Plasma Disappearance of Albumin and Impact of Capillary Thickness in Idiopathic Dilated Cardiomyopathy and After Heart Transplantation

Søren Galatius, MD; Lasse Bent-Hansen, MD, PhD; Henrik Wroblewski, MD, PhD; Vibeke B. Sørensen, MD; Tove Nørgaard, MD, PhD; Jens Kastrup, MD, PhD

Background—The increased plasma disappearance of albumin has previously been described in decompensated congestive heart failure (CHF); this disappearance normalized after diuretic treatment. Cardiac transplantation (HTX) and current medical treatment affect microvascular structure and function. We investigated the plasma disappearance of albumin and the impact of microvascular thickness and electrostatic properties in patients with compensated CHF and after HTX.

Methods and Results—The fraction of intravascular albumin that passes to the extravascular space per unit time, as determined from the plasma disappearance of intravenously injected $^{131}$I-labeled albumin, was increased to $7.8\pm 1.7\%$ in 16 patients with CHF compared with 18 controls ($6.5\pm 1.9\%, P<0.05$); these levels normalized after HTX ($5.8\pm 2.6\%, P<0.01, n=17$). The change in ratio between $^{131}$I-albumin and simultaneously injected negatively charged glycosylated $^{125}$I-albumin (selectivity index, $>1$/hour in controls) was lower in patients with HTX ($0.993\pm 0.022$/hour) than in controls ($1.008\pm 0.019$/hour; $P<0.05$), which indicated a relatively increased plasma disappearance of negatively charged albumin in HTX patients. Capillary basement membrane thickness was evaluated semiquantitatively from skin biopsies and showed no difference in the 3 groups (control, CHF, and HTX patients). However, in all 3 study groups, subjects with thicker capillary basement membranes had lower albumin escape rates ($6.1\pm 1.8\%, n=32$, versus $7.6\pm 2.6\%$ in subjects without thickening of capillary basement membranes, $n=19$; $P<0.05$).

Conclusions—The plasma disappearance of albumin increased in patients with compensated CHF and it normalized after HTX. The present normalized capillary basement thicknesses in patients with CHF and the direct association between this parameter and plasma albumin disappearance indicate that previous compensatory microvascular basement membrane growth results in restricted permeability. Microvascular electrostatic properties did not relate to plasma albumin disappearance. (Circulation. 2000;102:319-325.)

Key Words: heart failure ■ microcirculation ■ serum albumin ■ permeability

Both regulatory and structural abnormalities of peripheral microcirculation are present in patients with congestive heart failure (CHF). Cardiac transplantation (HTX) and long-term treatment with angiotensin-converting enzyme (ACE) inhibitors seem to reverse some of these abnormalities. However, edema may still be present both before and after HTX. One of several factors in the pathogenesis of peripheral edema may be the increased loss of intravascular albumin, which may be influenced by the degree of microvascular abnormalities. More than 2 decades ago, Hesse et al$^4$ demonstrated that the plasma disappearance of albumin was increased in patients with decompensated CHF and peripheral edema; however, these levels normalized after 1 to 2 weeks of diuretic treatment. In accordance with this observation, short-term volume expansion increased the transcapillary escape rate of albumin (TER$_{alb}$) in healthy controls.$^5$ TER$_{alb}$ was directly related to right atrial pressure in these studies,$^4,5$ but it was normal in patients who had elevated right atrial pressure due to chronic obstructive lung disease with pulmonary hypertension.$^6$ TER$_{alb}$ is also related to mean arterial pressure in both type 1 diabetes and essential hypertension.$^7$ However, treatment with ACE inhibitors, which is a cornerstone of the modern treatment of CHF, reduced TER$_{alb}$ in normotensive patients with type 1 diabetes.$^8$ Thus, factors other than those which are directly pressure- and volume-dependent seem to be of importance to the degree of plasma albumin disappearance. The degree of plasma albumin disappearance is unknown in CHF patients who are treated with modern treatment modalities, and it has never been investigated after HTX.

