Clinical Studies on the Cardiac Performance by Means of Transseptal Left Heart Catheterization

—The Acute Effects of Digitalis on Left Ventricular Function in Patients with Valvular Stenosis—

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The acute effects of digitalis on the left ventricular performance were studied by transseptal left heart catheterization using external monitoring of radioisotope dilution.

1) In patients with mitral stenosis, in whom heart rate was not altered after digitalization, the cardiac output did not increase significantly presumably because of mitral obstruction, while the left ventricular end-diastolic pressure and volume was decreased, perhaps due to positive inotropic effect of digitalis.

2) In patients with mitral stenosis, in whom heart rate was decreased, the cardiac output increased significantly in association with an increase of left ventricular end-diastolic pressure and volume, perhaps due to negative chronotropic effect of digitalis (increased left ventricular filling secondary to increased diastolic filling period) and Starling's effect.

3) In patients with aortic stenosis, left ventricular systolic and end-diastolic pressure and volume increased after digitalization perhaps due to increased resistance at aortic ostium and increased contractility of left ventricle.

It is concluded that the modes of action of digitalis on left ventricular function are multiple depending on the structural state of the heart, and that the effects may generally be expressed as the summation of positive inotropic and negative chronotropic effect.

THE mechanism of digitalis action on cardiovascular system has been studied by numerous investigators in both animals and man. Since 1945, when cardiac catheterization was introduced into clinical cardiology, the effects of digitalis on the circulatory system using this technique have been reported in normal subjects as well as in patients with various heart diseases. However, these were the results of right heart catheterization and the left heart performance was accessed only from these results.¹⁾⁻⁵⁾ With a recent develop-

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ment of left heart catheterization, left ventricular function could be measured directly.⁶⁾⁻⁸⁾ But because of the difficulty of measuring left ventricular volume in man, only the left ventricular pressure was determined in the evaluation of left ventricular function. As Jones⁹⁾ has shown, however, there is no parallelism between left ventricular pressure and volume, and the left ventricular stroke volume is more closely related with end-diastolic volume than with diastolic filling pressure. Therefore, it is important to measure left ventricular volume in addition to left heart pressure. In this report, left ventricular volume was measured by radioisotope dilution techniques before and after digitalization.

There are some reports^{6),10)} showing that the hemodynamic effects of digitalis are multiple by the underlying diseased states. Therefore, it is also important to evaluate the effects in various heart diseases. For this purpose, patients with mitral or aortic valve stenosis were selected in this report focusing our view point to the influence of mechanically obstructive factor of the hearts.

MATERIALS

Thirteen patients treated as hospitalized or as out-patients at the Second Department of Internal Medicine, Tokyo University Hospital have been studied. They were divided to 3 groups; Group A: 4(0) cases with predominant mitral stenosis, whose heart rate was not influenced by digitalis, Group B: 5(4) cases with predominant mitral stenosis, whose heart rate decreased by more than 10% by digitalis, Group C: 4(2) cases with predominant aortic stenosis. The figures in parenthesis indicate the number of cases with atrial fibrillation. The diagnosis was determined by the physical findings, chest X-ray film, electrocardiogram, phonocardiogram and cardiac catheterization. The functional severity of the patients was in Class II or III of the classification by New York Heart Association.

METHOD

For the measurement of intracardiac pressure, right and transseptal left heart catheterization were simultaneously performed via the antecubital and femoral veins of the patients lying in the supine position. In the cases of atrial fibrillation, the pressures were calculated as the mean of 20 beats.

