Myocardial Infarction Following Coronary Ligation in Dogs

HEMODYNAMIC EFFECTS OF ISOPROTERENOL AND ACETYLSYROPHANTHIDIN

By William B. Hood, Jr., M.D., Brian McCarthy, Ph.D., and Bernard Lown, M.D.

ABSTRACT

In the subacute phase of myocardial infarction following coronary ligation in dogs, a relationship was noted between the extent of infarction and the degree of elevation of left ventricular end-diastolic pressure. Left ventricular filling pressure was consistently increased when 25% or more of the left ventricle was infarcted. Isoproterenol infusion resulted in enhanced left ventricular function in both control and infarcted dogs, but the response was clearly weakened in those animals in which more than 20% of the left ventricle was infarcted. Acetylstrophanthidin caused no improvement in left ventricular function in infarcted dogs as judged by the relationship between filling pressure and cardiac output. The peak rate of rise of left ventricular pressure did increase in animals with infarcts, but was less than that in controls. Animals with infarcts had a lowered threshold for production of ventricular tachycardia by acetylstrophanthidin. These results in dogs suggest the need for further assessment of the role of digitals in the treatment of heart failure following acute myocardial infarction.

ADDITIONAL KEY WORDS

Heart failure and shock commonly accompany acute myocardial infarction but hemodynamic measurements have failed to show a consistent pattern (1, 2). Furthermore, in both man and in animals, the degree of circulatory impairment does not appear to correlate well with the extent of myocardial infarction.

In patients, the discrepancy between the degree of myocardial injury and performance probably stems from variations in function of the remaining viable myocardium, from arrhythmias, from reflex changes in the myocardium and in resistance and capacitance vessels, and from secondary factors such as hypoxia and electrolyte derangement due to prolonged circulatory insufficiency. Acute experiments in animals present the same limitations, and in addition are often carried out in open-chest animals following protracted anesthesia and extensive instrumentation.

The present study was designed to explore the relationship between the extent of myocardial injury following coronary ligation and the degree of hemodynamic changes, while attempting to minimize the influence of other variables. This was accomplished by studying the close-chest animal several days after ligation at a time when arrhythmia and shock were absent. In addition, isoproterenol and acetylstrophanthidin were administered in an...
attempt to demonstrate defects in the responsiveness of the infarcted ventricle, and to determine potential usefulness in therapy.

Methods

Twenty-eight mongrel dogs of both sexes were anesthetized with pentobarbital 30 mg/kg iv and subjected to thoracotomy and ligation of the left anterior descending coronary artery. The two-stage method devised by Harris was employed (3). Ligation was carried out at or just below the tip of the left atrial appendage, at a distance that averaged 2.2 cm (range, 1.8 to 3.2 cm) from the mouth of the left main coronary artery, as was measured post-mortem. Six animals died of ventricular fibrillation during the procedure, and an additional 10 animals died during the period of sustained ventricular tachycardia which usually begins several hours after ligation and lasts through the second postoperative day. The 12 surviving animals were studied on the third or fourth day after ligation as will be described. All had normal sinus rhythm at the time of study. In 7 additional animals, the thorax and pericardium were opened, but the coronary vessels were not dissected or ligated; these animals comprised the control group referred to hereafter as "sham-operated" animals.

