THE NATURE OF THE RENAL CIRCULATORY CHANGES IN
CHRONIC CONGESTIVE FAILURE AS REFLECTED BY
RENAL TUBULAR MAXIMAL FUNCTIONS 1,2

BY J. GROSSMAN, R. E. WESTON, J. P. HALPERIN,3 AND L. LEITER
(From the Medical Division, Montefiore Hospital, New York City)

(Submitted for publication June 2, 1950; accepted, July 3, 1950)

Intermittency of glomerular activity in man has
not been demonstrated (1). Therefore, functional
changes in the renal hemodynamics of human sub-
jects generally have been attributed to proportional
changes in the flow to all nephrons. Thus, the
well-established decrease of glomerular filtration
rate and renal blood flow in chronic congestive
failure (2, 3) has been considered a result of in-
adequate cardiac output and secondary renal vaso-
constriction, occurring without reduction in the
mass of functioning tubules. Since the decrease
in filtration reduces the quantity of electrolyte
delivered to tubules normally adapted to handle a
larger load (4, 5), it has been postulated that the
resulting glomerulo-tubular imbalance contributes
significantly to the salt and water retention of
congestive failure.

Recent studies from this and other laboratories
(6, 7) indicate, however, that despite the mark-
edly increased renal A-V oxygen difference, there
is a significant reduction in renal oxygen con-
sumption in chronic congestive failure. Although
this could represent a diffuse depression of paren-
chymal metabolism, resulting from generalized
renal ischemia and hypoxia, an alternative hypoth-
esis exists. In the light of True's demonstration of
an intrarenal vascular shunting mechanism in other species (8), this lower oxygen consump-
tion may reflect an intrarenal diversion of blood
away from the cortex, bypassing entire nephrons
and thereby diminishing the functional mass of
actively metabolizing parenchyma. Such a shunt-
ing mechanism would result in a decrease in func-
tioning tubules, proportionate to the reduced
filtration, and thus would minimize the role of

1 Presented before the Association of American Physi-
2 Supported in part by grants from the National Heart
Institute, U. S. Public Health Service, Campbell Prod-
ucts, Inc., and the Martha M. Hall Foundation.
3 Eli Lilly Research Fellow in Medicine.

glomerulo-tubular imbalance in the salt retention
of congestive failure.

Previously, we (6) and others (7) had found,
by renal vein catheterization, that renal extraction
of para-aminohippurate (PAH) in congestive
failure is normal. Although some have consid-
ered such data as evidence against the existence of
intrarenal shunts, this conclusion is not justified.
In these earlier studies low plasma levels of PAH
were employed to measure renal blood flows.
Therefore, were blood shunted away from part of
the kidney through juxtamedullary glomeruli and
related tubules, as postulated by True, these
nephrons could extract the normal fraction of
PAH until the PAH load reaching the perfused
tubules exceeded that received at normal renal
blood flows when the plasma PAH concentration
is at the self-depression limit. Since tubular load
is a function of plasma flow and plasma concen-
tration, the greatly reduced renal plasma flow of
congestive failure obviously will enhance this
capacity.

Therefore, to determine whether the reduced
renal hemodynamics in chronic congestive failure
proportionately affects all nephrons, the following
determinations were performed:

(1) Glomerular filtration rate (GFR).
(2) Renal plasma flow (RPF).
(3) Maximal tubular capacity for excreting
para-aminohippurate (TmPAH), a measure of
functional tubular excretory mass.
(4) Maximum tubular capacity for reabsor-
bining glucose (TmG), a measure of the number of
functioning intact nephrons.

From the data obtained, it is possible to estab-
lish the nature of the renal circulatory changes
in congestive failure.

METHODS AND MATERIAL
The subjects were five males and ten females with
rheumatic heart disease in well-established chronic con-
gestive failure. Their mean age was 38 years. Although they exhibited varying degrees of edema, all retained salt and water when their sodium intake was increased. Moreover, they showed the usually accepted criteria of congestive failure—elevated venous pressure or hepato-jugular reflux, prolonged circulation times, hepatomegaly, pulmonary rales, and the usual symptoms (Table I). Most of the subjects were digitalized, and received mercurials only as indicated. Patients with a history or clinical evidence of hypertension, arteriosclerosis, or any organic renal disease were excluded from the study.

