45	83	0.58			
59	1.12	mean $\pm$ SD	(0.8392 $\pm$ 0.3303)			
mean $\pm$ SD	1.136 $\pm$ 0.2932	(Range)	(0.37 - 1.55)			
(Range)	(0.47 - 1.49)					
ANOVA						
Source	df	SS	MS	F	Prob	Fcrit
Between	1	0.7137	0.7137	7.47	0.0106	4.20
Within	28	2.5768	0.0954			
Total	29	3.2906				

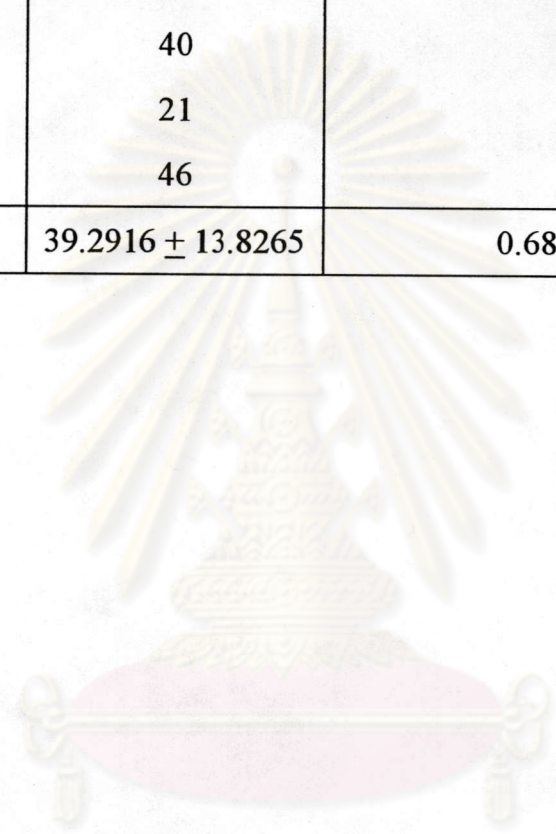


**Table XIV** Measured digoxin steady state level in patient aged 20-60 years after taking digoxin 0.125 mg. per day

Patient Number n = 23	Age (years)	Measured digoxin level (ng/ml)
7	44	0.47
24	54	0.79
29	48	0.67
31	35	0.70
36	41	0.94
45	50	0.41
46	43	0.50
48	23	0.51
50	37	0.41
54	21	0.36
55	58	0.66
56	36	0.65
60	58	0.62
64	47	1.37
66	23	1.00
71	45	0.73
73	55	1.19
75	36	0.99

Table XIV (Continuing)

Patient Number	Age (years)	Measured digoxin level (ng/ml)
78	47	0.53
79	35	0.59
80	40	0.45
82	21	0.37
83	46	0.58
mean $\pm$ SD	39.2916 $\pm$ 13.8265	0.6874 $\pm$ 0.2605



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**Table XV** Measured digoxin steady state level in patient aged above 60 years after taking digoxin 0.125 mg. per day

Patient Number n=7	Age (years)	Measured digoxin level (ng/ml)
3	70	0.74
4	68	0.84
5	66	0.80
16	68	1.45
23	81	1.31
51	70	0.75
72	66	1.21
means $\pm$ SD	69.8571 $\pm$ 5.1777	1.0142 $\pm$ 0.2991

**Table XVI** Comparison of the measured digoxin steady state level after taking digoxin 0.125 mg. per day

ANOVA

Source	df	SS	MS	F	Fcrit	Prob.
Between	1	0.5734	0.5734	7.9063	4.18	0.0088
Within	28	2.0308	0.0725			
Total	29	2.6042				

**Table XVII** Measured digoxin steady state level in patient aged <20 years after taking digoxin 0.25 mg. per day

Patient Number n = 3	Age (years)	Measured digoxin level (ng/ml)
43	19	0.72
65	19	0.66
70	17	1.03
means $\pm$ SD	18.3333 $\pm$ 1.1547	0.8033 $\pm$ 0.1985

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**Table XVIII** Measured digoxin steady state level in patient aged 20-60 years

