Use of Drugs in Cardiogenic Shock due to Acute Myocardial Infarction

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SUMMARY
As a plan of therapy for shock associated with acute myocardial infarction in a general hospital and assuming that septic and hemorrhagic shock has been eliminated as diagnostic possibilities we would suggest the following:

1. Pain should be relieved using morphine or pentazocine, and atropine if bradycardia is present. Oxygen by mask should be administered to bring the arterial oxygen tension to about 100 mm Hg. The airway must be examined and, if air exchange is poor and the arterial oxygen very low or carbon dioxide high, respiratory assistance and occasionally intubation may be required.

2. Blood pressure must be stabilized at an adequate level for perfusion of vital organs, or progression may be so rapid that death will occur before proper evaluation can be made and more rational therapy started. For this purpose we would start a norepinephrine infusion at a rate just sufficient to keep the systolic blood pressure near 100 mm Hg. If the shock syndrome is present but arterial pressure is normal or only slightly reduced, we would eliminate this step in therapy.

3. Arrhythmias or heart block should be corrected by methods discussed elsewhere in this symposium.

4. A venous catheter should be inserted so that the catheter tip is just within the thorax. If the central venous pressure (CVP) is below 10 cm H2O we would begin a regimen of plasma volume expansion giving 100 cc of 40dextran over a period of 10 min, waiting 10 min, and if the CVP has not risen 1 cm H2O repeat the process until shock is relieved, the CVP continues to increase or is above 15 cm H2O, or 1000 cc of 40dextran has been given. If the patient accepts more than 1000 cc of fluid in this manner without elevating the CVP it is most likely that some other major process causing fluid loss is complicating the myocardial infarction.

5. If or when CVP is above 10 cm H2O, and if the patient remains in shock and is hypotensive, we would add norepinephrine infusion at a rate just sufficient to bring the systolic pressure between 100 and 110 mm Hg. If this cannot be accomplished with small amounts of norepinephrine then intraarterial pressure must be measured since the discrepancy between the cuff pressure and actual pressure may be increasing with further pressor infusion.

6. If the patient is normotensive and has a CVP above 10 cm H2O but manifests the shock syndrome, an isoproterenol infusion should be instituted, but to use this regimen one must be able to measure intraarterial pressure. If CVP falls, simultaneous plasma volume expansion may be necessary. If arterial pressure begins to fall, norepinephrine should be substituted. We would use dopamine first in this particular situation, but this agent is not as yet generally available.

7. With the CVP elevated and blood pressure stable, arterial oxygenation established, and arrhythmias corrected, if the patient is still in a low cardiac output state with continued oliguria and poor tissue perfusion, digitalization with about half to two thirds the normal digitalizing dose should be undertaken.

8. If a further inotropic response is needed glucagon may be added at this point. With an initial bolus injection efficacy should be established and if found helpful a constant infusion should follow. Aminophylline should be given simultaneously to potentiate the action of glucagon.

9. The patient who at this point remains oliguric and with a small pulse pressure may be benefited by cautious vasodilation with chlorpromazine or phentolamine and simultaneous further plasma volume expansion.

10. A patient who remains pressor-dependent or responds poorly to pressors will probably need circulatory assistance. However, unless some definitive measure can be
undertaken to restore or replace nonfunctioning myocardium this too will be of little benefit.

(11) A patient who stabilizes well but experiences a fall in blood pressure as the pressor infusion is being discontinued should have plasma volume expansion as the pressor infusion is decreased. The physician must resist the temptation to restart the infusion as the pressure falls, unless the shock syndrome accompanies the hypotension.

SHOCK IS A CLINICAL syndrome which includes obtundation, oliguria (urine flow <30 cc/hour), cold cyanotic extremities, and small pulses. Blood pressure as measured by the standard cuff method is usually low but intraarterial pressure measured directly may be low, normal, or high. Since the clinical syndrome is not dependent on a low intraarterial pressure one should classify shock as being with or without intraarterial hypotension. The shock syndrome associated with acute myocardial infarction has multiple factors in its etiology, and although ventricular dysfunction is usually the most significant component the terms myocardial infarction shock and cardiogenic shock must not be used interchangeably. Cardiogenic shock refers to that portion of the syndrome which is due to malfunction of the heart as a pump but ignores the reflex changes in the peripheral vascular system, the effective plasma volume deficit, and ventilatory abnormalities which occasionally become dominant.

