Hemodynamic Effects of Digoxin on Congestive Heart Failure in Old Myocardial Infarction, Dilated Cardiomyopathy, Acute Myocardial Infarction and Mitral Stenosis

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SUMMARY

The hemodynamic effects of digoxin (0.01 mg/Kg) on congestive heart failure were compared in 32 patients with old myocardial infarction (OMI) (n=9), dilated cardiomyopathy (DCM) (n=10), acute myocardial infarction (AMI) (n=5) and mitral stenosis (MS) (n=8).

The responses of heart rate (HR) and pulmonary capillary pressure (PCP) to digoxin in OMI, DCM and MS were marked but different in each of these groups and no significant changes were found in patients with AMI. The responses of cardiac index (CI) to digoxin in patients with OMI and DCM in whom left ventricular myocardial contractile force was impaired were divided into 2 groups (Group 1: CI increased more than 15% and Group 2: less than 15%). In Group 1, both CI and percent fractional shortening (%FS) before digoxin administration were lower than in Group 2, i.e., 1.97 ± 0.27 vs 2.80 ± 0.48 L/min/m² ($p < 0.001$) and 10.9 ± 8.0 vs $19.5 \pm 11.9\%$ ($p < 0.05$), respectively. In MS, CI increased after digoxin administration only in the 2 patients with low CI and rapid HR in the control state.

These results indicate that the mode of hemodynamic response to digoxin is considerably different in various diseases. They further suggest that digoxin should not be used in the early phase of AMI, although digoxin was of great clinical benefit in patients with OMI and DCM through such mechanisms as its positive inotropic and negative chronotropic effects and lowering of PCP.

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DIGITALIS glycosides have been used in the therapy of congestive heart failure for the more than 200 years since the report of Withering and continue to be recognized as extremely useful drugs. The postulated mechanism of the hemodynamic effects of digitalis on congestive heart failure is still based upon study results obtained more than 10 years ago. These studies involved acute observations from 30 to 120 min after intravenous administration of digitalis. However, there are some problems that remain unsolved, e.g., whether digitalis is effective in acute myocardial infarction and mitral stenosis and whether digitalis can necessarily increase cardiac index in congestive heart failure.¹⁾

The hemodynamic responses are now easily observed over a longer period of time using a Swan-Ganz thermodilution catheter. However, except in cases of acute myocardial infarction and circulatory shock,²⁾⁻⁶⁾ there have been few reports on the hemodynamic effects of digitalis in recent years. Marked progress has been made in the drug treatment of congestive heart failure since diuretics and vasodilator drugs have been employed. Accordingly, the indication for the use of digitalis in the treatment of congestive heart failure is now more strictly defined.

To clarify these problems and to decide on appropriate indications for the use of digitalis, we compared the hemodynamic responses to digoxin of patients with congestive heart failure secondary to old myocardial infarction, dilated cardiomyopathy, acute myocardial infarction and mitral stenosis.

METHODS

Thirty-two patients with congestive heart failure of NYHA functional classes II-IV were studied. There were 23 men and 9 women with a mean age of 55 years, ranging from 27 to 82 years. The etiology of congestive heart failure was either old myocardial infarction (OMI) (n=9), dilated cardiomyopathy (DCM) (n=10), acute myocardial infarction (AMI) (n=5) or mitral stenosis (MS) (n=8). Myocardial infarction was documented by a history of characteristic chest pain, the development of pathologic Q waves on the ECG and an increase in creatine phosphokinase. AMI and OMI were defined as those cases where the period from the onset of attack was within 3 days and 1 month or more, respectively. DCM was diagnosed on the basis of its typical clinical course in the absence of any other heart diseases based upon echocardiography, coronary arteriography and myocardial biopsy. The diagnosis of MS was confirmed by echocardiography and no MS patient had any other valvular disease. Atrial fibrillation was present in a DCM case and all MS cases. None of the 32 patients had been given digitalis

before. The administration of diuretics and vasodilator drugs was stopped for 24 hours before the study.

Hemodynamic measurements: Before the study, echocardiographic parameters such as left ventricular end-diastolic dimension (LVDD), left ventricular end-systolic dimension (LVDs) and fractional shortening (%FS) were measured. After informed consent had been obtained, a Swan-Ganz triple lumen thermodilution catheter was inserted via the cubital vein and its tip was positioned in the pulmonary artery. Cardiac output was measured by computer model 9520 and determined in triplicate. Heart rate (HR) was measured by ECG and blood pressure (BP) by sphygmomanometer. Pulmonary capillary pressure (PCP) and right atrial pressure (RAP) were measured with

Fig. 1. Response of pulmonary capillary pressure to digoxin in 6 patients.

