
**MEDICAL PROGRESS**

**MEDICAL THERAPY OF ACUTE MYOCARDIAL INFARCTION BY APPLICATION OF HEMODYNAMIC SUBSETS**

(Second of Two Parts)

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**Physiologic Basis for Therapeutic Decisions — Effects of Drugs on Cardiac Function**

The selection of therapy for a patient with disordered function in acute myocardial infarction involves both assessment of the level of cardiac performance and prediction of the response to therapy. Table 5 summarizes the reported hemodynamic effects of commonly used therapeutic methods in acute myocardial infarction. The effects of therapeutic agents on cardiac function in acute myocardial infarction are usefuly considered in four classes: diuretics, vasodilators, inotropes and others. This classification is of particular value in clinical practice, for although there are substantial variations in the magnitude of effects, the direction of the hemodynamic response to various agents within each group is similar.

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the pulmonary-capillary pressure falls, and there is little change in heart rate. The probable mechanism responsible for this response is shown in Table 6. A reduction in the resistance to ejection increases the percentage of blood ejected on a single beat — that is, the ejection fraction increases. This increase in ejection fraction is accompanied by an increase in stroke volume, resulting in augmented cardiac output. Simultaneously, an increase in ejection fraction results in a decrease in left ventricular volume, leading to a reduction in ventricular diastolic pressure that is transmitted "backward" as reduced left atrial and pulmonary-capillary pressure. Pulmo-

this difference in action may be explained by the exponential shape of the ventricular pressure-volume relation and the logarithmic shape of the Starling relation shown in Figure 6. When left ventricular diastolic pressure (and pulmonary-capillary pressure) is high, a small change in ventricular volume causes a major reduction in diastolic pressure. This small change in diastolic pressure, however, causes little reduction in cardiac output by the Starling mechanism. On the other hand, when left ventricular diastolic pressure (and pulmonary-capillary pressure) is normal, a small reduction in diastolic pressure reflects a large reduction in diastolic volume, which may substantially reduce cardiac output.

**Periphera l Vasodilators**

These drugs are dramatically effective in improving hemodynamics in patients with heart failure due to acute myocardial infarction. Cardiac output im-

<table>
<thead>
<tr>
<th>Table 5. Hemodynamic Effects of Commonly Used Therapies on Cardiac Hemodynamics in Acute Myocardial Infarction.</th>
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<tbody>
<tr>
<td><strong>Therapy</strong></td>
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<td></td>
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<tr>
<td><strong>Control</strong></td>
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<td><strong>Mean (%)</strong></td>
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<tr>
<td><strong>CONTROL</strong></td>
</tr>
<tr>
<td><strong>Mean (%)</strong></td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
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<tr>
<td>Bezek*</td>
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<tr>
<td>Balcon*</td>
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<tr>
<td>Malmcrona*</td>
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<tr>
<td>Norepinephrine</td>
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<td>Ahrama*</td>
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<td>Muller*</td>
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<tr>
<td>Gunnar*</td>
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<tr>
<td>Isoprotrenol</td>
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<td>Muller*</td>
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<td>Gunnar*</td>
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<td>Glucagon</td>
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<tr>
<td>Diamond*</td>
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<td>Nitropreside</td>
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<td>Franciosa*</td>
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<td>Chatterjee'</td>
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<tr>
<td>Photomolinne</td>
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<td>Kelly*</td>
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<td>Walinsky*</td>
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<tr>
<td>Nitroglycerin</td>
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<td>Gold*</td>
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<td>Furosemide</td>
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<td>Mond*</td>
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<td>Dikbit*</td>
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<tr>
<td>Propranolol</td>
</tr>
<tr>
<td>Mulder*</td>
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<tr>
<td>Circulatory Assist.</td>
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<td>Dilley*</td>
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<td>Dunkman*</td>
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</table>

*Data, reported as cardiac output, have been divided by an average body-surface area of 1.8 m² to obtain cardiac index for comparative purposes.

