Plasma Volume Prior to and Following Volume Loading During Shock Complicating Acute Myocardial Infarction

By PROTASIO L. DA LUZ, M.D., MAX HARRY WEIL, M.D., VINNIE Y. LIU, M.S., and HERBERT SHUBIN, M.D.

SUMMARY

Blood volume was measured following onset of shock in 19 patients who had sustained acute myocardial infarction. The plasma volume was measured by dilution technique utilizing R\textsuperscript{125}ISA and the red cell mass by \textsuperscript{51}Cr red cell tag, at the time of admission.

The plasma volume in six survivors was 41.1 ± 3.3 ml/kg; in 13 fatal cases it was 44.7 ± 4.0 ml/kg; this difference was not significant. The red cell mass in four survivors was 27.2 ± 1.75 ml/kg and in four fatal cases, 24.7 ± 1.60 ml/kg. Since these measurements are within normal ranges, we excluded absolute hypovolemia as a significant factor in accounting for the circulatory failure. Infusion of fluids in amounts which maintained a positive fluid balance selectively increased the plasma volume (57.1 ± 4.4 ml/kg), cardiac index, stroke volume and central blood volume in survivors, and reversed arterial vasoconstriction and lactic acidosis. However, the plasma volume was unaffected in the fatal cases (44.4 ± 4.0 ml/kg) and this was associated with progressive hemodynamic and metabolic deterioration.

These observations support the hypothesis that recovery from shock is associated with expansion of plasma volume. To the contrary, during fatal progression of shock, plasma volume expansion does not occur despite volume loading.

Additional Indexing Words:
Cardiogenic shock Blood volume Hypovolemia Fluid infusion Lactic acidosis

SHOCK FOLLOWING acute myocardial infarction is a reflection of power failure and is related to the mass of myocardium which is disabled by ischemic injury or cell death.\textsuperscript{1} In a report by Page et al.\textsuperscript{2} of 20 patients who were in shock and died after myocardial infarction, there was necrosis and/or fibrosis of at least 40% of the left ventricular myocardium. In 12 additional patients who died suddenly without the clinical picture of shock, there was destruction of only 30% or less of the left ventricle.\textsuperscript{2} An additional factor which may contribute to circulatory failure is hypovolemia.\textsuperscript{3} In the absence of massive myocardial injury, the correction of volume deficits would be expected to improve the prognosis. Even when hypovolemia was suspected, clinicians have been conservative in administering colloid or sodium-containing fluids for fear of precipitating congestive heart failure. In earlier studies, prior to the availability of intravascular monitoring techniques, infusion of moderate amounts of blood or plasma failed to improve survival.\textsuperscript{4-6} More recently, administration of relatively large amounts of fluid, guided by concurrent measurements of intravascular pressure and cardiac output, have demonstrated beneficial effects.\textsuperscript{7-9} In the present study, plasma volume and hemodynamic variables were measured in 19 patients and the effects of a systematic fluid challenge on the intravascular volume and hemodynamic status were assessed. These investigations were undertaken to determine whether shock associated with acute myocardial infarction is...
related, in part, to a deficit in intravascular volume.

Clinical Material
There were 15 men and four women whose ages ranged from 48 to 84 years (mean 63). Diagnosis of myocardial infarction was based on clinical history, the presence of characteristic Q waves and ST-T wave changes on the electrocardiogram and/or autopsy confirmation. Shock was defined as systolic blood pressure less than 90 mm Hg, clammy skin, urinary output of less than 30 ml/hr and arterial blood lactate concentration exceeding 1.4 mM/liter. The incidence of previous myocardial infarction and congestive heart failure was higher among the fatal cases than in survivors. Physical signs of congestive heart failure were more common among the fatal cases. Six patients recovered from shock, but four died before discharge from the hospital, with death attributed to arrhythmia (1), extension of infarction (2), and recurrence of shock (1). The interval between the acute myocardial infarction, as estimated on the basis of the patient’s history, and the onset of shock averaged 58 hours in survivors and 26 hours among those who died. Prior to admission to the Critical Care Ward, clinical signs of circulatory failure were present for a mean period of 23 (1 to 132) hours. Pertinent clinical data are summarized in table 1.