Myocardial infarction results in decreased cardiac output. The ischemic myocardium bulges with systole and the remaining functioning muscle not only has to substitute for the nonfunctioning tissue but also must overcome the damping effect of the expanding infarcted area. The resultant decreased rate of pressure rise activates the baroreceptors of the carotid sinus and aorta thus calling for vasoconstriction to maintain arterial pressure. The surprising finding is that more than half of the patients with myocardial infarction, shock, and hypotension have normal rather than elevated systemic vascular resistance.

Aggress called attention to this lack of vasoconstriction, and by injecting beads into the coronary arteries to produce infarction constructed an experimental model to simulate the clinical syndrome. In his animals the cardiac output and arterial pressure fell while the vascular resistance remained constant. If, in addition, the animals had dorsal sympathectomy and vagotomy, the decrease in cardiac output was accompanied by vasoconstriction and arterial pressure was maintained. He attributed the inhibition of vasoconstriction to a reflex arising in the coronary arteries but differing from the Jarish-Bezold reflex in not being abolished by vagotomy. More recently, it has been postulated that ischemia activates receptors in the ventricular myocardium causing inhibition of the vasoconstrictor response. These receptors may be stretch receptors activated when the ischemic muscle bulges during systole. The afferent fibers have been located as being vagal or sympathetic and cause central inhibition of sympathetic tone. In addition to these studies in the experimental animal, it has recently been demonstrated that patients with acute myocardial infarction have decreased vasoconstriction during head-up tilt, again indicating inhibition of normal sympathetic responses.

The lack of vascular response to a fall in cardiac output seen in the patient with acute myocardial infarction is not easily recognized clinically. Such patients without generalized vasoconstriction demonstrate the best recovery rate with pressor infusion, have higher cardiac outputs, and may have lesser amounts of myocardial damage. Since long-term survival is most likely to occur in the patients with the least myocardial destruction, identification of the patient in shock with normal resistance is important.

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Myocardial infarction is in general associated with diffuse disease of the coronary arteries. Partial occlusion of a vessel causes a pressure gradient over the narrowing and, therefore, a significant pressure difference may exist between aortic diastolic pressure and the perfusion pressure at the level of the arterioles. It is probable that vessels distal to areas of partial occlusion as well as vessels in the ischemic zone will be maximally vasodilated. For these reasons very significant amounts of the myocardium may have a blood supply which is pressure-dependent and no longer able to adjust by autoregulation. This same situation may also pertain to cerebral and renal blood flows if there is partial occlusion of the major arteries to these organs.

Hypovolemia may be a significant factor in shock associated with myocardial infarction. A loss of intravascular volume may occur not only as a result of reduced fluid intake but also due to prolonged vasoconstriction, vomiting associated with the pain of infarction or medication, sweating, or the use of potent diuretic agents which can reduce intravascular volume precipitously. Circulatory arrest may produce such profound acidosis at the capillary level that vascular integrity is lost, fluid rapidly leaves the intravascular compartment, and dilatation of the capacitance vessels occurs. Since the injured myocardium needs a higher filling pressure to maintain an adequate cardiac output the reduced filling pressure associated with hypovolemia may result in shock in a patient with acute myocardial infarction even though the extent of myocardial damage is only moderate. Sudden loss of intravascular volume in acute myocardial infarction therefore may set off a chain of events (hypotension → use of pressor agents → further loss of intravascular volume → decreasing cardiac output) which will increase the extent of myocardial damage.

The appearance of clinical shock in a patient with acute myocardial infarction should not preclude considering noncardiac causes of shock such as sepsis or hemorrhage. The clue may not be obvious but a low central venous pressure (CVP), a fever out of proportion to the myocardial necrosis, a sudden fall in hematocrit, shock in a patient lacking electrocardiographic changes of transmural infarction, or shock associated with a normal or high cardiac output should all initiate a search for additional nonmyocardial causes of shock.

