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# Filtration as the main mechanism of increased protein extravasation in liver cirrhosis

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Transvascular escape rates of albumin and immunoglobulin-G, IgG ($TER_{alb}$ and $TER_{IgG}$, i.e. the fractions of intravascular mass of albumin and IgG passing to the extravascular space per unit time) were determined simultaneously from the disappearance of intravenously injected $^{131}$I-labelled human serum albumin and $^{125}$I-labelled human IgG in eight patients with cirrhosis of the liver. The mean wedged hepatic venous pressure was 22 mmHg (range 13–34). $TER_{alb}$ and $TER_{IgG}$ were on average 8.4 ± 0.8 %/h (SD), and 7.4 ± 1.9 %/h (SD), respectively and these values are significantly increased compared to normal subjects [$TER_{alb}$ = 5.2 ± 1.0 %/h (SD) and $TER_{IgG}$ = 3.0 ± 0.7 %/h (SD), $P < 0.001$]. The $TER_{IgG}/TER_{alb}$ ratio was on average 0.88 ± 0.20 (SD), which is significantly higher than that of normals [0.58 ± 0.08 (SD), $P < 0.005$]. The results indicated that increased filtration (bulk flow) is the dominant process of the increase microvascular protein escape in cirrhosis, due most likely to increased hepatic, but also to increased extrahepatic splanchnic transcapillary protein flux.

*Key-words:* albumin; ascites; immunoglobulin-G (IgG); liver cirrhosis; lymphatic return; protein extravasation; protein kinetics; portal hypertension; transvascular escape rate of protein

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Recently we have found that the transvascular escape rate of albumin (i.e. the fraction of the intravascular mass of albumin that passes into the extravascular space per unit time) in patients with cirrhosis of the liver, is approximately twice the value of normal controls [8, 17]. The transvascular escape rate of albumin ($TER_{alb}$) and immunoglobulin-G, IgG ($TER_{IgG}$) is increased in diabetes and arterial hypertension, but the $TER_{IgG}/TER_{alb}$ ratio remains normal [16, 18]. To get further information on the mechanism of the microvascular protein escape in patients with liver cirrhosis, the transvascular escape rate of albumin (mol. wt 69,000) and IgG (mol. wt 160,000) were determined simultaneously. Our main result is an elevated

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$TER_{IgG}/TER_{alb}$ ratio, suggesting filtration (bulk flow) as the dominant mechanism of the increased protein extravasation in cirrhosis.

## MATERIAL AND METHODS

The material comprises seven males and one female with biopsyverified cirrhosis of the liver. The mean age was 49 years (range 35–65 years). The average body weight was 66 kg (range 52–81 kg) and the average height 172 cm (range 163–184 cm). All subjects had a history of alcohol abuse. The time-interval from diagnosis to the present investigation was on average 5 weeks (range 1 week–5 months). The clinical data are summarized in Table I. All patients, except one (no. 6), received diuretics, the daily dose ranged: Spironolactone (INN) 0–200 mg, Furosemide (INN) 0–160 mg, and Bumetanide (INN) 0–1 mg. All patients had normal arterial blood pressure and no signs of diabetes mellitus. None of the patients had a past history or present evidence of skin disease, cardiac failure or renal disease. All patients had normal serum creatinine concentration, and none had proteinuria. There was no evidence of any other serious disease than liver cirrhosis and alcoholic hepatitis. At the time of investigation no patient had any evidence of hepatic coma or gastrointestinal bleeding, and all were considered to be in steady state and without peripheral oedema.

Hepatic venous catheterization was performed in all subjects, either through an antecubital vein, or due to increased bleeding tendency in two patients (nos 5 & 7), as a transjugulovenous catheterization associated with liverbiopsy [22]. The pressure was measured in free and wedged hepatic venous position, as well as in the right atrium, the inferior vena cava, and in the femoral artery with a capacitance transducer. The transvascular escape rate of albumin and IgG was determined within 3 days of the pressure measurements, except in one patient (no. 1), where the interval was 2 weeks. The investigative procedure and the theoretical basis for calculation of $TER_{alb}$ and $TER_{IgG}$ have been described in detail previously [15, 18]. The investigation was preceeded by 12 h of fasting and was carried out in the morning after 1 h at rest in the supine position.