The electrostatic properties of the microvascular wall may have a barrier function; the disappearance of albumin and the disturbance of the electrostatic properties of the vascular wall were most pronounced in diabetic patients with nephropathy.$^9$

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From the Heart Center, the Rigshospital, Copenhagen (S.G., H.W., V.B.S., J.K.); the Department of Cardiology, Hvidovre Hospital, Copenhagen (L.-B.H.); and the Department of Pathology, Hillerød Hospital, Hillerød (T.N.), Denmark.

Correspondence to S. Galatius, MD, The Heart Center B2014, The Rigshospital, DK 2100 Copenhagen Ø, Denmark. Galatius@dadlnet.dk

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Such patients also had the highest degree of thickening in the basement membranes of terminal arterioles and capillaries. This resembles the structural microangiopathy found in CHF. However, the pathogenesis of this thickening may be different because it may be more metabolically dependent in diabetes and more pressure dependent in CHF. The roles played by the thickening of capillary basement membranes and the electrostatic properties of the vessel wall on the loss of intravascular albumin are unknown in patients with CHF and after HTX.

The aims of the present study were (1) to determine the plasma disappearance of albumin in patients with compensated CHF caused by idiopathic dilated cardiomyopathy (IDCM) who are treated with long-term ACE inhibition and/or HTX and (2) to test the impact of capillary thickness and the electrostatic properties of the vessel wall on plasma albumin disappearance.

Methods

Subjects

Demographic data are given in Table 1. The study population consisted of 18 healthy control subjects, 16 patients with CHF due to IDCM, and 17 patients who had HTX because of end-stage CHF due to IDCM. Four patients were studied both before and after HTX. All subjects were male, and the groups were age-matched. The diagnosis of IDCM was based on clinical and hemodynamic findings. No patient had a history of diabetes, hypertension, chronic obstructive lung disease, angina, or myocardial infarction.

All heart transplant recipients were clinically stable and free from clinical or biopsy-verified rejection, infection, or other major illness. All patients with CHF were treated with diuretics (mean furosemide-equivalent dose, 100 mg; range, 20 to 300 mg) and an ACE inhibitor (mean captopril-equivalent dose, 100 mg; range, 37.5 to 150 mg). In addition, 13 patients with CHF were also treated with digoxin (mean dose, 312.5 μg; range, 125 to 500 μg), 11 were treated with anticoagulants, 3 with aspirin, and 1 with a calcium antagonist from the dihydropyridine class. Because all the patients in the present study had CHF due to IDCM, the disease was diagnosed at the time of first symptoms of CHF. Treatment with ACE inhibitors and diuretics began at the time of diagnosis for all patients who had their first symptoms <3 years before this study took place; treatment had lasted ≥3 years in patients who were diagnosed earlier. After HTX, all patients were treated with triple immunsuppression, including cyclosporine, azathioprine, and low-dose glucocorticoid. In addition, 12 HTX patients were treated with diuretics, 14 were on aspirin, and 10 were treated with a calcium antagonist from the dihydropyridine class.

Because the aim of the study was to investigate patients in the clinical setting, all medication was continued, and patients’ diets were not modified. The patients had been stable without any change in medication for ≥4 weeks before the study. All patients were in a compensated state, ie, no jugular venous stasis, no basal pulmonary rales, no signs of congestion at x-ray, no clinical signs of ascites, and no peripheral edema. All subjects gave written informed consent, and the protocol was approved by the local ethics committee. The study conforms with the guidelines of the Declaration of Helsinki.

Procedure

The investigations were performed in the morning after an overnight fast. The subjects were lightly dressed and placed in the supine position. Room temperature was kept constant during the investigations at ~23°C. A canula was inserted into the antecubital vein of both forearms. The right arm was placed on a heating cushion to ensure abundant blood flow and the immediate mixing of injected albumin. Investigations began after a minimum of 30 minutes in the supine position. Arterial blood pressure was measured at the upper arm with a standard clinical sphygmomanometer at heart level; diastolic blood pressure was recorded at Korotkoff phase 5.

