Pathophysiology of Cardiogenic Shock
Quantification of Myocardial Necrosis, Clinical, Pathologic and Electrocardiographic Correlations

By Daniel R. Alonso, M.D., Stephen Scheidt, M.D., Martin Post, M.D., and Thomas Killip, M.D.

SUMMARY
Clinical and pathologic data were correlated in 22 patients with cardiogenic shock and 10 “control” patients who died suddenly after infarction without shock. A pathologic technique of ventricular mapping allowed quantification of recent as well as old infarction. Total left ventricular (LV) damage averaged 51% (range 35-68%) in the shock patients and 23% (range 14-31%) in the control group. Shock was associated with recent infarction (all 22 patients), old infarction (21 patients) and extension of infarction (18 patients). Extension, often in a subepicardial manner, averaged 6% of LV mass (range 3-10%) in 18 patients with shock; it preceded shock in four, coincided with the onset of shock in six, and followed shock in seven patients with shock. In contrast, small extensions averaging 2% of LV mass were found in three, and multiple recent infarctions in two control patients. Although progressive myocardial damage was a common pathologic finding, it was infrequently recognized clinically. The electrocardiogram reflected evidence of recent infarction in 56%, old infarction in 31%, and extension in only 30% of patients. These data suggest that appropriate early therapeutic intervention might limit myocardial damage by preventing extension or reinfarction. Since shock was best correlated with total LV damage, such limitation of infarction might reduce the incidence and mortality of cardiogenic shock.

Additional Indexing Words:
Myocardial infarction Quantification of infarct size Extension of infarction

CARDIOGENIC shock remains the major cause of death among patients hospitalized with acute myocardial infarction. Mortality is high in spite of pharmacologic agents, mechanical circulatory assistance and surgery. Development of optimal therapy requires better understanding of the pathophysiology of the cardiogenic shock syndrome.

We present herein a detailed clinical-pathologic study of patients who died with cardiogenic shock. The data demonstrate that shock is associated with massive myocardial damage and that myocardial injury frequently occurs in a stepwise or progressive fashion. Interruption of the cycle of clinical deterioration and progressive damage through therapy directed at limiting the amount of myocardial damage during the episode of acute infarction might reduce the incidence and mortality of cardiogenic shock.

Methods
Clinical, physiologic and postmortem studies have been obtained in 32 patients over a two-year period. Twenty-two patients died with cardiogenic shock complicating acute myocardial infarction. All had intrarhegystolic pressure less than 90 mm Hg and abnormal renal or cerebral perfusion manifested by hourly urine flow less than 20 ml or abnormalities of mental status. Hypovolemia was excluded either by measurement of left ventricular filling pressure, which exceeded 12 mm Hg whenever obtained, or by trial expansion of intravascular volume. Severe pain, significant arrhythmias, disorders of electrolyte or acid base balance, and abnormalities of ventilation or oxygenation were corrected whenever possible.

The findings in the patients with shock were compared to those of a control group, composed of ten patients who died suddenly and unexpectedly during convalescence in the hospital following acute myocardial infarction.

Table 1 lists characteristics of the shock and control groups. Differences in age, time of admission to the Cardiac Care Unit and total duration of illness between
Table 1

Comparison of Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Cardiogenic shock</th>
<th>Sudden death after myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>66 (50-85)</td>
<td>70 (57-89)</td>
</tr>
<tr>
<td>Median time from clinical &quot;moment of infarction&quot; to CCU admission, hr</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Median survival after infarction, hr</td>
<td>100</td>
<td>172</td>
</tr>
<tr>
<td>Number of patients with complications at CCU admission</td>
<td>none</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>mild or moderate CHF</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>pulmonary edema</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>cardiogenic shock</td>
<td>4</td>
</tr>
<tr>
<td>Median time from infarction to onset of shock, hr, (range)</td>
<td>66 (0-331)</td>
<td></td>
</tr>
<tr>
<td>Median survival after onset of shock, hr</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCU = Cardiac Care Unit, CHF = congestive heart failure.

The two groups are not statistically significant. Patients who developed shock did so at varying times after admission. Only seven of the 22 patients developed shock within 24 hr of the acute myocardial infarct.

In the group who died suddenly two patients had ventricular rupture and eight had unexpected cardiac arrest.