About 5 $\mu$Ci of $^{125}$I-labelled human IgG prepared by DEAE-cellulose chromatography [19] and 5 $\mu$Ci of $^{131}$I-labelled human albumin ([$^{131}$I]RISA, code MIMS, Institute of Atomic Energy, Kjeller, Noway) were used as tracers and injected simultaneously in an arm vein. The tracer preparations contained less than 1.0% non-protein bound iodide. Previous studies have shown that the preparations are of satisfactory physical, chemical and metabolic quality [1, 23, 24]. Venous blood samples (4 ml) were drawn from the contra-lateral arm: 0, 10, 15, 20, 30, 35, 40, 50, 55, and 60 min after injection of the tracers. The radioactivity of the serum samples was measured in a well-type

TABLE I. Clinical data and pressure measurements from eight patients with alcoholic cirrhosis

| Patient no. | Age (years) | Sex | Additional diagnosis | Ascites* | Pressures (mmHg) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Systemic artery | Right atrium (≦5)** | Wedged hepatic vein (<15) | Free hepatic vein | Inferior vena cava |
| 1 | 54 | M | Alcoholic hepatitis polyneuropathia | 0 | 140/73 | 4 | 19 | 9 | 9 |
| 2 | 35 | M | | + | 94/49 | 6 | 21 | 6 | 6 |
| 3 | 45 | F | Alcoholic hepatitis, oesophageal varices | +++ | 118/77 | 5 | 34 | 16 | 14 |
| 4 | 57 | M | | 0 | 143/77 | 2 | 13 | 8 | 6 |
| 5 | 65 | M | Oesophageal varices, duodenal ulcer | (+) | 140/70*** | 1 | 22 | 4 | 4 |
| 6 | 41 | M | Oesophageal varices | 0 | 135/63 | 0 | 21 | 0 | 0 |
| 7 | 47 | M | | + | 105/70*** | 2 | 24 | 8 | 7 |
| 8 | 47 | M | | (+) | 120/56 | 2 | 20 | 2 | 2 |
| Mean | | | | | 124/67 | 2.8 | 22 | 6.6 | 6.0 |

* Clinical evaluation of ascites at the time of investigation: 0 no, (+) doubtful, + slight, +++ tense ascites with umbilical hernia.
** 95% upper limit in normal subjects.
*** Cuff blood pressure; all other pressures are intravascular measurements.

scintillation detector (Selectronik), 10,000 counts were recorded, and the activity was expressed in relation to the total protein concentration measured by refractometry (CPM/g). The transvascular escape rates of albumin ($TER_{alb}$) and IgG ($TER_{IgG}$) were determined as the rate constants of monoexponential fits (least squares method) of the plasma specific activity-time curves, 10–60 min after injection of the tracers. The calculated total radiation dose was less than 200 mrem, and the thyroid uptake of radioactive iodide was blocked with 450 mg potassium iodide given orally. *Plasma volume* (PV) was determined as the amount of injected radioactivity of [$^{131}$I]RISA divided by the plasma concentration of [$^{131}$I]RISA, retropolated to injection time. *Plasma albumin and IgG concentration* were measured immunologically [11, 14]. *Intravascular masses* of albumin ($IVM_{alb}$) and IgG ($IVM_{IgG}$) were calculated as PV multiplied by the plasma concentration of albumin and IgG, respectively.

The significance of differences between mean values was tested by using Student's *t* test. $P \leq 0.05$ was considered as significant. The results of the TER measurements were compared with those obtained in nine normal adult male subjects [18].

## RESULTS

The results of the pressure measurements are given in Table I. All patients, except one (no. 4) had significantly elevated portal pressure, measured as wedged hepatic venous pressure. PV was $3.42 \pm 0.73$ l (SD), which is not significantly different from that of controls. From Table II it is seen, that the plasma albumin concentration and $IVM_{alb}$ were significantly decreased, and the plasma IgG concentration and $IVM_{IgG}$ were significantly increased.