Methods
Measurements were obtained on admission to the Critical Care Ward and after an average interval of 28 (3 to 59) hours. A red Odman-Ledin catheter, 28.5 cm in length (internal diameter 1.2 mm, external 2.2 mm), was inserted into the femoral artery by percutaneous guide-wire technique and advanced for a distance of approximately 10 cm. A polyethylene catheter, 83 cm in length (internal diameter 1.57 mm, external 2.04 mm), was inserted into the median basilic vein and advanced into the right ventricle and then withdrawn to a position 5 cm proximal to the tricuspid valve. The position was, in each case, confirmed by portable chest X-ray after the dead space of the catheter was filled with 50 percent diatrizoate. Both catheters were connected to a strain gauge pressure transducer (Statham P23AA and 23 PDb), and arterial and central venous pressures were recorded on a direct-writing Sanborn multichannel recorder (Hewlett-Packard Company, No. 984). The catheters were flushed intermittently under pressure with saline solution containing heparin 2 units/ml. Since most of these patients were studied prior to the availability of the Swan-Ganz catheter\(^1\) or the use of left ventricular pressure measurements in acutely ill patients,\(^11\) such data was not available in a sufficient number of patients to warrant its inclusion in this report.

Cardiac output was calculated by indicator dilution technique. Indocyanine green, in a bolus of 2.5 or 5 mg, was injected into the central venous catheter. A Gilford photoelectric densitometer, Model 103, was employed in connection with a Harvard pump and withdrawal syringe, No. 600-900, for measurement of arterial dye concentration. Each indicator dilution curve was calibrated, using 0, 2, 4, and 6 \(\mu\)g/ml dye. The curves were analyzed by standard methods of numerical integration\(^12\) applying appropriate correction for dead space of the arterial catheter and cuvette. Paired measurements of cardiac output were performed in 12 patients. The standard error of the difference was 0.026 liters/min/m\(^2\) (\(P > 0.80\)). The cardiac index, stroke volume, central blood volume, and total peripheral resistance were calculated using standard formulae.\(^13\)

Plasma volume was measured using radiiodinated human serum albumin (RI\(^125\)SA, RI\(^131\)SA). Red cell mass was measured using \(^{51}\)Cr. Isotope activity was determined at intervals of 15, 25, 35 and 45 min with subsequent extrapolation of the values to zero time by methods previously reported.\(^14\) Results were expressed in relation to body weight.

In 16 instances, red cell mass was measured concurrently with that of plasma volume and the total blood volume was derived from the sum of the two values. The values of the total blood volume obtained from these two techniques were then compared to an estimate of total blood volume (ETV) based on the following formula:

\[
ETV = \frac{\text{Plasma Vol. (ml) \times 100}}{100 - (\text{Hct.} \times 0.87)}
\]

in which 0.87 represents the combined correction factor for “trapped” plasma (0.96) and the ratio of peripheral to central hematocrit (0.91). These conform to values reported by McGovern et al.\(^15\) and Chaplin et al.\(^16\)

Lactate concentration was measured by a semi-automated method previously described by Marbach and Well.\(^17\)

After admission to our Unit, metaraminol and/or levarterenol were administered to the majority of the patients. The dose of metaraminol averaged 0.58 mg/min among seven patients who died and 0.38 mg/min in four survivors. This difference was not statistically significant. Two survivors and three patients who died received levarterenol in doses which did not differ significantly and which averaged 20 mcg/min. Crystalloid fluids, primarily 5\% dextrose in water, were infused into all patients. Patients who ultimately died received an average of 79.5 (± 13.5)

### Table 1

<table>
<thead>
<tr>
<th>Clinical Features on Admission to the Critical Care Ward</th>
<th>Survivors (6)</th>
<th>Died (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Physical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck vein distension</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Two or more of the above</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

_Circulation, Volume XLIX, January 1974_
ml/hr, for a period of 22 hours. Survivors received a significantly larger volume of fluid, which averaged 117.0 (± 16.7) ml/hr over a period of 35 hours (fig. 1).