Pathologic Studies

The heart was removed intact from the chest. A radiograph was obtained in various projections, and the coronary arteries were then perfused with a mixture of barium sulfate and gelatin through polyethylene catheters placed in each coronary ostium and secured by a ligature around the origin of the vessel. A nonpulsatile perfusion pressure of 100 mm Hg was applied until all visible epicardial branches were filled. At the completion of the perfusion, the heart was fixed by immersion in a solution of 20% formalin for 48 hr. Care was taken to fill the cardiac chambers with formalin to complete fixation. The heart was weighed before and after fixation; no significant difference in the weights was found.

After 48 hr of fixation radiographs of the heart were obtained in four projections. The coronary arteries were then dissected free from the epicardial surface. The entire length of major vessels was resected. The arteries were decalcified in 7% nitric acid for 24-48 hr, according to the amount of calcium present in each vessel. Radiographs were taken of isolated coronary arteries by placing them directly on mammography X-ray film.

Quantification of infarcted ventricular myocardium was accomplished by sectioning the heart in a standardized manner, determining the degree of necrosis in each standard segment and calculating total damage through comparison with data obtained from normal hearts. The method employed is a modification of one originally devised by Dr. Donald B. Hackel of Duke University Medical Center.

The method is as follows: After completion of arteriography the crux of the heart was identified. A cut was made 2 cm below the crux parallel to the atrioventricular groove (fig. 1). Thus, the heart was divided into a basal and a ventricular portion. The latter was then cut into six equal and parallel coronal slices. These coronal slices were labelled A through F, from the apex to the base. The ventricular myocardium of the basal portion was separated by sharp dissection from the atria along the atrioventricular groove and labelled G.

Each of the seven coronal slices (A through G) was then cut into six radial segments in a standard manner. The interventricular septum was divided into equal anterior and posterior halves (segments 5 and 1 respectively). The perimeter of the epicardial aspect of the remaining free wall of the left ventricle was measured with a flexible plastic ruler and divided into three equal segments. The segments were labelled 4 (anterior), 3 (lateral) and 2 (diaphragmatic). The entire free wall of the right ventricle was separated and assigned number 6, but was not included in the calculation to follow. Thus a total of 35 segments (5

Figure 1

(Top) Method of sectioning the heart for quantification of ventricular myocardial damage. (Bottom) Method of dividing each coronal slice of myocardium into radial segments. Five radial segments (1-5) in each of 7 coronal slices (A-G) provide 35 standard segments comprising the entire mass of the left ventricular myocardium.
radial segments in each of 7 coronal slices) of myocardium of left ventricular wall and interventricular septum was obtained.

In the hearts from patients with shock or sudden death, areas of myocardial infarction and fibrosis were identified grossly and mapped in each coronal section. Microscopic sections were then obtained from areas of obvious infarction as well as from grossly normal myocardium. A minimum of 20 large blocks of left ventricular myocardium were studied microscopically in each heart.

The technique of sectioning the heart in a standard manner was performed in 25 normal adult hearts obtained at autopsy from patients who died from noncardiac causes. The percent contribution of each standard segment to the total left ventricular weight of the normal heart is shown in figure 2.

In hearts with infarction, viable myocardium in each standard segment was estimated by gross and microscopic observations. If viable myocardium was totally absent, either due to recognizable recent necrosis or as a result of old infarction with subsequent fibrosis and loss of mass, the percent of left ventricular mass represented by that standard segment (as determined from the expected percent in the 25 normal hearts) was subtracted from 100%. If, for example, the anterior septal segment in section C (fig. 2) was totally infarcted, the necrosis represented 5.5% of ventricular mass. Loss of myocardium in part of a standard segment was subtracted in proportion to the amount of damage or loss of tissue in the segment. Thus this method accounts for not only recognizable recent damage, but also old necrosis which has resulted in loss of ventricular mass.

The age of infarcts was estimated by conventional histopathologic criteria. Three categories were established: recent infarct (less than 2 weeks old), intermediate infarct (2 weeks to 3 months old) and old infarct (more than 3 months old). While this separation according to age was both workable and useful, it is recognized that aging of a myocardial infarct is not a precise process.

Results

The hearts of patients who died with cardiogenic shock showed massive left ventricular destruction and the extent of infarction was significantly greater than in the patients who died without shock. Thus the total mass of left ventricular infarction averaged 51% (range 35-68%) in the 22 patients with shock and 23% (range 14-31%) in the 10 patients with sudden death (fig. 3). The mass of old or intermediate infarction was not different in the shock and sudden death groups; the highly significant difference in total infarction between the two groups was explained by the difference in mass of recent infarction which averaged 31% in the

![Figure 2](image-url)

Mean percent of left ventricular myocardial mass contained in each of the 35 standard segments as determined from 25 normal hearts.

