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Evaluation of digitalis in cardiac failure

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Abstract

Ten patients in sinus rhythm with symptomatic cardiac failure participated in a study investigating the value of digitalis at rest and during dynamic exercise. A haemodynamic profile and left ventricular ejection fraction were measured before treatment, after intravenous ouabain, and after six weeks of maintenance treatment with digoxin.

There was no significant change in the haemodynamic profile or in the left ventricular ejection fraction at rest after either glycoside. During exercise there was a

significant reduction in left ventricular filling pressure from 39 ± 3 mm Hg to 34 ± 3 mm Hg ($p < 0.05$) after ouabain and to 33 ± 3 mm Hg ($p < 0.02$) after digoxin. Cardiac index improved from 3.3 ± 0.3 l/min/m² to 4.0 ± 0.4 l/min/m² ($p < 0.01$) after ouabain and to 3.8 ± 0.4 l/min/m² ($p < 0.01$) after digoxin. During exercise stroke volume index and stroke work index also improved significantly with both glycosides. This was accompanied by an increase in left ventricular ejection fraction from $29 \pm 2\%$ to $36 \pm 3\%$ ($p < 0.05$) after ouabain and digoxin.

In this study both intravenous ouabain and maintenance treatment with oral digoxin exerted a modest positive inotropic effect in patients with cardiac failure in sinus rhythm. The haemodynamic benefit, however, was manifest only during exertion.

Introduction

For many years digitalis preparations have been advocated as the principal positive inotropic agents for cardiac failure. Experiments showed a cardiotonic effect, while studies of acute administration confirmed improved myocardial performance.¹⁻⁷ Nevertheless, the translation of these findings into clinical

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benefit in patients receiving maintenance treatment who remain in sinus rhythm has been more controversial. Some reports have suggested continued improvement,⁸⁻¹⁰ while other workers have been less impressed^{11,12}; and the ease with which maintenance treatment can be withdrawn without clinical deterioration has been noted.¹³⁻¹⁵ Thus the role of maintenance treatment with digitalis is still not clear. Moreover, the question of efficacy during exercise has seldom been examined.^{7,10}

We describe the use of digitalis given acutely and as maintenance treatment in 10 patients with chronic cardiac failure. A haemodynamic profile and left ventricular ejection fraction were obtained at rest and during upright dynamic exercise before treatment, after intravenous ouabain, and after six weeks of oral digoxin.

Patients and methods

We studied nine men and one woman aged 42-65 years (mean 51) with class III or IV (NYHA) disability despite diuretics (thiazide in one case; frusemide in the remainder). In seven patients the cardiac failure was caused by coronary disease, and in three it was idiopathic; all were in normal sinus rhythm. None of the patients had been given digitalis before. All patients gave informed consent to the study.

Study design (fig 1)—Control haemodynamic data were obtained at rest and during upright dynamic exercise using a bicycle ergometer.

FIG 1—Study design. Haemodynamic data and left ventricular ejection fraction measured at rest (open columns) and during dynamic exercise (shaded columns) after intravenous ouabain and after six weeks' maintenance with oral digoxin.

The level of exercise achieved (25-75 watts) permitted three to five minutes of exercise and was identical for each patient at each phase of the study. Measurements were repeated at rest and during exercise 30-60 minutes after intravenous ouabain (0.5 mg). Patients were then given oral digoxin for six weeks and the study repeated. The dose of digoxin was adjusted to maintain the plasma concentration within the therapeutic range (1.3-2.6 nmol/l; 1.0-2.0 ng/ml). Patients continued with their diuretic treatment throughout the study, but no other cardioactive drug was prescribed.

Haemodynamic measurements—Heart rate was measured from the electrocardiogram and arterial blood pressure by sphygmomanometer. A flow-directed thermodilution catheter was inserted to give pulmonary arterial and wedge pressures. Left ventricular filling pressure was accepted as mean pulmonary capillary wedge pressure or pulmonary artery diastolic pressure. Cardiac output was measured in triplicate by thermodilution. The following calculations were used: cardiac index (cardiac output/body surface area; l/min/m²); stroke volume index (cardiac index/heart rate; ml/m²); mean arterial pressure ((one-third pulse pressure)+diastolic pressure; mm Hg); left ventricular systolic mean pressure ((two-thirds pulse pressure)+diastolic pressure; mm Hg); left ventricular stroke work index (stroke volume index × (left ventricular systolic mean pressure—left ventricular filling pressure) × 0.0136; g m/m²); total vascular resistance ((mean arterial pressure/cardiac output) × 80; dyn/s/cm⁵).

