Effects of Digitalis on Resting and Isometric Exercise Myocardial Perfusion in Patients with Coronary Artery Disease and Left Ventricular Dysfunction

ROBERT VOGEL, M.D., DENNIS KIRCH, M.S.E.E., MICHAEL LEFREE, B.S., JOHN FRISCHKNECHT, M.D., and PETER STEELE, M.D.

SUMMARY Digitalis has been shown to improve the impaired ventricular function associated with coronary artery disease as well as to increase myocardial oxygen consumption and produce coronary vasoconstriction. To elucidate the net result of these contrasting effects, six patients with coronary artery disease and left ventricular ejection fractions < 0.50 had 1.0 mCi thallium-201 injected intravenously at rest and during three minutes of 33% of maximal handgrip, off and on 0.25 mg daily maintenance digoxin. Thallium-201 scintigram images were taken 30 minutes later and were computer processed with orthogonal linearly interpolated background subtraction and maximal count density equalization. Processed images were visually graded on a 0, 1, or 2 scale for 18 sectors — nine from the AP projections and nine from the 40° left anterior oblique projections. A score resulting from the summation of the 18 sector grades was made for each study, the maximum score being 36. Off digitalis, patients performing handgrip exercise decreased their scintigram scores from 25.7 ± 1.5 (mean ± SEM) to 23.0 ± 1.0, P < 0.05. When patients were on maintenance digoxin, scores did not change significantly during handgrip exercise. Post exercise scores were significantly higher on digoxin than off (P < 0.05), whereas, resting scores were unaffected by digoxin. These data suggest that myocardial perfusion, as measured by thallium-201 uptake, is improved in patients on digitalis who have coronary artery disease and left ventricular dysfunction.

LEFT VENTRICULAR FUNCTION AND DYSFUNCTION associated with coronary artery disease improves with digitalis, but the drug also increases myocardial oxygen consumption and acutely administered, can be a coronary vasoconstrictor. In addition, isometric exercise depresses ventricular function in individuals with diminished cardiac reserve, producing left ventricular dilatation, a factor which decreases myocardial perfusion. From these observations it is not clear what net effect digitalis and isometric exercise will have on the myocardial oxygen consumption-delivery ratio in patients with coronary artery disease and diminished cardiac function. In recent years, myocardial scintigraphic imaging using thallium-201 has been used to identify areas of hypoperfusion. This study measures the effects of chronically administered digoxin on thallium-201 myocardial perfusion scans in patients with coronary artery disease and left ventricular dysfunction at rest and during performance of isometric exercise.

Methods

Patients

Six male patients, 46 to 61 years old, were informed of the nature of the study and consented to the procedure. Prior cardiac catheterization had revealed three vessel coronary occlusive disease (> 70%) in four, and total occlusion of the left anterior descending coronary artery only in two. These latter two individuals had had coronary artery bypass surgery with demonstrated graft occlusion. Single right anterior oblique plane left ventriculography had demonstrated left ventricular ejection fractions ranging from 0.30 to 0.48. All patients had evidence of anterior wall dysfunction, and four patients had inferior wall dysfunction as well. Four patients required diuretic therapy for clinical congestive heart failure, and all experienced daily angina pectoris. No patient had taken digitalis or propranolol within two weeks of the start of the procedure, and none had taken nitrate therapy within six hours of testing; diuretic therapy was continued.

Myocardial Imaging and Processing

Each patient had his heart rate and blood pressure (by sphygmomanometry) measured in the seated position and was injected with 1 mCi thallium-201 intravenously. A myocardial scan using a 37.5 cm field Picker 415 nuclear camera was made in the anterior-posterior and 40° left anterior oblique projections 30 minutes later. This delay was found optimal due to the high early lung background activity of these individuals with clinical congestive heart failure. Due to the lack of significant cardiac output rise with handgrip, 30 minute delay was also employed for the exercise studies. Dual pulse height counting at 69-80 and 168 KeV and a dynamic parallel hole collimator were employed. The ten minute duration scintigrams were recorded on a Ohio-Nuclear 75 recorder. The central 19 by 19 cm region of the scintigram containing the cardiac image was displayed on the 64 by 64 element matrix of a Digital Equipment Corporation PDP-12 digital computer and the outer boundaries of the cardiac silhouette were visually identified. The noncardiac contribution to each matrix element within the cardiac boundaries was estimated from the mean of the linearly weighted values of the four elements immediately outside the cardiac silhouette on the element's horizontal and vertical intercepts with the cardiac border. These noncardiac counts were subtracted from the scintigram image and the matrix element with the highest count density was set to fixed level, with all other matrix elements being adjusted...
Process scintigrams were photographically taken from the computer display screen at identical photographic settings, and total cardiac and background counts were recorded. One week following the control resting determination, each patient underwent three minutes of 33% of maximal handgrip, sitting, with 1 mCi of thallium-201 injected intravenously at the end of the first minute of handgrip. Blood pressure and heart rate were measured immediately thereafter. A cardiac scintigram was taken thirty minutes later. Each patient was then placed on oral digoxin 0.25 mg daily and resting and handgrip scintigrams were made one and two weeks thereafter, respectively.

