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Experimental Myocardial Infarction

VI. EFFICACY AND TOXICITY OF DIGITALIS IN ACUTE AND HEALING PHASE IN INTACT CONSCIOUS DOGS

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ABSTRACT Use of digitalis in myocardial infarction is controversial. To determine the efficacy and toxic threshold, serial infusions of 3 μg/kg per min of acetylstrophanthidin were given to six intact conscious dogs 24 hr before and 1 hr, 2 days, and 7 days after myocardial infarction induced by inflation of a balloon cuff implanted on the left anterior descending coronary artery. Within 1 hr after myocardial infarction, heart rate increased by 28%. Left ventricular end-diastolic pressure increased from 7 to 20 mm Hg, and stroke volume decreased by 25%. At this time acetylstrophanthidin caused no beneficial hemodynamic change. 1 wk later, the heart rate and left ventricular end-diastolic pressure had declined toward normal but remained elevated. At this time, acetylstrophanthidin lowered left ventricular end-diastolic pressure by 25%, and increased the stroke volume and cardiac output by 25% and 21% respectively, without any change in heart rate or aortic pressure. Tolerance to acetylstrophanthidin, defined as appearance of ventricular tachycardia, declined the 1st hr after myocardial infarction by 24% ($P < 0.05$) from the control level of 43 ±4 μg/kg (SEM), but subsequently returned to control.

Thus, immediately after myocardial infarction, tolerance to acetylstrophanthidin was reduced, and left ventricular failure was not ameliorated. 1 wk later in the healing phase of myocardial infarction, tolerance to acetylstrophanthidin returned to normal and left ventricular performance was improved by this drug. The study suggests a limited therapeutic role for digitalis in the treatment of left ventricular failure in the acute phase immediately after myocardial infarction, but beneficial effects may occur in the healing phase 1 wk later.

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INTRODUCTION

The use of digitalis in acute myocardial infarction has been controversial since its inception. Little is known about the efficacy of digitalis in left ventricular failure of myocardial infarction. In patients with myocardial infarction without shock and congestive heart failure, the only hemodynamic alteration observed during digitalization was a 5% increase in arterial pressure (1). In another study, a fall in cardiac output after intravenous digitalization was reported in patients with myocardial infarction and poor left ventricular function (2). Similarly, no beneficial effect of digitalis was demonstrated 3 days after experimental canine myocardial infarction (3). Despite the lack of objective data, digitalization has been recommended in heart failure of acute myocardial infarction by various authors (4–10).

The toxic effects of digitalis in acute myocardial infarction have been studied in more detail. No alteration of tolerance to digitalis immediately after experimental coronary ligation, and decreased tolerance in the subacute phase has been reported (3, 11–13). On the contrary, decreased tolerance to digitalis has been reported in the early stages of myocardial infarction in pigs, although the exact time of onset of infarction was not known (14). In only one clinical study was an attempt made to determine whether patients with myocardial infarction are unduly sensitive to digitalis (15). In this investigation, limited to uncomplicated cases, 1.2 mg of digitoxin given orally in the first 48 hr after admission did not produce any untoward effects.

The present investigation in experimental canine myocardial infarction was designed to answer the following questions: (*a*) Is digitalis beneficial in acute myocardial infarction? (*b*) Does the efficacy of digitalis change

from the acute to the healing stage of myocardial infarction? (*c*) Does digitalis tolerance change between acute and healing stages of myocardial infarction?

METHODS

Six mongrel dogs weighing 23.3 ±2.3 (SEM) kg were studied consecutively. The technic of producing myocardial infarction in the intact conscious dog has been reported in detail (16, 17). 10–15 days before the initial study, a thoracotomy was performed under pentobarbital anesthesia, and an inflatable balloon cuff device was placed around the left anterior descending coronary artery.