The left ventricular volume was measured by the radioisotope dilution method by external cardiac monitoring modified after Folse and Braunwald.¹¹⁾ Thirty or 200 μ c. of I¹³¹ hippuran or I¹³¹ labeled human serum albumin was injected into the left ventricular cavity through the left heart catheter, and its dilution process of the radioactivity in the left ventricle was counted by a scintillation detector, which was focused over the left ventricle with an inclination of about 30 degrees against the horizontal plane in the supine position. The apparatus used for the external count-

ing was already reported.¹²⁾ The scintillation detector consists of a 1.5 inch (diameter) $\times$ 1 inch (depth) talliated sodium iodide crystal (Harshaw Chemical Co.) coupled to a photomultiplier tube (RCA 6199). The crystal detector was collimated with a lead flat field collimator. The dilution process counted by the scintillation detector was recorded using a galvanometer type pen recorder which was connected to the detector. The paper speed was 50 mm./sec. Calculation of left ventricular end-diastolic volume and end-systolic volume was made by the method reported by Donato et al.¹³⁾ and slightly modified by us (see Appendix).

For comparison of the individual cases, each value of blood flow and volume was corrected by square meters of body surface area.

The left ventricular mean systolic ejection rate (MSER, ml./sec.) (Levine),¹⁴⁾ which indicates the blood volume ejected per unit ejection period, was calculated as stroke volume divided by systolic ejection period (SEP), as the original method. Circumferential shortening rate (CSR, cm./sec.) (Gorlin),¹⁵⁾ which indicates the contracting speed of left ventricle, and which can be regarded as an indicator of left ventricular contractility, was calculated by the following formula; $CSR = 2\pi(r_{EDV} - r_{ESV})/SEP$ (r_{EDV} = radius at the end-diastolic period of left ventricle, r_{ESV} = radius at the end-systolic period. Radii were calculated by assuming the left ventricle as a cube.) Systolic tension (T, dyne/sec.) was calculated by the following formula; $T = r_m \times P_s \times 1,332/2$ (r_m = mean radius, P_s = systolic peak pressure of left ventricle). Minute work (MW, Kg. M./min./M.²) was calculated as; $MW = CI \times 1.055 \times (BAm - 5) \times 13.6/1,000$ (CI = cardiac index, BAm = mean brachial artery pressure), and stroke work (SW, Gm. M./beat/M.²) was calculated as minute work divided by the mean heart rate.

These measurements were made during steady state, and then 0.4 mg. of Lanatoside C was injected slowly into pulmonary artery using right heart catheter followed by additional injection of 0.2 mg. of Lanatoside C after 30 min. Then measurements were repeated again 60 min. after the first injection.

RESULTS

The hemodynamic data of all the patients in the resting state are presented in Table I and II.

1) *Heart Rate* In Group A heart rate was 88/min. in average, ranging from 80 to 98/min.; in Group B, 127/min. in average, ranging from 96 to 164/min.; and in Group C, 108/min. in average, ranging from 87 to 118/min. It is remarkable that in Group B heart rate was increased more than in Group A.

2) *Cardiac Index* Group A averaged 3.76 L./min./M.² with a range of 2.24–6.40 L./min./M.²; Group B, 2.88 L./min./M.² with a range of 2.19–4.47 L./min./M.²; and Group C, 2.74 L./min./M.² with a range of 2.65–2.85 L./min./M.²

3) *Stroke Volume Index* Group A averaged 42.3 ml./M.² with a range of 22.0–76.8 ml./M.²; Group B, 24.6 ml./M.² with a range of 14.8–46.6 ml./M.²; and Group C, 26.1 ml./M.² with a range of 22.4–33.0 ml./M.² Cardiac

index and stroke volume index tended to decrease in Group B and C than in Group A.

4) *Pulmonary Artery Systolic Pressure* Group A averaged 53 mm. Hg with a range of 31–83 mm. Hg; Group B, 62 mm. Hg with a range of 45–90 mm. Hg; and Group C, 40 mm. Hg with a range of 23–62 mm. Hg.

5) *Mean Left Atrial Pressure* Group A averaged 29 mm. Hg with a range of 14–49 mm. Hg; Group B, 33 mm. Hg with a range of 26–36 mm. Hg; and Group C, 15 mm. Hg with a range of 4–32 mm. Hg. Pulmonary artery systolic and mean left atrial pressure were increased in Group A and B (mitral stenosis).

