Distribution and Transeapillary Exchange of Albumin in Congestive Heart Failure

By Richard S. Ross, M.D., W. Gordon Walker, M.D., and John D. S. Hammond, M.B., M.D.

With the technical assistance of Miss Ann Meyerhoff

In general, previous investigators have concluded that the capillary permeability to proteins is either normal or increased in patients with congestive failure. It is difficult to reconcile such results with the consistent finding of increased plasma volume in congestive heart failure. In a previous study of normal individuals, iodinated serum albumin was used to measure the transcapillary exchange rate of proteins, and in the present study this method is applied to the study of capillary permeability in patients with congestive failure.

Methods

Nineteen patients with congestive heart failure resulting from various underlying conditions have been studied. This group of patients has been compared statistically with a control group of 17 patients suffering from a variety of chronic diseases but without heart failure or edema. Three patients were studied during heart failure and after recovery.

The methods for determination of mean capillary permeability from the serum disappearance curve of radioactively labeled albumin have already been presented in detail. Briefly, between 12 and 100 μc. of radioiodinated human serum albumin was injected intravenously, the larger dose being used in the 7 patients from whom edema fluid was to be collected. Eight or more venous blood samples were obtained without stasis during the subsequent 36 hours and at daily intervals thereafter for 10 to 14 days.

Edema fluid was collected from 7 of the patients by means of Southey tubes inserted into the patients' legs 4 to 6 hours after the intravenous injection of the albumin. Approximately 25 ml. of edema fluid was collected from each leg, fluid contaminated with blood being discarded. The Southey tubes were then removed and pressure was applied to the puncture sites to prevent further fluid loss. The tubes were inserted in the same way at other sites on the legs on the next 2 days and thereafter at intervals of 1 or 2 days for as long as sufficient blood-free fluid could be obtained. The series of collections covered a period of from 3 to 10 days after the injection of labeled albumin.

The radioactivity was measured as previously described. After initial counting, the edema fluid was mixed with an equal volume of 50 per cent trichloracetic acid, filtered, and the filtrate counted. The difference between these 2 counts represented protein-bound radioactivity. Protein was measured by the macro-Kjeldahl technic as previously described.

The edema fluid was dialyzed against 12 per cent dextran solution until its total protein concentration was about equal to that in the serum. Paper electrophoresis was employed to determine the albumin fraction in the concentrated edema fluid and in the serum. The protein-bound radioactivity in each sample of blood and edema was expressed in terms of specific activity, defined as counts per minute per milligram of albumin. The over-all coefficient of variation of the estimate of specific activity was 3.0 per cent for the blood and 5.5 per cent for the edema.

The experiment shown in figure 1 is typical of the 7 patients in which edema fluid was collected.
# Albumin Exchange in Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Heart failure group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. dev.</td>
<td>Mean</td>
</tr>
<tr>
<td>Initial serum albumin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gm./100 ml.</td>
<td>2.57</td>
<td>0.50</td>
<td>2.39</td>
</tr>
<tr>
<td>Plasma volume L.</td>
<td>2.13</td>
<td>0.56</td>
<td>3.38</td>
</tr>
<tr>
<td>ml./Kg.</td>
<td>39.4</td>
<td>12.4</td>
<td>48.8</td>
</tr>
<tr>
<td>Vascular albumin mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gm.</td>
<td>53.9</td>
<td>10.0</td>
<td>81.1</td>
</tr>
<tr>
<td>Gm./Kg.</td>
<td>1.01</td>
<td>0.42</td>
<td>1.15</td>
</tr>
<tr>
<td>Extravascular albumin mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gm.</td>
<td>94.3</td>
<td>44.2</td>
<td>100.0</td>
</tr>
<tr>
<td>Gm./Kg.</td>
<td>1.77</td>
<td>0.94</td>
<td>1.51</td>
</tr>
<tr>
<td>Total exchangeable albumin mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gm.</td>
<td>148.1</td>
<td>60.6</td>
<td>100.2</td>
</tr>
<tr>
<td>Gm./Kg.</td>
<td>2.78</td>
<td>1.31</td>
<td>2.66</td>
</tr>
<tr>
<td>Fraction intravascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kpo* Hr.⁻¹</td>
<td>0.38</td>
<td>0.08</td>
<td>0.43</td>
</tr>
<tr>
<td>kpm* Hr.⁻¹</td>
<td>0.026</td>
<td>0.008</td>
<td>0.026</td>
</tr>
<tr>
<td>Metabolism* Gm./hr.</td>
<td>0.40</td>
<td>0.10</td>
<td>0.43</td>
</tr>
<tr>
<td>λa†</td>
<td></td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td>λe‡</td>
<td></td>
<td>0.0027</td>
<td></td>
</tr>
<tr>
<td>λm†</td>
<td></td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

*Rates:

kpo = fraction of plasma protein exchanged with extravascular protein per unit time.
kpm = fraction of vascular protein metabolized per unit time.

