Clinical significance of positive inotropic action of digoxin in patients with left ventricular disease

C. Davidson¹ and D. Gibson²

From the Department of Cardiology, St. Bartholomew's Hospital, London

Oral digoxin was administered for 10 days to 9 patients with aortic Starr-Edwards prostheses. Its effect on the initial phase of left ventricular ejection was measured using a phonocardiographic method reflecting the initial acceleration of blood into the ascending aorta, and was correlated with plasma levels of the drug. A positive inotropic effect was present, maximum 4 to 6 hours after first administration. The response was not correlated with the plasma levels which reached a peak at 2 to 3 hours. The magnitude of the effect was approximately one-third of that produced by mild supine exercise, and in individual patients there was close correlation between the effects of the two positive inotropic stimuli, suggesting variation in responsiveness from one patient to another. No significant positive inotropic effect attributable to digoxin could be demonstrated later in the study though plasma levels of the drug were within the therapeutic range throughout.

It was concluded that the positive inotropic effect of digoxin in these patients with left ventricular disease was small, compared with that of mild exercise. Chronic digoxin administration did not appear to cause a significant increase in left ventricular contractility. A concomitant reduction in sympathetic activity may be responsible for masking an inotropic effect in patients with intact cardiovascular reflexes, and could also play a part in producing a fall in venous pressure after digoxin.

Digitalis preparations are widely used in the treatment of heart disease. Their therapeutic action in patients in sinus rhythm is usually attributed to a positive inotropic action which has frequently been demonstrated in man, both at cardiac catheterization (Mason and Braunwald, 1963), and by such externally measured variables as left ventricular ejection time and pre-ejection period (Weissler *et al.*, 1966; Shapiro, Narahara, and Taubert, 1970; Weissler and Schoenfeld, 1970). It was the purpose of the present study to document this positive inotropic effect after the administration of digoxin in therapeutic doses to patients with left ventricular disease, and to correlate the results with plasma levels of the drug measured by radioimmunoassay. Observations were made in patients with aortic Starr-Edwards prostheses (Gibson, Broder, and Sowton, 1970), allowing changes in left ventricular function due to digoxin to be assessed phonocardiographically over a period of 10 days' continuous treatment and

to be compared with those of mild, supine exercise in the same individual.

Subjects and methods

Patients

Clinical details of the 9 patients who took part in the study are given in Table 1. All had isolated aortic valve disease, which had been treated by aortic valve replacement with a Starr-Edwards prosthesis at St. Bartholomew's Hospital in the previous 2 weeks to 3 years, and all were in sinus rhythm. None had had any digitalis preparation over the preceding 6 weeks, though maintenance diuretic treatment, required in 4 patients, was not interrupted for the study. All the patients had normal blood urea values. One patient (Case 2) was in pulmonary oedema throughout the acute study, and a further one developed atrial fibrillation during the chronic study (Case 5). The results from these 2 patients were not included in the analysis of the chronic study, which was therefore based on the 7 patients whose cardiac status remained stable throughout. The nature and purpose of the investigation were explained to the patients, and their consent obtained. There were no side effects.

Phonocardiographic observations

Phonocardiograms were recorded with Sanborn equipment, using a high-frequency filter system. The micro-

Received 19 April 1973.

¹ Present address: Department of Medicine, The General Infirmary, Leeds, Yorkshire.

² Present address: Department of Cardiology, Brompton Hospital, London SW3 6HP.

TABLE I

Case No.	Age (yr)	Aortic valve replacement (mth previously)	Chest x-ray		ECG	Diuretic treatment
			CTR (%)	Pulm. vasc. congestion*		
Female						
1	62	14	61	+	LVH	Nil
2	58	0.5	54	++	LVH	Frusemide
Male						
3	65	48	58	0	LBBB PR 0.22	Nil
4	51	0.5	53	0	LVH	Nil
5	53	3	46	0	LVH	Bendrofluazide
6	43	18	48	+	LVH	Nil
7	66	72	53	+	LVH	Frusemide
8	40	3	52	0	LVH	Frusemide
9	42	0.5	49	0	LVH	Nil

* Pulmonary vascular congestion: +, dilated upper lobe vessels, ++ additional lymphatic lines and interstitial oedema.

