Augmentation of Serum CPK Activity by Digitalis in Patients with Acute Myocardial Infarction

YURI VARONKOV, M.D., WILLIAM E. SHELL, M.D., VLADIMIR SMIRNOV, PH.D., DAVID GUKOVSKY, PH.D., AND EUGENE I. CHAZOV, M.D.

SUMMARY The effect of acetyl strophanthadin on the rate of creatine phosphokinase (CPK) efflux was evaluated in 59 predominantly class I and II patients randomly allocated between treated and control. Therapy (0.5 mg) was begun 11–15 hours after the onset of symptoms and repeated four hours later (0.25 mg). Accumulated CPK activity (ACA) was determined from serial serum CPK changes sampled every two hours and compared to predicted CPK activity (PACA) determined from the first seven hours of CPK changes. In the control group, ACA was not significantly different from PCA. Digitalis consistently resulted in an augmentation of CPK efflux into serum which was temporally related to drug administration and resulted in a corresponding increase in ACA (P < 0.001). Thus acetyl strophanthadin appears to increase apparent CPK activity in serum in class I and II patients.

THE THERAPEUTIC ROLE of digitalis during acute myocardial infarction remains controversial. Digitalis has been recommended since 19121 for the treatment of acute myocardial infarction because of the similarity of the hemodynamic state associated with myocardial infarction to that of heart failure. Since digitalis can increase the contractility of both normal2 and ischemic tissue,3 digitalis theoretically will increase myocardial function following myocardial infarction. Although digitalis can improve myocardial performance, its effect on performance during an evolving infarction appears dependent on the time of administration, clinical class of the patient and degree of hemodynamic impairment.4 Moreover, experimental evidence in open-chest animals suggests that digitalis may be deleterious to ischemic regions in the nonfailing heart, resulting in increasing signs of electrical injury, and beneficial to ischemic regions of failing hearts resulting in decreasing epicardial ST-segment elevation.5, 7 Changes in serial serum creatine phosphokinase (CPK) have been used to estimate "infarct size" in experimental animals and in man,8 the analysis of these changes by a one compartment model can be referred to as the accumulated CPK activity (ACA). Early changes in CPK activity have also been used to predict the time course of later CPK changes by computer curve fitting9 these projected CPK

1. From the Laboratory of Cardiac Metabolism, Myasniov Institute of Cardiology, Moscow, USSR and the Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California.
2. These experiments were performed in Moscow under the joint auspices of the Ministry of Health, USSR, and the National Institutes of Health, Bethesda, Maryland, USA. Dr. Shell’s exchange visit was supported by the agreement between the USA and USSR on Cooperation in the Field of Medical Science and Public Health, signed May 23, 1972.
3. Address for reprints: Division of Cardiology, Publication Office, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, California 90048.
4. Received June 25, 1976; revision accepted December 10, 1976.
values are used to predict the CPK accumulation in serum and can be referred to as the predicted CPK activity (PCA). By comparison of the ACA to the PCA, it is possible to determine if a given therapeutic intervention increases or decreases CPK activity in serum.6,11

Accumulated CPK activity (ACA) is an estimate of infarct size conceived in traditional anatomic terms. There are several lines of evidence to support the association between ACA and anatomic infarct size. CPK depletion from myocardium following coronary artery occlusion appears to reflect cell death when necrosis is defined by reduction in blood flow to ischemic zones,12,13 abnormal mitochondrial function,12 abnormal histologic appearance consistent with necrotic cells,6,14 presence of inflammatory infiltrate (which many observers consider the most reliable index of necrosis),14 and subsequent fibrosis with scar formation.16 ACA as assessed by the one compartment model in dogs correlates with estimation of total myocardial CPK depletion \( r = 0.96 \) original calculation6 and 0.82 recalculated by Roe18. In man, ACA presages subsequent survival and morbidity,17 predicts ventricular performance18 and presages the degree of acontractile segments on a ventriculogram.19 Moreover, in 17 patients, Bleifeld and colleagues20 have found that the relation between ACA and infarct size determined pathologically at autopsy was close \( r = .93, N = 17 \). Accordingly, ACA appears to be an estimate of infarct size determined pathologically both in experimental animals and man.

Moreover, in experimental animals, CPK appearance in serum can be increased by ventricular pacing, isoproterenol and atropine;21 the expected CPK appearance rate can be retarded by propranolol.16 When the ACA following an intervention is compared to infarct size estimated by myocardial CPK depletion, the correspondence remains close — i.e., the myocardial CPK depletion reflects either the augmented CPK activities or the apparent reduction of CPK activities in serum.18 Reperfusion following coronary artery occlusion in the dog appears to be a complex intervention leading to an increased rate of CPK release,22,23 myocardial hemorrhage,23 temporary deterioration of electrolyte efflux,24 temporary deterioration of function \( r = .93, N = 17 \) and apparent long-term salvage of tissue as assessed two weeks following reperfusion.25 Accordingly, ACA, as an index of response to potentially therapeutic interventions, appears to reflect cell death in the absence of the massive reflow associated with reperfusion. In man, the effect of various therapies on ACA has undergone only preliminary evaluation; trimethaphan decreases ACA in hypertensive patients,8 nitroprusside increases ACA in normotensive patients28 and glucocorticoids increases ACA when given in pharmacologic doses.17 To date, the relationship between a therapeutically induced change in ACA and a change in patient survival, ventricular performance or anatomically measured infarct size is unknown. Moreover, the correspondence between predictions of CPK accumulation in serum and subsequently observed ACA has not been evaluated in randomized untreated patients.

