Effect of digoxin on the heart in normal subjects: influence of isometric exercise and autonomic blockade: A noninvasive study

JUHANI PARTANEN, JUHANI HEIKKILÄ, TIMO PELLINEN & MARKKU S. NIEMINEN

Cardiovascular Laboratory and First Department of Medicine, University Central Hospital, Helsinki, Finland

1 Eight healthy subjects were studied before digoxin and after successive therapy periods of 1 week 0.125, 0.25 and 0.50 mg of digoxin. The mean serum concentrations ($\pm$ s. d.) were 0.4 ± 0.2 , 0.6 ± 0.3 and 1.4 ± 0.5 nmol l⁻¹, respectively. The effects of digitalis were studied by echocardiography and systolic time intervals at rest and after 3 min handgrip exercise. Effects of simultaneous autonomic blockade induced by atropine and propranolol were also examined.

2 Digoxin in increasing doses slowed the heart rate at rest; with the daily dose of 0.50 mg from 63 ± 10 to 53 ± 6 beats min⁻¹, and fractional shortening rose from 28 ± 6 to $33 \pm 3\%$ ($P < 0.05$ for both). Preload, afterload and cardiac output did not change. The electro-mechanic systolic time index (QS₂I) decreased ($P < 0.001$) and the observed alteration of QS₂I was dose-related.

3 The influence of digoxin was similar during isometric exercise, except for unchanged fractional shortening.

4 During autonomic blockade digoxin slowed the intrinsic heart rate from 93 ± 6 to 86 ± 6 beats min⁻¹ (0.25 mg) and to 83 ± 6 beats min⁻¹ (0.50 mg) ($P < 0.01$ for both). QS₂I was shortened ($P < 0.01$). Echocardiographically determined ejection phase indices remained unchanged.

5 When handgrip stress was induced during autonomic blockade, digoxin evoked a clear-cut increase in contractile function, resembling the effects of digoxin alone at rest. Thus, fractional shortening increased by 14% and QS₂I decreased by 16 ms ($P < 0.01$ for both).

6 We conclude that digoxin increases the contractility in normal heart without changes in loading conditions. The rise in inotropy at rest is obvious from both fractional shortening by echo and systolic time intervals. The same takes place during handgrip with autonomic blockade, when the heart lacks sympathetic support. The influence of long-term digoxin on heart rate is partly direct without autonomic mediation. The effect of digoxin is dose-dependent.

Keywords digoxin isometric exercise autonomic blockade
left ventricular contractility echocardiography systolic time intervals

Introduction

Digitalis glycosides exert a positive inotropic effect and a negative chronotropic influence on both healthy and decompensated hearts, when administered acutely (Braunwald *et al.*, 1961;

Murphy *et al.*, 1964; Sonnenblick *et al.*, 1966; Arnold *et al.*, 1980). The inotropic effect continues for at least 10–14 days on the normal left ventricle (Crawford *et al.*, 1976) and has been

also demonstrated during dynamic exercise (Saito *et al.*, 1979). The value of digitalis glycosides in sinus rhythm in chronic treatment of congestive heart failure is disputable (Arnold *et al.*, 1980; Fleg *et al.*, 1982). The effect of digoxin on heart rate is thought to be mediated via autonomic reflexes but the stimulation of the inotropic state is direct, without contribution of the autonomic nervous system (Gillis & Quest, 1979).

Isometric exercise increases the contractility of the normal left ventricle by withdrawal of vagal nerve activity and stimulation of sympathetic tone (Grossman *et al.*, 1973; Martin *et al.*, 1974; Stefadourous *et al.*, 1974). The effect of digoxin on the inotropic state during isometric exercise has not yet been studied.

The aim of our study was to examine the effect of increasing digoxin doses on contractility of the left ventricle at rest and during isometric exercise. The direct effect of digoxin without parasympathetic and β -adrenoceptor reflexes was evaluated by also recording the variables during autonomic blockade with atropine and propranolol (Jose & Taylor, 1969). The loading conditions were taken into account as they may have an important influence on factors related to contractility.

Methods

Subjects

The study group comprised eight healthy young volunteers, four women and four men, aged 23–27 years (mean 24 years). The mean body weight was 60.8 ± 10.9 kg (s.d.). The subjects were selected to the study on a basis of repeatedly obtainable high quality echocardiograms. Clinical examination, resting electrocardiography and echocardiography revealed no abnormalities.