As shown in Table II, $TER_{alb}$ and $TER_{IgG}$ were on the average $8.4 \pm 0.8$ % IVM/h (SD), and $7.4 \pm 1.9$ % IVM/h (SD), respectively, and these values are substantially increased compared to normals ($TER_{alb}$ = $5.2 \pm 1.0$ (SD), and $TER_{IgG} = 3.0 \pm 0.7$ (SD), $P < 0.001$). The $TER_{IgG}/TER_{alb}$ ratio was on average $0.88 \pm 0.20$ (SD), which is significantly larger than that of normal subjects [$0.58 \pm 0.08$ (SD), $P < 0.005$]. $TER_{alb}$ and $TER_{IgG}$ were not correlated to the portal pressure or the pressures in the right atrium, inferior vena cava or systemic artery.

## DISCUSSION

$TER_{alb}$ and $TER_{IgG}$ were significantly higher than that of normals. The control group [18] consisted of males, who were younger than the patient studied, but this is of minor importance, since the TER values are largely age-independent in adults [15].

TABLE II. Transvascular escape rates of albumin ($TER_{alb}$) and IgG ($TER_{IgG}$), concentrations and intravascular masses (IVM) of albumin and IgG from eight patients with alcoholic cirrhosis.

| Patient no. | $TER_{alb}$ (%IVM/h) | $TER_{IgG}$ (%IVM/h) | $\frac{TER_{IgG}}{TER_{alb}}$ | Concentrations (μmol/l) | | Intravascular protein masses (μmol) | |
|---|---|---|---|---|---|---|---|
| | | | | Albumin | IgG | Albumin | IgG |
| 1 | 8.5 | 10.4 | 1.22 | 488 | 86 | 1482 | 262 |
| 2 | 9.4 | 9.7 | 1.03 | 372 | 118 | 1771 | 562 |
| 3 | 7.9 | 8.3 | 1.05 | 332 | 101 | 1168 | 356 |
| 4 | 7.5 | 5.8 | 0.77 | 597 | 73 | 1448 | 178 |
| 5 | 7.5 | 6.2 | 0.83 | 449 | 90 | 1436 | 288 |
| 6 | 8.0 | 5.8 | 0.73 | 471 | 78 | 1783 | 296 |
| 7 | 9.5 | 5.5 | 0.58 | 397 | 86 | 1536 | 332 |
| 8 | 9.0 | 7.3 | 0.81 | 419 | 148 | 1159 | 410 |
| Mean | 8.4 | 7.4 | 0.88 | 440 | 98 | 1473 | 336 |
| ±SD | 0.8 | 1.9 | 0.20 | 81 | 25 | 234 | 114 |
| Controls: | | | | | | | |
| Mean | 5.2 | 3.0 | 0.58 | 581 | 71 | 1870 | 231 |
| ±SD | 1.0 | 0.7 | 0.08 | 32 | 14 | 203 | 67 |
| *P* | <0.001 | <0.001 | <0.005 | <0.02 | <0.02 | <0.005 | <0.05 |

Controls are from Parving & Rossing, 1973 [18]

One of the assumptions of the method by which TER is determined, is that no back-transport of the tracers to the vascular system occurs during the time of investigation. Under normal conditions this back-transport is negligible within 1 h, as discussed previously [15], and a semilogarithmic plot of the initial plasma disappearance of albumin fits a straight line during the first 60 min, Fig. 1 [17]. The cumulative curves of the disappearance of IgG and albumin from the present study are shown in Fig. 1. In the semilogarithmic plot, these curves from the eight patients with cirrhosis are found to be somewhat bent in the final part, and it is furthermore seen that the courses of both curves are almost identical.

Increased lymph flow is present in patients with cirrhosis [13], and the bending of the tracer curves is probably due to enhanced protein return through the lymphatics, as discussed later. Table III shows $TER_{alb}$ and $TER_{IgG}$ calculated 10–20 min, 10–30 min, 10–40 min and 10–60 min after injection of tracers. By using more initial data, higher (although due to scarcity of data, less precise) values of the transvascular escape rates are obtained by both tracers, as the back-transport of tracer is smallest immediately after injection. A relatively high lymphatic flow through a small volume is necessary to create early bending of the semilogarithmic plot of the tracer curves, as discussed in appendix 1.