Plasma Volume Expansion in Shock of Myocardial Infarction

Most patients with shock and myocardial infarction have severe myocardial damage and have an elevated CVP. However, there are some patients who, as noted above, have an inadequate effective blood volume. If the CVP is below 10 cm H₂O, fluid challenge should precede all forms of therapy unless hypotension is so profound that immediate stabilization of arterial pressure is mandatory. Langsjoen et al. reported a reduced mortality rate in patients treated with low molecular-weight dextran after acute myocardial infarction. Although the therapy was designed to decrease intravascular sludging, the authors postulated that correction of undetected hypovolemia might have contributed to the improved survival. Nixon et al. pointed out the need for fluid to elevate the cardiac filling pressure of patients in shock with myocardial infarction and advocated infusion of dextrose solution as initial therapy of all patients with this syndrome. Allen et al. reported hypovolemia to be present in 20% of patients with cardiogenic shock and advocated initial dextrose infusion as therapy.

Normal or slightly reduced blood volumes have been reported in patients with shock and myocardial infarction. However, without knowing the individual’s normal blood volume prior to shock it is difficult to use blood volume measurements in adjusting fluid therapy. For this reason Weil et al. have advocated fluid challenge and careful monitoring of the CVP for diagnosis and treatment of hypovolemia. The information needed to monitor fluid infusion in myocardial infarction, in order to be certain that pulmonary edema is not precipitated, is the left atrial or pulmonary venous pressure. At the same time
a measure of left ventricular end-diastolic pressure (LVEDP) must be known in order to assure that the left ventricle is working at peak performance on the function curve, utilizing the Frank-Starling mechanism. Scheinman et al. used pulmonary artery end-diastolic pressure as an equivalent of mean left atrial pressure. Swan and Ganz have constructed a catheter with a balloon cuff near the tip. This catheter can be floated into the pulmonary artery and by inflating the balloon the pulmonary artery is occluded and pulmonary venous pressure as transmitted through the pulmonary capillaries can be measured from the tip of the catheter distal to the balloon. Both of these methods assess pulmonary venous pressure and fulfill the requirements for monitoring to avoid the danger of pulmonary edema, but neither method gives a measure of the pressure which is a determinant of ventricular function (LVEDP).

We have been impressed with the ease of measuring left ventricular pressure directly by passing a small catheter retrograde across the aortic valve under fluoroscopic guidance. Cohn has used a coiled catheter inserted without visual guidance. Ventricular irritability occurs less frequently than with right heart catheterization. We have measured pulmonary artery diastolic pressure (PADP) simultaneously with left ventricular diastolic pressure in 10 patients with acute myocardial infarction who had LVEDP in excess of 20 mm Hg (fig. 1). PADP underestimated LVEDP by an average of 11 mm Hg. PADP appears to give a good estimate of LV pressure just prior to atrial contraction and thus can be used to predict the onset of pulmonary edema. However, to determine the functional state of the myocardium and be certain peak performance has been achieved it would appear necessary to measure left ventricular pressure directly, and this becomes particularly urgent when considering therapy by mechanical circulatory assistance or emergency cardiac surgery. If the LVEDP is less than 20 mm Hg, plasma volume expansion should be attempted before classifying the severity of the myocardial lesion and committing the patient to a drastic therapeutic intervention.

Recognizing that measurements of pulmonary artery or left ventricular pressures are at present not feasible in most hospitals, we have compared CVP and LVEDP in a large group of patients in shock and found that as a static measurement there was poor correlation. With addition of plasma volume, however, both values tended to rise proportionately and therefore the CVP seemed to be valuable for monitoring fluid infusion (fig. 2). However, during infusion of norepinephrine (fig. 3), isoproterenol, or dopamine this relationship between the CVP and LVEDP was inconsistent and the LVEDP could rise while the CVP was falling. This limits the usefulness of the CVP as a means of monitoring changes in LVEDP to periods of plasma volume infusion when no pressor agent is being given or if

Figure 1

Pulmonary artery diastolic pressure (PADP), left ventricular diastolic pressure (LVEDP) before atrial contraction (AC), and LVDP at end-diastole (ED) are shown for each of 17 patients with uncomplicated acute myocardial infarction. In some patients large increases in LVDP occur coincident with AC and elevate LVDP at ED.
Changes in CVP and LVEDP following Infusion of Low Molecular Weight Dextran in 17 Patients

- Pre LMWD
- Post LMWD

Figure 2

Central venous pressure (CVP) and left ventricular end-diastolic pressure (LVEDP) before and after infusion of low molecular-weight dextran (LMWD) in patients with various types of shock. Although the CVP and LVEDP did not correlate well before LMWD, with LMWD infusion LVEDP and CVP showed parallel changes.

