Intrarenal Blood Flow in Congestive Heart Failure

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SUMMARY
Intrarenal blood flow distribution was measured by the $^{133}$Xenon washout technic in 10 patients with heart disease who were studied at time of left and right heart catheterization. Renal washout curves were analyzed by computer using a weighted least-squares nonlinear regression technic. In three patients with heart disease without edema the compartment I blood flow rates (outer cortex) were not significantly different from those found in nine normal kidney donors. In seven patients with hemodynamic evidence of heart failure and clinical edema the compartment I flow rates were significantly lower than those of the normal control group and of a group of sodium-depleted hypertensive patients. The rate constants of isotope removal from more central regions of the kidney (compartments II and III) were not depressed to a similar degree. Infusion of furosemide into the renal artery induced diuresis in eight studies which was accompanied by preferential increases in compartment I flow rates in six. The data suggest that preferential vasoconstriction of renal cortical vessels may contribute to increased sodium retention by the kidneys and to edema formation in patients with congestive heart failure.

Additional Indexing Words:
Intrarenal blood flow $^{133}$Xenon washout technic
Furosemide Edema formation

The mechanisms responsible for abnormal renal sodium retention in congestive heart failure remain unclear, despite evidence that both hemodynamic and hormonal influences are operative. Increased secretion and urinary excretion of aldosterone have been observed in patients and animals with heart failure and circulatory congestion, but these are not invariable findings. The possible roles in the edema formation of heart failure of an extraadrenal factor which increases the responsiveness of the kidneys to aldosterone or of natriuretic hormones remain to be elucidated.

In advanced congestive heart failure, total renal blood flow and glomerular filtration rate decline as the kidneys share in the vasoconstrictive response to diminished cardiac output. However, normal values of glomerular filtration rate have been observed in patients with mild degrees of heart failure who were forming edema. The overriding importance of increased tubular reabsorption of sodium in heart failure was demonstrated by Barger who observed that dogs with congestive failure due to surgically induced pulmonic stenosis and tricuspid insufficiency failed to excrete a salt load which was infused directly into the renal artery. At the time of these studies plasma aldosterone levels were not measured; however, the degree of sodium retention appeared related to the degree of hemodynamic alteration since pulmonary banding alone led to decreased sodium excretion but not ascites formation.

In later studies, Barger and co-workers reported that the distribution of blood flow within the kidneys was altered in this model of chronic congestive heart failure and that sodium retention correlated with reductions of blood flow in the outer cortex. Accordingly, the present studies were undertaken to investigate whether alterations of intrarenal hemodynamics might contribute to edema formation in human heart failure. The results obtained in patients with heart disease and clinical manifestations of edema are compared to patients with heart disease without edema and to a control population of normal kidney donors and sodium-restricted hypertensive patients.
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Methods

Intrarenal blood flow distribution was measured in 10 patients with heart disease and 14 control subjects from the renal washout of 133Xenon by the method of Thorburn et al. The theoretic basis for the measurement of nutrient blood flow from the washout of inert radioactive gases has been described by Kety. It is based upon the assumption that the diffusibility of the inert gas is sufficiently high to maintain equilibrium under physiologic conditions between the tissue and the venous capillary blood flow leaving the tissue. When a bolus of 133Xenon is injected into the main renal artery, it is distributed among the intrarenal compartments of flow; the quantity (%) of 133Xenon received by each of the compartments is directly proportional to the fraction of total renal blood flow constituting the respective compartment. The xenon can be removed from the renal tissue only by urine, lymph, or capillary blood flow. Since urine and lymph flow are small relative to the renal blood flow, and because Thorburn et al. have indicated that free xenon activity is lost in urine at low flow rates, the rate of disappearance of 133Xenon from the kidney is a measure of capillary (nutrient) blood flow.

