DIGITALIS has been documented to have an inotropic effect after acute myocardial infarction. Why, then, is its use to treat acute infarction with congestive heart failure controversial? A digitalis-induced increase in contractility may be prevented from causing an increase in stroke volume and a decrease in left ventricular filling pressure by several mechanisms. First, enhanced contractility may increase bulging of ischemic or infarcted segments, thereby dissipating the inotropic effect that it exerts on the nonischemic or partially ischemic myocardium. Second, increased systemic vascular resistance induced by digitalis causes an increase in afterload, and this effect may oppose the mild inotropic effect of digitalis.

Investigations in animals show that there is an attenuated global inotropic response to digitalis and other inotropic drugs immediately after infarction, and that responsiveness to digitalis may be partially regained within hours after the onset of infarction. From these experiments one can appreciate that the hemodynamic effect of digitalis is the result of the interplay of the direct inotropic effect of the drug on responsive myocardial segments as well as the possible dissipation of this inotropic action on nonresponsive areas of myocardium. The net effect of this interaction is further modulated by the variable effect of digitalis on systemic vascular resistance. Digitalis enhancement of systemic vascular resistance is partially due to a direct arteriolar vasoconstrictive effect. This peripheral effect of digitalis is greater if the drug is given intravenously as a bolus and may be minimized if given slowly over 10 minutes. The vasoconstrictive action of digitalis occurs within minutes after an i.v. dose and may precede the peak inotropic effect of the drug. This increased afterload may aggravate left ventricular failure. Digitalis-induced pulmonary edema has indeed been documented. Therefore, digitalis preparations must not be given as a bolus, but should be infused over 10 minutes or longer. This effect of increased afterload after i.v. digitalis administration is not uncommon. Lown et al. found that 59% of patients with acute myocardial infarction who were treated with sequential rapid i.v. injections of acetyl choline had an increase in blood pressure. An increase in systolic pressure exceeding 20 mm Hg was noted in 16 patients; in two instances it was greater than 40 mm Hg and in one it was 60 mm Hg. It is not known what causes individual differences in response of systemic vascular resistance to i.v. digitalis, nor whether the digitalis-induced increase in afterload may be avoided entirely by oral administration of this drug. Increased systemic vascular resistance after i.v. administration of digitalis can explain why some patients with acute myocardial infarction may not respond with significant hemodynamic improvement.

When systemic vascular resistance decreases in patients treated with digitalis it is due to a cascade of events after improvement in cardiac output. Under these circumstances, the inotropic effect of digitalis leads to an increase in cardiac output. This is followed by a decrease in the sympathetic tone that is augmented in left ventricular failure, and then a return to the usual dominance of parasympathetic tone. This sympatholytic effect, probably mediated by arterial baroreceptors, results in a decrease in systemic vascular resistance. In the absence of failure, this sympatholytic effect is less pronounced and the direct arterial vasoconstrictive effect of digitalis, and the stimulatory effect of digitalis on the brainstem, may predominate.

How can these adverse effects of digitalis be minimized or prevented? As previously mentioned, a digitalis-induced increase in afterload may be diminished by slow i.v. infusion of the drug. Bolus injection should be avoided. The use of afterload-reducing agents in conjunction with digitalis is a promising approach to the treatment of congestive failure in patients with acute myocardial infarction.

This background information, as well as clinical experience, forms the basis for the following suggestions regarding the use of digitalis in acute myocardial infarction.

**Digitalis in Acute Myocardial Infarction**

**by Clinical Classification of Severity**

For Patients without Clinical Signs of Heart Failure (Killip Class 1)

Digitalis should not be given to patients with acute myocardial infarction who are not in cardiac failure because it may increase infarct size. An increase in serum creatine phosphokinase activity has been found in patients with myocardial infarction who were not in failure and who were given digitalis. This adverse effect, which has also been documented in experimentally induced myocardial infarction, may be explained by the direct vasoconstrictor action of digitalis on vascular smooth muscle which results in an increase in systemic vascular resistance. The increased peripheral resistance and the enhanced myocardial contractility caused by digitalis increase myocardial oxygen consumption. Since oxygen delivery is impaired with acute infarction, an increase in infarct size may result.
For Patients with Moderate Heart Failure as Evidenced by an S, Gallop, Pulmonary Rales, and/or Pulmonary Congestion by X-ray (Killip Class 2)

Digitalis alone or in conjunction with mild diuretics such as the thiazides are particularly useful in treatment of patients with mild-to-moderate congestive heart failure that persists for several days. In this issue of Circulation, Morrison and co-workers have shown that digitalis exerts a minimal but significant effect on increasing the ejection fraction in patients with acute myocardial infarction, most of whom had moderate-to-severe decreases in left ventricular function. This was accomplished without evidence of a decrease in myocardial perfusion or an increase in infarct size. These data are consistent with those obtained by others who have measured the hemodynamic effects of digitalis in patients with moderate congestive heart failure. Most of these studies have demonstrated a modest increase in cardiac output and small decreases in left ventricular filling pressure.