Results

Hemodynamic Measurements

On admission to the Critical Care Ward, there were no significant differences in mean arterial pressure, heart rate, cardiac index, stroke volume, central blood volume and peripheral resistance between survivors and fatal cases. The only hemodynamic variable which differed significantly among the two groups was the central venous pressure, which was higher in patients who died (fig. 2). However, lactate concentration on admission to the Critical Care Ward was significantly higher ($P < 0.05$) among patients who died (table 2), reflecting a more severe degree of perfusion failure.18

Validation of Calculated Values of Total Blood Volume

The values of total blood volume based on simultaneous measurements of red cell mass and plasma volume on 16 occasions in 11 patients and those computed from plasma volume and hematocrit (ETV) differed by 1.78 ($± 1.08$ SEM) ml/kg. This difference was not statistically significant. The linear correlation between the total blood volume based on simultaneous measurement of plasma volume and red cell mass and that calculated from plasma volume and hematocrit was 0.96, $P < 0.0005$.

Intravascular Volume and Fluid Infusion

The initial values of plasma volume were within the normal range in 13 patients. In four patients the plasma volume was less than 35 ml/kg. It exceeded 60 ml/kg in two patients. However, there was no significant difference between the initial values of plasma volume measured among survivors and fatal cases.

The peripheral hematocrit was within the normal range in both survivors and fatal cases. However, an unexpected difference was a statistically significant lower hematocrit in fatal cases at the time of the initial study. This finding, previously observed by others,19 was not explained by differences in those hemodynamic measurements performed by us, or by concurrent disease.

The plasma volume following infusion of fluid provided a basis on which the survival group could be separated from the fatal cases (table 3). An increase in plasma volume of at least 10 ml/kg was observed in five of six survivors ($P < 0.05$). However, in patients who ultimately died, no significant increase in plasma volume was noted. When the intravascular volume was expanded, the cardiac index, stroke volume and central blood volume were significantly increased ($P < 0.05$) but a concurrent increase in central venous pressure was statistically insignificant. Among survivors, peripheral resistance decreased to approximately 50% of the initial values. The increase in systemic blood flow was balanced by the reduction in

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**Figure 1**

Fluid intake and urine output among survivors and fatal cases.

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**Figure 2**

Central venous pressure and plasma volume in relation to fluid infusion.

Circulation, Volume XLIX, January 1974
calculated peripheral resistance so that the mean arterial pressure remained essentially unchanged. A slight reduction in heart rate also followed volume repletion. The improvement in hemodynamic status was associated with increased urine output and a reversal of lactic acidosis.

The red cell mass averaged 27.2 (±1.75) ml/kg before fluid challenge in five survivors and did not change significantly following infusion of fluid. However, a statistically significant reduction in hematocrit was observed among both survivors and fatal cases. In survivors this was accounted for by the selective increases in plasma volume during fluid repletion and losses stemming from the withdrawal of blood during the course of management, for purposes of repetitive laboratory measurements. The relatively smaller decline of hematocrit in the fatal cases could be ascribed only to repetitive blood sampling.

The total blood volume increased in parallel with improvement in the hemodynamic status of survivors. To the contrary, there was a decrease in total blood volume and central venous pressure together with persistent depression of cardiac index and stroke volume among the fatal cases. The increase in peripheral resistance was unaffected in the fatal cases.

Because of clinical signs of pulmonary edema, the volumes of fluid administered to patients who subsequently died were significantly smaller. Since there was a comparably smaller urine output in these patients, a positive fluid balance was maintained in both survivors and fatal cases (Table 4).

