MEDICAL PROGRESS

MEDICAL THERAPY OF ACUTE MYOCARDIAL INFARCTION BY APPLICATION OF HEMODYNAMIC SUBSETS (First of Two Parts)

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IN the broadest sense, current hospital therapy of acute myocardial infarction attempts to prevent, or promptly and effectively treat, the electrical and mechanical consequences of regional myocardial ischemia or infarction, while preserving jeopardized ischemic myocardium. Prevention and effective therapy of arrhythmias have largely been realized through the development of coronary-care units. The goals of prompt and effective therapy of disordered cardiac function and preservation of ischemic muscle, although far from achieved, have been greatly advanced in the past several years by the widespread use of hemodynamic monitoring. As a result, new concepts concerning the disease itself and new therapies have been developed. Nevertheless, the systematic application of this new knowledge in the clinical practice of cardiology in the community has lagged behind these advances. This discussion, therefore, has three purposes: to describe the method of hemodynamic monitoring; to summarize and interpret the large body of clinically relevant information that has resulted from use of the method; and to apply this knowledge to the development of a logical approach to therapy of patients with acute myocardial infarction.

HEMODYNAMIC MONITORING — THE METHOD

Hemodynamic monitoring uses a balloon-tipped catheter (Swan-Ganz)[1] that is advanced from a peripheral vein to the pulmonary artery at the bedside without the use of fluoroscopy. When inflated, the balloon serves to guide the catheter in the direction of blood flow, through the chambers of the right side of the heart into the pulmonary artery, where the balloon ultimately impacts in a vessel of equal diameter. In this position, the tip of the catheter no longer records pulmonary arterial pressure, since this wave form is totally damped through the air-filled balloon; rather, it records the downstream pressure, termed pulmonary-capillary pressure. By adding a lumen with an orifice 30 cm from the catheter tip and implanting a thermistor in the external surface of the catheter just proximal to its tip,[2] one can determine cardiac output by the thermodilution technic. A known quantity of cold solution is injected into the right atrium, and the resultant change in pulmonary-artery blood temperature is measured by the thermistor. This method therefore measures output of the right side of the heart, which is normally equal to that of the left in the absence of intracardiac shunts. Cardiac output determined by this method is both accurate and highly reproducible.[3] Thus, with a single catheter in the right side of the heart, the effects of acute myocardial infarction and its complications upon right atrial, pulmonary-artery and pulmonary-capillary pressures, and cardiac output can be assessed continuously (Fig. 1). Alterations in the magnitude and morphology of these wave forms are of major diagnostic importance in a number of pathologic cardiovascular conditions encountered in the coronary-care unit (Table 1).

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INTERPRETATION OF HEMODYNAMIC MEASUREMENTS — MAGNITUDE AND MORPHOLOGY

Right Atrial Pressure

Right atrial pressure is equivalent to both the right ventricular pressure in diastole (when the tricuspid valve is open, the right atrium and right ventricle are common chambers) and to the central venous pressure. Reduced right atrial pressure is generally secondary to hypovolemia. Elevation of pressure has three major causes: right ventricular failure of any origin, tricuspid regurgitation and pericardial tamponade. In patients with acute myocardial infarction, elevated right atrial pressure most commonly reflects right ventricular failure.

Clues to the diagnosis of tricuspid insufficiency and pericardial tamponade come from inspection of the pressure wave forms. The diagnosis of tricuspid insufficiency can be made in the presence of a "giant v wave" in the right atrial tracing (Fig. 2). Pericardial tamponade may be suspected in the presence of an elevated right atrial pressure when diastolic-pressure measurements from right atrium, right ventricle, pulmonary artery and pulmonary capillaries are of equal magnitude and similar contour.

Pulmonary-Artery Pressure

Pulmonary-artery pressure is equal to right ventricular pressure during systole, while the pulmonic valve is open. It is increased in the presence of either increased pulmonary vascular resistance (as with