Fig. 2. % change of heart rate and pulmonary capillary pressure by digoxin administration.

Table I. Hemodynamic Responses to Intravenous Digoxin in (OMI), Dilated Cardiomyopathy (DCM), Acute My-

	OMI			DCM	
	C	2	24	C	2
HR (beats/min)	93.6±22.0	83.2±13.0†	81.4±18.8*	102.6±16.0	87.2±12.0†
Systolic BP (mmHg)	118.1±13.1	113.7±16.1	110.6±12.8	114.6±46.2	133±27.9
Diastolic BP (mmHg)	77.4±7.9	76.3±10.5	75±6.9	82±11.1	83±15.4
PCP (mmHg)	24±3.9	19.2±5.4*	16.2±4.8*	24.5±7.8	17.2±3.9*
CI (L/min/m ²)	2.40±0.61	2.52±0.40	2.42±0.41	2.58±0.58	2.48±0.41
SVI (ml/beats/m ²)	26.5±9.6	30.5±5.9	31.0±9.3	25.7±6.1	30.2±5.1†
SVWI (gm·m/m ²)	27.1±6.4	32.1±9.3	34.1±13.7	25.2±7.8	34.1±10.9†
SVR (dynes·sec·cm ⁻⁵)	2223±836	2017±544	2041±683	1944±522	2079±484

Values are expressed as mean±SD.

Abbreviations: C=control; HR=heart rate; BP=blood pressure; PCP=pulmonary capillary pressure; CI=cardiac index; SVI=stroke volume index; SVWI=stroke volume work index;

a Siemens 746 transducer and recorded on a Siemens mingograph. Hemodynamic values were calculated using standard formulas. Mean BP (mBP) was calculated from the formula $1/3 (sBP - dBP) + dBP$ mmHg, stroke volume index (SVI) was CI/HR ml/m², stroke volume work index (SVWI) was calculated from the formula $(sBP - PCP) \times SI \times 1.36/100$ gm·m/m². Systemic vascular resistance (SVR) was derived from the formula $BP \times 80/CI$ dynes·sec·cm⁻⁵.

Protocol: After control hemodynamic measurements were obtained, digoxin 0.01 mg/Kg was administered intravenously for 10 min and hemodynamic measurements were carried out at 1, 2, 4 and 24 hours after the administration. Thereafter, digoxin 0.05 mg/Kg p.o. was administered every 24 hours. In 6 patients (2 with OMI, 2 with DCM and 2 with MS), further measurements were made 48 and 72 hours after drug administration.

Statistical analysis was performed using Student's paired t-test.

RESULTS

As a preliminary study, we observed the hemodynamic effects of digoxin in 6 patients (2 with OMI, 2 with DCM, 2 with MS) for 72 hours after its administration. PCP was lowered during the first 24 hours after drug administration but thereafter no significant change was found and the response in patients with MS was different from that in other diseases during the first 24 hours (Fig. 1). Based upon these results, we compared the hemodynamic changes in patients with various diseases associated with congestive heart failure in the 24 hour period after digoxin administration.

Congestive Heart Failure Due to Old Myocardial Infarction
Myocardial Infarction (AMI) and Mitral Stenosis (MS)

	AMI			MS		
24	C	2	24	C	2	24
88.5±12.7*	113.4±17.1	111.8±15.4	111.3±17.2	99.9±24.7	80.4±21.0*	84.3±19.0*
126.1±23.6	120.5±9.3	121.5±10.0	120±18.8	123.5±21.9	120.8±17.4	114.8±18.1
79.8±9.8	89.2±7.2	88±10.3	85.2±13.2	80.5±7.7	79.1±8.0	74.3±9.8
16.1±4.9*	20.6±5.2	18±6.4	17±5.6	20.9±4.5	16.5±5.6*	16.6±4.8*
2.57±0.48	2.90±1.06	2.96±1.06	2.81±1.08	2.25±0.40	2.23±0.37	2.38±0.26
29.3±5.5†	25.7±9.2	26.7±9.0	25.4±9.4	24.0±8.9	29.2±11.8†	28.7±6.9†
32.3±6.6*	28.1±6.4	30.4±5.4	27.4±5.6	25.4±10.8	31.6±14.9†	29.2±9.1†
1985±523	1872±700	1823±631	1872±704	2338±532	2271±397	1945±202

SVR=systemic vascular resistance.

† $p < 0.05$, * $p < 0.005$.

