Blood Volume Prior to and Following Treatment of Acute Cardiogenic Pulmonary Edema

JAIME FIGUERAS, M.D., AND MAX HARRY WEIL, M.D., PH.D.

SUMMARY Following onset of acute cardiogenic pulmonary edema in 21 patients, increases in hematocrit, plasma protein concentration, and colloid osmotic pressure were associated with decreases in plasma volume. Accordingly, there was a loss of hypo-osmotic fluid into the extravascular spaces. Following treatment with oxygen, furosemide, and morphine sulfate and reversal of clinical and radiographic signs of pulmonary edema, declines in hematocrit, plasma protein concentration, and colloid osmotic pressure were associated with increases in plasma volume. Hypo-osmotic edema fluid was therefore reabsorbed into the vascular compartment.

The concept that acute heart failure with pulmonary edema is associated with an increase in intravascular volume is therefore not supported. To the contrary, there is a reduction of blood volume during acute pulmonary edema. During reversal of acute pulmonary edema with diuresis, there was re-expansion rather than contraction of blood volume.

DURING HEART FAILURE in which there is a rise in left ventricular filling pressure and secondarily in mean left atrial and pulmonary artery pressures and pulmonary blood volume, hydrostatic forces account for increased pulmonary capillary filtration with extravasation of fluid into the interstitium and subsequently into the alveoli of the lung. At the same time, renal and endocrine mechanisms account for salt and water retention. Acute cardiogenic pulmonary edema (PE) has been attributed, at least in part, to retention of fluid, increases in plasma volume, and consequently increases in the preload on the heart.\(^1\) However, acute cardiogenic pulmonary edema is associated more often with increases than decreases in hematocrit and plasma protein concentration.\(^2\) The changes would be more consistent with a decrease rather than an increase in plasma volume. In the present study, intravascular volumes were measured during cardiogenic pulmonary edema to quantitate plasma and total blood volumes following onset of acute pulmonary edema.

Loop diuretics have been remarkably effective for immediate management of cardiogenic pulmonary edema.\(^6\) However, the mechanisms by which the diuretic agents produce their favorable effects are not securely established. The most widely held concept has been that potent diuretics like furosemide re-establish cardiac competence by decreasing intravascular volume during the course of diuresis.\(^9\) Preload would therefore be decreased and the effective workload on the heart would be reduced. However, in the present studies, measurements of intravascular volume after treatment with oxygen, morphine, and furosemide demonstrated an expansion rather than contraction of the intravascular volume.

Methods

Patients

Studies were performed in 21 patients, 11 men and 10 women, ranging from 44 to 83 (median 67) years in age. In 16 of the patients, PE was observed at the time of admission to the Center for the Critically Ill and in five patients, PE appeared during the course of in-patient care. Each patient presented with acute onset of respiratory distress, orthopnea, and unequivocal evidence of myocardial disease.
Bilateral moist rales and radiographic signs of grade 3 or 4 pulmonary edema, according to the criteria of Turner, Lau, and Jacobson, were documented in each instance. In 11 patients, there was expectoration of frothy fluid. Patients who had evidence of bleeding, clinical signs of shock, or patients who had either colloid infusions or blood transfusions were excluded.

Previous history of acute pulmonary edema was elicited in nine of the 21 patients; 11 patients had been treated with diuretics prior to the occurrence of acute pulmonary edema; and six patients had evidence of peripheral edema on admission. In two instances acute myocardial infarction was subsequently demonstrated by electrocardiographic and enzyme changes. Clinical data are summarized in table 1.

The initial set of measurements were obtained immediately after referral to the Center for the Critically Ill from either the emergency department or general medical services following onset of acute PE. Oxygen was the only agent administered prior to the initial set of measurements. A second set of measurements was obtained between 4 and 12 hours after admission in each of the patients. A third set of measurements was obtained between the 12th and 36th hour in a subgroup of ten of the patients. Except for one patient who succumbed within 30 hours following initial measurements, all patients responded favorably to treatment and were discharged from the hospital.