Changes in CVP and LVEDP during Infusion of Norepinephrine in 12 Patients

- Pre-norepinephrine
- During norepinephrine

Figure 3

CVP and LVEDP before and during norepinephrine infusion in 12 patients with shock. No clear relationship between changes in CVP and LVEDP is apparent during infusion of norepinephrine.
pressors are being infused to periods when the rate of pressor infusion is not altered. We have used \(^{40}\) dextran as the agent for volume expansion as have Cohn et al.\(^{29}\) This agent has the advantage of dispersing red-cell aggregates and preventing platelet clumping. Nixon et al. have advocated the use of 5% dextrose solution\(^{31}\) as have Swan et al.\(^{30}\) who suggested monitoring pulmonary artery pressure and giving 20 cc/min of 5% dextrose for 5–15 min or until the pulmonary artery diastolic pressure increased more than 4 mm Hg. Dextrose solutions, if used, must be given rapidly so that they challenge the extent to which the intravascular compartment is filled. When dextrose solutions are given slowly the fluid may leave the intravascular compartment as rapidly as the infusion adds volume and thereby edema may develop and the cardiac filling pressure not rise. A 3.5% solution of serum albumin would also be an adequate substitute for dextran and might not leave the intravascular compartment as rapidly as either dextrose or dextran. We have used a modification of Weil's method for volume challenge by giving 100 cc of \(^{40}\) dextran over a 10-min period, waiting 10 min, and then if CVP has not increased by more than 1 cm of H\(_2\)O repeating the process. This is continued until the CVP continues to increase, exceeds 15 cm H\(_2\)O, or shock is relieved, or 100 cc has been given. With treatment of 10 patients in this manner we witnessed recovery from shock in seven and long-term survival in five.\(^{19}\) A 50% survival is so remarkable in this illness that it suggests that myocardial damage in these patients was only moderate and that hypovolemia was the added complication which produced the shock syndrome.

**Norepinephrine**

Using a definition of shock in myocardial infarction which includes systolic blood pressure below 80 mm Hg, Binder et al. found the survival rate without vasopressors to be about 10%.\(^{31}\) If patients with volume depletion are excluded, the survival rate with the use of pressor agents in most series has been between 20 and 30%.\(^{32}\) Pure vasoconstrictors such as methoxamine, neosynephrine, or angiotensin are not of value in the treatment of shock with acute myocardial infarction.\(^{15}\) Increasing afterload merely increases the work of the heart, and since these agents are without inotropic effects the ventricle dilates. As this increases wall tension and oxygen needs, the ventricle is thereby required to work from an even greater mechanical disadvantage.

The first hemodynamic studies of response to pressors were by Malmcrona, Schröder, and Werkö who reported on nine patients with recent myocardial infarction, five of whom had periods of systolic blood pressure below 100 mm Hg.\(^{33}\) They showed increases in cardiac output during metaraminol infusion in seven of the nine patients. Smulyan, Cuddy, and Eich studied seven patients in shock with myocardial infarction measuring the effects of norepinephrine in five and metaraminol in two patients.\(^{34}\) Cardiac output increased in only two patients although in most of the patients systemic arterial pressure was brought above 110 mm Hg during treatment. Shubin and Weil treated 10 patients with either norepinephrine or metaraminol and demonstrated an increase in cardiac output and arterial pressure.\(^{35}\) They made the very important observation that when the arterial pressure was brought above 90 mm Hg there was a decrease in cardiac output and an increase in systemic vascular resistance. We have reported on the use of norepinephrine in 33 patients in shock with acute myocardial infarction and all except one had control mean arterial pressure below 75 mm Hg.\(^{1}\) Cardiac output increased an average of 18%, arterial pressure increased 43%, and systemic vascular resistance increased 37%.

We have reviewed our experience with the use of norepinephrine in patients with various forms of medical shock (table 1) and have confirmed the observations of Weil and Shubin\(^{36}\) that increasing the arterial pressure above levels just adequate to perfuse the vital organs (brain, heart, and kidney) merely increases the work of the heart at the expense of a decrease in blood flow. Laks et al. have demonstrated in the intact dog that at very small infusion rates norepinephrine increases
cardiac output with little effect on systemic vascular resistance.37 Much of the animal experimental work that shows the detrimental effects of norepinephrine has been at infusion rates which elevated mean arterial pressure above 120 mm Hg.