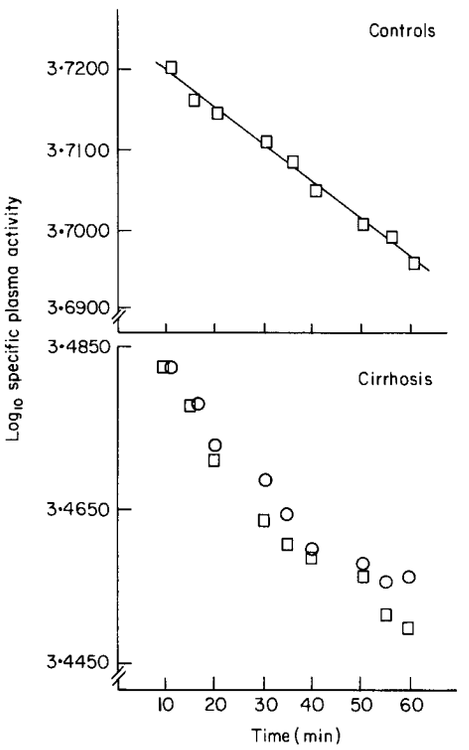



FIG. 1. Comparison of the decrease in plasma specific activity of albumin (□) and IgG (○) during the first 60 min after the injection of the tracers, compiled from twelve control subjects (top, from Parving *et al.*, 1977, [17]) and the eight cirrhotics in the present study (bottom). The control curve fits a straight line during the first 60 min (semilogarithmic plot), while the cirrhotic curves are found to be curved in the final part.

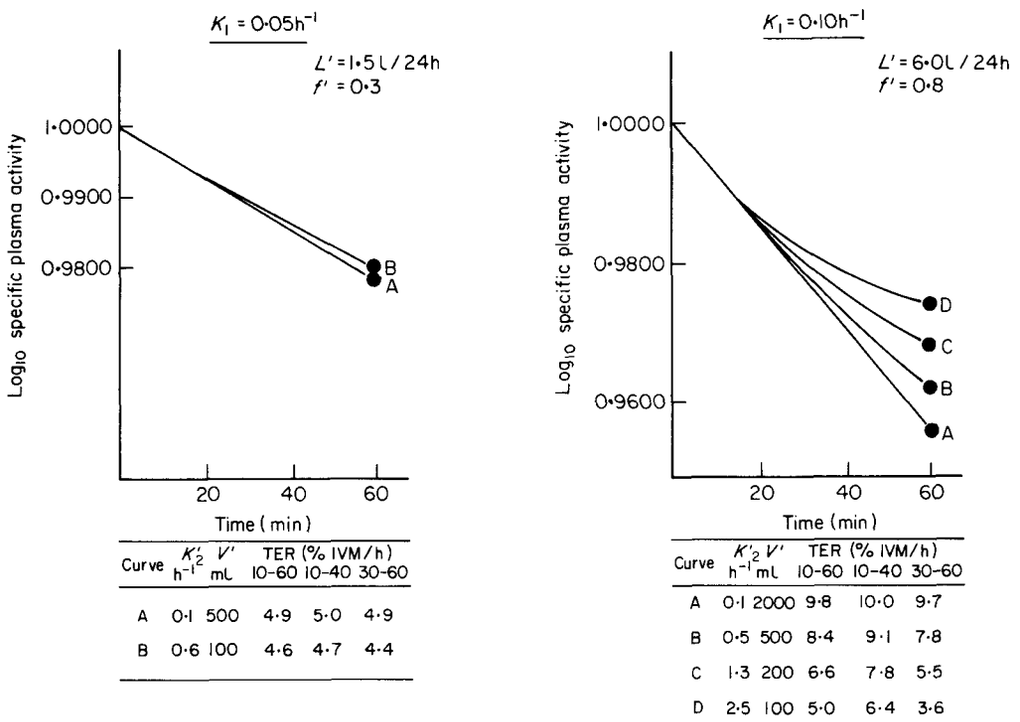
TABLE III. Transvascular escape rates of albumin and IgG from eight patients with cirrhosis, calculated from cummulated data in different time intervals after tracer injection.