Treatment included oxygen administered by rebreathing mask, ventimask, or nasal prongs in oxygen concentrations ranging from 28 to 60 (mean 40) %. After an initial set of measurements had been obtained, morphine sulfate was injected intravenously in bolus doses ranging from 2 to 5 mg with total dose ranging from 5 to 15 mg until acute anxiety was relieved. Furosemide was administered by intravenous bolus injection in amounts of 40 or 80 mg. Additional doses of 40 or 80 mg of furosemide were administered after 1 hour in the absence of a diuretic response. The total dose of furosemide during the initial 24 hours of management ranged from 40–160 (mean 71.4) mg.

Thirteen healthy volunteer physicians, nurses, or technicians in whom plasma volume was measured after at least 3 hours of bed rest, constituted a reference (group 1) for comparison of intravascular volume. The volunteers, 10 men and 3 women, ranged from 19 to 34 (median 25) years in age.

Fifty additional patients, 24 men and 26 women ranging from 22 to 86 (median 62) years in age served as a second reference group (group 2). These patients were referred to our Center for the Critically Ill for emergency care and admitted for observation because of chest pain. None had clinical or radiographic evidence of heart failure or PE. Acute myocardial infarction was subsequently excluded in each patient on the basis of sequential electrocardiographic and enzyme studies. There were no complicating illnesses or deaths prior to hospital discharge.

Methods

Arterial blood pressure was directly measured following catheterization of the femoral artery by percutaneous methods previously described in four patients, or indirectly by sphygmomanometer in 17 patients. Samples of arterial blood were obtained by percutaneous puncture of the femoral artery or from the arterial catheter. Duplicate measurements of the pH of arterial blood (pH), arterial oxygen tension (PaO2), arterial carbon dioxide tension (PaCO2), oxygen saturation (SaO2), hematocrit, total plasma protein concentration, plasma colloid osmotic pressure, plasma osmolality, plasma sodium, plasma potassium and arterial blood lactate (lactate) were obtained on a single sample of 6 ml of heparinized blood.

Arterial blood gases were measured by standard electrode technique utilizing a Radiometer Model pH M 27 System. Oxygen saturation was measured with an Instrumentation Laboratory Cooximeter Model 182. Hematocrit was measured by microhematocrit technique. Total protein concentration was estimated by refractometry (American Optical Refractometer TS meter Model 10400). Plasma colloid osmotic pressure was measured with a transducer-membrane system by methods previously described. Plasma osmolality was determined by freezing point depression utilizing an Advanced Digimatic Osmometer Model 3D. Plasma sodium and potassium were measured with an IL Flame Photometer Model 143. Arterial blood lactate was analyzed by an automated technique developed in our laboratory.

Plasma volume (PV) was measured in each case using radio-iodinated human serum albumin (RI125SA). Red cell mass was measured on 15 occasions in 14 patients using 51Cr labeled autologous red blood cells. Isotope activity was determined at intervals of 15, 25, 35, and 45 min after injection of the tracer with subsequent extrapolation of the radioactive counts to zero time by methods previously reported.

Total blood volume (TBV) was estimated from the plasma volume and hematocrit with appropriate corrections as follows:

\[
TBV = \frac{PV \times 100}{100 - (Hct \times 0.87)}
\]