Patient Number n = 38	Age (years)	Measured digoxin level (ng/ml)
2	38	1.32
8	36	0.63
9	36	1.32
10	49	1.00
11	35	1.30
12	33	1.10
13	56	0.77
15	36	0.98
17	38	1.12
19	42	1.30
21	21	1.31
22	48	0.91
25	39	1.52
26	44	0.64
28	46	1.04
33	46	0.97
34	53	1.80
37	48	0.85
38	53	0.86
39	44	1.03
40	28	0.72
41	39	1.17
42	36	0.94

Table XVIII (Continuing)

Patient Number	Age (years)	Measured digoxin level (ng/ml)
44	28	0.16
47	34	0.80
49	60	1.36
52	48	1.31
53	37	2.11
57	36	0.98
59	50	1.12
62	56	0.77
63	34	1.61
67	21	1.37
68	43	1.10
74	27	1.23
76	25	0.67
77	46	0.83
81	56	1.14
mean $\pm$ SD	40.6579 $\pm$ 9.9519	1.1094 $\pm$ 0.3189

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**Table XIX** Measured digoxin steady state level in patient aged above 60 years after taking digoxin 0.25 mg. per day

Patient Number n = 8	Age (years)	Measured digoxin level (ng/ml)
1	62	0.88
14	76	1.12
20	71	1.49
27	63	1.55
30	63	1.35
32	73	1.41
58	68	1.45
69	63	1.08
means $\pm$ SD	67.375 $\pm$ 5.4232	1.2912 $\pm$ 0.2367

**Table XX** Comparison of the measured digoxin steady state level between patient aged <20 years, 20-60 years and above 60 years after taking digoxin 0.25 mg. per day

ANOVA

Source	df	SS	MS	F	Fcrit	Prob.
Between	2	0.5396	0.2698	2.93	3.23	0.0610
Within	46	4.2361	0.0920			
Total	48	4.7757				

**Table XXI** Measured digoxin steady state level in patient aged 20-60 years after taking digoxin 0.125 alternate with 0.25 mg. per day

Patient Number	Age (years)	Measured digoxin level (ng/ml)
18	44	0.9

**Table XXII** Measured digoxin steady state level in patient aged above 60 years after taking digoxin 0.125 alternate with 0.25 mg. per day

Patient Number	Age (years)	Measured digoxin level (ng/ml)
n = 3		
6	73	1.21
35	69	0.86
61	67	1.05
means $\pm$ SD	69.6666 $\pm$ 3.0550	1.04 $\pm$ 0.1752

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#### 4. Comparison between the measured and the predicted digoxin serum concentrations.

Digoxin is distributed in the body in a two-compartment model. It distributed initially into the plasma compartment and other rapidly equilibrating tissues, and then passed into a more slowly equilibrating tissue compartment where it exerts its pharmacological effects on the myocardium. The manner which digoxin distributed in the body must be considered of the interpretation on plasma levels. Plasma sample must be taken at the proper time for meaningful indication of the clinical effects. In this study, the serum digoxin level was obtained by eight hours after the administration of the last dose of digoxin. Every patients must take digoxin at the same dosage regimen every day for at least five days to assure steady state concentration before the blood sample was drawn. The mean measured serum digoxin concentration was  $0.9859 \pm 0.3462$  ng/ml (means  $\pm$  SD) and the range was 0.36-2.11 ng/ml while the mean predicted serum digoxin concentration was  $0.9753 \pm 0.3235$  ng/ml (means  $\pm$  SD) and the ranges was 0.39 - 1.74 ng/ml respectively.

Table XXIII presented the comparison between the measured and predicted serum digoxin level.

The predicted digoxin concentrations calculated by using patient serum creatinine and some physical characteristics. When the measured and predicted concentrations were compared by the unpaired t-test statistical method, showed on table XXIII, indicated no significant difference between the mean measured and predicted concentrations at the 95% level of confidence. Figure 5 presented the measured and predicted concentrations versus the number of patients.



Table XXIII Predicted and measured serum digoxin concentrations in patients.