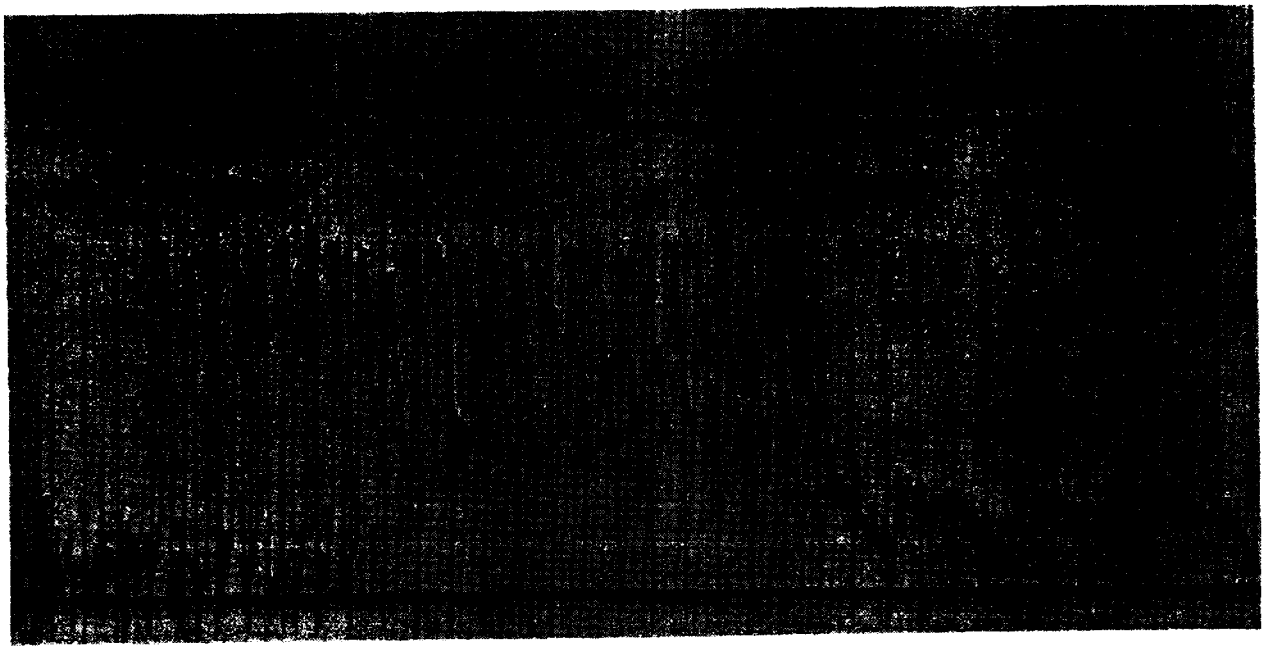

Figure 1. Continuous Pressure Recording as the Pulmonary-Artery Balloon Catheter Is Passed through the Chambers of the Right Side of the Heart.

RA denotes right atrium, RV right ventricle, PA pulmonary artery, and PCW pulmonary-capillary-wedge pressure (see text for discussion of the interpretation of these pressures).

existent chronic lung disease or pulmonary embolism) or elevated pulmonary flow (as in ventricular septal defect). The pulmonary arterial diastolic pressure is virtually equal to pulmonary-capillary pressure when pulmonary vascular resistance is normal. For this reason, pulmonary arterial diastolic pressure is often substituted for pulmonary-capillary pressure, since balloon inflation is not required for its measurement.[4-7] When pulmonary vascular resistance is increased, however, pulmonary arterial diastolic pressure is substantially elevated in comparison to pulmonary-capillary pressure. This distinction can be of diagnostic value in the differentiation of pulmonary embolism from cardiogenic shock, since in pulmonary embolism, pulmonary arterial diastolic pressure may be elevated while pulmonary-capillary pressure is normal, whereas in cardiogenic shock, both pressures are elevated and more nearly equal.

The morphology of the pulmonary arterial pressure wave is of value in the diagnosis of acute mitral regurgitation,[8-10] in which the tracing is often distorted by a giant regurgitant wave transmitted backward through the low-resistance pulmonary vascular bed (Fig. 2).

Pulmonary-Capillary Pressure

Since there are no valves between the pulmonary capillaries and the left atrium, and since the pulmonary vascular bed normally has a low resistance, pulmonary-capillary pressure is a phase-delayed and amplitude-damped version of left atrial pressure. During diastole, with an open, non-stenotic mitral valve, the pulmonary venous bed, left atrium and left ventricle become a common chamber, and pulmonary-capillary pressure is then also equal to left ventricular diastolic pressure. Because the mitral valve begins to close before the onset of ventricular systole, however, pulmonary-capillary pressure may not be equal to left ventricular pressure at end-diastole.*

The level of pulmonary-capillary pressure is critical in the assessment of a patient's clinical status for two reasons. In the first place, it is the hydrostatic pressure that forces fluids out of the pulmonary vascular space into the interstitial and intra-alveolar spaces. When elevated, therefore, it is the hemodynamic "cause" of pulmonary congestion. Secondly, cardiac function is frequently defined by Starling's law of the heart, which states that the strength of cardiac contraction is proportional to myocardial fiber length (or left ventricular volume) at the onset of contraction. Since the level of pulmonary-capillary pressure is directly related to this diastolic fiber stretch, it may be used as a readily obtained index of left ventricular volume. When applied in this manner to construct a cardiac function curve, it is often termed left ventricular filling pressure.