in which 0.87 represents the combined correction factor for

<table>
<thead>
<tr>
<th>Pt/Age/Sex</th>
<th>Etiology</th>
<th>Complications</th>
<th>Radiographic pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/S.H./70/M</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>2/M.K./59/F</td>
<td>ASHD</td>
<td>DM</td>
<td>4+</td>
</tr>
<tr>
<td>3/N.A./69/M</td>
<td>CM</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>4/F.K./75/M</td>
<td>ASHD</td>
<td>CLD</td>
<td>4+</td>
</tr>
<tr>
<td>5/L.S./83/F</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>6/G.M./67/M</td>
<td>CM</td>
<td>DM</td>
<td>4+</td>
</tr>
<tr>
<td>7/T.A./69/M</td>
<td>HHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>8/E.W./81/F</td>
<td>ASHD</td>
<td></td>
<td>3+</td>
</tr>
<tr>
<td>9/L.Z./67/F</td>
<td>HHD</td>
<td></td>
<td>3+</td>
</tr>
<tr>
<td>10/D.W./55/F</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
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<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
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<td>HHD</td>
<td></td>
<td>3+</td>
</tr>
<tr>
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<td>ASHD</td>
<td></td>
<td>3+</td>
</tr>
<tr>
<td>14/J.C./67/M</td>
<td>ASHD</td>
<td>CLD</td>
<td>4+</td>
</tr>
<tr>
<td>15/J.H./72/F</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>16/M.J./65/F</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
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<tr>
<td>17/P.V./81/F</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>18/F.B./57/F</td>
<td>ASHD</td>
<td>DM</td>
<td>3+</td>
</tr>
<tr>
<td>19/D.C./53/M</td>
<td>CM</td>
<td></td>
<td>3+</td>
</tr>
<tr>
<td>20/M.D./59/M</td>
<td>ASHD</td>
<td></td>
<td>4+</td>
</tr>
<tr>
<td>21/J.H./50/M</td>
<td>HHD</td>
<td></td>
<td>4+</td>
</tr>
</tbody>
</table>

* = Non-survivor.

† According to criteria of Turner et al. A

Abbreviations: ASHD = arteriosclerotic heart disease; HD = hypertensive heart disease; CM = myocardial infarction; DM = diabetes mellitus; CLD = chronic lung disease.
"trapped" plasma (0.96) and the ratio of peripheral to central hematocrit (0.91). Hematocrit was measured in duplicate and in no instance was the difference between duplicate measurements greater than one percent. The plasma volume was measured on 34 occasions in the 21 patients. Because of the relatively prolonged periods of time required for intravascular equilibration of the radioactive tracer following intravenous injection, blood volume was measured prior to treatment in only six of the 21 patients. In the remaining 15 patients, blood volumes were computed from subsequent measurements on the basis of changes in hematocrit. Adjustments were made for the volumes of blood which had been removed for laboratory testing. The following formula was derived for this purpose:

\[
P V_1 = \frac{P V_2}{1 - H c t_2 \cdot 0.87} - P V_2 + B \cdot H c t_1 \cdot 0.96 \left(1 - H c t_1 \cdot 0.87\right)
\]

(2)

in which \( P V_1 \) represents the initial plasma volume in ml/kg. \( P V_2 \) represents measured plasma volume on a subsequent occasion in ml/kg. \( H c t_1 \) and \( H c t_2 \) represent corresponding values of measured hematocrit expressed as decimals. \( B \) represents total volume of blood withdrawn for laboratory testing in the time interval between measurements 1 and 2 (averaging 95 ml). Since the largest volume withdrawn was in close time proximity to the initial measurement of hematocrit, \( H c t_1 \), was used for adjustment of effects of blood removal. The correction factor of 0.87 represents adjustment for the combined effects of trapped plasma and the ratio between peripheral and central hematocrit. Total blood volume was then computed with formula (1). In four instances, \( P V_2 \) was computed from \( P V_1 \) in an analogous manner:

\[
P V_2 = \frac{P V_1}{1 - H c t_1 \cdot 0.87} - P V_1 - B \cdot H c t_1 \cdot 0.96 \left(1 - H c t_2 \cdot 0.87\right)
\]

(3)

\( H c t_2 \cdot 0.87 \)

The applicability of these computations was empirically tested as part of the investigation. In six patients measurements of plasma volume were available on two consecutive occasions, immediately after admission and on a second occasion after an interval of 4 to 10 hours. The differences between measured plasma volume and the plasma volume computed from changes in hematocrit with formula (2) were compared for purposes of this validation.

The estimate of total blood volume based on measurement of plasma volume and hematocrit was separately validated. The total blood volume representing the sum of the measured plasma volume, and red cell mass was compared to the total blood volume derived from measurement of plasma volume and hematocrit by formula (1) on 15 occasions.