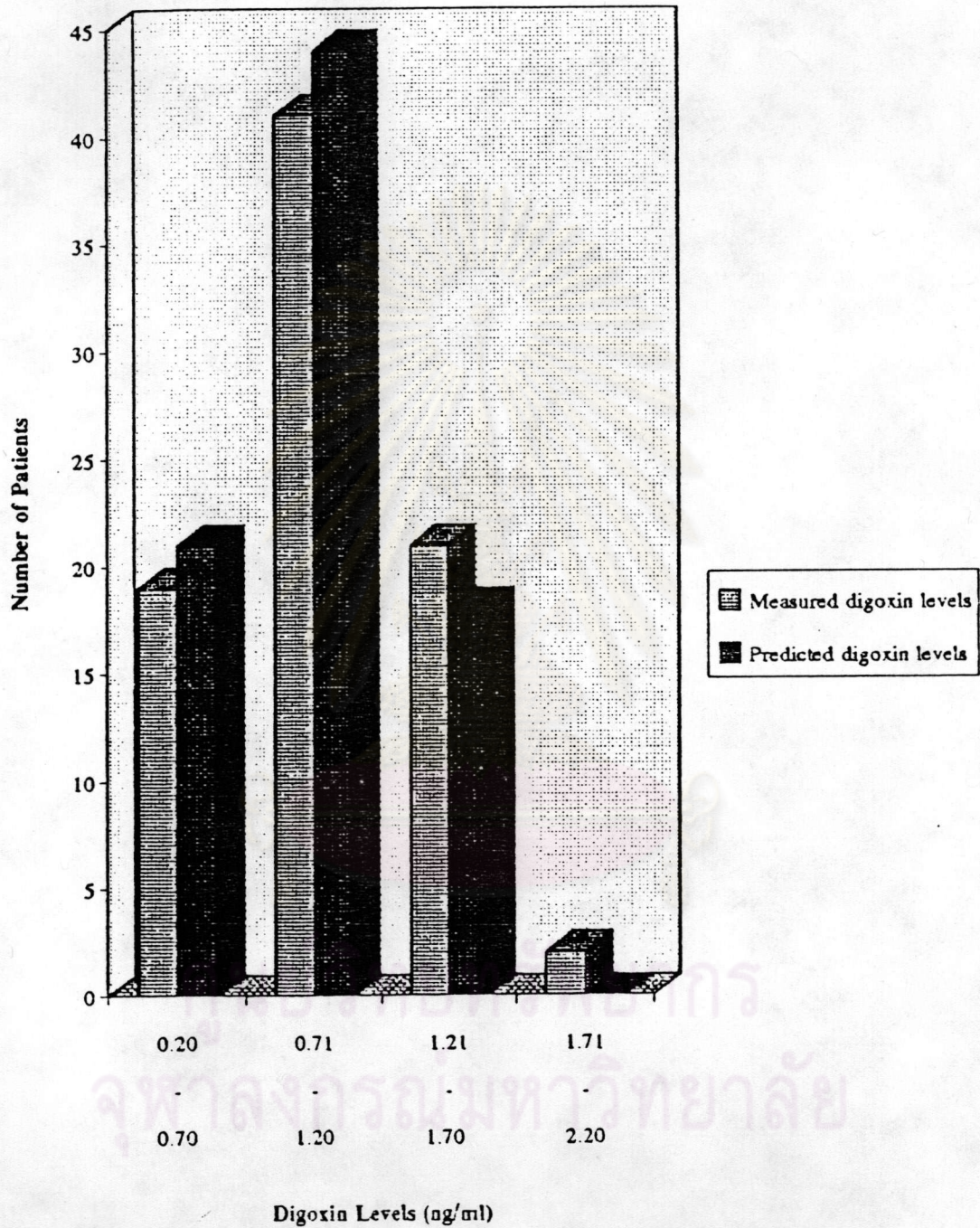
Patient Number	Measured (ng/ml)	Predicted (ng/ml)
1	0.88	1.37
2	1.32	1.18
3	0.74	0.63
4	0.84	0.87
5	0.80	0.75
6	1.21	0.95
7	0.47	0.46
8	0.63	0.93
9	1.32	1.45
10	1.00	0.99
11	1.30	1.64
12	1.10	1.02
13	0.77	0.96
14	1.12	1.60
15	0.98	1.29
16	1.45	0.83
17	1.12	1.09
18	0.90	0.92
19	1.30	1.41
20	1.49	1.19
21	1.31	1.125
22	0.91	1.74
23	1.31	0.99
24	0.79	0.77
25	1.52	1.35
26	0.64	0.68
27	1.55	1.07
28	1.04	1.09
29	0.67	0.74
30	1.35	1.55
31	0.70	0.63
32	1.41	1.37
33	0.97	1.11
34	1.80	1.01
35	0.86	0.51
36	0.94	0.64
37	0.85	1.22
38	0.86	1.36
39	1.03	1.20
40	0.72	0.78
41	1.17	1.13
42	0.94	1.13
43	0.72	1.05
44	1.16	0.75
45	0.73	0.73
46	0.50	0.70
47	0.80	0.95
48	0.51	0.62
49	1.36	1.17



