Hemodynamic Response to Acute Intravenous Digoxin in Patients with Recent Myocardial Infarction and Coronary Insufficiency with and without Heart Failure*

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Intravenous digoxin was administered to 12 patients, ten with acute myocardial infarction and two with acute coronary insufficiency. Six patients had clinical failure and six did not. There was no beneficial hemodynamic response in the group without heart failure and only slight response in the group with mild to moderate heart failure. No significant rise in cardiac index or fall in pulmonary artery end-diastolic pressure occurred in either group. Maintenance digoxin therapy did not prevent the development of heart failure in two patients. A significant incidence of ventricular dysrhythmias occurred. The limited hemodynamic response in patients with heart failure may be due to the systemic vascular effects of digoxin, high levels of circulating catecholamines, and altered properties of the acutely ischemic or infarcted myocardium. The prophylactic use of digitalis glycosides in uncomplicated myocardial infarction cannot be advocated. Modifications are suggested in the indications for, and dose regimens of cardiac glycosides in heart failure complicating myocardial infarction.

Although well defined in the treatment of left heart failure and atrial dysrhythmias, the role of digitalis glycosides in the management of patients with acute myocardial infarction remains uncertain. Clinical studies report that therapeutic doses given rarely have toxic effects. The hemodynamic evaluation of digitalis has been limited, and although the response in the uncomplicated patient with acute myocardial infarction has been defined, the effects of administering digitalis when significant myocardial depression complicates myocardial infarction is less well established.

The following study was designed to assess the hemodynamic response to digoxin administered intravenously as a single dose to patients with acute coronary heart disease. Two groups of patients were considered, one with definite clinical left ventricular failure and the other without. The prophylactic value of maintenance digoxin therapy to prevent the development of clinical heart failure in the latter group was investigated.

**Material and Methods**

*Patients:* Twelve patients were studied, ten of whom had sustained a recent myocardial infarction as defined by history, serum enzymes and typical electrocardiographic changes; the remaining two patients were diagnosed as having acute coronary insufficiency since episodes of prolonged cardiac pain were associated with ST segment depression in the precordial ECG leads, but without any detectable serum enzyme abnormality.

The mean age of the patients was 63.6 years (range from 48 to 78 years); eight were men and four women. Six patients, mean age 68 years, were in left ventricular failure at the time of study, as characterized by persistent rales at the lung bases, audible left ventricular third heart sounds and
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cardiomegaly as shown on chest x-ray film; five were in sinus rhythm, and the remaining patient was in atrial fibrillation. Six other patients, whose mean age was 62 years, were not in cardiac failure either clinically or radiographically, and all but one had a normal-sized heart on chest x-ray examination.

All patients were investigated in the myocardial infarction research unit within 12 hours of their admission to the coronary care unit. The average duration between onset of the acute episode which precipitated admission and the hemodynamic studies was 22 hours.

Methods: Under local anesthesia a No. 5 French flow-directed balloon catheter was inserted into the right or left antecubital vein and advanced without fluoroscopy into the pulmonary artery. A fine Teflon catheter (inner diameter 1.1 mm) was inserted into the corresponding brachial artery for monitoring arterial pressure.

Table 1—Myocardial Infarction, Mean Hemodynamic Responses to Intravenous Digoxin in the Presence and Absence of Heart Failure

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>No Heart Failure</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Heart rate</td>
<td>83</td>
<td>78</td>
</tr>
<tr>
<td>±7.4</td>
<td>±7.6</td>
<td>±7.1</td>
</tr>
<tr>
<td>Mean</td>
<td>118</td>
<td>118</td>
</tr>
<tr>
<td>±8.5</td>
<td>±7.7</td>
<td>±6.5</td>
</tr>
<tr>
<td>Mean PABP</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>±1.6</td>
<td>±2.0</td>
<td>±2.0</td>
</tr>
<tr>
<td>PA EDP</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>±1.2</td>
<td>±4.4</td>
<td>±1.1</td>
</tr>
<tr>
<td>CI</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>±0.29</td>
<td>±1.9</td>
<td>±1.4</td>
</tr>
<tr>
<td>SI</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>±2.9</td>
<td>±2.2</td>
<td>±8.6</td>
</tr>
<tr>
<td>SVR</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>±6.1</td>
<td>±5.5</td>
<td>±5.9</td>
</tr>
<tr>
<td>LVMW1</td>
<td>5.7</td>
<td>5.4</td>
</tr>
<tr>
<td>±0.67</td>
<td>±0.41</td>
<td>±0.64</td>
</tr>
<tr>
<td>LVSWI</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>±8.7</td>
<td>±9.1</td>
<td>±4.6</td>
</tr>
<tr>
<td>TTI</td>
<td>3419</td>
<td>3197</td>
</tr>
<tr>
<td>±300</td>
<td>±331</td>
<td>±369</td>
</tr>
</tbody>
</table>

Abbreviations:
C—Control
30, 60—30 and 60 minutes after IV digoxin
BP—Blood pressure mm Hg
PA—Pulmonary artery
EDP—End-diastolic pressure
CI—Cardiac index L/min/m²BSA
SI—Stroke index ml/m²
SVR—Systemic vascular resistance, units
LVMW1—Left ventricular minute work index kg-m/min/M²
LVSWI—Left ventricular stroke work index gm-m/M²
TTI—Tension time index mm Hg-sec/min

Degree of significance is indicated by the following:
*p < 0.005  +p < 0.01  #p < 0.025  Mean values ± standard error of the means are given.