<table>
<thead>
<tr>
<th>Table 6. Effect of Peripheral Vasodilators in Normal and Depressed Cardiac Function.*</th>
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<tbody>
<tr>
<td><strong>ACTION</strong></td>
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<tr>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Decreased resistance</strong></td>
</tr>
<tr>
<td><strong>Increased capacitance</strong></td>
</tr>
<tr>
<td><strong>Decreased</strong></td>
</tr>
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<td><strong>Increased</strong></td>
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</table>

*The peripheral arterial & venous effects are "competitive" in relation to their effect on cardiac output. Decreased resistance to ejection increases ejection fraction, whereas increased venous capacitance decreases venous return. In patients with depressed cardiac function, the sum of the peripheral arterial & venous effects is to increase cardiac output & decrease left ventricular filling pressure; but in individuals with normal left ventricular function, the peripheral venous effect usually predominates, so that cardiac output and filling pressure both decrease.
nary-capillary pressure is also reduced by concomitant peripheral venodilation, which may result in diminished venous return. Thus, an improvement in effective cardiac performance is obtained through manipulation of the milieu in which the heart works without necessarily changing the function of the muscle itself.

Like that of diuretic agents, the effect of peripheral vasodilators differs between patients in the pulmonary-congestion subsets and those in the subsets with normal pulmonary-capillary pressure. Peripheral vasodilators increase stroke volume in patients with elevated pulmonary-capillary pressure and depressed cardiac index, but decrease stroke volume and increase heart rate in patients with normal levels of pulmonary-capillary pressure. The probable mechanism for this difference involves the effect of the drug on vascular resistance and venous capacitance, as shown in Table 6. Persons with normal levels of left ventricular filling pressure more often have a normal ejection fraction and, therefore, little capability for augmentation of function by reducing resistance to ejection. Since peripheral vasodilators reduce left ventricular filling pressure by increasing peripheral venous pooling, stroke volume may decrease by the Starling effect in these patients. In contrast, patients with increased left ventricular filling pressure and decreased cardiac index can experience a substantial increase in ejection fraction with reduction in peripheral vascular resistance, and the reduction in cardiac output that ensues from reduction in left ventricular filling pressure is minimal.

One might reasonably expect that the use of vasodilating agents would be limited by their propensity to aggravate hypotension in patients with severe heart failure. Hemodynamic monitoring has shown that the response to infusion of a peripheral vasodilator tends to follow a three-step progression determined by infusion rate.48 At low doses, cardiac output increases, and pulmonary-capillary pressure decreases, with little change in arterial pressure, the increase in output balancing the decrease in resistance. As infusion rate is increased to a medium range, cardiac output further increases and pulmonary-capillary pressure falls with a concomitant fall in arterial pressure. With high infusion rates, profound vasodilatation can occur, leading to a reduction in cardiac output, pulmonary-capillary pressure and arterial pressure. It is at this latter level that the peripheral vasodilating agents change from being dramatically effective to potentially lethal by seriously compromising coronary perfusion. For this reason it is important to observe the following two guidelines for employment of vasodilator therapy when cardiac output levels are not available: During infusion, pulmonary-capillary pressure should not be allowed to fall below 15 to 18 mm Hg; and arterial pressure should be maintained within the physiologic range. In the hypotensive patient, reduction in arterial pressure should not be allowed to exceed 5 mm Hg. When these "rules" are observed, peripheral vasodilating agents may safely and therapeutically increase cardiac output and decrease capillary pressure.

Inotropic Agents

Among the variety of inotropic agents employed in acute myocardial infarction, digitalis,46-48 isoproterenol,47-48 norepinephrine,47-48 glucagon47-48 and dopamine81-86 have been studied for specific hemodynamic effects. Each drug in this class exerts its effect predominantly by increasing myocardial contractility. Isoproterenol and glucagon are also peripheral vasodilators and can increase cardiac output by this mechanism, whereas in the doses usually employed clinically, norepinephrine produces peripheral vasoconstriction. The hemodynamic effects of inotropic agents differ predominantly in their effect on arterial pressure: isoproterenol and glucagon cause no change or a decrease, digitalis generally has little effect, and the effect of norepinephrine and dopamine is predominantly dose related. At low doses the beta-adrenergic effects of these agents predominate, causing no change in pressure, whereas at higher doses, the alpha effects are more apparent.