The equations by which the Kety modification of the Fick principle has been applied to measure the distribution of intrarenal blood flow from the externally monitored renal washout curve of a radioactive inert gas have been detailed by Thorburn et al. and Ladefoged. For analysis of curves obtained in animal experiments these groups have assumed that the curves were composed of four exponential terms corresponding to four flow compartments arranged in parallel. Radioautographic studies utilizing 85Kr have localized the four components of the isotope washout curve as follows: (1) the outer cortex, (2) the juxtamedullary region (inner cortex and outer medulla), (3) the inner medulla, and (4) the hilar and perirenal fat. Recirculation of indicator does not interfere with measurements of blood flow in the first two regions because 133Xenon or 85Krypton is largely eliminated in one passage through the lungs. A bolus of 1–3 mCi of 133Xenon dissolved in isotonic saline was injected into a catheter positioned in the renal artery and was followed by a flushing dose of 5 ml of saline. The rate of disappearance of the isotope was monitored externally by a 2-in NaI scintillation crystal located 3 in from the end of a cylindrical collimator which was positioned perpendicular to the abdominal wall over the kidney under study. The output from each crystal was led through a dual pulse-height analyzer (window settings 50–100 kev) to a dual rate computer and digital printer. Counts were integrated and printed every 2 sec for the first 2 min, every 6 sec for the next 10 min, and every 12 sec for the subsequent 8 min. In four studies the washout was recorded for a duration of 40 min. Peak radioactivity recorded over the kidney ranged from 150,000 to 1,500,000 counts/min with background of 150–300 counts/min.

The data from each study were analyzed by means of a nonlinear regression technic using an IBM 360/91 computer. Sequentially multieponential equations containing two, three, or four exponential terms were applied to the data by the method of weighted least squares, and the parameters (intercepts and rate constants) and their confidence limits were calculated. Whether the addition of another exponential term to the equation describing the data produced a statistically significant reduction of the residual error of the data about the fitted curve was calculated by an F test. From the parameters of the equation which contained the greatest number of statistically significant terms the tissue blood flow rates in the two most rapid flow compartments within the kidney were calculated by the Kety formula: F (ml/100g/min) = α × λ/ρ where α is the rate constant of 133Xenon washout from the compartment and λ is the blood tissue partition coefficient for 133Xe in the kidney, and ρ is the specific gravity of the tissue (1.01). The weighted arithmetic mean blood flow was also calculated from the parameters describing each 133Xe washout curve, because Ladefoged has reported that this mean flow correlates with flow/g calculated from electromagnetic flowmeter renal blood divided by kidney weight. In 17 133Xenon renal washout curves from dog studies analyzed in this way, the weighted arithmetic flow times the kidney weight was directly related to the simultaneously measured total renal blood flow measured with a Statham M 4000 electromagnetic flowmeter (r = 0.83, P < 0.001).

The study group was comprised of 10 patients with heart disease, five females and five males, aged 26 to 63 years, who were studied at the time of diagnostic right and left heart catheterization. In seven of the patients there was evidence of pulmonary or peripheral edema, despite digitalis, diuretics, and dietary salt restriction (table 1). Control studies of the intrarenal circulation were obtained in seven normal individuals who had renal arteriograms and radioisotope studies as part of their evaluation as prospective kidney donors, and in seven hypertensive individuals undergoing diagnostic workup. Members of the latter group had normal urinalyses and serum creatinine concentrations and had no evidence of heart disease. The hypertensive subjects received sodium-restricted diets (10 mEq Na/day) in a metabolic balance ward for 3–5 days prior to study.

In the patients with heart disease, right and left heart catheterization was performed in the basal state using standard technics. After completion of the cardiovascular hemodynamic measurements, a Cordis end-hole (no. 8 French) catheter was advanced via the brachial artery retrograde into the main renal artery. Cardiovascular hemodynamics were not measured in the control subjects; in these the renal artery was catheterized via the femoral artery using the Seldinger technic. The position of the catheter in the renal artery was checked by fluoroscopy during the injection of 2 ml of Conray 60 (iothalamic acid); absence of reflux of injectate into the aorta and a complete view of the kidney were the criteria for optimal catheter placement. Ten minutes

*Obtained as Xenisol from Mallinkrodt Chemicals, St. Louis, Missouri.

