EFFECTS OF CARDIOPULMONARY BYPASS ON PLASMA DIGOXIN LEVELS, AND ITS CORRELATION BETWEEN EARLY POSTBYPASS ARRYTHMIAS IN DIGITALIZED PATIENTS(*)

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Effects of cardiopulmonary bypass (CPB) on plasma digoxin levels, and its relation with early postbypass arrythmias in chronnicaly digitalized patients were studied in two groups. The first group consisted of 20 patients who were taking digoxin for a long time and had a cardiac valve replacement or valve r onstruction. The second group consisted of 5 digitalized patients who had closed cardiac procedures.

A significant fall in plasma digoxin levels at 30, 60, 240 minutes and 8 hours after establishment of CPB was observed in the first group. (P< 0.001, P<0.05, P< 0.01). The mean decrease in plasma digoxin levels was 0.54± 0.06 ng/dl. A decrease of serum digoxin levels in the second group was not detected. In all of the post-bypass patients, the plasma digoxin levels where under the accepted toxic levels (1.00± 0.07ng/dl). Although the decrease observed in digoxin levels of the patients, post bypass arrythmias were seen in 6 patients. In 4 of these patients additional digitalis was given while weaning from CPB. The types of arrythmia were nodal tachycardia, bigeminy ventricular extrasystols and atrioventricular dissociation. After excluding all of the other factors effecting the pathogenesis of postbypass arrythmias, digitalis hypersensitivity was thought to be the cause of the rythm disturbances.

Key words: cardiopulmonary bypass, post-bypass arrythmia, plasma digoxin level.

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Cardiac arrythmias in the early postbypass period, especially tachyarrythmias and premature contractions, are not uncommon complications following cardiac surgery[1,2]. Early diagnosis and intervention of these rythm disturbances are life saving measures.

Many factors are responsible of early postbypass arrythmias. Experimental studies have shown that without performing a ventriculotomy, prolonged perfusion periods can cause metabolic disturbances of the myocardium, and can initiate cardiac arrythmias[3]. It has been documented that, during the early period following cardiopulmonary bypass (CPB), the myocardium is more susceptible to the toxic effects of digitalis glycosides[4,5].

Increased myocardial sensitivity against digitalis glycosides and the positive effects of digoxin on early postbypass arrythmias were observed in this prospective study.

Materials and Methods

Two groups of patients, receiving digitalis glycosides for a long time at the Hacettepe University Medical School were investigated. The first group consisted of twenty patients undergoing CPB and receiving one or more valve replacement or a mitral reconstrictive procedure. Ten of these patients were male and the other ten female. The youngest patient was 16 and the oldest 64 years old with a mean age of 30.5 years.

The second group of patients consisted of five atients undergoing closed heart procedures who had been receiving digitalis for a long period. Four of these patients had a closed mitral valvotomy and one had a patent ductus arteriosus (PDA) closure. The youngest patient in this group was 4 and oldest patient was 44 years old with a mean age of 25.4 years. Table I shows clinical characteristics of Group I and II.

Blood samples were taken from patients in group I to determine plasma digoxin, Magnesium (Mg^{++}), Potasium (K^{+}), blood urea nitrogen (BUN), creatinine (Cr) levels during induction of anesthesia (CPB_0). Plasma digoxin levels were determined within 30 minutes(CPB_1), 120 minutes (CPB_2), 4 hours (CPB_3), and 8 hours (CPB_4) after cardiopulmonary bypass was established. Plasma Mg^{++}, K^{+}, BUN, Cr, arterial pH, PO_2 values were determined again with CPB_4. Table II shows the results of blood samples during the various stages of the study.

One patient with a complete AV block, who had a tricuspid annuloplasty was excluded from the study. The renal functions of all patients were accepted normal, and were evaluated according to urine output (35-45 ml / hour), plasma BUN, and Cr levels.

Blood samples were taken from patients in group II during and 8 hours after induction of anesthesia. All of the blood samples were taken from a peripheral vein and inferior vena cava. All of the samples were centrifuged with a speed of 10.000 r/min for 15 minutes.

CPB was established in standart techniques with a perfusion rate of 2.2-2.4 L/min/m^2. Myocardial preservation was performed with cold potassium cardioplegia and systemic hypothermia between 28-32 °C. Technical data of the operated patients are shown in Table 1.