For Patients with Severe Heart Failure:
Acute Pulmonary Edema (Killip Class 3)

Digitalis is not the initial drug of choice because of its mild inotropic effect and because of the delay in time to peak action, particularly since the drug should be titrated by administration of several doses. Nevertheless, digitalis should not be discarded as an important therapeutic agent in this condition. Lown et al. found that pulmonary edema cleared entirely after acetyl strophanthidin in two patients with acute myocardial infarction. Also, in patients with heart failure who are treated initially with nitroprusside, digitalis can further increase cardiac output. Many of these patients remain in heart failure, so digitalis can be useful in the subacute and chronic treatment of severe congestive failure.

Digitalis in Patients with Cardiogenic Shock (Killip Class 4)

Digitalis should not be used for the acute management of cardiogenic shock in the absence of atrial arrhythmias. In this condition, digitalis only tends to complicate an already difficult management problem.

Digitalis in Acute Myocardial Infarction Associated with Atrial Arrhythmias

Atrial arrhythmias, especially atrial fibrillation or flutter, frequently herald congestive heart failure or may precipitate cardiac congestion. These arrhythmias are particularly hazardous in acute myocardial infarction because the rapid ventricular response increases myocardial ischemia manifest by coronary insufficiency or congestive heart failure. Infarct size may be increased. Digitalis is the drug of choice under these circumstances because, by its inotropic effect, it acts to reverse the underlying cause of the atrial arrhythmias — myocardial failure. This primary action of digitalis diminishes heightened sympathetic tone and restores vagal tone. These actions of digitalis, in addition to the direct neural effects of the drug, increase the refractory period of the atrioventricular (AV) node, enhance AV block, and result in a decrease in ventricular response as evidenced by a slowing of the heart rate. Because ventricular rate must be decreased as early as possible, a digitalis preparation should be used that has a short onset of action and short time to peak effect. An ideal drug for this purpose is ouabain because it has a rapid onset and reaches its maximum effect in 30–45 minutes. The initial dose is 0.25 mg, which should be given over 10 minutes. The drug can be given in increments of 0.1 mg every hour. Cardioversion may be necessary if there is a rapid onset of pulmonary edema or hypotension after the onset of atrial arrhythmias. Digitalis is not needed if the ventricular response to atrial fibrillation or flutter is less than 110–120 beats/min. In fact, it is contraindicated if the ventricular response is slow, i.e., 60–80 beats/min, because this slow ventricular response soon after the onset of atrial fibrillation or flutter in patients with acute myocardial infarction is suggestive of AV nodal disease. Complete AV block with a slow heart rate may occur if digitalis is administered under these circumstances.

Other drugs, such as β-adrenergic blocking agents, may be useful in decreasing the rapid ventricular response, but their negative inotropic effect can enhance congestive heart failure. These drugs can also suppress sinus node activity and cause marked bradycardia. Verapamil, a calcium antagonist, quickly reduces the ventricular rate in patients with atrial fibrillation. Verapamil causes reverse of atrial flutter to sinus rhythm in most patients. It may produce sinus arrest, AV block or cardiac standstill in patients with impaired function of the sinus node or AV conduction.

Pharmacokinetics of Digitalis in Acute Myocardial Infarction

The absorption of digoxin is frequently delayed in patients with acute myocardial infarction. This may be due to a decrease in intestinal motility. The delay in absorption is further accentuated in the presence of morphine. However, the bioavailability of digoxin is not impaired in patients with acute myocardial infarction. This delayed absorption may argue for the use of an i.v. preparation if the desired effects of digitalis are required promptly.

Digitalis Sensitivity and Acute Myocardial Infarction

Digitalis sensitivity has been well documented in experimentally induced infarction. Ku and Lucchesi found that there was a 43% decrease in the dose of acetyl strophanthidin needed to produce ventricular arrhythmias compared with the preischemic dose. Similar experiments by Morris et al. using the pig, also documented myocardial sensitivity after coronary occlusion. Digitalis sensitivity appears, in part, to be caused by a direct myocardial sensitivity to the toxic effect of digitalis. Infusion of small amounts of digitalis
directly into a coronary vessel after acute ligation or after reperfusion was associated with local myocardial sensitivity over the ischemic muscle.\(^7\) Whether these findings have any clinical relevance was addressed by Lown et al.,\(^11\) who found that acetyl strophanthidin in the usual therapeutic doses was well tolerated in acute myocardial infarction. Reicansky et al.\(^29\) did not observe any increased incidence of ventricular arrhythmias or other toxic effects when the usual therapeutic doses were given to man.

Should Other Drugs Replace Digitals?

Physicians frequently question whether drugs that cause afterload reduction, diuretics, or intravenous sympathomimetic amines, alone or in combination, should entirely replace the use of digitals in acute myocardial infarction. The use of diuretics, particularly the potent loop diuretics, such as furosemide, are not without complications. The most common cause of hypovolemic shock in acute myocardial infarction is the overuse of diuretics.\(^30\) Afterload-reducing agents must be administered by constant infusion. The rate of infusion must be rigorously controlled to avoid serious hypotension. In addition, catheterization and bedside monitoring are generally required. These procedures may cause discomfort or complications.\(^31\) There is no other effective inotropic agent that can be administered orally to patients with acute myocardial infarction. For these reasons, digitals will probably continue to be an important drug in the management of acute myocardial infarction complicated by congestive heart failure.

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