Metabolism = metabolism of albumin expressed as grams synthesized and degraded per hour.

†See figure 1.

## Results

The mean values of the measured albumin masses and exchange rates for the patients with congestive heart failure are shown in table 1, together with the mean values for the control group. The weight of the patient at the beginning of the study has been used for the expression of various masses and volumes in terms of unit body weight. Edema present initially in the heart failure group makes this weight greater than the true dry weight of the patient. Volumes or masses expressed as ml./Kg. or Gm./Kg. of body weight are, therefore, smaller in edematous patients than they would have been if a true measure of dry weight could have been used. Thus, the differences between the heart failure and the normal groups are minimized by this presentation.

The mean plasma volume for the group with heart failure is 3.38 L. or 48.8 ml./Kg., compared with 2.13 L. or 39.4 ml./Kg. for the control group. The absolute plasma volume and the plasma volume per unit weight are both significantly increased in the group with heart failure (total: p < .01; per Kg.: p < .05). The total vascular albumin mass is significantly greater in the heart failure group (p < .01), but the vascular albumin mass per unit weight is not. Neither the extravascular nor the total exchangeable albumin masses differ significantly in the 2 groups and the mean transcapillary albumin exchange rates (kpo) are the same. The fractional rate of metabolism (kpm) is greater for the control group.

*Table 1 is a summary of a complete table of results which has been deposited as Document number 6313 with the AM Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A copy may be obtained by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.
ALBUMIN IN HEART FAILURE

The product of $k_{pm}$ and vascular albumin mass, or the number of grams of albumin metabolized and synthesized per hour, is not, however, significantly different. The absolute values for metabolism of albumin in grams per hour are lower than those reported by others, but this discrepancy is easily explained by the differences in serum albumin concentration. Other investigators, using different methods of protein analysis, obtained higher values for albumin concentration, total vascular mass and, hence, metabolism.

Figures 2 and 3 compare relationships obtained in the heart failure group with data from the control group. In the control group (fig. 2 right), the plasma volume and the mean fractional transcapillary albumin exchange rate ($k_{pe}$) are positively correlated ($r = 0.75; p < .001$). As plasma volume increases, a larger fraction of the vascular albumin mass is transferred to the extravascular compartment per unit time. This highly significant positive relationship does not exist in the group with congestive heart failure (fig. 2 left). A similar relationship is demonstrated between vascular albumin mass (plasma volume × serum albumin concentration) and the mean transcapillary exchange rate ($k_{pe}$) ($r = 0.53; p < .05$) in normal individuals, but this relationship is not found in the group with heart failure.

In figure 3 bottom, the relationship between the vascular and extravascular albumin masses in the 16 control subjects is shown. These 2 quantities are positively correlated ($r = 0.84; p < .001$). A fourfold variation in vascular albumin is associated with a fifteenfold variation in extravascular albumin mass. Figure 3 top is a similar plot for the 19 patients with heart failure. In this group, there is no correlation between the vascular and extravascular albumin masses. The variation in vascular albumin mass is similar in both groups of patients, whereas that in extravascular albumin mass is much smaller in the patients with heart failure.

The relationship between the vascular albumin mass and the fraction of the total exchangeable albumin within the circulation has been studied. In the control group, no correlation can be demonstrated between these quantities, but a positive or direct relationship exists in the group of patients with heart failure ($r = +0.60; p < .01$).
In 3 instances, it was possible to perform complete studies on the same patient during heart failure and after recovery. In all 3 patients, recovery was associated with a decrease in plasma volume and vascular albumin mass and an increase in the mean fractional transcapillary albumin exchange rate ($k_{pe}$). The relation between plasma volume and $k_{pe}$ is shown in Figure 4.

The average concentration of albumin in the edema fluid collected from 7 of the patients was 2.1 mg./ml. with a range from 0.2 to 5.3 mg./ml. The albumin mass of the local edema pool could not be measured accurately, and therefore the local transcapillary rate of albumin exchange into the edema could not be determined. Hence, in comparing the mean rate of appearance of labeled albumin molecules in the extravascular compartment with the local rate of appearance in the edema, it has been possible only to make use of the constants $\lambda_1$ and $\lambda_E$ (figs. 1 and 5; table 1).