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were allowed to dissipate the vasocostricte efects of the dye prior to isotope injection.23

Following control measurements of renal 133xenon washout in eight patients (two normal control subjects, three hypertensives, and three patients with heart disease) an injection of furosemide (80 mg dissolved in 10 ml of saline) was made over 1–2 min into the renal artery of the kidney under study. The measurement of intrarenal blood flow distribution was repeated 5 and/or 30 min later.

In one patient the renal washout of 133xenon was monitored by means of a multiple-crystal scintillation camera (the Baird Atomic Autofluoroscope, model 5600) and a 1.5-in multichannel collimator. This instrument is a radiation detector composed of 294 individual NaI scintillation crystals arranged in a x-y rectangular matrix. The counts recorded by each crystal are recorded on magnetic tape in a position corresponding to the location of the crystal in the matrix. The radioactivity by each crystal can also be displayed on an oscilloscope as light of proportional intensity. Thus radioactivity within an organ can generate an isotope picture, a scintiphotograph. In the study of the patient, counts recorded by all the crystals overlying the kidney were summed during each counting interval in order to generate a renal washout curve similar to that obtained with one large crystal. Scintiphotographs showing gamma radition from 133xenon within the organ were obtained at various points along the curve.

The results were analyzed by standard statistical technics.24 Differences between groups of patients were compared by the Student t test and were declared significant if P was < 0.05.

Results

Table 2 summarizes the measurements of renal 133xenon washout in the control studies. In nine of 12 kidneys in the seven normal kidney donors, the renal washout curve was fitted best by an equation containing four exponential terms; in three kidneys the best statistical fit was obtained using an equation containing three exponential terms. The rate constants of 133Xe washout from the most rapid flow compartment (compartment I) in all normal curves were similar (compartment I α = 5.65 ± 1.18 sp) as were the rate constants of isotope loss from the slowest compartment in all curves (α = 0.01). In the three curves described best by an equation containing three exponentials, the midcurve exponential had a rate constant (αII = 0.47 ± 0.10) which was midway between the rate constants describing compartments II and III in the normal curves which were fitted by equations containing four exponential terms (αII = 1.14 ± 0.58; αIII = 0.18 ± 0.10).

In the 12 normal kidneys the most rapid flow compartment (compartment I) received 84 ± 10% of the injected isotope. Calculated tissue blood flow
### Table 2

**Intrarenal Blood Flow Distribution in Normal Kidney Donors on Unselected Salt Diet and Patients with Uncomplicated Essential Hypertension on Salt-Restricted Diets**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compartment I*</th>
<th>Compartment II</th>
<th>Compartment III</th>
<th>Compartment IV</th>
<th>Arith mean flow (ml/min/100 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A* (%)</td>
<td>a</td>
<td>Flow (ml/min/100 g)</td>
<td>A* (%)</td>
<td>a</td>
</tr>
<tr>
<td>4 Exponential curves (N = 9)</td>
<td>83 ± 11</td>
<td>5.68 ± 1.13</td>
<td>412 ± 82</td>
<td>12 = 8</td>
<td>1.14 ± 0.58</td>
</tr>
<tr>
<td>3 Exponential curves (N = 3)</td>
<td>84 ± 5</td>
<td>5.53 ± 1.59</td>
<td>400 ± 15</td>
<td>9 = 5</td>
<td>0.47 ± 0.10</td>
</tr>
<tr>
<td>Mean (N = 12)</td>
<td>84 ± 10</td>
<td>5.65 ± 1.18</td>
<td>400 ± 86</td>
<td>12 = 9</td>
<td>0.88 ± 0.23</td>
</tr>
<tr>
<td>4 Exponential curves (N = 6)</td>
<td>80 ± 16</td>
<td>4.36 ± 0.67</td>
<td>316 ± 49</td>
<td>12 = 9</td>
<td>0.88 ± 0.23</td>
</tr>
<tr>
<td>3 Exponential curves (N = 4)</td>
<td>84 ± 9</td>
<td>4.35 ± 0.5</td>
<td>315 ± 36</td>
<td>13 = 5</td>
<td>0.4 ± 0.08</td>
</tr>
<tr>
<td>Mean (N = 10)</td>
<td>82 ± 13</td>
<td>4.36 ± 0.58</td>
<td>315 ± 42</td>
<td>13 = 5</td>
<td>0.4 ± 0.08</td>
</tr>
</tbody>
</table>

*Compartments correspond to the respective components of the multiexponential $^{133}$Xe washout curve.

