catecholamine neurons: evidence for a stimulation of central dopamine neurons. J Pharm Pharmacol 25:409-411, 1973
35. Johnson AM, Loew DM, Vigouret JM: Stimulant properties of bromocriptine on central dopamine receptors in comparison to apomorphine, amphetamine and L-dopa. Br J Pharmacol 56:59-68, 1976
36. Miyamoto T, Battista A, Goldstein M, et al: Long-lasting anti-tremor activity induced by 2-Br-α-ergocryptine in monkeys. J Pharm Pharmacol 26:452-454, 1974
37. Goldstein M, Battista AF, Matsumoto Y: Pre and postsynaptic effects of dopaminergic agonists: anti-Parksonian efficacy and effects on dopamine synthesis, International Symposium on Parkinson's Disease, Vienna, September 17-20, 1975 (in press)
38. Calne DB, Teychenne PF, Claveria LE, et al: Bromocriptine in Parkinsonism. Br Med J 4:442-444, 1974
39. Lieberman A, Zolfaghari M, Boal D, et al: The antiparkinsonian efficacy of bromocriptine. Neurology (Minneap) 26:405-409, 1976
40. Parkes JD, Marsden CD, Donaldson I: Bromocriptine treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 39:184-193, 1976
41. Lieberman A, Miyamoto T, Battista AF, et al: Studies on the antiparkinsonism efficacy of lergotrile. Neurology (Minneap) 25:459-462, 1975
42. Teychenne PF, Leigh PN, Reid JL, et al: Idiopathic Parkinsonism treated with bromocriptine. Lancet 2:473-476, 1975
43. Kartzinel R, Shoulson I, Calne DB: Studies with bromocriptine. II. Double-blind comparison with levodopa in idiopathic parkinsonism. Neurology (Minneap) 26:511-513, 1976
44. Kartzinel R, Perlow M, Teychenne P, et al: Bromocriptine and levodopa (with or without carbidopa) in Parkinsonism. Lancet 2:272-275, 1976
Lieberman A, Kupersmith M, Estey E: The anti-Parkinsonian efficacy of lergotrile. Lancet (in press)
46. Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality. Neurology (Minneap) 17:427-442, 1967
47. Alba A, Trainor FS, Ritter W, et al: A clinical disability rating for Parkinson patients. J Chronic Dis 21:507-522, 1968
48. McDowell F, Lee JE, Swift T: Treatment of Parkinson's syndrome with l-dihydroxyphenylalanine (levodopa). Ann Intern Med 72:29-35, 1970
49. Kartzinel R, Calne DB: Studies with bromocriptine. I. "On off" phenomena. Neurology (Minneap) 26:508-510, 1976
50. Gerlach J: Effect of CB 154 (2-bromo-alpha-ergocryptine) on paralysis agitans compared with madopar in a double-blind, cross-over trial. Acta Neurol Scand 53:189-200, 1976
Klawans HL, Lupton M, Simon L: Calcification of the basal ganglia as a cause of levodopa-resistant parkinsonism. Neurology (Minneap) 26:221-225, 1976
52. Adams RD, Van Bogaert L: Striato-nigral degeneration response to levodopa therapy. J Neuropathol Exp Neurol 23:584-608, 1964
53. Rajput AH, Kazi KH, Rozdilsky B: Striatonigral degeneration response to levodopa therapy. J Neurol Sci 16:331-341, 1972
54. Sharpe JA, Reucastle NB, Lloyd KG, et al: Striatonigral degeneration: response to levodopa therapy with pathological and neurochemical correlation. J Neurol Sci 19:275-286, 1973
55. Mones RJ: An analysis of six patients with Parkinson's disease who have been unresponsive to l-dopa therapy. J Neurol Neurosurg Psychiatry 36:362-367, 1973
56. Lieberman AN, Goodgold AL, Goldstein M: Treatment failures with levodopa in parkinsonism. Neurology (Minneap) 22:1205-1210, 1972
Klawans HL Jr, Zeitlin E: L-Dopa in Parkinsonism associated with cerebellar dysfunction (probable olivopontocerebellar degeneration). J Neurol Neurosurg Psychiatry 34:14-19, 1971
58. Lieberman A: Parkinson's disease: a clinical review. Am J Med Sci 267:66-80, 1974

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 usefully 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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Diuretic Agents

Diuretic agents such as furosemide reduce pulmonary-capillary pressure and cause little change in cardiac output or heart rate in patients with heart failure due to acute infarction.[42-44] It has only recently been recognized that furosemide reduces pulmonary-capillary pressure within minutes of administration — long before an important diuretic effect has occurred.[43] The primary mechanism for reduction of pulmonary-capillary pressure is apparently a substantial change in the distribution of venous blood, as reflected by a 5 per cent increase in venous capacitance within five minutes of drug administration. A secondary fall in capillary pressure is then generally observed about one hour after administration of the drug, reflecting the drug's diuretic effect.