Inotropic agents generally become increasingly ineffective as the magnitude of the left ventricular failure increases: administration of inotropic agents to patients with cardiogenic shock frequently results in no detectable change in the cardiac output or pulmonary-capillary pressure. The mechanism for this difference pertains to the fact that the magnitude of left ventricular failure predominantly reflects the magnitude of myocardial infarction. With increasing infarct size, there is less myocardium to respond to an inotropic agent. Furthermore, the remaining noninfarcted muscle may be functioning at near maximum potential as a result of endogenous catecholamine release secondary to diminished cardiac output. When the capability of the heart to respond to inotropic stimulation is substantially reduced, inotropic agents that increase peripheral vascular resistance may actually cause a decrease in cardiac output and an increase in pulmonary-capillary pressure, and rarely may precipitate acute pulmonary edema.91 Ironically, therefore, the patients who most require therapy show the least response, and those who do not require the drug tend to exhibit the desired effect.

Mechanical Circulatory Assist

Because special equipment and a circulatory-assist team are required, intra-aortic balloon counterpulsation has been used predominantly in patients with cardiogenic shock.92-101 Substantial improvement in cardiac hemodynamics can be obtained with intra-aortic balloon counterpulsation, and the shock state is frequently reversed. The hemodynamic response frequently diminishes with time, however, and long-term results with this therapeutic method alone have been relatively poor. This type of therapy, therefore, is most commonly employed as an effective short-term mea-
ure for circulatory support. When combined with vasodilator therapy, circulatory assistance may protect against the deleterious effect of decreased arterial diastolic pressure induced by vasodilator therapy, and thereby provide a margin of safety by permitting a more rapid infusion of the drug.

The preceding discussion may be summarized as a second principle: the response to therapy is determined by the re-treatment level of left ventricular performance. As a useful generalization, inotropic agents become progressively as effective as the magnitude of left ventricular failure increases. In contrast, agents that reduce capillary and arterial pressure, such as peripheral vasodilators, are ineffective in the therapy of uncomplicated myocardial infarction but extremely useful as adjuncts.

**Physiologic Basis of Therapeutic Decisions — Effect of Drugs on Cardiac Metabolism**

The variable response to therapy observed in different subsets implies that the choice of therapy for a given patient will be determined in part by the level of pulmonary-capillary pressure and cardiac index. In the presence of acute myocardial ischemia, however, one must also consider whether the drug affects the ability of ischemic myocardium to increase oxygen extraction from each milliliter of blood as it passes through the heart. In acute myocardial infarction, an upper limit of flow to ischemic myocardium is established by the presence of fixed proximal arterial stenoses. Whereas oxygen supply in other tissues can be increased by increasing oxygen extraction, it is near maximal at rest even in the normal heart, and any increase in oxygen demand is met by an increase in coronary flow. We are, therefore, currently unable to substantially increase oxygen supply to ischemic myocardium by medical means.

Medical therapy, however, may have substantial effects on myocardial oxygen demand. Four major factors increase myocardial oxygen demand: preload, afterload, contractility and heart rate. Clinically, we assess preload by pulmonary-capillary pressure and afterload by arterial systolic pressure. Although a substantial amount of information exists concerning the effects of drugs on myocardial metabolism in animals, there are only a limited number of such studies in patients with acute myocardial infarction. Nevertheless, the data available (Table 7) are consistent with animal studies and support the following conclusions.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSE</th>
<th>N</th>
<th>MEAN CORONARY BLOOD FLOW (%)</th>
<th>MEAN MYOCARDIAL OXYGEN CONSUMPTION (%)</th>
<th>LACTATE (% CHANGE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis (7)</td>
<td>0.3 - 0.5 mg of digitoxin intravenously</td>
<td>9</td>
<td>38</td>
<td>35</td>
<td>+44 - +38</td>
</tr>
<tr>
<td>Norepinephrine (11)</td>
<td>2 - 8 µg/min</td>
<td>8</td>
<td>38</td>
<td>29</td>
<td>-4 - +12</td>
</tr>
<tr>
<td>Isoproterenol (11)</td>
<td>2 - 4 µg/min</td>
<td>6</td>
<td>16</td>
<td>20</td>
<td>-8 - -19</td>
</tr>
<tr>
<td>Nitroxprusside (16)</td>
<td>16 - 200 µg/min</td>
<td>19</td>
<td>-6</td>
<td>-27</td>
<td>+17 + +16</td>
</tr>
<tr>
<td>Propranolol (22)</td>
<td>0.1 mg/kg</td>
<td>20</td>
<td>-17</td>
<td>-22</td>
<td>-14 + +26</td>
</tr>
</tbody>
</table>

