Transcapillary Escape Rate of Albumin and Right Atrial Pressure in Chronic Congestive Heart Failure before and after Treatment

BIRGER HESSE, M.D., HANS-HENRIK PARVING, M.D., HENRIK LUND-JACOBSEN, M.D., and IVAN NOER, M.D.

SUMMARY The transcapillary escape rate of albumin (TER alb), i.e., the fraction of intravascular mass of albumin that passes to the extravascular space per unit of time, was determined from the disappearance of intravenously injected 111I-labeled human serum albumin during the first 60 minutes after injection in 10 subjects with chronic right heart failure. The investigation was repeated after sodium and water depletion. Before treatment TER alb was significantly elevated (mean 83 ± 1.6%/hour, in comparison to values for normal subjects (mean 5.4 ± 1.1%/hour, P < 0.001). With treatment TER alb decreased significantly (mean 5.9 ± 1.2%/hour, P < 0.01). Right atrial pressure decreased from an average of 10 mm Hg to 6 mm Hg during treatment. A statistically significant, positive correlation was found between TER alb and right atrial pressure (r = 0.77, P < 0.001). Our results best can be explained by increased filtration, mainly through the venous end of the microvasculature, due to the increased venous pressure in heart failure.

THE FINDING of a normal or low protein concentration in edema fluid from subjects with congestive heart failure (CHF) has led to the conclusion that the protein permeability of the capillaries is normal or reduced and thus of no importance in relation to the formation of cardiac edema. However, the use of qualitative, nonkinetic methods to study a dynamic process, viz., the escape of proteins from plasma into the interstitial fluid, is highly questionable. Kinetic methods have yielded conflicting results concerning the microvascular-protein permeability in CHF; some have found a decreased permeability, some a normal permeability, and others have reported a markedly elevated protein permeability. Recently we found the transcapillary escape rate of albumin (TER alb), the fraction of intravascular mass of albumin that passes to the extravascular space per unit of time, to be significantly increased and this change to be accompanied by increases in central venous pressure during acute plasma volume expansion in man. This condition simulates heart failure because intravascular volume is enlarged and filling pressures of the ventricles are elevated. The aim of the present study was to measure the transcapillary escape rate of albumin before and after diuretic treatment of subjects with right heart failure.

Methods The study comprises 10 patients with chronic heart failure referred for hemodynamic investigation. Clinical data are presented in Table 1. All patients except patient 3 were on maintenance treatment with digoxin. Five (patients 1, 5, 6, 8, and 10) received thiazide diuretics at the time of admission. For two of the patients (nos. 5 and 6) the diuretic therapy was stopped 1 week before the first investigation. Then a potent diuretic (bumetanide, 2 mg daily) was given and the second investigation was carried out after 1 or 2 weeks when the patients no longer were losing weight. All the patients had clinical signs of right-sided failure with liver enlargement and intermittent or constant peripheral edema. Three patients (nos. 1, 3, and 8) had gross edema and ascites at the time of their first examination. No patient but no. 7 had hypertension. None had diabetes mellitus or any major
medical or surgical disease other than their heart disease, except patient 6, who had a history of chronic bronchitis. Informed consent of the patients was obtained in each case. Patient 8 was not reexamined until 5 months later, 3 months after pericardectomy. Because pericardectomy had not yet been performed.

The day before the determination of TER_{Hb}, the patients underwent a right-sided heart catheterization according to the routine of our cardiovascular laboratory. The investigative procedure and the theoretical basis for calculation of TER_{Hb} from the initial disappearance rate of labeled plasma albumin has been described in detail previously. Briefly, the patients were studied in the morning after fasting for at least 12 hours and after resting for 30 minutes in the supine position. Human serum albumin labeled electrolytically with ^{125}I (code MIAK, Institute for Atomic Energy, Kjeller, Norway) was used. This tracer preparation contains less than 1.0% free radioactive iodide and has been demonstrated by metabolic studies to behave like endogenous albumin. About 5 $\mu$Ci of the tracer was used for the first investigation and about 20 $\mu$Ci for the second. The tracer was injected into one arm vein, and nine venous blood samples, each of 6 ml, were drawn from the other arm 10, 15, 20, 30, 35, 40, 50, 55, and 60 minutes after injection. TER_{Hb} was determined as the rate constant of the practically monoexponential decrease in plasma specific activity during the first 60 minutes after injection as calculated by the least squares method.