Abbreviations: $A*$ = initial percentage of isotope distributed to the compartment; $a$ = slope of the exponential from which flow is calculated; Compartment I = rapid flow - outer renal cortex; Compartments II, III = intermediary regions (possibly inner cortex and medulla); Compartment IV = perirenal fat; all $a = \sigma$.

In compartment 1 was 406 ± 86 ml/100g/min.

Several groups using radioautographs in animals have provided evidence that the most rapid washout study. It is apparent that the oval image, produced by $^{133}$Xe, was absorbed, presumably from the outer cortical region of the kidney. The fact that in these normal kidneys the posterior cortex was not shown to be the second region of interest is that the normal kidneys were not shown to have the greatest isotope removal rate. The data on $^{133}$Xe washout from the normal kidneys (0.01) suggest that this compartment is not represented by perirenal or hilar fat.
Figure 1
Scintiphotographs taken during the washout of \(^{133}\text{Xenon}\) from the human kidney. The upper scintiphotograph depicts the oval image of the kidney produced by the isotope during seconds 8–16 of the washout curve. A concentric reduction of the renal image is apparent in the lower scintiphotograph taken during seconds 110–120 where the first component of the curve is nearly complete, suggesting that compartment I corresponds with blood flow through the outer renal cortex.

Weighted arithmetic mean flow in the 12 kidneys from the normal subjects was 340 ± 70 ml/100g/min.

Seven hypertensive patients were studied while receiving sodium-restricted diets (table II); mean urinary sodium excretion during the 24 hours preceding the study was 34 ± 14 mEq. The \(^{133}\text{Xe}\) washout curves were fitted best by equations containing four exponentials in six kidneys and by equations with three exponential terms in four. There was no significant difference in the percentage of isotope received by compartment I in the hypertensive kidneys compared to the normal group (82 vs 84%). However, compartment I nutrient blood flow was significantly reduced below normal, averaging 315 ± 42 ml/100g/min (\(P < 0.01\)).

Compartment II received 12% of the \(^{133}\text{Xe}\) in the six studies with four-term curves and in these kidneys the compartment II flow rate was 64 ± 16 ml/100g/min, a value not significantly different from the compartment II flow rate in the four-term curves obtained from the normal kidney donors. In the four curves which were fitted by three exponential equations, the \(\alpha_{11}\) and the blood flow rates calculated from \(\alpha_{11}\) were not significantly different from the values obtained in three-term curves from the normal group. The weighted arithmetic mean flow in the sodium-restricted hypertensives averaged 259 ± 38 ml/100g/min.

The \(^{133}\text{Xe}\) renal washout curves from the three nonedematous patients with heart disease were described best by equations containing three exponentials (table 3); that of patient A appears in figure 2 (bottom). In the three patients, an average of 85% of injected isotope was distributed to compartment I and the mean compartment I ("cortical") blood flow rate was 372 ± 45 ml/100g/min; these values are not significantly different from the normal control patients. The \(\alpha_{11}\) and calculated compartment II blood flow rate of 37 ± 12 ml/100g/min were also not significantly different from the comparable parameters of the three exponential washout curves obtained from studies of normal kidneys. Weighted arithmetic mean renal

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blood flow in the three nonedematous patients with heart disease was also not significantly different from the normal flow of 316 ± 39 ml/100g/min.