*Figures in parentheses represent no. of patients.

The effect of inotropic agents on the imbalance between myocardial oxygen supply and demand is somewhat variable. Isoproterenol consistently increases myocardial oxygen demand by a substantial degree, aggravating the imbalance between oxygen supply and demand, as evidenced by an increase in the concentration of lactate in cardiac venous blood. Norepinephrine also substantially increases myocardial oxygen demand, but this increase may be equaled by an increase in oxygen delivery secondary to increased aortic diastolic pressure, particularly if severe hypotension exists. Therefore, the metabolic response varies from patient to patient, depending on relative effects on oxygen supply and demand. Digitalis causes a substantial increase in myocardial oxygen demand through its effect upon increasing myocardial contractility. In cases in which the drug is effective in reducing preload (and therefore heart size) or heart rate, however, the increase in myocardial oxygen demand may be minimized. As with norepinephrine, therefore, the effect of digitalis upon the imbalance between myocardial oxygen supply and demand is variable. Nevertheless, it seems likely that inotropic agents seldom improve the imbalance between myocardial supply and demand and frequently aggravate it substantially in patients with acute infarction.

Properly administered, peripheral vasodilators substantially lower myocardial oxygen demand by reducing both preload and afterload, without affecting heart rate or contractility. Therapeutic reduction of afterload must be undertaken with considerable caution, however, since too vigorous administration of peripheral vasodilators may result in substantial fall in aortic diastolic pressure, in which case the decrease in myocardial perfusion and reflex increase in heart rate may exceed the reduction in oxygen demand. Careful control of the infusion rate of peripheral vasodilators, therefore, is essential to produce a reduction in myocardial oxygen requirement with little change in coronary blood flow.

No data are currently available on the effects of diuretic agents on myocardial oxygen supply and demand. Nevertheless, it may be hypothesized that these agents reduce oxygen demand by lowering pulmonary-capillary pressure while arterial pressure, heart rate and contractility remain unchanged. Propranolol is perhaps the most effective drug currently...
available for decreasing myocardial oxygen demand through its effect of reducing myocardial contractility and heart rate. Improvement in myocardial lactate metabolism is frequently observed after propranolol administration in patients with acute infarction.62

Mechanical circulatory assistance affects both myocardial oxygen supply and demand.94 By inflation of an intra-aortic balloon or external leg compression in diastole, mechanical circulatory assistance increases aortic diastolic and coronary perfusion pressure. This elevation in perfusion pressure should augment flow to ischemic myocardium. In practice, the actual increase in myocardial perfusion is probably limited by the presence of fixed, proximal coronary-artery stenoses and by the development of coronary arterial thromboses. Myocardial oxygen demand, however, can be substantially decreased by effective mechanical circulatory assistance. In intra-aortic balloon counterpulsation, the balloon is evacuated at the onset of systole, creating a "potential space" in the aorta, and in effect a reduction in resistance to ejection by the failing heart. This reduction in impedance can cause a decrease in systolic arterial pressure with an increase in stroke volume, and because of improved emptying, a subsequent reduction in pulmonary-capillary pressure. Thus, effective mechanical circulatory assistance improves myocardial oxygen supply by increasing coronary perfusion pressure and reduces myocardial oxygen demand by decreasing preload and afterload.