*In cases in which the atrial contribution to ventricular filling is substantial, or in which left ventricular compliance is reduced, left ventricular end-diastolic pressure may exceed mean left ventricular diastolic pressure and pulmonary-capillary presure by as much as 20 mm Hg.

Table 1. Normal and Abnormal Intracardiac Pressures.*

Area Tested	Normal Pressure Range (Mm Hg)	Conditions in Which Increased	Specific Patterns
RA	0 - 8	RV failure; PE; COPD; tricuspid-valve abnormality; pericardial tamponade.	TI: giant V wave ("ventricularized" wave form); tamponade: "diastolic plateau," with paradoxical inspiratory rise.
PA	15 - 30 / 5 - 12†	Systolic: ↑ resistance: PE; COPD; ↑ flow: VSD; Diastolic: ↑ resistance: PE; COPD; All causes of ↑ PCP.	MI: retrograde V wave; VSD: wide pulse pressure; tamponade: narrow pulse pressure; COPD: marked respiratory fluctuation.
PCP	5 - 12†	LV failure mitral valve disease tamponade ↓ LV compliance: hypertrophy; infarction.	MI: giant V wave; tamponade: "diastolic plateau," with paradoxical inspiratory rise; COPD: marked respiratory fluctuation.

*RA denotes right atrium, PA pulmonary artery, RV right ventricle, PE pulmonary embolism, TI tricuspid insufficiency, MI mitral insufficiency, COPD chronic obstructive pulmonary disease, VSD ventricular septal defect, LV left ventricle, & PCP pulmonary-capillary pressure.

†Although clinical signs of pulmonary congestion begin at approximately 18 mm Hg, the generally accepted upper limit of normal is 12 mm Hg.

An increase in pulmonary-capillary pressure in acute myocardial infarction generally reflects increased left ventricular volume.[11] Increased volume most commonly results from a diminution of ejected systolic volume, and thus is related directly to the mechanisms that decrease cardiac output. In addition, an increase in left ventricular stiffness follows the development of acute myocardial infarction,[12-15] and has a role of unknown magnitude in increasing pulmonary-capillary pressure. Less commonly, acute mitral insufficiency occurs, causing increased left atrial pressure, which is transmitted directly back to the pulmonary capillaries.

Clinical assessment of right atrial pressure ("central venous pressure") is sometimes used to gauge the risk of pulmonary congestion (i.e., the level of pulmonary-capillary pressure) during volume loading. This approach carries substantial risk. Since the level of right atrial pressure is determined predominantly by function of the right side of the heart, it may not reflect the level of pulmonary-capillary (or left atrial) pressure in many pathologic states.[16] Right atrial pressure (RAP) does reflect the approximate level of pulmonary-capillary pressure (PCP) (roughly by RAP + 7 = PCP) when right ventricular function is approximately comparable to that of left ventricular function — e.g., in the normal heart and in chronic biventricular failure. When right ventricular function is different from left ventricular function, however, the predictive value of this relation becomes nonexistent. Thus, right atrial pressure may be relatively greater than pulmonary-capillary pressure when performance of the right side of the heart is impaired: acutely, with pulmonary embolism; or chronically, with chronic obstructive pulmonary disease. Conversely, pulmonary-capillary pressure will be substantially greater than right atrial pressure when left ventricular dysfunction predominates, as in acute myocardial infarction.[16] Thus, although elevation of right atrial pressure remains a useful index of the magnitude of right-sided heart failure, it must be recognized that florid pulmonary edema may occur in the presence of a normal right atrial pressure (or central venous pressure) in patients with acute myocardial infarction.[17,18]

The pulmonary-capillary wave form, like that of the right atrium, is bifid and of low magnitude. Acute mitral regurgitation alters this wave form in the same manner as tricuspid regurgitation alters right atrial pressure: the diagnostic "giant V wave" of this disorder is a direct reflection of the marked increase in left atrial pressure caused by a rapid increase in left atrial volume during ventricular systole (Fig. 2).