The individual response to diuretic agents, however, varies substantially within hemodynamic subsets. Thus, diuretic agents may reduce cardiac output in persons with normal levels of pulmonary-capillary pressure but have no such effect on cardiac output in those with elevated pressure.[43] The mechanism for

Table 5. Hemodynamic Effects of Commonly Used Therapies on Cardiac Hemodynamics in Acute Myocardial Infarction.

Therapy	No. of Cases	Dose	Cardiac Index		Left Ventricular Filling Pressure	
			Control	Mean (%)	Control	Mean (%)
			liters/min/m²		mm Hg	
Digitalis:						
Bezdek[62]	9	0.3 - 0.5 mg of ouabain	2.4	14	17	−6
Balcon[61]	11	0.25 mg acetyl strophantidin or 0.5 mg of digoxin	2.7*	−6		
Malmcrona[62]	10	0.8 mg of Lanatoside	3.1	0		
Norepinephrine:						
Abrams[75]	27	8 - 10 μg/min	2.2*	20		
Mueller[70]	8	2 - 8 μg/min	1.5	12		
Gunnar[72]	11	q.s. AP 80	1.8	19		
Isoproterenol:						
Mueller[73]	6	2 - 4 μg/min	1.4	61		
Gunnar[72]	11	1 - 7 μg/min	1.8	35		
Glucagon:						
Diamond[77]	8	70 μg/min	2.4	25	15	−6
Nitroprusside:						
Franciosa[49]	13	79 μg/min	2.5*	9	24	−50
Chatterjee[115]	27	16 - 200 μg/min	1.5	17	25	−35
Phentolamine:						
Kelly[56]	11	0.75 mg/min	3.0	23	20	−35
Walinsky[50]	14	5-mg bolus, then 0.3 mg/min	2.2	26	19	−42
Nitroglycerin:						
Gold[47]	17	0.3 mg sublingually	2.9	6	19	−26
Furosemide:						
Mond[42]	17	40 mg/min	3.2*	−13	18	−22
Dikshit[43]	20	40 mg intravenously	2.1	4	20	−28
Propranolol:						
Mueller[110]	8	0.1 mg/kg/5 min × 3	2.6	−30	12	+16
Circulatory Assist:						
Dilley[97]	6		1.5	67	25	−36
Dunkman[98]	40		1.7	47	22	−23

*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.

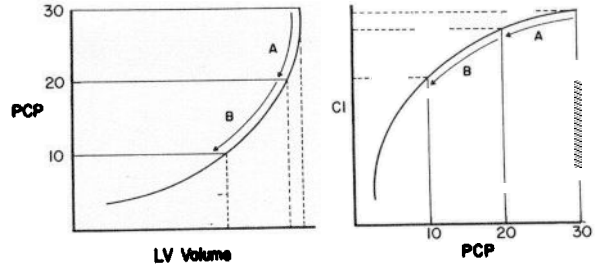

Figure 6. Schematic Illustration of the Exponential Relation between Left Ventricular Pulmonary-Capillary Pressure (PCP) and Left Ventricular (LV) Volume (Left Panel) and the Logarithmic Relation between Cardiac Index (CI) and Capillary Pressure (Right Panel).

With a decrease in pulmonary-capillary pressure from 30 to 20 mm Hg (A), there is little change in left ventricular volume. In contrast, when capillary pressure falls from 20 to 10 mm Hg (B), there is a substantial reduction in left ventricular volume. The different cardiac-index response associated with these two equal reductions in pulmonary-capillary pressure is shown in the right panel. With a small change in left ventricular diastolic volume (A), there is little change in preload, and therefore, little change in cardiac output. When preload is more substantially reduced by the reduction of capillary pressure (B), however, a substantial reduction in cardiac output may occur, represented by movement down the "steep" portion of the Starling-function curve.

this difference in action may be explained by the exponential shape of the ventricular pressure-volume relation[45] and the logarithmic shape of the Starling relation[11] 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 volume, 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.

Peripheral Vasodilators

These drugs are dramatically effective in improving hemodynamics in patients with heart failure due to acute myocardial infarction.[46-58] Cardiac output improves substantially, 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-

Table 6. Effect of Peripheral Vasodilators in Normal and Depressed Cardiac Function.*

Action	Abnormal Heart	Normal Heart
Decreased resistance	Increased ejection fraction	No change in ejection fraction
Increased capacitance	Reduced capillary pressure	Reduced capillary pressure
Hemodynamic result	Increased cardiac output	Decreased cardiac output
	Lowered capillary pressure	Lowered capillary pressure

*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 venodilatation, 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.[48] 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[16,59]; 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,[60-66] isoproterenol,[67-73] norepinephrine,[73-76] glucagon[76-80] and dopamine[81-90] 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-

ire for circulatory support. When combined with isodilator therapy, circulatory assistance may protect against the deleterious effect of decreased arterial iastolic pressure induced by vasodilator therapy, and iereby provide a margin of safety by permitting a iore rapid infusion of the drug.