From the equations describing the transcapillary exchange of labeled molecules, it can be shown that $\lambda_1$, which represents the mean rate of decrease of specific activity of albumin in the serum, is equal to the mean rate of increase of specific activity throughout the extravascular albumin mass. It can be demonstrated that the rate of increase of labeled molecules in the extravascular albumin mass, which is equal to $\lambda_1$, is always greater than the fractional exchange rate of this compartment. Thus, a comparison of $\lambda_1$ and $\lambda_E$ is, in fact, a comparison of the mean rate of increase of specific activity throughout the extravascular compartments ($\lambda_1$), with the rate of increase in the segment of this compartment represented by the edema fluid ($\lambda_E$). In all 7 patients studied, $\lambda_1$ was greater than $\lambda_E$ (fig. 5), indicating that the mean rate of increase of specific activity throughout the extravascular compartment was more rapid in every case than the local rate of increase in the edema fluid.

No significant correlation exists between the slope of the concentration time plot of the edema radioactivity, $\lambda_E$, and the concentration of albumin in the edema. A rough estimate of the local extravascular mass of protein in the edema was obtained from the product of the albumin concentration in edema fluid and the
Discussion

In normal individuals, the transcapillary exchange of albumin is directly related to the vascular albumin mass and plasma volume (fig. 2). As the plasma volume rises, the rate of transfer of protein to the extravascular compartment increases. The extravascular albumin mass increases more rapidly than the vascular mass in response to an increase in total protein (fig. 3). The extravascular protein mass serves as a reservoir and the relation of the transcapillary exchange rate to plasma volume provides a mechanism whereby changes in plasma volume are minimized.

This normal regulatory mechanism does not operate in the patients with heart failure. The transcapillary exchange rate of albumin does not rise with plasma volume and vascular mass, and hence the normal relation between the vascular and extravascular albumin masses does not exist (fig. 3 top). In congestive failure, as vascular albumin mass increases, this mass constitutes a larger fraction of the total exchangeable albumin and the fraction in the extravascular compartment becomes proportionately smaller. The mean values for plasma volume and transcapillary exchange (table 1) reflect the relations illustrated in figures 2 and 3. The mean plasma volume of the group of patients with heart failure is significantly larger than that of the control group, while the mean value for transcapillary exchange in congestive failure is identical with that of the control group. If the normal relation had existed between these 2 variables, a larger mean value for the transcapillary exchange rate would have been expected in association with the larger plasma volumes of the congestive failure group. Thus, the exchange rate, though not reduced in the absolute sense, is decreased relative to the plasma volume and vascular albumin mass in patients with congestive failure.

From this comparison of 2 populations, we have concluded that capillary permeability is reduced relative to the plasma volume in heart failure. This conclusion is strongly supported by the results of studies on 3 patients studied during heart failure and after recovery. In all 3 patients, an increase in the transcapillary exchange rate of protein was associated with a fall in plasma volume (fig. 4) and in vascular albumin mass. Thus, the albumin exchange rate, and hence presumably capillary permeability, must have been decreased relative to the expanded plasma volume of the patients prior to recovery. It seems reasonable to assume that this decreased capillary permeability preceded, and was indeed responsible for, the increase in vascular albumin mass and subsequent expansion of plasma volume.

The fractional redistribution between vas-
cular and extravascular compartments must entail either a decrease in the rate of transfer of albumin through the walls of the blood capillaries into the extravascular space or an increase in its rate of return to the circulation via the lymphatic capillaries. It is known that the walls of lymphatic capillaries, in contrast to those of the blood capillaries, offer no resistance to the large plasma protein molecules, and it thus seems unlikely that changes in their permeability could effect an increase in the rate of albumin transfer back into the circulation. Thus, it seems reasonable to assume that the fractional increase in vascular albumin which occurs as the vascular albumin mass and plasma volume increase in patients with heart failure results from a decrease in the permeability of the blood capillaries to albumin.

There are 3 possible mechanisms which might explain the observed results: (1) a decrease in permeability per unit area of all capillary membranes; (2) a decrease in the total area available for transfer with permeability per unit area remaining constant; or, (3) the elimination of some areas of high capillary permeability with shunting of a larger fraction of total blood flow to areas of low permeability. All seem plausible as explanations. From the present study, we have no evidence in preferential support of any of these 3 possibilities. The observed reduction in hepatic blood flow in heart failure may lend support to the last possibility, since reduction in flow to this area, which is relatively highly permeable to protein, may significantly lower the "mean" capillary permeability to albumin as measured by the present method.

It is to be emphasized that the present analysis of the serum disappearance curve yields a mean value consisting of both faster and slower rates distributed about this average. The uncertainties inherent in this type of analysis were discussed in the previous paper. Though the mean transcapillary exchange rate is reduced in heart failure, it is possible that the local rate of exchange in edematous areas is greater than the whole body mean rate. The edema fluid studies demonstrate that this was not the case as the edema fluid specific activity rose at a rate which was slower than the rate of increase in specific activity throughout the extravascular space. No conclusions can be drawn regarding the relation of the local exchange rate as measured in heart failure to that in the normal limb, as it is not possible to obtain blood-free extravascular fluid from normal individuals under physiologic circumstances in sufficient quantity for control studies.