Plasma digoxin levels were determined with radio immunassey (RIA) method, using BYK - Mallinkrodt SPAC RIA kits. With this method plasma digoxin levels could be detected specificly between 0.2 - 5 ng/dl. The normal range of plasma digoxin levels are accepted to be between 0.5 and 2 ng/dl.

Plasma Mg^{++} levels were determined according the titan yellow method with a Coleman Model 6120 spectrophotometer, K^{+} levels with a Instrumentation Laboratory Model 243 flame photometer, BUN and Cr values with a Technicon Autoanalyzer Model SMA-417, arterial pH, PaO_2 values with a Radiometer Copenhagen-M72- Digital acid -base analyzer microsystem instrument.

All of the patients were monitorized intra and postoperatively.Electrocardiographic patterns were taken from patients who had rythm disturbances. The criteria for digital

	CASE NO	AGE, GENDER	PROTOCOL NO	DIAGNOSIS	OPERATION	CROSS CLAMP TIME (min)	HYPO-THERM (°C)	AMOUNT OF FLUID GIVEN DURING CPB	DIGITALIS APPLICATION WHILE WEANING FROM CPB	ARRYTHMIA
Group I	1	50, M	1552566	MS (Calc)	MVR	25	28	1700 ml	-	-
	2	28, F	1113615	MS-MI	MVR	32	27	1900 ml	0.2 mg Cedilanid	-
	3	26, F	1527616	MS-MI-AS	MVR-AVR	105	26	2300 ml	-	-
	4	36, F	1131572	MS-MI	MVR	27	30	2200 ml	-	-
	5	34, F	1514581	MS-MI	MVR	38	30	1300 ml	-	-
	6	16, F	1544923	MS	OMV	18	32	1500 ml	0.4 mg Cedilanid	Nodal Tachycardia
	7	45, F	1564359	MS (restenosis)	MVR	33	30	1600 ml	0.2 mg Cedilanid	AV Dissociation
	8	25, M	1563990	MS-TS	OMV-OTV	24	28	1500 ml	-	Nodal Tachycardia
	9	26, F	1544505	MS (restenosis)	MVR	28	32	1700 ml	-	-
	10	27, M	1376601	MS (calc)	MVR	21	30	1500 ml	-	-
	11	16, M	1564331	MS (embolism)	OMV	26	31	1600 ml	-	Nodal Tachycardia
	12	34, F	1537651	MS-MI-AI	MVR-AVR	90	28	2300 ml	0.2 mg Cedilanid	Bigem vent extrasyst
	13	29, M	1553371	AI	AVR	55	29	2200 ml	-	-
	14	29, M	1552321	MS (calc)	MVR	25	30	1700 ml	-	-
	15	64, M	1543864	AI	AVR	69	28	2200 ml	-	-
	16	28, F	1500414	MS (calc)	MVR	21	30	1500 ml	-	-
	17	31, F	1338361	MI-AI-TS	MVR-AVR-TVR	115	28	3100 ml	0.6 mg Cedilanid	Bigem vent extrasyst
	18	36, F	1975660	MI-AI-AS	MVR-AVR	90	28	2900 ml	-	-
	19	31, F	1362723	MS-MI-AI-TS	MVR-AVR-TVR	129	28	3300 ml	-	-
	20	25, M	1510033	AS-AI	AVR	88	28	2100 ml	-	-
Group II	1	4, F	1495582	PDA	Transfiction-ligation					
	2	25, M	1558992	MS	CMC					
	3	44, M	1537080	MS	CMC					
	4	34, M	1575777	MS	CMC					
	5	20, M	1377510	MS	CMC					

MS: mitral stenosis, MI: mitral insufficiency, AS: aortic stenosis, AI: aortic insufficiency,
TS: tricuspid stenosis, Calc: calcification, MVR: mitral valve replacement, AVR: aortic valve replacement, OMV: open mitral valvatomy
OTV: open tricuspid valvotomy, PDA: patent ductus arteriosus, CMC: closed mitral comissurotomy.