**TER**

The procedure and theoretical basis for the calculation of TER have been described in detail previously. Briefly, 4 to 8 μCi of nonglycosylated I-albumin and glycosylated 125I-albumin (both tracers from Kjeller) produced from human serum albumin by electrolytic labeling were injected simultaneously. Both tracer preparations were approved for use in humans and contained <1% free radioactive iodide. The radioiodelabeled nonglycosylated albumin was demonstrated by metabolic studies to behave like endogenous albumin, and glycosylation did not seem to alter metabolism. The tracer preparations were injected into the vein of one arm, and 5-mL blood samples were drawn from the opposite arm at 2, 10, 15, 20, 30, 40, 50, and 60 minutes to determine TER. Plasma radioactivity was counted in duplicate in each sample, and the counts were corrected for radio decay. To correct for changes in plasma water during the TER measurements, counts were expressed as cpm/μmol albumin. After logarithmic transformation of this ratio, TER was determined from the slope of the regression line.
Plasma volume was calculated from the radioactivity at time zero by retrolapolation of the plasma disappearance curve and the injected amount of radioiodinated albumin, as measured by weighing the syringes before and after injection. The intravascular mass of albumin equals the plasma volume $\times$ plasma concentration of albumin. The serum albumin concentration was determined with a coefficient of variation of $<3\%$ on a Hitachi 917 by immunoturbi-dimetry with reagents from Dakopatts A/S using the procedure recommended by the manufacturer. The outflux of albumin (\(\mu\)mol/hour) was calculated by multiplying the intravascular mass of albumin (mmol) by the TER, measurement. Finally, the volume of plasma water cleared for albumin (mL $\cdot$ kg$^{-1} \cdot$ min$^{-1}$) was calculated by multiplying plasma volume and TER.$^{13,15}$

**Selectivity Index**

The theoretical basis for the comparison of the plasma disappearance of nonglycosylated/glycosylated labeled albumin by calculating the selectivity index was described in detail by Bent-Hansen et al.$^{15,16}$ The glycosylation of $^{125}$I-albumin was performed in sterile, closed vials. The incubation mixture consisted of 4 \(\mu\)Ci of $^{125}$I-albumin 0.03 mg/\(\mu\)Ci, 550 mmol/L glucose, and 0.9% benzyl alcohol in 25 mmol/L phosphate buffer (pH 7.8) to a final volume of 2.0 mL. Before use, the vials were kept incubated at 37°C for 48 hours. At all other times, they were kept at a temperature $<4^\circ$C. This procedure results in a degree of glycosylation of 5.5 mol of glucose per mol albumin. Glycosylation increases the net anionic charge of the compound$^{12}$ without significantly altering its size.$^{18}$ The selectivity index is the $^{131}$I-albumin/$^{125}$I-albumin clearance ratio per hour, and it expresses the relative disappearance of nonglycosylated versus glycosylated albumin. It will be $>1$ in controls,$^{16}$ and it is calculated from the slope of the correlation line (method of least squares) of the zero ratio (the sample at 2 minutes was drawn to determine the $\approx$ zero ratio) divided by the ratio at 10, 15, 20, 30, 40, 50, and 60 minutes. The comparison of the simultaneously determined plasma activities, instead of comparing the calculated TER of nonglycated albumin and that of glycated albumin, yields a much more sensitive analysis, which cancels some of the considerable variation in the calculation of TER.$^{16}$

**Histological Examination**

The histological examination was performed as previously described.$^{11}$ In brief, sections from cutaneous biopsies of the lower leg were used for a blinded, light microscopic, semiquantitative grading of the thickness of basement membranes in terminal arterioles and capillaries (Figure 1). Grading was as follows: grade 1, no thickening (Figure 1A); grade 2, thickening comprising $\leq50\%$ of the vascular wall; grade 3, thickening comprising $>50\%$ but not the entire circumference of the vessel (Figure 1B); and grade 4, thickening and severe narrowing of the entire vessel.

**Statistics**

Normally distributed data according to Shapiro Wilk’s W test were compared between groups by 1-way ANOVA and, if significant, by Student’s t test for unpaired data. When data were not normally distributed, the corresponding nonparametric test was used. Fischer’s exact test was used to test for differences in vascular structure between the groups. Simple regression analysis was performed between relevant parameters and albumin permeability parameters and histological grading of biopsies. In all analysis, \(P<0.05\) was considered significant. Values are presented as mean $\pm$ SD in the text and as mean $\pm$ SE in figures, if not otherwise indicated.

**Results**

Systolic and diastolic blood pressures and serum creatinine levels were significantly higher in cardiac transplant recipients than in controls and CHF patients; the latter 2 groups did not differ from each other. CHF patients and cardiac transplant recipients had significantly higher heart rates than controls. The cardiac transplant recipients had the highest heart rates (Table 1).