Plasma volume was determined by extrapolating the plasma disappearance curve of tracer albumin to zero time and the injected volume of tracer was measured by weighing. Plasma albumin concentration was measured by the method of Laurell.

The TER_{Hb} values were compared with those obtained for 28 normal adults by exactly the same techniques.

For statistical analysis, Wilcoxon’s test for paired and unpaired observations was used.

Results

The results of the hemodynamic investigations are given in Table 2. All subjects had markedly elevated pulmonary artery wedge pressures and right atrial pressures at the first examination. During sodium depletion the pressures decreased significantly ($P < 0.001$) and a few became normal. Cardiac index was low and did not change significantly during therapy.

Table 3 demonstrates that TER_{Hb} was markedly elevated during the first investigation. The average was 8.3 ± 1.6% (SD)/hour in comparison to normal values that average 5.4 ± 1.1%/hour ($P < 0.001$). The treatment caused a significant reduction in TER_{Hb}; the average value was 5.9 ± 1.2%/hour ($P < 0.01$). This did not differ statistically from the control value ($P > 0.10$). Figure 1 illustrates a significant positive correlation between TER_{Hb} and right atrial pressure ($r = 0.77, P < 0.001$).

Plasma volume decreased significantly after treatment ($P < 0.05$). Plasma volume and intravascular mass of albumin were markedly enlarged in the two subjects with constrictive pericarditis.

Discussion

All the subjects presented here had CHF, but with differing etiology. However, for each the hemodynamic state

<table>
<thead>
<tr>
<th>Sub-</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Edema*</th>
<th>Hepatomegaly</th>
<th>Weight (kg)</th>
<th>Functional class (NYHA)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Constrictive pericarditis</td>
<td>4+</td>
<td>4+</td>
<td>120.0</td>
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<td>2</td>
<td>47</td>
<td>M</td>
<td>Mitral stenosis and regurgitation</td>
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<td>+</td>
<td>69.0</td>
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<td>55</td>
<td>M</td>
<td>Cardiomyopathy</td>
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<tr>
<td>5</td>
<td>57</td>
<td>F</td>
<td>Mitral stenosis and aortic regurgitation</td>
<td>2+</td>
<td>2+</td>
<td>47.0</td>
<td>III</td>
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<tr>
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<td>63</td>
<td>F</td>
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<td>F</td>
<td>Mitral stenosis</td>
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<td>Mitral stenosis</td>
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<td>+</td>
<td>61.3</td>
<td>II</td>
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<tr>
<td>10</td>
<td>62</td>
<td>M</td>
<td>Ischemic heart disease with mitral regurgitation</td>
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<td>0</td>
<td>71.5</td>
<td>II</td>
</tr>
</tbody>
</table>

1 – first examination; II – second examination; NYHA = New York Heart Association.

*0, no edema; +, intermittent, dependent edema; 2+, persistent, dependent edema; 3+, gross, dependent edema ± ascites; 4, universal edema
TABLE 3  Transcapillary Escape Rate of Albumin (TER alb), Plasma Volume (PV), and Intravascular Mass (IVM), in Congestive Heart Failure

<table>
<thead>
<tr>
<th>Subject</th>
<th>TER alb (% IVM/hr)</th>
<th>Albumin (g/liter)</th>
<th>PV (liters/m²)</th>
<th>IVM (g/m²)</th>
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</thead>
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<td>1*</td>
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<td>32.8</td>
<td>3.78</td>
<td>64</td>
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<td>7*</td>
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<td>35.3</td>
<td>1.65</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>10.7</td>
<td>40.9</td>
<td>2.00</td>
<td>115</td>
</tr>
<tr>
<td>9</td>
<td>6.7</td>
<td>32.7</td>
<td>1.57</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>8.1</td>
<td>53.1</td>
<td>1.64</td>
<td>52</td>
</tr>
</tbody>
</table>

| P       | <0.01            | NS               | <0.05         | NS         |

I - first examination; II - second examination; P values denote paired differences; NS - not significant.

* Subjects 1 and 7 were omitted in average values.