Study design

The studies were performed between 0730 h and 0830 h after an overnight fast. At each examination blood pressure, echocardiogram, phonocardiogram, electrocardiogram and carotid pulse wave were recorded by two investigators to ensure that the recordings were as simultaneous as possible. After the baseline data were obtained increasing oral doses of digoxin (0.125, 0.25 and 0.50 mg each) were given once a day for 1 week. No wash-out periods or placebo were interposed.

The subjects lay semisupine for at least 15 min before the start of the study programme. Blood pressure was measured from the resting arm with a sphygmomanometer. Diastolic blood

pressure (DBP) was recorded at the point of disappearance of the heart sounds (Korotkoff stage 5). Mean blood pressure (MBP) was calculated from the formula:

$$\text{MBP (mmHg)} = \text{DBP} + 1/3 (\text{SBP} - \text{DBP}),$$

where SBP = systolic blood pressure.

Isometric exercise was induced by handgrip using an electrical device especially constructed for this purpose (Malinen *et al.*, 1979). The maximal voluntary contraction was determined as the average of three squeezes 15 min before the beginning of the study program. After the resting recordings, the subjects performed an isometric exercise by squeezing the handle with 30% of maximal voluntary contraction for 3 min. Recordings began 2 min and 45 s after the beginning of handgrip and continued for 30 s.

Thereafter atropine (0.04 mg kg^{-1}) and propranolol (0.2 mg kg^{-1}) were injected simultaneously to each subject during 3 min (Jose & Taylor, 1969). The influence of autonomic blockade was recorded 7 min after the injection. Handgrip began 12 min after the injection, and the measurements were repeated as before.

Echocardiography

The subjects were studied semisupine, each time in the same left lateral oblique position. An Irex System II echocardiograph and a 2.25 MHz medium focused transducer were used for the recordings. Lead II electrocardiogram, phonocardiogram and M-mode echocardiogram were recorded simultaneously on dry silver paper at a speed of 50 or 100 mm s^{-1} . The left ventricular internal diameters were recorded carefully in the standard way just below the level of the tip of the anterior mitral leaflet. The subjects were asked to avoid Valsalva manoeuvre during handgrip.

Echocardiograms were analysed semiautomatically using a Digital PDP 11/34 minicomputer and an x-y digitizer according to the method of Upton & Gibson (1978). The leading edges were used for analysis of dimension loops, the measurement being performed according to the European standard (Roelandt & Gibson, 1980). The left ventricular end-diastolic diameter (LVEDD) was measured at the beginning of the Q-wave, and the left ventricular end-systolic diameter (LVESD) at the first high frequency deflections of the aortic component of the second heart sound. Fractional shortening (FS) was calculated with the formula:

$$\text{FS (\%)} = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}} \times 100.$$

The total peripheral vascular resistance (TPR) was estimated as follows (Stefadouros *et al.*, 1973):

$$\text{TPR (dyn} \times \text{s/cm}^5\text{)} = \frac{\text{MBP}}{\text{CO}} \times 80.$$

The maximal velocity of left ventricular circumferential fibre shortening was obtained from the digitized cardiac cycles as the maximum value of the first derivate of the systolic shortening of the internal diameter divided by left ventricular end-diastolic diameter (Upton & Gibson, 1978).

Left ventricular systolic wall stress (WS) was derived with the formula (Ratshin *et al.*, 1974):

$$\text{WS (dyn/cm}^2\text{)} = \frac{\text{SBP} \times \text{LVMSD}}{2 \times \text{PWMST}} \times \left(1 - \frac{\text{LVMSD}}{8 \times (\text{LVMSD} + \text{PWMST})}\right) \times 1332,$$

where LVMSD = left ventricular mid-systolic diameter, PWMST = left ventricular posterior wall mid-systolic thickness.

The values of the recordings were calculated as the mean value of five consecutive or nearly consecutive cardiac cycles.

Systolic time intervals

Systolic time intervals were measured indirectly from simultaneous tracings of the carotid pulse, phonocardiogram and electrocardiogram (Weissler *et al.*, 1968). The paper speed was 100 mm s⁻¹. The total electromechanic systole (QS₂, pre-ejection period (PEP) and left ventricular ejection time (LVET) were determined. QS₂ and LVET were corrected for heart rate using Weissler's regression equations (Weissler *et al.*, 1968). The PEP/LVET ratio was determined from uncorrected values. Since PEP seems to be rate-independent (Cokkinos *et al.*, 1976; Spodick *et al.* 1984), it was not corrected for heart rate. The measurements were derived from 10 consecutive cardiac cycles.