Experimental design. For each of the serial digitalizations carried out in this study, acetylstrophanthidin 3 μg/kg per min was infused continuously into the inferior vena cava until the animals developed ventricular tachycardia. Ventricular tachycardia was defined as a consecutive run of more than 10 ventricular beats at a rate exceeding 100 beats/min, however the infusion was continued until stable fast ventricular tachycardia developed. Since all animals received a little more acetylstrophanthidin than was required to induce ventricular tachycardia, the duration of ventricular tachycardia was not analyzed.

Four separate digitalizations were carried out in each animal. In three of these studies, continuous electrocardiographic and hemodynamic measurements were made: (*Study No. 1*) A control infusion of acetylstrophanthidin was carried out. (*Study No. 2*) 24 hr later myocardial infarction was produced as previously described (16, 17). In two of the six animals, occasional ventricular ectopic beats occurred approximately 15 min after onset of infarction, however, antiarrhythmic agents were not employed. 1 hr after infarction, acetylstrophanthidin was again infused. (*Study No. 3*) 48 hr after myocardial infarction, when postinfarction ventricular arrhythmias had subsided and the animals had returned to normal sinus rhythm, acetylstrophanthidin was again infused. At this time the electrocardiogram was recorded, but no hemodynamic measurements were made. (*Study No. 4*) 1 wk after myocardial infarction, the acetylstrophanthidin infusion study was repeated.

In all studies, Nos. 1–4, the animals were sedated with 15 mg of morphine sulfate given intramuscularly 1 hr before the procedure. All the animals survived the four studies.

Procedure. The animals were positioned on their right sides. Under local anesthesia, a femoral artery and vein were isolated. Under fluoroscopic control Cournand catheters Nos. 7 to 9 were placed in the left ventricle and pulmonary artery. Two polyethylene catheters (I.D. 0.045 inch) were inserted into the same artery and vein, one into the aorta and the other into the inferior vena cava. For studies Nos. 1, 2, and 4, pressures were measured continuously in the aorta, left ventricle, and pulmonary artery. Cardiac output was measured before and every 4 min during infusion of acetylstrophanthidin into the inferior vena cava until the onset of ventricular tachycardia. At the end of each study, the catheters were withdrawn and the arteriotomy repaired. All the animals were sacrificed after study No. 4, and the presence of anterior wall myocardial infarction was confirmed at postmortem examination.

All recordings were made on a multichannel photographic recorder (Hewlett-Packard Co., Palo Alto, Calif.). The zero for pressure measurements was taken at mid-chest level. Pressures were measured using Statham P23Db transducers. Left ventricular pressure was recorded at high and low gain simultaneously. Cardiac output was determined by injecting 2.5 mg of indocyanine green dye into the pulmonary artery and continuously withdrawing blood from the aorta by a Harvard withdrawal pump, through a Gilford densitometer. After each measurement, the withdrawn blood was returned to the animal. Arterial blood P_{O_2}, P_{CO_2}, pH, and serum sodium, potassium, and chloride were measured in studies 1, 2, and 4 before digitalization and again after onset of digitalis toxicity. In addition, in study No. 2, these parameters were measured before myocardial infarction. P_{O_2} was measured with a modified electrode system (Clark Micro-Capillary Reservoir Electrode 2-100R, model 113-S, Instrumentation Laboratory Inc., Watertown, Mass.) and P_{CO_2} and pH by the same apparatus using a capillary electrode (Severinghaus and Sanz, model 107-0). Serum sodium and potassium were measured in duplicate by flame photometry and serum chloride by the method of Cotlove, Trantham, and Bowman (18). Oxygen saturation was calculated from P_{O_2} and pH (19). In the majority of the studies, hematocrit was measured in duplicate by the microcrit method. The quantity of blood withdrawn from the animal on each experimental day was 31 ml, or a total of 93 ml for the three experiments.

The data were analyzed in the following manner:

(*a*) For studies Nos. 1, 2, and 4, the hemodynamic data before acetylstrophanthidin infusion were compared with the last complete set of hemodynamic measurements before the onset of ventricular tachycardia.