Our present finding of an increased TER alb in subjects was characterized by elevated pressures in the right side of the heart and, in most cases, by a low cardiac index when the subject first was examined. The hemodynamic changes after partial relief of the decompensation—pressure reduction or partial relief of the decompensation—are in agreement with an earlier report on the treatment of chronic heart failure.18

FIGURE 1  Correlation between transcapillary escape rate of albumin (TER alb) and right atrial pressure in subjects with congestive heart failure. r = 0.77; P < 0.001; ● = first examination; ○ = second examination.

TABLE 4  Transcapillary Escape Rate of Albumin (TER alb) Determined from the Initial Slope, Compared with Values Obtained by Multicompartment Exponential Analysis of Long-term Plasma Albumin Disappearance Curves

<table>
<thead>
<tr>
<th>Authors</th>
<th>TER alb (% IVM/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.</td>
<td>6.9</td>
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<tr>
<td>Beeken et al.</td>
<td>4.6</td>
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<td>Takeda and Reeve</td>
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<td>Dykes</td>
<td>6.4</td>
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<tr>
<td>Parving</td>
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</table>

IVM = intravascular albumin mass.

* Initial slope.
hepatic outflow which increases the hepatic lymph and protein transport.17 In addition, studies on animals have clearly demonstrated that the liver is the main source of "early" lymphatic backflux of tracer albumin.22 This will tend to cause an underestimate of the true value for \( \text{TER}_{\text{in}} \) and induce a systematic curvilinearity in the initial plasma disappearance curves in CHF. However, a semilogarithmic plot of the initial plasma disappearance revealed no detectable signs of this curve form, either in the study by Moir et al.1 or in our present one.

Unfortunately, it is not possible to make a correct comparison between the present \( \text{TER}_{\text{in}} \) values and those obtained by Moir et al. or Ross et al., because no information about the clinical condition of the subjects or pressure data were given in their reports. This is crucial because normal \( \text{TER}_{\text{in}} \) values also were found in our study after sodium depletion in spite of slightly elevated right atrial pressures.

The present finding of an increased \( \text{TER}_{\text{in}} \) is in agreement with the demonstration of a marked increase in lymph flow and protein transport through the thoracic duct in subjects with chronically elevated central venous pressures due to constrictive pericarditis4 and various types of CHF.5 24 Furthermore, albumin clearance from subcutaneous tissue is elevated in CHF.25 26 Thus it seems fair to conclude that increased microvascular protein escape is present in CHF with increased right atrial pressure. In this connection it is of interest to mention that acute plasma volume expansion, as well as venous pressure elevation, induce an increased microvascular protein escape in animals and man (see review by Parving et al.).

The value for \( \text{TER}_{\text{in}} \) was found to correlate significantly with right atrial pressure in this study. As a simple explanation one might suggest an increased filtration rate of plasma albumin due to an increase in the transmural hydrostatic pressure difference, particularly in the venous end of the microvasculature, which is the most permeable part of the microvasculature.27 28 Even under normal conditions, filtration may well be the dominant transport mechanism for the overall transcapillary escape of albumin, as discussed by Lassen et al.29 In addition, venous pressure elevation can stretch the pores between the endothelial cells in the microvasculature.20 31 However, this phenomenon does not seem to be operative in our study because we found a slope that decreased with increasing right atrial pressure. Pinocytosis also might explain the increased \( \text{TER}_{\text{in}} \) if the ad hoc assumption is made that this process is pressure-dependent. Electronmicroscopic observations show no evidence of an increased number of pinocytotic vesicles27 32 during elevated capillary pressure. However, this does not rule out the possibility of a shortened transit time for the vesicles.

The increased \( \text{TER}_{\text{in}} \) found in our study might be explained by an increased contribution to the albumin escape from highly permeable organs such as the liver. However, the abovementioned studies on lymph and subcutaneous clearance in CHF6 5 14 24 29 and the investigations on animals with acute venous pressure elevation30 31 34 strongly support the occurrence of increased microvascular protein escape in nearly all organs except the brain in CHF.

The increased \( \text{TER}_{\text{in}} \) in CHF must, other factors being equal, contribute to the formation of edema by increasing the interstitial albumin concentration and colloid osmotic pressure. However, it is documented that the albumin concentration is very low in cardiac edema fluid, indicating that the water flux is even more increased than loss of albumin from the intravascular space. As it appears, the interstitial colloid osmotic pressure is lowered in CHF, counteracting the increased intravascular hydrostatic pressure, as discussed by Aukland,42 but this edema-preventing mechanism is reduced as a result of the increased \( \text{TER}_{\text{in}} \).