On the third or fourth day following operation, animals were given 1.5 mg/kg of morphine sulfate intramuscularly, then anesthetized with 0.3 ml/kg of a mixture containing 200 mg urethane, 50 mg allobarbital, and 30 mg pentobarbital/ml iv. Heparin (50 mg) was administered intravenously. Intravascular pressures were recorded using Sanborn model 267BC pressure transducers from catheters placed in the arch of the aorta and right atrium, and from a 0.84-mm bore stainless steel tube 44 cm long inserted through the right carotid artery into the left ventricle. This system responded adequately to frequencies of 25 cycle/sec, as determined by application of a square wave of 150 mm Hg pressure (bursting a balloon affixed to tip of tubing). In 2 other dogs, contrast material was injected into the aortic root with the tube in place in the left ventricle; aortic regurgitation was absent. The first derivative of left ventricular pressure \((dP/dt)\) was obtained by electronic differentiation. Left ventricular end-diastolic pressure was taken as the mean of the values obtained during one or more complete respiratory cycles. Indicator dilution cardiac output curves were inscribed by injecting indocyanine green dye into the right atrium and recording from a fiberoptic catheter situated in the ascending aorta, using methods previously described (4). Dye injections were always made at end-expiration. All tracings were recorded on an Electronics for Medicine Model DR-8 recorder. Ventilation was maintained through a cuffed endotracheal tube using a Harvard respiratory pump. Arterial oxygen saturation was greater than 90% in all animals. In 2 of the animals with infarcts this required the administration of 100% oxygen. The remaining animals were ventilated with room air. Bectal temperature was monitored and kept within 1°C of the baseline value by using a heating pad. The animals lay on their left sides throughout the procedure, and the zero level for pressure measurements was set at the mid-chest position as determined by careful measurement. Following baseline control measurement of pressures and cardiac output, isoproterenol was infused intravenously at a rate of 5 μg/min. At the third minute of isoproterenol infusion, measurements were repeated. A steady state was achieved at the time of this measurement, as indicated by a stable heart rate and mean arterial pressure. Following a 15-min recovery period another set of baseline measurements was obtained, then acetylstrophanthidin was infused at a rate of 100 μg/min until ventricular tachycardia (defined as 4 successive beats of ventricular origin) ensued. This is referred to hereafter as the "toxic dose." During the infusion, pressures and cardiac output were measured at 1, 3, and 5 min, and every 3 min thereafter during which normal sinus rhythm persisted. The data in Table 3 and in Figures 7 and 8 represent the average values for the last set of measurements prior to the onset of ventricular tachycardia. At the time of this measurement, the percentage of the toxic dose of acetylstrophanthinid infused was 85 ± 2% (SEM) for sham-operated dogs and 81 ± 3% (SEM) for dogs with a coronary artery ligated. All procedures were carried out within 2 hr to minimize the effects of prolonged anesthesia.

![Graph](http://circres.ahajournals.org/)

**FIGURE 1**

Left ventricular end-diastolic pressure under baseline conditions in relation to size of infarct. \(r = +0.56 (0.01 < P < 0.05)\), \(y = 0.265x + 6.12\).
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Calculations of stroke index and peripheral vascular resistance were made as previously described (5). The time integral of pressure during systole (pressure-time per beat) was calculated as the product of systolic mean pressure and the systolic ejection period, both measured from the aortic root pressure tracing. Statistical evaluation was carried out using Student's t-test (6).

Following the procedure, animals were killed with an overdose of pentobarbital. The hearts were excised, and the entire heart and its individual chambers were weighed. The infarct was excised and weighed separately. Relative infarct size was expressed according to the percentage of total left ventricular weight which it represented. Anatomically, the infarct usually comprised a well-demarcated oval segment of ventricle extending with long axis down the anterolateral surface of the left ventricle to the apex, and sparing the right ventricle. Occasionally there were uneven margins or layers of viable tissue in the infarct; if so, these were carefully trimmed away before weighing.

Results

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Under baseline conditions left ventricular end-diastolic pressure (LVEDP) was 10 mm Hg or higher in all 4 animals that had infarcts larger than 25% of the left ventricle. LVEDP was also increased in 2 of the 4 animals that had 20 to 25% of the left ventricle with infarcts, and in 1 of the remaining 4 animals with infarcts of smaller size (Fig. 1). All of the sham-operated animals showed LVEDP of less than 10 mm Hg. Right heart filling pressures were not elevated: The mean right atrial pressure in sham-operated animals was \( -0.8 \pm 0.3 \text{ mm Hg (SEM)} \), \( +0.8 \pm 0.3 \text{ mm Hg (SEM)} \) in animals that had infarcts smaller than 25% of the left ventricle, and \( +1.9 \pm 0.8 \text{ mm Hg (SEM)} \) in animals that had infarcts larger than 25% of the left ventricle.

Despite the defect in the left ventricular wall in dogs with myocardial infarction, there were no significant differences in mean arterial blood pressure, heart rate, cardiac index, dP/dt, or peripheral vascular resistance between sham-operated animals and those with myocardial infarction (Table 1). However, stroke index was low in animals with large infarcts (Fig. 2), suggesting that these animals did not have the same capacity to eject blood.