The preceding discussion may be summarized as a econd principle: *the response to therapy is determined by the retreatment level of left ventricular performance*. As a useful eneralization, inotropic agents become progressively ss effective as the magnitude of left ventricular failre increases. In contrast, agents that reduce capilry pressure, such as diuretics, or those that reduce apillary and arterial pressure, such as peripheral asodilators, are ineffective in the therapy of uncomlicated myocardial infarction but extremely useful as he magnitude of left ventricular failure becomes more evere.

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 iven patient will be determined in part by the level of ulmonary-capillary pressure and cardiac index. In he presence of acute myocardial ischemia, however, ne must also consider whether the drug affects the iability of ischemic myocardium[102-105] by altering the mbalance between myocardial oxygen supply and demand.[106]

The amount of oxygen supplied to myocardial tisue is the product of coronary blood flow and the mount of oxygen extracted from each milliliter of lood as it passes through the heart. In acute myocarial infarction, an upper limit of flow to ischemic nyocardium is established by the presence of fixed roximal arterial stenoses. Whereas oxygen supply in ther tissues can be increased by increasing oxygen xtraction, it is near maximal at rest even in the norhal heart, and any increase in oxygen demand is met y an increase in coronary flow. We are, therefore, urrently 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.[106] 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.

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,[73] 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.[73] 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.[107,108] 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.[107,108] 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.

Table 7. Effects of Therapeutic Agents on Coronary Blood Flow and Myocardial Metabolism during Acute Myocardial Infarction in Man (See Text for Discussion).

Agent	Dose	N	Mean Coronary Blood Flow (%)	Mean Myocardial Oxygen Consumption (%)	Lactate (% Change)
Digitalis (7)[620]	0.3 - 0.5 mg of ouabain intravenously	9	38	35	+44 - +38
Norepinephrine (11)[70]	2 - 8 μg/min	8	38	29	−4 - +12
Isoproterenol (11)[73]	2 - 4 μg/min	6	16	20	−8 - −19
Nitroprusside (16)[115]	16 - 200 μg/min	19	−6	−27	+17 - +16
Propranolol (22)[110]	0.1 mg/kg	20	−17	−22	−14 - +26

*Figures in parentheses represent no. of patients.

Properly administered, *peripheral vasodilators* substantially lower myocardial oxygen demand[48,109] 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*[68,110-113] is perhaps the most effective drug currently

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

Drug	Hemodynamics		MVO_2	
	CO	PCP	Effect	Mechanism
Inotropes	Unchanged or increased	Unchanged or decreased	Increase	Increased contractility; increased heart rate or blood pressure.
Diuretics	Unchanged	Decreased	Decrease	Decreased heart size
Vasodilators	Increased	Decreased	Decrease	Decreased atrial pressure & heart size
Beta-adrenergic blockers	Decreased	Unchanged or increased	Marked decrease	Decreased heart rate, contractility & atrial pressure

*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 subsets. 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_2 myocardial oxygen consumption.

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.[68]

Mechanical circulatory assistance affects both myocardial oxygen supply and demand.[92] 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.

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[38-41]; there is a causal relation between capillary pressure and pulmonary congestion[16,26] and between cardiac index and peripheral hypoperfusion[35]; cardiac-pump dysfunction is related to infarct size[133]; 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

*The data in this section were collected as part of the Myocardial Infarction Units at Cedars-Sinai Medical Center,[26,34,43,48,50,58,59,75-77,114-116,121,122,126,129] and from other institutions.[117-120,123,124,128,133]

improve pump function. Nevertheless, a number of recent investigations have suggested that infarct size may be reduced by administration of certain pharmacologic agents.[103,104,117,118] Such therapy may be appropriate in this subset, especially when abnormalities in the major determinants of myocardial oxygen consumption are present. In our 200-patient population described earlier, approximately one third of those in Subset I had a systolic pressure exceeding 140 mm Hg, one fifth had a heart rate exceeding 100 beats per minute, and one fourth had a pulmonary-capillary pressure >18 mm Hg.[34] Each of these altered determinants of myocardial oxygen consumption may be normalized by therapy. For instance, increased heart rate and arterial pressure may be reduced by propranolol[110] (Fig. 7*a*), and elevated arterial pressure by nitroprusside,[129] trimethephan,[128] or other antihypertensive agents or more simply by bed rest and sedation. Although this approach has theoretical and experimental support, no data in man are available to recommend such therapy directly, and a number of nonspecific agents, including hyaluronidase,[119] steroids,[120-122] oxygen,[123] glucose-insulin-potassium,[124] and mannitol,[125] are also undergoing clinical trials.

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 that which would cause a deleterious reduction in cardiac output by the Starling mechanism.[16,59] 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,[26] whereas there is little if any decrease in cardiac output when the pressure is reduced from high levels to 15 mm Hg[59] (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.