Radionuclide ventriculography—Radionuclide left ventriculography was performed after sequential in-vivo red-cell labelling with 20 mCi ^{99m}Tc Pyrolite. Equilibrium data were obtained in the modified left anterior oblique projection using an IGE Maxi Camera interfaced to a Varian 620L computer. Data were acquired in list mode and 16 frames per cardiac cycle reconstructed using a 32 × 32 matrix with about 200 000 counts per frame. Global left ventricular ejection fraction was calculated using a series of algorithms based on contouring validated in our laboratory. Left ventricular ejection fraction so calculated correlated closely with that obtained at contrast angiography (r=0.90; n=63), is relatively free from observer variation, and is reproducible at rest and on exercise.

Statistical analysis was by Student's paired *t* test. Differences were taken as significant at *p*<0.05. Results are expressed as means ± SEM.

Results

Resting haemodynamic data (table I)—Control left ventricular filling pressure was 19 ± 2.6 mm Hg and was not influenced by intravenous ouabain or oral digoxin. Cardiac index was 2.0 ± 0.2 l/min/m² before treatment and was also unchanged by acute or maintenance digitalis treatment. The calculated measurements of stroke volume index, stroke work index, and systemic vascular resistance were unchanged, and left ventricular ejection fraction was 33 ± 2.7% during the control period, 32 ± 2.3% after ouabain, and 35 ± 2.3% after digoxin. Thus the glycoside did not significantly alter the resting haemodynamic profile.

Exercise haemodynamic data (table II) were obtained in eight patients (two were unable to sustain exercise to permit data acquisition).

TABLE I—Resting haemodynamic data (values are means ± SEM)

	Control	Ouabain	Digoxin
Heart rate (beats/min)	69 ± 3.6	67 ± 2.7	67 ± 2.9
Mean arterial pressure (mm Hg)	89 ± 3.1	88 ± 3.5	91 ± 3.2
Left ventricular filling pressure (mm Hg)	19 ± 2.6	17 ± 1.8	18 ± 1.8
Cardiac index (l/min/m ²)	2.0 ± 0.2	2.1 ± 0.1	2.0 ± 0.1
Stroke volume index (ml/beat/m ²)	29 ± 3	32 ± 2	29 ± 2
Total systemic resistance (dyn/s/cm ⁵)	2080 ± 200	1849 ± 84	2121 ± 129
Stroke work index (g m/m ²)	35 ± 4.2	38 ± 3.6	35 ± 3.2
Left ventricular ejection fraction (%)	33 ± 2.7	32 ± 2.3	35 ± 2.3

TABLE II—Exercise haemodynamic data (values are means ± SEM)

	Control	Ouabain	Digoxin
Heart rate (beats/min)	125 ± 8.6	120 ± 7.3	122 ± 4.5
Mean arterial pressure (mm Hg)	109 ± 4.5	111 ± 3.3	120 ± 8.0
Left ventricular filling pressure (mm Hg)	39 ± 3.2	34 ± 2.6*	33 ± 3.4**
Cardiac index (l/min/m ²)	3.3 ± 0.3	4.0 ± 0.4***	3.8 ± 0.4***
Stroke volume index (ml/beat/m ²)	27 ± 2	33 ± 3***	31 ± 3*
Total systemic resistance (dyn/s/cm ⁵)	1460 ± 112	1291 ± 131	1416 ± 140
Stroke work index (g m/m ²)	36 ± 4.7	47 ± 5.6***	49 ± 8.2***
Left ventricular ejection fraction (%)	29 ± 1.7	36 ± 2.9*	36 ± 3.1**

Compared with control: **p*<0.05; ***p*<0.02; ****p*<0.01.