Serum digoxin concentrations

Serum digoxin concentrations were determined by radioimmunoassay with a kit manufactured by Farnos Co., Finland. The samples were taken about 24 h after the previous digoxin dose.

Reproducibility

The subjects were studied twice at rest prior to

digitalization. The interval between recordings ranged from 3 to 26 days, mean 9 days.

Statistical methods

Analysis of variance with repeated measures (ANOVA) was used to test the significance of the changes in the variables. Student's *t*-test for paired observations was used when appropriate after testing by analysis of variance. The results are given as group means $\pm$ s.d. The reproducibility was tested with estimation of coefficients of variation between two measurements before digoxin. Individual coefficients of variation were calculated as a percentage by dividing the standard deviation with the mean of the variables. The group mean of coefficients of variation was derived by averaging the individual values. A *P* value lower than 0.05 was taken to be statistically significant.

Results

Reproducibility

The mean values of coefficients of variation of all haemodynamic variables, except cardiac output and total peripheral vascular resistance, were below 9% (Table 1). The coefficients of variation of these two were 12.2 ± 7.9 and $12.0 \pm 7.7\%$ because of day-to-day variation, though the group means were nearly similar 3.3 ± 1.1 and 3.3 ± 0.8 min⁻¹ and 2335 ± 673 and 2223 ± 548 dyn s cm⁻⁵, respectively.

Serum concentrations of digoxin

Serum concentrations with the daily digoxin doses of 0.125, 0.25 and 0.50 mg were 0.4 ± 0.2 and 0.6 ± 0.3 and 1.4 ± 0.5 nmol l⁻¹ respectively.

Effect of digoxin at rest

Digoxin 0.50 mg daily decreased heart rate from 63 ± 10 to 53 ± 6 beats min⁻¹ ($P < 0.05$) (Table 2). Left ventricular end-diastolic diameter, systolic blood pressure, systolic wall stress, total peripheral resistance and cardiac output did not change. Ejection fraction and fractional shortening rose, the latter from 28 ± 6 to $33 \pm 3\%$ ($P < 0.05$ for both). QS₂I decreased. QS₂I was shorter with 0.50 mg than with 0.25 mg of digoxin daily ($P < 0.05$).

Effect of digoxin during autonomic blockade

Digoxin decreased the intrinsic heart rate from 93 ± 6 to 87 ± 5 , to 86 ± 6 and to 83 ± 6 beats min⁻¹ ($P < 0.01$ for all) with the increasing doses (Table 3). There was no change in any of

Table 1 Reproducibility of variables measured at intervals of 3 to 26 days, mean 9 days, numbers are means $\pm$ s. d. ($n = 8$)

Variable	Measurement I	Measurement II	CV mean % (range)
HR (beats min ⁻¹)	63 $\pm$ 10	62 $\pm$ 10	5.9 (1.6–12.6)
SBP (mmHg)	111 $\pm$ 9	114 $\pm$ 4	5.1 (1.2–9.5)
DBP (mmHg)	79 $\pm$ 9	73 $\pm$ 8	7.9 (0.0–18.4)
MBP (mmHg)	90 $\pm$ 8	86 $\pm$ 6	4.9 (1.4–7.8)
LVEDD (mm)	46.0 $\pm$ 4.7	45.6 $\pm$ 3.9	2.5 (0.7–6.4)
SV (ml)	53 $\pm$ 17	53 $\pm$ 13	8.8 (2.6–20.2)
CO (l min ⁻¹)	3.3 $\pm$ 1.1	3.3 $\pm$ 0.8	12.2 (0.3–19.4)
WS (10 ³ dyn cm ⁻²)	274 $\pm$ 69	266 $\pm$ 58	7.5 (0.2–10.6)
EF (%)	54 $\pm$ 8	55 $\pm$ 8	3.6 (0.6–10.0)
FS (%)	28 $\pm$ 5	29 $\pm$ 5	4.8 (1.0–12.0)
VCFmax (lengths s ⁻¹)	1.94 $\pm$ 0.32	1.89 $\pm$ 0.24	5.8 (0.0–13.1)
TPR (dyn s cm ⁻⁵)	2335 $\pm$ 673	2223 $\pm$ 547	12.0 (0.0–22.5)
PEP (ms)	101 $\pm$ 20	102 $\pm$ 16	8.2 (0.0–26.2)
LVETI (ms)	402 $\pm$ 20	398 $\pm$ 17	1.1 (0.2–4.5)
PEP/LVET	0.342 $\pm$ 0.071	0.349 $\pm$ 0.059	8.6 (0.3–24.7)
QS ₂ I (ms)	529 $\pm$ 10	525 $\pm$ 17	1.1 (0.0–3.5)