Figure 7*b* shows the use of the diuretic furosemide in Subset II. After diuresis, pulmonary-capillary pressure decreased 25 per cent from the abnormal to the high-normal range. Heart rate, arterial pressure and cardiac index were unchanged. Thus, diuretic therapy reduced the hemodynamic determinant of pulmonary congestion without reducing forward flow. Myocardial oxygen demand may have been lowered by reduction in heart size, as reflected by the decrease in pulmonary-capillary pressure.

In the presence of substantial systolic hypertension, peripheral vasodilators may be appropriate, since these agents reduce both pulmonary-capillary pressure and systemic arterial pressure. Thus, since arterial systolic pressure is a major determinant of myocardial oxygen consumption, the use of these agents is theoretically preferable. The effect of nitroprusside[48] in patients with elevated pulmonary-capillary pressure and systolic hypertension with a normal cardiac index is shown in Figure 7*c*. This therapy resulted in a 27 per cent fall in capillary pressure, with no change in heart rate or cardiac index. Arterial systolic pressure fell 20 mm Hg, but remained within the physiologic range. Since pulmonary-capillary pressure and arterial pressure were both reduced, it is likely that myocardial oxygen demand also diminished, but it is also possible that reduction in aortic diastolic pressure resulted in an equal or even greater reduction in myocardial oxygen supply.

Some patients clinically diagnosed as having pulmonary congestion have a normal pulmonary-capillary pressure.[34] In such cases both diuretic and vasodilator therapy may decrease cardiac output. This effect is most commonly encountered clinically when rapid diuresis results in a fall in capillary pressure to normal levels, whereas x-ray and physical findings exhibit "phase lag" in returning to normal. Further diuretic administration, based on the clinical diagnosis of pulmonary congestion, may lead to hypovolemia and, in extreme cases, shock. When uncertainty about the magnitude of elevation in pulmonary-capillary pressure exists, therefore, hemodynamic evaluation can be employed to prevent this occurrence.

Peripheral 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.[59]

The effect of volume infusion in patients with depressed cardiac index and normal pulmonary-capil-

