The Change in Digitalis Tolerance After Open Heart Surgery

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The present investigation was undertaken to evaluate the change in digitalis tolerance immediately after extracorporeal circulation with eleven patients undergoing open heart surgery for the correction of congenital or acquired heart diseases who were ranged in age from 4 to 56 years and experimentally with eleven mongrel dogs by means of acetyl strophanthidin tolerance test.

The decrease of digitalis tolerance following total body perfusion has been clinically observed in all cases of the prolonged duration of perfusion of longer than one hour within a period of 4 to 7 hours after perfusion and experimentally in all dogs of one hour perfusion within a period of 2 hours after perfusion. Metabolic acidosis after perfusion may primarily be connected with the decreased digitalis tolerance. Of the electrolyte measurement, no consistent change was observed.

THE EFFECT of the total body perfusion on digitalis tolerance has not been thoroughly elucidated. The present investigation was undertaken to further evaluate the change in digitalis tolerance immediately after extracorporeal circulation clinically and experimentally. Acetyl strophanthidin was used as a digitalis tolerance test to evaluate the status of digitalization pre- and post-perfusion as previously reported¹.

CLINICAL STUDIES

I. Methods and Materials

Acetyl strophanthidin tolerance test was performed to determine the status of digitalization. One ml of the alcoholic solution of acetyl strophanthidin containing 0.5 mg, equivalent of 3 cat units, of acetyl strophanthidin was diluted with 19 ml of 5 per cent glucose. Prior to the test, the electrocardiogram was taken and superintended continuously during the test. One ml of this diluted solution containing 0.025 mg of acetyl strophanthidin was

Fig. 1. Acetyl strophanthidin tolerance test in pre-perfusion period.

Lead II-A, just prior to acetyl strophanthidin tolerance test

B, 10 minutes after a total of 0.5 mg acetyl strophanthidin has been injected

C, 13 minutes after B.

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injected intravenously during one minute at 3 to 5 minutes intervals. With the initial sign of digitalis intoxication such as nausea, vomiting, or appearance of ventricular premature beat, ventricular tachycardia and atrioventricular block on the electrocardiogram, the test was discontinued. This test was intended to determine the minimal dosage of this drug which produced these signs of intoxication (Fig. 1).

Forty-five acetyl strophanthidin tolerance tests were undertaken in eleven patients who had undergone extracorporeal circulation for the correction of congenital or acquired heart diseases at the period of pre- and post-perfusion. The total body perfusion was performed at a flow rate of 1.4 to 2.3 L/M²/min under mild hypothermia except one, as showed in Table I, with a disc-typed oxygenator and a DeBakey pump for a period of 20 to 170 minutes. These patients were ranged in age from 4 to 56 years. All patients were digitalized with Lanatoside C or Digitoxin for one to seven weeks as pre-operative digitalization before the intracardiac surgery and were administered 6 hours prior to extracorporeal circulation. No digitalis was administered for at least 12 hours following the total body perfusion except acetyl strophanthidin to any patient. Acetyl strophanthidin tolerance test

was performed 24 hours prior to perfusion, at a period of 4 to 7 hours following perfusion, and at a period of 16 to 18 hours after perfusion. Severe complications due to acetyl strophanthidin tolerance test were not observed.

Moreover, a total of 16 acetyl strophanthidin tolerance tests on five patients of mitral stenosis was performed before and after transventricular mitral commissurotomy.

2. Results

In all five patients undergoing transventricular mitral commissurotomies, the dosages of acetyl strophanthidin prior to surgery were equal to them at a period of 4 to 7 hours and of 16 to 18 hours after surgery. Consequently, digitalis tolerance during and after closed heart surgery was considered unaltered due to the surgical procedure.

On the contrary, some change in digitalis tolerance was observed immediately after open heart surgery. The result of alteration in digitalis tolerance after extracorporeal circulation is summarized in Table I. In all six patients undergoing the intracardiac surgery within a perfusion period of one hour, no alteration in digitalis tolerance was observed following perfusion. However, in the other five patients undergoing the total body perfusion during a perfusion period of 80 to 170 minutes, the occurrence of the sign of digitalis intoxication

TABLE I RESULT OF ACETYL STROPHANTHIDIN TOLERANCE TEST PRE- AND POST-PERFUSION IN CLINICAL CASES

Case	Age (years)	Sex	Diag.	Extracorporeal Circulation			Total amount of A. S. (mg.)		
				flow rate (L/M ² /m.)	perfusion period (min.)	body temperat. (°C)	Pre-Perf.	Post-Perfusion	
								4 to 7 hrs.	16 to 18 hrs.
1	4	Male	ASD	1.5	30	29	0.3	0.275	0.3
2	4	Female	VSD	1.8	20	32	0.3	0.3	
3	16	Female	ASD	2.3	25	32	0.9	0.9	
4	17	Male	VSD	2.2	50	32	0.8	0.9	1.0
5	20	Female	VSD	1.4	30	32	0.8	0.8	0.8
6	21	Female	PS	2.2	30	36	0.9	0.9	1.0
7	20	Female	MI	2.1	170	31	0.9	0.6	0.85
8	21	Female	TOF	1.7	80	32	0.75	0.6	
9	21	Female	MSI	1.6	140	29	0.65	0.5	0.6
10	23	Female	ECD	2.0	100	30	0.7	0.4	0.6
11	56	Female	Aneurysma of ascend. Aorta & AI	1.6	150	28	0.5	0.35	