One can block the vasoconstriction caused by norepinephrine by adding alpha-blocking agents such as phentolamine (Regitine) or chlorpromazine but it is our impression that this is best done as a separate therapeutic maneuver after arterial pressure has been stabilized (vide infra).

Isoproterenol

Isoproterenol is a potent synthetic activator of beta-receptors and thereby is an active inotropic and chronotropic agent increasing the force and rate of contraction as well as the myocardial oxygen consumption. It increases renal blood flow but the proportion of the cardiac output going to the kidneys is reduced.

This agent has been used with success in the treatment of shock due to sepsis and trauma and in cardiogenic shock following cardiac surgery.38 Smith et al. advocated its use in patients with myocardial infarction and demonstrated it to be a better agent than metaraminol.39 However, in patients with “driving pressures” less than 80 mm Hg it appeared to be of no benefit. Morse, Danzig, and Swan used isoproterenol in conjunction with volume expansion and thought it a valuable agent,40 but did not compare it to small amounts of norepinephrine. We compared isoproterenol infusion in amounts of 1–7 μg/min to norepinephrine infusion in 13 patients with hypotension and shock following acute myocardial infarction.41 None of the patients showed clinical improvement during isoproterenol infusion. There was rapid clinical deterioration in four patients on switching from norepinephrine to isoproterenol, and this was reversed by reinstituting norepinephrine in one.

The most conclusive report negating the usefulness of isoproterenol in shock and hypotension due to coronary disease has been that of Mueller et al.42, 43 They demonstrated that isoproterenol increased myocardial lactate production in all patients given this agent while with norepinephrine infusion lactate production shifted to extraction or extraction increased. This metabolic deterioration during isoproterenol infusion in spite of an increase in coronary blood flow may represent the “coronary steal syndrome” described by Sharma et al.17 The maximally dilated vessels surrounding an infarct and behind areas of fixed obstruction have blood flow which is pressure-dependent. An agent such as isoproterenol which drops perfusion pressure and decreases coronary resistance in uninvolved areas would divert blood away from the ischemic areas while increasing the oxygen needs of the ischemic myocardium. Bing et al. have shown that in ischemic muscle isoproterenol enhances peak tension but that deterioration occurs more rapidly than in ischemic muscle not exposed to isoproterenol.44 This increased rate of deterioration could be slowed but not reversed by the addition of glucose. The authors proposed that isoproterenol causes rapid depletion of high energy stores. Thus isoproterenol not only diverts blood from the ischemic areas but enhances myocardial deterioration in the ischemic area.

Despite these arguments against its use, isoproterenol may be an effective agent in the

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<th>Control MAP (mm Hg)</th>
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<td></td>
<td>Mean Δ CO (%)</td>
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<tr>
<td>&lt; 50</td>
<td>+32 ± 34.0</td>
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<td>50 – 70</td>
<td>+16 ± 26.5</td>
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<tr>
<td>&gt; 70</td>
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Table 1

Response to Norepinephrine Infusion in 122 Patients with Shock of Various Etiologies

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presence of the shock syndrome when intraarterial pressure is normal. Under these circumstances, isoproterenol should be given in small amounts of 0.5–2.0 μg/min and discontinued if arterial pressure falls or if arrhythmias appear. In patients with severe mitral insufficiency and acute myocardial infarction any increase in systemic vascular resistance only enhances the regurgitant flow and, therefore, isoproterenol is the catecholamine to be used first.

Isoproterenol can also be used after atropine in the presence of bradycardia but in most instances this will be a temporary measure while placing a pacing catheter. Idioventricular rhythms should not be brought much above 60 beats/min with this drug because of the danger of inducing ventricular tachycardia or fibrillation.