Table XXIII (Continuing)

Patient Number	Measured (ng/ml)	Predicted (ng/ml)
50	0.41	0.39
51	0.75	0.85
52	1.31	1.69
53	2.11	1.11
54	0.36	0.73
55	0.66	0.45
56	0.65	0.63
57	0.98	1.29
58	1.45	1.20
59	1.12	1.39
60	0.62	0.58
61	1.05	1.01
62	0.77	1.17
63	1.61	1.16
64	1.37	0.61
65	0.66	0.48
66	1.00	0.71
67	1.37	0.72
68	1.10	1.29
69	1.08	0.68
70	1.03	1.02
71	0.73	0.63
72	1.21	1.48
73	1.19	0.68
74	1.23	0.93
75	0.99	0.86
76	0.67	1.00
77	0.83	1.16
78	0.53	0.57
79	0.59	0.80
80	0.45	0.61
81	1.14	1.15
82	0.37	0.48
83	0.58	0.60
mean $\pm$ SD (Range)	0.9859 $\pm$ 0.3462 (0.36 - 2.11)	0.9753 $\pm$ 0.3235 (0.39 - 1.74)
		Probability
Pooled SE	5.2003 E-02	0.4193
Pooled t	0.2038	
Degree of Freedom	164	





**Figure 5** Comparison between the measured and predicted serum digoxin concentration



## **The Adjustment of the dose using pharmacokinetic parameters**

The dosage regimen of five patients were adjusted.

The first patient showed sign of digoxin intoxication, she suffered from nausea, vomiting, anorexia and tiredness. After her dosage regimen had been adjusted using pharmacokinetic theory, these signs were disappeared, revealed clinical improvement.

The second patient, her present disease was mild mitral stenosis, mitral stenosis and tricuspid regurgitation which was the severe heart disease, and she also had anemia as her underlying disease. The patient showed sign of abnormal heart rate ( $>50$  beats per minute) and the serum digoxin level was low. When the dosage regimen was adjusted, the patient had the improvement. Table XXIV showed the dosage regimens given, measured serum digoxin concentrations before and after the adjustment.

The other three patients had been given digoxin for a period of time. Two patients had aortic regurgitation and one had severe tricuspid regurgitation with mitral regurgitation. Other drugs had been added to these three patients to control their diseases. Diuretics and ACEI were the group of drugs which had been used in addition to digoxin. Potassium sparing diuretics were most oftenly used. No evidence of any undesired effect was occurred in all three patients. However, the physicians decided to discontinue digoxin in these patients, the days of discontinuation were 24, 36, 40 days for the third, fourth and fifth patients, respectively. After monitoring the patients clinical outcome for sometime, no evidence of undersired symptoms had been observed, indicated that these three patients did not need digoxin for their



present status, diuretics and ACEI may sufficiently control the status of their diseases.

Table XXIV Dosage regimen along with the measured serum digoxin levels after an adjustment in five patients.