Processed Scintigram Analysis

Each scintigram was analyzed by two observers, in conjunction, without knowledge of the patient's exercise or drug status. Nine sectors within the cardiac silhouette were graded for both the anterior-posterior and the 40° left anterior oblique projections. A central circular sector of 1/3 the cardiac silhouette diameter and eight 45° arc circumferential sectors were delineated for each scintigram. Each sector was graded on a 0, 1, 2 scale: representing no visualized activity, partial or inhomogeneous visualized activity, and fully bright homogeneous activity, respectively.

The results of the study are shown in table 1. Normal scintigram mean scores are 34.7 ± 0.4 (SEM) at rest and 35.1 ± 0.4 at exercise in our laboratory, based upon 15 angiographically proven coronary disease free individuals. Both resting and exercise scores ranged normally from 32 to 36. Handgrip exercise in patients not receiving digitals decreased scintigram mean scores from 25.7 ± 1.5 to 23.0 ± 1.0, P < 0.05. In contrast, patients on maintenance digoxin did not change their scores during exercise significantly (25.5 ± 2.1 to 26.5 ± 1.9). Post exercise scores were significantly higher in patients on digoxin than off (P < 0.05), whereas resting scores were unaffected by digoxin. Two patients off digoxin experienced short episodes of angina pectoris during handgrip but none on digoxin had chest pain. No other untoward reactions were observed.

The anterior-posterior and 40° left anterior oblique scintigrams of a patient with a large heart are shown in figures 1 and 2. A large defect is seen following handgrip in the central and upper anterior regions of the anterior-posterior and

**TABLE 1. Scintigraphic and Hemodynamic Data in Six Patients with Coronary Artery Disease and Left Ventricular Dysfunction**

<table>
<thead>
<tr>
<th>Pt Status</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>Scan scores</th>
<th>Cardiac background ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 R O</td>
<td>66</td>
<td>128/78</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>H O</td>
<td>76</td>
<td>150/120</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>R D</td>
<td>56</td>
<td>114/80</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>H D</td>
<td>84</td>
<td>132/98</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>2 R O</td>
<td>65</td>
<td>114/74</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>H O</td>
<td>70</td>
<td>120/88</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>R D</td>
<td>65</td>
<td>110/80</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>H D</td>
<td>65</td>
<td>120/87</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>3 R O</td>
<td>80</td>
<td>106/80</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>H O</td>
<td>88</td>
<td>128/84</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>R D</td>
<td>72</td>
<td>98/72</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>H D</td>
<td>96</td>
<td>126/90</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>4 R O</td>
<td>68</td>
<td>96/68</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>H O*</td>
<td>74</td>
<td>126/96</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>R D</td>
<td>66</td>
<td>98/70</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>H D</td>
<td>72</td>
<td>120/90</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>5 R O</td>
<td>72</td>
<td>132/78</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>H O*</td>
<td>100</td>
<td>160/92</td>
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<td>11</td>
</tr>
<tr>
<td>R D</td>
<td>78</td>
<td>128/76</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>H D</td>
<td>112</td>
<td>170/90</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>6 R O</td>
<td>78</td>
<td>114/82</td>
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<td>14</td>
</tr>
<tr>
<td>H O</td>
<td>80</td>
<td>164/114</td>
<td>12</td>
<td>14</td>
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<tr>
<td>R D</td>
<td>68</td>
<td>127/80</td>
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<td>13</td>
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<tr>
<td>H D</td>
<td>72</td>
<td>148/106</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Mean R O</td>
<td>72 ± 2.6</td>
<td>115/77</td>
<td>25.7 ± 1.5</td>
<td>0.292 ± 0.026</td>
</tr>
<tr>
<td>*Experienced angina pectoris. Abbreviations: R = rest; H = handgrip; O = off digoxin; D = on digoxin; AP = anterior-posterior projection; LAO = left anterior oblique projection; SEM = standard error of mean.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
left anterior oblique projections, respectively. As can be seen, no defects developed following handgrip for this patient while he was on digoxin therapy. Figures 3 and 4 are those of a patient with a small heart who develops small defects (arrows) following handgrip. All of five patients who had left ventricular wall regional akinesis had corresponding resting scintigram defects, but mean resting scores were unaffected by digitalis.

