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(Part 4)

Present Status of Digitalis Treatment of Acute Myocardial Infarction

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SUMMARY
The available experimental and clinical data still leave many unanswered questions concerning the role of digitalis therapy after acute myocardial infarction. It seems clear that little is to be gained by glycoside administration to patients with uncomplicated infarctions who do not have cardiomegaly. The precise role of digitalis therapy in the treatment of cardiogenic shock remains undefined on the basis of the available data. However, until evidence to the contrary appears, its use should be continued on the basis of experience with experimental cardiogenic shock and the presumption that this state, when observed clinically, is a form of extreme left ventricular failure.

Digitalis appears to be indicated in the treatment of atrial fibrillation with rapid ventricular rate complicating acute myocardial infarction. Other supraventricular arrhythmias, such as atrial flutter and ectopic atrial tachycardia, frequently require larger doses of the glycoside, and other means of therapy, such as antiarrhythmic agents or electrical conversion, may be preferable in such instances.

Digitalis is commonly utilized early in the treatment of congestive heart failure and cardiomegaly complicating acute myocardial infarction, despite the paucity of experimental and clinical evidence in support of such therapy. Whether the digitalis glycosides should continue to be used routinely in such patients is an important subject for clinical investigation.

Although digitalis therapy in patients with acute myocardial infarction has been advocated since the original systematic account in English of this syndrome by Herrick in 1912,1 considerable controversy concerning the indications and usefulness of digitalis in such patients still exists. In recent years substantial information regarding the mechanisms of action of digitalis glycosides has accumulated, and it is the purpose of this communication to examine these developments as they relate to the use of this important drug in the patient with acute myocardial infarction.

Effects on the Inotropic State of the Myocardium

A. Normal Myocardium
It is now generally accepted that the beneficial effects of digitalis in patients with congestive cardiac failure result from direct stimulation of the contractile state of the myocardium. Thus, in hemodynamic studies on patients exhibiting chronic heart failure of the low-output type, it has been shown that digitalis augments the cardiac output and
lowers the abnormally elevated left ventricular end-diastolic pressure.\textsuperscript{2-5} In patients in whom myocardial infarction has eliminated significant quantities of myocardium from contributing to the contractile process, cardiac output can be sustained only by an increased extent of shortening of the surviving myocardium, some of which may be ischemic but much of which is adequately perfused and may in fact be normal.\textsuperscript{6} For this reason it is pertinent to consider the action of cardiac glycosides both on normal, nonischemic heart muscle and on ischemic myocardium.

Considerable information concerning the action of digitalis glycosides on the nonfailing heart is now available.\textsuperscript{7} The contractile force of the nonfailing right ventricle of anesthetized patients undergoing cardiopulmonary bypass for correction of atrial septal defect or pulmonic stenosis was found to be augmented strikingly by the administration of intravenous acetylstrophanthidin.\textsuperscript{8} Similarly, in conscious subjects with atrial septal defect, in whom the hemodynamic burden placed on the left ventricle presumably is normal, administration of intravenous ouabain significantly augmented the rate of rise of left ventricular pressure (dp/dt).\textsuperscript{9} In the absence of concurrent changes of heart rate, left ventricular end-diastolic pressure, or systemic arterial pressure, the observed increases in left ventricular dp/dt produced by the glycoside may be considered to reflect a true improvement in myocardial contractility.

Recent investigations have suggested that the concepts derived from skeletal muscle mechanics\textsuperscript{10} can be effectively utilized in the analysis of cardiac function.\textsuperscript{11} This approach makes use of the finding that at any given ventricular end-diastolic volume (myocardial fiber length), there is an inverse relation between the force of muscle contraction, i.e., the load the muscle can lift, and its velocity of shortening. The position of the curve relating these two variables, the force-velocity curve, serves as a useful and sensitive index of the inotropic state of the myocardium. In order to utilize this approach for studying the effects of cardiac glycosides on the function of nonfail-

ing, nonischemic heart muscle, cineradiograms of roentgen-opaque markers sutured to the external surfaces of the ventricles of patients who had undergone corrective cardiac operations were obtained. The velocity of movement of these markers was compared to the simultaneously recorded intraventricular pressure, and the resultant calculated force-velocity relation indicated again that ouabain augmented contractility of the nonfailing, nonischemic human myocardium.\textsuperscript{12} This conclusion is also supported by the observation that the drug lowers the postexercise oxygen debt in patients with cardiomegaly but without heart failure.\textsuperscript{13} From these clinicopharmacologic studies it appears that, even though cardiac glycosides have little effect on the pumping action of the normal ventricle as expressed in the cardiac output,\textsuperscript{14} they do exert a stimulating influence on normal cardiac muscle. This action provides a theoretic basis for the possible beneficial action of the drug in patients with myocardial infarction in whom the surviving normal myocardium must sustain the entire contractile effort.