Accordingly, this study was designed to evaluate the effect of digitalis, administered early in the course of an infarction, on the time course of CPK accumulation in serum during evolving myocardial infarction in unselected patients randomized between treated and control groups. Patients were treated 14 hours after the onset of infarction with acetyl strophanthin; the effect of this agent on ACA was evaluated.

Materials and Methods

A. Patient Selection

Fifty-nine patients with definite acute myocardial infarction were randomly allocated between treatment and non-treatment with digitalis. Consecutive patients with acute transmural myocardial infarction with evidence of ST-segment change and Q waves were randomly allocated between four hospitals by central dispatch system at the Ministry of Health in Moscow. The first 30 admissions to two hospitals were allocated to the treatment group, and the first 29 patients admitted to two additional hospitals were allocated to the control group. This randomization scheme was used to facilitate completion of the study within a short time interval; all patients were under direction of the Ministry of Health of the USSR and received uniform therapy. The control patients received only lidocaine, morphine and oxygen. The treated patients received these medications and the acetyl strophanthin. A diagnosis of myocardial infarction was made on the basis of the electrocardiogram, characteristic chest pain, and subsequent elevation of the serum CPK activity. Patients were excluded from the study if they had evidence of shock, persistent hypotension, or demonstrated an arrhythmia requiring digitalis therapy. There were no other exclusions. Patients were included in the study if they were admitted to the hospital within four hours after the onset of chest pain.

B. Treatment Protocol

Following admission of patients to the hospital, serum CPK activity was sampled every two hours for the first three days of hospitalization. A chest X-ray was obtained in both control and treated groups, a prospective clinical protocol was evaluated and a 12-lead electrocardiogram was obtained. Fourteen hours after the onset of chest pain, 0.5 mg of acetyl strophanthin was given, which was followed four hours later by a second dose of 0.25 mg intravenously. Twelve-lead electrocardiograms were sampled just prior to the onset of therapy, one hour after the first dose of acetyl strophanthin in the treated group of patients. A chest X-ray was obtained 12 hours after the second dose of acetyl strophanthin in both groups of patients. All patients were seen by one author to assess clinical class.

C. Biochemical Procedures

Serum CPK activity was sampled in EGTA as previously described.8 The serum activity was assayed by the Rosalki method.27 The samples were brought to a central laboratory and analyzed by automated spectrophotometer; the identity of the treated patients was not available prior to analyzing the CPK activity.

Analysis of Data

A. Observed CPK Activity

ACA was estimated by serial serum CPK changes as previously described.8 In essence, the ACA is determined
from the equation \( \frac{dE}{dt} = f(t) + K_dE \) which relates the rate of enzyme change in serum to both the rate of clearance of CPK from serum and the rate of release of enzyme into serum. When this equation is rearranged and corrected for the CPK distribution volume (D.V.), the amount of CPK released during the infarction can be estimated:

\[
CPK-R = \int_0^t \left( \frac{dE}{dt} + K_dE \right) dt \times D.V.
\]  

(1)

ACA is then found by two constants — a proportionality constant relating serum and tissue CPK (CPK-R/CPK-D) and a constant representing the amount of CPK lost from an infarct (CPK-I):

\[
ACA = \frac{CPK-R}{[(CPK-R/CPK-D) \times (CPK-I)]}
\]

We evaluated the integral in equation from the initial value until the last available value which varied from 30-72 hours.

The appropriate constants used were: \( K_d = 0.01 \) min\(^{-1}\), D.V. = 6% of body weight, CPK-R/CPK-D = 0.15, CPK-I = 500 IU/g. ACA estimated in this manner is expressed in CPK gram-equivalents,\(^\text{(17)}\) which approximates the amount of myocardium undergoing ischemic necrosis releasing the same amount of CPK as 1 gram of myocardium undergoing homogeneous necrosis; this unit is a convenient measure of total CPK accumulation in serum and is intended only to approximate true anatomic infarct size.