Statistical analysis of differences between the measurements on 21 patients and the two control groups was by Student's \( t \)-test for unpaired observations. Differences between initial measurements and measurements after reversal of pulmonary edema on the 21 patients were analyzed by the Student's \( t \)-test for paired observations.

Results

Comparison of Measured and Computed Values of Plasma and Blood Volume

In the six patients in whom plasma volume was measured consecutively within an interval of 4 to 10 hours, the measured plasma volume on the first occasion was 41.0 ± 4.7 ml/kg (mean ± SEM) and the volume computed by formula (2) was 39.6 ± 2.9 ml/kg (fig. 1). The correlation between measured plasma volume and plasma volume estimates computed from the changes in hematocrit was \( r = 0.95 \). These observations provide evidence that changes in hematocrit may be utilized for calculation of changes in plasma volume in this context.

The total blood volume computed as the sum of 15 separate measurements of plasma volume and red cell mass averaged 62.4 ± 2.7 ml/kg. Total blood volume computed from plasma volume and hematocrit formula (1) averaged 61.9 ± 2.8 ml/kg. These differences were not statistically significant (fig. 2). The correlation coefficient between measured and computed blood volume was \( r = 0.90 \). These
TABLE 2. Initial Plasma and Total Blood Volumes (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Plasma vol. (ml/kg)</th>
<th>Total blood vol. (ml/kg)</th>
<th>Het. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(group 1)</td>
<td>13</td>
<td>44.6 ± 1.4</td>
<td>73.3 ± 2.3</td>
<td>42.9 ± 0.9</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>21</td>
<td>36.6 ± 1.7*</td>
<td>60.6 ± 2.6*</td>
<td>45.1 ± 1.7</td>
</tr>
</tbody>
</table>

*P <0.005, control vs PE.

Initial Measurements

The values of the initial total blood volume (TBV) and plasma volume (PV) in patients with acute PE were compared to those of reference group 1 (table 2). Differences between the two groups were highly significant. In 17 of the 21 patients the TBV was less than 70 ml/kg and in 16 patients the plasma volume was less than 38 ml/kg, indicating a significantly lower vascular volume. There were no significant differences in the parameters measured or calculated between nine patients with prior history of acute pulmonary edema and the 12 patients in whom pulmonary edema occurred for the first time. There were also no significant differences in these parameters between the 11 patients who had been previously treated with diuretics and the remaining ten patients. The reduction in total blood and plasma volumes was associated with an increase in total protein concentration of plasma and in the plasma colloid osmotic pressure which were significantly larger than reference group 2 (table 3).

Effects of Therapy

Following treatment, heart rate declined significantly but a concurrent decrease in arterial pressure was not statistically significant. Reversal of clinical signs of pulmonary edema was paralleled by increases in arterial oxygen saturation to normal values and a significant reduction in PaCO2 and arterial blood lactate with reversal of acidemia (table 4). Although urine output exceeded fluid intake by 1053 ± 143 ml, hematocrit declined, plasma volume was significantly increased, and the total protein concentration and colloid osmotic pressure were significantly decreased (fig. 3 and table 5). Weak associations between changes in plasma volume and changes in total protein (r = -0.460), changes in COP (r = -0.644), and changes in hematocrit (r = -0.440) were observed. A decline in plasma osmolality was observed between the initial and second measurement (306 ± 3.1 vs 297 ± 3.2 mOsm/kg, P < 0.005), but plasma sodium and potassium were not significantly changed (table 4).

In the ten patients in whom a third set of measurements was available, an additional increase in plasma volume and a further reduction in total protein and colloid osmotic pressure were observed. However, only the differences between the initial and third measurements were statistically significant (table 6). The relationships between plasma volume, colloid osmotic pressure, and hematocrit during reversal of pulmonary edema in these ten cases are graphically shown in figure 4.