![Figure 3](image-url)

Mass of left ventricular infarction in 22 patients who died from cardiogenic shock compared to 10 with sudden death. There is no significant difference in mass of old (clear portion of bar) or intermediate (lightly stippled) infarction. The highly significant difference in mass of total infarction is explained by the much larger recent infarction (dark stippling) in the shock patients.
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shock group but only 12% in the sudden death group.

Figure 4 depicts the distribution of damage by age of infarct in each of the patients with shock and sudden death. The relative proportions of old, intermediate and recent damage are highly variable. In 16 of the 32 patients most of the myocardial damage was due to recent necrosis. Six patients, only two of whom died from shock, had relatively small recent infarcts combined with larger old or intermediate infarcts. In general, the appearance of shock seems best correlated with total left ventricular damage.

Duration of Shock

The 22 patients with shock were divided into two groups according to the clinical duration of shock. Group 1 consisted of patients in shock longer than 24 hr. Group 2 was comprised of patients who died within 24 hr of the onset of shock. The mean duration of shock was 88 hr for Group 1 and 12 hr for Group 2. The two groups do not differ significantly with respect to the total or recent mass of left ventricular infarction, the frequency or mass of extension, or the extent of coronary artery thrombosis (Table 2). Figure 5 demonstrates that there is no relationship between the mass of left ventricular infarct and the duration of shock. Thus length of survival following the onset of shock does not appear to influence the pathologic findings.

Extension of Infarction

An infarct was considered to have extended when myocardial necrosis of a more recent vintage was demonstrated at the edges of an established infarct. This was distinguished from “multiple recent infarction” (hereafter “reinfarction”), where several discrete infarcts in scattered locations were apparent.

Two patterns of extension, type A and type B, were observed. Type A extension occurred at the edges of a subendocardial infarct, usually involving the subepicardial aspect of the ventricular wall. Type B extension developed at the lateral margins.

![Figure 4](http://circ.ahajournals.org/)

Mass of left ventricular infarction in individual patients.

Circulation, Volume XLVIII, September 1973
Table 2

<table>
<thead>
<tr>
<th>Influence of Duration of Shock on Pathologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Prolonged shock (duration &gt;24 hrs)</td>
</tr>
<tr>
<td>N 9</td>
</tr>
<tr>
<td>Mean duration of shock, onset to death, hr 88</td>
</tr>
<tr>
<td>Mass of LV infarct, % of LV 54</td>
</tr>
<tr>
<td>Mass of recent LV infarct, % of LV 36</td>
</tr>
<tr>
<td>Extension of infarction, patients 8 (89%) 10 (83%)</td>
</tr>
<tr>
<td>Mass of extension, % of LV 5.4</td>
</tr>
<tr>
<td>Recent coronary artery thrombosis, patients 6 (67%) 10 (83%)</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Rapid demise (duration &lt;24 hrs)</td>
</tr>
<tr>
<td>P</td>
</tr>
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</tr>
</tbody>
</table>

Abbreviations: LV = left ventricle, NS = not significant

of transmural infarcts since no viable subepicardial myocardium remained (fig. 6).

Extension of infarction was observed in 18 of the 22 shock patients but in only 3 of the 10 sudden death patients (P < .005). Type A extension occurred in 9 and type B extension in 9 of the 18 patients with shock in whom extension was documented. The mass of left ventricle involved by extension averaged 6% (range 3-10%) in the shock group. There were three small extensions in the

sudden death group, comprising 2, 2 and 3% of left ventricular mass, respectively.

Seven of the patients in the shock group and one in the sudden death group had two or more anatomically distinct reinfarctions.

The pathologic determination of the infarcts recognized at autopsy was correlated with clinical events as described in the medical record. Chronologic relationships for the 22 patients are depicted in figure 7 and table 3. Extension or reinfarction followed the onset of shock in seven patients. In six patients an extension or reinfarction clearly preceded and perhaps precipitated shock. In six instances the onset of shock and extension or reinfarction occurred at about the same time, so that the pathophysiologic sequence could not be determined.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5**

Mass of left ventricular infarct plotted against the duration of cardiogenic shock. Apparent lack of any relationship suggests that shock itself is not responsible for the pathologic findings.