\textbf{B. Hypoxic Myocardium}

It is essential also to consider the effects of the cardiac glycosides on hypoxic myocardium. Hypoxia of surviving myocardium occurs for a number of reasons in patients with acute myocardial infarction. First of all, systemic hypoxemia is common in these patients and it is presumably related to impaired pulmonary gas exchange, as a consequence of the elevated pulmonary capillary pressure, resulting from impairment of left ventricular performance.\textsuperscript{15-19} A second important mechanism responsible for myocardial hypoxia is related to the relatively large zone of heart muscle surrounding an infarct which receives a portion of its blood supply from the occluded coronary vessel.\textsuperscript{20} The oxygen available to this portion of myocardium, which Edwards\textsuperscript{21} has aptly termed the "twilight zone," is reduced to a varying extent, although not totally eliminated. A third cause of myocardial hypoxia in patients with acute
infarction is arteriosclerotic narrowing in the unoccluded coronary vessels. Coronary arteriosclerosis is a diffuse disease, and segments of myocardium quite remote from the acute infarct may also suffer from an impairment of oxygen delivery resulting from coronary arterial stenosis, particularly during hypotensive episodes.

The effect of acetylstrophanthidin on ischemic myocardium was studied by Sarnoff and co-workers in an isolated heart preparation in which aortic pressure, heart rate, and stroke volume were held constant. Even when coronary flow was reduced to 30% of control values, direct coronary injection of acetylstrophanthidin produced a marked increase in contractility without significant changes in myocardial oxygen consumption or external efficiency. In studies carried out on dogs rendered hypoxic by breathing 7–10% oxygen without coronary occlusion, Donlon and Yu reported an average rise of 25% in left ventricular dp/dt and a mean increase of 34% in stroke work after acetylstrophanthidin, without a consistent change in left ventricular diastolic pressure. In nonhypoxic animals given intravenous acetylstrophanthidin, the comparable increments in left ventricular dp/dt and stroke work were 84 and 40%, respectively. These data suggest that the response of hypoxic myocardium to digitalis, while attenuated, is not abolished.

From the above experimental observations it appears that the contraction of ischemic myocardium can be stimulated acutely by positive inotropic agents, including the digitalis glycosides. As will be evident, however, this enhancement of contractility may, under certain circumstances, exert a deleterious effect. In this connection, the effects of hypoxia may be of importance in the genesis of arrhythmias seemingly precipitated by digitalis therapy. Clinical studies have indicated that hypoxic, hypercapnic patients with chronic obstructive pulmonary disease tend to develop arrhythmias after bolus injections of acetylstrophanthidin. The enhanced tendency to arrhythmias in large groups of patients with chronic pulmonary disease has also been noted. More recent studies have indicated that hypoxia alone, even without hypercapnia and acidosis, sensitizes the dog to the toxic effects of acetylstrophanthidin. It should be noted, however, that the degree of hypoxia produced in the experimental animal (mean pO2 of 31–34 mm Hg) far exceeds that usually observed clinically, except in the most seriously ill patients who are at the greatest risk from digitalis therapy.