Table I. Clinical and operative data of the study groups

	CASE NO	PLASMA DIGOXIN LEVELS (ng/dl)					OTHER PARAMETERS DURING ARRYTHMIA						
		CPB0	CPB1	CPB2	CPB3	CPB4	Mg (mEq/L)	K (mEq/L)	PaO2	pH	BUN (mg/dl)	Cr (mg/dl)	ARRYTHMIA
Group I	1	1.6	1.2	1.3	1.4	1.2	1.4	4.2	8.6	7.44	20	0.9	-
	2	1.8	1.4	1.2	0.9	1.0	1.8	3.7	70	7.48	16	0.7	-
	3	1.3	1.3	1.1	0.9	0.7	2.0	3.9	80	7.38	10	1.7	-
	4	1.3	1.0	1.0	0.8	0.7	1.7	4.5	94	7.36	10	1.5	-
	5	1.5	1.0	0.9	0.7	0.5	1.8	3.7	105	7.44	18	1.2	-
	6	1.5	1.2	1.6	1.5	1.5	2.8	4.2	85	7.48	10	0.8	Nodal Tachycardia
	7	1.6	1.4	1.0	0.9	0.9	1.8	4.2	90	7.38	12	0.6	AV Dissociation
	8	1.8	1.7	1.4	1.2	1.2	1.7	4.7	95	7.4	16	1.2	Nodal Tachycardia
	9	1.8	1.6	1.2	1.0	1.1	1.8	3.9	80	7.42	18	1.7	-
	10	1.4	1.2	1.0	0.8	0.8	1.8	4.2	110	7.42	26	0.8	-
	11	1.6	1.6	1.4	1.4	1.2	2.4	4.5	80	7.48	10	0.9	Nodal Tachycardia
	12	1.4	1.4	1.3	1.1	0.8	1.6	3.9	85	7.46	14	0.6	Bigem vent extrasyst
	13	1.8	1.5	1.3	1.1	0.9	1.4	3.9	95	7.38	18	1.2	-
	14	1.7	1.4	1.3	1.1	1.0	1.8	4.2	80	7.35	12	1.7	-
	15	1.4	1.6	1.4	1.3	1.1	2.2	4.5	85	7.38	14	1.3	-
	16	1.9	1.8	1.8	1.6	1.6	1.6	3.9	80	7.44	14	0.9	-
	17	1.9	1.5	2.0	1.8	1.5	2.4	3.9	115	7.42	20	0.9	Bigem vent extrasyst
	18	1.9	1.7	1.0	0.8	0.7	1.8	4.2	90	7.44	22	1.3	-
	19	1.8	1.4	1.2	1.1	0.8	2.0	4.2	80	7.48	16	1.2	-
	20	1.7	1.3	1.1	0.8	0.8	1.8	4.5	80	7.39	22	1.7	-

		PLASMA DIGOXIN LEVELS (ng/dl)	
		Induction	Postoperative (8 th hour)
Group II	1	1.2	1.4
	2	1.5	1.6
	3	1.1	1.9
	4	1.7	1.8
	5	1.3	1

Table II: Plasma digoxin, Mg++, K+, PaO2 and arterial pH, BUN, Cr levels and arrythmias encountered during early postbypass period.

entoxication was as following.

1. Second or third degree atrioventricular (A-V) block, which was not due to surgical trauma,
2. Supraventricular tachycardia with A-V block,
3. Low rate atrial fibrillation (below 50 beats/min) with premature ventricular complexes,
4. A-V dissociation,
5. Nodal tachycardia,
6. Multifocal ventricular complexes,
7. Ventricular bigeminy extrasystoles,
8. Ventricular tachycardia,
9. Cessation of rythm disturbance when digitalis administration was stopped.

Results

Plasma digoxin, Mg^{++}, K^{+}, arterial pH, PaO_2, BUN, Cr levels and the rythm disturbances encountered are shown in Table II. Univariate and Multivarite analysis between groups are shown in Table III.

The mean plasma digoxin levels observed in 20 open heart and 5 closed heart patients are shown in Table IV. The plasma digoxin values during induction of anesthesia were in normal ranges in group I and group II, (1.54± 0.16 ng/dl) and (1.56± 0.16 ng/dl) respectively.

In the open heart group, a significant decrease in total plasma digoxin levels was observed (CPB_1: $p<0.001$, CPB_2: $p<0.001$, CPB_3: $p<0.01$, CPB_4: $p<0.001$). Post bypass arrythmias were detected in 6 patients although the significant decrease in plasma digoxin levels. When all of the arrythmogenic factors were screened, no etiological factor could be found except the moderately low serum values. Arrythmias due to surgical trauma were excluded from this study.