LVH, Left ventricular hypertrophy.

CTR, Cardiothoracic ratio, measured from PA chest radiograph.

phone was placed in the position down the left sternal edge where the clicks of the prosthesis were most clearly audible, and, in addition, during the control period, an indirect carotid pulse record was taken using a Phillips differential transformer. It was not possible to obtain technically satisfactory recordings of the carotid pulse during exercise. Phonocardiogram, electrocardiogram, and carotid pulse were recorded photographically at a paper speed of 100 mm/sec using an SE 2005 ultraviolet recorder. A representative record is shown in Fig. 1. RR interval was measured from successive R waves on the electrocardiogram. Since the exact origin of the q wave was difficult to determine on account of somatic tremor, QA₁ interval was measured as the time between the most prominent part of the R wave and the first high frequency component of the opening sound of the prosthesis (A₁), to which was added the qR interval, determined from 10 successive beats, at rest. Measurement of the QA₁ interval in this way was found to give more reproducible values during exercise. Ejection time was measured as the interval between the onset of the rapid upstroke of the carotid pulse and its incisura, and ball travel time as ejection time less A₁A₂ interval. These measurements are indicated in Fig. 1 (Gibson *et al.*, 1970). In all cases, mean values from 10 successive beats were used.

Control values

Control measurements were made at 9 a.m., noon, and 5 p.m. on the day before the acute study, as well as immediately before the first dose of digoxin. There were no consistent differences between values taken at these times, so that the control value for each patient was taken as the average of the four readings.

Effect of exercise

After the control measurements had been taken, at 9 a.m. on the day before the acute study, the patients performed straight leg raising, at a rate of approximately 60 times a minute, for a period of two minutes, and phonocardiogram and electrocardiogram were recorded at the end of this period. The aim was to increase the heart rate by about 10 beats a minute, and all the patients were able to manage this exercise without difficulty.

Acute study

This was designed to document the effects on heart rate and QA₁ interval of a single oral dose of digoxin. After control measurements had been made, the patients took 1 mg digoxin at 9 a.m., and further records were made at 10 a.m., 11 a.m., 1 p.m., and 3 p.m. and 5 p.m. Blood samples were taken, without occlusion, immediately after the phonocardiograms had been performed. Patients remained in bed throughout the acute study.

Chronic study

This was designed to assess the effect of more prolonged oral treatment with digoxin at a dose of 0.25 mg three times daily, a dose commonly used in clinical practice. Measurements were made on alternate days. Phonocardiograms were recorded at 9 a.m. before the patients had risen, and digoxin was taken at 9.30 a.m., 2 p.m., and 8 p.m. As in the acute study, blood for digoxin levels was taken immediately after the phonocardiogram had been performed and therefore at least 12 hours after the last dose of digoxin. The chronic study was started on the day after the acute study had been completed.

FIG. 1 Record of electrocardiogram (ECG), phonocardiogram (PCG), and indirect carotid pulse, indicating measurements made. ET, left ventricular ejection time; time marker 0.1 sec.

Digoxin assay

This was by radio immunoassay, using methods previously reported from this laboratory (Chamberlain *et al.*, 1970). All samples were estimated in duplicate, the mean difference between duplicate determinations being 0.2 ng/ml.

TABLE 2 Analysis of variance: acute study

Source of variance	Sum of squares	Degrees of freedom	Variance estimate	F
Patients	1191	8	149	5.32†
Times	410	4	103	3.68*
Residuals	887	32	28	
Total	2488	44		

* $P < 0.05$.

† $P < 0.01$.

TABLE 3 Analysis of variance: chronic study

Source of variance	Sum of squares	Degrees of freedom	Variance estimate	F
Patients	1575	6	262	5.8†
Times	168	5	33.6	NS
Residuals	1353	30	45.1	
Total	3096	41		

† $P < 0.01$

Statistical analysis

This was by an analysis of variance. The statistical significance of reductions in QA_1 interval with respect to control at each time interval after administration of digoxin in the acute study, or on each day in the chronic study, was assessed from the residual variance estimate, using Student's 't' test. The individual effects of RR interval, and plasma digoxin level in predicting QA_1 interval in each patient, were assessed by multiple

TABLE 4 Effect of RR interval and digoxin level on QA_1 : acute study $QA_1 = a(\text{dig. level}) + b(\text{RR interval}) + c$.