Cardiac Output

Diminished cardiac output is often the result of several mechanisms operating simultaneously. By far the most common factors are decreased contracting muscle mass,[19,20] which may be either infarcted or ischemic but noncontractile,[21,22] and cardiac arrhythmias.[23,24] Less frequently, specific defects of cardiac structure diminish cardiac output, often in association with a substantial reduction in contracting muscle mass. These mechanical defects include mitral insufficiency and ventricular septal defect. In addition, a wide variety of noncardiac factors, including dimin-

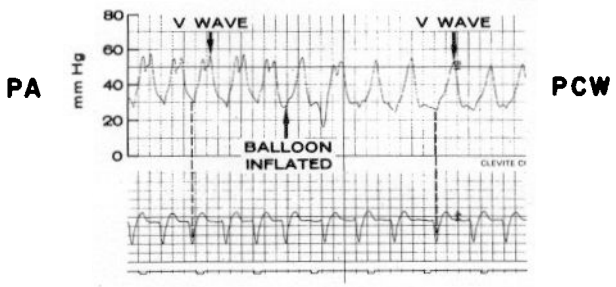

Figure 2. The "Giant V Wave" of Mitral Insufficiency.
In the left-hand portion, the pulmonary-artery pressure is recorded. Its characteristic morphology is a second pressure wave that becomes apparent in late systole: this is the left atrial "v wave," which has been transmitted retrograde to the pulmonary artery through the pulmonary veins and capillaries. When the balloon at the catheter tip is inflated, the catheter records pulmonary-capillary pressure more clearly, revealing the giant V wave. When recorded from this position, the giant V wave is diagnostic of mitral insufficiency. when recorded from the right atrium, it suggests the diagnosis of tricuspid insufficiency. PA denotes pulmonary-artery pressure, and PCW pulmonary-capillary-wedge pressure.

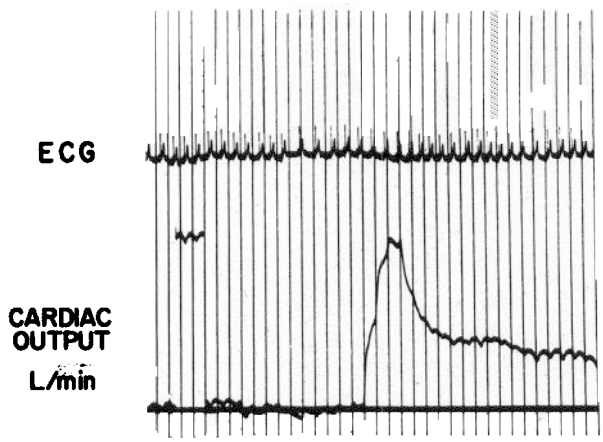

Figure 3. Cardiac-Output Curve from a Patient with Ventricular Septal Defect.
The tracing exhibits a secondary "recirculation peak," which is typical of left-to-right shunts (see text for discussion of mechanism).

ished intravascular volume, increased vascular resistance and metabolic factors, may contribute substantially to diminished cardiac output in acute infarction.

The normal cardiac output curve has a smooth exponential downslope. This morphology is characteristically distorted by ventricular septal defect.[25] In this disorder, large quantities of cooler blood that have already traversed the pulmonary circuit reappear a second time at the pulmonary-artery sampling site, producing a second, diagnostic "recirculation peak" characteristic of left-to-right shunts (Fig. 3). This recirculation may cause current bedside computers to miscalculate true cardiac output grossly, and the curve must be calculated by hand. The result is that output of the right side of the heart equals flow in the left side of the heart plus shunt flow. The ratio of pulmonary to systemic flow ("shunt ratio") may be assessed by determination of the oxygen saturation of blood from the right atrium, pulmonary artery and a systemic artery. Output of the left side of the heart is calculated by dividing output of the right side of the heart by this ratio.[25]

Relation of Hemodynamics to Clinical State

Although the hemodynamic changes that occur with acute myocardial infarction are numerous, *increased pulmonary-capillary pressure and diminished cardiac output are the final common pathways* for production of virtually all the clinical signs and symptoms of heart failure. Increased pulmonary-capillary pressure is expressed clinically as the signs and symptoms of pulmonary congestion. Thus, as the pressure increases, radiologic manifestations of acute pulmonary congestion ordinarily follow a specific pattern[26] as follows: 18 to 20 mm Hg, onset of pulmonary congestion; 20 to 25 mm Hg, moderate congestion; 25 to 30 mm Hg, severe congestion; and >30 mm Hg, onset of pulmonary edema.