Changes in the plasma digoxin levels of the second group patients were found to be unsignificant. When first group and second group plasma digoxin levels were compared CPB_3 and CPB_4 values were significantly lower than the second group ($p<0.05$, $p<0.01$) respectively (Table III).

Although serum plasma levels decreased significantly following CPB institution, arrythmias suggesting digitalis entoxication were observed in 6 patients in group I (Table II). In four out of six of these patients additional doses of digitalis was administered immediately after weaning from CPB. Serum digoxin levels fell to the lowest values at the 8th hour after induction of anesthesia (1.00± 0.07 ng/dl)) (Table IV).

Discussion

Patients with acquired heart disease usually are treated with digitalis glycosides. Preoperative digitalis adminstration to these patients is still a controversy. Early postbypass arrythmias are common complications of CPB[1,3]. Studies have shown that there is an increase in the myocardial susceptibility to digitalis intoxication following CPB[6,7]. Animal experiments have shown myocardial irritability to digitalis glycosides following extracorporeal circulation[8,9]. Determination of plasma digitalis levels with RIA method has provided us to regulate the proper dose of the drug, and to

		OPEN HEART					CONTROL	
		CPB0	CPB1	CPB2	CPB3	CPB4	Induction	Postop (8 th hour)
OPEN HEART	CPB0		P<0.001	P<0.001	P<0.001	P<0.001	P>0.05	P>0.05
	CPB1			P>0.05	P<0.001	P<0.001	P>0.05	P>0.05
	CPB2				P<0.001	P<0.001	P>0.05	P>0.05
	CPB3					P<0.01	P<0.01	P<0.05
	CPB4						P<0.01	P<0.01
CONTROL	Induction							P>0.05
	Postop (8 th hour)							

Table III: Univariate and multivariate analysis between patient groups.

	PARAMETER	CPB0	CPB1	CPB2	CPB3	CPB4
OPEN HEART	PLASMA DIGOXIN LEVEL (ng/dl)	1.54±0.06	1.41±0.05	1.28±0.06	1.11±0.07	1.00±0.07

		Induction	Postop (8 th hour)
CONTROL	PLASMA DIGOXIN LEVEL (ng/dl)	1.56±0.16	1.54±0.16

Table IV: Mean plasma digoxin levels observed in open heart and control patient groups.

recognize arrythmias due to digitalis intoxication in early postbypass period.

It has been shown that tissue digitalis concentrations of the myocardium does not change significantly following CPB[9-13]. It has been observed that plasma digoxin levels of these patients decrease to some extent during CPB, and then exceeds the preoperative values with a rebound phenomenon[6,7,14]. In this study decrease in plasma levels have encountered, but a rebound phemonenon has not been observed (Table II). In the 20 digitalized patients a significant decrease in plasma digoxin levels was recorded and this lasted untill the end of 8th hour. The mean plasma digoxin level was 1.54± 0.06ng/dl during induction of anesthesia, and fell to 1.00±0.07ng/dl.

Many factors could be a reason of rythm disturbances in early postbypass period. In this study arrythmogenic factors such as plasma digoxin, Mg^{++}, K^+ levels, ascidosis and hypoxemia were investigated. Rythm disturbances due to surgical trauma was excluded.

In all of the patients with rythm disturbance arterial pH, PaO_2 values were with in normal ranges. Hypo or hypertension was not seen in any patient. These parameters could not be responsible of rythm disturbances.

Plasma K^+ concentrations have an important place in the etiopathogenesis of rythm disturbances in cardiac surgery[1,13]. In hypokalemia, depolarization rate increases while repolarization rate decreases. This phenomenon causes myocardial irritability. Ectopic supraventricular or ventricular focuses may couse important rythm disturbances. Hyperkalemia may be another cause of arrythmia. Low cardiac output syndrome, hemolysis, acute tubular necrosis could be a cause of hyperkalemia. Hyperkalemia could be a reason for sinus bradycardia, AV block, interventricular conduction disturbance or ventricular fibrillation[1]. In this study all of the patients who had arrythmia had normal plasma K^+ concentrations.

Myocardial susceptibility to digitalis glycosides following CPB although low serum concentrations, has been documented[6,7,14]. Other causes of myocardial irritability to digitalis glycosides other than CPB has been observed. Following acute myocardial infarction, digitalis intoxication with low serum digitalis concentrations are encountered[15]. During experimental arterial hypoxemia, when PaO_2 falls below 40 mm Hg the same effect is seen[16,17].