2, 24=2 and 24 hours after i.v. digoxin.

Hemodynamic responses to digoxin in each disease group are shown in Table I and Fig. 2. HR (beats/min) significantly decreased at 2 hours from 93.6 ± 22.0 to 83.2 ± 13.0 in OMI, from 102.6 ± 16.0 to 87.2 ± 12.0 in DCM and from 99.9 ± 24.7 to 80.4 ± 21.0 in MS and a further reduction was found at 24 hours to 81.4 ± 18.8 in OMI and to 88.5 ± 12.7 in DCM, but in MS, on the contrary, a slight elevation to 84.3 ± 19.0 was found.

There were no significant changes in systolic and diastolic blood pressure in these disease groups. PCP (mmHg) was decreased significantly at 2 hours from 24 ± 3.9 to 19.2 ± 5.4 in OMI, from 24.5 ± 7.8 to 17.2 ± 3.9 in DCM and from 20.9 ± 4.5 to 16.5 ± 5.6 in MS and at 24 hours it further decreased to 16.2 ± 4.8 in OMI, and to 16.1 ± 4.9 in DCM, but no further reduction was found in MS. In terms of these parameters, no significant change was demonstrated in AMI at either 2 or 24 hours after digoxin administration. CI was not significantly increased in any disease group at either 2 or 24 hours. SVI and SVWI were significantly increased in DCM and MS at both periods although no significant change was found in OMI and AMI. No significant change in SVR was found in any disease group at either period.

According to the summarized data, no significant change in CI was demonstrated as mentioned above. However, when looking at individual cases, it was noted that there were cases with and other without digoxin induced changes in CI. Therefore, patients with OMI and DCM, where the mechanism of heart failure is due to impaired left ventricular contractile force were divided into 2 groups. Group 1 consisted of 7 patients in whom CI increased by 15% or more at 2 hours after digoxin administration and Group 2 consisted of 12 patients in whom CI increased by less than 15% at the same

Table II. Comparison of Clinical Features, Hemodynamic Parameters and Echocardiographic Parameters in Responders (Group 1) and Non-responders (Group 2) to Intravenous Digoxin

	Group 1		Group 2	
Number of patients	7		12	
Old Myocardial Infaction	5		4	
Dilated Cardiomyopathy	2		8	
NYHA IV	4		4	
III	2		7	
II	1		1	
Hemodynamic parameters	control	after 2 hours	control	after 2 hours
HR (beats/min)	100.3±18.1	90.3±10.0	96.9±19.9	80.4±13.0
Systolic BP (mmHg)	111.4±17.7	116.6±16.5	121.8±22.5	128.1±28.0
Diastolic BP (mmHg)	77.1±7.6	81.1±10.7	81.4±10.8	79.1±15.1
PCP (mmHg)	25.9±5.9	20.3±5.1	23.3±6.2	16.9±4.1
CI (L/min/m ²)	1.97±0.27	2.46±0.37	2.80±0.48*	2.52±0.42
SVI (ml/beats/m ²)	19.8±2.8	26.9±2.0	29.7±7.3*	32.3±5.7
SVWI (gm·m/m ²)	18.2±3.6	28.2±4.8	30.8±10.0*	36.0±11.2
SVR (dynes·sec·cm ⁻⁵)	2701±576	2268±381	1712±435*	1922±530
Echocardiographic Parameters				
LVDD (mm)	62.6±7.3		70.0±8.0	
LVDs (mm)	55.8±8.0		55.8±9.9	
%FS (%)	10.9±8.0		19.5±11.9†	

Values are expressed as mean±SD.

Abbreviations: same as Table I.

LVDD=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; %FS=fractional shortening.

† $p<0.05$
* $p<0.005$] compared between control in Groups 1 and 2.

period. In these 2 groups, clinical features and hemodynamic and echocardiographic parameters were compared (Table II).

CI before digoxin administration was lower in Group 1 than that in Group 2 (1.97 ± 0.27 vs 2.80 ± 0.48 L/min/m², $p<0.05$). After digoxin administration CI increased to 2.46 ± 0.48 L/min/m² in Group 1, while it decreased to 2.52 ± 0.42 L/min/m² in Group 2. PCP, on the other hand, decreased to nearly the same level in both groups (Fig. 3). SVI, SVWI and %FS before digoxin administration in Group 1 were significantly lower than those in Group 2, while SVR in Group 1 was higher than that in Group 2 ($p<0.001$). In other hemodynamic and echocardiographic parameters, no significant difference was found between the 2 groups. The severity of heart failure expressed by NYHA functional classification was greater in Group 1 than in Group 2. In MS, CI increased after digoxin administration in only 2 cases whose HR were markedly increased and CI were markedly decreased

Fig. 3. Response of cardiac index and pulmonary capillary pressure to digoxin in patients with old myocardial infarction and dilated cardiomyopathy.