The earliest change associated with an increase in pulmonary-capillary pressure is *redistribution of flow*[27-30] to the upper lobes of the lung. As pressure is further increased, fluid passes from the capillaries to the perivascular and interstitial tissue, resulting in diminished clarity of the borders of medium-sized pulmonary vessels and the development of *perihilar haze*.[28,30-32] As pressure is increased still further, fluid moves to the perialveolar space, resulting in the appearance of radiolucent grapelike clusters surrounded by radiodense fluid called the *"peri-acinar rosette."*[28,31] Finally, with very high pulmonary-capillary pressure, rosettes coalesce, and other signs are accentuated, resulting in the radiologic appearance of *acute pulmonary edema*.[33]

In a similar manner, the signs and symptoms of peripheral hypoperfusion to the brain, kidney and skin are the clinical expression of reduced cardiac output and become increasingly severe as cardiac output is reduced. Thus, normalized cardiac output* relates to peripheral hypoperfusion as follows[34]: 2.7 to 4.3 liters per minute per square meter, normal range; 2.2 to 2.7, subclinical depression; 1.8 to 2.2, onset of clinical hypoperfusion; and <1.8, cardiogenic shock.

These correlations of pulmonary-capillary pressure and cardiac index with clinical state are shown in Figure 4.*The single value for pulmonary-capillary pressure and cardiac index that most precisely separates patients with and without pulmonary congestion and peripheral hypoperfusion are 18 mm Hg and 2.2 liters per minute per square meter respectively.[34] Conversely, on the basis of clinical criteria, one can predict whether cardiac index and pulmonary-capillary pressure are abnormal in slightly more than 80 per cent of patients. There are two major limitations of clinical prediction of the hemodynamic state. The first is that approximately one fourth of the patients designated clinically as not having hypoperfusion have a cardiac index of <2.2 liters per minute per square meter. Most cases of this error occur in patients who have clinical evidence of pulmonary congestion. The second important clinical limitation is failure to recognize elevation of pulmonary-capillary pressure (>18 mm Hg), which occurs in approximately 15 per cent of patients. Thus, clinical criteria can be used to reflect the range of cardiac hemodynamics accurately in the majority of cases, and the most common clinical errors involve underdiagnosis of hemodynamic depression.

*To normalize for differences in cardiac output due to body size, cardiac output is divided by body-surface area (in square meters) to obtain cardiac index. Body-surface area is determined from the height and weight of the patient with use of published tables.

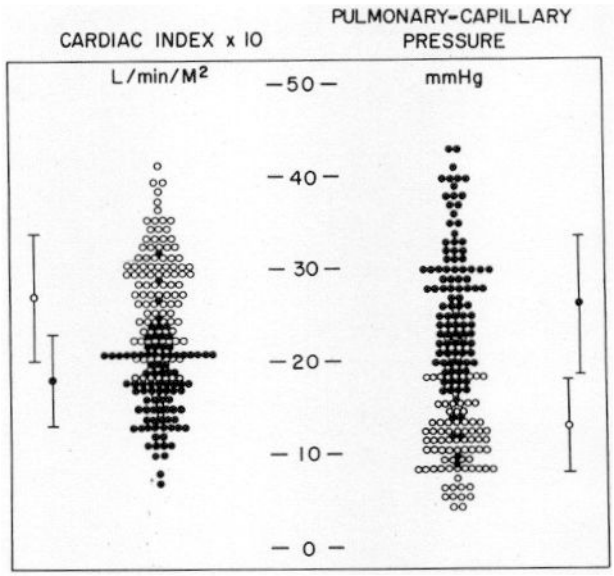

Figure 4. Relation between Altered Cardiac Hemodynamics and the Clinical Signs of Heart Failure.

The left panel shows the relation between cardiac index and peripheral hypoperfusion, and the right panel that between pulmonary-capillary pressure and pulmonary congestion. Solid dots indicate the presence of clinical findings of peripheral hypoperfusion in the left panel, and pulmonary congestion in the right panel. The data suggest that signs of peripheral hypoperfusion begin to become apparent at a cardiac-index level of approximately 2.2 liters per minute per square meter and that clinical pulmonary congestion begins to become apparent at a pulmonary-capillary pressure of approximately 18 mm Hg. Mean ±1 S.D. are shown.