In the study plasma digoxin concentrations of arrythmic patients, have been found much more lower than the accepted toxic levels. If plasma digoxin concentrations are an index of myocardial digitalis concentrations, it could be said that in early postbypass period myocardial susceptibility increases to digitalis intoxication[18-20]. The mechanisms of this interaction is not known exactly, but it is thought to be a cause of metobolic variations and the changes in ion flux during cardiopulmonary bypass[21]. Especially, low plasma Mg^{++} concentrations seen in these patients should be considered seriously. Schinman has desribed postperfusion hypomagnesemia for the first time[6,22,23]. Bozer has reported that postperfusion hypomagnesemia can reside until the

postoperative 24 th hour[22,24]. It has been observed that, administration of additional Mg^{++} to the patients before and after cardiopulmunary bypass does not prevent hypomagnesemia exactly[22,25]. The effect of Mg^{++} ion on digitalis related arrythmias has not been understood clearly. It has been proposed that, Mg^{++} ion reactivates the Na^{+}-K^{+} ATP-ase enzyme, which digitalis glycosides inhibit[26]. According to Goldman hypomagnesemia causes myocardial digitalis intake to increase, while hypermagnesemia causes an decrease[27]. The inhibition of ATP-ase enzyme and intracellular K^{+} loss could be an important factor in the pathogenesis of early postbypass arrythmias[28,29]. In this study Na^{+}-K^{+} ATP-ase and Mg^{++} ATP-ase determinations have not been studied. Experimental studies have shown that, the significant difference of blood K^{+} levels seen in digitalis intoxication, at the coronary sinus and femoral artery disappears when Mg^{++} is administrated[25]. It has shown that Mg^{++}, with K^{+} or alone has an effect on digitalis action. Thus perfusion hypomagnesemia could explain the myocardial irritability during the post bypass period[22]. Three of the 6 arrythmic patients had low Mg^{++} concentrations (cases7,8,12). Two of these patients received additional digitalis immediately after weaning from CPB.

While evaluating arrythmias that appear during postbypass period, plasma digoxin concentrations should be known besides factors such as hypoxemia, ascidosis, hypo -hyperkalemia. Determination of preoperative and postbypass digitalis concentrations, and to consider that the myocardium is more susceptible to digitalis glycosides provides a more accurate diagnosis and therapy in the management of postbypass arrythmias.

Especially in acutely digitalized patients, there is often a heightened sensitivity to digitalis in the postoperative period primarily due to metabolic disturbances and also due to a higher myocardial concentration[7,30]. Patients receiving chronic digitalis therapy particularly before cardiac surgery, do appear to have a reduced incidence of postoperative supra ventricular arrhythmias[31]. If preoperative digitalization is performed, ideally it should be done several weeks before surgery. Digitalis is usually required for managing fast rate atrial fibrillation in the post bypass and postoperative period. Even in these patients the additional dose should be given carefully, and if arrythmia occurs, digitalis intoxication should be taken into consideration.

Conclusion

Digitalis glycosides are administered frequently to tachycardic patients with atrial fibrillation while weaning from CPB. It should be remembered that in these patients postbypass myocardial irritability to digitalis could be significantly more than the normal population. Digitalis intoxication, although decreased plasma digoxin levels, should be in mind in postbypass arrythmias in digitalized patients. Early diagnosis and intervention of these rythm disturbances are life saving measures.

References

1- Braimbridge MU: Postoperative cardiac intensive care, 2nd ed. Oxford, London and Edinburg. Blackwell Scientific Publications 1972;pp, 32-39.

2- Mundth ED: Postoperative intensive care in the cardiac surgical patients. Prog Cardiovasc Dis 1968;11: 229-233.

3- İliçin G: Açık kalb cerrahisinde postoperatif bakım ve komplikasyonlar. Ankara. Hacettepe Üniversitesi Yayınları 1974;pp, 37-41.

4- Ebert PA, Morrow AG, Austen WG: Clinical studies of the extracorporeal circulation on myocardial digoxin concentrations. Am J Cardiol 1963;11:201-207.

5- Magin RR, Cooper T: Digitalis tolerance following extracorporeal circulation. Surg Forum 1961;12:196-201.