In 4 of the 7 patients, specimens of edema fluid were collected for a sufficiently long period of time for the specific activities of the blood and the edema to become equal. In 3 of these 4 patients, the concentration time plot of the radioactivity of the serum had assumed.

\[ \lambda_1: \text{the slope of the first phase of the double exponential serum disappearance curve of serum radioactivity.} \]

\[ \lambda_E: \text{the slope of the edema appearance curve. (See text.)} \]
the slope $\lambda_2$ at least 2 days before the specific activity of serum and edema fluid had become equal (fig. 1). This disparity between the equilibrium times of the total extravascular albumin mass and that of the local edema pool indicates that the albumin of edema fluid constitutes a very small fraction of the total extravascular albumin mass. The slow rate of transfer of labeled albumin molecules from serum to edema fluid has little effect on the apparent time taken for the specific activity of the total extravascular compartment to equilibrate with that of the serum.

From measurements of extravascular albumin mass and estimates of extracellular water, it can be calculated that the mean concentration of albumin throughout the extravascular space would be approximately 5 mg./ml. The observed concentration in edema fluid was usually approximately 2 mg./ml., indicating that the extravascular albumin space is not uniform and the edema being sampled constitutes a subdivision in which the albumin concentration is much lower than the average concentration for the entire extravascular albumin mass.

A significant quantity of radioactivity was found in the edema fluid filtrates after the protein had been precipitated by trichloracetic acid (see Methods). This radioactivity present in the filtrate represented radioiodine ($^{131}$I) which had been separated from protein but which was not promptly excreted. In 6 of the 7 patients studied, the quantity of this nonprecipitable radioiodine present in edema increased progressively and the highest levels were reached from 48 to 240 hours after injection. In the sample containing the largest amounts of nonprecipitable radioactivity, this fraction constituted from 20 to 65 per cent of the total radioactivity of the sample. The persistence of this material and the progressive rise in concentration with time indicates that this is not simply $^{131}$I present as the iodide. It seems likely that this nonprecipitable fraction in the edema fluid may be equivalent to the nonexchanging compartment 6 postulated by Lewallen et al.

Summary

The distribution and transcapillary exchange of albumin have been studied in patients with congestive heart failure and the results compared with a group of control subjects who did not have heart failure.

The normal relation between vascular albumin mass and plasma volume on the one hand and transcapillary albumin exchange on the other does not exist in patients with congestive failure. The transcapillary albumin exchange rate, which presumably reflects capillary permeability, is decreased relative to the plasma volume and vascular albumin mass. It appears that decreased permeability of capillaries to albumin is associated with congestive failure and may be responsible for the increased plasma volume characteristic of this disease.

The appearance of labeled protein in edema fluid has been studied in 7 patients and compared with the simultaneously determined serum disappearance curves. The albumin contained in the edema fluid constitutes a small fraction of the total extravascular albumin pool. The vascular albumin mass equilibrates less rapidly with the local edema albumin mass than with the total extravascular albumin mass.

Interlingua in Summario

Le distribution e le echange transcapillar de albumina esseva studiate in patientes con congestive disfallimento cardiae, e le resultatos obtenite esseva comparate con illos ab un gruppo de subjectos de controlo qui non suffrova de disfallimento cardiae.

Le relation normal inter le massa de albumina vascular e le volumine de plasma (de un latere) e le echange transcapillar de albumina (del altere) non existe in patientes con disfallimento congestive. Le intensitate del echange transcapillar de albumina, que presumitemente reflete le permeabilitate capillar, es reducite relative al volumine de plasma e al massa de albumina vascular. Il pare que un reducite permeabilitate del capillares pro albumina es associate con disfallimento congestive e es possibilemente responsabile pro le augmento del volumine de plasma que es characteristic de iste morbo.

Le re-apparition de materie proteina in liquido edematose esseva studiate in 7 patientes e comparate con le simultaneamente determinate curvas de disparition ab le sero. Le albumina continite in le liquido edematose representa un micre fraction del total thesaurus...
de albumina extravascular. Le massa de albumina vascular se pone in equilibrio minus rapidemente con le massa de albumina de edema local que con le massa de albumina extravascular total.

References
Distribution and Transcapillary Exchange of Albumin in Congestive Heart Failure
RICHARD S. ROSS, W. GORDON WALKER and JOHN D. S. HAMMOND

Circ Res. 1960;8:1041-1048
doi: 10.1161/01.RES.8.5.1041

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/8/5/1041

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/