Discussion

In patients with chronic heart failure and especially in the presence of generalized edema, prior investigations have demonstrated either increases in intravascular volume or no consistent changes. During acute cardiogenic pulmonary edema, however, blood volume is more frequently reduced. In 16 of the 21 patients herein reported, the

TABLE 3. Initial Colloid Osmotic Pressure (COP), Total Protein (TP) and Hematocrit (Hct) (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>COP (mm Hg)</th>
<th>TP (g/dl)</th>
<th>Hct %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>50</td>
<td>23.5 ± 0.4</td>
<td>7.1 ± 0.1</td>
<td>41.7 ± 0.8</td>
</tr>
<tr>
<td>(group 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>21</td>
<td>26.7 ± 0.7**</td>
<td>8.1 ± 0.2**</td>
<td>45.1 ± 1.7*</td>
</tr>
</tbody>
</table>

**P <0.001, control vs PE.

*P <0.005, control vs PE.

PLASMA VOL ml/kg
TOTAL PROT gm/dl
PLASMA ONCOTIC PRESS mm Hg

FIGURE 3. Comparison of plasma volume, total protein, and plasma oncotic (colloid osmotic) pressure in reference groups (C) and in patients with acute cardiogenic pulmonary edema before (I) and following (Rx) treatment.
initial volume measured or calculated after onset of acute dyspnea demonstrated a lower than normal intravascular volume. To this extent, volume changes during acute pulmonary edema differ from those which were observed during chronic congestive heart failure.

The mechanism by which volume is depleted during acute pulmonary edema may be clarified, in part, from concurrent measurements of hematocrit, total protein, and colloid osmotic pressure. Hematocrit, plasma total proteins, and colloid osmotic pressure were greater than those observed in the reference groups prior to reversal of pulmonary edema. Accordingly, plasma water had been removed from the intravascular compartment. The evidence points to extravasation of fluid from the intravascular compartment that is low in colloid content. The likelihood that this represents, at least in part, fluid which is extravasated into the lung is consistent with observations on the protein content and colloid osmotic pressure of pulmonary edema fluid. In a group of patients with frothy pulmonary edema recently studied in our center, as much as one-half liter of fluid was collected during endotracheal suction within an interval of less than 30 min. The colloid osmotic pressure of this fluid averaged approximately one-half of the colloid osmotic pressure plasma, a level which is consistent with values of total protein in pulmonary edema fluid previously reported by Katz and his co-workers. The amounts of fluid extravasated during pulmonary edema may exceed 2 liters in the adult. Extravasation of this fluid into the lung is trace to increases in capillary hydrostatic pressure in excess of colloid osmotic pressure in consequence of increases in left ventricular filling pressure. Accordingly, the loss of substantial volumes of hypo-oncotic fluid into the lung would explain a reduction in volume and the increases in hematocrit and plasma protein concentrations observed by us.

Decreases in intravascular volume may also stem from increases in capillary filtration pressure in the systemic circuit in consequence in increases in right atrial filling pressure and increases in venous tone during heart failure. Muscular exercise in the struggling patient with or without heart failure, fluid losses associated with hyperventilation, and the extravasation of fluid related to the secretion of large amounts of endogenous catecholamines may also be cited as additional causes for volume depletion.

Effects of Therapy

All but one patient promptly improved following treatment with oxygen, morphine, and furosemide. Reversal of pulmonary edema was associated with highly significant decreases in hematocrit, colloid osmotic pressure, and total protein. An increase in plasma volume was confirmed in 14 of the 21 patients.

The present observations on patients with acute heart failure contrast to those reported by Davidov, Kakaviatos, and Finnerty in five patients with chronic congestive heart failure. Their patients had long-standing congestive heart failure with generalized edema which had been refractory to both thiazide and organomercurial diuretic agents. Plasma volume was initially increased. After furosemide diuresis, a decrease in plasma volume and an increase in hematocrit were observed. Similar observations were made by Ramirez and Abelmann in five patients with chronic heart failure. This differs from the present group of patients in whom pulmonary edema appeared as an acute event.

Following administration of the diuretic agent, intravascular volume was expanded over a mean period of 7.4 hours, a time interval during which fluid excretion exceeded fluid intake by more than 1 liter. The findings suggest that the rate of fluid refill into the intravascular compartment exceeded the net volume of fluid excreted in the urine.