Abbreviations: CF = coefficient of variation; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; LVEDD = left ventricular end-diastolic diameter; SV = stroke volume; CO = cardiac output; WS = systolic wall stress; EF = ejection fraction; FS = fractional shortening; VCFmax = maximal velocity of left ventricular circumferential fibre shortening; TPR = total peripheral vascular resistance; PEP = pre-ejection period; LVET = left ventricular ejection time; LVETI = index of LVET; QS₂I = electromechanic systolic time index.

Table 2 Effect of digoxin on haemodynamic data at rest ($n = 8$)

Variable	No digoxin	Digoxin (mg daily)		
		0.125	0.25	0.50
HR (beats min ⁻¹)	63 $\pm$ 10	59 $\pm$ 11	60 $\pm$ 9	53 $\pm$ 6*†
SBP (mmHg)	111 $\pm$ 9	113 $\pm$ 6	112 $\pm$ 10	111 $\pm$ 18
DBP (mmHg)	79 $\pm$ 9	70 $\pm$ 7	70 $\pm$ 7	68 $\pm$ 11*
MBP (mmHg)	90 $\pm$ 8	84 $\pm$ 7	84 $\pm$ 7	82 $\pm$ 13
LVEDD (mm)	46.0 $\pm$ 4.7	45.0 $\pm$ 3.6	45.3 $\pm$ 4.1	46.7 $\pm$ 4.2
SV (ml)	53 $\pm$ 17	51 $\pm$ 11	53 $\pm$ 12	62 $\pm$ 13†
CO (l min ⁻¹)	3.3 $\pm$ 1.1	3.0 $\pm$ 0.8	3.2 $\pm$ 0.8	3.3 $\pm$ 0.8
WS (10 ³ dyn cm ⁻²)	274 $\pm$ 69	264 $\pm$ 62	271 $\pm$ 61	249 $\pm$ 52
EF (%)	54 $\pm$ 8	56 $\pm$ 9	56 $\pm$ 6	61 $\pm$ 4*†
FS (%)	28 $\pm$ 6	29 $\pm$ 6	29 $\pm$ 4	33 $\pm$ 3*†
VCFmax (lengths s ⁻¹)	1.94 $\pm$ 0.32	1.97 $\pm$ 0.36	1.91 $\pm$ 0.25	2.06 $\pm$ 0.23
TPR (dyn s cm ⁻⁵)	2335 $\pm$ 673	2399 $\pm$ 749	2204 $\pm$ 496	2101 $\pm$ 538
PEP (ms)	101 $\pm$ 20	99 $\pm$ 12	95 $\pm$ 15	90 $\pm$ 13
LVETI (ms)	402 $\pm$ 20	397 $\pm$ 9	395 $\pm$ 11	393 $\pm$ 16
PEP/LVET	0.342 $\pm$ 0.071	0.335 $\pm$ 0.047	0.325 $\pm$ 0.052	0.299 $\pm$ 0.049
QS ₂ I (ms)	529 $\pm$ 10	520 $\pm$ 14*	514 $\pm$ 8**	505 $\pm$ 15***†

Abbreviations as in Table 1. Values are means $\pm$ s. d. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, the variables with increasing digoxin doses compared with those before digoxin. † $P < 0.05$; ‡ $P < 0.01$, the values with the dose of 0.50 mg compared with the values with the dose of 0.25 mg digoxin daily.

Table 3 Effect of digoxin on haemodynamic data during autonomic blockade ($n = 8$)