**Effects on Myocardial Oxygen Consumption**

Under ordinary circumstances, the myocardium derives essentially all of its energy from the oxidation of substrate through the Krebs cycle. Since, as already indicated, oxygen availability to nonnecrotic areas of myocardium may be severely limited in patients with coronary arteriosclerosis and acute infarction, it is important to consider the effects of digitalis on myocardial oxygen consumption (MVO2). It has been shown in a number of investigations that digitalis does not increase MVO2, either exerting no effect on this variable or actually reducing it. However, this finding was not consistent with the observation that the drug augments the velocity of fiber shortening, which is an important determinant of MVO2. In a nonfailing canine heart, in which heart rate, stroke volume, and mean aortic pressure were held constant, it was found that acetylstrophanthidin increased MVO2 significantly, even in the face of a reduction in integrated and peak systolic tension. In contrast, when this agent was administered to failing hearts it had no effect and, in some experiments, even reduced MVO2 presumably due to a fall in end-diastolic volume, which resulted in a decline in systolic tension. It appears that the increase in contractility produced by digitalis tends to increase MVO2, but, in the dilated, failing heart which becomes smaller after glycoside administration, the concurrent reduction in wall tension counteracts the O2 cost of augmented contractility. Thus, the effects of digitalis on MVO2 are conditioned importantly by the state of compensation existing at the time the drug is administered.
Recently, the effects of a variety of agents, including digitalis, on the extent and severity of ischemic injury in dogs with acute coronary occlusion were evaluated by use of an epicardial mapping technique.\textsuperscript{33} In dogs without ventricular enlargement or impaired performance, ouabain increased the severity and extent of the ischemic injury. In contrast, in animals with coronary occlusion and pharmacologically induced heart failure and ventricular dilatation, identical doses of the glycoside tended to reduce the extent and severity of ischemic damage.\textsuperscript{31} It is postulated that the fate of the perinfarction zone, with the limited oxygen available to it, is influenced profoundly by the O\textsubscript{2} requirements of the tissue. Increasing the latter in the nonfailing heart, by means of ouabain and other inotropic stimuli such as isoproterenol, intensifies ischemia, resulting ultimately in more extensive infarction. In contrast, reducing myocardial O\textsubscript{2} demands, by administering digitalis to the failing heart, or by means of synchronized aortic balloon counterpulsation,\textsuperscript{34} evidently allows for survival of the underperfused zone bordering the infarct.

Several investigators have studied the effects of digitalis on overall cardiac performance in experimental myocardial infarction. In anesthetized dogs studied several days after acute experimental myocardial infarction, Hood et al. demonstrated no improvement of cardiac performance after acetylthorphanthidin, as judged by the relationship between left ventricular filling pressure and cardiac output.\textsuperscript{35} Moreover, in the unanesthetized dog with an elevated left ventricular end-diastolic pressure and a reduced stroke volume studied 1 hour after acute myocardial infarction, ouabain did not cause a beneficial hemodynamic change.\textsuperscript{36} Seven days later, however, during the healing phase of acute infarction, acetylthorphanthidin caused a reduction of left ventricular end-diastolic pressure and an elevation of stroke volume and cardiac output.\textsuperscript{36}

Thus, in experimentally produced acute myocardial infarction, the effects of digitalis on cardiovascular dynamics appear to depend upon the timing of its administration in relation to the infarction and its effect on the extent and severity of myocardial ischemic injury. The latter is related to the degree of impairment of cardiac function and the attendant degree of cardiomegaly.

Effects of Catecholamine Depletion

It has been demonstrated that cardiac catecholamine depletion is a biochemical hallmark of chronic congestive cardiac failure.\textsuperscript{37} In experimental canine myocardial infarction, norepinephrine cannot be detected after the second day in the infarcted area.\textsuperscript{38} In addition, uninvolved left ventricular muscle exhibits a rapid decline in norepinephrine stores, which reaches its nadir by the tenth day.\textsuperscript{38} Although it has been postulated repeatedly that the inotropic action of digitalis is dependent on cardiac norepinephrine stores,\textsuperscript{39–42} there is now abundant evidence that catecholamine depletion or adrenergic blockade does not diminish the positive inotropic effects of digitalis preparations.\textsuperscript{43, 44} Therefore, the absence of prominent hemodynamic effects of digitalis in myocardial infarction should not be attributed to catecholamine depletion.