was observed in about 70 per cent doses of preperfusion acetyl strophanthidin at a period of 4 to 7 hours after perfusion. The increased sensitivity to digitalis returned to pre-perfusion levels at a period of 16 to 18 hours following perfusion.

When the perfusion period was over one hour, the transitional mild acidosis (arterial pH came down near 7.30) was sometimes observed at a period of 3 to 8 hours after the total body perfusion. However, the decreasing arterial pH was immediately corrected all the time, and so the relationship between the alteration in digitalis tolerance and the acidosis following perfusion was uncertain.

Blood chemical studies containing serum electrolyte have not shown a significant change. The systolic arterial blood pressure due to the administration of acetyl strophanthidin increased 10 to 40 mmHg either prior to perfusion or following perfusion. The effect of increased arterial blood pressure was maintained for 30 to 40 minutes.

ANIMAL STUDIES

1. Methods and Materials

Six adult mongrel dogs, weighing 12 to 16 kilograms were digitalized with digitalis lanata

for 20 to 30 days period. A digitalizing dose of 0.09 to 0.1 mg/Kg was given. Maintenance dosage from 0.015 to 0.02 mg/Kg/day was used. As a control, five non-digitalized dogs were used. Acetyl strophanthidin tolerance tests were performed to determine the minimal effective dosage same as of clinical studies. Eleven dogs underwent total body perfusion using a disc-typed oxygenator and a DeBAKEY pump with normothermic perfusion period of one hour at a flow rate of 70 to 90 ml/Kg/min. The electrocardiogram, femoral arterial blood pressure, and central venous pressure were continuously monitored during the procedure. The body temperature was kept between 36 and 38°C. The following measurement were undertaken before, during and after perfusion. The arterial and venous blood pH, PO_2 and PCO_2 were intermittently measured with a blood gas analysis machine of Instrumentation Laboratory, Inc., and serum electrolytes (potassium, sodium and calcium) were measured with a flame photometer. The plasma bicarbonate was read from the SIGGARD-ANDERSEN Nomogram. Additionally, the myocardial contractile force was measured by the strain-gauge method in four of the eleven dogs.

2. Results

TABLE II PRE- AND POST-PERFUSION ACETYL STROPHANTHIDIN TOLERANCE TESTS IN DOGS

Digitalized Dogs

No. Dogs	Weight (kg)	Flow rate (ml/kg/m.)	Pre-Perfusion		Post-Perfusion			
			Dosage of A. S. (mg/kg)	Duration of A. S. intoxicat. (min.)	0~2 Hours		2~6 Hours	
					Dosage of A.S. (mg/kg)	Duration of A.S. (min)	Dosage of A.S. (mg/kg)	Duration of A.S. (min.)
1	16	70	0.006	17	0.004	20		
2	14	85	0.006	16	0.005	22	0.004	20
3	14	75	0.007	20			0.004	25
4	13	70	0.01	17	0.009	18	0.007	23
5	12	80	0.015	18	0.015	18	0.01	30
6	14	70	0.006	17	0.005	12		

Non-Digitalized Dogs

7	14	70	0.03	12	0.02	15		
8	12	80	0.03	9	0.03	9	0.018	16
9	16	75	0.02	12	0.02	7	0.015	12
10	15	70	0.023	14	0.027	18		
11	16	90	0.025	17	0.028	20	0.025	16

Fig. 2. Effect of acetyl strophanthidin after perfusion in dog.

The result of pre- and post-perfusion acetyl strophanthidin tolerance tests is summarized in Table 2. The minimal effective dose of acetyl strophanthidin before perfusion was 0.009 mg/Kg (0.006 to 0.015 mg/Kg) in the digitalized group, and, on the contrary, 0.026 mg/Kg (0.02 to 0.03 mg/Kg) in the non-digitalized group. However, the acetyl strophanthidin tolerance after perfusion decreased either in digitalized or in non-digitalized group. Although acetyl strophanthidin tolerance was almost equal to preperfusion during a period of 2 hours following perfusion, a decrease of tolerance to 60 to 65 per cent of preperfusion value was shown during a period of 2 to 6 hours after perfusion in both groups. However, the arterial blood pressure and myocardial contractile force due to the administration of acetyl strophanthidin increased even after the perfusion (Fig. 2).