Dopamine

Dopamine is a precursor of norepinephrine and activates both the beta- and alpha-adrenergic receptors.45 In addition this drug has vasodilator effects on the renal and mesenteric vessels not mediated through adrenergic receptors.46 Dopamine, by increasing myocardial oxygen consumption, reduces coronary vascular resistance.47 A direct effect of dopamine on the coronary circulation has not as yet been demonstrated. Because its action on the adrenergic receptors is intermediate between norepinephrine and isoproterenol and due to its renal vasodilator properties, dopamine has been considered a useful agent in the treatment of various shock states.48 Dopamine has been shown to improve hemodynamic abnormalities caused by experimental myocardial infarction as it tends to reverse the depression of myocardial function that follows coronary artery ligation.49 MacCannell et al. reported improvement in urine flow as well as arterial pressure and cardiac output during dopamine infusion in patients with shock of several etiologies.50 Talley et al. reported seven patients who had a better hemodynamic response to dopamine than to isoproterenol.51

We have reported on the effects of dopamine on 62 patients with shock.52 In 13 patients, five of whom had acute myocardial infarction, the shock was primarily cardiogenic. In patients with cardiogenic shock dopamine increases cardiac output and LVEDP and can increase mean arterial pressure if it is reduced. Systemic vascular resistance tends to fall as cardiac output increases in those who are initially vasoconstricted. When compared to norepinephrine and isoproterenol, dopamine increases cardiac output more than norepinephrine and less than isoproterenol and increases arterial pressure more that isoproterenol and less than norepinephrine. Urine flow appears to improve as often with norepinephrine as with dopamine. Comparison of the latter two agents by therapeutic trial is often necessary if improved urine flow is the object of therapy.

Dopamine can be infused at rates of 0.1–1.6 mg/min, and careful ECG monitoring is necessary because ventricular arrhythmias may be precipitated.

Digitalis

Digitalis has been used in treatment of shock with myocardial infarction but few studies of the hemodynamic effects have been published. Gorlin measured cardiac output in two patients before and after rapid digitalization and found increases in both patients.53 In an experimental model of cardiogenic shock Cronin and Zsoter showed that digitalis causes an increase in blood pressure, a slight increase in cardiac output, and a very significant increase in stroke volume with a fall in LVEDP.54 The increase in blood pressure preceded the increase in cardiac output and they suggested that the direct vasoconstrictor effects of digitalis preceded the inotropic action.

We have reported the effects of acute digitalization in a group of patients in shock with myocardial infarction and the averages of the changes in cardiac output, arterial pressure, CVP, and systemic vascular resistance tended to show no effect of the digitalis on any of these parameters.1 Some patients improved but others deteriorated or continued to deteriorate following administration of digitalis. Morrison and Killip have stressed the
increased ventricular irritability induced by digitalis in acute myocardial infarction, and therefore it should be used judiciously and only after elevating the arterial pressure and by ensuring an adequate filling pressure by fluid infusion, if necessary. It should be given in amounts calculated to be one half to two thirds of the accepted “digitalizing” doses. The best effects will be in the patients in overt failure, but almost all patients with acute myocardial infarction given digitalis will decrease LVEDP and increase LV stroke work and rate of pressure development.

The question remains as to whether this effect is of benefit to the heart. The increase in stroke work and the increase in rate of pressure development would be at the expense of an increase in myocardial oxygen consumption. However, the decrease in LVEDP, if it represents a decrease in diastolic volume and not just a change in myocardial compliance, should decrease myocardial oxygen needs. The law of LaPlace indicates that the pressure in the ventricle varies directly with the tension in the wall and inversely with the radius of the cavity. Therefore, if left ventricular pressure develops from a smaller ventricular radius, myocardial tension, a major determinant of myocardial oxygen consumption, could decrease even as pressure rises. It is probable that the dilated heart benefits from administration of digitalis while the normal-sized heart does not. The answer to whether the effects in acute myocardial infarction are beneficial awaits studies of changes in ventricular volume or measurements of myocardial oxygen consumption. There is some indication from clinical observations that changes in ventricular volume may determine the efficacy of digitalis in ischemic heart disease, since patients with angina and small hearts not infrequently accelerate their angina with digitalization while patients with big hearts may be relieved of angina when given digitalis. Digitalis should not be given in the presence of heart block unless a pacemaker catheter is in place.