The $^{133}$Xe renal washout curves of the seven patients with heart failure and circulatory congestion were best fitted by equations containing three exponential terms (table 3); that of patient B appears in figure 2 (top). In this group, the percentage of isotope delivered to compartment I was slightly reduced to 78 ± 13%. However, the blood flow rate of compartment I, the "cortical" compartment, was 164 ± 48 ml/100g/min, a value significantly lower than that found either in the normal subjects or the sodium-restricted hypertensive patients ($P < 0.001$). The $\alpha_{1}$ and blood flow calculated from compartment II of these curves were also reduced slightly, but not significantly, below comparable values obtained in three component curves from the two groups of control studies. Weighted arithmetic mean flow was markedly reduced to 135 ± 46 ml/100g/min in the patients with heart failure and edema.

Cardiovascular hemodynamic measurements in the 10 patients with heart disease also appear in table 3. Normal mean values for cardiac index and for ventricular end-diastolic pressures were obtained in the three patients with no clinical evidence of edema. In the seven patients with congestive heart failure, the mean cardiac index was below normal and there were significant elevations of the mean end-diastolic pressures in the left and right ventricles. There was no significant correlation between cardiac index and compartment I blood flow ($r = 0.32$) in the 10 patients with heart disease. Left ventricular end-diastolic pressure ($r = 0.42$) and pulmonary wedge pressure ($r = 0.56$) were also unrelated to altered flow in compartment I. However, a significant inverse relationship was found between blood flow in compartment I (outer cortex) and the right ventricular end-diastolic pressure (fig. 3).

Following initial renal hemodynamic measurements, eight patients received a renal arterial injection of furosemide (80 mg) and the recording of $^{133}$xenon washout was repeated 5 min later in all studies and 30 min later in three of these studies.

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**Figure 2**

$^{133}$Xenon washout curves in two subjects with rheumatic heart disease. Patient A (lower curve) had no clinical evidence of edema and the washout curve is not significantly different from normal. Patient B (upper curve) was clinically edematous and the renal washout curve revealed marked reduction in "critical" blood flow.

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All subjects experienced a diuresis within 30 min. The renovascular response to the drug was variable (fig. 4). In two patients there was a reduction of compartment I flow 5–10 min following furosemide with a return toward control values at 30 min (one patient). Apparent renal vasodilatation occurred in six patients, however. In four of these, compartment I flow rates increased to an extent proportionately greater than \( \alpha_{II} \) or arithmetic mean blood flow. In two other patients with heart failure (not shown in table 3), whose control washout curves had been described only by two exponentials, there was such an increase in the \(^{133}\)Xe washout rate following the diuretic that an equation with three and four exponential terms now provided the best statistical fit of the data. In these two studies the blood flow rates calculated from compartment I after furosemide were not significantly different from those obtained in the normal control subjects.

**Discussion**

In the present study, the intrarenal distribution of nutrient blood flow was measured with \(^{133}\)Xe in patients with and without edema secondary to heart disease. The data indicate that the tissue blood flow in compartment I, the outer cortex of the kidney, was significantly reduced in the patients with congestive heart failure. Isotope washout from the remaining flow compartments within the kidney was not increased, but was either unchanged or reduced to a lesser degree. These data when combined with other studies in experimental

