The Acute Hemodynamic Effects of Ethacrynic Acid and Furosemide in Patients with Chronic Postcapillary Pulmonary Hypertension

STEPHEN M. AUSTIN, M.D., BERNARD F. SCHREINER, M.D., DAVID H. KRAMER, M.D., PRAVIN M. SHAH, M.D., AND PAUL N. YU, M.D.

SUMMARY The acute hemodynamic effects of either ethacrynic acid or furosemide were studied in 27 patients who underwent diagnostic right and transseptal left heart catheterization. Twenty-three patients had postcapillary pulmonary hypertension secondary to isolated or predominant mitral stenosis. Of these, 21 patients were in New York Heart Association functional class III, and one each in class II and IV. In the remaining four patients pulmonary artery pressures were normal. Two patients had aortic stenosis and one each coronary artery disease and nonobstructive cardiomyopathy. All four patients were in class II. Cardiac index, pressures, and pulmonary blood volume (PBV) were measured in the control state and 20, 40, and 60 min after diuretic administration. Pulmonary extravascular fluid volume (PEV) was measured in the control state and at 60 min post drug infusion. A similar hemodynamic response was observed for each drug. Significant reductions in pulmonary artery and left atrial mean pressures, cardiac index, and plasma volume occurred over the one hour observation period and were accompanied by a significant diuresis. However, despite reductions in central pressures and blood flow, PBV, PEV, and PEV/PBV remained unchanged, as did systemic arterial pressure. Since 23 of the subjects had postcapillary pulmonary hypertension it is postulated that the failure of PBV to decrease significantly despite significant decreases in pulmonary artery mean pressure is related to altered pressure volume characteristics in the pulmonary vascular bed in which the lung is operating on a steep portion of its pressure volume curve. The failure of the PEV to decrease supports the concept that the pulmonary extravascular space is relatively resistant to early decreases in pulmonary capillary pressure induced acutely. The failure of the pulmonary extravascular fluid volume to decrease despite a fall in plasma volume and pressures corresponds to the well recognized delay in resolution of radiologic evidence of pulmonary congestion.

THE RAPID AND POTENT DIURETIC EFFECTS of ethacrynic acid and furosemide are well-known. Although chemically dissimilar, both drugs act primarily to inhibit sodium reabsorption in the ascending limb of Henle's loop.1-3 Despite their widespread clinical use, the acute hemodynamic effects of furosemide and ethacrynic acid in the relief of pulmonary congestion and edema are not completely understood. Several studies have demonstrated a decline in pulmonary arterial and left atrial pressures in the presence of postcapillary pulmonary hypertension.4-10 However, in patients with normal pressures no significant changes have been observed.11, 12 Changes in cardiac output have also been variable.4-12 In a few studies plasma volume and pulmonary blood volume have decreased.5, 10-12 It has been suggested that a reduction in left atrial pressure should result in a decrease in pulmonary extravascular fluid volume or lung water (PEV).13 In a previous study from our laboratory, either no change or only a slight decrease in PEV occurred, depending upon whether patients received concomitant fluid replacement.6

The purpose of this study is to further investigate the acute hemodynamic effects of furosemide and ethacrynic acid, particularly the interrelationships among pressures, flow, and volumes in the pulmonary circulation.

Materials and Methods

Twenty-seven adult patients undergoing diagnostic cardiac catheterization were studied. Twenty-three patients had isolated or predominant mitral stenosis; (21 in New York Heart Association functional class (FC) III and one each in FC II and IV). Two patients had valvular aortic stenosis (both FC II), one had coronary artery disease, (FC II) and one had nonobstructive cardiomyopathy (FC II). These four patients had normal pulmonary artery mean (PAm) pressures, while all 23 patients with mitral valve disease had postcapillary pulmonary hypertension. The mean age of the entire group was 42 years. Twenty-two patients were women and five were men. Eighteen patients were on digitalis therapy and 13 received daily oral diuretic. Informed consent was obtained from each patient and no complications were encountered.