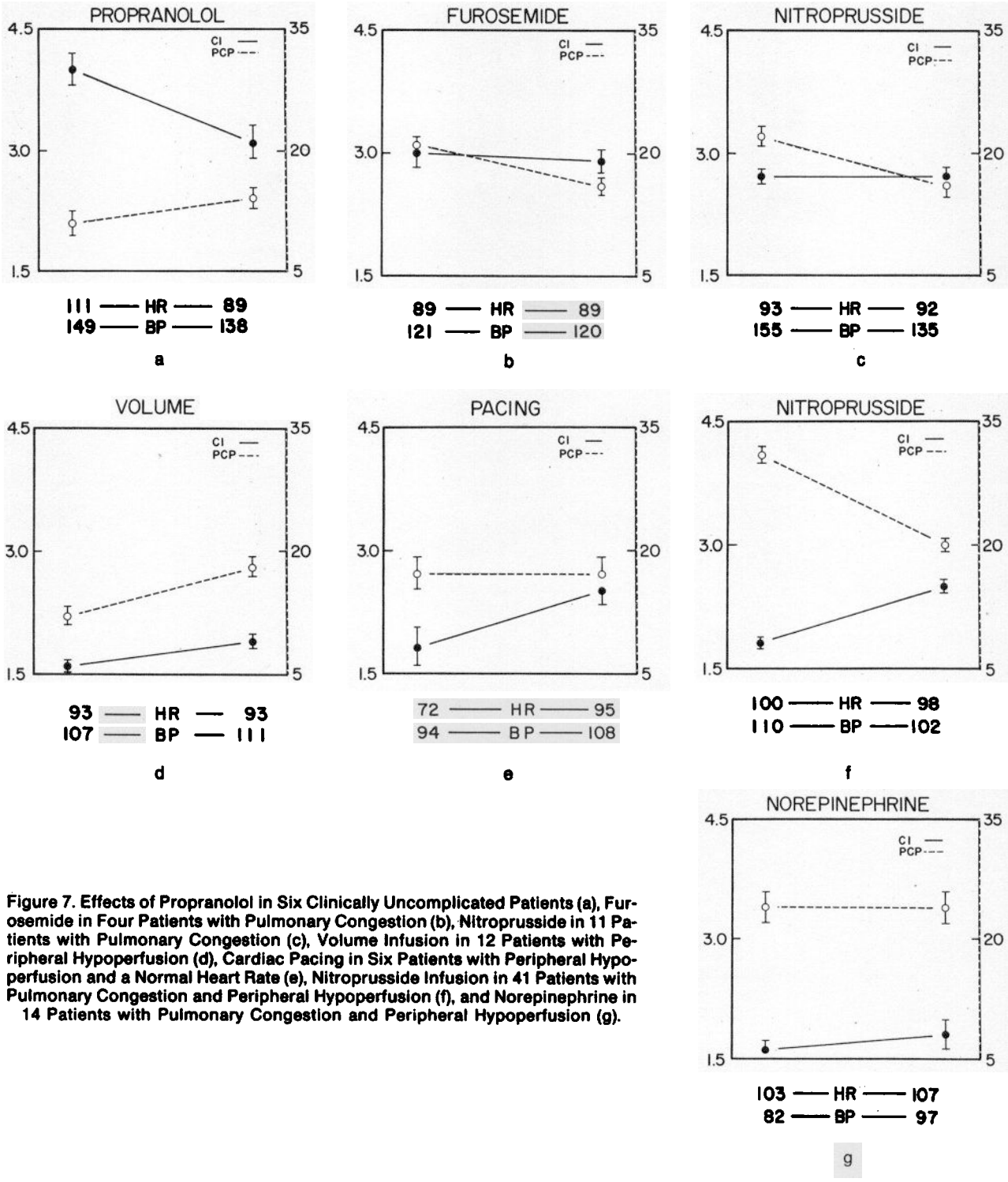

Figure 7. Effects of Propranolol in Six Clinically Uncomplicated Patients (a), Furosemide in Four Patients with Pulmonary Congestion (b), Nitroprusside in 11 Patients with Pulmonary Congestion (c), Volume Infusion in 12 Patients with Peripheral Hypoperfusion (d), Cardiac Pacing in Six Patients with Peripheral 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).

lary pressure is shown in Figure 7*d*. 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. 7*e*). 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 re-

ponse is limited: little increase in cardiac index occurs beyond a rate of 90 to 100 beats per minute.[12] Although intravenously administered atropine will increase heart rate (and cardiac output), recent data suggest that such therapy may worsen arrhythmic risk.[127] Temporary transvenous pacing may therefore be a safer alternative.

Although cardiac index may be improved by both volume expansion and increased heart rate in appropriately selected patients in Subset III, this hemodynamic benefit probably occurs at the expense of increasing myocardial ischemia, since both therapies increase a major determinant of myocardial oxygen demand[106] (heart size and heart rate, respectively). The long-term effects of this therapy, therefore, remain unknown.

The logical goal of therapy in this high-risk subset is the simultaneous improvement of both cardiac index and pulmonary-capillary pressure. "Afterload reduction"[129] via peripheral vasodilators appears particularly suited to this goal. Figure 7*f* 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.[48,128] Substantial reduction in in-hospital mortality has been observed with vasodilator therapy, although the long-term prognosis for patients surviving hospitalization remains poor.[129] 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 systolic pressure.[130,131] 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.[132] 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 7*g* 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,[60-66] 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.[115] 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 disordered 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-

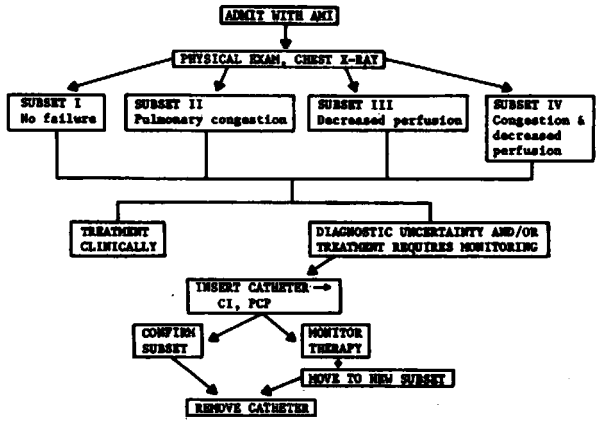

Figure 8. Estimation of the Prognosis and Level of Pulmonary-Capillary Pressure (PCP) and Cardiac Index (CI) in Acute Myocardial Infarction by Means of an Initial Clinical Evaluation.

On the basis of this evaluation a decision to employ catheterization can be made that allows confirmation of the hemodynamic estimate and the monitoring of the effect of therapy. When the patient achieves the desired hemodynamic stability, the catheter can be removed.

dicating 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.