Patient Number	Dose <sup>1</sup> (mg/day)	Measured <sup>1</sup> (ng/ml)	Dose <sup>2</sup> (mg/day)	Measured <sup>2</sup> (ng/ml)
54	0.125	0.36	0.25	0.76
77	0.25	0.83	off	-
81	0.25	1.14	0.125	0.88
82	0.125	0.37	off	-
83	0.125	0.58	off	-

1 = before the adjustment

2. = after the adjustment

Digoxin is often used to control the atrial fibrillation. Patient who have ever had the history of having this disease must be given digoxin alone or with other drugs. Along the treatment, the atrial fibrillation may disappear if they can control their environment. Patients with heart failure should restrict their salty diet and take the drug as directed from the physician. So, the use of digoxin may be stopped but the monitoring of their clinical outcome must be concentratly analyzed for sometime. The three patients had the history of atrial fibrillation. When all had been admitted in the hospital, a positive improvement were observed. All three were waiting for the heart surgery. Nevertheless, further collection of the data was required, before any conclusion could be made.





### Prediction of Creatinine Clearance from Serum Creatinine

The serum creatinine of eighty-three patients were obtained from the patients' data charts. Table XXV showed the ranges of the serum creatinine, number of the patients and the percentage in various ranges. The creatinine clearances were calculated from equation 1-4 in Appendix A. Table XXVI showed the number of patients the percentage of patients in various ranges of creatinine clearances. . The serum creatinine represented the evaluation of renal function. Riergies et al. (1994) reported that the difference in creatinine clearance result in various digoxin toxicity. The same publishers suggested that each milliliter per minute increment in creatinine clearance decreased the risk of digoxin toxicity.

**Table XXV** The ranges of serum creatinine along with the number of patients and the percentage

serum creatininine (mg/dl)	Number of patients (percent)
< 0.70	2 (2.41)
0.70 - 0.90	24 (28.91)
0.91 - 1.50	47 (56.63)
1.51 - 2.00	8 (9.638)
> 2.00	2 (2.41)



**Table XXVI** The range of creatinine clearance along with the number of patients and the percentage


creatinine clearance (L/day)	Number of patients (percent)
< 50	27 (32.53)
50.0 - 70.00	37 (44.58)
70.01 - 90.00	15 (18.07)
> 90.00	4 (4.82)

### **Digoxin Clearances versus Creatinine clearances**

In this study, the means serum creatinine, creatinine clearance and volume of distribution were  $1.0710 \pm 0.3075$  mg. per dl.,  $57,8593 \pm 19.7273$  ml. per min.,  $387.0267 \pm 75.9311$  ml. per min., respectively. The estimation of digoxin clearance from creatinine clearances using patients' physical characteristic data and pharmacokinetic equations, the volume of distribution was also calculated by the same method and were concluded in Table XXVII Digoxin clearances were plotted against creatinine clearances. The linear equation obtained was identified as the equation generated from Thai patients. The result of the linear regression analysis of digoxin clearance on creatinine clearance showed the correlation coefficient ( $r^2$ ) equal to 0.1325. These results were presented in figure 6. So, we can concluded from our data that the digoxin clearance could be estimated from the creatinine clearance of the patient. From this study, there was no evidence of toxicity when the serum creatinine was higher than the normal value since only two patients' serum creatinine were higher than 2 mg. per dl., both of them were equal to 2.2 mg. per dl. which were only slightly higher than the normal values. The normal serum clearances value is 0.7-2 mg/dl, but it varies from patients to patients and it is up to the



serum clearances value is 0.7-2 mg/dl, but it varies from patients to patients and it is up to the clinical status of the patient, for instances, the underlying disease or the renal function are important factors influencing the variable of this value of the two patients who required dosage regimen adjustment, the serum creatinine of one patient who showed the side effects of digoxin which disappeared by the new adjustment of the dosage regimen was 1.0 mg/ml, the serum creatinine of the other patient who showed undesired sign of the disease, was 0.8. The relationship of digoxin toxicity to patients' the serum creatinine should be observed in a much greater number of patients before any conclusion could be made.