Ratios of total cardiac to estimated noncardiac counts falling within the cardiac silhouette did not change significantly off digoxin (0.232 ± 0.026 to 0.220 ± 0.023) with handgrip, but increased significantly, from 0.217 ± 0.027 to 0.242 ± 0.022 (P < 0.02) with handgrip on maintenance digoxin. Individual variation was observed in blood pressure responses to exercise on and off digitalis, but mean values rose to statistically similar levels. Changes in scintigram scores and ratios did not correlate with such blood pressure responses to exercise.

Discussion

Isometric exercise in the form of sustained handgrip may cause electrocardiographic changes in patients with coronary artery disease but this happens less frequently than following bicycle exercise.78-21 Handgrip exercise does consistently result in a worsening of left ventricular function in individuals with resting ventricular dysfunction or diminished functional reserve.9, 10, 15, 14 Third and fourth heart sounds are frequently produced or accentuated following isometric exercise,14 and the resulting prompt increase in blood pressure7 is greater than following rhythmic exercise.8, 12 The 18% and 23% increases in heart rate and mean blood pressure, respectively, observed in the present study.
are close to the 20% and 23% values reported by Fisher et al.\textsuperscript{12} Using rubidium-84, Lowe et al.\textsuperscript{13} reported a 17% drop in mean myocardial blood flow in six individuals experiencing angina pectoris associated with handgrip. Although not strictly equivalent, the two individuals who experienced angina in our study had the greatest decreases in cardiac-background ratio of the six tested (19% and 32%).

Thallium-201 myocardial uptake has been shown by Strauss et al.\textsuperscript{14} to correlate closely with potassium-43 uptake, and by Mueller et al.\textsuperscript{15} to correlate well with myocardial perfusion as measured by the microsphere technique. Using unprocessed images, however, regions of hypoperfusion smaller than 4.9 grams in weight or of more than 45% of normal perfusion were not detected.\textsuperscript{16} Goris et al.,\textsuperscript{17} using a similar background subtraction method, has found improved visualization of defects in a patient and in phantoms. In order to obtain comparable scintigrams in which the only variation would be produced by the drug, we processed all scintigrams identically with fixed maximal scintillation count densities and contrast proportional to the scintillation count densities themselves. In addition, as high background (lung) count rate has been observed often in patients in clinical congestive heart failure and was found in the present patients, we used estimated background subtraction. The close association of the changes in the mean visually graded summed scores and the cardiac-background count ratios suggest that the processing did not introduce new information.

In this study, chronic digitalis administration reversed the handgrip induced regional myocardial hypoperfusion, abolishing the significant reduction in visually graded scores associated with and producing a significant increase in the cardiac-background ratio with handgrip. This cannot be attributed to a direct effect of digitalis on thallium-201 uptake, as digitalis is known to decrease thallium-201 uptake as an independent variable.\textsuperscript{18} The improved myocardial perfusion during exercise agrees with the clinically assessed reduction in exercise-induced angina pectoris following acute digitalization found by Malmborg\textsuperscript{19} and Sharma et al.\textsuperscript{20} Kahler et al.\textsuperscript{21} have reported a reduced oxygen debt with exercise following digitalization. More recently, Mahler et al.\textsuperscript{22} and this laboratory\textsuperscript{23} have reported improved left ventricular hemodynamics with increased afterload in dogs and in eight individuals with coronary artery disease, respectively, following chronic digitalis administration. Six of these eight patients are those of the current study, all having been demonstrated to have improved hemodynamics with exercise following digitalization.