Effects on Vascular Resistance

A. Coronary Vascular Resistance

Although the effects of cardiac glycosides on the coronary vascular bed have received considerable attention, the results of studies on coronary flow in the anesthetized dog have not been consistent.\textsuperscript{45–48} Here, as in the case of the effect on cardiac output and MV\textsubscript{O\textsubscript{2}}, the action of the drug appears to be conditioned by the state of the animal at the time of administration. The effects of anesthesia and surgical manipulation appear to play a particularly important role in modifying the results of the drug on the coronary vascular bed. Recently the effects of ouabain on the coronary vascular bed in conscious dogs were examined in our laboratories by Vatner et al., after the animals' full recovery from implantation of Doppler flow probes on the aorta and left circumflex coronary artery. Despite the increase in MV\textsubscript{O\textsubscript{2}} induced by digitalis in
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nonfailing hearts, which would have been expected to produce dilatation of the coronary vascular bed, ouabain caused coronary vasoconstriction,49 coronary vascular resistance rising by an average of 23% 15 min following the administration of a subtoxic dose of the glycoside. In contrast, when the same animals were studied in the anesthetized state, an identical dose of the drug did not cause an increase in calculated coronary vascular resistance. There is little information regarding the effects of cardiac glycosides on the human coronary arterial bed, but these animal studies imply that a bolus intravenous injection of a rapidly acting glycoside might constrict the coronary vascular bed and therefore this may not be an advisable method of administration in patients with acute myocardial infarction. Of course, the extent to which the results of studies in normal dogs are applicable to patients with coronary vascular disease remains to be demonstrated.

B. Effect on Systemic Resistance Vessels

There is abundant experimental evidence, in both anesthetized dogs and in patients studied at a constant cardiac output on cardiopulmonary bypass, that a direct action of digitalis on vascular smooth muscle, unaffected by autonomic influences, is responsible for the increase in total systemic vascular resistance produced by the drug.50 More recently, experiments were carried out in conscious dogs with chronically implanted flowmeters.51 The results indicate that in normal dogs digitalis causes constriction in the renal and iliac beds, but dilatation in the mesenteric bed. In contrast, in dogs with heart failure induced by tricuspid avulsion and creation of pulmonary stenosis, vasodilation occurred and flow increased in all beds studied in response to ouabain, presumably as a consequence of increasing cardiac output, thereby reducing the reflex vasoconstriction which characterizes the low-output state.51 Systemic arterial pressure, however, increased in both the normal animals and those with heart failure after ouabain.51 Both generalized systemic and regional arteriolar constrictor

and venoconstrictor effects of cardiac glycosides have been demonstrated in conscious, intact human subjects without heart failure52,53 with opposite effects occurring in patients with heart failure.53

In both conscious animals51 and in human subjects, regardless of the state of compensation, large doses of cardiac glycosides administered intravenously,55 produce a rise in systemic arterial pressure. The afterload of the myocardium, which is directly related to active pressure development during systole and to ventricular radius by the Laplace relation,54 is an exceedingly important determinant of the extent of myocardial fiber shortening and therefore of stroke volume and cardiac output. Thus, even in the normal heart, when end-diastolic volume is held constant, progressive increases in aortic pressure cause reciprocal reductions in stroke volume,55 while in the depressed heart such increases may produce a fall in stroke volume even when end-diastolic pressure rises.56 From these considerations the possible deleterious effect of the systemic vasoconstrictor actions of rapidly acting glycosides is evident, and it is pertinent that the constrictor action of cardiac glycosides on vascular smooth muscle is more rapid in onset and shorter in duration than is the positive inotropic effect. The transient elevation in systemic arterial pressure resulting from rapidly acting glycosides51,53 might therefore be undesirable in patients with acute myocardial infarction. Indeed, Cohn et al. demonstrated that the early pressor effect of intravenously administered ouabain may be harmful in some patients with cardiogenic shock.57

Effects on Cardiac Rhythm

The propensity to develop ventricular irritability in patients with acute myocardial infarction has led to the fear that such patients may be more sensitive to the arrhythmogenic properties of the glycosides. Early experimental evidence indicated, however, that digitalis facilitates ectopic activity in the presence of infarction only at toxic dose levels.58-60 On the other hand, more recent studies in the conscious unrestrained farm pig have suggested

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that the average intoxicating dose of acetylstrophanthinid is reduced by one third, i.e., from 2.2 to 1.5 mg, after acute myocardial infarction. Clinical evidence that patients with acute myocardial infarction are particularly prone to develop digitalis-induced arrhythmias, however, is lacking. The role of the drug in the production of primary ventricular fibrillation complicating acute myocardial infarction is not known since many other factors in such patients, including bradycardia, increased sympathetic activity, hypoxia, and hypokalemia, may contribute to the genesis of serious arrhythmias. It is possible that cautious replacement of potassium in hypokalemic patients may allow the administration of additional amounts of glycoside, which may further enhance myocardial contractile force.