Variable	No digoxin	Digoxin (mg daily)		
		0.125	0.25	0.50
HR (beats min ⁻¹)	93 ± 6	87 ± 5**	86 ± 6**	83 ± 6**†
SBP (mmHg)	118 ± 10	113 ± 8	116 ± 7	112 ± 10
DBP (mmHg)	83 ± 8	79 ± 4	81 ± 7	77 ± 12
MBP (mmHg)	95 ± 8	90 ± 5	92 ± 7	89 ± 11
LVEDD (mm)	43.8 ± 4.4	43.1 ± 4.3	44.0 ± 4.0	44.1 ± 5.5
SV (ml)	44 ± 11	41 ± 9	45 ± 9	46 ± 12
CO (l min ⁻¹)	4.1 ± 0.9	3.5 ± 0.7	3.9 ± 0.8	3.8 ± 0.9
WS (10 ³ dyn cm ⁻²)	276 ± 63	265 ± 67	278 ± 62	269 ± 44
EF (%)	50 ± 6	49 ± 8	51 ± 6	52 ± 6
FS (%)	25 ± 4	25 ± 5	26 ± 4	27 ± 3
VCFmax (lengths s ⁻¹)	1.93 ± 0.22	1.95 ± 0.21	1.94 ± 0.26	1.97 ± 0.27
TPR (dyn s cm ⁻⁵)	1949 ± 467	2125 ± 502	1975 ± 429	1974 ± 621
PEP (ms)	108 ± 13	108 ± 12	101 ± 13	99 ± 13
LVETI (ms)	417 ± 11	405 ± 12*	406 ± 9*	400 ± 12**
PEP/LVET	0.412 ± 0.065	0.412 ± 0.065	0.384 ± 0.049	0.379 ± 0.062
QS ₂ I (ms)	561 ± 8	547 ± 6**	541 ± 13**	533 ± 13**‡

Abbreviations as in Table 1. Statistics and symbols as in Table 2.

the other variables except in LVETI and QS₂I which decreased. QS₂I fell with 0.50 mg from 561 ± 8 to 533 ± 13 ms ($P < 0.01$) and it was shorter with the dose of 0.50 mg digoxin than with 0.25 mg ($P < 0.01$).

Effect of digoxin during handgrip

Digoxin 0.50 mg daily decreased heart rate during handgrip from 75 ± 17 to 59 ± 9 beats min⁻¹ ($P < 0.05$) (Table 4). Left ventricular end-diastolic diameter, systolic wall stress, cardiac output, stroke volume, total peripheral vascular resistance and echocardiographically determined ejection phase indices did not change. LVETI decreased and QS₂I declined from 552 ± 11 to 524 ± 12 ms ($P < 0.01$) with the dose of 0.50 mg digoxin daily.

Effect of digoxin during handgrip and autonomic blockade

Digoxin decreased the intrinsic heart rate also during handgrip with the incremental dose from 94 ± 6 to 87 ± 7, to 86 ± 6 and to 82 ± 7 beats min⁻¹ ($P < 0.01$ for all) (Table 5). There were no changes in ventricular end-diastolic diameter or systolic wall stress, blood pressure, cardiac output or total peripheral vascular resistance. Ejection fraction and fractional shortening rose, the latter from 22 ± 5 to 25 ± 3% ($P < 0.05$ for both). QS₂I shortened from 571 ± 4 to 555 ± 10 ms ($P < 0.01$) with the dose of 0.50 mg digoxin daily.

Discussion

Reliability of the results

Except for cardiac output and total peripheral vascular resistance, our results showed good or satisfactory reproducibility estimated twice with mean interval of 9 days. The mean group values of these two variables were nearly unchanged. The good reproducibility is consistent with previous results with longer observation periods (Ladipo *et al.*, 1980; Kupari, 1983, 1984). We had no placebo phase in our study design. However, the total number of the echo and systolic time interval recordings was 272 and they were randomly digitized. The data were analyzed after all the recordings were digitized. We consider the reliability of the results to be good with this arrangement even without placebo.

Physiological and methodological aspects

Left ventricular performance is a function of heart rate, preload, afterload and inotropic state (Braunwald, 1984). The simultaneous influence of these other determinants of pump function must also be considered when evaluating myocardial contractility. A variation in loading conditions or in heart rate may induce marked changes in ejection phase indices or in systolic time intervals. These changes do not then reflect an alteration in contractility (Braunwald, 1984; Lewis *et al.*, 1977; Hassan & Turner, 1983). Ventricular preload is best estimated as end-diastolic stress, which correlates with end-diastolic

Table 4 Effect of digoxin on haemodynamic data during isometric exercise ($n = 8$)