Table I. Hemodynamic Data Before

	Case	Diagnosis	Sex	Age	Digitali- zation	HR (/min.)	CI (L./M. ²)	SVI (ml./M. ²)	Art. pr. (pulse pr.)
A	Y. S.	MS	M	18	before after	98 101	3.67 3.78	37.5 37.5	105/62 (76) 123/74 (90)
	A. K.	MS	F	31	before after	83 81	2.74 2.68	33.0 33.1	106/70 (82) 115/70 (85)
	H. N.	MS	F	23	before after	92 98	2.24 2.33	22.0 24.7	106/74 (85) 108/76 (85)
	Y. K.	MS	F	19	before after	80 85	6.40 6.47	76.8 75.4	123/73 (90) 132/97 (109)
B	Y. H.	MS	F	30	before after	96 82	4.47 4.88	46.6 59.5	120/92 (101) 124/90 (101)
	H. I.	MSI+Ar +A.F.	M	38	before after	107 75	3.09 2.89	28.8 33.6	157/102 (120) 184/116 (139)
	T. H.	MSI+A.F.	F	19	before after	132 88	2.18 3.09	16.6 35.1	120/84 (100) 136/72 (90)
	H. O.	MSI+A.F.	M	35	before after	138 110	2.22 2.64	16.1 24.0	122/72 (85) 110/68 (82)
	U. M.	MS+A.F.	F	33	before after	164 113	2.43 3.14	14.8 27.8	150/85 (93) 140/60 (87)
C	K. Y.	ASI+MI	M	23	before after	87 88	2.85 3.44	33.0 39.0	128/64 (85) 140/68 (85)
	H. W.	ASI+MI +A.F.	M	36	before after	106 89	2.71 3.06	25.9 34.4	108/60 (88) 136/72 (96)
	M. E.	ASI+A.F.	F	30	before after	120 110	2.75 3.05	23.0 28.0	130/76 (94) 136/80 (99)
	M. K.	AS+A.F.	M	30	before after	118 124	2.65 2.50	22.4 20.1	106/61 (78) 117/61 (81)

MS: mitral stenosis, MI: mitral insufficiency, AS: aortic stenosis, AI: aortic insufficiency, AF: atrial fibrillation, HR: heart rate, CI: cardiac index, SVI: stroke volume index, PA: pulmonary systolic pressure, LA: mean left atrial pressure, LVEDP: left

6) *Left Ventricular End-diastolic Pressure* In all cases, they were within normal limits. Group A averaged 8.5 mm. Hg with a range of 5.0–13.0 mm. Hg; Group B, 8.8 mm. Hg with a range of 4.0–14.0 mm. Hg and Group C, 7.7 mm. Hg with a range of 7.0–8.0 mm. Hg.

7) *Left Ventricular End-diastolic Volume* Group A averaged 147 ml./M.² with a range of 100–228 ml./M.²; Group B, 178 ml./M.² with a range of 128–258 ml./M.²; and Group C, 159 ml./M.² with a range of 116–202 ml./M.² Left ventricular end-diastolic volume in these groups was increased in comparison with the normal value.¹⁶⁾

8) *Valvular Orifice Area* The mean and range of the calculated area of and After Digitalization

PA (mm. Hg)	LA (mm. Hg)	LV		LVEDV (ml./M. ²)	MSER (ml./sec.)	CSR (cm./sec.)	T (dyne/ sec.)	MW (Kg·M./ M. ²)	SW (Gm·M./ M. ²)
		Syst. pr. (mm.Hg)	EDP (mm.Hg)						
83	49	111	6	153	266	6.60	26.7	1.42	14.5
80	36	129	2	150	259	9.23	26.3	2.92	29.7
	31	101	5	127	185	7.72	23.3	2.01	24.2
	37	105	4	105	143	9.54	21.4	1.85	22.8
45	22	132	13	100	88	7.04	27.7	2.03	22.0
45	20	130	3	78	96	8.80	24.7	2.18	22.2
31	14	119	10	228	228	10.5	32.2	6.70	83.9
28	12	119	10	226	227	11.3	31.9	8.06	94.7
52	32	117	7	128	232	11.6	24.8	6.14	61.5
48	16	120	12	185	297	11.4	29.0	6.70	81.7
45	36	151	4	258		4.50	43.7	3.72	34.8
35	20	184	6	224		6.65	50.1	4.92	65.7
66	26	110	14	191	94	2.85	28.7	2.98	22.4
48	17	116	12	279	188	3.40	32.0	3.78	42.9
58									
48									
90	36	137	10	135	78	4.31	31.4	1.97	12.1
60	20	140	11	159	132	7.20	33.5	2.44	21.5
40	4	136	8	116	170	7.70	30.0	3.30	37.9
32	8	176	16	200	232	7.13	47.5	3.98	45.3
28	10	144						3.03	28.6
28	11	152						3.74	42.0
62	32	180	8					3.51	29.3
44	26	188	16					4.11	37.3
23		200	7	202	112	3.35	54.5	2.98	25.0
30		280	7	283	109	2.68	86.2	2.85	23.0