In the two subjects with constrictive pericarditis plasma volume and intravascular mass of albumin were grossly enlarged. The explanation of this gross volume expansion in constrictive pericarditis is unknown. However, it seems attractive to combine the abnormal volume regulation in such subjects with malfunction of cardiac stretch receptors, which in other cases of CHF might antagonize the mechanisms for intravascular fluid retention.

References

22. Dykes PW: Rates of distribution and catabolism of albumin in normal
Intrarenal Distribution of Blood Flow in Rats Determined by $^{125}$I-Iodoantipyrine Uptake

ARVID HOPE, CAND. REAL., GUNNAR CLAUSEN, CAND. REAL., AND KNUT AUMLAND, DR. MED.

SUMMARY. Local renal blood flow was estimated in pentobarbital-anesthetized rats with $^{125}$I-Iodoantipyrine (Ap) according to the method of Kety: Arterial blood was sampled continuously on rotating filter paper during 9- to 16-second intravenous Ap infusion; 1-second blood sample volumes were determined from their hemoglobin content. After snapfreezing the kidneys, 1- to 6-mg samples were cut out from outer and inner half of cortex (OC and IC) and outer and inner half of outer medulla (OM, and OM,). Ap concentration and blood flow were determined in 20-30 tissue samples in each experiment. A tissue-blood solubility ratio (partition coefficient) for Ap of 0.97 ml/g was determined in vivo by infusing Ap iv at decreasing rate for 80 seconds. Blood flow within each zone appeared remarkably homogeneous. After correction for methodological errors estimated from partition experiments, the coefficient of variation averaged 7.0% and 10.6% in OC and IC, respectively, obviously including errors due to inconsistent zonal dissection. Average zonal flow (ml/min per g) in 13 rats was: OC, 7.09 ± 1.13 (SD); IC, 4.65 ± 0.83; OM, 2.17 ± 0.37; and OM, 0.89 ± 0.25. Average renal blood flow (RBF) was calculated at 4.62 ml/min per g, and the relative fractions of OC through OM, at 65, 28, 6.5, and 1.6% of RBF. The high flow in IC compared to published data on microsphere measurements will give no direct information on regional peritubular flow, which may well be of importance in the regulation of tubular reabsorption of salt and water. Furthermore, under pathological conditions peritubular blood flow may become critical for tubular nutrition. For the purpose of measuring tissue perfusion ("nutritional flow"), determination of local uptake or washout of inert diffusible substances would seem to offer the most adequate methodological approach. Our present paper reports measurements of regional renal blood flow in anesthetized rats based on the local $^{125}$I-antipyrine uptake rate by the method originally devised by Kety. The results have been presented in part in abstract form.

ALTHOUGH a large number of studies have dealt with the regional distribution of blood flow in the dog kidney, relatively few attempts have been made to measure intranidal blood flow in rats. This seems unfortunate because the majority of studies on single-nephron filtration rate and tubular functions are performed on rats, and therefore lack readily comparable data on regional blood flow.

Up to now, the most direct estimate of regional flow in the rat kidney has been obtained from microsphere distribution. Apart from the uncertainties regarding the distribution of microspheres relative to blood flow, the microsphere method will give information only on inflow to glomeruli in the various cortical layers, or average inflow in special anatomical groups of glomeruli. Since the postglomerular flow pattern and distribution are incompletely known, microsphere measurements will give no direct information on regional peritubular flow, which may well be of importance in the regulation of tubular reabsorption of salt and water. Furthermore, under pathological conditions peritubular flow may become critical for tubular nutrition. For the purpose of measuring tissue perfusion ("nutritional flow"), determination of local uptake or washout of inert diffusible substances would seem to offer the most adequate methodological approach. Our present paper reports measurements of regional renal blood flow in anesthetized rats based on the local $^{125}$I-antipyrine uptake rate by the method originally devised by Kety. The results have been presented in part in abstract form.

Methods

PRINCIPLE

As developed by Kety: When a freely diffusible, biologically inert tracer substance is carried to a tissue by arterial...
Transcapillary escape rate of albumin and right atrial pressure in chronic congestive heart failure before and after treatment.

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doi: 10.1161/01.RES.39.3.358

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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