Differences between Clinical and Hemodynamic Assessment — How Discrepancies May Occur

Although there are a number of mechanisms by which the physical examination may be misleading about the state of cardiac function, several are noteworthy. Table 2 shows four cases, each illustrating one mechanism by which gross discrepancies between the clinical and hemodynamic evaluations of cardiac performance may occur. The first patient, examined soon after intravenous administration of furosemide, had clinically moderate pulmonary congestion, but normal pulmonary-capillary pressure. The difference in clinical and hemodynamic evaluation reflected the rapid reduction in pulmonary-capillary pressure to within the normal range after furosemide, with persistence of rales and x-ray changes. In such cases there may be a *phase lag*[24] of as much as 48 hours between hemodynamic stabilization and resolution of abnormal physical and radiologic signs. The second patient, with associated *chronic obstructive pulmonary disease,* was clinically diagnosed as having moderate pulmonary congestion because of dyspnea and rales. Hemodynamics, however, were within the normal range, indicating that the patient's physical signs were extracardiac in origin. The third patient, with long standing hypertension, had clinically severe pulmonary congestion on examination and radiographic evidence of pulmonary edema. Hemodynamic measurements revealed a high normal cardiac output and a markedly increased pulmonary-capillary pressure. The normal cardiac output with elevated pulmonary-capillary pressure in this patient, therefore, was probably secondary to *left ventricular hypertrophy* and *reduced ventricular compliance.*[12-15] The fourth patient, with long standing *chronic compensated heart failure,* was asymptomatic, but was considered to have minimal left ventricular failure on the basis of an audible third heart sound. Hemodynamics, however, revealed substantial reduction of cardiac output and a marked elevation in pulmonary-capillary pressure. In such a case, selective peripheral vasoconstriction may mask the presence of low cardiac output, and thickening of the pulmonary vascular walls can allow the lung to tolerate a substantial elevation in pulmonary-capillary pressure without clinical congestion. Thus, a substantial disparity between clinical and hemodynamic evaluation secondary to such *compensatory mechanisms* can occur.

Table 2. Discrepancies between Clinical and Hemodynamic States *

Clinical State	Basis	CI	PCP	Possible Mechanism
Moderate "LV failure"	Rales, congestion by x-ray study	2.6	12	"Phase lag" after diuretic therapy
Moderate "LV failure"	Dyspnea, diaphoresis S_4, S_3	3.1	15	Noncardiac
Severe "LV failure"	Rales, pulmonary edema by x-ray study	3.6	28	Decreased diastolic compliance
Mild "LV failure"	S_3, normal by x-ray study	2.2	30	Chronic failure with substantial compensation

*LV denotes left ventricle, CI cardiac index (in liters/min/m²), & PCP pulmonary-capillary pressure (in mm Hg).

Assessment of Left Ventricular Pump Performance

The second use of pulmonary-capillary pressure and cardiac index, beyond determining the magnitude of pulmonary congestion and peripheral hypoperfusion, is for assessing left ventricular pump performance. Figure 5 plots cardiac index vs. pulmonary-capillary pressure (the Starling relation) in 200 patients with acute myocardial infarction at the time of admission.[34] From these graphic data, several important conclusions become apparent. First of all, there is a wide degree of variability in left ventricular performance in patients with acute myocardial infarction. Secondly, the level of cardiac performance at the time of hospitalization bears a direct relation to in-hospital mortality, as defined by the highly important difference in mortality rates established by a cardiac index of 2.2 liters per minute per square meter and a pulmonary-capillary pressure of 18 mm Hg.

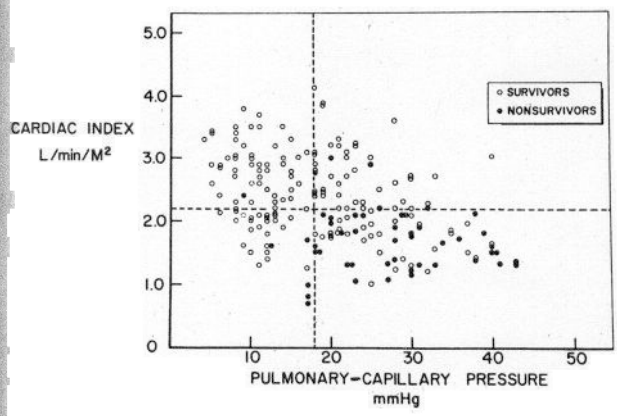

Figure 5. Relation between Pulmonary-Capillary Pressure and Cardiac Index in 200 Patients at the Time of Admission to Cedars–Sinai Medical Center Myocardial Infarction Research Unit.