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**Table 3**

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Diagnosis</th>
<th>Compartment I</th>
<th>Compartment II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( A^* (%), \alpha )</td>
<td>( A^* (%), \alpha )</td>
</tr>
<tr>
<td>Heart Disease without Edema ( (N = 3) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RHD: MS</td>
<td>83, 5.63, 409</td>
<td>13, 0.433, 32</td>
</tr>
<tr>
<td>2</td>
<td>ASHD</td>
<td>84, 5.29, 385</td>
<td>13, 0.380, 28</td>
</tr>
<tr>
<td>3</td>
<td>RHD: AI, MI</td>
<td>89, 4.36, 322</td>
<td>9, 0.690, 50</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>85, 5.09, 372</td>
<td>12, 0.498, 37</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>3, 0.66, 45</td>
<td>2, 0.160, 12</td>
</tr>
<tr>
<td>Heart Disease with Edema ( (N = 7) )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RHD: AI</td>
<td>79, 3.01, 218</td>
<td>18, 0.485, 35</td>
</tr>
<tr>
<td>2</td>
<td>RHD: AI, MI</td>
<td>54, 1.61, 116</td>
<td>35, 0.315, 23</td>
</tr>
<tr>
<td>3</td>
<td>UHD</td>
<td>69, 1.65, 84</td>
<td>19, 0.308, 22</td>
</tr>
<tr>
<td>4</td>
<td>RHD: MS, MI, AS, AI</td>
<td>85, 2.78, 204</td>
<td>7, 0.249, 18</td>
</tr>
<tr>
<td>5</td>
<td>RHD: MI</td>
<td>79, 2.30, 166</td>
<td>18, 0.473, 34</td>
</tr>
<tr>
<td>6</td>
<td>RHD: MS, MI</td>
<td>91, 2.48, 180</td>
<td>6, 0.304, 22</td>
</tr>
<tr>
<td>7</td>
<td>Left atrial myxoma</td>
<td>92, 2.49, 180</td>
<td>4, 0.374, 27</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>78, 2.33, 164</td>
<td>15, 0.358, 26</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>13, 0.53, 48</td>
<td>11, 0.09, 6</td>
</tr>
</tbody>
</table>

Abbreviations: RHD = rheumatic heart disease; ASHD = arteriosclerotic heart disease; UDH = unknown heart disease; LA myxoma = left atrial myxoma; MS = mitral stenosis; MI = mitral insufficiency; AS = aortic stenosis; AI = aortic insufficiency; intracardiac pressures are denoted as: RA = right atrium; RV = right ventricular end-diastolic; PA = pulmonary artery; PAV = pulmonary artery wedge; LV = left ventricular end-diastolic; CI = cardiac index. Intrarenal compartments (exponentials of \(^{133}\)Xe washout curve) AO = initial quantity of isotope per compartment; \( \alpha \) = slope of exponential; mean blood flow = weighted arithmetic mean.
animals suggest that preferential vasoconstriction of renal cortical vessels may contribute to the increased renal sodium retention which characterizes edema formation in clinical heart failure.

The inert gas technic, an adaptation of the Fick principle developed by Kety for studies of capillary blood flow in many tissues, was first applied to the measurement of intrarenal blood flow distribution by Thorburn et al. The assumptions and equations involved in the method have been reviewed previously. The data from each washout curve (tables 2, 3) were analyzed on an IBM 360/91 computer by a weighted least-squares nonlinear regression technic. This computer technic avoids some of the subjective errors which occur with graphic curve peeling methods of analysis and it also applies statistical technics to parameter assessment. Studies using data with known parameters also indicated that the computer program could separate exponential terms whose rate constants differed by 1.6 (vs the threefold difference required to separate exponentials by graphic methods).

The washout curves in the seven normal kidneys of prospective kidney donors were described “best” in a statistical sense by applying equations containing four exponential terms to the data in nine studies, and by an equation containing three exponentials in three studies. Rosen et al. and Hollenberg et al., using a graphic analysis, also found four terms in normal human renal washout curves, whereas Ladefoged used a three-term model in his analysis of curves obtained in normal and hypertensive patients. The values obtained for compartment I flow rates have been similar in all published studies. The study with the scintillation camera (fig. 1) confirms a similar report of
Blaufax et al. suggests that compartment I of human renal washout curves represents blood flow to the outer cortex. While we do not attempt to provide an anatomic localization for compartment II, the mean flow rate in normal subjects of normal four-term curves is comparable to that reported for juxtamedullary flow in animals. The apparent “fusion” of compartments II and III found in many curves (tables 2, 3) may result from inability of the computer to separate compartments with rate constants of similar magnitude; such inability to separate exponentials is probably a complex function of the Poisson error of radioactivity counting, biologic flow fluctuations, the time intervals of data collection, and the magnitude of counts recorded.