All patients underwent right and transseptal left heart catheterization. Cardiac output and pulmonary blood volume were determined in duplicate by the indicator dilution technique, as reported previously from our laboratory.13, 14 Indocyanine green was injected sequentially into the main pulmonary artery and left atrium, with sampling of dye from a brachial artery cannula. Using a program incorporating the Stewart-Hamilton equation, the data were analyzed by an XDS Sigma 3 computer for determination of cardiac output and mean transit time of each curve.

Pulmonary blood volume (PBV) was calculated from the equation:

\[ PBV = CI \times (Tm_{PA/BA} - Tm_{LA/BA}) \]

where PBV = pulmonary blood volume (ml/m²) 
CI = mean cardiac index (ml/sec/m²)
Tm_{PA/BA} = mean transit time of indocyanine green
from pulmonary artery to brachial artery (sec)

\[ T_{\text{d}L-\text{BA}} = \text{mean transit time of indocyanine green from left atrium to brachial artery (sec)} \]

Central blood volume (CBV), that volume from the main pulmonary artery to a systemic artery and all temporally equivalent arterial sites, was calculated from the equation:

\[ \text{CBV} = C\text{I} \times (T_{\text{d}PA-\text{BA}}) \]

Pulmonary extravascular fluid volume was measured by the simultaneous injection of a mixture of radioiodinated serum albumin (RISA) and titrated water (THO), into the main pulmonary artery, according to the method of Chinard and Enns. Sequential samples of 1.5 to 2.0 ml were collected from the brachial arterial cannula at two second intervals. Plasma aliquots were counted in a 3-channel Beckman LS 250 beta scintillation counter, as reported elsewhere. The mean transit time was determined for each indicator, and PEV calculated by the equation:

\[ \text{PEV} = C\text{I} \times (T_{\text{d}THO-\text{PA-BA}} - T_{\text{d}RISA-\text{PA-BA}}) \]

where

- PEV = pulmonary extravascular fluid volume (ml/m²)
- \( C\text{I} \) = mean cardiac index (ml/sec/m²)
- \( T_{\text{d}THO-\text{PA-BA}} \) = mean transit time of THO from pulmonary artery to brachial artery (sec)
- \( T_{\text{d}RISA-\text{PA-BA}} \) = mean transit time of RISA from pulmonary artery to brachial artery (sec)

The observed PEV was multiplied by a correction factor of 0.8, as suggested by Chinard et al., and reported previously from this laboratory.

In order to test the reproducibility of the method, duplicate measurements of PEV over a 15–20 minute period were made in 16 patients not included in the present series, in whom no hemodynamic intervention was performed. The mean value of the entire group of duplicate observations was 138 ml/m², with a standard deviation of ± 15 ml/m², a standard error of the difference of 3.9 ml/m², and correlation coefficient of \( r = 0.96 \). During this period of observation no significant changes occurred in cardiac index, heart rate, PEV, pulmonary artery, left atrial or systemic artery mean pressures. The constancy of these parameters was also investigated in eight additional patients during a control period and after 20 minutes of a sham infusion in a study previously reported from this laboratory. During these sham infusion studies four patients were also observed during a 20 minute "recovery" period during which the hemodynamic parameters remained stable. Furthermore, duplicate PEV determinations in a series of 57 patients previously reported from our laboratory had a standard deviation of 15.6 ml/m² and standard error of the difference of 2.1 ml/m². Triplicate determinations of PEV were also made in 19 patients over a 20 to 40 min period with excellent reproducibility. From these studies we are confident that steady-state conditions can be maintained for periods of 40 min and probably longer.

Plasma volume was determined from RISA blood concentrations ten minutes after each PEV measurement, using an equilibration sample of plasma and a previously prepared standard. Both samples were counted in a Nuclear-Chicago gamma counter.