**Autopsy Findings**

Postmortem examination on nine patients confirmed the presence of a massive myocardial infarction in each instance, more often of the anterior wall (Figure 3). Pulmonary edema was present in all cases and accounted for the increase

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**Table 2**

Hemodynamic and Metabolic Measurements Before (b) and After (a) Fluid Infusion

<table>
<thead>
<tr>
<th></th>
<th>Survivors (6)</th>
<th>Died (13)</th>
<th>Survivors vs. Died</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>a</td>
<td>P</td>
</tr>
<tr>
<td>Mean arterial pressure, torr</td>
<td>75.1*</td>
<td>74.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>±6.1</td>
<td>±1.58</td>
<td>4</td>
</tr>
<tr>
<td>Central venous pressure, torr</td>
<td>6.6</td>
<td>7.6</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>±1.81</td>
<td>±1.49</td>
<td>1.24</td>
</tr>
<tr>
<td>Heart rate, beat/min</td>
<td>96.0</td>
<td>87.0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>±7.0</td>
<td>±9.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Cardiac index, liter/min./m²</td>
<td>1.49</td>
<td>2.77</td>
<td>&lt;01</td>
</tr>
<tr>
<td></td>
<td>±0.25</td>
<td>±0.32</td>
<td>0.15</td>
</tr>
<tr>
<td>Stroke volume, ml/beat</td>
<td>28.0</td>
<td>62.0</td>
<td>&lt;05</td>
</tr>
<tr>
<td></td>
<td>±4.53</td>
<td>±10.0</td>
<td>2.78</td>
</tr>
<tr>
<td>Central blood volume, liters</td>
<td>1.38</td>
<td>1.87</td>
<td>&lt;05</td>
</tr>
<tr>
<td></td>
<td>±0.17</td>
<td>±0.18</td>
<td>0.21</td>
</tr>
<tr>
<td>Peripheral resistance, dynes sec. cm⁻²</td>
<td>2659</td>
<td>1280</td>
<td>&lt;05</td>
</tr>
<tr>
<td></td>
<td>±683</td>
<td>±190</td>
<td>380</td>
</tr>
<tr>
<td>Lactate, mM/liter</td>
<td>2.32</td>
<td>1.32</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>±0.75</td>
<td>±0.24</td>
<td>1.42</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

---

**Table 3**

Intravascular Volumes Before (b) and After (a) Fluid Challenge

<table>
<thead>
<tr>
<th></th>
<th>Survivors (6)</th>
<th>Died (13)</th>
<th>Survivors vs. Died</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>a</td>
<td>P</td>
</tr>
<tr>
<td>Plasma volume, ml/kg</td>
<td>41.1*</td>
<td>57.1</td>
<td>&lt;05</td>
</tr>
<tr>
<td></td>
<td>±3.3</td>
<td>±4.4</td>
<td>4</td>
</tr>
<tr>
<td>Total blood volume, ml/kg</td>
<td>70.4</td>
<td>80.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>±4.8</td>
<td>±4.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>45.6</td>
<td>32.0</td>
<td>&lt;01</td>
</tr>
<tr>
<td></td>
<td>±2.9</td>
<td>±1.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
Table 4

<table>
<thead>
<tr>
<th>Period of observation hr</th>
<th>Total intake ml</th>
<th>Total output ml</th>
<th>Fluid balance ml</th>
<th>Plasma volume % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>4027* ± 701</td>
<td>2160 ± 809</td>
<td>+1867 ± 739</td>
<td>+39 NS</td>
</tr>
<tr>
<td>Died (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1765 ± 582</td>
<td>451 ± 208</td>
<td>+1341 ± 408</td>
<td>0 NS</td>
</tr>
<tr>
<td>*Mean ± SEM.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P: Survivors vs. died <0.025 <0.025 NS <0.05

in lung weight. Since neither plasma volume nor urine output was increased during fluid infusion in the fatal cases, these findings provide evidence that at least part of the fluid was sequestered in the lungs. The observed increases in heart weight are indicative of preceding cardiac hypertrophy.

Discussion

Measurements of intravascular volumes with radioisotope techniques in patients with low output states have been performed in this laboratory for more than ten years. In 1967, Ryström et al.\(^1\) reported on observations based on 25 patients in shock in whom measurements of plasma volume and red cell mass had been performed. They confirmed that the delayed mixing of the tracer material did not invalidate the use of the dilution technique. An important feature of this technique is extrapolation after multiple sampling over a period of 45 minutes, when mixing of the tracers has been

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Figure 3

The change in the organ's weight (gm) is expressed as a percentage of the predicted value, based on the patient's weight at autopsy. Numbers at the bottom represent the predicted values.
completed. In the present series, we also confirmed the observations of Albert et al. in that the values of estimated total blood volume based on measurements of plasma volume and hematocrit correlated well with those obtained from separate measurement of plasma volume and red cell mass.