(*b*) To compare the efficacy of an equivalent dose of acetylstrophanthidin before and 1 hr and 1 wk after myocardial infarction (studies Nos. 1, 2 and 4), the data were also analyzed after administration of 24 μg/kg of the drug. This was done to eliminate possible dose-dependent effects, since the amount of acetylstrophanthidin tolerated was reduced 1 hr after acute myocardial infarction.

(*c*) The total dose of acetylstrophanthidin, which induced ventricular tachycardia, was compared in studies Nos. 1–4.

All comparisons were made by paired *t* test (20), and the data are presented as mean ±SEM.

RESULTS

The hemodynamic changes are summarized in Table I, and serum electrolytes, blood gases, and pH in Table II.

Hemodynamic effects of digitalis

Control study (study No. 1) (Table I). Acetylstrophanthidin did not significantly alter heart rate, aortic, left ventricular end-diastolic, or pulmonary arterial pressures, nor total systemic and pulmonary resistance; however, stroke volume increased by 20% ($P < 0.05$). Cardiac output increased by 16%, but was not statistically significant.

Acute myocardial infarction (study No. 2). The control hemodynamic measurements before myocardial infarction were comparable with those observed in study No. 1. 1 hr after acute myocardial infarction, there was a 25% decrease in stroke volume ($P < 0.05$), and a 28% increase in heart rate ($P < 0.05$). Left ventricular end-diastolic pressure increased from 7.1 ±1.1 to 19.6 ±4.1 mm Hg ($P < 0.01$), and mean pulmonary arterial pressure increased by 44% ($P < 0.05$). There were no

TABLE I

Hemodynamic Data (Mean ±SEM) before and during Digitalization in the Control State (Study No. 1), Acute Myocardial Infarction (Study No. 2), and 7 Days after Myocardial Infarction (Study No. 4)

	n	Toxic dose	Heart rate	Cardiac output	Stroke volume	Pressures: Mean aortic	Pressures: Left ventricular end-diastolic	Pressures: Mean pulmonary arterial	Resistances: Total pulmonary	Resistances: Total systemic
		%	*beats/min*	*liters/min*	*ml/beat*	*mm Hg*	*mm Hg*	*mm Hg*	*dyne-sec/cm⁵*	*dyne-sec/cm⁵*
Control (study No. 1)										
Pre-AS	6		82 ±3	3.37 ±0.26	40.7 ±2.2	115 ±6	9.3 ±1.5	12.6 ±1.3	309 ±45	2880 ±415
AS, 24 μg/kg	6	58 ±5	75 ±5	3.42 ±0.29	45.8 ±3.5*	115 ±7	8.1 ±0.8	12.8 ±1.6	305 ±41	2984 ±503
AS, pre-VT	6	81 ±5	79 ±6	3.90 ±0.56	48.8 ±4.7‡	115 ±4	7.6 ±1.0	12.8 ±1.7	273 ±39	2803 ±528
Acute myocardial infarction (study No. 2)										
Pre-MI	6		82 ±3	3.68 ±0.36	43.6 ±3.1	108 ±6	7.1 ±1.1	12.0 ±1.0	283 ±30	2503 ±258
1 hr after MI	6		105 ±6§	3.44 ±0.22	32.9 ±3.3§	123 ±4	19.6 ±4.1§	17.3 ±2.4§	367 ±50	2990 ±300
AS, 24 μg/kg	5	70 ±6	97 ±11	3.15 ±0.22	34.0 ±5.6	141 ±11‖	15.6 ±3.7	15.5 ±2.0	390 ±56	3589 ±390‖
AS, pre-VT	6	78 ±4	92 ±9	3.04 ±0.35¶	33.4 ±5.3	140 ±8¶	16.1 ±3.1	14.8 ±1.6	425 ±89	3865 ±403¶
Healing myocardial infarction (study No. 4)										
Pre-AS	6		99 ±4	3.21 ±0.38	31.8 ±2.8	113 ±6	15.6 ±3.0	15.6 ±2.3	437 ±61	3113 ±417
AS, 24 μg/kg	5	60 ±10	96 ±9	3.81 ±0.65**	39.5 ±4.8‡‡	117 ±8	11.6 ±3.2‡‡	16.6 ±3.8	376 ±105	2818 ±591
AS, pre-VT	6	75 ±5	95 ±7	3.70 ±0.61**	38.7 ±4.5‡‡	116 ±7	12.0 ±2.5‡‡	16.3 ±3.3	391 ±90	2861 ±514