EFFECTS OF ISOPROTERENOL

Results of administration of isoproterenol are shown in Table 2 and in Figures 3 and 4. The increase in dP/dt, heart rate, and cardiac index noted in the sham-operated animals was markedly less in animals with large infarcts (Fig. 3). Using the relationship between stroke index and left ventricular filling...
### TABLE 1

**Hemodynamic Measurements under Baseline Conditions**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>% of left ventricular infarct</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Heart rate (beat/min)</th>
<th>Cardiac index (liter/min per m²)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>Peripheral vascular resistance index (dyne • sec • cm⁻² • m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (7 dogs)</td>
<td>Ligated (12 dogs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.9* ±0.9</td>
<td>20.2 ±0.7</td>
<td>21 ±5</td>
<td>114 ±9</td>
<td>108 ±6</td>
<td>116 ±9</td>
<td>3.17 ±0.21</td>
</tr>
<tr>
<td>16.5</td>
<td>20.3</td>
<td>36</td>
<td>119</td>
<td>148</td>
<td>109</td>
<td>3.38 ±0.21</td>
</tr>
<tr>
<td>22.5</td>
<td>17.5</td>
<td>29</td>
<td>147</td>
<td>110</td>
<td>181</td>
<td>3.48 ±0.24</td>
</tr>
<tr>
<td>19.5</td>
<td>15.5</td>
<td>28</td>
<td>100</td>
<td>87</td>
<td>178</td>
<td>2.32 ±0.21</td>
</tr>
<tr>
<td>23.0</td>
<td>20.5</td>
<td>26</td>
<td>114</td>
<td>124</td>
<td>120</td>
<td>3.78 ±0.24</td>
</tr>
<tr>
<td>20.0</td>
<td>24.5</td>
<td>22</td>
<td>119</td>
<td>112</td>
<td>122</td>
<td>3.34 ±0.21</td>
</tr>
<tr>
<td>19.5</td>
<td>19.0</td>
<td>21</td>
<td>145</td>
<td>72</td>
<td>106</td>
<td>3.74 ±0.24</td>
</tr>
<tr>
<td>18.0</td>
<td>19.5</td>
<td>21</td>
<td>119</td>
<td>129</td>
<td>147</td>
<td>3.34 ±0.21</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

### TABLE 2

**Change in Hemodynamic Measurements with Isoproterenol Infusion**

<table>
<thead>
<tr>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Heart rate (beat/min)</th>
<th>Cardiac index (liter/min per m²)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>Peripheral vascular resistance index (dyne • sec • cm⁻² • m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (7 dogs)</td>
<td>Ligated (12 dogs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5 ±5*</td>
<td>-3 ±3</td>
<td>+50 ±5</td>
<td>+29 ±7</td>
<td>+3.10 ±0.43</td>
</tr>
</tbody>
</table>

Significance

*Mean ± SEM.
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Change in Hemodynamic Measurements with Acetylstrophanthidin Infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham (7 dogs)</th>
<th>Ligated (12 dogs)</th>
<th>Ligated - Sham (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure</td>
<td>+24 ± 16*</td>
<td>+18 ± 5</td>
<td>0.60 &lt; P &lt; 0.70</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>39 ± 10</td>
<td>38 ± 9</td>
<td>0.90 &lt; P &lt; 0.95</td>
</tr>
<tr>
<td>Cardiac index (liter/min/m²)</td>
<td>5.60 ± 0.12</td>
<td>5.60 ± 0.12</td>
<td>0.80 &lt; P &lt; 0.90</td>
</tr>
<tr>
<td>Change in dP/dt (mmHg/sec)</td>
<td>+1540 ± 770</td>
<td>+640 ± 110</td>
<td>0.05 &lt; P &lt; 0.10</td>
</tr>
<tr>
<td>Change in LVEDP (mmHg)</td>
<td>+1690 ± 1020</td>
<td>+1910 ± 110</td>
<td>0.70 &lt; P &lt; 0.80</td>
</tr>
</tbody>
</table>

FIGURE 3
Relationship between change in various hemodynamic variables following isoproterenol infusion and size of infarct.

pressure as a measure of ventricular function, larger infarcts were associated with a diminished efficacy of isoproterenol in reducing LVEDP and in raising stroke index (Fig. 4). These results show that both inotropic and chronotropic responsiveness to isoproterenol was impaired in animals with infarcts, especially in those with large infarcts.

EFFECTS OF ACETYLSYROPHANTHIDIN

The mean dose of acetylstrophanthidin required to produce ventricular tachycardia was significantly lower in animals with infarcts than in sham-operated animals (Fig. 5). However there was great variation in the toxic dose of acetylstrophanthidin among animals with infarcts, and many of them tolerated amounts of this agent that were in the control range (Fig. 5).
Relationship between mean stroke index and mean left ventricular end-diastolic pressure under baseline conditions (open symbols) and with isoproterenol infusion (closed symbols). Circles represent sham-operated animals (6 dogs), triangles animals with infarcts smaller than 25% of the left ventricle (8 dogs), and squares animals with infarcts larger than 25% of the left ventricle (4 dogs). Brackets indicate SEM.