From these data a third principle becomes apparent: knowledge of the effect of an intervention on both cardiac function and metabolism is critical to therapeutic decisions in patients with acute infarction.

Ideally, therefore, the development of criteria for therapy of altered cardiac function should be based on assessment of cardiac function in a given patient, and knowledge of the effect of the therapeutic agent on both cardiac function and metabolism. The effect of commonly used therapeutic agents on function and metabolism in patients with abnormal performance is summarized in Table 8.

Table 8. Effects of Commonly Used Pharmacologic Agents on Cardiac Hemodynamics and Myocardial Oxygen Requirement in Patients with Acute Myocardial Infarction.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>HEMODYNAMICS</th>
<th>MVO&lt;sub&gt;1&lt;/sub&gt;</th>
<th>MECHANISM</th>
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<tbody>
<tr>
<td></td>
<td>CO</td>
<td>PCP</td>
<td>EFFECT</td>
</tr>
<tr>
<td>Inotropes</td>
<td>Unchanged or increased</td>
<td>Unchanged or decreased</td>
<td>Increase</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Unchanged</td>
<td>Decreased</td>
<td>Decrease</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decrease</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>Decreased</td>
<td>Unchanged or increased</td>
<td>Marked decrease</td>
</tr>
</tbody>
</table>

*The data refer to the effects of the drug in the situations in which it would be clinically indicated — i.e., propranolol would be used in the hyperdynamic subset, & other drugs would be used in the heart-failure subset. Both hemodynamic & metabolic effects refer only to patients with acute myocardial infarction (see text for discussion). CO denotes cardiac output, PCP pulmonary-capillary pressure, & MVO<sub>1</sub> myocardial oxygen consumption.

**Optimization of Cardiac Hemodynamics — An Approach to Therapy**

This section outlines a practical hemodynamic approach to therapeutic decision making based on the previous discussion. The following assumptions are basic to this approach: the relation between pulmonary-capillary pressure and cardiac index defines the function of the heart as a pump;11 cardiac-pump dysfunction is associated with increased mortality and morbidity in acute myocardial infarction;16-41 there is a causal relation between capillary pressure and pulmonary congestion;42,43 and between cardiac index and peripheral hypoperfusion;44 cardiac-pump dysfunction is related to infarct size42,43, and infarct size is influenced by hemodynamic determinants of myocardial oxygen consumption.102 By logical deduction, therefore, three basic therapeutic goals in acute myocardial infarction are to relieve pulmonary congestion by reducing elevated pulmonary-capillary pressure, to relieve peripheral hypoperfusion by increasing reduced cardiac output, and to accomplish this end without increasing the imbalance between myocardial oxygen supply and demand.

Although innumerable other factors must receive consideration in the choice of therapy for a specific patient, one or more of these goals is generally central to therapeutic decision making in acute myocardial infarction. In the following section, the hemodynamic response to therapy that occurs in subsets of patients with acute myocardial infarction is described in relation to these goals, and the possible effects of these complex hemodynamic alterations on the imbalance between myocardial oxygen supply and demand are discussed.

The Uncomplicated Patient (Subset I)

Hemodynamics are generally within the normal range in Subset I, and therapy is not required to improve cardiac performance.

Pulmonary (Subset II)

According to current understanding of the hemodynamics of left ventricular failure, many patients with acute myocardial infarction are in a deleterious hemodynamic state, following mechanical circulatory assistance. Hemodynamics are generally within the normal range in Subset I, and therapy is not required to improve cardiac performance.
Hemodynamic Therapy of Myocardial Infarction — Forrester et al.

Pulmonary Congestion without Peripheral Hypoperfusion (Subset II)

According to the previously stated assumptions, the logical goal of therapy in Subset II is to reduce pulmonary-capillary pressure below a level causing pulmonary congestion but above which would cause a deleterious reduction in cardiac output by the Starling mechanism. The specific aim, therefore, is to reduce the pressure to the range of 15 to 18 mm Hg; below 18 mm Hg the signs and symptoms of pulmonary congestion disappear over a period of 12 to 48 hours after reduction of capillary pressure, whereas there is little if any decrease in cardiac output when the pressure is reduced from high levels to 15 mm Hg (as capillary pressure falls to the range of 5 to 10 mm Hg, substantial reductions in cardiac output can occur).