Case No.	a	b	c	SE _a	SE _b
1	-1.02	+0.13*	+23.3	5.00	0.042
2	+2.72	+0.11	+52.0	5.60	0.10
3	+0.19	+0.14*	+67.9	3.17	0.064
4	-2.22	+0.14	+3.7	1.37	0.072
5	+13.77	+0.18†	+2.5	6.52	0.043
6	+0.03	+0.09	+33.2	2.86	0.016
7	+0.56	+0.23*	-89.2	4.77	0.082
8	-4.37	+0.06	+39.6	4.86	0.042
9	+1.56	+0.08	+41.9	9.22	0.039

SE, standard error.

* $P < 0.05$.

† $P < 0.01$.

TABLE 5 Effect of RR interval and digoxin level on QA_1 : chronic study

Case No.	a	b	c	SE _a	SE _b
1	-0.72	+0.14†	+35.0	3.82	0.036
3	-0.65	+0.15	61.6	4.73	0.085
4	-9.23	-0.027	+112.7	3.10	0.046
6	-0.78	+0.099†	+31.1	1.55	0.007
7	+1.65	+0.22†	-78.0	5.82	0.066
8	+1.67	+0.14*	-14.9	4.73	0.051
9	+17.9	+0.044	+65.2	11.83	0.059

* $P < 0.05$.† $P < 0.01$.

regression analysis for the acute and chronic studies separately. The results were expressed in the form

$$QA_1 = a(\text{digoxin level}) + b(\text{RR interval}) + c,$$

where a, b, and c are constants. These, together with the standard errors of a and b and the probability of individual values differing from zero are shown in Tables 4 and 5. Statistical methods were those of Dixon and Massey (1969).

Results

1) Effect of exercise

Exercise caused a reduction in QA_1 interval in all patients, by a mean of 22 msec (standard deviation 16) associated with an increase in heart rate from a mean of 87 to a mean of 97 beats per minute. Both changes were significant at the 1 per cent level.

2) Acute study

Digoxin levels Values of plasma digoxin, measured by radioimmunoassay, are shown diagrammatically as a function of the time after an oral dose of 1 mg digoxin in Fig. 2. The peak value was 1.4 ng/ml, which was achieved after 2 hours, while by 8 hours the mean plasma level had dropped to 0.6 ng/ml.

FIG. 2 Changes in QA_1 interval and plasma digoxin level caused by oral administration of 1 mg digoxin. Mean values from 9 patients.

QA_1 interval Changes in QA_1 interval are also shown in Fig. 2. A reduction of 8 msec at 4 hours and 5 msec at 6 hours are significant at the 1 and 5 per cent levels, respectively. The results of the overall analysis of variance are given in Table 2.

Relation between QA_1 interval, RR interval, and plasma digoxin level The results of multiple regression analysis in which the dependence of QA_1 interval or RR interval on plasma digoxin level were examined are given in Table 4. In no patient was the coefficient 'a' significantly different from zero, indicating that QA_1 interval was not determined to any significant degree by plasma digoxin level. In 4 patients, the coefficient 'b' differed significantly from zero, showing that in these subjects only, QA_1 was dependent on heart rate.

Relation between digoxin and exercise-induced changes in QA_1 interval There was significant correlation between the reduction in QA_1 caused by digoxin and that due to exercise in the same patient (Fig. 3, $r = 0.81$, $P < 0.01$, standard error of the estimate 13 msec), the regression equation being: Exercise reduction of QA_1 interval (msec) = 2.83 (digoxin reduction) + 2.6 msec.

In 2 of the patients, the greatest reduction in QA_1 interval occurred after 6 hours, while in the remainder it was 4 hours after the initial oral dose. There was no significant correlation between the maximum change in QA_1 interval due to digoxin and resting value of ball travel time ($r = 0.11$).