Pressures were recorded by conventional methods using Statham P23 db transducers and a direct writing oscillograph (Brush Instruments, Model 480). Mean pressures were obtained by electronic integration.

Cardiac index was determined from the average of at least two pulmonary artery and left atrial dye injections performed over a 6–8 min period. The PBV was measured in duplicate during the control period and at each time interval after drug intervention. Prior to the control period dye curves were recorded after injection into both pulmonary artery and left atrium in order to adjust amplifier gain and accustom the patient to the procedure. Left ventricular end-diastolic pressure was also recorded in each patient and found to be normal (<13 mm Hg). Subsequently the catheter was withdrawn to the mid left atrium under fluoroscopic control and was not moved in order to maintain a constant site for left atrial dye injection.

Nine patients received furosemide, 40–60 mg, and 18 patients, ethacrynic acid, 25–50 mg, infused through the pulmonary artery catheter.

The control period averaged 15 min during which patient composure was evaluated by constancy of heart rate, cardiac output, pulmonary artery, left atrial, and systemic artery pressures. At predetermined intervals following diuretic administration the cardiac output was determined in quadruplicate and the PBV in duplicate. In order to avoid blood loss, the blood sampled aseptically in a syringe was re-infused into the patient after each determination. Pressures and heart rate were recorded every five minutes after diuretic administration and before and after each pair of pulmonary artery and left atrial dye curves.

In the majority of patients cardiac index, heart rate, pulmonary artery, left atrial and systemic artery mean pressures, PBV and CBV were measured in the control state and 20, 40, and 60 minutes after drug administration. Pulmonary extravascular volume was determined during the control period and at 40 and 60 minutes after drug administration. At 40 minutes and one hour post diuretic administration PEV and PBV data were available in five and 17 patients respectively. Thus complete data were available in 22 of the 27 patients. In five patients the data were incomplete. In three of these PEV was not determined; in one the PBV was not recorded at 60 min due to inadvertent dislodgment of the transseptal catheter from the left to the right atrium and in the remaining one no PBV was available due to inability to perform a satisfactory transseptal puncture. Paired PEV determinations were available in 24 patients while paired plasma volume measurements were made in 25 patients.

Statistical analysis was performed using the paired \( t \)-test in which each patient served as his own control. Because of the similar pharmacologic effects and time course of diuretic action of furosemide and ethacrynic acid, the data analysis was performed for the entire group.

**Results**

The hemodynamic data for the 27 patients who received either furosemide or ethacrynic acid are summarized in table...
1. The average pulmonary artery mean pressure (PAm) decreased from 36 to 30 mm Hg at 20 min post drug infusion, and thereafter fell to 28 mm Hg by one hour. Compared to the control values the decreases in PAm pressure at 20, 40, and 60 min were each highly significant (P < 0.001). Average left atrial mean pressure (LAm) also decreased from 22 mm Hg during the control period to 18 mm Hg at 20 min and to 15 mm Hg at 60 min post drug infusion (P < 0.001). Similarly, the average pulmonary vascular distending pressure (PD) (the average of the PAm and LAm pressures) declined significantly at each time interval following diuretic administration. Despite the fall in these pressures average systemic artery mean pressure (SAm) was well maintained throughout the study period.

The decrease in PAm and LAm pressures was accompanied by a concomitant fall in cardiac index from 2.62 L/m²/min during the control period to 2.34 L/m²/min at 20 min post drug infusion. This flow level was maintained for the remaining 40 min of observation. Since heart rate did not change, stroke index fell significantly from 33 ml/beat/m² during the control period to 28 ml/beat/m² at 20 min and remained at this level during the remainder of the study.

Calculated pulmonary vascular resistance remained unchanged throughout the periods of observation.