The dotted lines are placed at the levels of 18 mm Hg for pulmonary-capillary pressure and 2.2 liters per minute per square meter for cardiac index. There is a wide degree of variability in left ventricular performance in patients with acute myocardial infarction, and mortality rate increases as cardiac performance deteriorates.

Lastly, approximately one third of the patients had normal levels of left ventricular performance during the time they were having an acute myocardial infarction. Thus, the first important principle in the approach to therapy of disordered cardiac function: *acute myocardial infarction cannot be viewed as a single functional disorder; rather it is a series of subsets.*

To this end, a number of classification methods for patients with acute myocardial infarction have been proposed. Two basic approaches have been used.[35-41] The first, of which the best known is probably the method of Killip, defines clinically relevant syndromes (such as pulmonary edema and cardiogenic shock), whereas the second method uses multiple clinical or hemodynamic criteria, appropriately weighted, to establish a numerical probability of survival. Both approaches are useful for establishing prognosis in groups of patients, but neither method relates the clinical presentation to its specific hemodynamic determinants, nor are they directly based on the level of cardiac performance. These methods, therefore, have only limited relevance to therapeutic decision making.

A more broadly relevant subset classification relates the clinical presentation to specific hemodynamic determinants of left ventricular pump performance (Table 3). Clinical subsets are defined by the manifestations of pulmonary congestion (reflecting increased pulmonary-capillary pressure) and peripheral hypoperfusion (reflecting decreased cardiac index).[34] On the basis of these findings, four clinical subsets (C) are defined: CI, no pulmonary congestion or peripheral hypoperfusion; CII, pulmonary congestion without hypoperfusion; CIII, peripheral hypoperfusion without congestion; and CIV, both hypoperfusion and congestion. These clinical subsets are of substantial value in assessing short-term prognosis. Although clinically uncomplicated patients virtually always survive hospitalization (1 per cent mortality), mortality increases to approximately 10 per cent when pulmonary congestion is present and to 60 per cent when both pulmonary congestion and peripheral hypoperfusion are detectable.

Since pulmonary congestion is due to increased pulmonary-capillary pressure, and peripheral hypoperfusion to depressed cardiac index, four comparable *hemodynamic subsets* are established by the specific levels of cardiac index and pulmonary-capillary pressure described earlier in the discussion of clinical and hemodynamic correlations. The comparable hemodynamic subsets (H), therefore, are defined as follows: HI, pulmonary-capillary pressure ≤18 mm Hg, and cardiac index >2.2 liters per minute per square meter; HII, pulmonary-capillary pressure >18 mm Hg, and cardiac index >2.2 liters per minute per square meter; HIII, pulmonary-capillary pressure ≤18 mm Hg, and cardiac index ≤2.2 liters per minute per square meter; and HIV, pulmonary-capillary pressure >18 mm Hg, and cardiac index ≤2.2 liters per minute per square meter. Clinical subset classification correctly predicts into which hemodynamic subset a patient will fall in approximately 70 per cent of the cases. Because of this high correlation, the mortality rates in the four hemodynamic subsets are comparable to those in clinical subsets (Table 4). Most striking is the fact that the presence of peripheral hypoperfusion, diagnosed either by clinical evaluation or by a cardiac index ≤2.2 liters per minute per square meter, is associated with an increase of approximately 10 times in mortality rate.

Table 3. Hemodynamic Basis of Clinical Presentation.

Basis	Increased Pulmonary-Capillary Pressure	Decreased Cardiac Index
Subjective	Dyspnea	Obtundation, fatigue
Objective	Rales, x-ray evidence of congestion	Reduced blood pressure, increased heart rate, cold skin & oliguria

Table 4. Mortality Rates in Clinical and Hemodynamic Subsets.

Subset	Pulmonary Congestion*	Peripheral Hypoperfusion†	% Mortality	
			Clinical	Hemodynamic
I	–		1	3
II	+		11	9
III	–	+	18	23
IV	+	+	60	51

*Pulmonary-capillary pressure >18 mm Hg.
†Cardiac index <2.2 liters/min/m².

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