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**Table XXVII** Comparison of the serum creatinine, creatinine clearance, digoxin clearance and the volume of distribution in eighty-three patients.

Patient Number	Scr <sup>1</sup> (mg/dl)	Cl <sub>cr</sub> <sup>2</sup> (ml/min)	Cl <sub>dig</sub> <sup>3</sup> (ml/min)	Cl <sub>dig</sub> <sup>3</sup> (L/day)	Vd <sup>4</sup> (L/Kg)
1	1.0	45.93	198.86	286.35	332.38
2	1.0	60.07	132.57	190.90	387.62
3	0.9	50.12	118.24	170.26	75.77
4	2.2	21.82	104.16	149.99	295.64
5	1.1	38.87	109.37	157.49	318.09
6	1.0	46.15	108.47	156.19	348.26
7	1.0	74.67	186.17	268.08	451.88
8	1.5	63.94	277.77	399.98	513.61
9	1.3	41.22	132.57	19090	329.18
10	1.6	54.35	175.00	252.00	495.28
11	1.6	35.29	134.60	193.82	293.32
12	1.0	71.33	150.09	216.13	449.12
13	1.2	62.22	227.27	327.27	496.88
14	1.0	35.55	156.25	225.00	300.20
15	1.0	55.47	178.57	257.14	354.35
16	2.2	22.91	60.34	86.88	310.42
17	0.85	70.83	156.25	225.00	409.57
18	1.2	53.83	145.83	209.99	383.47
19	1.0	50.90	134.61	193.83	324.99
20	0.9	54.30	117.44	169.11	358.33
21	1.0	33.64	133.54	192.29	277.18
22	1.1	38.50	192.30	276.91	267.55



Table XXVII (Continuing).

Patient Number	Scr <sup>1</sup> (mg/dl)	Cl <sub>cr</sub> <sup>2</sup> (ml/min)	Cl <sub>dig</sub> <sup>3</sup> (ml/min)	Cl <sub>dig</sub> <sup>3</sup> (L/day)	Vd <sup>4</sup> (L/Kg)
23	1.4	23.38	66.79	96.18	251.08
24	1.55	35.37	110.75	159.48	314.85
25	1.0	53.65	115.13	165.79	337.32
26	0.9	108.80	273.43	393.74	662.60
27	0.8	66.36	112.90	162.57	427.64
28	0.9	27.19	168.26	242.29	415.38
29	1.0	38.25	130.59	188.05	308.57
30	1.0	38.37	129.62	186.65	297.55
31	1.0	56.08	125.00	180.00	360.05
32	0.7	51.98	124.11	178.72	335.94
33	1.0	63.25	180.41	259.79	412.67
34	0.8	73.95	97.22	139.99	448.13
35	0.9	63.52	152.61	219.76	456.07
36	1.1	54.40	93.08	134.03	363.20
37	1.0	56.74	205.88	296.47	378.81
38	0.9	52.49	203.48	293.01	337.52
39	1.2	58.55	169.90	244.65	382.79
40	0.6	119.26	243.00	349.92	544.51
41	0.9	70.92	149.57	215.38	392.75
42	1.0	69.33	186.17	268.08	397.32
43	0.9	81.23	243.05	349.99	417.11
44	0.5	124.29	150.86	217.23	563.89
45	0.8	51.79	119.86	172.59	308.75
46	0.9	53.47	175.00	252.00	322.69

Table XXVII (Continuing)

Patient Number	Scr <sup>1</sup> (mg/dl)	Cl <sub>cr</sub> <sup>2</sup> (ml/min)	Cl <sub>dig</sub> <sup>3</sup> (ml/min)	Cl <sub>dig</sub> <sup>3</sup> (L/day)	Vd <sup>4</sup> (L/Kg)
71	0.9	61.15	119.86	172.59	400.46
72	1.0	77.74	72.31	104.13	463.50
73	0.8	64.08	73.52	105.87	374.21
74	1.1	50.85	142.27	204.87	359.03
75	1.0	41.52	88.38	127.27	349.53
76	1.5	40.47	261.19	376.11	355.36
77	1.0	79.10	210.84	303.61	484.61
78	0.7	45.33	165.00	237.60	349.52
79	0.8	81.79	148.30	213.55	436.71
80	0.8	66.58	194.44	279.99	388.79
81	0.9	54.77	153.50	221.04	371.19
82	1.5	38.84	236.48	340.53	299.00
83	1.2	47.22	150.86		328.78
mean + SD	1.0710±0.3075	57.8593 ±	101.9931 ±	146.8258 ±	387.0267 ±
(Range)	(0.5 - 2.2)	19.7273 (21.82-124.29)	22.5235 (60.98-177.92)	32.4631 (100.37 - 256.20)	75.9311 (277.40 - 665.60)