| Interval (min) | $TER_{alb}$ (%IVM/h) | $TER_{IgG}$ (%IVM/h) | $\frac{TER_{IgG}}{TER_{alb}}$ |
|---|---|---|---|
| 10–20 | 14.2 | 13.3 | 0.94 |
| 10–30 | 12.7 | 10.9 | 0.86 |
| 10–40 | 10.8 | 9.4 | 0.87 |
| 10–60 | 8.4 | 7.4 | 0.88 |

The ratio between $TER_{IgG}$ and $TER_{alb}$ was high, compared to normal subjects as well as patients with diabetes mellitus [18] and arterial hypertension [16,20]. In these groups, the $TER_{IgG}/TER_{alb}$ ratio was close to 0.6, which is the ratio between the diffusion coefficients of IgG and plasma albumin in aqueous solution [26]. $IVM_{IgG}$ and plasma IgG concentration were increased, and $IVM_{alb}$ and plasma albumin concentration were decreased, as characteristic in alcoholic cirrhosis [12]. Since TER is expressed as a fraction of the intravascular mass of the protein in question, the disproportional rise of $TER_{IgG}$ is not due to the increased plasma concentration of IgG or increased $IVM_{IgG}$. Diffusion is widely assumed to be the most important mechanism by which proteins pass from the plasma into the interstitial space [2, 4]. No diffusive process can, however, bring the $TER_{IgG}/TER_{alb}$ ratio to exceed that of the free diffusion coefficients, and it is thus concluded that diffusion is *not* the main process of the increased microvascular protein escape in cirrhosis. The present results are, together with earlier studies of the distribution of IgG and albumin between plasma and interstial space in cirrhosis [1, 6, 27], consistent with filtration as the dominant transport

mechanism (see appendix 2), as earlier suggested by Lassen *et al.* [10]. The finding of almost identical values of the protein escape of IgG and albumin indicates furthermore that the filtration takes place through large pores, as IgG (Stokes-Einstein radius 55Å) exceeds the size of the small pore system, e.g. in skeletal muscle capillaries [9]. The fenestra (1000–10,000Å) of the sinusoids of the liver [3] make the perisinusoidal space (Disse) immediately accessible to substances present in the circulating plasma, and the flux of albumin from plasma into the perisinusoidal space (and back) is very rapid as shown by Goresky [5]. For this reason, the hepatic part of the overall transvascular escape rate of protein is the escape rate from the perisinusoidal space into the lymphatics of the liver. Although the sinusoids and perisinusoidal space may be abnormal in cirrhosis ('capillarization' with wall tightening due to hyalin sclerosis [25]), the appearance of radioiodinated albumin in the hepatic lymph is fast [13], consistent with a high hepatic protein escape in cirrhosis (see appendix 2). The capillary wall of the intestine is fenestrated (300–600Å), [3], and it is likely that apart from a large hepatic protein escape the extrahepatic splanchnic organs (stomach, intestine and spleen) contribute significantly to the increased overall protein escape in patients with increased portal pressure. Increased pressure in the inferior vena cava might be present in patients with cirrhosis [28], but congestion in this part of the circulation only increases TER slightly in animal experiments [7].

In the present material, four patients had slight ascites, and only one had tense ascites. As illustrated in Fig. 2 (appendix 1), the return of tracer through a large extravascular volume will diminish the bending of the semilogarithmic plot of the intravascular tracer time-activity curves. Lymph derived from the liver is either returned to the circulation through the lymphatics or enters the peritoneal cavity directly [29]. From the shape of the tracer curves in the




| Curve | $K'_2$ $h^{-1}$ | $V'$ mL | TER (% IVM/h) 10-60 | 10-40 | 30-60 |
|---|---|---|---|---|---|
| A | 0·1 | 500 | 4·9 | 5·0 | 4·9 |
| B | 0·6 | 100 | 4·6 | 4·7 | 4·4 |

| Curve | $K'_2$ $h^{-1}$ | $V'$ mL | TER (% IVM/h) 10-60 | 10-40 | 30-60 |
|---|---|---|---|---|---|
| A | 0·1 | 2000 | 9·8 | 10·0 | 9·7 |
| B | 0·5 | 500 | 8·4 | 9·1 | 7·8 |
| C | 1·3 | 200 | 6·6 | 7·8 | 5·5 |
| D | 2·5 | 100 | 5·0 | 6·4 | 3·6 |