Heart rate and mean arterial pressure were unchanged by ouabain and digoxin. Left ventricular filling pressure fell significantly from 39 ± 3.2 mm Hg to 34 ± 2.6 mm Hg (13%) with ouabain and to 33 ± 3.4 mm Hg (15%) with digoxin. Cardiac index increased significantly from 3.3 ± 0.3 l/min/m² to 4.0 ± 0.4 l/min/m² (21%) after ouabain and to 3.8 ± 0.4 l/min/m² (15%) after digoxin. Stroke work index increased significantly from 36 ± 4.7 g m/m² to 47 ± 5.6 g m/m² (31%) with ouabain and to 49 ± 8.2 g m/m² (36%) with digoxin. Figures 2 and 3 show the relation between change in left ventricular filling pressure and stroke work index in individual patients. An increase in stroke work index with a concomitant fall in left ventricular filling pressure during exercise indicating improved left ventricular performance occurred in six of the eight patients after both ouabain and digoxin. These changes were accompanied by a significant increase in ejection fraction from 29 ± 1.7% to 36 ± 2.9% with ouabain and to 36 ± 3.1% with digoxin. Systemic vascular resistance was unchanged.

Discussion

Despite experiments on isolated heart muscle and intact hearts showing the inotropic effect of digitalis, the ability of glycosides to improve cardiac performance remains controversial. Our data suggest that digitalis may improve cardiac function but that this may be manifest only during dynamic exercise, an aspect of digitalis seldom mentioned.^{7,10} The haemodynamic response to treatment at rest was variable and no clear benefit could be detected, which agrees with other studies.^{11,12,16} On exercise, however, left ventricular filling pressure fell, cardiac

index increased, and stroke work index increased. These changes occurred after acute ouabain administration, were maintained with oral digoxin, and suggest an improvement in left ventricular function. This improvement was apparently mediated by improved contractility. Since systemic vascular resistance and arterial pressure were unchanged, alteration in impedance to left ventricular outflow was probably not responsible. Left ventricular filling pressure fell; hence it is unlikely that the increase in stroke volume was related to an increase in preload. Of the three determinants of stroke volume

FIG 2—Comparison of changes in left ventricular filling pressure and stroke work index during exercise after intravenous ouabain. Concomitant fall in left ventricular filling pressure and increase in stroke work index indicating improved left ventricular performance occurred in six of eight patients.

FIG 3—Comparison of changes in left ventricular filling pressure and stroke work index during exercise after maintenance with digoxin. Concomitant fall in left ventricular filling pressure and increase in stroke work index occurred in same six of eight patients as in fig 2.

(impedance to left ventricular outflow, preload, and contractility), probably increased contractility was responsible for the observed increase in stroke volume. This is supported by the significant increase in left ventricular ejection fraction. The reduction in left ventricular filling pressure may also be explained by augmented stroke volume resulting in a reduction in left ventricular end-diastolic volume. Digitalis, however, may reduce venous tone,¹⁷ so that venous pooling may have been partly responsible.

Improved left ventricular performance did not occur in all patients: an increase in stroke work index with a concomitant fall in left ventricular filling pressure during exercise occurred in six of the eight patients (figs 2, 3). This contrasts with the study of Arnold *et al.*¹⁰ in which the glycoside produced a uniform improvement in left ventricular function. In that study patients with class IV symptoms were excluded, possibly eliminating a group of patients who do not respond to digoxin.

There was also a discrepancy between subjective symptoms and haemodynamic profile, which has been noted before.¹⁸ Despite the overall improvement in haemodynamics during exercise there was no consistent improvement in symptoms, five patients having a reduction in effort dyspnoea and the remainder being unchanged.

Perhaps the strongest indictment of the failure of digoxin is the ease with which it can be withdrawn without clinical deterioration.¹³⁻¹⁵ Nevertheless, the indications for long-term treatment in these heterogeneous populations were variable and in some may have been inappropriate. Some patients did indeed develop acute cardiac failure after digoxin withdrawal, while some required alteration in diuretic treatment.

Our purpose was to investigate the haemodynamic effect of introducing and maintaining glycoside treatment in patients with established left ventricular dysfunction. Although the number of patients studied was small and the results somewhat variable in individual patients, left ventricular performance improved in most during exertion. These results therefore suggest that in chronic cardiac failure digoxin is appropriate and should not be withheld.

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