There are several options, since diuretics, peripheral vasodilators and inotropic agents all reduce pulmonary-capillary pressure. In general, diuretics offer substantial practical and theoretical advantages. These agents can be administered by mouth or by intravenous infusion with a wide margin of safety (in contrast to the more potent peripheral vasodilators) and do not increase myocardial oxygen demand (as inotropic agents do). Since reduction in pulmonary-capillary pressure generally signifies a reduction in left ventricular volume, even in the presence of reduced left ventricular compliance, diuretic agents may decrease the magnitude of myocardial ischemia by this mechanism.

Periipheral Hypoperfusion without Pulmonary Congestion (Subset III)

The clinical diagnosis of isolated peripheral hypoperfusion is of major prognostic importance because the mortality rate is four times greater in Subset III than in patients without hypoperfusion. The logical goal of therapy is to improve cardiac index to a level adequate to relieve the signs of hypoperfusion at the least cost to the heart in terms of oxygen consumption. The majority of patients in this subset demonstrate a reduction in stroke volume and compensatory tachycardia. In such patients, cardiac output may be increased by volume expansion. The cardiac-output response is of very limited magnitude, however, beyond a capillary pressure of approximately 15 to 18 mm Hg.

The effect of volume infusion in patients with depressed cardiac index and normal pulmonary-capil-
lary pressure is shown in Figure 7d. As capillary pressure was increased 50 per cent, the mean cardiac index increased 19 per cent whereas arterial systolic pressure remained unchanged. Thus, improvement in cardiac index occurred while capillary pressure was maintained below the level of pulmonary congestion. Since cardiac index did not increase to the level observed in Subset I (>2.2 liters per minute per square meter), however, it is apparent that depression of cardiac performance in Subset III may persist after volume expansion.

A smaller group of patients in Subset III demonstrate a normal stroke volume and a relatively low heart rate. This group often responds favorably to an induced increase in heart rate (Fig. 7e). The most substantial rise in cardiac index is generally observed in patients with resting heart rates of 50 to 70 beats per minute. As with volume loading, however, the response occurs be though increase suggest be a safe long-term unknown.

Although volume propria and change in decrease in long-term known.

Figure 7. Effects of Propranolol in Six Clinically Uncomplicated Patients (a), Furosemide in Four Patients with Pulmonary Congestion (b), Nitroprusside in 11 Patients with Pulmonary Congestion (c), Volume Infusion in 12 Patients with Peripheral Hypoperfusion (d), Cardiac Pacing in Six Patients with Peripheral Hypoperfusion and a Normal Heart Rate (e), Nitroprusside Infusion in 41 Patients with Pulmonary Congestion and Peripheral Hypoperfusion (f), and Norepinephrine in 14 Patients with Pulmonary Congestion and Peripheral Hypoperfusion (g).
The logical goal of therapy in this high-risk subset is the simultaneous improvement of both cardiac index and pulmonary-capillary pressure. "Afterload reduction" via peripheral vasodilators appears particularly suited to this goal. Figure 7f shows the effect of nitroprusside in Subset IV: cardiac index increased 38 per cent, and capillary pressure fell 33 per cent. Afterload reduction returned hemodynamics to Subset I levels in 20 per cent of patients, whereas another 55 per cent improved to Subset II and III. In addition, the marked reduction in capillary pressure and slight reduction in arterial systolic pressure with no change in heart rate suggest that myocardial oxygen demand may also have decreased. This presumed reduction in myocardial oxygen demand has been corroborated by direct measurement, although coronary perfusion pressure also may be reduced. Therefore, the effect of different intravenous vasodilators on the magnitude of ischemia remains a source of considerable controversy.44 Substantial reduction in in-hospital mortality has been observed with vasodilator therapy, although the long-term prognosis for patients surviving hospitalization remains poor.112 Because of the potential danger of overtreatment, such therapy requires continuous hemodynamic monitoring, with careful attention to both pulmonary-capillary pressure and blood-pressure levels, as discussed earlier.