Paired t test was used in defining significant response from control at 30 and 60 minutes. The hemodynamic data of the two control groups were compared using the t test.

RESULTS

The table depicts the mean values and standard errors of the mean in the two groups of six patients, with and without clinical heart failure. Comparison of the mean control values indicates significantly reduced stroke index and increased heart rate, mean and end-diastolic pulmonary arterial pressure in those patients with clinical heart failure. Although mean cardiac index, left ventricular minute and stroke work indices were lower and systemic vascular resistance higher in this group, the differ-

*Detailed individual results are available on request to the authors.
ences were not statistically significant at the 5 percent level.

**Comparison of Response to Digoxin within the Two Groups:** The results are depicted in the table indicating mean values, standard errors of the mean and degree of significance as determined by the Student t test for paired samples.

**Heart Rate:** A significant fall in heart rate occurred both at 30 and 60 minutes in the group of patients without clinical heart failure \( (P < 0.025) \). Mean heart rate remained unchanged in the other group.

**Cardiac and Stroke Indices:** No significant change in cardiac or stroke indices occurred in either group following digoxin administration.

**Mean Systemic Arterial Blood Pressure:** Systemic blood pressure rose at 30 minutes \( (P < 0.025) \), remained elevated at 60 minutes \( (P < 0.005) \) in those patients with clinical heart failure. No significant changes occurred in the nonfailure group.

**Pulmonary Arterial Pressure:** No significant changes occurred in mean and diastolic pulmonary arterial pressures in either clinical group, although these parameters tended to fall at 30 minutes in the clinical failure group of patients.

**Systemic Vascular Resistance:** Mean systemic vascular resistance became further elevated in the group of patients with clinical failure \( (P < .01) \) 30 minutes after digoxin administration, and subsequently returned to the control value at 60 minutes.

**Left Ventricular Work Indices:** An increase in both LVMWI and LVSWI was calculated for the group of patients with clinical heart failure caused largely by the associated increase in systemic arterial blood pressure.

**Tension-Time Index:** This did not change significantly in either group. In those patients with cardiac failure, its constancy resulted from the associated fall in ejection time, whereas the reduction in tension-time index in patients without clinical heart failure was due primarily to a fall in heart rate.

**Acute Coronary Insufficiency (Two Patients):** The following minimal changes followed digoxin administration. Pulmonary arterial diastolic pressure increased from 18 to 22 mm Hg 30 minutes after intravenous digoxin in the patient in heart failure associated with a slight fall in cardiac index and a slight rise in systemic vascular resistance. The second patient only developed slowing of the heart rate.

**Toxicity:** Three patients developed ventricular dysrhythmias. In one, short runs of ventricular tachycardia were recorded 20 minutes following administration of digoxin; he was not in cardiac failure, and the serum potassium level was 3.7 mEq/L. The second patient who also was not in cardiac failure and whose serum potassium level was 3.8 mEq/L developed frequent premature ventricular beats during the study, and the third patient developed a short episode of ventricular tachycardia one hour after completing the study. This last patient had clinical evidence of heart failure and was receiving diuretic therapy at the time of study. The level of the serum potassium was 4.0 mEq/L immediately prior to the investigation.

**Late Follow-Up:** Of the six patients without heart failure at the time of study, two developed clinical failure over the ensuing 48 hours without evidence of either extension of the infarct or significant dysrhythmia. Both were receiving 0.25 mg of digoxin per day as maintenance therapy.

**DISCUSSION**

Direct left ventricular filling pressure is a useful parameter following myocardial infarction but usually requires retrograde arterial catheterization of the aortic valve. A reasonable approximation of this pressure may be given by pulmonary arterial diastolic pressure. When LVEDP is raised, a pulmonary arterial 'a' wave can frequently be defined (in sinus rhythm) and correlated well with LV filling pressure unless the pulmonary vascular resistance is elevated. In the presence of a heart rate exceeding 124 beats per minute, however, Bouchard and co-workers have shown that the PA diastolic pressure correlates poorly with direct LVEDP especially when LV dysfunction is present. Their study was not, however, performed in patients with acute myocardial infarction, and furthermore the heart rate was never more than 120 beats per minute in the patients of the present series. In the single patient with atrial fibrillation, PA diastolic pressure was averaged over 15 beats and compared with an immediately consecutive pulmonary arterial "wedge" pressure to obtain an approximation of LV filling pressure.