The compartment I (outer cortical) blood flow rates in the patients with heart disease without historic or clinical evidence of edema were not statistically different from those found in the normal control subjects; compartment II flows were also similar in the two groups (three exponential curves). The patients in both groups were receiving unrestricted salt diets at the time of study.

In contrast, the cortical flow rates were significantly subnormal in the cardiac patients with hemodynamic evidence of heart failure and edema. Because dietary sodium restriction has been reported to reduce cortical perfusion rates in animals and man, it was necessary to compare the results obtained in the edematous patients (who were on low-salt diets) with a control group of subjects who also had been depleted of sodium. The cortical blood flow rates in the patients with heart disease and edema were significantly lower than those found in seven hypertensive patients, who had received a low-sodium diet for 3–5 days prior to study.

Diminished cortical blood flow has also been reported in several other experimental situations in which renal tubular sodium reabsorption was increased: acute partial occlusion of the thoracic inferior vena cava, hemorrhage, stimulation of the sympathetic nerves, infusion of norepinephrine, and in dogs with heart failure due to pulmonary stenosis and tricuspid insufficiency. In man, cortical blood flow rates have been reported to be reduced in salt-depleted normal subjects and in patients with cirrhosis and ascites.

In the study of Barger and co-workers of dogs with heart failure, the flow rate in compartment II increased, as that in compartment I diminished. In the present studies, the rate constants of 133Xe washout from compartments II and III were not increased in the patients with congestive heart failure; rather the washout rate constants of compartments II and III were only slightly reduced (insignificantly) in studies in which there were proportionately greater reductions in the rate constants of 133Xe washout from compartment I. These data suggest preferential vasoconstriction in the renal cortex, rather than reciprocal changes in flow between renal cortex and more central regions of the kidney.

There is no readily apparent explanation for different intrarenal flow patterns in congestive heart failure. Possibly there may be differences in the intrarenal responses to myocardial failure in the canine and human kidneys. Alternatively the difference may result from the pronounced degree of renal vasoconstriction present in the population of patients with heart failure who were studied (table 3). In several types of animal experiments, redistribution of flow was most apparent when the renal vasoconstrictive stimulus was mild and it was less apparent when there were marked reductions of total renal blood flow (e.g., hemorrhage, thoracic caval occlusion, infusion of norepinephrine, or angiotensin).

The mechanism by which a reduced outer cortical blood flow might induce increased renal sodium retention in heart failure is unclear. Reduced hydrostatic pressure or increased colloid osmotic pressure in the peritubular capillaries of the most populous nephron population is one plausible explanation. The work of many investigators has demonstrated that these physical factors play a significant role in the control of tubular sodium reabsorption. Alternatively, changes in single nephron glomerular filtration rate within the kidney might be involved. Horster and Thurau found that reductions of single-nephron GFR in cortical nephrons during sodium depletion were associated with increased single-nephron GFR in juxtamedullary nephrons, so that total kidney GFR was unchanged. A similar change occurring in response to intrarenal blood flow redistribution in heart failure could result in increased net sodium reabsorption even if the fraction of filtrate reabsorbed in both nephron populations remained unchanged. Such changes in intrarenal blood flow and GFR per nephron in different regions of the kidney might also provide an alternative explanation (to efferent arteriolar vasoconstriction) for the
increased filtration fraction which has been observed in mild heart failure.\textsuperscript{14, 15, 89}

An increasing body of micropuncture evidence suggests that the increased tubular sodium reabsorption characteristic of edema formation occurs in portions of the nephron beyond the proximal tubules.\textsuperscript{46, 41} The data of present studies suggest that in edematous patients the reductions in outer cortical perfusion were proportionately greater than elsewhere in the kidney. Relative increases in blood flow to juxtamedullary nephrons and the inner medulla of the kidney conceivably might act to promote increased distal sodium reabsorption by diminishing interstitial corticomedullary sodium gradients, an effect which reduces transstubular passive back flux. Alternatively, the blood flow redistribution observed in studies of thoracic caval occlusion and in experimental and human heart failure might explain the enhanced effect of aldosterone to promote tubular sodium reabsorption in these disorders.\textsuperscript{42} In normal man, aldosterone has been shown to enhance tubular sodium reabsorption in the loop of Henle and distal nephron.\textsuperscript{48} Direct evidence for these and a third hypothesis,\textsuperscript{17} that juxtamedullary nephrons have an intrinsically greater capacity for sodium transport, is lacking at this time, however.