Variable	No digoxin	0.125	Digoxin (mg daily)	
			0.25	0.50
HR (beats min ⁻¹)	75 ± 17	65 ± 14	65 ± 13	59 ± 9*
SBP (mmHg)	136 ± 11	127 ± 7	130 ± 9	128 ± 14
DBP (mmHg)	99 ± 4	89 ± 7**	93 ± 9*	89 ± 13*
MBP (mmHg)	112 ± 6	102 ± 6**	105 ± 8	102 ± 12*
LVEDD (mm)	47.3 ± 4.7	45.2 ± 4.6	45.8 ± 5.5	46.8 ± 5.0
SV (ml)	53 ± 9	51 ± 13	52 ± 15	56 ± 12
CO (l min ⁻¹)	4.0 ± 1.3	3.2 ± 0.8	3.3 ± 0.8	3.3 ± 0.8
WS (10 ³ dyn cm ⁻²)	362 ± 74	324 ± 103	324 ± 70	336 ± 104
EF (%)	51 ± 9	54 ± 8	53 ± 7	55 ± 5
FS (%)	26 ± 5	28 ± 5	27 ± 5	29 ± 3
VCFmax (lengths s ⁻¹)	1.80 ± 0.32	2.05 ± 0.36	1.84 ± 0.41	1.82 ± 0.19
TPR (dyn s cm ⁻⁵)	2409 ± 587	2633 ± 587	2678 ± 680	2630 ± 734
PEP (ms)	100 ± 27	100 ± 15	101 ± 18	93 ± 13
LVETI (ms)	420 ± 16	407 ± 14*	403 ± 14**	406 ± 16**
PEP/LVET	0.348 ± 0.091	0.341 ± 0.052	0.350 ± 0.058	0.309 ± 0.044
QS ₂ I (ms)	552 ± 11	534 ± 11**	531 ± 13**	524 ± 12**

Abbreviations as in Table 1. Statistics and symbols as in Table 2.

Table 5 Effect of digoxin on haemodynamic data during isometric exercise with autonomic blockade ($n = 8$)

Variable	No digoxin	0.125	Digoxin (mg daily)	
			0.25	0.50
HR (beats min ⁻¹)	94 ± 6	87 ± 6**	86 ± 6**	82 ± 7**†
SBP (mmHg)	131 ± 14	127 ± 7	128 ± 9	130 ± 11
DBP (mmHg)	100 ± 11	97 ± 6	97 ± 8	94 ± 9
MBP (mmHg)	110 ± 11	107 ± 6	108 ± 8	106 ± 9
LVEDD (mm)	45.7 ± 5.5	45.8 ± 5.6	44.6 ± 5.6	45.1 ± 5.6
SV (ml)	43 ± 13	48 ± 15	44 ± 13	46 ± 14
CO (l min ⁻¹)	4.0 ± 1.2	4.1 ± 1.2	3.7 ± 1.0	3.8 ± 1.1
WS (10 ³ dyn cm ⁻²)	342 ± 53	335 ± 87	293 ± 57	326 ± 59
EF (%)	44 ± 8	49 ± 9*	48 ± 8**	49 ± 6*
FS (%)	22 ± 5	25 ± 5*	24 ± 5**	25 ± 3*
VCFmax (lengths s ⁻¹)	1.69 ± 0.25	1.72 ± 0.28	1.81 ± 0.41	1.79 ± 0.27
TPR (dyn s cm ⁻⁵)	2445 ± 915	2234 ± 621	2433 ± 563	2366 ± 569
PEP (ms)	116 ± 14	107 ± 15	103 ± 13	106 ± 14
LVETI (ms)	418 ± 11	416 ± 14	416 ± 13	416 ± 16
PEP/LVET	0.442 ± 0.069	0.393 ± 0.069	0.379 ± 0.056	0.383 ± 0.071
QS ₂ I (ms)	571 ± 4	558 ± 11*	554 ± 9**	555 ± 10**

Abbreviations as in Table 1. Statistics and symbols as in Table 2.

pressure and diameter and is inversely related to ventricular wall thickness (Braunwald, 1984). Changes in left ventricular end-diastolic diameter correlate with changes in left ventricular end-diastolic pressure (Quinones *et al.*, 1976; Gaasch *et al.*, 1976). Thus, left ventricular end-diastolic diameter may be adopted as an indirect measure of preload when evaluating effects of interventions in the same subjects. Afterload, which can be defined as systolic wall stress (Braunwald, 1984), may be determined noninvasively with

echocardiography and systolic blood pressure (Ratshin *et al.*, 1974).

We did not observe any changes in preload or afterload with incremental digoxin doses. Therefore the loading conditions did not affect the echocardiographically determined ejection phase indices or systolic time intervals, a finding that helps to explain the observed effects of digoxin on myocardial contractility. Heart rate was taken into account by using indices of systolic time intervals (Weissler *et al.*, 1968) except

for PEP, which seems to be rate-independent (Cokkinos *et al.*, 1976; Spodick *et al.*, 1984). The effect of heart rate on ejection fraction and fractional shortening is small or negligible. (Hirschleifer *et al.*, 1975; DeMaria *et al.*, 1979; Ricci *et al.*, 1979; Erbel *et al.*, 1984). Velocity of circumferential fibre shortening is also heart rate-dependent (DeMaria *et al.*, 1979).