Hemodynamic studies in patients with uncomplicated acute myocardial infarction have not demonstrated any significant acute circulatory improvement. Our study is in keeping with this conclusion. With the exception of a fall in heart rate which may have been due to parasympathetic stimulation, no significant change in the measured hemodynamic parameters was induced by digoxin. One patient (No. 8) (Fig 1) did, however, develop marked elevation in left ventricular filling pressure which was associated with a rise in systemic vascular resistance and a fall in cardiac index. These changes may reflect the significant effect of digoxin on the peripheral circulation; the resultant increase
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In the present series of patients with left ventricular failure, significant increases were produced in systemic blood pressure and vascular resistance and also in left ventricular stroke and minute work indices. In contrast to the group of patients without cardiac failure, heart rate remained unaltered, and pulmonary arterial end-diastolic pressure fell slightly at 30 minutes. No significant alteration in systemic tension-time index occurred despite the rise in systemic blood pressure. Maintenance of the cardiac output and fall in left ventricular filling pressure in spite of a rise in afterload could well reflect some improvement in overall myocardial function.

The relationship between the positive inotropic myocardial and peripheral vascular responses to digitalis in patients with acute myocardial infarction in whom varying degrees of endogenous catecholamine secretion is occurring cannot be overemphasized and may be responsible for the variable hemodynamic effects recorded. Peripheral vascular resistance falls in patients with chronic heart failure following the administration of cardiac glycosides due to improved cardiac output and compensatory suppression of endogenous catecholamine release. In one patient (No. 3) with severe left ventricular failure, a fall in systemic vascular resistance was accompanied by a rise in cardiac index and reduction in the left ventricular filling pressures (Fig 2). Catecholamine suppression may be less manifest when acute heart failure is due to myocardial infarction, and inappropriate responses have been documented in such patients the causes for which are as yet poorly defined.

Digitalis augments myocardial oxygen consumption in the nonfailing heart of the experimental animal, but surface ECG mapping techniques in animals with induced myocardial damage have demonstrated extension of the zones of ischemia following ouabain administration. Clinically, Balcon and associates noted angina in one patient following administration of digoxin. In the failing heart, however, reduction in left ventricular size and therefore myocardial wall tension and slowing of the heart rate may oppose the increasing oxygen requirements of increased contractility, thereby improving overall myocardial efficiency. In the present study, alteration in myocardial oxygen consumption could not be assessed from the tension-time index. Left ventricular work indices increased primarily as a result of pressure work, and the left ventricular function curve was shifted to the left in those patients with cardiac failure at a constant heart rate, but changes in heart size were, however, not known.

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The hemodynamic response to digoxin in patients with acute myocardial ischemia but without defined infarction was poor, and the lack of significant positive inotropic effect in the patient with heart failure may have been due to an increased myocardial oxygen requirement in response to digoxin, which resulted in further ischemia and myocardial dysfunction.

Digitalis administration later in the course of the infarct, both in experimental animals and in patients has demonstrated a more significant improvement in function, although the validity of Vmax determinations as an index of ventricular function following myocardial infarction can be seriously questioned. Failure of any early response may relate to additional energy expenditure needed to distend noncontractile or dyskinetic zones of the myocardium. Possible compensatory hypertrophy in adjacent noninfarcted areas, metabolic effects and changes in left ventricular wall compliance may all alter the response to digitalis later in the course of the infarct.

Prophylactic digitalization has been recommended in specific instances of heart disease without clinical failure, including before surgery, anesthesia and pregnancy or in myocardial infarction before any cardiac decompensation is evident. Maintenance digoxin therapy did not, however prevent the development of clinical failure in two of six patients studied.

The incidence of ventricular dysrhythmias associated with the acute administration of digoxin is of great concern. Animal studies have indicated a reduced myocardial tolerance for digitalis glycosides following acute infarction. Clinical studies, however, have not reported any increased incidence of ventricular dysrhythmias or sudden death in patients with acute myocardial infarction receiving digitalis preparations. One of the patients with cardiac failure in the present series had received diuretics and a second patient showed marked elevation in pulmonary arterial pressure immediately following digoxin administration. The dysrhythmias may relate to sudden loss of potassium from the myocardial cell, in all three instances intravenous lidocaine easily controlled the rhythm disturbances.

Although the number of patients in the current series is small, the following conclusions seem justified. Digoxin is of no circulatory benefit in patients with acute myocardial infarction who are not in cardiac failure. In patients with associated heart failure, significant hemodynamic improvement occurs only when the failure is severe. The rise in systemic arterial pressure resulting from the peripheral effects of digoxin offsets its beneficial myocardial effect and cardiac output may remain constant. The prophylactic use of digitalis to prevent the subsequent emergence of cardiac failure cannot therefore be advocated, particularly in view of the significant incidence of ventricular dysrhythmias. Similarly, the beneficial effects of digitalis in early left ventricular failure are slight, and diuretic therapy may well be preferable as the initial therapy with due attention paid to the level of the serum potassium.

When digoxin therapy is decided on for severe cardiac failure following myocardial infarction, modification in the dose scheme should be considered; smaller doses of a more rapidly acting preparation are recommended so that the response can be readily assessed, the dose titrated, and the patient protected against the emergence of ventricular dysrhythmias.

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