**Albumin Permeability Parameters**

The albumin permeability parameters are listed in Table 2. Plasma volume did not differ significantly between the 3 groups, although patients with HTX tended to have the lowest plasma volume (borderline significance compared with CHF patients, \(P=0.08\); not significant compared with controls). An inverse correlation existed between time since HTX and plasma volume \((r=-0.47, P<0.05)\). TER$_{ab}$ was highest in CHF patients and lowest in patients after HTX. The plasma volume clearance of albumin was significantly higher in CHF patients compared with controls and HTX patients. The serum albumin concentration was lower in HTX patients compared with controls and CHF patients, as was the total plasma content of albumin (intravascular mass of albumin). Thus, the resulting total flux of albumin across the capillary membrane was significantly higher in CHF patients than in controls or HTX patients; the latter 2 groups differed little (borderline significance of \(P=0.06\)). The TER$_{ab}$, plasma volume, intravascular mass of albumin, and albumin flux in the 4 patients investigated before and after HTX generally showed a pattern similar to that found in the entire population (Figure 2).
The plasma disappearance of the nonglycosylated albumin versus negatively charged glycosylated albumin expressed as the selectivity index (change in simultaneous transport ratio per hour) showed a significant difference between cardiac transplant recipients and the control group; the plasma disappearance of nonglycosylated albumin was favored in controls (Table 2).

Microvascular Histology and Albumin Transport
The semiquantitative light microscopic examination showed a thickening of basement membranes in terminal arterioles and in capillaries in a number of subjects in all 3 study groups; none of the groups differed from each other (Table 2). However, subjects from all 3 groups with thickening of the capillary basement membranes (grade 2 to 3) showed significantly lower TERalb levels than subjects without thickening of the capillary basement membrane (6.1 ± 1.8%, n = 32, versus 7.6 ± 2.6%, n = 19; P < 0.05; Figure 3). The pattern was similar in the 3 individual study groups as well, although it was only significant in controls (P < 0.05; Figure 3). The subjects with basement membrane thickening of the capillar-

| TABLE 2. Albumin Permeability Parameters, Plasma Volume, and Microvascular Histology |
|---------------------------------|--------|--------|
|                                 | Controls (n = 18) | CHF (n = 16) | HTX (n = 17) |
| Plasma volume, mL/kg           | 44 ± 8.2 | 47 ± 13.3 | 41 ± 8.4* |
| TERalb, %/hour                  | 6.5 ± 1.9 | 7.8 ± 1.7† | 5.9 ± 2.5‡ |
| Cl (TERalb), mL·kg⁻¹·min⁻¹      | 0.047 ± 0.15 | 0.061 ± 0.019¶ | 0.040 ± 0.018§ |
| Serum-albumin, μmol/L          | 648 ± 66 | 631 ± 79 | 578 ± 70‡# |
| IVMalb, mmol                   | 2.3 ± 0.5 | 2.5 ± 0.6 | 2.0 ± 0.4‖ |
| Albumin flux, μmol/hour        | 146 ± 43 | 195 ± 60# | 116 ± 52§¶ |
| Selectivity index, hour⁻¹      | 1.008 ± 0.019 | 0.997 ± 0.019 | 0.993 ± 0.022¶ |
| Capillary basement membrane thickness, grade I/II/III | 5/12/1 | 6/7/3 | 8/7/2 |
| Arteriolar basement membrane thickness, grade I/II/III | 9/9/0 | 9/6/1 | 9/7/1 |

Values are means ± SD unless otherwise indicated. Cl (TERalb) indicates plasma volume clearance of albumin; IVM, intravascular mass.

*P < 0.1, †P < 0.05, ‡P < 0.01, §P < 0.001 compared with CHF patients.

¶P < 0.1, ‖P < 0.05, #P < 0.01 compared with controls.

Figure 2. TERalb (A), plasma volume (B), intravascular mass of albumin (IVMalb, C), and albumin flux (D) in 4 patients before and after HTX. Each patient is marked with an individual designation throughout.
ies also had higher serum albumin levels than subjects without thickening (641±78 versus 580±63 mmol/L; P<0.01).