B. Predicted CPK Accumulation

The rate of CPK activity subsequent to therapy was predicted from the first seven hours of CPK activities. The concept underlying prediction of CPK release (PCA) is that early enzyme changes presage later changes and that the time course of enzyme release tends to be reproducible; the reproducibility of CPK changes is reflected in the common clinical experience that CPK activity following myocardial infarction peaks 24-36 hours after the initial chest pain. To describe the CPK changes, we utilize an empiric equation, the lognormal function:

\[
CPK\text{-activity} = \frac{b}{t^e} e^{-\left(\frac{1n t - c}{d^t}\right)^2}
\]

where \( E = \) lognormal function. Thus, PCA =

\[
\text{predicted ACA} = \frac{CPK-R}{\left(\frac{CPK-R}{CPK-D}\right)} \times CPK-I
\]

The PCA is an estimate of the total amount of CPK which would be released without therapy. It must be stressed that the terms ACA and PCA are intended to provide an estimate of total enzyme release; the relation of these measures of ischemic injury to the volume of necrotic tissue or the number of dead cells is undergoing continuous investigation including studies of anatomy, function and most importantly patient prognosis.

C. Statistical Analysis

In this group of patients a paired \( t \)-test was used to compare predicted and observed accumulated CPK activities in both the treated and control groups\(^\text{28}\) and to test the mean difference. A nonpaired Student’s \( t \)-test was used to compare observed accumulated CPK activities (ACA) between the treated and nontreated groups.\(^\text{28}\) A nonpaired \( t \)-test was used to compare predicted ACA between the treated and control groups.\(^\text{28}\) A linear regression of ACA on PCA was obtained in both the treated and control groups; the slope and intercept were compared by standard means.\(^\text{28}\) Discrete data were compared by a chi square analysis.\(^\text{28}\)

Results

A. Patient Characteristics

There were 59 patients randomized into a control (\( N = 29 \)) and a treated group (\( N = 30 \)). The characteristics of the two populations were not remarkably different. The mean age was 56.5 ± 2.1 years in control patients and 54.1 ± 1.7 in treated patients. The mean weight was 74.5 ± 2.5 kg in control patients, 72.0 ± 1.2 kg in treated patients. The mean systolic blood pressure in the treated group was slightly higher (141 ± 6.1 treated vs 138 ± 5.7). The diastolic blood pressure was also slightly higher in the treated group (96 ± 4.3 treated vs 92 ± 3.9 control), the heart rate in the two groups of patients was not substantially different (80 ± 1.8 treated vs 78 ± 2.9 control). The respiratory rate was slightly higher in the treated group (25.9 ± 4.4 treated vs 22.8 ± 2.9 control), and the \( \Sigma T \) obtained from standard 12-lead electrocardiograms at the time of admission was not substantially different between the two groups (11.7 ± 2.6 treated vs 8.4 ± 1.42 control).

The clinical characteristics of the two populations were not remarkably different (table 1). There were 85% males in the control group and 76% males in the treated group (\( \chi^2 = .770 \)). Thirty-seven percent of the control patients had a history of hypertension while 48% of the treated group had a history of hypertension (\( \chi^2 = .728 \)). When the treated patients were classified according to the Killip clinical classification, there were 46% class I, 43% class II and 11% class III (\( \chi^2 = 2.92 \)). There was 28% incidence of third heart sounds in the control and the treated groups (\( \chi^2 = .001 \)).
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>Treated</th>
<th>x²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>85*</td>
<td>76</td>
<td>.770</td>
<td>.38</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>37</td>
<td>48</td>
<td>.728</td>
<td>.396</td>
</tr>
<tr>
<td>Killip class I</td>
<td>46</td>
<td>46</td>
<td>2.92</td>
<td>.23</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S_s</td>
<td>28</td>
<td>28</td>
<td>.001</td>
<td>.97</td>
</tr>
<tr>
<td>Neck vein distension</td>
<td>0</td>
<td>14</td>
<td>3.87</td>
<td>.0491</td>
</tr>
<tr>
<td>Enlarged liver</td>
<td>8</td>
<td>23</td>
<td>2.36</td>
<td>.124</td>
</tr>
<tr>
<td>History of previous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infarction</td>
<td>25</td>
<td>12</td>
<td>1.38</td>
<td>.24</td>
</tr>
<tr>
<td>History of angina</td>
<td>44</td>
<td>41</td>
<td>0.46</td>
<td>.83</td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values listed are percentage of patients displaying listed characteristic.

None of the patients in the control group had neck vein distension while 14% of the treated group had neck vein distension ($x^2 = 3.87$, $P = 0.05$). Eight percent of the control patients had an enlarged liver, while 23% of the treated group had an enlarged liver on physical examination ($x^2 = 2.36$). Twenty-five percent of the control group had a history of myocardial infarction, while 12% had a history of myocardial infarction in the treated group ($x^2 = 1.38$). Forty-four percent of the control group had a history of angina pectoris, while 41% of the treated group had a history of angina pectoris ($x^2 = 0.46$). Thus, it appears that the control and treated groups were evenly matched as to initial characteristics.