ventricular end-diastolic pressure, LVEDV: left ventricular end-diastolic volume, MSER: mean systolic ejection rate, CSR: circumferential shortening rate, T: systolic tension, MW: minute work, SW: stroke work.

the mitral orifice in the cases of Group A was 1.26 cm.², ranging from 0.50 cm.² to 2.74 cm.²; of Group B, 0.81 cm.², ranging from 0.65 cm.² to 0.99 cm.²; and that of the aortic orifice in the cases of Group C, 0.83 cm.², ranging from 0.25 cm.² to 1.34 cm.²

The results after the digitalization (Table I) were as follows:

Table II. Mean Values of Hemodynamic Data in Each Group

Group	Cases	HR	CI (L./M. ²)	SVI (ml./M. ²)	PA (mm.Hg)	LA (mm.Hg)	LVEDP (mm.Hg)	LVEDV (ml./M. ²)
A	4	88	3.70	42.3	53**	29	8.5	147
B	5	127	2.88	24.6	62	33*	8.8*	178*
C	4	108	2.74	26.1	40	15**	7.7	159***

* 4 cases, ** 3 cases, *** 2 cases

(Abbreviations are same as in Table I)

1) *Heart Rate* In Group A, heart rate increased by 3.6% in an average. It was decreased by 25.4% in Group B; and 4.5% in Group C. All cases of Group A had sinus rhythm, and 4 of 5 cases of Group B had atrial fibrillation.

2) *Cardiac Index* The average increase of cardiac index was 2.6% in Group A, 18.6% in Group B and 9.7% in Group C. The increase in Group B was considered significant. In one case of severe aortic stenosis (M.K.), cardiac index was decreased.

3) *Stroke Volume Index* (Fig. 1). The average increase in stroke volume

Fig. 1. Changes in stroke volume index after digitalization.

Fig. 2. Changes in pulmonary systolic pressure after digitalization.

Fig. 3. Changes in mean left atrial pressure after digitalization.

Fig. 4. Changes in left ventricular end-diastolic pressure (LVEDP) after digitalization.

index was 3.0% in Group A and 62% in Group B. In Group C, stroke volume index was increased except in 1 case of severe aortic stenosis (M.K.).

4) *Systemic Blood Pressure* Systemic systolic and pulse pressure increased in all of the cases. The average increase of pulse pressure in Group A was 18.3%, in Group B 32.9%, and in Group C 4.3%.

5) *Pulmonary Systolic Pressure* (Fig. 2) The average decrease of pulmonary systolic pressure was 2.0 mm. Hg in Group A; 14.0 mm. Hg in Group B and 5.0 mm. Hg in Group C, in which only the case M.K. showed the elevation of pulmonary systolic pressure.

6) *Mean Left Atrial Pressure* (Fig. 3) The average decrease of mean left atrial pressure was 2.8 mm. Hg in Group A; 14.3 mm. Hg in Group B; and 1.0 mm. Hg in Group C. The change in Group B was remarkable.

7) *Left Ventricular Systolic Pressure* The average increase of left ventricular systolic pressure was 4.6% in Group A; 8.0% in Group B; and 19.5% in Group C. Particularly the increase of pressure gradient at the aortic ostium was remarkable in the case of severe aortic stenosis.