FIG. 2. Semilogarithmic plots of different, calculated plasma tracer curves. *Left.* Simulating a normal person. The curves are almost straight, and the TER values calculated in different time intervals are similar. *Right.* Simulating a patient with cirrhosis of the liver. The larger the 'liver lymph space' ($V'$) is, the more straight is the plasma activity curve. TER, calculated in different intervals varies considerably. For explanation of symbols, see text.

present study, it seems likely, that only a smaller part of the increased splanchnic protein escape enters the peritoneal cavity directly. In so far as the escaped protein is not returned to the circulation through the lymphatics, it will contribute to increased protein content in the peritoneal cavity and thereby to formation of ascitic fluid. According to this hypothesis, ascitic fluid is, at least partly, governed by impeded lymphatic protein return.

In conclusion the microvascular escape rate, not only of albumin but also of larger protein molecules as IgG, is significantly elevated in patients with cirrhosis. Our results point to filtration (bulk flow) as the dominant process of the protein flux from the plasma to the interstitium and further into the lymphatics. The liver and the extrahepatic splanchnic areas are most likely, due to the increased transmural pressure difference in the venous parts of splanchnic microvasculature, the main sources of the increased overall protein escape in cirrhosis. Ascitic fluid is probably governed as inbalance between the filtrative forces and the transport capacity of the lymphatics.

## APPENDIX 1

A general mathematical model of albumin distribution is described by Reeve & Bailey [21]. The differential equation of change in intravascular specific activity of tracer [$P(t)$] is:

$$(1) \qquad -dP(t)/dt = K_1 \cdot P(t) - K_1 \cdot X(t)$$

where catabolism is neglected during a short time-interval (1 h), [15]. $K_1$ is the fraction of intravascular mass of albumin passing to the extravascular space per unit time. $X(t)$ is a function describing the return of extravascular leaking tracer, i.e. $X(t)$ is the convolution of $P(t)$ by the frequency function of extravascular transit times.

Assuming the interstitial space to consist of two well-mixed compartments: a liver (C′) and non-liver compartment (C″), the following equation, derived from (1), will express the plasma specific activity of tracer:

$$(2) \qquad P(t) = e^{-K_1 \cdot t} + f' \cdot \int_0^{t-T'} C'(t)dt + f'' \cdot \int_0^{t-T} C''(t)dt$$

where $C'(t) = (K_1 e \cdot {}^{-K_1 \cdot t}) * (K_2' \cdot e^{-K_2' \cdot t})$, $t > T'$

$(C'(t) = 0$ for $t \leqslant T')$

and $C''(t) = (K_1 \cdot e^{-K_1 \cdot t}) * (K_2'' \cdot e^{-K_2'' \cdot t})$, $t > T''$

$(C''(t) = 0$ for $t \leqslant T'')$

$f'$ and $f''$ are the fractions of tracer passing to liver and non-liver compartments respectively; $T'$ and $T''$ are the appearance time of tracer through the liver and non-liver compartment, respectively; $K_2' = L'/V'$, $L'$ is the flow rate of liver lymph, and $V'$ is the liver lymph space; $K_2'' = L''/V''$, $L''$ is the flow rate of non-liver lymph, and $V''$ is the non-liver interstitial space.