Effect of digoxin at rest

Digoxin has been shown to increase myocardial contractility of the normal and non-failing heart (Braunwald *et al.*, 1961; Sonnenblick *et al.*, 1966; Crawford *et al.*, 1976; Saito *et al.*, 1979). Ejection fraction and fractional shortening increased in the present study without any changes in loading conditions. Fractional shortening has been shown to be independent of heart rate (DeMaria *et al.*, 1979). Ejection fraction does not depend on heart rate until a rise of 30 beats min^{-1} in pulse frequency (Ricci *et al.*, 1979) or then it decreases by only 1% of the left ventricular volume with each 10 beats min^{-1} rise in heart rate (Erbel *et al.*, 1984). Hence, the increase in fractional shortening and ejection fraction is not due to the fall in heart rate by 10 beats min^{-1} , but to the rise in contractility.

The observed increase in maximal velocity of circumferential fibre shortening from 1.94 ± 0.32 to 2.06 ± 0.23 lengths s^{-1} was insignificant. However, with a decrease in heart rate by 10 beats min^{-1} with digoxin the expected parallel rate-related 5% fall in maximal velocity of circumferential fibre shortening did not appear: the mean velocity of circumferential fibre shortening has been shown to increase by 5% for each 10 beats min^{-1} rise in heart rate (DeMaria *et al.*, 1979). Mean and maximal velocities in circumferential fibre shortening change similarly (Quinones *et al.*, 1976). These findings again suggest that a stimulated inotropic state was achieved with digoxin.

QS₂I decreased with digoxin in a dose-related manner. Other systolic time intervals tended to diminish. Our data concur with previous observations that QS₂I appears to be the most useful of the systolic time intervals when judging the overall effects of inotropic agents (Lewis *et al.*, 1977). The changes in systolic time intervals also proved digoxin to have an inotropic effect on healthy heart.

Effect of digoxin during autonomic blockade

As sympathoadrenergic drive and vagal responses may markedly alter cardiac performance during both rest and stress, we studied the effects of

digoxin on the 'bare' heart, after autonomic blockade. It has been demonstrated that the heart does not respond to moderate autonomic stimulations after used doses of atropine and propranolol (Jose & Taylor, 1969). In spite of autonomic blockade the inotropic effect of digoxin was obvious: heart rate decreased, and neither loading conditions nor ejection phase indices changed when both LVETI and QS₂I were shortened. In accordance with a widely held belief, the enhancement of contractility seems to be a direct effect of digoxin without β -adrenoceptor or vagal mediation (Gillis & Quest, 1979).

Human heart contains α -adrenoceptors both in atrial and ventricular myocardium (Mügge, 1985). Acetylcholinesterase constricts muscular blood vessels and those effects are reversed by phenoxybenzamine, an α -adrenoceptor antagonist, suggesting that digitalis may mediate its vascular effects via α -receptors (Stark *et al.*, 1972). The used autonomic blockade does not rule out that digoxin might also have affected via cardiac α -adrenoceptors when increasing contractility. However, this seems unlikely, since there was no variation in peripheral α -adrenoceptor stimulation determined by unchanged total peripheral vascular resistance.

In our study long-term digitalization seemed to have a direct effect on heart rate since it decreased also during autonomic blockade. To date, the chronotropic effect of digitalis glycosides has been thought to be mediated by the autonomic nervous system (Gillis & Quest, 1979). Digoxin was not reported to change heart rate during long-term treatment in patients with transplanted hearts (Ricci *et al.*, 1978), which, however, are responsive to humoral catecholamines. The heart rate response in this study is unlikely to be mediated by α -adrenoceptors, since their increased activity does not induce constant effects on heart rate (Mügge, 1985; Tung *et al.*, 1985). Stable peripheral vascular resistance also indicated unchanged α -adrenoceptor activity. Consistently with that intravenous digoxin did not change heart rate during autonomic blockade (Treese *et al.*, 1983; Partanen *et al.*, 1986).