The arterial blood pH was within normal limits before, during perfusion and one hour after perfusion. However, it decreased gradually after the period of one hour postperfusion and it tended to become acidosis. The arterial blood pH was 7.27 at a period of 2 hours after perfusion, and 7.23 at a period of 4 hours postperfusion. The decreasing of arterial blood pH after perfusion appeared to be nearly parallel with the increased sensitivity to digitalis. However, these relationships were not always observed in each case. This acidosis may be

caused by metabolic factor, because the base excess was decreased almost in parallel with the decreasing arterial blood pH (Fig. 3) and, on the other hand, the arterial blood PCO_2 was always maintained at a level of 25 to 35 mmHg. Consequently, the increased sensitivity to digitalis after extracorporeal circulation may be concerned in metabolic acidosis following perfusion.

Of the electrolyte measurement, no consistent change which would explain the altered tolerance to digitalis was observed (Fig. 4).

Fig. 3. Alteration of arterial pH and base deficit in perfused dogs.

Fig. 4. Change of serum electrolytes in perfused dogs.

DISCUSSION

Acetyl strophanthidin is a synthetic ester of strophanthidin first described by CHEN² (1942), and was first used as a digitalis tolerance test by LOWN and LEVEINE³ (1954), which was later found very accurate by SOLOFF⁴, GILBERT⁵ and CAPELLER⁶. Acetyl strophanthidin tolerance test, from our experience, is a method convenient to evaluate the status of digitalization, because accurate results are rapidly obtainable from this test. However, in some cases, severe side effects have been reported; previous workers^{4,5,7} have reported death due to ventricular fibrillation induced by acetyl strophanthidin tolerance test. We have had no severe side effects which can be related to the use of acetyl strophanthidin, in so far as it is used by the method of the divided administering small amount in the clinical and laboratory observations. We believe acetyl strophanthidin tolerance test is a useful method for all digitalized patients inclusive of children to evaluate the status of digitalization without any side effects.

As to the digitalization before cardiac surgery in our clinic, all patients undergoing open heart surgery for correction of acquired or congenital heart diseases regardless of the cardiac failure are digitalized.

Hitherto, it has been reported⁸⁻¹⁰ that the tolerance to digitalis decreased immediately after open heart surgery with extracorporeal circulation. However, the explanation of this change has been not known. DOHERTY et al.⁹, HERNANDEZ et al.¹², and KOUCHOUKOS et al.¹³ indicated that an increased rate of tissue bind-

ing of the glycoside, rather than changes in the rate of excretion, in distribution, or in muscle sensitivity, is the primary factor in the etiology of the decreased tolerance after the total body perfusion. On the other hand, TASSOPOULOS et al.¹⁰ reported that total body perfusion was associated with no significant change in sensitivity to "tissue fixed" digitalis, although all of the animals that have been tested showed a decreased tolerance to digitalis immediately after perfusion. Previous workers⁸⁻¹⁰ reported that the changes returned to normal level within the first 24 hours after perfusion. LOWN et al.¹¹ reviewing on the shift of electrolytes in the postoperative period, stressed that the low levels of intracellular potassium would play an important role of the increase in sensitivity to digitalis. TASSOPOULOS et al.¹⁰ reported also that the alteration of myocardial tissue electrolyte may be related to the alteration in digitalis tolerance in spite of no change of blood electrolyte.

The effect of extracorporeal circulation on digitalis tolerance, from our experience, has been observed in all cases of total body perfusion except for clinical cases perfused within 60 minutes; it showed acetyl strophanthidin tolerance decreased within a period of 4 to 7 hours after clinical perfusion, and within a period of 2 hours after experimental one, and the duration of the period of heightened sensitivity to digitalis was 16 to 18 hours after clinical perfusion. The metabolic acidosis frequently persisted for hours after extracorporeal circulation and this metabolic acidosis following perfusion may primarily be connected with the decreased digitalis tolerance,

which would be related to the disturbance in myocardial electrolytes.

The administration of acetyl strophanthidin after extracorporeal circulation may be useful for treatment in some case, as showed in our experiment, because this drug is effectively to increase the arterial blood pressure and the myocardial contractile force even after perfusion. BLOODWELL et al.¹⁴⁻¹⁵ showed that mean arterial blood pressure rose due to increased myocardial contractile force by digitalis administered at a time during postperfusion period. Digitalis may heighten the myocardial contractility in non-failing heart. Accordingly, digitalis can be administered during preperfusion period, as well as during the period of postperfusion for all patients undergoing open heart surgery under careful regulation of metabolic acidosis.

SUMMARY

The effect of extracorporeal circulation on digitalis tolerance has been clinically studied with eleven patients undergoing open heart surgery and experimentally with eleven mongrel dogs by means of acetyl strophanthidin tolerance test. The alteration of digitalis tolerance following perfusion has been clinically observed in all cases of the prolonged duration of perfusion of longer than one hour and experimentally in all dogs of one hour perfusion.

Metabolic acidosis after perfusion may be the primary cause of the change in digitalis tolerance.

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