Abbreviations: AS, acetylstrophanthidin; VT, venticular tachycardia; MI, myocardial infarction.
* Borderline significance, $0.05 < P < 0.10$, study No. 1.
‡ Significantly different from Pre-AS values, $P < 0.05$, study No. 1.
§ Significantly different from Pre-MI values, $P < 0.05$, study No. 2.
‖ Significantly different from values 1 hr after MI, $P < 0.05$, study No. 2.
¶ Borderline significance, $0.05 < P < 0.10$, study No. 2.
** Borderline significance, $0.05 < P < 0.10$, study No. 4.
‡‡ Significantly different from Pre-AS values, $P < 0.05$, study No. 4.

significant changes in cardiac output, total peripheral, and pulmonary resistances. After infusion of 24 μg/kg of acetylstrophanthidin, the mean aortic pressure and total systemic resistance increased in every animal; the average increase was 15 and 20%, respectively ($P < 0.05$). There were no significant changes in heart rate, stroke volume, cardiac output, and pulmonary arterial pressure. Left ventricular end-diastolic pressure decreased slightly in four animals, did not change in one, and increased in one animal. These changes were not significant. With further infusion of acetylstrophanthidin, the last complete set of observations made before the onset of ventricular tachycardia showed changes which were qualitatively similar to those observed after 24 μg/kg of acetylstrophanthidin. However, cardiac output decreased 12% from the pre-acetylstrophanthidin level ($0.05 < P < 0.10$), and total peripheral resistance increased further.

Healing myocardial infarction (study No. 4). 7 days after myocardial infarction, all the animals had a persistently elevated left ventricular end-diastolic pressure and heart rate compared with study No. 1 ($P < 0.05$). Now, after infusion of 24 μg/kg of acetylstrophanthidin, left ventricular end-diastolic pressure decreased from 15.6 ±2.3 to 11.6 ±3.2 mm Hg ($P < 0.05$), and the stroke volume increased 24% ($P < 0.05$). There were no significant changes in heart rate, aortic and pulmonary pressures, or total pulmonary and systemic resistances. With further infusion of acetylstrophanthidin, the observations made just before the onset of ventricular tachycardia were similar to those made after 24 μg/kg of acetylstrophanthidin. The fall in left ventricular end-diastolic pressure and rise in stroke volume were maintained ($P < 0.05$). An increase in cardiac output of 15% was present, but was of borderline significance ($0.05 < P < 0.10$).

Blood gases, pH, serum electrolytes, and hematocrit

There was no significant change in blood gases, pH, and serum electrolytes at any phase of the experiment except for slight but significant hypocapnea coinciding with acetylstrophanthidin administration, both 1 hr after myocardial infarction, and again 1 wk later. There were no effects observed due to myocardial infarction per se; specifically, acute myocardial infarction produced no

TABLE II

Blood Gases, pH, and Serum Electrolytes before Acetylstrophanthidin Infusion and after Acetylstrophanthidin-Induced Ventricular Tachycardia in the Control State (Study No. 1), Acute Myocardial Infarction (Study No. 2), and 7 Days after Myocardial Infarction (Study No. 4), in Six Dogs