B. Projected CPK Activity in Untreated Patients

In individual patients, there was a generally close correspondence between the observed CPK values and those projected from the first seven hours of CPK determinations (fig. 1). In this untreated patient, the CPK values projected from the first seven hours (420 min) are similar to the observed values and the observed curve fell within the two standard deviation confidence limits. Accordingly, the observed and predicted CPK accumulations determined from these values are also quite close (ACA = 10.5 CPK gm·eq, PCA = 8.8). This type of close correspondence is a "best" case example; it can be expected that this type of analysis will lead to gross inconsistencies between ACA and PCA in at least 5% of cases thereby precluding use of each patient as his own control.

In this series of patients, we did not exclude patients with signs of clinical extensions, determined either by chest pain or by enzyme changes. Thus, a number of patients are included in whom there were signs of clinical extension along with the appropriate deviation of the observed and projected CPK values; in patient C-24 (fig. 2), the observed CPK values deviated from those projected from the lognormal function, suggesting an extension of necrosis; the ACA was 31.8 and the predicted PCA was 24.9. Theoretically, the terminal portion of the lognormal curve does not conform to a simple monoeXponential decay; thus, the projected CPK values in the completely idealized case should be higher than those observed. When the observed CPK values are higher than those projected, substantial augmentation of CPK accumulation has occurred, suggesting extension of necrosis. In this series of patients, we did not attempt to exclude patients with spontaneous extension of their necrosis as estimated from CPK accumulation rates from the control group.

C. Influence of Digitalis on Projected CPK Accumulation in Treated Patients

The observed CPK activities in these class I and II patients without heart failure followed a consistent pattern after the administration of acetyl strophanthin. Following the administration of the first dose of digitalis (fig. 3), there was a sudden acceleration in the rate of CPK accumulation.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** The observed and projected CPK values for an untreated patient. The CPK activity in mlU/ml is on the ordinate and time in hours on the abscissa. The projection was made based on the CPK activity during the first seven hours after enzyme rise. The open circles refer to the observed values and the Xs refer to the projected values. The hatched line represents two standard deviation confidence limits.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** The observed and projected CPK activities in a patient experiencing spontaneous extension of enzyme release.
CPK AND DIGITALIS IN AMI/Varonkov et al. 723

with a deviation of the projected and observed CPK values. Following the second dose of digitalis, there was a further increase in CPK accumulation and a second peak. In addition, the terminal portion of the CPK curves rarely conformed to a single monoexponential decay rate in contrast to the untreated patients who frequently demonstrated a monoexponential decay rate. The failure to achieve a monoexponential decay suggests continued accumulation of enzyme into serum. In this example, the PCA was 49.7 CPK gm-eq and the observed ACA was 104.2, indicating a 110% increase in the amount of observed CPK activity seen in serum. Similar responses were observed in four other treated patients (fig. 4) — indicating a rapid increase in the CPK accumulation into serum after the first dose, and a tendency for the curve to be nonmonoexponential during the terminal phase. In control patients, deviation of observed and predicted values tended to be spontaneous and unpredictable.

D. Comparison of Observed and Predicted CPK Activities in the Treated and Control Groups

In this series, 29 of 30 patients experienced an increase in CPK accumulation in serum following the administration of acetyl strophanthanin when compared to the control group (tables 2 and 3). In the control group, there was a close correspondence between the observed and predicted ACA (fig. 5). The regression was ACA = .93 PCA + 1.12 with \( r = 0.96, N = 30 \). However, in the treated group (fig. 6), the regression line relating observed and predicted ACA was shifted upward to the left. The observed and the predicted

![Figure 3](image-url)

**Figure 3.** The observed and projected CPK activities in a patient treated with acetyl strophanthanin. The CPK projection was based on the first seven hours of CPK activity and the treatment was initiated at 11 hours. The first dose is indicated by the first arrow (0.5 mg) and the second dose indicated by the second arrow (0.25 mg). The predicted accumulated CPK activity (ACA) was 49.7; the observed ACA was 104.2 CPK gm-eq.

![Figure 4](image-url)