![Figure 6](http://circ.ahajournals.org/)

**Figure 6**

Schematic representation of two types of extension of myocardial infarction. Type A (top) was observed at the edges of an infarct, usually subepicardially. Type B (bottom) occurred at the lateral margins.
Arranging the data in another way, the onset of shock was related to the original infarct in 9 episodes of shock, followed extension or reinfarction in 6, occurred simultaneously with extension or reinfarction in 6, and was not closely related to an obvious pathologic event in 3 instances.

**Coronary Artery Pathology**

Thrombosis was common in both groups of patients. Recent occlusive thrombosis of major coronary arteries was found in 16 of the 22 (72%) patients with shock and 6 of the 10 (60%) patients with sudden death. The thrombi averaged 18.4 mm

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**Table 3**

<table>
<thead>
<tr>
<th>Extension or reinfarction (patients)</th>
<th>Clinical onset of shock: (episodes of shock)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Followed shock</td>
<td>Related to original infarct 9</td>
</tr>
<tr>
<td>Preceded shock</td>
<td>Followed extension or reinfarction 6</td>
</tr>
<tr>
<td>Occurred simultaneously with the</td>
<td>Occurred simultaneously with extension or</td>
</tr>
<tr>
<td>onset of shock</td>
<td>reinfarction 6</td>
</tr>
<tr>
<td>No extension or reinfarction</td>
<td>No obvious pathologic event 3</td>
</tr>
<tr>
<td></td>
<td>22</td>
</tr>
</tbody>
</table>
(range 2.0 to 52.0 mm) in length in the shock group, and 28.6 mm (range 13.0 to 47.0 mm) in the sudden death group. The presence and size of recent thrombi could not be correlated with the duration of shock, survival after the onset of acute myocardial infarction or the presence, type or mass of extension.

Table 4 compares the distribution of major coronary artery stenoses (≥75% of luminal area) in the shock and sudden death patients. Extensive three-vessel disease was the dominant finding in patients who died with cardiogenic shock, but 3 patients had involvement of one vessel only (left anterior descending coronary artery in two, right coronary artery in one).  

**Electrocardiographic Correlations**

Scalar electrocardiograms were evaluated for evidence of old and new myocardial infarction using standard criteria. Forty discrete old infarcts were identified pathologically in the 32 patients. Electrocardiographic diagnosis was not possible in six instances because of left bundle branch block, acute infarction in the same location as old infarction (thus obscuring any old changes) or inadequate electrocardiograms. Of the remaining 34 old infarctions, only 12 (35%) could be diagnosed from the scalar electrocardiogram (fig. 8).

Of the 38 discrete recent infarcts identified pathologically, chronologically suitable electrocardiograms were available in 33 instances. Nineteen of the 33 acute infarctions (58%) could be diagnosed from the electrocardiogram.

In 19 instances of acute transmural infarction, an average of 32% of left ventricular mass was destroyed. Of these transmural infarcts, only three could not be diagnosed from the electrocardiogram, for a diagnostic accuracy of 84%. In contrast, 19 acute nontransmural infarcts were small, averaging 12.5% of left ventricular mass. Only four nontransmural infarcts were apparent from the electrocardiogram, for a diagnostic accuracy of 21% (fig. 8).

**Figure 8**

Diagnostic utility of the standard scalar electrocardiogram according to mass and type (transmural, central or subendocardial) of infarction. Transmural infarctions were larger and usually produced diagnostic electrocardiographic changes.

In ten instances an electrocardiogram was available after the presumed chronologic time of extension of infarction. In only three of these instances could acute injury (new ST-segment elevation or Q wave) be recognized electrocardiographically.

**Discussion**

This study demonstrates that when cardiogenic shock complicates acute myocardial infarction, massive left ventricular infarction is to be expected. Furthermore, the extent of myocardial damage is much greater in patients who die from shock than in those who die unexpectedly while convalescing in the hospital from acute infarction. Our observations are in agreement with recent clinical-pathologic studies in which the mass of left ventricular

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**Table 4**

Coronary Artery Pathology in Patients with Shock and Sudden Death

<table>
<thead>
<tr>
<th>Major coronary vessels with ≥75% stenosis</th>
<th>Shock pts</th>
<th>%</th>
<th>Sudden death pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vessel</td>
<td>3</td>
<td>14</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>2 vessels</td>
<td>7</td>
<td>32</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>3 vessels</td>
<td>12</td>
<td>54</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviation. pts = patients.
infarction was established by other pathologic techniques.  