**Glucagon**

Glucagon has been noted to have an inotropic effect in isolated muscle preparations and in the intact animal. In man it has been shown to be effective in increasing cardiac output, rate of pressure development, and heart rate. It was first used therapeutically as an inotropic agent by Linhart who reported improvement in a patient with depressed cardiac function after heart-valve replacement. With administration of glucagon to this patient he noted that the blood pressure returned to normal, heart rate increased slightly, and further pharmacologic support was unnecessary. Parmley reported on the administration of this agent to 16 patients in the first postoperative day after prosthetic-valve replacement and found an increase in mean arterial pressure, heart rate, and cardiac index. There was no change in systemic vascular resistance, although Glick had previously shown glucagon to be a mild vasodilator. Vander Ark and Reynolds treated 16 patients with cardiogenic shock for 1–12 days with continuous glucagon infusions. They noted improvement in 12 of the patients who experienced increased blood pressure, decreased heart rate, and increased urine flow. Murtagh et al. gave glucagon to eight patients with myocardial infarction and noted an increase in pulmonary and systemic vascular resistances. Diamond et al. treated 10 patients with acute myocardial infarction, nine of whom had left ventricular failure. They noted an increase in heart rate, cardiac output, and arterial pressure. There was a consistent increase in pulmonary vascular resistance, and they attributed this to a direct effect of glucagon on the pulmonary vasculature. They also report the use of glucagon in treating two patients with severe myocardial infarction and shock, and credited survival in one of the patients to the use of glucagon. Studies in patients with chronic congestive failure have been less conclusive than studies in patients with acute failure. In studies of papillary muscles from patients having mitral-valve replacement Goldstein et al. found glucagon had no inotropic effect on muscles from patients who had prolonged cardiac failure.
adenyl cyclase but through a different receptor mechanism. Aminophylline will potentiate the effects of glucagon by blocking phosphodiesterase which deactivates cyclic AMP. Glucagon, therefore, has the advantage of acting through a nonadrenergic receptor mechanism and can be effective in the patient who has received beta-receptor blocking agents. It does not cause arrhythmias and can be used in the patient with digitalis excess. It has also been shown to reverse the prolongation of action potential produced by quinidine.

Administration is either by single injection of 4-5 mg intravenously or by constant intravenous infusion at the rate of 4-12 mg/hour. The single injection shows onset of action almost immediately, peak action at 10 min, and action is dissipated within 30 min. Hyperglycemia is a constant finding but is usually only to levels of 140 mg% and seldom exceeds 200 mg%. Hypoglycemia may occur, particularly on discontinuation after prolonged infusion. Hypokalemia occurs consistently and should be prevented by K+ supplementation during glucagon infusion. Glucagon infusion should be augmented by simultaneous aminophylline infusion. Nausea and vomiting are uncomfortable side effects and the resultant vagal stimulation may decrease cardiac output. By limiting the infusion rate or keeping the single injection below 5 mg this side effect usually can be avoided.

Glucagon has a direct effect on the renal tubules leading to diuresis and natriuresis. In chronic intractable cardiac failure we have noted marked diuresis far in excess of the hemodynamic effect and suggest that the direct renal effects deserve further study (fig. 4).

**Chlorpromazine and Phenolamine**

Chlorpromazine and phenolamine have been used as vasodilators in myocardial infarction. They can be used in conjunction with norepinephrine to decrease the vasoconstrictor activity of the latter agent and thus allow more inotropic activity. Both agents also cause a decrease in venous tone and should be

![Figure 4](https://example.com/figure4.png)

**Figure 4**

The effects of isoproterenol (ISP), phenolamine, and glucagon in a patient with chronic congestive heart failure. Cardiac output (CO) increased more with isoproterenol than with glucagon but urine flow (UF) was greater during glucagon infusion. Phenolamine infusion had little effect on either CO or UF. Changes in mean arterial pressure (MAP), heart rate (HR), and left ventricular end-diastolic pressure (LVEDP) are also shown.

although these same muscles responded positively to norepinephrine. Papillary muscle from patients with mitral stenosis and no left ventricular failure showed an inotropic response to both glucagon and norepinephrine. This discrepancy is probably due to uncoupling or disruption of the glucagon receptor mechanism in chronic congestive heart failure. Glucagon acts by activating adenyl cyclase which converts adenosine triphosphate to cyclic AMP (adenosine 5'-monophosphate) and this in turn activates the contractile mechanism. Catecholamines also activate
accompanying volume administration unless the vasodilator is being used in management of pulmonary edema. Chlorpromazine is given in amounts of 5–10 mg intravenously in a single injection and may be repeated only once at 20–30 min. Larger amounts of this agent will increase drowsiness and may enhance arrhythmias. Phentolamine is given as a constant intravenous infusion at a rate of 2–4 mg/hour. Phenoxycbenzamine, although a very potent alpha-adrenergic blocking agent, is not available for general use and its action is so prolonged that we would not think it should be used in acute myocardial infarction.

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