**Figure 4.** Four patients treated with acetyl strophanthanin, as indicated by the arrows. These changes depict typical responses to digitalis.
TABLE 2.  **Control Patients**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Predicted CPR activity</th>
<th>Observed CPR activity</th>
<th>Difference</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>8.58</td>
<td>100.3</td>
<td>-14.5</td>
<td>-16.9</td>
</tr>
<tr>
<td>C-2</td>
<td>20.6</td>
<td>15.2</td>
<td>5.4</td>
<td>26.2</td>
</tr>
<tr>
<td>C-3</td>
<td>40.0</td>
<td>37.0</td>
<td>3.0</td>
<td>7.5</td>
</tr>
<tr>
<td>C-4</td>
<td>3.4</td>
<td>4.5</td>
<td>-1.1</td>
<td>-22.4</td>
</tr>
<tr>
<td>C-5</td>
<td>8.2</td>
<td>11.4</td>
<td>-3.2</td>
<td>-27.4</td>
</tr>
<tr>
<td>C-6</td>
<td>2.6</td>
<td>2.3</td>
<td>-0.3</td>
<td>-11.5</td>
</tr>
<tr>
<td>C-7</td>
<td>48.5</td>
<td>49.9</td>
<td>-1.4</td>
<td>-2.8</td>
</tr>
<tr>
<td>C-8</td>
<td>8.8</td>
<td>10.5</td>
<td>-1.7</td>
<td>-19.3</td>
</tr>
<tr>
<td>C-9</td>
<td>41.6</td>
<td>40.1</td>
<td>1.5</td>
<td>3.6</td>
</tr>
<tr>
<td>C-10</td>
<td>20.8</td>
<td>45.9</td>
<td>-25.1</td>
<td>-120.7</td>
</tr>
<tr>
<td>C-11</td>
<td>34.6</td>
<td>37.9</td>
<td>-3.3</td>
<td>-9.5</td>
</tr>
<tr>
<td>C-12</td>
<td>45.9</td>
<td>36.6</td>
<td>9.3</td>
<td>20.3</td>
</tr>
<tr>
<td>C-13</td>
<td>45.2</td>
<td>44.8</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>C-14</td>
<td>53.3</td>
<td>38.8</td>
<td>14.5</td>
<td>27.2</td>
</tr>
<tr>
<td>C-15</td>
<td>34.2</td>
<td>45.1</td>
<td>-10.9</td>
<td>-31.9</td>
</tr>
<tr>
<td>C-16</td>
<td>80.4</td>
<td>84.5</td>
<td>-4.1</td>
<td>-5.1</td>
</tr>
<tr>
<td>C-17</td>
<td>115.7</td>
<td>121.2</td>
<td>-5.5</td>
<td>-4.8</td>
</tr>
<tr>
<td>C-18</td>
<td>48.2</td>
<td>73.6</td>
<td>-25.4</td>
<td>-52.7</td>
</tr>
<tr>
<td>C-19</td>
<td>76.8</td>
<td>81.2</td>
<td>-4.4</td>
<td>-5.7</td>
</tr>
<tr>
<td>C-20</td>
<td>12.3</td>
<td>12.9</td>
<td>0.6</td>
<td>4.9</td>
</tr>
<tr>
<td>C-21</td>
<td>42.7</td>
<td>44.9</td>
<td>-2.2</td>
<td>-5.1</td>
</tr>
<tr>
<td>C-22</td>
<td>93.1</td>
<td>96.8</td>
<td>-3.7</td>
<td>-4.0</td>
</tr>
<tr>
<td>C-23</td>
<td>53.1</td>
<td>52.6</td>
<td>0.5</td>
<td>9</td>
</tr>
<tr>
<td>C-24</td>
<td>24.9</td>
<td>31.8</td>
<td>-6.9</td>
<td>-27.7</td>
</tr>
<tr>
<td>C-25</td>
<td>26.6</td>
<td>28.5</td>
<td>-1.9</td>
<td>-7.1</td>
</tr>
<tr>
<td>C-26</td>
<td>25.4</td>
<td>25.3</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>C-27</td>
<td>50</td>
<td>53.3</td>
<td>-3.3</td>
<td>-6.6</td>
</tr>
<tr>
<td>C-28</td>
<td>48.7</td>
<td>44.7</td>
<td>4.0</td>
<td>8.2</td>
</tr>
<tr>
<td>C-29</td>
<td>108.1</td>
<td>97.3</td>
<td>11.6</td>
<td>10.7</td>
</tr>
<tr>
<td>C-30</td>
<td>36.3</td>
<td>38.5</td>
<td>-2.2</td>
<td>-6.1</td>
</tr>
<tr>
<td>Mean</td>
<td>44.53</td>
<td>46.9</td>
<td>-2.38</td>
<td>-5.3%</td>
</tr>
</tbody>
</table>