The metabolic half-times and excretion rates of short, intermediate, and long-acting glycosides have been well characterized. It has been demonstrated that both renal insufficiency and advanced age are associated with impaired renal excretion of digitalis glycosides. Since alterations in renal hemodynamics commonly occur after acute myocardial infarction, it is likely that digitalis dosage should be modified appropriately in such patients. With the availability of newer techniques of serum digitalis assay, it should be possible critically to analyze digitalis dosage schedules in relation to evidence of beneficial effects as well as toxicity and to determine definitively whether acute myocardial infarction sensitizes patients to digitalis-induced arrhythmias.

Clinical Observations

Herrick in 1912 and Hamman in 1926 advocated the use of digitalis in all patients with acute myocardial infarction. In contrast, Friedberg recommends the use of digitalis only when heart failure is not controlled by bed rest, opiates, or oxygen therapy. Unless they persist after the first week, basilar rales alone, according to Friedberg, are not sufficient indication for digitalis. The criteria for digitalis therapy after acute myocardial infarction proposed by Logue and Hurst are somewhat broader and include the presence of gallop sounds, pulmonary rales, radiographic evidence of interstitial pulmonary edema, and a sinus rate exceeding 110 beats/min. Although Lown and co-workers agree with the latter recommendations, in their experience 22% of patients with congestive symptoms demonstrated an inadequate response to digitalis, and diuretic measures were required. A somewhat different approach is advocated by Swan and associates, who recommend administration of digoxin to patients with congestive heart failure who do not respond adequately to an initial trial of diuretic therapy.

The specific digitalis preparation recommended differs according to the circumstance. For urgent situations, such as acute pulmonary edema complicating myocardial infarction, ouabain has been suggested. Because of its rapidity of onset and dissipation and the ease of dosage adjustment, Lown and associates also advocate ouabain as the preparation of choice. Logue and Hurst, on the other hand, have indicated that switching to other preparations for maintenance therapy may pose a problem; hence, they favor the use of digoxin. If digitalis is to be used in the therapy of acute myocardial infarction, it might be best for the individual clinician to prescribe the preparation with which he is most familiar. The potential hazard of bolus intravenous injections of rapidly acting glycosides has already been commented upon.

As indicated earlier, animal studies do not support the concept that the patient with acute myocardial infarction is more susceptible to the arrhythmogenic properties of the glycosides in the usual dose range. Prior to the advent of routine cardiac monitoring in the coronary care unit, Askey treated 50 patients with uncomplicated myocardial infarction with digitoxin and noted no difference in the incidence of ventricular ectopic beats or of sudden death in this group compared with a control group of 50 untreated subjects. It is likely that any increase in susceptibility to digitalis toxicity relates to the severity of the

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complication accompanying the acute infarction rather than to the presence of myocardial cell damage per se. For example, Lown and associates reported that patients with profound heart failure, hypoxia, acidosis, or with advanced renal or hepatic disease often appeared to be unusually sensitive to ouabain. They reported the development of ventricular fibrillation in two patients critically ill with pulmonary congestion, who had previously been on maintenance digitalis therapy and who had received intravenous ouabain 20 min previously.\(^6\)

While the glycosides may exert arrhythmogenic effects in profoundly ill patients, digitalis is frequently useful in the treatment of certain arrhythmias complicating acute myocardial infarction. Atrial fibrillation with rapid ventricular rate occurring during the course of acute infarction appears to be a clear indication for the use of digitalis.\(^7\) Since fatal systemic embolism has been reported after such treatment, even without return to sinus rhythm,\(^6\) it appears prudent to anticoagulate such patients when initiating digitalis therapy. Atrial and nodal tachycardias are frequently transient, and it has been suggested that digitalis may provide effective prophylaxis against their recurrence.\(^6\) Persistent atrial tachycardia causing hypotension should be treated with electrical conversion followed by digitalis. Atrial flutter should be treated in a similar fashion, with the addition of both digitalis and quinidine as prophylactic measures.\(^6\)