The specific relationship between the improved myocardial performance and thallium-201 scintigrams with digitalis is not identified by this study. It is known, however, that isometric exercise produces a significant increase in left ventricular preload in patients with initially abnormal or borderline ventricular function.\textsuperscript{10, 12, 13} In turn, increased preload has been shown to reduce endomyocardial perfusion in dogs induced ischemic.\textsuperscript{14} Additionally, chronic digitalis administration, in reducing left ventricular volume during isometric exercise,\textsuperscript{25} reduces systolic left ventricular wall tension, thus decreasing myocardial oxygen requirements. The lack of resting change following digitalization suggests that digitalis itself does not alter myocardial perfusion. In response to the improved hemodynamics, with a fixed degree of exercise in a patient on digitalis, however, scintigram hyperperfusion is lessened. It is unknown whether digitalis affects thallium-201 scintigrams in patients with normal ventricular function or those maximally stressed, but the drug does alter exercise scintigrams in patients with coronary artery disease and left ventricular dysfunction at submaximal levels of exertion.

**Acknowledgment**

The authors wish to express their appreciation for the expert secretarial assistance of Mrs. Carol Vandello.

**References**

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Serum Glycoproteins in Coronary Artery Disease

STUART SNYDER, M.D., EUGENE L. COODLEY, M.D., BEATRICE C. DURHAM, M.A., AND RONALD S. PENNOCK, M.D.

SUMMARY Serum glycoprotein levels were compared in two groups of age- and sex-matched patients, 15 with coronary artery disease and 14 normal controls. While total glycoprotein levels were increased in the coronary group, significantly higher levels were found in only five of 16 glycoproteins — Cp, haptoglobin, GC-
globulin, α1-acid glycoprotein, and Ca activator — with no change in 10 other glycoproteins and significant decrease in transferrin.

This study demonstrates what appears to be a glycoprotein profile in coronary artery disease and reviews possible interactions of glyco-
proteins with known risk factors in atherogenesis.

ELEVATION OF SERUM PROTEIN-BOUND CAR-
BOHYDRATE has been reported in a number of unrelated disease entities including diabetes, infections and inflam-
mations, malignancy, and hyperlipidemic subjects of all types. To account for this elevation in hyperlipidemic sub-
jects, a specific profile of glycoprotein response has been described. This is characterized by elevations of α1-acid glycoprotein, hemopexin, haptoglobin, ceruloplasmin, and the complement proteins C3, C4, and Ca activator.

In addition, there have been reports describing elevation of total serum glycoproteins in chronic atherosclerotic cardio-
vascular disease. However, because there is no information as to the precise glycoprotein changes in this latter condition and also because of a possible association between glyco-
protein abnormalities and increased atherosclerosis, the following study was undertaken.

Methods

Fifteen patients who had documented chronic sympto-
matic coronary arterial disease but were free of any other disease entities were selected for this study. These patients all had had myocardial infarctions at least one year in the past, as defined by the usual clinical and laboratory criteria or else had significant symptomatic angina pectoris with coronary visualization documenting significant atherosclerosis. None were hypertensive or diabetic nor were any hyperlipidemic subjects included (based on their having normal lipid profiles). In addition, no patient who had an acute infarction was included if it had occurred within a year of the study. None of the patients showed evidence of diabetes even with the occurrence of myocardial infarction.

Also excluded were patients with a history of any recent infectious process or acute inflammatory process within the year preceding the study.

Fourteen normal control subjects were used for compar-
ison. These were free of any apparent disease and were age and sex-matched. The mean age of the normal controls was 48.9 ± 3.8 and this group contained six females and eight males. The mean age for the coronary patients was 50.1 ± 5.5 and there were also six females in this group. They were also matched for race.

Both groups of patients and controls were recruited from volunteers. In the case of controls they were hospital employees. The patients were ambulatory outpatients who have informed consent for venipuncture. No patient was on any drug (including estrogens, androgens or steroids) which has ever been shown to affect blood protein concentrations. Random glucose values in the study patients were at all times under 105 mg%, fasting cholesterol under 240 mg%, and fasting triglyceride under 130 mg%. In the control group, these studies were also in the same limits.

Single samples from both patients and controls were collected over a three week period. Red blood cells were removed from plasma by centrifugation and the serum stored at -10° C for studies.

Protein-bound carbohydrate — a measure of the total serum glycoprotein level — was determined by the Phenol-
Sulfuric method using a standard composed of galactose, mannose, and fucose in the ratio of 5:5:1. This is similar to the carbohydrate composition in serum glycoproteins.

Quantitation of individual serum glycoproteins was per-
formed by standard radial immunodiffusion using plates containing monospecific antiserum obtained from Behring.
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