se 5.4 5.6

TABLE 3.  **Digitalis Treated Patients**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Predicted CPR activity</th>
<th>Observed CPR activity</th>
<th>Difference</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1</td>
<td>25.2</td>
<td>53.1</td>
<td>-27.9</td>
<td>-110.7</td>
</tr>
<tr>
<td>S-2</td>
<td>20.7</td>
<td>40.4</td>
<td>-19.7</td>
<td>-95.2</td>
</tr>
<tr>
<td>S-3</td>
<td>23.3</td>
<td>44.3</td>
<td>-21.0</td>
<td>-90.1</td>
</tr>
<tr>
<td>S-4</td>
<td>22.1</td>
<td>49.1</td>
<td>-27.0</td>
<td>-122.2</td>
</tr>
<tr>
<td>S-5</td>
<td>49.9</td>
<td>69.1</td>
<td>-19.2</td>
<td>-31.5</td>
</tr>
<tr>
<td>S-6</td>
<td>19.1</td>
<td>39.2</td>
<td>-20.1</td>
<td>-105.2</td>
</tr>
<tr>
<td>S-7</td>
<td>49.7</td>
<td>104.2</td>
<td>-54.5</td>
<td>-109.7</td>
</tr>
<tr>
<td>S-8</td>
<td>72.0</td>
<td>54.1</td>
<td>17.9</td>
<td>24.9</td>
</tr>
<tr>
<td>S-10</td>
<td>21.3</td>
<td>41.8</td>
<td>-20.5</td>
<td>-96.2</td>
</tr>
<tr>
<td>S-11</td>
<td>61.6</td>
<td>83.9</td>
<td>-22.3</td>
<td>-36.2</td>
</tr>
<tr>
<td>S-12</td>
<td>98.1</td>
<td>130.0</td>
<td>-31.9</td>
<td>-32.5</td>
</tr>
<tr>
<td>S-13</td>
<td>42.3</td>
<td>53.2</td>
<td>-10.9</td>
<td>-25.8</td>
</tr>
<tr>
<td>S-14</td>
<td>44.8</td>
<td>60.9</td>
<td>-16.1</td>
<td>-35.9</td>
</tr>
<tr>
<td>S-15</td>
<td>25.2</td>
<td>76.4</td>
<td>-51.2</td>
<td>-203.2</td>
</tr>
<tr>
<td>S-16</td>
<td>27.1</td>
<td>46.7</td>
<td>-19.6</td>
<td>-72.3</td>
</tr>
<tr>
<td>S-17</td>
<td>63.9</td>
<td>94.0</td>
<td>-30.1</td>
<td>-47.1</td>
</tr>
<tr>
<td>S-18</td>
<td>27.4</td>
<td>48.4</td>
<td>-21.0</td>
<td>-76.6</td>
</tr>
<tr>
<td>S-19</td>
<td>39.2</td>
<td>58.9</td>
<td>-29.7</td>
<td>-95.0</td>
</tr>
<tr>
<td>S-20</td>
<td>23.8</td>
<td>54.7</td>
<td>-30.9</td>
<td>-129.8</td>
</tr>
<tr>
<td>S-21</td>
<td>60.1</td>
<td>120.3</td>
<td>-60.2</td>
<td>-75.1</td>
</tr>
<tr>
<td>S-22</td>
<td>55.1</td>
<td>86.5</td>
<td>-31.4</td>
<td>-57.0</td>
</tr>
<tr>
<td>S-23</td>
<td>13.0</td>
<td>43.5</td>
<td>-30.5</td>
<td>-224.6</td>
</tr>
<tr>
<td>S-24</td>
<td>44.5</td>
<td>69.4</td>
<td>-24.9</td>
<td>-56.0</td>
</tr>
<tr>
<td>S-25</td>
<td>15.3</td>
<td>30.0</td>
<td>-14.7</td>
<td>-96.1</td>
</tr>
<tr>
<td>S-26</td>
<td>41.5</td>
<td>37.4</td>
<td>-3.1</td>
<td>-7.6</td>
</tr>
<tr>
<td>S-27</td>
<td>50.4</td>
<td>74.8</td>
<td>-24.4</td>
<td>-48.4</td>
</tr>
<tr>
<td>S-28</td>
<td>15</td>
<td>40.9</td>
<td>-25.9</td>
<td>-172.7</td>
</tr>
<tr>
<td>S-29</td>
<td>57.7</td>
<td>79.3</td>
<td>-21.6</td>
<td>-37.4</td>
</tr>
<tr>
<td>S-30</td>
<td>16.7</td>
<td>41.1</td>
<td>-24.4</td>
<td>-146.1</td>
</tr>
<tr>
<td>Mean</td>
<td>37.9</td>
<td>62.9</td>
<td>-24.2</td>
<td>-86.04%</td>
</tr>
</tbody>
</table>

se 4.02 4.7

FIGURE 5. Regression analysis of observed and predicted accumulated CPK activity in untreated patients. The observed ACA (CPK gm-eq) is indicated on ordinate and the predicted ACA on the abscissa. The line of identity is indicated by the xs while the observed values are indicated by open circles.

ACA, however, tended to cluster around the offset regression line (ACA = .72 PCA - 7.9, r = 0.86, N = 29). Moreover, 28 of the 29 patients fell above the line of identity, indicating that the observed infarct sizes were larger to account for shift of the regression line while maintaining a linear relationship with those predicted. The regression analysis suggests that a consistent increase in observed CPK efflux occurred which was associated with the administration of acetyl strophantin.

The observed and predicted ACA in the control group were in close agreement (fig. 7). The mean predicted ACA was 44.53, while the mean observed ACA was 46.9. This represents a 2.38 gm-eq difference or a 5.35% difference. These differences were not statistically significant. However, as indicated above, the observed accumulation in serum should theoretically be smaller than the predicted ACA, the results of this study of randomized, unsolicited patients suggest that a number of patients underwent spontaneous acceleration of enzyme accumulation.

In the treated group (fig. 8), the mean observed ACA was 85% larger than the mean predicted. The mean predicted ACA was 37.9 ± 4.02, while the mean observed ACA was 62.9 ± 4.7 (P < 0.001), t = 10.2. This represents a 24.2 gm-eq increase in observed rate of CPK accumulation over that predicted. This difference was highly significant and could not be accounted for by spontaneous deviations in the parameters associated with calculation of ACA which would also occur randomly in the nontreated group.