Since three agents were used for treatment, namely oxygen and morphine in addition to furosemide, the role of each individual drug is not clarified. However, recent observations by Dikshit, Vyden, Forrester et al., and Mond, Hunt and Sloman are pertinent. These workers demonstrated hemodynamic effects of furosemide which were not directly related to its diuretic action. Within 15 min after administration of furosemide, an increase in venous capacitance was associated with a significant decrease in left

**Table 5. Changes in Plasma Volume, Hematocrit (Hct), Total Protein (TP), Colloid Osmotic Pressure (COP), and Net Fluid Loss After an Average Interval of 7.4 ± 0.6 Hours of Treatment in 21 Patients with Acute Pulmonary Edema (mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Prior</th>
<th>Following</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume, ml/kg</td>
<td>38.6 ± 1.7</td>
<td>40.6 ± 2.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hct, %</td>
<td>45.1 ± 1.7</td>
<td>41.5 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP, g/dl</td>
<td>8.1 ± 0.2</td>
<td>7.3 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COP, mm Hg</td>
<td>26.7 ± 0.7</td>
<td>22.4 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine output-fluid intake</td>
<td>1053 ± 143</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6. Changes in Plasma Volume, Hematocrit (Hct), Total Protein (TP), Colloid Osmotic Pressure (COP), and Net Fluid Loss after an Average Interval of 21.3 ± 2.1 Hours of Treatment in 10 Patients with Acute Pulmonary Edema (mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Prior</th>
<th>Following</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume, ml/kg</td>
<td>37.2 ± 2.9</td>
<td>43.1 ± 2.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hct, %</td>
<td>42.8 ± 1.9</td>
<td>36.7 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP, g/dl</td>
<td>8.2 ± 0.3</td>
<td>6.9 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COP, mm Hg</td>
<td>26.1 ± 0.9</td>
<td>21.5 ± 1.0</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Urine output-fluid intake</td>
<td>2823 ± 848</td>
<td></td>
<td></td>
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</table>

**Figure 4. Sequential changes in total blood volume, plasma volume, hematocrit, total protein concentration, plasma oncotic pressure (colloid osmotic) pressure and net fluid loss in ten patients with acute cardiogenic pulmonary edema during the course of therapy.**

ventricular filling pressure. Moreover, reversal of pulmonary edema following administration of furosemide may occur in the absence of diuresis. The fall in left ventricular filling pressure may be related to increased venous compliance, sequestration of blood in the venous capacitance bed, and therefore a decrease in preload.

Morphine has a similar effect in that it also acts to increase venous capacitance. Oxygen reduces pulmonary vascular resistance stemming from hypoxia, and therefore reduces the workload on the right ventricle. The effects on venous capacitance also favor a reduction in venular and small vein pressure and, accordingly, they account for a reduction in capillary hydrostatic pressure. Because colloid osmotic pressure is increased, the net hydrostatic-oncotic gradient favors capillary refill. Experimentally, furosemide also increases thoracic lymph flow and thereby augments intravascular volume. Since the fluid which is returned into the intravascular compartment has a colloid content which is only a fraction of that of plasma, concurrent reduction in plasma total proteins, colloid osmotic pressure and hematocrit would be anticipated and were, in fact, found. To this extent our results are in close agreement with the case reported by Biagi in which dramatic improvement of acute pulmonary edema after administration of furosemide was associated with a 12% decline in the hematocrit in the absence of diuresis.

Both physical exertion in the struggling patient during acute pulmonary edema and bed rest following hospitalization may affect vascular volume. In cardiac patients Iseri demonstrated a decrease in plasma volume during exercise and a return to control levels after 30 min of rest. Therefore, reduction in intravascular volume observed during acute pulmonary edema may be accentuated by the physical struggle and increased work of breathing. Bed rest in itself, on the other hand, accounts for a decrease in plasma volume following a transient initial increase. This reduction in plasma volume can already be appreciated after 6 hours of bed rest. The absence of such a decline in plasma volume in the patients who are the subject of this report and who were at bed rest lends further credence to our observations. We therefore conclude that plasma volume is more often re-expanded rather than contracted during a 36 hour interval of therapy during which diuresis with reversal of acute cardiogenic pulmonary edema is documented.