The finding of reduced cortical perfusion rates in edematous patients with normal renal arterial pressure is indicative of active renal cortical vasoconstriction. Pomeranz et al.,\textsuperscript{51} Kilcoyne and Cannon,\textsuperscript{32} and Schrier and co-workers\textsuperscript{44} have provided experimental evidence that the carotid sinus reflex and sympathetic nervous outflow may reduce outer cortical blood flow rates in experimental preparations which are used as models for heart failure. Demonstrations of renal vasodilatation and natriuresis after sympathectomy or dibenzylamine infusions suggest that sympathetic nervous outflow plays a role in the vasoconstriction of human heart failure as well.\textsuperscript{45, 46}

Whether augmented intrarenal renin levels also participate in the renal cortical vasoconstriction of heart failure through local formation of angiotensin I and II is unclear. Several lines of evidence are suggestive: (1) superficial cortical nephrons are higher in renin than those of the juxtamedullary nephrons;\textsuperscript{47} (2) renal venous renin levels have been reported to be increased in patients with congestive heart failure;\textsuperscript{48} (3) angiotensin II has been reported to constrict cortical vessels;\textsuperscript{94} (4) redistribution of blood flow away from the cortex has been reported in both animals\textsuperscript{82} and in normal human subjects studied\textsuperscript{28} under conditions of reduced sodium intake, a situation in which endogenous renin production increases; and (5) Kilcoyne and Cannon\textsuperscript{32} found that cortical vasoconstriction and the renal vasoconstrictive response to intrarenal norepinephrine infusions were greater in salt-depleted (high renin) animals than in control (low renin) animals treated with high-salt diets and desoxycorticosterone. These observations raise the possibility that the renin-angiotensin system may coparticipate with the renal nerves in influencing intrarenal blood flow distribution in heart failure.

The afferent signal which triggers renal cortical vasoconstriction in heart failure is unknown. In the present studies there was no correlation between renal cortical blood flow and cardiac index, pulmonary wedge, or left ventricular end-diastolic pressures. However a significant inverse relationship between renal cortical blood flow and right ventricular end-diastolic pressure was demonstrated. Barger, Rudolf, and Yates have reported slight reductions of renal blood flow in dogs with increased right atrial pressure (and otherwise normal cardiac hemodynamics) after surgically induced pulmonic stenosis and tricuspid insufficiency,\textsuperscript{46} and Hollander and Judson found that renal sodium retention was present in patients with heart failure when there were significant elevations of right ventricular end-diastolic pressure.\textsuperscript{50}

The studies with intrarenal infusion of furosemide indicate that this diuretic can induce preferential renal cortical vasodilatation both in normal man and in patients whose renal vascular resistance was markedly increased as a consequence of cardiac failure. This result confirms previous results of Birtch et al.,\textsuperscript{51} in dogs, and it may also provide a rationale for use of furosemide in edematous patients with prerenal azotemia. The observations that diuresis resulted from drug administration to four patients whose \textsuperscript{133}Xe washout curves were unchanged from control values or showed renal vasoconstriction is consistent with a host of other studies which indicate that furosemide induces a potent inhibition of active sodium chloride transport mechanisms within the renal tubular cells.\textsuperscript{92} The cortical vasodilatation seen after furosemide in six patients with heart failure, however, suggests that induced alterations of intrarenal blood flow distribution may contribute to the diuretic effects of this agent in the therapy of cardiac patients with circulatory congestion.

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INTRARENAL BLOOD FLOW IN CHF
Intrarenal Blood Flow in Congestive Heart Failure
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