References

42. Mond H, Hunt D, Sloman G: Haemodynamic effect of furosemide in patients suspected of having acute myocardial infarction. Br Heart J 36:44-53, 1974
43. Dikshit K, Vyden JK, Forrester JS, et al: Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 288:1087-1090, 1973
44. Kiely J, Kelly DT, Taylor DR, et al: The role of furosemide in the treatment of left ventricular dysfunction associated with acute myocardial infarction. Circulation 48:581-587, 1973
45. Diamond G, Forrester JS, Hargis J, et al: The diastolic pressure-volume relationship of the canine left ventricle. Circ Res 29:267-275, 1971
46. Sweatman T, Strauss G, Selzer A, et al: The long-acting hemodynamic effects of isosorbide dinitrate. Am J Cardiol 29:475-480, 1972
47. Gold HK, Leinbach RC, Sanders CA: Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction. Circulation 46:839-845, 1972
48. Chatterjee K, Parmley WW, Ganz W, et al: Hemodynamic and metabolic responses of vasodilator therapy in acute myocardial infarction. Circulation 48:1183-1193, 1973
49. Franciosa JA, Guiha NH, Limas CJ, et al: Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. Lancet 1:650-654, 1972
50. Walinsky P, Chatterjee K, Forrester J, et al: Enhanced left ventricular performance with phentolamine in acute myocardial infarction. Am J Cardiol 33:37-41, 1974
51. Gould L, Ettinger S, Carmichael A, et al: The use of phentolamine in experimental hemorrhagic shock. Angiology 21:330-335, 1970
52. Gould L: Phentolamine. Am Heart J 78:276-278, 1969
53. Taylor SH, Sutherland GR, MacKenzie GJ, et al: The circulatory effects of phentolamine in man with particular respect to changes in forearm blood flow. Clin Sci 28:265-284, 1965
54. Gould L, Zahir M, Ettinger S: Phentolamine and cardiovascular performance. Br Heart J 31:154-162, 1969
55. Taylor SH, Sutherland GR, MacKenzie GJ, et al: The circulatory effects of intravenous phentolamine in man. Circulation 31:741-754, 1965
56. Kelly DT, Delgado CE, Taylor DR, et al: Use of phentolamine in acute myocardial infarction associated with hypertension and left ventricular failure. Circulation 47:729-735, 1973
57. Majid PA, Sharma B, Taylor SH: Phentolamine for vasodilator treatment of severe heart-failure. Lancet 2:719-724, 1971
58. Gray R, Chatterjee K, Vyden JK, et al: Hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure. Am Heart J 90:346-352, 1975
59. Crexells C, Chatterjee K, Forrester JS, et al: Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. N Engl J Med 289:1263-1266, 1973
60. Rahimtoola SH, Sinno MZ, Chuquimia R, et al: Effects of ouabain on impaired left ventricular function in acute myocardial infarction. N Engl J Med 287:527-531, 1972
61. Balcon R, Hoy J, Sowton E: Haemodynamic effects of rapid digitalization following acute myocardial infarction. Br Heart J 30:373-376, 1968
62. Malmcrona R, Schröder G, Werkö L: Haemodynamic effects of digitalis in acute myocardial infarction. Acta Med Scand 180:55-63, 1966
63. Rahimtoola SH, DiGilio MM, Sinno MZ, et al: Cardiac performance three to eight weeks after acute myocardial infarction. Arch Intern Med 128:220-228, 1971
64. *Idem:* Effects of ouabain on impaired left ventricular function during convalescence after acute myocardial infarction. Circulation 44:866-876, 1971
65. Hodges M, Friesinger GC, Riggins RCK, et al: Effects of digoxin on early left ventricular failure in acute myocardial infarction. Circulation 40: Suppl 3:107, 1969
66. Rahimtoola SH, Gunnar RM: Digitalis in acute myocardial infarction: help or hazard? Ann Intern Med 82:234-240, 1975
67. Kuhn LA, Kline HJ, Goodman P, et al: Effects of isoproterenol on hemodynamic alterations, myocardial metabolism, and coronary flow in experimental acute myocardial infarction with shock. Am Heart J 77:772-783, 1969
68. Misra SN, Kezdi P: Hemodynamic effects of adrenergic stimulating and blocking agents in cardiogenic shock and low output state after myocardial infarction. Am J Cardiol 31:724-735, 1973
69. Smith HJ, Oriol A, Morch J, et al: Hemodynamic studies in cardiogenic shock: treatment with isoproterenol and metaraminol. Circulation 35:1084-1091, 1967
70. Mueller H, Ayres SM, Giannelli S Jr, et al: Cardiac performance and metabolism in shock due to acute myocardial infarction in man: response to catecholamines and mechanical cardiac assist. Trans NY Acad Sci 34:309-333, 1972
71. Mueller H, Ayres SM, Grace WJ: Principle defects which account for shock following acute myocardial infarction in man: implications for treatment. Crit Care Med 1:27-38, 1973
72. Gunnar RM, Loeb HS, Pietras RJ, et al: Ineffectiveness of isoproterenol in shock due to acute myocardial infarction. JAMA 202:1124-1128, 1967
73. Mueller H, Ayres SM, Giannelli S Jr, et al: Effect of isoproterenol, l-norepinephrine, and intraaortic counterpulsation on hemodynamics and myocardial metabolism in shock following acute myocardial infarction. Circulation 45:335-351, 1972
74. Haft JI: Cardiovascular injury induced by sympathetic catecholamines. Prog Cardiovasc Dis 17:73-86, 1974
75. Abrams E, Forrester JS, Chatterjee K, et al: Variability in response to norepinephrine in acute myocardial infarction. Am J Cardiol 32:919-923, 1973
76. Diamond G, Forrester J, Danzig R, et al: Acute myocardial infarction in man: comparative hemodynamic effects of norepinephrine and glucagon. Am J Cardiol 27:612-616, 1971
77. Diamond G, Forrester J, Danzig R, et al: Haemodynamic effects of