The human heart may respond to autonomic stimulations during heavy exercise despite atropine and propranolol in the doses we used (Caruthers *et al.*, 1976). Digitalis glycosides induce vagal stimulation and sympathetic withdrawal (Gillis & Quest, 1979). However, the decrease of heart rate during long-term digoxin administration under autonomic blockade is unlikely to be attributed to the possible incompleteness of the blockade. Autonomic blockade abolished the clear decrease of heart rate seen during intravenous digoxin with intact reflexes (Partanen

et al., 1986). Isometric exercise did not affect heart rate in the present work during autonomic blockade without digoxin as demonstrated before (Martin *et al.*, 1974) proving the sufficiency of the blockade during these interventions.

The reason for the different action on heart rate during autonomic blockade between intravenous and long-term digoxin administration is not known. The mechanism for the decrease in the intrinsic heart rate might be digitalis-induced long-term changes in autonomic nervous system activity (Gillis & Quest, 1979). This occurs in athletes, whose intrinsic heart rate decreases during training (Frick *et al.*, 1967), though digoxin induces no diastolic volume changes in the heart.

Effect of digoxin during handgrip

Digoxin did not induce variation in echocardiographically determined ejection phase indices during handgrip. Since no changes occurred in loading conditions or stroke volume, the shortened LVETI is due to left ventricular stimulation. This effect is consistent with the decrease in QS₂I.

Isometric exercise induces vagal withdrawal and sympathetic stimulation (Martin *et al.*, 1974). Owing to these autonomic reflexes, left ventricular contractility is enhanced during isometric exercise (Grossman *et al.*, 1973; Stefadourous *et al.*, 1974). Heart rate increases with no changes in stroke volume. Blood pressure rises with unchanged total peripheral vascular resistance in healthy subjects (Grossman *et al.*, 1973; Martin *et al.*, 1974; Stefadourous *et al.*, 1974).

The inotropic effect of digoxin was evident at rest but not so clearly discernible during isometric exercise. Improved contractility due to sympathetic activation itself during handgrip may well mask the quantitatively lesser effect of digoxin. Also autonomic reflexes might be weaker during isometric exercise under digoxin. Digoxin decreased heart rate during autonomic blockade by 11% probably by an effect directly on the sinus node. The resting rate fell by 16% after digoxin and by 21% during handgrip. Thus more vagal and less sympathetic stimulation may take place during handgrip with than without digoxin. Such reflexes may be attributed either to the direct effect of digoxin on the autonomic nervous system (Gillis & Quest, 1979) or to increased contractility after digoxin.

Effects of digoxin during handgrip with autonomic blockade

Since autonomic reflexes may modify digoxin-induced changes in contractility during handgrip,

isometric exercise was also performed with autonomic blockade.

A 13% reduction in heart rate confirmed that digoxin has a direct chronotropic effect.

There were no changes in loading conditions. The increase in fractional shortening and ejection fraction thus indicates a rise in myocardial contractility. Maximal velocity of circumferential fibre shortening increased by 6% ($P < 0.05$ in a single paired Student's *t*-test) in contrast to the expected 6% decrease with heart rate reduction of 12 beats min^{-1} (DeMaria *et al.*, 1979). Improved maximal circumferential fibre shortening and shortened QS₂I indicate enhancement in left ventricular performance.

The abolishment of vagal and β -adrenoceptor mediated reflexes during handgrip with autonomic blockade makes the inotropic effect of digoxin obvious, whether measured with ejection phase indices or systolic time intervals. This confirms that these reflexes partly mask the cardiac response to digoxin during static exercise without blockade. It also corroborates the notion that the inotropic effect of digoxin is direct.

Sustained oral use of digoxin increased inotropy during static exercise under autonomic blockade. This is in consistency with our previous results with intravenous digoxin. However, intravenous digoxin did not change intrinsic heart rate at rest or during isometric exercise in contrast to long-term administration of the drug (Partanen *et al.*, 1986).

Conclusions

Our results indicate that digoxin increases left ventricular contractility in intact and pharmacologically blocked hearts both at rest and during isometric exercise. The findings corroborate the view that the inotropic effect of digoxin is direct, without autonomic mediation. The heart rate-slowing effect of digoxin seems to be partly direct, and only partly mediated by the autonomic nervous system. The effect of digoxin is more readily noticed at rest than during isometric exercise. When the heart lacks sympathetic support during static exercise with autonomic blockade the inotropic effect of digoxin becomes clearly evident from both systolic time intervals and from ejection phase indices by echocardiography. The influence of digoxin is dose-related. The most sensitive variable of systolic time intervals when measuring the effects of digoxin seems to be QS₂I.

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