The difference in mass of infarcted left ventricle between the cardiogenic shock and sudden death groups is highly significant and is not related to the duration of shock, the use of drugs or of mechanical circulatory assistance with the intra-aortic counterpulsating balloon.

On the average, more than half of the left ventricular mass is destroyed in patients who die from cardiogenic shock. Stated another way, in the patients with cardiogenic shock less than half of the left ventricular myocardium remains to maintain ventricular function. The theoretical consequences of such loss of myocardium are considered with reference to a conceptual model by Swan et al.  

Under certain circumstances, loss of half of the left ventricular myocardium is sufficient to explain the hemodynamic and clinical consequences of shock, and contractility of the remaining viable tissue need not be impaired. One implication of this analysis is that preservation of functioning myocardium is of paramount importance. Current and past experience have amply demonstrated that therapy directed at the remaining viable tissue (which is already functioning at normal or perhaps above-normal levels of contractility) does little to improve salvage.

We have further shown that patients dying during hospitalization from myocardial infarction often have a stepwise increase or progression of myocardial necrosis, usually from marginal extension of infarction. Thus, extension was found in 18 of 22 patients with shock but in only three of ten with sudden death. Multiple recent infarctions were found in seven patients with shock and two with sudden death. Page et al. observed extension to be present only in patients with shock and suggested that extension was a consequence of the shock state.  

In our patients, although extension followed the onset of shock in some, it clearly preceded (and perhaps caused) shock in others. These observations indicate that extension is an important mechanism resulting in progressive myocardial necrosis following acute myocardial infarction.

Extension of infarction is often a process which goes unrecognized clinically. None of the three extensions recognized pathologically in the patients with sudden death were suspected despite close observation in a cardiac care unit. In the patients with shock, only three of ten electrocardiograms available after the presumed time of extension demonstrated an acute injury pattern. Only three of the 18 extensions were suspected clinically because of renewed or protracted chest pain. Although diagnosis of extension is infrequent, the process may not be silent. Perhaps more frequent recording of electrocardiograms, serial precordial ST-segment maps or assay of serum enzymes several times daily would improve diagnostic accuracy.

The limitations of the standard scalar electrocardiogram in the diagnosis of myocardial infarction have been previously recognized.  

In our study, after excluding patients with left bundle branch block and intraventricular block, old infarction could be diagnosed in only 31% and acute infarction in only 59% of hearts with pathologically confirmed areas of myocardial necrosis. Our findings closely parallel those of Levine and Phillips. Infarcts that are nontransmural, diaphragmatic and posterior, or those that comprise less than 10% of left ventricular mass are often not apparent electrocardiographically. At least part of the difficulty is due to the fact that a significant Q wave, evidence of a transmural scar, is generally necessary for diagnostic certainty. Others have noted the inadequacies of the electrocardiogram in the diagnosis of purely subendocardial infarction. It must be recognized therefore, that although cardiogenic shock is usually temporally related to acute infarction or recent extension, the electrocardiogram will be of diagnostic value only about half of the time.

There was a preponderance of patients with disease of all three major coronary arteries in the shock group, although three patients developed shock with a single major coronary artery occlusion. The frequency of coronary thrombosis encountered in our patients with shock is comparable to that reported by Page. The incidence of thrombi in the sudden death group, higher than that reported in other studies of sudden death, is probably explained by the fact that our group comprised hospitalized patients who died suddenly during convalescence, often many days following acute infarction. Other studies of sudden death generally deal with patients dying within a short time of the onset of symptoms. Our inability to determine the age of thrombus precludes any attempt to establish a causal relationship between thrombosis and infarction or extension of the original injury.

The apparent temporal association between extension of infarction and the clinical onset of shock suggests that progression of myocardial damage plays an important role in the pathogenesis of shock. Extension probably represents loss of viability of an ischemic zone which surrounds the initial infarct. Infarction of this zone of
marginal viability could be precipitated by any factor that unfavorably influences its metabolic milieu. The balance of factors which regulate metabolic demands and the supply of nutrients to the myocardium becomes crucial in controlling the progressive necrosis which may follow the initial insult. Perhaps treatment designed to improve oxygenation and substrate utilization or to reduce myocardial oxygen needs can enhance the viability of the marginal ischemic zone. The hypothesis that progressive loss of functioning myocardium following acute infarction is preventable requires further investigation as specific therapeutic interventions are critically evaluated. Limitation of myocardial damage, rather than intensive therapy after cardiogenic shock is manifest, may succeed in reducing both the incidence and mortality of progressive power failure complicating acute myocardial infarction.

References
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