Despite significant decreases in cardiac index, PAm and LAm pressures, there was no significant change in PBV, CBV, PEV or in the ratio of PEV/PBV throughout the study period. However, a substantial diuresis which averaged 850 ml (range 300 to 1390 ml) was observed. This was accompanied by a significant decrease in plasma volume from 1617 to 1499 ml/m² at 60 min post diuretic infusion.

Figure 1 depicts the change in PBV compared to the fall in PAm pressure. The mean change in PBV was from 341 to 321 ml/m², as average PAm pressure fell from 36 to 28 mm Hg. Only the fall in average PAm pressure was significant. However in patients 1, 2, 3, 4, (i.e., two with aortic stenosis and one with nonobstructive cardiomyopathy and one with coronary artery disease) PAm and LAm were normal in the control period and in three of the four diuretics caused a significant fall in PBV (greater than 45 ml/m²) despite only a slight decrease in pressure. In these four patients control PEV averaged 94 ml/m² and fell an average of 34 ml/m² during diuretic intervention. However, plasma volume decreased by an average of 125 ml/m² which was comparable to that observed in the other patients.

### Table 1. Summary of the Hemodynamic Response to Acute Diuresis

<table>
<thead>
<tr>
<th>Condition</th>
<th>CI (L/min)</th>
<th>HR (b/min)</th>
<th>SI (ml/beat/m²)</th>
<th>PAm (mmHg)</th>
<th>LAm (mmHg)</th>
<th>SAm (mmHg)</th>
<th>PD (mmHg)</th>
<th>Volume (ml/m²)</th>
<th>PBV</th>
<th>PEV</th>
<th>CBV</th>
<th>Pl. Vol</th>
<th>PEV/PBV</th>
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<tr>
<td>A (mean)</td>
<td>2.62</td>
<td>83</td>
<td>33</td>
<td>36</td>
<td>22</td>
<td>93</td>
<td>25.9</td>
<td>341</td>
<td>152</td>
<td>644</td>
<td>1617</td>
<td>1617</td>
<td>.42</td>
</tr>
<tr>
<td>(SEM)</td>
<td>(0.10)</td>
<td>(2.6)</td>
<td>(2.9)</td>
<td>(2.4)</td>
<td>(1.3)</td>
<td>(2.6)</td>
<td>(1.8)</td>
<td>(12)</td>
<td>(12)</td>
<td>(27)</td>
<td>(42)</td>
<td>(42)</td>
<td>(.03)</td>
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<tr>
<td>B (mean)</td>
<td>2.34</td>
<td>83</td>
<td>28</td>
<td>30*</td>
<td>18*</td>
<td>95</td>
<td>24.3*</td>
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<td>(SEM)</td>
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<td>(3.7)</td>
<td>(1.8)</td>
<td>(2.7)</td>
<td>(1.5)</td>
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<td>(2.2)</td>
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<tr>
<td>C (mean)</td>
<td>2.30</td>
<td>81</td>
<td>29</td>
<td>31*</td>
<td>17*</td>
<td>94</td>
<td>24.0*</td>
<td>332</td>
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<tr>
<td>(SEM)</td>
<td>(0.09)</td>
<td>(2.1)</td>
<td>(0.5)</td>
<td>(2.9)</td>
<td>(1.3)</td>
<td>(2.8)</td>
<td>(1.9)</td>
<td>(15)</td>
<td></td>
<td></td>
<td></td>
<td>(18)</td>
<td></td>
</tr>
<tr>
<td>D (mean)</td>
<td>2.28</td>
<td>82</td>
<td>29</td>
<td>28*</td>
<td>15*</td>
<td>90</td>
<td>21.8*</td>
<td>321</td>
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<td>(18)</td>
<td>(50)</td>
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<tr>
<td>(SEM)</td>
<td>(0.08)</td>
<td>(3.0)</td>
<td>(0.6)</td>
<td>(2.6)</td>
<td>(1.4)</td>
<td>(3.2)</td>
<td>(1.9)</td>
<td>(13)</td>
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### Discussion