6- Fatourechi V: Plasma digoxin and magnesium concentration in open heart surgery. J Cardiovasc Surg 1979;20:151-155.

7- Morrison J, Killip T: Serum digitalis and arrythmia in patients undergoing cardiopulmonary bypass. Circulation 1973;47:341-343.

8- Austen WG, Ebert PA: The effect of cardiopulmonary bypass on tissue digoxin concentrations in the dog. Surg Res 1962;2:85-89.
9- Hernandez A, Kouchoukos N, Goldring D: The effect of cardiopulmonary bypass upon digoxin-H3 tissue concentration. Pediatrics 1963;31:952-957.
10- Cooley DA, Beall AC, Driscoll TB: Effect of total cardiopulmonary bypass on myocardial and blood digoxin concentration in man. Am J Cardiol 1963;11:194-199.
11- Krasula RA, Sidney L: Serum digoxin levels during and following open heart surgery in children. Circulation 1972;46 (Suppl 2):177-180.
12- Molokhia FA, Smith TW: Constancy of myocardial digoxin concentration during experimental cardiopulmonary bypass. Ann Thorac Surg 1971;11:222-226.
13- Molokhia FA, et al: Constancy of myocardial digoxin concentration during cardiopulmonary bypass. Circulation 1970;42:III-112-115.
14- Coltard DJ, Chamberlain DA, Smith TW: Effect of cardiopulmonary bypass on plasma digoxin concentrations. Brit Heart J 1971;33:334-337.
15- Kumar JC, Ableman WH: Experimental myocardial infarction: Efficacy and toxicity of digitalis in acute and healing phase of myocardial infarction in intact couscious dogs: J Clin Invest 1970;49:358-361.
16- Harrison DC, Robinson MD: Role of hypoxia in digitalis toxicity. Am J Med Sci 1968;256:352-356.
17- Lown B, Black H, Moore F: Digitalis, electrolytes and the surgical patient. Am J Cardiol 1960;6: 309-312.
18- Doherty JE: The clinical pharmacology of digitalis glycosides. Review Amer J Med Sci 1968;255:382-386.
19- Doherty JE, Perkins, WH, Glanighan WS: The distiribution and concentration of triatriated digoxin in human tissues. Ann Intern Med 1967;66:116-121.
20- Smith GD, Everest MS: Measurement of digoxin in plasma and its use in diagnosis of digoxin intoxication. Brit Med J 1969;1:286-290.
21- Cooper J, Jellinek M, Willman VL: Biochemical studies of myocardium and blood during extracorporeal circulation in man. Circulation, 1965;31:144-149.
22- Bozer AY: Ekstrakorporeal dolaşım ve hipotermi. Ankara. Hacettepe Üniversitesi Basımevi 1973;144-143.
23- Turnier E, Osborn JJ, Gerbode J: Magnesium and open heart surgery. J. Thorac Cardiovasc Surg 1972;64:694-697.
24- İliçin G, Bozer AY, Saylam A: Effect of extracorporeal circulation on magnesium metabolism. Hacettepe Bull Med Surg 1971;4:103-106.
25- Garcia RE, Castillo OJ: Prevention of hypomagnesemia and hypocalcemia in open heart surgery. J Cardiovasc Surg 1977;18:257-261.
26- Neff S, Seller RH: Magnesium sulfate in digitalis toxicity. Am J Cardiol 1972;29:377-380.
27- Goldman RH, Coltard DJ: The inotropic effects of digoxin in hyperkalemia. Relation to "sodium-potassium ATPase" inhibition in the intact heart. Circulation 1973;48:830-838.
28- Palmer E, et al: Hypomagnesemia as a persistent cause of hypokalemia. JAMA 1975; 233:23-26.
29- Schwartz A, Allen JC: Furtherstudies on the correlation between inotropic actions of quabain and its interaction with the sodium-potassium ATPase. J Pharmacol Exp Ther 1974;191:119-123.
30- Lewis RP: Digitalis. in: Leier CV, ed. Cardiotonic drugs- A clinical survey. New York-Basel: Marcel Dekker, Inc. 1986;pp,85-151.
31- Chee TP, Desser KB, Benchimol A: Postoperative supraventricular arrythmias and the role of prophylactic digoxin in cardiac surgery. Am Heart J 1982;104:974-977.