Discussion
The major finding of this study is that compensated patients with CHF caused by IDCM have an increased plasma albumin disappearance that normalizes after HTX. In addition, the thickening of capillary basement membranes is associated with a reduced plasma albumin disappearance and a higher plasma albumin level in patients with CHF before and after HTX, as well as in healthy control subjects; neither patient group differed from controls in capillary morphology. Finally, after HTX, patients seem to have a reduced selectivity index, which suggests reduced microcirculatory negative charge sites. This apparently has no association with the degree of plasma albumin disappearance.

The plasma disappearance of albumin has been thoroughly characterized in patients with type 1 diabetes of differing severities. In contrast, the most recent study of this parameter in CHF patients is >2 decades old, and no studies exist describing the whole-body microvascular disappearance of albumin after HTX. Present studies in these 2 patient populations seem warranted because (1) peripheral edema possibly affected by capillary permeability is still a clinical problem before and after HTX and (2) previous studies concerned patients with CHF of various causes who were treated in a manner far different from today.

Plasma Disappearance of Albumin in CHF
In the study by Hesse et al., patients with peripheral edema and elevated right atrial pressure had increased TERab. This normalized, despite slightly elevated right atrial pressures, after 1 to 2 weeks of sodium depletion and volume reduction. In contrast, the patients in the present study all had no visible peripheral edema and had plasma volumes similar to those of controls. Therefore, it is interesting that these patients had increased TERab. However, a rate constant may not be an exact measure of permeability. Thus, both a volume and a concentration factor were included; these factors illustrated that CHF patients also had increased albumin clearance and whole-body albumin flux. This may mirror the present use of ACE inhibitors and aspirin or warfarin, because both treatment modalities may increase capillary area through either reduced procoagulant state and microvascular clotting or through reduced vasoconstriction. ACE inhibition may also reduce basement membrane hyalinosis, which may influence microvascular permeability. In the present study, all but one patient with CHF were on aspirin or other anticoagulant therapy, and all were on long-term treatment with an ACE inhibitor.

Structural Microangiopathy and TERab
The association between increased capillary basement membrane thickness and reduced TERab indicates that a thicker microvascular wall may act as a more solid and less permeable barrier. Our findings support the view that the structural microvascular alterations previously demonstrated in CHF were compensatory and secondary to increased microvascular hydrostatic pressure. In addition, the present data suggest that this compensatory structural alteration may have restricted colloid permeability and thus acted as an edema-protective factor. These results agree with the finding of reduced pulmonary microvascular permeability in CHF and a thickened capillary-to-alveolar space-layer ratio in pulmonary hypertension. However, these results are in direct contrast to findings in type 1 diabetes, in which increasing microvascular basement membrane thickness occurs with increased TERab and increased severity of diabetic complications. Thus, our data support the view that the microvascular alterations seen in diabetes may be primary (metabolically and genetically determined according to the Steno hypothesis) rather than secondary (early alterations in capillary pressure). The relationship between TERab and cutaneous capillary basement membrane alterations is based on the assumption that the observed alterations in skin capillaries are a general microvascular phenomenon, because much of TERab comes from albumin clearance from visceral organs and skeletal muscle. The assumption seems relevant because differences in organ albumin clearance seem to be caused by differences in capillary density and perfusion rather than differences in the permeability of the individual vessels. In addition, cutaneous arteriolar basement membrane alterations and the distensibility of skin and skeletal muscle were interrelated.

The 3 study groups did not differ with respect to capillary and arteriolar basement membrane thickness. In previous studies from our laboratory, patients with CHF had increased arteriolar basement membrane thicknesses, and no or very few controls had alterations >grade 1. Angiotensin II has vascular mitogenic properties, and ACE inhibitors may reverse vascular structural alterations. Thus, the fact that all CHF patients in the present study were on long-term treatment with an ACE inhibitor may explain the similar distribution of basement membrane thickness of capillaries. In contrast, at the time when the previous investigations were performed, fewer patients had been treated for a shorter period with ACE inhibitors. The evaluation of biopsies was performed blindly and semiquantitatively by one person in the present study, which is in accordance with previous studies. Therefore, the semiquantitative grading of biopsies, all apparently within a normal range, may have resulted in a
differentiated grading within a more narrow spectrum of basement membrane thickness.