FIGURE 5
Total dose of acetylstrophanthidin per kilogram of body weight required to produce ventricular tachycardia in sham-operated animals and animals with infarcts. Mean value for sham-operated animals = 61.6 ± 4.3 µg/kg (SEM) and for animals with infarcts = 46.5 ± 4.8 µg/kg (SEM). (0.01 < P < 0.05). There is no clear relationship between toxic dose and size of infarct.

FIGURE 6
Mean values for percentage change in dP/dt during infusion of acetylstrophanthidin. Figures in parentheses show the number of animals still having sinus rhythm when the point was plotted. Arrows indicate the average time of onset of ventricular tachycardia.

A positive inotropic response to acetylstrophanthidin, as measured by increased dP/dt, was present in both sham-operated animals and those with infarcts, but was less marked in those with infarcts (Table 3, Fig. 6). This was especially apparent in animals with infarcts that tolerated larger doses of acetylstrophanthidin. These animals showed a plateau in dP/dt response at a point when only half the toxic dose had been infused (Fig. 6).

Sham-operated animals and those with infarcts both showed a similar rise in mean arterial pressure and peripheral vascular resistance, and reduction in heart rate and cardiac index with acetylstrophanthidin infusion. The decline in cardiac index, present in almost every animal, was associated with variable changes in LVEDP in both sham-operated animals and those with infarcts (Fig. 7). Of the 4 animals with the largest infarcts, all of which had elevated LVEDP (Fig. 1), none showed a fall in LVEDP with infusion of acetylstrophanthidin (Fig. 7).

The presence of a decline in cardiac index, with no consistent change in LVEDP may imply a decrease in left ventricular contractility, or shift to a lower ventricular function curve; however, the rise in dP/dt with acetylstrophanthidin infusion depicted in Figure 6 indicates that an increase in contractility occurred.
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Change in Cardiac Index
(liter/min/m²)

Change in Left Ventricular End-Diastolic Pressure (mmHg)

BASELINE AS BASELINE

FIGURE 7
Changes in cardiac index and left ventricular end-diastolic pressure during acetylstrophanthidin infusion. Sham-operated animals on the left, and animals with infarcts on the right. For animals with infarcts the dotted lines represent animals with infarcts larger than 25% of the left ventricle. The majority of animals showed a reduction in cardiac index. Left ventricular end-diastolic pressure showed no consistent change in either group. Data obtained from last set of observations prior to onset of ventricular tachycardia (see Methods).

Rise in arterial pressure and increased afterload to contraction may be responsible in part for this discrepancy. As shown in Figure 8, there was a correlation between changes in pressure-time per beat and changes in LVEDP with acetylstrophanthidin infusion. In 1 animal with an infarct, an extreme elevation of pressure-time per beat clearly was associated with acute left ventricular failure (top right corner). This animal also had a 41% reduction in cardiac index with acetylstrophanthidin, the largest such change observed in any animal.

Discussion
Acute myocardial infarction in experimental animals produces an unstable shocklike state (7), in which reflex peripheral vasodilatation may play a prominent role (8). These changes in the peripheral circulation may result in diminished venous return, fall in cardiac output, and hypotension, quite apart from changes in myocardial contractility. However, when filling pressures are artificially raised by transfusion, cardiac output may be elevated to normal (9). A clinical counterpart has been noted in some instances of myocardial infarction with shock in patients, in whom elevation of filling pressure by infusions resulted in improved cardiac output (10).

Compared with animals immediately following infarction, the subacute preparation possesses the advantages of hemodynamic stability, lack of susceptibility to sudden death from arrhythmia, presence of an anatomically well defined lesion of the left ventricle which can be measured, and a circulatory defect which appears to depend exclusively upon myocardial factors.

Maintenance of a cardiac output which is normal, or nearly so, in the presence of substantial infarction of the left ventricle indicates that compensatory mechanisms are brought into play. These may include elevation of left ventricular filling pressure, and
Increased inotropism from release of endogenous catecholamines may also play a role (11). Obviously if ventricular destruction is extensive enough, the remaining myocardium will not be able to support the circulation. Since the largest infarct observed among the survivors in this series was 36% of the left ventricle, it may be that this figure approaches the limit compatible with survival.