Since the glycosides increase the contractile force developed by the myocardium, concern has been expressed that digitalis might lead to rupture of the heart in patients with acute infarction.\(^7\) Although rupture of the heart has been noted in 8.6% of fatal acute infarctions,\(^7\) Maher et al. reported that the incidence of rupture was actually lower in patients receiving digitalis.\(^8\) Other clinical studies have concluded that there is little evidence that digitalis contributes to cardiac rupture after acute infarction.\(^81,\)\(^82\)

The various hemodynamic patterns which may occur after acute myocardial infarction have recently been summarized.\(^83\) Transmural myocardial infarction is almost always accompanied by an elevated left ventricular end-diastolic pressure.\(^84\) In uncomplicated patients, the cardiac output remains normal, the systemic arterial pressure is normal or only mildly reduced, and peripheral vascular resistance and central venous pressure tend to be normal. A fourth heart sound is almost always present and does not necessarily indicate cardiac failure.\(^85\) It is unlikely that such patients would benefit from digitalis therapy. Measurements of cardiac output after intravenous administration of digitalis in patients with uncomplicated acute transmural myocardial infarction have revealed either no change\(^86\) or actually a fall\(^87\) in cardiac output. Indeed, intravenous administration of glycosides in such patients has been reported to be associated occasionally with the sudden development of ischemic chest pain.\(^87\) On the other hand, administration of intravenous ouabain to patients recovering uneventfully from uncomplicated acute myocardial infarction produces a decrease in previously elevated levels of left ventricular end-diastolic pressure as well as a significant rise in left ventricular stroke work, without changes in cardiac index or heart rate.\(^88\)

With congestive heart failure or shock, the left ventricular end-diastolic pressure tends to be substantially elevated, but the degree of elevation does not necessarily coincide with the severity of the shock state.\(^84\) In general, the more severe the congestive heart failure or hypotension, the lower the systemic arterial pressure and cardiac output, and the higher the peripheral vascular resistance. Viewed in this context, cardiogenic shock is an extreme form of left ventricular failure, comprising the end of a spectrum of impaired left ventricular function that occurs to varying degree in all patients with acute myocardial infarction. Although digitalis appears to exert a beneficial effect in experimentally induced cardiogenic shock,\(^89,\)\(^90\) Cohn et al. reported that the rapid intravenous administration of various digitalis preparations may actually be deleterious in some patients due to the early peripheral...
vasoconstrictor effect of the glycosides.\textsuperscript{57} Because treatment of cardiogenic shock usually involves a variety of therapeutic modalities,\textsuperscript{89} of which digitalis is only one, it is difficult to evaluate its effectiveness in comparison with or as an adjunct to other methods of treatment. Nonetheless, on the basis of existing information, treatment with this drug appears to be indicated in all patients with cardiogenic shock before considering more-radical forms of therapy, such as assisted circulation or operation.

Although numerous authors have advocated digitalis therapy for congestive heart failure complicating acute myocardial infarction,\textsuperscript{74-77} there are few studies in man which document benefit from the cardiac glycosides in this setting. Recently Ratshin et al. noted small increases in cardiac index and stroke work as well as a reduction in left ventricular end-diastolic pressure in seven patients with left ventricular failure and acute myocardial infarction 30-45 min after receiving 0.5-0.75 mg of intravenous digoxin.\textsuperscript{92} These data suggest that digoxin, administered acutely, may be of small but demonstrable benefit in patients with left ventricular failure complicating acute myocardial infarction.

Although most patients with acute transmural myocardial infarction develop left ventricular wall motion abnormalities, particularly paradoxical expansion, within the first few hours after the infarction,\textsuperscript{80} there is little pertinent work concerning the possible effects of digitalis therapy on these areas of disordered contractility. However, it has been shown that positive inotropic stimulation of surviving myocardium may accentuate the amplitude of paradoxical systolic excursion.\textsuperscript{94} Moreover, Herman et al. have speculated that any area of paradoxical motion may act as a "slack" elastic element in series with the contractile portions of the left ventricle, thereby acting to increase cardiac work,\textsuperscript{95} an effect which could further increase M\textsubscript{V}o\textsubscript{2}.\textsuperscript{96, 97} Whether the digitalis glycosides exert a salutary effect on areas of disordered left ventricular contractility is an important question which requires further study.

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