**HTX and TER\(_{\text{alb}}\)**

TER\(_{\text{alb}}\) and the clearance of albumin were reduced after HTX compared with levels in CHF patients. The whole-body albumin flux was lower in HTX patients than in controls and CHF patients as a result of (1) the low TER\(_{\text{alb}}\), (2) the relatively low plasma volume, and (3) the low serum albumin found in HTX patients. The low TER\(_{\text{alb}}\) despite high arterial pressure, may be a result of reduced capillary permeability (diffusion coefficient), perhaps through a reduction in inflammatory mediators; for example, cyclosporin reduced proteinuria in glomerulonephritis.\(^9,22\) The low levels of serum albumin do not seem to be caused by an increased extracorporal loss of albumin because none of the patients had proteinuria. More likely, reduced albumin synthesis may explain the low serum albumin levels after chronic illness. Alternatively, the overall albumin mass was not reduced, but rather distributed in a larger extracellular fluid volume in HTX patients.\(^23\) However, we did not demonstrate increased plasma volume in HTX patients.

**Selectivity Index**

The glycation of albumin takes place at free lysine amino terminals, thereby increasing the net anionic charge of the molecule.\(^24\) The size increases to a lesser degree, making the simultaneous transport index (ie, the selectivity index of the 2 albumins) a sensitive tool for a charge-dependent permeability analysis. In the kidney, the glomerular basement membrane functions not only as a simple molecular sieve, but also as an electrostatic barrier. The degeneration of this barrier in the kidney of patients with type 1 diabetes is probably a factor in the degree of urinary albumin excretion.\(^25\) The single earlier investigated comparing human whole-body disappearance of glycosylated and nonglycosylated albumin suggested a similar role of charge-dependency in relation to TER\(_{\text{alb}}\) in progressive type 1 diabetes.\(^16\)

In the present study, controls had a significantly higher selectivity index (a more electronegative barrier) than HTX patients, which suggests that a reduction in negative charge sites occurs in HTX patients. The anionic properties of the microvascular wall are likely caused by the high content of negatively charged glycosaminoglycans,\(^16\) thus indicating a defect synthesis of glucosaminoglycans in HTX patients. However, neither HTX patients who had an entirely normal plasma disappearance of albumin nor CHF patients, who had a selectivity index that did not differ from those of controls, had any association with TER\(_{\text{alb}}\). Nevertheless, the permeability to albumin and lipoproteins was highly correlated.\(^26\) Therefore, an increased transfer of negatively charged lipoproteins and of glycosylated products across the endothelium may cause vascular injury and be a factor in the characteristic vasculopathy seen after HTX.\(^27\) However, the role of whole-body microcirculation as an electric barrier is relatively vague and unclear and based only on data from the present and one previous study.\(^15\) Therefore, further studies are warranted. The glycosylation procedure of the present and previous investigation were identical, differing only in patient population. Nevertheless, the selectivity index was numerically lower in the controls of the present study.\(^15\)

Existing data have established the dependence of TER\(_{\text{alb}}\) on body fluid volume and pressure in subjects without diabetes.\(^4,5,7\) We extend this knowledge on factors that impact TER\(_{\text{alb}}\) by illustrating its dependence on microvascular morpholgy and its apparent independence of charge in subjects without diabetes. However, in addition to the mentioned factors, numerous other factors, such as endothelial function, general vascular function, exterior pressure, and air composition,\(^28\) may also have an important, independent impact on TER\(_{\text{alb}}\). Furthermore, although all patients investigated were selected among subjects who previously had no disease, we cannot entirely exclude the possibility that the results generated reflect a late stage of a disease of systemic origin.

In conclusion, compensated CHF due to IDCMI is associated with an increased plasma disappearance of albumin, which normalizes after HTX. These patients have a microvascular basement morphology similar to that of healthy controls. However, in all 3 groups, an increasing basement membrane thickness was directly associated with a reduced plasma disappearance of albumin. Thus, increasing basement membrane thickness may act as one edema-protective mechanism in certain pathophysiological states. In HTX patients, a possible reduction in microvascular charge-negative sites was found; this apparently did not influence overall plasma albumin disappearance.

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