Another therapeutic alternative is that of vasopressor therapy, which increases systemic and coronary-artery perfusion pressure. In theory, a rise in arterial diastolic pressure might improve coronary perfusion and myocardial oxygen supply more than the increase in oxygen demand occasioned by higher systemic pressure.126,127 The level of aortic diastolic pressure at which this effect might be achieved cannot be determined in man, since intracoronary pressure falls across each stenosis, so that the resultant perfusion pressure to the ischemic muscle is unpredictably different from the aortic diastolic pressure.122 For this reason, use of pressor agents like vasodilators remains empirical. Pressors are generally used when arterial systolic pressure falls below 90 to 100 mm Hg in association with peripheral hypoperfusion. Since the optimal level of arterial pressure is unknown, and presumably varies from patient to patient, no firm guidelines can be established, although clinical response often seems to be optimal when arterial systolic pressure is kept in the range of 90 to 110 mm Hg. Combination therapy, particularly nitroprusside and dopamine, is often used to maintain both cardiac output and arterial pressure in this circumstance. Figure 7g shows the intravenous use of norepinephrine in patients with depressed cardiac index, elevated pulmonary-capillary pressure and systemic hypotension. Neither cardiac index nor capillary pressure was distinctly improved, although arterial systolic pressure increased 15 per cent. Thus, the administration of norepinephrine caused little change in the determinants of either pulmonary congestion or peripheral hypoperfusion, although both myocardial oxygen supply and demand were probably increased via increased arterial pressure and myocardial contractility.

Other inotropic agents such as digitalis increase cardiac index and decrease pulmonary-capillary pressure in some cases,64,64 but may also increase myocardial oxygen consumption.

**Variant Subsets**

Two specific complications of acute myocardial infarction, mitral insufficiency and ventricular septal defect, are often treated with vasodilator therapy regardless of the magnitude of reduction in cardiac index.111 Such therapy generally increases cardiac index and diminishes pulmonary-capillary pressure. The mechanism by which peripheral vasodilators improve cardiac performance in heart failure was discussed earlier. The rationale for use of afterload-reducing agents in mitral insufficiency and ventricular septal defect is similar. Although the total quantity of blood ejected from the ventricle during systole may remain unchanged, reduction in peripheral resistance results in a greater percentage of the blood delivered forward and thus a smaller percentage delivered backward into the left atrium or right ventricle. As a result, forward cardiac output increases, and capillary pressure diminishes. The magnitude of change in these indexes in the therapy of mitral insufficiency is often quite large, and the clinical result can be dramatic.

**Conclusions**

There are three principles basic to therapy of disorderly function in individual patients with acute infarction: acute infarction is a series of subsets; the response to therapy varies with the level of resting function; and the choice of therapy must include consideration of its effect on both cardiac function and myocardial metabolism.

The use of these concepts in the therapy of patients with acute infarction has led to substantial short-term improvement in clinical state. Nevertheless, major limitations in current understanding should be recognized. First of all, there are as yet no data clearly in-
indicating that any therapy reduces infarct size or improves long-term survival in man. Secondly, the use of subsets for establishing prognosis or as an aid to selecting therapy represents a synthesis of relevant clinical and hemodynamic information. Since new treatments and improved methods of evaluation are certain to emerge in the future, the approach to therapeutic decision making discussed herein should be considered to be a description of a process and not a standard for therapy of cardiac dysfunction in acute myocardial infarction. As therapy continues to be modified with additional experience, however, a schema of "acute coronary triage" may be developed, whereby each patient admitted to a coronary-care unit will undergo prompt and systematic evaluation aimed at detection and correction of electrocardiographic and hemodynamic defects. By such an approach, acute morbidity and long-term mortality may be reduced through establishment of optimal cardiac function and limitation of infarct size.

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