	P_{O_2}	P_{CO_2}	pH	O_2 sat	Sodium	Potassium	Chloride
	mm Hg	*mm Hg*		%	*mEq/liter*	*mEq/liter*	*mEq/liter*
Control (study No. 1)							
Pre-AS	89 ±8	35 +1	7.40 ±0.02	96 ±1	147 ±3	3.4 ±0.2	107 ±4
Post-AS	79 ±8	35 ±4	7.35 ±0.02	93 ±1	148 ±6	3.6 ±0.1	113 ±3
Acute myocardial infarction (study No. 2)							
Pre-MI	85 ±3	34 ±2	7.37 ±0.01	95 ±1	148 ±6	3.7 ±0.2	113 ±3
Post-MI, pre-AS	84 ±2	31 ±2*	7.35 ±0.01	95 ±1	156 ±6	4.0 ±0.3	117 ±5
Post-AS	87 ±4	25 ±3‡	7.40 ±0.02	96 ±1	145 ±4	3.7 ±0.2	112 ±7
Healing myocardial infarction (study No. 4)							
Pre-AS	80 ±6	32 ±1	7.42 ±0.01	95 ±1	154 ±7	3.9 ±0.4	111 ±6
Post-AS	75 ±7	27 ±2§	7.41 ±0.02	93 ±2	143 ±2	4.0 ±0.1	116 ±5

Abbreviations: AS, acetylstrophanthidin; MI, myocardial infarction; sat, saturation.
* Significantly different from pre-MI, $P < 0.05$.
‡ Significantly different from pre-AS; $P < 0.05$.
§ Significantly different from pre-AS; $P < 0.05$.

evidence of arterial hypoxemia (Table II). Hematocrit ranged from 32.5 to 46% in the six animals; the three in which serial measurements were made showed an average decline of 4% over the period of study.

Tolerance to acetylstrophanthidin (Fig. 1)

In the control state (study No. 1), animals required 42.9 ±3.7 μg/kg of acetylstrophanthidin before the onset of ventricular tachycardia. Ventricular tachycardia was of sudden onset in four animals and occurred gradually in two animals. 1 hr after myocardial infarction, animals tolerated 32.6 ±3.7 μg/kg of acetylstrophanthidin, representing a 24% reduction in toxic threshold ($P < 0.05$) (Fig. 1). Onset of ventricular tachycardia was sudden in three animals and gradual in three other animals. This decrease in tolerance to acetylstrophanthidin was noted in five of the six animals; the remaining animal showed no change in tolerance. An increase in tolerance towards normal was noted 48 hr and 7 days after myocardial infarction, when 39.3 ±2.9 and 43.1 ±9.8 μg/kg of the drug were required, respectively. These values did not differ significantly from control. In study Nos. 3 and 4, the onset of ventricular tachycardia was sudden in three and gradual in the other three animals. In individual animals, the sudden or gradual onset of acetylstrophanthidin-induced ventricular tachycardia did not follow a consistent pattern in study Nos. 1–4. All the animals appeared comfortable throughout the procedure and retching and emesis were not seen.

DISCUSSION

Despite the fact that use of digitalis is generally recommended in treating heart failure accompanying acute myocardial infarction (4–10), there has always been some hesistancy on the part of clinicians to use the drug energetically in this situation (21–23). This hesitancy is

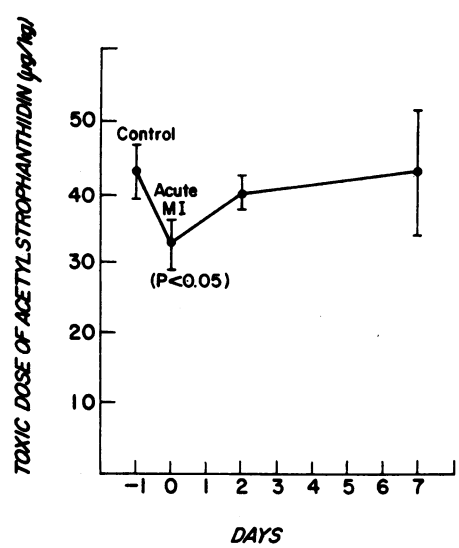

FIGURE 1 The dose of acetylstrophanthidin which induced ventricular tachycardia mean ±SEM in control state (study No. 1), 1 hr (study No. 2), 2 days (study No. 3), and 7 days (study No. 4) after myocardial infarction.