However, when observed ACA was compared in the treated and control group, there was no statistical difference between the two (fig. 9). The mean observed ACA in the control group was 44.3, while the mean observed ACA in the treated group was 62.9 (t = 2.19, P = 0.25). Thus, although there was an 85% difference between observed and predicted...
ACA in the treated group and although there was a trend toward increased observed ACA in the treated group, statistical difference was not achieved with this sample size. These data demonstrate the utility of CPK prediction in reducing sample size necessary to ascertain a change in the rate of CPK accumulation.

The mean PCA in the two groups was also similar. The concordance of PCA provides further support of the similarity of the treated and untreated patients and tends to support the conclusion that digitalis was associated with increased CPK accumulation in serum.

**Discussion**

Administration of acetyl strophanthidin 14 hours after the onset of symptoms to class I and II patients with acute evolving myocardial infarction but without heart failure results in an increase in CPK accumulation into serum and an 85% augmentation of observed accumulated CPK activity (ACA) as compared to predicted CPK accumulation (predicted during the first seven hours of CPK change). In a randomized control group, the observed CPK and predicted CPK accumulated activity were closely correlated, \( r = 0.96 \), demonstrating a 2 CPK gm-eq difference, while in the treated group the observed ACA was 24.2 gm-eq larger than predicted. The treated and control groups appeared to be identical in regard to clinical attributes, and were matched according to initial predicted ACA. These data indicate that administration of digitalis to class I and II patients with uncomplicated acute myocardial infarction leads to increased accumulation of CPK in serum.

The untreated patients in this study were a randomized control group who did not receive therapy. They represent the first series of randomized untreated patients in whom observed ACA estimated from serum CPK values obtained from approximately the first three days of an evolving infarction could be compared to predicted CPK accumulation derived from the first seven hours of CPK change in the same patients. Previous studies comparing observed and predicted ACA have utilized control groups which were either idealized smooth curves or selected patients matched according to predicted accumulation rates; thus these groups did not represent a truly randomized control group. In this randomized control group the observed ACA exceeded the predicted CPK release rate by 5.3%. Because the terminal portion of the lognormal function is not truly monoeponential, computer curve fitting utilizing the lognormal function should lead to a predicted ACA larger than the observed ACA. Our control patients demonstrated observed ACA which were larger than predicted ACA. The difference is probably due to nonexclusion of patients with clinical extension of necrosis. Since it has been shown by ST-segment precordial mapping and by analysis of

---

**FIGURE 6.** The regression analysis of observed and predicted ACA in the acetyl strophanthidin treated patients. The open circles are the observed values.

**FIGURE 7.** The observed and predicted ACA in untreated patients. This graph illustrates the mean and one standard error.

**FIGURE 8.** The predicted and observed ACA in the treated group. The predicted ACA was 37.9 ± 4.02. The observed ACA was 62.9 ± 4.7, indicating a 24.2 CPK gm-eq difference, or 60%.

**FIGURE 9.** The predicted ACA in the treated and untreated patients.
serial serum CPK curves that a substantial number of unex-
plained and clinically undetected extensions of myocardial
ischemic injury occur, it is not surprising that in a truly ran-
donized control series in which extensions are not excluded,
the observed ACA would exceed that predicted by the
lognormal function. Accordingly, studies designed to test the
efficacy of a given intervention, using a comparison between
predicted and observed ACA, must take cognizance of the
fact that the observed ACA in the control patients will ex-
ceed the predicted ACA by 5.3%.

These studies indicate, in class I and II patients, that the
administration of acetyl strophanthanin to patients with
evolving myocardial infarction leads to a relatively consis-
tent increase in CPK accumulation into serum. Following
the first dose of digitalis, there is increased CPK activity and
following the second dose of acetyl strophanthanin, 29 of the
30 treated patients showed a further acceleration of CPK ac-
tivities. Moreover, when the observed and predicted curves
were compared in control patients, although some patients
demonstrated late CPK extensions, the CPK curves event-
ually reached a smooth terminal decay for which it would be
possible to calculate an individual $K_a$ as suggested by
Norris. However, in treated patients, the terminal parts of
the CPK curves tended not to become monoeponential; this
observation suggests that not only was an initial acceleration
of CPK accumulation induced by the two doses of acetyl
strophanthanin but also that substantial further acceleration
of CPK accumulation occurred several hours after the ad-
ministration of the digitalis.