glucagon during acute myocardial infarction with left ventricular failure in man. Br Heart J 33:290-295, 1971
78. Eddy JD, O'Brien ET, Singh SP: Glucagon and haemodynamics of acute myocardial infarction. Br Med J 4:663-669, 1969
79. Vander Ark CR, Reynolds EW Jr: Continuous infusion of glucagon in cardiogenic shock. Circulation 40: Suppl 3:206, 1969
80. Williams JF Jr, Childress RH, Chip JN, et al: Hemodynamic effects of glucagon in patients with heart disease. Circulation 39:38, 1969
81. Holloway EL, Stinson EB, Derby GC, et al: Action of drugs in patients early after cardiac surgery. I. Comparison of isoproterenol and dopamine. Am J Cardiol 35:656-659, 1975
82. Holzer J, Karliner JS, O'Rourke RA, et al: Effectiveness of dopamine in patients with cardiogenic shock. Am J Cardiol 32:79-84, 1973
83. Talley RC, Goldberg LI, Johnson CE, et al: A hemodynamic comparison of dopamine and isoproterenol in patients in shock. Circulation 39:361-378, 1969
84. MacCannell KL, McNay JL, Meyer MB, et al: Dopamine in the treatment of hypotension and shock. N Engl J Med 275:1389-1398, 1966
85. Crexells C, Bourassa MG, Biron P: Effects of dopamine on myocardial metabolism in patients with ischaemic heart disease. Cardiovasc Res 7:438-445, 1973
86. Rosenblum R, Tai AR, Lawson D: Dopamine in man: cardiorenal hemodynamics in normotensive patients with heart disease. J Pharmacol Exp Ther 183:256-263, 1972
87. Goldberg LI: Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol Rev 24:1-29, 1972
88. *Idem:* Use of sympathomimetic amines in heart failure. Am J Cardiol 22:177-182, 1968
89. Goldberg LI, McDonald RH Jr, Zimmerman AM: Sodium diuresis produced by dopamine in patients with congestive heart failure. N Engl J Med 269:1060-1064, 1963
90. Loeb HS, Winslow EBJ, Rahimtoola SH, et al: Acute hemodynamic effects of dopamine in patients with shock. Circulation 44:163-173, 1971
91. Cohn JN, Tristani FE, Khatri IM: Cardiac and peripheral vascular effects of digitalis in clinical cardiogenic shock. Am Heart J 78:318-330, 1969
92. Leinbach RC, Buckley MJ, Austen WG, et al: Effects of intra-aortic balloon pumping on coronary flow and metabolism in man. Circulation 43 and 44: Suppl 1:77-81, 1971
93. Brown BG, Goldfarb, Topaz SR, et al: diastolic augmentation by intraaortic balloon: circulatory hemodynamics and treatment of severe, acute left failure in dogs. J Thorac Cardiovasc Surg 53:789-804, 1967
94. Yehr WZ, Butner AN, Krakauer JS, et al: Cardiogenic shock: dynamics of coronary blood flow with intra-aortic phase-shift balloon pumping. Surg Forum 19:142-143, 1968
95. Powell WJ Jr, Daggett WM, Magro AE, et al: Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption, and coronary blood flow in dogs. Circ Res 26:753-764, 1970
96. Buckley MJ, Laird JD, Madras PN, et al: Left heart assist system: intra-aortic balloon pump. Surg Clin North Am 49:505-511, 1969
97. Dilley RB, Ross J Jr, Bernstein EF: Serial hemodynamics during intra-aortic balloon counterpulsation for cardiogenic shock. Circulation 47 and 48: Suppl 3:99-104, 1973
98. Dunkman WB, Leinbach RC, Buckley MJ, et al: Clinical and hemodynamic results of intraaortic balloon pumping and surgery for cardiogenic shock. Circulation 46:465-477, 1972
99. Corday E, Swan HJC, Lang TW, et al: Physiologic principles in the application of circulatory assist for the failing heart: intraaortic balloon circulatory assist and venoarterial phased partial bypass. Am J Cardiol 26:595-602, 1970
100. Meerbaum S, Lang TW, Corday E: Effect of counterpulsation on renal circulation during cardiogenic shock. Circulation 46 Suppl 2: 191, 1972
101. Lang TZ, Meerbaum S, Lozano J, et al: Ascending aorta synchronized pulsation (AASP) — a new form of circulatory assist for the treatment of cardiogenic shock. Am J Cardiol 25:137, 1970
102. Maroko RP, Kjekshus JK, Sobel BE, et al: Factors influencing infarct size following experimental coronary artery occlusion. Circulation 43:67-82, 1971
103. Maroko PR, Braunwald E: Modification of myocardial infarction size after coronary occlusion. Ann Intern Med 79:720-733, 1973
104. Braunwald E, Maroko PR: The reduction of infarct size: an idea whose time (for testing) has come. Circulation 50:206-209, 1974
105. Forrester JS, Chatterjee K: Preservation of ischemic myocardium. Adv Cardiol 11:158-160, 1974