8) *Left Ventricular End-diastolic Pressure (LVEDP)* (Fig. 4) In Group A, LVEDP was decreased by 3.8 mm. Hg in an average; in Group B, it was elevated by 4.0 mm. Hg; and in Group C, also elevated by 5.3 mm. Hg.

9) *Left Ventricular End-diastolic Volume (LVEDV)* (Fig. 5) In Group A, LVEDV decreased by 10.8% in an average. On the contrary, in Group B, it increased by 20.2% and in Group C it increased by 56.3% in an average.

Fig. 5. Changes in left ventricular end-diastolic volume (LVEDV) after digitalization.

10) *Mean Systolic Ejection Rate (MSER)* MSER increased in all of the groups, especially in Group B, except one case in Group C (M.K.).

11) *Circumferential Shortening Rate (CSR)* (Fig. 6) In Group A, CSR increased by 25.2% in an average; in Group B, increased by 41.9% and in Group C, decreased by 13.7%.

Fig. 6. Changes in circumferential shortening rate (CSR) after digitalization.

12) *Systolic Tension (T)* (Fig. 7) In Group A, T decreased by 5.1%; in Group B, increased by 12.5%; and in Group C, increased by 58.3%. The

Fig. 7 Changes in systolic tension (T) after digitalization.

increase in Group C was remarkable.

13) *The Relationship between CSR and T* (Fig. 8) In Group A, CSR increased in association with the slight decrease of T, in Group B, CSR increased with the slight increase of T, and in Group C, CSR decreased with the marked increase of T.

Fig. 8. Relationship between circumferential shortening rate and systolic tension. (○—A ●—B ×—C)

Fig. 9. Changes in stroke work (SW) after digitalization.

14) *Minute Work (MW) and Stroke Work (SW)* (Fig. 9) They increased in all cases, except in one case of severe aortic stenosis (M.K.).

DISCUSSION

In this study, effects of digitalis were analysed on the basis of structural changes of the heart.

I) Hemodynamic changes in mitral stenosis (Group A and B)

1) Resting observation;

The principal changes of the heart in these groups are the mechanical obstruction at the mitral ostium, which inhibits the blood flow, causing the elevation of left atrial pressure and pulmonary artery pressure and making overload upon right ventricle, and which tends to decrease in cardiac index and stroke volume, while in the left heart, left ventricular end-diastolic pressure was within normal range, which shows that the left ventricular function was maintained in almost normal.

After digitalization 2 types of response were obtained in these patients. In Group A heart rate remained unchanged, while in Group B the decrease in heart rate was observed within the observation period. In the resting state, heart rate was more increased in Group B than that in Group A, and stroke volume was more decreased in Group B. Clinical state in Group B was more severe than that in Group A.

2) Observation after digitalization;

a) Group A: LVEDP and LVEDV decreased without changes in heart rate and CSR increased with the decrease of T. These changes may be

considered as a result of increased contractility of the left ventricle by digitalis—positive inotropic effect of digitalis. MW and SW were also increased. The decrease of mean left atrial pressure can be considered as the secondary change due to the improvement of left ventricular function.

Some have reported that digitalis induced the elevation of pulmonary systolic pressure in the patients of mitral stenosis, while others have denied.^{10), 17)–20)} In our cases, it was not observed.

Cardiac index and LVEDV remained unchanged, presumably because the blood inflow into left ventricle during the diastolic phase was restricted due to stenosis at mitral ostium.

b) Group B: The cases of this group were divided from Group A by their characteristics that their heart rate decreased remarkably by digitalis. But as mentioned above, they show the tendency of cardiac decompensation. As is well known, digitalis reduces the heart rate when there is tachycardia which is due to heart failure, especially in the cases of atrial fibrillation, by the vagal stimulation or direct myocardial action on A-V node and bundle and improvement of the heart failure, reducing the venous pressure and abolishing the Bainbridge reflex responsible for the compensation tachycardia.²¹⁾ In this group stroke volume and cardiac index increased remarkably by digitalis. This is presumably compatible with the fact, as observed by many investigators,^{1), 5), 17), 22)–26)} that digitalis increases stroke volume and cardiac index in failing heart.