The conclusion of this study is based on the reliability of
CPK projections. Since CPK projection, using the method-
ology outlined, is a nonlinear mathematical problem,
there is not a unique solution to the equations. The non-
unique solution of nonlinear systems introduces potential
subjectivity and variability into the projections. Precise and
reproducible predictions depend on appropriate choice of
initial parameter estimates used in the computer program and
appropriate selection of limits on parameters associated with
a lognormal function. In our previous studies, we limited
parameters and chose the initial estimate of parameters on
an arbitrary but consistent basis. Inconsistent choice of ini-
tial parameters and manipulation of the limits will lead to
imprecise prediction, variation of predictions between
various institutions and various laboratories, and potential
inaccurate conclusions. In an effort to obviate these
problems, the computer program used in these studies
allowed the computer to set the limits of the parameters and
applied a linear approximation to the lognormal function to
reach the initial parameter estimates. Accordingly, the
user presented to the computer only the patient's name, the
CPK data and patient weight from which an observed and
predicted infarct size were calculated. The algorithms
utilized in this study resulted in reproducible ACA esti-
mations standardized between individuals and between in-
vestigators.

The correlation coefficient between the observed and
predicted ACA in untreated patients was 0.96 with a 5.3%
difference between the observed and predicted ACA
(N = 29). There was a 2.38 CPK gm-eq difference between
the observed and predicted ACA using the linear approxima-
tion to the initial parameters. In our earlier studies utilizing
nonrandomized patients with idealized CPK curves, we
reported a correlation coefficient of 0.96 with a 7.0%
difference between the observed and predicted ACA. In a study by Morrison in which arbitrary initial guesses for the
prediction were used, the difference between the observed
and the predicted ACA was 3.0 gm-eq with a correlation
coefficient of 0.97. Thus, there is a close relationship between
predicted and observed ACA in untreated patients which can
be standardized between investigators and between insti-
butions; these data suggest that prediction of CPK release
by computer curve fitting provides reliable estimates of the
time course and rate of CPK release. It must be stressed that
CPK projections are not dependent on the validity of the
parameters used in the one compartmental model, i.e., $D_V,
K_a$; the projections are dependent only on the cor-
respondence of observed curves to the lognormal function.

These data indicate that administration of acetyl
strophanthanin to uncomplicated patients with evolving
myocardial infarction is associated with an accelerated rate
of CPK appearance into serum. Several phenomena could
account for the observed acceleration of CPK release in
cluding: 1) augmentation of infarct size; 2) inhibition of en-
zyme clearance from serum; 3) increased washout of enzyme
from necrotic myocardium; and 4) noncardiac release of en-
zyme. Digitalis increases ST-segment elevation in dogs
without heart failure and reduces ST-segment elevation in
dogs with failing hearts. However, to date, the effect of
digitalis on anatomic estimates of infarct size in experi-
mental animals has not been examined nor has the effect of
digitalis on CPK release in animals been examined. In a
preliminary study, Morrison suggests that digitalis has little
influence on CPK release in patients with failing hearts. The
significance of the accelerated rate of CPK release will
depend on evaluation of patient survival and morbidity.

Clearance rates of injected purified CPK have been ex-
amined under a variety of conditions; there is no change in
the clearance rate following change in cardiac output, reduct
of renal clearance or volume change; alterations of hepatic
blood flow can influence the clearance rate of CPK although
the experimental results depend on the animal model. CPK
clearance rate can be dramatically influenced, however, by
acute inhibition of the reticuloendothelial system. Washout of
enzyme from a pool of enzyme bathing a necrotic zone has been suggested as an explanation for acceleration rates of CPK release. The washout question has been studied by examining the relation between serum enzyme release and myocardial enzyme depletion (so-called CPK-R/CPK-D ratio); interventions with pro-
pranolol, trimethaphan, heart rate acceleration and
isoproterenol do not result in a washout effect. Acute reper-
fusion in dogs may lead to disproportionate enzyme release
into serum although this effect has not been clearly es-
tablished. Acute increase in coronary blood flow in dogs with
evolving infarction results in a transient (one hour) spike of
CPK release which presumably represents washout but is
quantitatively insignificant (unpublished observations).

Observed ACA predicts short-term prognosis in patients
in the absence of discrete therapeutic interventions and
is related to anatomic infarct size in patients dying of acute
infarction. It is currently unclear if following a therapeutic
intervention, changes in CPK release translate into either an
increase or decrease in infarct size. Validation of CPK release as an index of therapeutic response will depend on verification in animals of the factors influencing enzyme activity in serum and close correlation between clinical course, i.e., mortality and morbidity, and rates of CPK release for various therapies.

In summary, the rate and amount of CPK release can be predicted in randomized untreated patients. Digitalis administration to uncomplicated patients with evolving infarction results in accelerated CPK accumulation in serum. Finally, interpretation of the significance of accelerated CPK accumulation in serum depends on correlation between clinical course and estimated infarct size.

Acknowledgment

The authors wish to acknowledge the editorial assistance of Mrs. Betty Garrigues.

References

Augmentation of serum CPK activity by digitalis in patients with acute myocardial infarction.

Y Varonkov, W E Shell, V Smirnov, D Gukovsky and E I Chazov

Circulation. 1977;55:719-727
doi: 10.1161/01.CIR.55.5.719

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/55/5/719

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/