Previous studies from our laboratory in which assessment of control hemodynamic pressures, PBV, and CBV was made during and after sham infusion have clearly demonstrated that a steady state can be maintained for 30-40 min and probably longer under controlled experimental conditions. It is therefore most unlikely that the hemo-

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Changes in pulmonary blood volume (PBV) abscissa are related to mean pulmonary artery pressure (PAm) ordinate before and after administration of the diuretic. The average values in control and post intervention periods are indicated by the heavy squares and the SEM by the short bars. Note that PAm decreases significantly without an appreciable change in PBV. Patients labeled 1-4 had normal PAm pressures. In three of four, diuretic administration was accompanied by significant decreases in PBV and minor falls in PAm.
dynamic changes observed in the present study could be due to the catheterization procedure itself. The decreases in PAm, LAm and cardiac index over a one hour period, but commencing within 20 min of diuretic infusion and accompanied by a significant diuresis and fall in plasma volume, strongly suggest that the observed changes were indeed due to the diuretic effect.

Consideration should also be given to the technique and methodology for the determination of PEV. We have indicated that the reproducibility of duplicate determinations is excellent in 16 patients not included in this study. The standard deviation was approximately ± 10%. This degree of reproducibility is similar to that found by other workers. Duplicate determination during the control and diuretic periods were not made in the present study because collection of relatively large amounts of blood would be required.

Values for PEV in patients with normal hemodynamics and in those with mitral valve disease previously reported from this and other laboratories are summarized in Table 2 (unpublished observations). In 35 normal patients the mean PEV ranged from 84 to 102 ml/m² (sd ± 15–26 ml/m²). It has been observed that in the presence of post-capillary pulmonary hypertension that elevations in PEV are proportional to the elevation in LAm and/or left ventricular diastolic pressure. In patients with mitral stenosis PEV is elevated as functional impairment increases and as LAm pressures rise. As shown in table 2, values for mean PEV vary from 109 in FC II patients to 144 and 158 ml/m² in FC III patients.

In the present study all patients with mitral stenosis had left atrial hypertension which averaged 24 mm Hg and a mean PEV of 161 ml/m². The remaining four patients had normal PAm and LAm pressures and PEV which averaged 94 ml/m². Thus the average PEV value for the entire group was 152 ml/m². The latter value is in agreement with those previously reported by others as well as ourselves and is significantly greater than values obtained in normal subjects (table 2). Although it is difficult to state with certainty the magnitude of PEV alteration which can be reliably measured, it can be estimated from studies of duplicate determinations that "real" changes in PEV would likely exceed two standard deviations or 20%. For patients in this study this would correspond to a deviation of 30 ml/m². However, changes in PEV were less than that magnitude and varied in both plus and minus directions. On the other hand, in another study reported in this issue of 114 patients supine leg exercise or rapid atrial pacing resulted in significant increases in PEV, greater than 35 ml/m² in many instances.

In our patients with postcapillary pulmonary hypertension, administration of ethacrynic acid or furosemide results in a significant and early decrease in pulmonary artery pressure, left atrial pressure, cardiac index and stroke index without accompanying changes in the mean systemic artery pressure. In 16 of the 27 patients a significant fall in pulmonary artery and left atrial mean pressures occurred in less than 20 min after administration of the diuretic. While our over-all findings support the concept that the fall in pressures and cardiac index may be secondary to decreased plasma volume and venous return, it should be pointed out that significant decreases in pressure and cardiac index may occur prior to the maximal diuretic effects of the drugs. In more than one half of our patients a substantial reduction in PAm and LAm pressures was observed within 10 min of drug administration. This finding suggests that another mechanism may be operative in decreasing venous return, such as systemic venodilatation, as proposed by Dikshit and associates. These investigators found a 52% increase in mean calf venous capacitance five minutes after the intravenous administration of furosemide to patients with acute myocardial infarction. Similar peripheral vasodilation have been described for ethacrynic acid in anephric dogs. The findings in the present study also support the thesis that clinical improvement with diuretics in patients with pulmonary congestion appears to result from the reduction in elevated pulmonary vascular pressures which outweigh the potentially deleterious effect of the decrease in cardiac output.