Fig. 4. Response of cardiac index and heart rate to digoxin in patients with mitral stenosis.

at baseline (Fig. 4).

The serum digoxin level was determined by radioimmunoassay in all patients after 24 hours of digoxin administration and was in the therapeutic range with levels of between 0.22 and 1.46 ng/ml (mean, 0.72 ± 0.35 ng/ml).

DISCUSSION

In AMI, no significant changes in hemodynamic parameters were revealed after digoxin administration. Three mechanisms to explain the lack of responsiveness to digoxin have been proposed as follows: (1) Tennant and

Wiggers implicated the paradoxical wall motion in the infarcted area.⁷⁾ Langley et al, more recently, pointed out the considerable amount of "wasted work" due to the paradoxical wall motion.⁸⁾ Digitalis may augment the contractility of the non-infarcted myocardium but such effect is cancelled out by the paradoxical wall motion of the infarcted area. (2) Circulating catecholamine is increased in the early stage of acute myocardial infarction.^{9),10)} This causes an increase in the contractility of the non-infarcted myocardium and in such a situation further augmentation of contractility by digoxin may not be expected. (3) Myocardial depressant factor (MDF) may play an important role in suppressing the myocardial contractility,¹¹⁾ whereby the action of digoxin may be equivocal. Since such a mechanism, if present, persists very briefly during the early phase of AMI, digoxin is considered to be effective several days after the onset of AMI. In addition, as other reports have suggested that digitalis augments serum CPK and increases mortality in patients with AMI,^{12),13)} it is advisable that digoxin not be used during the early phase of AMI.

The effect of digoxin on HR was most prominent in MS compared with other diseases, although its effect on PCP was small. An increase in CI was found in only 2 MS patients with rapid HR and low CI at baseline. In these 2 cases, digoxin resulted in the prolongation of diastole and thus augmented left ventricular filling volume and CI. In the other 6 MS cases whose CI did not increase, HR and PCP were reduced slightly. All MS cases exhibited atrial fibrillation. Previous reports have presented little evidence of a beneficial effect of digitalis in pure MS patients with normal sinus rhythm and it was suggested that digitalis might be harmful to such patients.¹⁴⁾ We observed the hemodynamic effects of digoxin according to the same protocol in 2 cases with pure MS and normal sinus rhythm who were in NYHA class I with normal CI and demonstrated that digoxin did not increase CI but decreased PCP and HR similar to the response in patients with atrial fibrillation.

The most significant improvement of various hemodynamic parameters was found in patients with DCM and OMI, in whom left ventricular contractile force was decreased, but CI was not necessarily increased. These results are in agreement with several other reports. Data reviewed by Selzer and Malmberg from all studies before 1962 revealed that in two thirds of 132 patients, digoxin increased CI but in the remaining one third, no beneficial effect was demonstrated.¹⁵⁾ They could not find any difference in the response to digoxin between the 2 groups, i.e., the group with increased CI and the group without increased CI. We also compared the hemodynamic parameters and clinical features of these 2 groups. CI and %FS before digoxin

administration in the former group was significantly lower than those in the latter group. Therefore, the improvement of left ventricular function due to digoxin administration in the former group was probably caused by the enhancement of myocardial contractility which is a well-known cardiac effect of digoxin. In the latter group, on the other hand, digoxin reduced PCP without increasing CI. Regarding its mechanism in this group, it was suggested that the vasoconstrictive effect of digoxin on veins, especially the hepatic vein, induced blood pooling in the portal venous system, which resulted in diminished venous return.¹⁶⁾ We could not differentiate between groups by their clinical features. However, in all patients in NYHA class IV (4 pts in each group), digoxin administration improved symptoms such as orthopnea and nocturnal dyspnea. Therefore, it was postulated that digoxin improved the clinical features as a result of its ability to lower PCP and an increase in CI was not necessarily needed.

In summary, we concluded the following.

1. Clinical use of digoxin is not advisable in the early phase of AMI.
2. In MS, digoxin reduced HR and PCP through its negative chronotropic effect and its effect was more pronounced in cases with markedly increased HR.
3. In DCM and OMI, digoxin increased CI only in cases with markedly lowered CI and %FS, but reduced PCP in all cases.

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