partly based upon the clinical impression held by many that digitalis may be less efficacious in treating heart failure due to acute myocardial infarction than that due to chronic coronary artery disease (21–23), and partly due to the fear that the acutely ischemic myocardium, which often spontaneously displays ventricular irritability, may be unduly sensitive to digitalis-induced arrhythmias. As noted in the Introduction, the few hemodynamic measurements which have been carried out in both animals and man have failed to show beneficial effects from digitalization in acute myocardial infarction (1, 2), and studies of toxicity have likewise uniformly revealed depression of the toxic threshold at various stages of infarction (3, 11–14).

An experimental canine model of left ventricular failure resulting from acute myocardial infarction, which simulates many of the features of the clinical syndrome of acute coronary occlusion in man, has recently been developed in this laboratory (16, 17). These features include sinus tachycardia, decreased stroke volume, increased left ventricular end-diastolic and pulmonary arterial pressures, and subsequent rise in serum enzymes. This model has provided the opportunity to study in serial fashion the hemodynamic effects of and toxic threshold to digitalis in intact conscious dogs before, during, and after anterior wall myocardial infarction.

Hemodynamic observations. The results of the initial digitalization with acetylstrophanthidin before myocardial infarction, which serve as a control study, are worthy of comment, since the results differ remarkably from those reported in anesthetized animals (24, 25). In the latter, digitalis causes an increase in peripheral vascular resistance, rise in aortic pressure, decrease in cardiac output, and slowing of heart rate. These effects, which are not seen in unanesthetized dogs (Table I), appear to result from altered autonomic tone due to anesthesia.[1] Indeed in the intact conscious dog, there is clear evidence of positive inotropic effects from acetylstrophanthidin, as manifested by increased stroke volume in the presence of unaltered heart rate, preload, and afterload (Table I).

At the time of acute myocardial infarction there was a rise in heart rate, left ventricular end-diastolic, and pulmonary arterial pressures, and a fall in stroke volume (Table I). These changes were stable over the ensuing hour of observation before digitalization. Now the administration of acetylstrophanthidin up to the point of toxicity led to changes which were quite different from those observed in the control study 1 day previously. There was a significant increase in peripheral vascular resistance and aortic mean pressure, and a decrease of borderline significance in cardiac output. There were no changes in left ventricular end-diastolic pressure or stroke volume which might suggest improved ventricular function, although in the presence of increased afterload, a minimal positive inotropic effect cannot be ruled out. However in terms of over-all ventricular performance, the effects of acetylstrophanthidin can only be described as deleterious, since the increase in afterload with unaltered stroke volumes would increase myocardial oxygen requirements (26).

It is noteworthy that these effects of acetylstrophanthidin following myocardial infarction, namely increased afterload and decreased cardiac output, bear some semblance to the changes resulting from digitalization in anesthetized animals (24, 25), when autonomic tone is altered (27). Thus it may be that a compensatory increase in sympathetic tone induced by onset of left ventricular failure in these animals, manifested primarily by sinus tachycardia, in some way facilitates the systemic vasoconstrictor effects of acetylstrophanthidin. It should be pointed out, however, that digitalis does not cause an increase in peripheral vascular resistance in the presence of increased sympathetic tone in all instances. In the presence of chronic heart failure, resulting in sympathetic overactivity and increased peripheral vascular resistance, the direct vasoconstrictor action of digitalis may be overridden by sympathetic withdrawal and decrease in peripheral vascular resistance in the presence of increased cardiac output (28).