We must reconcile the fact that following diuretic administration, cardiac index and stroke index fell as did PAm, LAm, and PD, while systemic mean pressure, PBV, CBV and PEV remained unchanged despite a significant fall in plasma volume and a significant diuresis. It is conceivable that the failure of the PBV and CBV to decrease may be related to the patients studied, drug dosage employed, or failure to detect real but subtle and statistically insignificant decreases in PBV.

It is unlikely that drug dosage was a factor since in most patients the falls in pressures and cardiac output were accompanied by a significant diuresis. The most likely factor was the patients studied. As noted in figure 1, 14 patients had a reduction in both PAm and PBV, eight had a decrease in PAm associated with a small increase in PBV, and three patients had minimal changes in PAm and PBV. A reduction in both PAm and PBV after diuretic administration would strongly suggest a passive change in the pulmonary vascular pressure volume relationship. This change could be initiated by extrarenal effects of the drugs and maintained by the ensuing reduction in plasma volume. The failure of the PBV to decrease significantly despite the fall in PAm and LAm

<table>
<thead>
<tr>
<th>Table 2. Review of Studies of Pulmonary Extravascular Fluid Volume in Patients with Normal Hemodynamics and Those with Mitral Valve Disease</th>
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<tr>
<td>Author</td>
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<tr>
<td><strong>Normal</strong></td>
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<tr>
<td>McCredie†</td>
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<td>Lilenfield</td>
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<td></td>
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<td>Schreiner</td>
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*Corrected by factor of 0.8.
†Arbitrarily corrected for a BSA = 1.8 m².
Abbreviations: FC = Functional Class (NYHA); LAm = left atrial mean pressure; PEV (ml/m²) = pulmonary extravascular fluid volume in ml/m² body surface area, SD = standard deviation.
pressure may be explained by pressure-volume relationship of the pulmonary vascular bed in patients with chronic left atrial hypertension secondary to mitral valve disease. As shown in previous studies from this laboratory, such patients have compromised pulmonary vascular distensibility and hence are operating on the steep portion of their pressure volume curves. Thus even a small reduction in PBV may result in a significant fall in pulmonary vascular pressure. The changes in pressures observed with diuretics are comparable to those observed in similar patients who undergo a 200-400 ml phlebotomy. Under the latter circumstances PAm and LAm pressures also fell with little or no change in PBV.

This interpretation is further strengthened by the observation made in patients 1 to 4 who had normal pulmonary vasculature. In all instances control PAm and LAm were normal and fell little after diuresis. However PBV decreased by an average of 58 ml/m² while PEV decreased from 94 to 60 ml/m². The data would suggest that these patients were operating on the flat portion of their pulmonary pressure-volume curves, in contrast to the other patients with pulmonary hypertension.

Other investigators have suggested that the combined use of PBV and PEV measurements with calculation of their ratio during the control period and during a given intervention would be helpful in deciding whether or not a change in PEV truly represented a change in the extravascular volume component. For example, we and other investigators have noted that the PEV/PBV in response to supine exercise of rapid atrial pacing for periods of less than 20-30 min does not change (despite absolute increase in both volumes during the intervention). It was postulated that recruitment of pulmonary vascular channels was responsible for the concomitant increase in both PBV and PEV. In the present study the PEV/PBV ratio remained constant after administration of diuretics, further substantiating that neither volume changed independently despite a fall in central pressures and in cardiac index. The relatively small change in PEV in the postdiuretic period suggests delayed mobilization of lung water, and insignificant changes in PBV supports the hypothesis that an elevated PBV is not the sine qua non of "pulmonary congestion." These findings are consistent with the delayed resolution of radiologic evidence of pulmonary congestion following decreases in pulmonary artery wedge pressure to normal levels.