106. Braunwald E: Control of myocardial oxygen consumption: physiologic and clinical considerations. Am J Cardiol 27:416-432, 1971
107. Covell JW, Braunwald E, Ross J Jr, et al: Studies on digitalis. XVI. Effects on myocardial oxygen consumption. J Clin Invest 45:1535-1542, 1966
Sonnenblick EH, Skelton CL: Oxygen consumption of the heart: physiological principles and clinical implications. Mod Concepts Cardiovasc Dis 40:9-16, 1971
Nagasawa K, Vyden JK, Forrester JS, et al: Effect of phentolamine on cardiac performance and energetics in acute myocardial infarction. Circulatory Shock 2:5-11, 1975
Mueller HS, Ayres SM, Religa A, et al: Propranolol in the treatment of acute myocardial infarction: effect on myocardial oxygenation and hemodynamics. Circulation 49:1078-1087, 1974
Pelides LJ, Reid DS, Thomas M, et al: Inhibition by β-blockade of the ST segment elevation after acute myocardial infarction in man. Cardiovasc Res 6:295-301, 1972
Norris RM, Caughey DE, Scott PJ: Trial of propranolol in acute myocardial infarction. Br Med J 2:398-400, 1968
Balcon R, Jewitt DE, Davies JPH, et al: A controlled trial of propranolol in acute myocardial infarction. Am Heart J 74:582-584, 1967
Parmley WW, Diamond G, Tomoda H, et al: Clinical evaluation of left ventricular pressures in acute myocardial infarction. Circulation 45:358-366, 1972
Chatterjee K, Parmley WW, Swan HJC, et al: Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvar apparatus. Circulation 48:684-690, 1973
Jobin G, Ostlund J, Stankus K, et al: Automated precordial mapping for ST-segment analysis: variability in serial mapping of normals and patients with stable ST onset elevation. Am J Cardiol (in press)
Shell WE, Lavelle JF, Covell JW, et al: Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction. J Clin Invest 52:2579-2590, 1973
Shell WE, Kjekshus JK, Sobel BE: Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity. J Clin Invest 50:2614-2625, 1971
119. Maroko PR, Libby P, Bloor CM, et al: Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. Circulation 46:430-437, 1972
120. Libby P, Maroko PR, Bloor CM, et al: Reduction of experimental myocardial infarct size by corticosteroid administration. J Clin Invest 52:599-607, 1973
121. da Luz PL, Forrester JS, Wyatt HL, et al: Myocardial reperfusion in acute experimental ischemia: beneficial effects of prior treatment with steroids. Circulation 53:847-852, 1976
122. Vyden JK, Nagasawa K, Forrester JS, et al: The clinical efficacy of corticosteroid administration in acute myocardial infarction, Steroids and Shock. Edited by TM Glenn. Baltimore, University Park Press, 1973, pp 425-437
123. Maroko PR, Radvany P, Braunwald E, et al: Reduction of infarct size by oxygen inhalation following acute coronary occlusion. Circulation 52:360-368, 1975
124. Maroko PR, Libby P, Sobel BE, et al: The effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. Circulation 45:1160-1175, 1972
125. Willerson JT, Powell WJ Jr, Guiney TE, et al: Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol. J Clin Invest 51:2989-2998, 1972
126. da Luz P, Forrester JS, Wyatt HL, et al: Opposing effects of increasing heart rate on global and regional ischemic myocardium: function and metabolism. Circulation 52: Suppl 2:173, 1975
127. Epstein SE, Redwood DR, Kent KM: Atropine and acute myocardial infarction. Circulation 47:1398-1400, 1973
128. Shell WE, Sobel BE: Protection of jeopardized ischemic myocardium by reduced ventricular afterload. N Engl J Med 291:481-486, 1974
129. Chatterjee K, Swan HJC, Forrester J, et al: Vasodilator therapy in patients with acute myocardial infarction (AMI) complicated by severe pump failure: immediate and long term prognosis. Circulation (in press)
130. Redwood DR, Smith ER, Epstein SE: Coronary artery occlusion in the conscious dog: effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia. Circulation 46:323-332, 1972
131. Smith ER, Redwood DR, McCarron WE, et al: Coronary occlusion in the conscious dog: effects of alterations in arterial pressure produced by nitroglycerin, hemorrhage and alpha-adrenergic agonists on the degree of myocardial ischemia. Circulation 47:51-57, 1973
132. Gould KL, Lipscomb K, Hamilton GW: Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol 33:87-94, 1974
133. Sobel BE, Bresnahan GF, Shell WE, et al: Estimation of infarct size in man and its relation to prognosis. Circulation 46:640-654, 1972