The plasma volume in 12 healthy normal volunteers previously studied in this laboratory ranged from 39 to 57 (mean 47.0 ± 6.43 S.D.) ml/kg. In comparison to these norms, the patients included in this study did not have a significant reduction in plasma volume. Even though plasma volume was normal in five of six survivors, an increase in cardiac index, stroke volume, and central blood volume and a reduction in peripheral resistance and lactic acidosis followed fluid infusion and expansion of the plasma volume. The increase in blood volume was associated with improved cardiac performance and peripheral perfusion.

The possibility that hypovolemia contributes to perfusion failure and the clinical manifestations of circulatory shock has been based almost entirely on the assumption that the response to volume repletion is by itself indicative of an intravascular volume deficit. At least two alternate explanations present themselves: (a) There may be an alteration in the capacitance of the vascular compartment rather than a quantitative deficit of volume and this may account for the beneficial response to volume loading. This explanation, previously cited by our group, invokes the concept of a disproportion between vascular volume and vascular capacitance. This alternate explanation is more consistent with previous reports by Smith et al. and Freis et al. who, like we, measured blood volume in patients after acute myocardial infarction and found it to be within a normal range or slightly reduced. (b) Therapeutic effect of volume infusion may also be explained by direct effects on myocardial performance which stem from the resulting increases in the preload on the heart. Russell et al. and Crexells et al. have previously observed that in patients with acute myocardial infarction increases in left ventricular filling pressures to levels of 14 to 24 mm Hg may substantially increase cardiac performance. Although other investigators have reported that increases in blood volume are associated with increases in left ventricular filling pressure, this can only be inferred in our patients in the absence of left ventricular pressure measurements.

Of the results herein reported, of central significance is the failure to expand volume in the patients who died. Even though a positive fluid balance was demonstrated following fluid administration, we have evidence that the fluid leaked from the intravascular space, and was sequestered, at least in part, in the lungs. The observed increases in central blood volume in survivors, but not in fatal cases, provide additional support for this mechanism.

Hyperactivity of the sympathetic nervous system, through an increase in hydrostatic capillary pressure, promotes egress of plasma from the intravascular compartment, thereby decreasing the intravascular volume. On the other hand, sympathetic blockade induces augmentation of the blood volume. Frye et al. demonstrated that in normal individuals who received large amounts of fluids intravenously, the cardiac output was increased only when sympathetic blockade had been previously established. The increased peripheral resistance among the fatal cases in our series in part reflects augmented sympathetic activity associated with a marked reduction in cardiac output. It is likely that the failure to increase plasma volume in response to fluid load is explained by the increased endogenous and neural sympathetic activity, as suggested by Frye et al. Both survivors and patients who died received metaraminol. Although the dosage was only slightly greater among patients who died, we cannot exclude the possibility that this also may have been a factor in limiting plasma volume expansion. The fluid which leaves the intravascular compartment accumulates in the interstitial space and appears as edema. The site of edema is largely determined by colloidal and hydrostatic pressures. When left atrial pressure is increased, the fluid accumulates as pulmonary edema and this would explain the selective increase in lung weight observed at autopsy in the fatal cases.

The present data must be cautiously interpreted with respect to the relationship between volume expansion and survival. The survivors had a lower incidence of previous myocardial infarction and congestive heart failure and the extent to which left ventricular function was impaired prior to the acute episode of infarction may be a major factor accounting for survival. Lactate values at the time of admission also were lower among survivors, indicating lesser severity of perfusion failure prior to institution of treatment. It is apparent from our data that circulatory failure following acute myocardial infarction may be reversed in some patients by volume expansion. In this series, five of the 19
patients (266) had an increase in plasma volume following fluid infusion and all survived. We are left with the observation, therefore, that an expansion of intravascular volume is associated with survival, but the extent to which exogenous fluid loads are ultimately beneficial should be the subject of more conventional double-blind studies.

Acknowledgment

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