Acknowledgments

The collaboration of Drs. Vinod Puri, William French, and Richard Carlson, and Ms. Sybil Michaels in the design and execution of these studies is gratefully acknowledged. Mr. Lawrence Portigal provided statistical consultation.

References

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The Rate of Atherosclerosis Change during Treatment of Hyperlipoproteinemia

DAVID H. BLANKENHORN, M.D., SAMUEL H. BROOKS, D.Sc., ROBERT H. SELZER, M.S., AND ROBERT BARNDT, JR., M.D.

SUMMARY The rate of change of femoral atherosclerosis has been determined in 25 treated hyperlipoproteinemic patients. There were 13 Type II patients and 12 Type IV patients. Serial angiograms had been performed at an interval averaging 13 months. Film densities were analyzed by digital image processing to yield a computer estimate of atherosclerosis (CEA). Serial measurements of CEA on each patient were used to determine atherosclerosis percent change per month in that patient. CEA percent change per month was significantly correlated with triglyceride and cholesterol level. Lower lipid levels were associated with more rapid regression. When hyperlipoproteinemic types were considered separately, significant single correlations were confined to Type IV. Triglyceride level and CEA/age significantly predicted atherosclerosis change rate and accounted for 72% of the variability observed in Type IV patients.

This paper presents information regarding rate of change of human femoral atherosclerosis during treatment of hyperlipoproteinemia. The estimates we report were obtained by assessment of two angiograms separated by an interval of approximately 13 months. Experiments of others with hyperlipoproteinemic animals suggest that change in fatty streaks can be detected in as short a period as eight months after alteration of lipid levels and is followed by change in more advanced plaques. To obtain this information, test and control animals have been sacrificed for direct examination of vessels at intervals after inducing or relieving hyperlipoproteinemia. Directly comparable experiments are not possible in man and what is known of blood lipid effect on atherosclerosis has been deduced from a few studies employing angiography plus many studies where lesions have been evaluated indirectly through atherosclerosis-related end points.

Interpretation of lipid lowering intervention trials, such as the Coronary Drug Project, Minnesota Coronary Survey, and Lipid Research Clinic Primary Prevention Trial, is ambiguous in regard to atherosclerosis change because myocardial infarction is the major end point studied. Myocardial infarction can occur when atherosclerosis becomes more severe and also when thrombosis is superimposed on unchanged atherosclerotic lesions. Myocardial infarction can occasionally occur when coronary arteries appear normal. The occurrence of myocardial infarction implies that vascular insufficiency has grown worse. There is no corresponding end point which can imply that vascular insufficiency has improved. This makes intervention trials based on myocardial infarction insensitive to changes which might follow atherosclerosis improvement. More direct information regarding human atherosclerosis change is desirable and now can be obtained from femoral angiograms. The information we report here reflects directly measured change in lesion state with equal sensitivity to change in either direction — regression or progression. A limitation in interpreting the results we present is that the relationship of femoral lesion change to long-term cardiovascular mortality rate is not known.

In a previous report we presented evidence that femoral atherosclerosis as determined by angiography is common in young patients with hyperlipoproteinemia, although they may have few symptoms. We have also reported that the visible extent of vessel wall involvement diminished in nine of these patients among 25 treated for hyperlipoproteinemia and studied by serial angiography. In a separate series of reports we described development of an instrumental method to assess angiograms. This method involves converting an X-ray image recorded on film into a digital array for computer processing using an optical image dissector. Edges of the vessel image are located by analyzing digital data in lines perpendicular to the long axis of the vessel. Irregularities of each vessel edge and densities of the vessel image are analyzed further to provide assessment of atherosclerosis through a combined measure, CEA (computer estimated atherosclerosis), which has previously been calibrated directly against atherosclerosis determined at autopsy. In this report, CEA has been determined on all films previously assessed by human readers and used to estimate rate of change in atherosclerotic lesions for correla-
Blood volume prior to and following treatment of acute cardiogenic pulmonary edema.
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