Chronic study The results of the chronic study were analysed in the same way as those of the acute. The mean plasma level of digoxin was 1.1 ng/ml, in specimens taken at least 12 hours after the last dose of digoxin. Throughout the study the QA_1 interval did not differ significantly from control, the results

FIG. 3 Relation between reduction in QA_1 interval caused by digoxin administration and that due to mild supine exercise in each of the 9 subjects. The regression line is indicated, together with limits set at 2 standard errors of the estimate.

of the analysis of variance being given in Table 3. From the residual variance estimate, it is apparent that the minimum change in QA_1 interval that would have differed significantly from control was 6 msec. The relation between QA_1 interval, RR interval, and plasma digoxin level is given in Table 5. In 4 patients rate-dependence of the QA_1 interval was demonstrated, while in 1 (Case 4) QA_1 interval was related to plasma digoxin level at the 5 per cent level of significance.

Discussion

Measurement of the interval between the Q wave of the electrocardiogram and the opening sound of an aortic Starr-Edwards prosthesis (A_1) has proved a sensitive method of assessing changes in left ventricular function, reflecting the forces causing ejection of blood into the aorta (Gibson *et al.*, 1970). It is relatively unaffected by tachycardia induced by atropine administration, ventricular pacing, or changes in posture, while it is consistently reduced by positive inotropic stimuli such as exercise on post-ectopic potentiation, and increased by beta-adrenergic blockade (Gibson, Broder, and Sowton, 1970, 1971; Crouchman, Gibson, and Hamer, 1972). Since the technique requires only an electrocardiogram and a phonocardiogram, frequent measurements can be made with little disturbance to the patient, and both short and long-term changes in ventricular function can be studied.

The demonstration of a positive inotropic stimulus may be influenced by a number of factors. In the presence of severe heart disease, the force generated by the left ventricle may be at a maximum under control conditions, and no further increase be possible, however strong the stimulus (Blinks and Koch-Weser, 1963). In order to demonstrate that the patients studied were capable of responding to a positive inotropic stimulus, a reduction in QA_1 interval was confirmed in all of them during mild exercise. Since changes in left ventricular function induced by alterations in end-diastolic fibre length do not appear to be wholly separable from those due to a change in contractile state (Pollack, 1970), it is possible that both might alter the QA_1 interval. However, previous studies have indicated that the effects of changes in left ventricular filling are small (Gibson *et al.*, 1970, 1971) and, in addition, if such changes did occur, they would be in the same direction as those caused by the positive inotropic action of digoxin on QA_1 interval. A possible separate effect of heart rate was defined in each patient by multiple regression analysis and dissociated from that of plasma digoxin level. In 4 patients significant positive correlation was present between RR interval

and QA_1 interval, while in the remainder the two were independent. This difference may reflect the mechanism by which changes in heart rate were mediated, being by alterations in sympathetic rather than vagal activity in those patients in whom QA_1 interval shortened with tachycardia. Such lack of uniformity suggests that the use of correction factors derived from pooled data to normalize results may not always be valid, since the relation between sympathetic and parasympathetic influences may be disturbed in heart failure or digoxin administration.

The results of this study show a significant reduction in QA_1 interval 4 to 6 hours after an oral dose of digoxin, indicating an increase in the force of left ventricular contraction. This occurred approximately 2 hours after peak plasma concentrations had been reached so that the delay probably reflected the time necessary for the drug to equilibrate between blood and myocardium. This accounts for the lack of correlation between plasma digoxin levels and the reduction in QA_1 interval, and consequently in the chronic study, measurements were made at least 8 hours after the last dose of digoxin had been given to allow a steady state to be reached. The maximum change in ventricular function after oral digoxin was earlier in the study than in previous reports and resembled more closely those in which the drug had been given intravenously (Weissler *et al.*, 1966; Shapiro *et al.*, 1970). This suggests that the delay in the onset of the action of digoxin is due to its uptake by myocardium rather than to its absorption from the gut, a conclusion supported by experimental work (Deutscher, Harrison, and Goldman, 1972).