LVEDP, LVEDV and T increased by digitalis in this group. The cause of this mechanism may be considered to be due to bradycardia; that is, bradycardia prolongs the diastolic phase, increases the blood flow into left ventricle and increases LVEDP, LVEDV and T. Stroke volume was increased in association with increasing LVEDV as was shown by Starling's law. Moreover, increased LVEDP and LVEDV were observed after the digitalization in this group. However, when the values of LVEDP before and after the digitalization were plotted against each preceding $\overline{RR}$ interval in electrocardiogram of the cases with atrial fibrillation, for example the case T.H., as seen in Fig. 10, LVEDP elevated in relation to the prolongation of preceding $\overline{RR}$ interval, and such relationship was illustrated as a ventricular function curve. Therefore, the elevation of LVEDP and LVEDV observed after digitalization may probably be explained as a result of bradycardia. Miller²⁷⁾ has showed the prolongation of the filling period by decrease of heart rate, and also showed the increased filling volume at that time by cineangiography. Other investigators^{28)–30)} also described that the important factor to determine the heart size at diastolic phase is the length of its filling phase.

Fig. 10. Relationship between LVEDP and preceding $\overline{RR}$ interval in electrocardiogram, before and after digitalization in case T.H. of Group B.

Moreover, in the cases of mitral stenosis, it is possible that the existence of pressure gradient between left ventricle and left atrium during the whole diastolic phase maintains the blood flow not only during the rapid filling period but also during the diastasis. It might have the particularly important role in the increase of blood flow in bradycardia. Especially in those with atrial fibrillation, which have no atrial contraction, the diastasis may play an important role in ventricular filling.

Fig. 11. Effect of digitalis, compared with theophylline ethylenediamine and induced hypervolemia.

The increase of CSR shows the existence of positive inotropic effect of digitalis, but this effect is so small in Group B, relative to the increase of filling, that it is covered by the latter, resulting in the increase of LVEDP, LVEDV and T.

In Group A, LVEDP and LVEDV decreased simultaneously as shown in Fig. 11. When this effect of digitalis is compared with that of theophylline ethylenediamine,¹⁶⁾ which is thought to be one of the drugs to cause positive inotropic effect on heart, the latter shows the same pattern as digitalis in Group A. Theophylline ethylenediamine also increases heart rate, cardiac index, stroke volume, MSER, CSR, SW and MW. It was recognized that digitalis showed this positive inotropic effect in Group A. On the other hand, in Group B, it is similar to the effect of acute hypervolemia induced by infusion of polyvinyl pyrrolidone,¹⁶⁾ as in Fig. 11. Acute hypervolemia also increased cardiac index, stroke volume and work, and CSR decreased.

II) Hemodynamic changes in aortic stenosis (Group C):

1) Resting observation;

Blood flow from left ventricle is inhibited by the mechanical obstruction at aortic valve, which makes overload upon left ventricle directly, causing left ventricular pressure elevation and enlargement. Cardiac index tended to decrease in comparison with normal values.

2) Observation after digitalization;

All of the measured cases showed the increase of LVEDP, LVEDV and T, and decrease of CSR. Cardiac index, stroke volume, MW and SW increased and pulmonary systolic pressure decreased except in case M.K. having severe aortic stenosis. Braunwald⁶⁾ observed that in valvular aortic stenosis digitalis maintained LVEDP almost the same or rather lower and increased cardiac index while in subaortic stenosis the increased contractility by digitalis makes the aortic orifice smaller and elevated LVEDP and left atrial pressure and decreased cardiac index. He also observed the effect of isuprel³¹⁾ on the subaortic stenosis and obtained the same result. Gorlin¹⁵⁾ observed the elevated LVEDP and LVEDV in valvular aortic stenosis by isoproterenol. These elevations may be caused by the increased afterload by the increased ventricular wall tension during systole generated by interaction of ventricular contraction and outflow resistance. There is a report³²⁾ of "functional aortic stenosis", which is characterized by resistance to left ventricular outflow without any anatomical obstruction. In the result of our study, Group C showed the responses which were different from those of Group A and B and had a some tendency similar to subaortic stenosis in Braunwald or valvular aortic stenosis in Gorlin. The differences of these reports might be due to some differences

in the conditions of cases or procedures. The possibility of existence of muscular hypertrophy near the aortic ostium could be considered even in valvular aortic stenosis.