The first monoexponential part of this equation describes the plasma specific activity of the tracer if no return of tracer is present. The integral parts describe the tracer return from liver and non-liver compartments, respectively. Solution for equation (2) with Laplace transforms gives:

$$(3) \qquad P(t) = e^{-K_1 \cdot t} + f' \cdot \left( -\frac{K_2'}{K_2' - K_1} \cdot e^{-K_1 \cdot (t-T')} + \frac{K_1}{K_2' - K_1} \cdot e^{-K_2' \cdot (t-T')} + 1 \right) + f'' \cdot \left( -\frac{K_2''}{K_2'' - K_1} \cdot e^{-K_1 \cdot (t-T'')} + \frac{K_1}{K_2'' - K_1} \cdot e^{-K_2'' \cdot (t-T'')} + 1 \right)$$

In Fig. 2, different tracer plasma curves are calculated by assuming different values of $K_1$, $f'$, $f''$, $L'$, $V'$ and $K_2'^{-}$. $L''$ is assumed to be 1.5 l/24h, and $V''$ to be 10 l ($K_2'' = 0.00625 h^{-1}$). $T' = T'' = 10$ min.

In Fig. 2, TER values are calculated in different time intervals from the different plasma tracer curves. To create a curved shape of the semilogarithmic plot, it is necessary to assume a relatively fast lymphatic tracer return through a relatively small space. An appearance time above 10 min will elongate the initial straight part of the curve, and thereby higher and more correct values of TER are obtained. Furthermore a longer appearance time will give a larger discrepancy between TER calculated from the

initial and TER calculated from the final data, as seen in the present study.

## APPENDIX 2

From the present results and from data of the distribution ratios of albumin and IgG between the intra- and the extravascular spaces, estimation of the hepatic share of the increased TER in patients with cirrhosis can be performed.

The extravascular protein space is assumed to consist of two compartments, a liver and a non-liver space, to which the overall escape of the intravascular proteins take place:

$$(1) \qquad TER_{alb} = TER'_{alb} + TER''_{alb}$$
$$(2) \qquad TER_{IgG} = TER'_{IgG} + TER''_{IgG}$$

where TER′ and TER″ are the escape rates to liver and non-liver extravascular protein spaces, respectively. In the liver, the sinusoids represent no restriction to protein flux, and thus

$$(3) \qquad TER'_{IgG} = TER'_{alb},$$

if the transport is filtration dominated.

R′ and R″ are the ratios, respectively, between liver and non-liver extravascular masses and the intravascular masses of albumin and IgG. Assuming a convective back-flow of proteins from the non-liver extravascular space into the vascular space, the $TER''_{IgG}/TER''_{alb}$ ratio will equal the $R''_{IgG}/R''_{alb}$ ratio, and

$$(4) \qquad TER''_{IgG} = \frac{R''_{IgG}}{R''_{alb}} \times TER''_{alb}$$

From equation (2), (3) and (4) follows:

$$(5) \qquad TER_{IgG} = TER'_{alb} + \frac{R''_{IgG}}{R''_{alb}} \times TER''_{alb}$$

Solution of equation (1) and (5) gives

$$(6) \qquad \frac{TER'_{alb}}{TER_{alb}} = \frac{(R''_{IgG}/R''_{alb}) - (TER_{IgG}/TER_{alb})}{(R''_{IgG}/R''_{alb}) - 1}$$

In cirrhosis, the distribution ratio between the extravascular and intravascular mass of IgG averages 0.7 [1]. The corresponding figure of albumin is 1.5 [6, 27]. As $R'_{IgG} \ll R''_{IgG}$ and $R'_{alb} \ll R''_{alb}$, the ratio $R''_{IgG}/R''_{alb}$ is approximately $0.7/1.5 = 0.47$ in patients with cirrhosis. Using this figure in equation (6) and the mean value of $TER_{IgG}/TER_{alb}$ found in this study: 0.88, the hepatic share of the overall transvascular escape rate of albumin ($TER'_{alb}/TER_{alb}$) is about 80%. This is consistent with increased hepatic protein escape as the main part of the overall increased TER in patients with cirrhosis. (In normal subjects, the ratios $R''_{IgG}/R''_{alb}$ and $TER_{IgG}/TER_{alb}$ are close to each other, and thus the hepatic share of the overall TER cannot be estimated with a reasonable accuracy from equation (6).) Conversely the assumption of an increased hepatic protein escape as the main cause of the increased TER in cirrhosis will together with the protein distribution ratios of albumin and IgG point to convective protein return, not only from the liver interstitial space but also from the non-liver interstitial space.

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