Catecholamines such as isoproterenol which stimulate β-adrenergic receptors exert a profound positive inotropic effect upon the myocardium (12). Administration of isoproterenol in this preparation resulted in increased stroke index and lowered LVEDP, indicating that improvement had occurred in ventricular function (Fig. 4). These changes and those in heart rate, dP/dt, and cardiac index (Fig. 3) were less marked in animals with infarcts than in sham-operated animals. These latter three variables appeared to be markedly affected when more than 20% of the left ventricle was infarcted, and their measurement may help to identify intact animals with large infarcts.

Previous authors have indicated that digitalis may decrease cardiac output in the normal open-chest dog by reducing venous return to the heart and so decreasing left ventricular filling pressure (13). In the present study LVEDP showed no consistent change during the infusion of acetylstrophanthidin either in sham-operated dogs or in those with left ventricular infarcts, and despite this, cardiac index declined (Fig. 7). That an increase in contractility did occur in both groups of animals is indicated by the increase in dP/dt (Fig. 6), but evidently this was not of sufficient magnitude to offset increases in afterload to contraction (Fig. 8). Beneficial effects of digitalis have previously been demonstrated in the acute phase after coronary embolization in dogs, with both reduction in filling pressure of the left ventricle and rise in cardiac output (14). In the subacute phase of infarction examined in the present study, when elevated left ventricular filling pressure was the predominating manifestation of left ventricular impairment, administration of acetylstrophanthidin resulted in no net improvement in ventricular function. A greater degree of heart failure, with marked lowering of cardiac output and elevated right heart filling pressures, with the attendant changes in arteriolar and venomotor tone (15) may be a prerequisite to obtaining beneficial effects from acetylstrophanthidin.

Clinical reports have suggested that ordinary doses of digitalis may be safely employed in patients with myocardial infarction (16). However no critical study of the minimal toxic dose of digitalis in such patients has yet been carried out. The present investigation demonstrates that ventricular tachycardia occurred with lower doses of acetylstrophanthidin in the subacute phase of infarction in dogs; similar findings have been previously reported (17, 18). These results indicate the need for continuing caution in giving large amounts of digitalis to human patients with acute myocardial infarction.

There are obvious differences between myocardial infarction in man and infarction from acute coronary ligation in dogs, in the nature of the pathologic process, in the performance of the uninfarcted myocardium, and in the degree of collateral circulation to the ischemic region. It is not certain how applicable these studies in animals are to clinical use. However, the dog ventricle with an infarct studied under stable conditions several days after ligation does provide a convenient model of mild left ventricular failure, with many reproducible and consistent features for the study of myocardial infarction.

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References


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greater excitability and rhythmicity of these hearts may be in part responsible for the fibrillary tendency, but this factor only accentuates the importance of the mass factor. The large size, slow conductivity, and relative independence of vascular nutrition, as compared with the mammalian heart, coupled with the pronounced tendency to fibrillate, made it feasible to conduct upon the ventricles of marine turtles some experiments which have a fundamental bearing on the nature of the fibrillary contractions.

The Ring Experiment.—It was found that rings, two centimetres broad, cut from the base of the fibrillating ventricles of large loggerhead turtles did not recover from the fibrillary contractions. A most striking phenomenon resulted when such broad fibrillating rings were narrowed by incising midway between the outer and inner margins, the incisions in these cases not being carried completely around the ring. In this way, by separation of the inner and outer portions, a figure 8 was formed, the two loops being connected by the broad fibrillating isthmus; a second cut across this mass connecting the inner margins of the two loops converted the tissue into a single large ring one centimetre broad and from six to ten centimetres in diameter. As soon as this narrowing was completed it was found that the inco-ordinated fibrillary contractions had resolved themselves into a number of contraction waves which followed each other successively and repeatedly around and around the ring, all progressing in the same direction, an exhibition to which we may apply the term "circus contractions." ¹ It usually so happened that the number of contraction waves gradually decreased until but a single contraction wave was left repeating its circuit again and again. In one instance such a wave continued around the ring for seven hours, making each circuit in from six to seven seconds, the diameter of the ring being ten centimetres. When such waves died out new ones were easily started by single mechanical stimuli. Faradic

¹ These experiments were conducted and publicly demonstrated at Woods Hole, Mass., before the appearance of the paper of R. G. Mines (Journal of physiology, 1913, xlvi, p. 349). Our rings were, however, cut from fibrillating tissue, which makes the results especially significant for the interpretation of the nature of the fibrillary process. Our conclusions are, in many respects similar to those of Mines (I. c., p. 373).
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