In summary, there are differences in hemodynamic effect of digitalis by the kind of heart diseases—by the basic hemodynamic state of the heart—particularly in cases with the mechanically obstructive heart diseases; The acute hemodynamic effect of digitalis could be illustrated as a sum of 2 main effects; positive inotropic effect and negative chronotropic effect as summarized in Fig. 12. One of these effects is exaggerated in each group, on the basis of their structural characteristics.

Fig. 12. Mechanism of effect of digitalis.

SUMMARY

In 13 patients with various heart diseases, the acute effects of digitalis on the left ventricular performance were studied by the transseptal left heart catheterization using external monitoring of radioisotope dilution and following results were obtained:

(1) In patients with mitral stenosis, in whom heart rate was not altered after digitalization, the cardiac output did not increase significantly presumably because of mitral obstruction, while the left ventricular end-diastolic pressure and volume decreased. This may be interpreted as a result of positive inotropic effect of digitalis.

(2) In patients with mitral stenosis, in whom heart rate was decreased,

cardiac output increased significantly in association with an increase of left ventricular end-diastolic pressure and volume. This may be interpreted as a result of negative chronotropic effect of digitalis; that is increased left ventricular filling secondary to increased diastolic filling period.

(3) In patients with aortic stenosis, left ventricular systolic and end-diastolic pressure and volume and systolic tension increased with decrease of left ventricular circumferential shortening rate. This may be interpreted as a result of increased resistance at the aortic ostium and increased contractility of the left ventricle.

These effects of digitalis were compared with those of theophylline ethylenediamine and induced hypervolemia. It is concluded that the modes of action of digitalis on left ventricular function are multiple depending on the state of the heart, and that the effects may generally be expressed as the summation of positive inotropic and negative chronotropic effect.

APPENDIX

Method of the Calculation of Left Ventricular Volume

When the values of the radioactivity measured from left ventricle are plotted on semilogarithmic paper, the descending limb of the curve goes down stepwise with the cardiac cycle, so that the fraction of left ventricular volume ejected per beat (FSV/EDV) can be calculated for each cycle. However, since the slope of the de-

Fig. 13

scending limb is considered to be a straight line, FSV/EDV can be calculated using the relationship between descending slope and $\overline{R-R}$ interval of electrocardiogram, by the modified method of Donato, as follows:

$$\frac{\text{FSV}}{\text{EDV}} = \frac{\text{Activity ejected per beat}}{\text{Total activity before ejection}} = \text{Rate in Emptying}$$

(FSV: forward stroke volume, EDV: end-diastolic volume)

$$Y_n = Y_0 \left(1 - \frac{\text{FSV}}{\text{EDV}} \right)^n$$

(Y_0 : radioactivity in left ventricle before ejection)
(Y_n : radioactivity in left ventricle after n beats)

$$\frac{\text{FSV}}{\text{EDV}} = 1 - \left(\frac{Y_n}{Y_0} \right)^{\frac{1}{n}} = 1 - \left(\frac{1}{2} \right)^{\frac{\overline{R-R}}{T_{\frac{1}{2}}}}$$

($\overline{R-R}$: means R-R interval, $T_{\frac{1}{2}}$: half life of the radioactivity in left ventricle)

Thus, EDV can be obtained.

In the cases of atrial fibrillation (Fig. 13), though FSV/EDV is different in each cycle, similar mean value is obtained using average descending slope and mean $\overline{R-R}$ interval as in those of sinus rhythm when the ventricular contractions are well controlled, and satisfactory reproducibility has been confirmed.

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