Our results differ from previous studies in that we failed to observe a statistically significant decrease in PBV for all our patients. The patients reported by Samet and Bernstein had normal pulmonary artery and left atrial pressures. In the study done by Bhatia and associates the patients had recovered from high altitude pulmonary edema 3-8 weeks previously and were otherwise healthy. Pulmonary artery and left atrial pressures in these patients were normal. Pulmonary blood volume was also normal in five of the seven patients studied.

The findings in our patients 1-4 are in agreement with these studies, i.e., that in the presence of normal pulmonary artery and left atrial pressure acute administration of diuretics causes a significant fall in PBV but little fall in normal PAm and LAm pressures. It is likely that these patients are operating on the flat portion of their pulmonary vascular pressure volume curves.

In conclusion, administration of potent diuretics may result in reductions of rate of blood flow, stroke index, PAm and LAm pressures and plasma volume without altering systemic arterial pressure, PBV, or PEV. Thus a major action is to reduce central pressures by reducing plasma volume and venous return. These studies have demonstrated that pulmonary extravascular volume in the presence of chronic left atrial hypertension changes rather slowly in response to an acute decrease in pulmonary "capillary" pressure induced over a relatively short period of time.

Acknowledgment

We wish to thank Drs. Donald Logan and John Farnham for their participation in some of these studies and Mr. Dennis Edwards and Mrs. Constance Katos for their expert technical assistance. The nursing skills of Miss Virginia Paddock, R.N., and Mrs. Janice Kucul, R.N., and the secretarial aid of Mrs. Nancy Tripp are gratefully acknowledged.

References

Lung Water and Urea Indicator Dilution Studies in Cardiac Surgery Patients
Comparisons of Measurements in Aortocoronary Bypass and Mitral Valve Replacement

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AND HARVEY W. BENDER, JR., M.D.

SUMMARY We measured transpulmonary indicator dilution curves of 51Cr-erythrocytes, 125I-albumin, 14C-urea, and 3H-water before and six and 24 hours after operation in seven patients undergoing aortocoronary bypass (ACB) and eight patients undergoing mitral valve replacement (MVR). We calculated cardiac output (CO), extravascular lung water (EVLW), the difference between 125I-albumin and 51Cr-erythrocyte distribution volumes (EV albumin), the difference between 14C-urea and 51Cr-erythrocyte distribution volumes (EV urea) and 14C-urea extraction (E) and permeability-surface area (PS) products. Comparisons between 16 ACB studies and 17 MVR studies showed the MVR group to have a higher EVLW (P < 0.01). Extravascular lung water decreased after operation. The ratio of EV urea to EV albumin averaged 1.35 in the MVR group and 0.91 in the ACB group (P < 0.001). 14C-urea E was also higher in the MVR group (P < 0.05), but PS was similar in the two groups. None of the differences was related to the time the studies were done. We showed that EVLW, calculated using both 125I-albumin and 51Cr-erythrocytes as intravascular indicators and measured blood water content, had a constant relationship to EVLW calculated using only 125I-albumin as the intravascular indicator and neglecting blood water content, over a broad range of cardiac outputs, hematocrits, and lung water volumes. We conclude that patients with mitral valve disease have an increased distribution volume and E for urea, probably due to hemodynamic changes but possibly due to increased vascular permeability. Extravascular lung water decreases after cardiac surgery regardless of the type of operation. A single intravascular indicator is adequate for estimating extravascular lung water in humans.

SEVERAL CLINICAL SYNDROMES characterized by respiratory distress and pulmonary edema are thought to result from increased leakage of lung exchanging vessels. A technique capable of detecting increased lung vascular permeability in living humans could contribute substantially to understanding the relationship of this abnormality to lung disease.

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