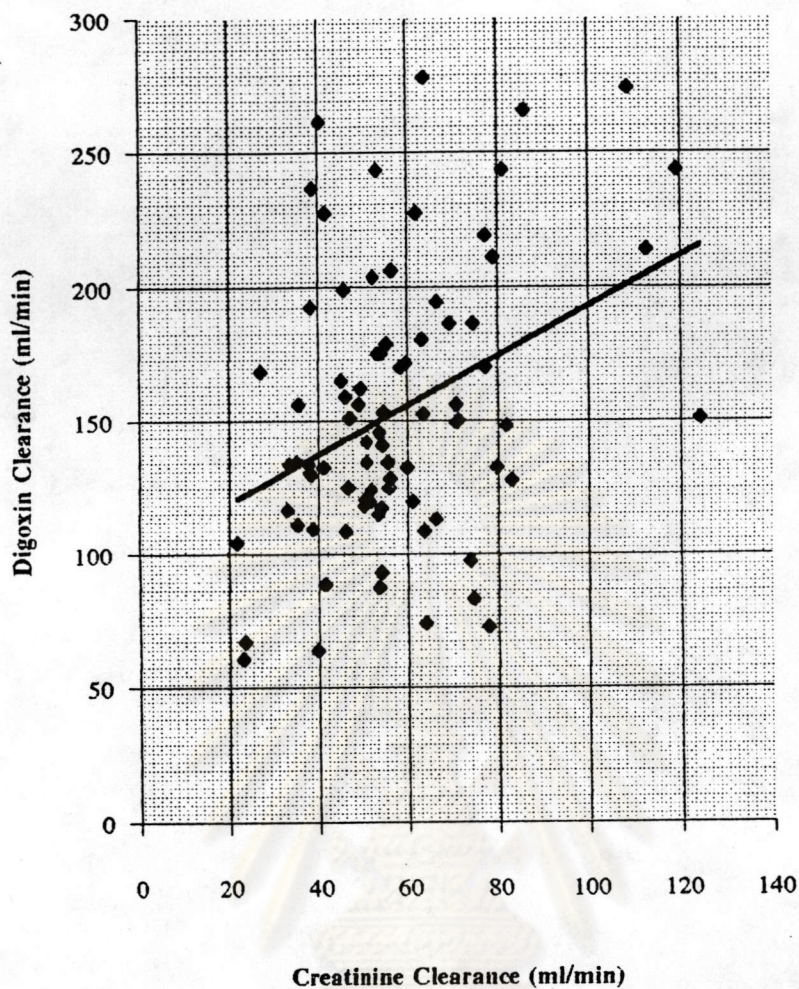
1 S<sub>cr</sub> = Serum creatinine

2 Cl<sub>cr</sub> = Creatinine clearance

3 Cl<sub>dig</sub> = Total Digoxin Clearance

4 V<sub>d</sub> = Volume of Distribution





### Regression of Y on X

Y = Digoxin clearance (ml/min)

X = Creatinine clearance (ml/min)

Y =  $0.9228 X + 100.5776$

1 Degree coefficient (slope) = 0.9228

0 Degree coefficient (Y-intercept) = 100.5776

Pearson's correlation coefficient (r) = 0.3640

$r^2$  = 0.1325

Residual Variance = 2253.0120

Residual Standard Deviation = 47.4659

**Figure 6** The linear regression of digoxin clearance and creatinine clearance