Although the reduction in QA_1 interval occurring after digoxin was statistically significant, its absolute magnitude was small, being less than one-third that of mild exercise. This figure compares closely with experimental work, in which maximal therapeutic doses of digoxin increased left ventricular dp/dt max of canine heart by 32 per cent above control, whereas an increase of 80 per cent could be achieved with isoprenaline (Beiser *et al.*, 1970). In addition, the magnitude of the reduction in QA_1 interval caused by digoxin correlated with that occurring during exercise in the same patient, indicating that the response to one inotropic stimulus could be predicted from observing the response to another unrelated one, and that differences in sensitivity to inotropic stimuli were probably the basis of the between-patient variance demonstrated in the acute study. However, this correlation could, theoretically, have resulted from the technique itself, since the initial acceleration of the ball of the prosthesis and therefore the force generated by the left ventricle at the onset of ejection, is inversely proportional to the square of the ball travel time, the time

taken by the ball to travel from the base to the apex of the cage. The greater the resting value of acceleration, the smaller the reduction in ball travel time for a given change in initial acceleration, so that the sensitivity of the method is correspondingly reduced. However, if the correlation between the effects of digoxin and those of exercise were solely due to this cause, the patients in whom the change in QA_1 interval was smallest would be expected to have the shortest values of ball travel time at rest, and this was not the case. It was concluded, therefore, that the between-patient variance was the result of real differences in the sensitivity of the myocardium to positive inotropic stimuli.

In contrast to the acute study, prolonged administration of digoxin was not associated with a statistically significant reduction in QA_1 interval below control values. This cannot be attributed to a concomitant increase in stroke volume, since this would, if anything, have caused a reduction in QA_1 interval. It is unlikely to have been due to failure of absorption of the drug, since a clear-cut response occurred in the acute study when the drug was given orally, and, in addition, therapeutic blood levels were demonstrated throughout. It is possible that prolonged reduction did occur, but that the method used was too insensitive to detect it: however, the maximum value of an effect which would have been missed for this reason can be estimated from the residual variance estimate, and was of the order of 6 msec, less than one-third of the change caused by mild exercise. The overall suitability of the method, however, for documenting such changes, had they occurred, was confirmed by the significant effect demonstrated in the acute study. It is, therefore, possible that the effect of the drug was modified by the presence of intact reflexes, and that its positive inotropic effect was masked by a corresponding reduction in the level of endogenous sympathetic activity, so that the overall level of the left ventricular contractile state remained unchanged. Indirect evidence for such a reduction in sympathetic activity has been obtained from observations of the effect of ouabain on the peripheral circulation (Mason and Braunwald, 1964). In patients in heart failure its administration was associated with a reduction in forearm venous tone and peripheral resistance which could not be attributed to a direct effect of the drug, but which was possibly to be due to sympathetic withdrawal secondary to improved cardiac function. Though the afferent stimulus was not defined, it is likely from the relative magnitudes of the effects of exercise and digoxin observed in the present study that a diminution of sympathetic tone, however mediated, might mask the positive inotropic effect of digoxin.

The present results may also have relevance in the clinical setting. Digitalis preparations are frequently recommended in low cardiac output states for their effect of left ventricular function (Wood, 1962b). However, in doses commonly employed in clinical practice, the magnitude of their effect is likely to be small compared with that of sympathetic stimulation, showing that infusion of adrenaline or isoprenaline is a much more effective method of increasing the force of left ventricular contraction if this is thought to be indicated. Theoretically, a group of patients might exist in whom catecholamines are without effect, but who are still capable of response to digitalis; but by showing close correlation between the effects of digitalis and exercise, the present study gives no support to this idea.

The failure to demonstrate a consistent reduction in QA_1 interval during chronic digoxin administration is in line with a previous study in which the effects of long-term digitoxin treatment were undetectable using a ballistocardiographic method (Starr and Luchi, 1969), and suggests that the use of digitalis preparations may not necessarily be associated with a sustained increase in left ventricular contractile state above control values. Such preparations would therefore resemble other positive inotropic stimuli such as isoprenaline (Gunnar *et al.*, 1967; Mueller *et al.*, 1968) or paired pacing (King and Taylor, 1968) where a long-term positive inotropic action may not be demonstrable due possibly to tachyphylaxis or to the effects of increased oxygen requirement on a diseased myocardium. The present results therefore raise the possibility that the therapeutic effects of digitalis in patients in sinus rhythm in causing, for example, diuresis or reduction in venous pressure (Wood, 1962a), may not be due to an increase in left ventricular contractile state. It is suggested, rather that they may result either from secondary reflex changes, in particular from a reduction in endogenous sympathetic activity, or from effects elsewhere in the cardiovascular system.

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Requests for reprints to Dr. C. Davidson, The General Infirmary, Leeds, Yorks.