The final hemodynamic study was performed 1 wk after coronary occlusion in the healing stage of myocardial infarction. Under baseline conditions, there was a persistent decrease in stroke volume and increase in heart rate and left ventricular end-diastolic pressure, although the latter two parameters had returned toward the preinfarction baseline. Other studies from this laboratory, in which ventricular function curves were performed, have likewise shown considerable recovery of cardiac function one week after coronary occlusion (29). At this stage of the study, these animals are in a state of mild chronic left ventricular failure. Now the administration of acetylstrophanthidin produced striking positive inotropic effects, as manifested by a significant increase in stroke volume, borderline increase in cardiac output, and a significant decrease in left ventricular end-diastolic pressure. Unlike the effects noted immediately after infarction, there was no increase in peripheral vascular resistance or aortic mean pressure.

The explanation for the observation that digitalis causes improvement in cardiac performance in the healing phase of myocardial infarction, but not immediately after occlusion remains unknown at present. As noted above, gradual diminution of sympathetic tone, which may reduce the peripheral vasoconstrictive effects of acetylstrophanthidin, may play a role. Perhaps even more

[1] Kumar, R. Unreported data.

important, however, is the possibility that aneurysmal bulging of the ischemic area, known to be uniformly present immediately after infarction (30), may be worsened by inotropic agents. Thus the increased contractility due to digitalis may be dissipated into the ballooning of the aneurysm. Such changes have been described in acute infarction with administration of catecholamines (31) and may also be applicable to other cardiotonic drugs.

During the healing phase of myocardial infarction, stiffening of the injured tissues and disappearance of the aneurysm are known to occur (32). Under these circumstances, the inotropic effects of digitalis may become manifest by increased stroke volume and diminished left ventricular end-diastolic pressure. The possible role of compensatory hypertrophy (33) or of metabolic changes (34) in the noninfarcted myocardium in altering digitalis-induced inotropy is not known at present. In any case, digitalis may well exert an equal inotropic action on the myocardium in both the early and late stages of infarction; presumably it is the translation of this effect on muscle into the action of the heart as a pump that is responsible for the difference between the early and late studies.

Observations regarding digitalis toxicity. Numerous previous studies in various species of animals have been carried out to determine whether tolerance to digitalis is reduced after experimental infarction (3, 11–14). All of these studies have shown a reduction in toxic threshold at some phase after coronary occlusion, although there is some disagreement about whether this occurs early (within hours) or later (within days or weeks) after infarction. Some of these studies were complicated by use of unpurified digitalis preparations (12, 13), and some by the use of anesthestics (3, 11, 13) and open-chest preparations (11). A more recent study in unanesthetized pigs indicated that a reduction in toxic threshold occurs within 24 hr after the onset of infarction, and is followed by a gradual return of threshold toward normal (14). Unfortunately, the exact time of onset of infarction could not be ascertained in this investigation.

The present study clearly demonstrates a significant depression of toxic threshold by 24% 1 hr after acute myocardial infarction, followed by a gradual return to normal over the next week. Other factors which are known to alter digitalis sensitivity, such as changes in arterial P_{O_2} (35) and serum electrolytes (36) were not present (Table II).

Therapeutic implications. The results of the present experiment and of other studies showing altered mechanical (29, 32) and biochemical (34) properties at various times after myocardial infarction indicate that recovery is a complex and dynamic process. The pharmacodynamic response to inotropic agents may depend upon the contractile behavior of the infarcted myocardium, which in turn may change with evolution of myocardial infarction.

Although caution must be exercised in extrapolation of experience from animal experiments to the clinical situation, the implications of the present study are clear. In the acute phase of experimental canine myocardial infarction resulting in left ventricular failure, digitalis has no beneficial therapeutic effects, and tolerance to the drug is reduced. However, during the healing phase of myocardial infarction, when mild chronic congestive failure is present, digitalis may prove useful, and toxicity is not enhanced. If these effects are present in human myocardial infarction, and the limited information available would appear to be in agreement, it might be anticipated that digitalis would have a limited therapeutic role in the early stages of acute myocardial infarction, but may offer distinct therapeutic benefits during later stages.

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