The renal studies were performed by means of the constant infusion technique of Smith and his associates (9). The patients were in the post-absorptive state, under moderate water diuresis. Urine specimens were collected at 15-30 minute intervals, by washing the catheterized bladder with sterile, distilled water and air. Blood specimens were obtained from an indwelling femoral arterial needle. Inulin, thiosulfate, and mannitol were used for the determination of GFR.

After three or more clearance periods during which GFR and RPF were measured, appropriate solutions to maintain the plasma glucose or PAH concentration at suitable levels were administered. After 30 minutes of equilibration, at least four 10-15 minute Tm determinations were performed. TmPAH and TmO determinations were carried out on separate days in all but three patients (E. K., M. V., and A. McD.). In four patients, TmPAH measurements were repeated prior to and following the intensification of failure by the addition of salt.

**Mannitol was used in a few experiments, although it was recognized that about 10 per cent of this hexitol is reabsorbed (10).**

**During these studies, including those on one patient (E. K.) with low Tm's, the load/Tm ratios, calculated in the usual manner (9), were adequate.**
to the low (0.4-0.6 gm.) sodium cardiac diet on which all patients were maintained.

Inulin, mannitol and PAH were determined by the usual methods (9). Prior to determination of mannitol, PAH was acetylated as suggested by Barker and Clark (11). Thiosulfate was determined by the method of Gilman, Phillips and Koelle (12), as modified by Elliott and Scott (13). True glucose was determined by the method of Nelson (14).

The higher concentrations of glucose required for Tma measurements because of the reduced filtration rate in cardinals were found to interfere with the mannitol determinations, as others (15) have reported in normal subjects. Since no glucose could be detected after yeasting of the samples, the falsely high mannitol values obtained were attributed to some product(s) of glucose fermentation. Because the degree of interference, in either mannitol-free blanks or solutions containing known amounts of mannitol, was directly proportional to the glucose content of the analyzed samples, the true mannitol levels theoretically could be calculated. However, on several occasions, Tma's calculated on the basis of such corrections differed significantly from the actual Tma determined with thiosulfate or inulin clearances. Therefore, thiosulfate or inulin was employed to measure filtration rate throughout. When inulin was used, additional inulin blanks, containing the same concentrations of glucose as the diluted plasma and urine samples, also were yeasted and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Weight</th>
<th>G.F.R.</th>
<th>R.P.F.</th>
<th>F.F.</th>
<th>T_{MPAR}</th>
<th>T_{Ma}</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. B.</td>
<td>F</td>
<td>52</td>
<td>58.1</td>
<td>74.0</td>
<td>295</td>
<td>.25</td>
<td>—</td>
<td>301</td>
</tr>
<tr>
<td>S. P.</td>
<td>M</td>
<td>30</td>
<td>61.1</td>
<td>86.8</td>
<td>258</td>
<td>.34</td>
<td>—</td>
<td>450</td>
</tr>
<tr>
<td>M. C.</td>
<td>F</td>
<td>55</td>
<td>36.3</td>
<td>82.7</td>
<td>272</td>
<td>.30</td>
<td>—</td>
<td>291</td>
</tr>
<tr>
<td>M. L.</td>
<td>F</td>
<td>39</td>
<td>47.3</td>
<td>68.0</td>
<td>—</td>
<td>—</td>
<td>234</td>
<td>—</td>
</tr>
<tr>
<td>M. V.</td>
<td>M</td>
<td>46</td>
<td>54.0</td>
<td>96.8</td>
<td>391</td>
<td>.25</td>
<td>70.5</td>
<td>419</td>
</tr>
<tr>
<td>M. S.</td>
<td>F</td>
<td>23</td>
<td>60.6</td>
<td>90.0</td>
<td>386</td>
<td>.23</td>
<td>—</td>
<td>364</td>
</tr>
<tr>
<td>G. S.</td>
<td>F</td>
<td>42</td>
<td>47.1</td>
<td>95.8</td>
<td>434</td>
<td>.22</td>
<td>79.5</td>
<td>—</td>
</tr>
<tr>
<td>E. B.</td>
<td>F</td>
<td>33</td>
<td>59.0</td>
<td>89.4</td>
<td>204</td>
<td>.44</td>
<td>78.8</td>
<td>—</td>
</tr>
<tr>
<td>J. McM.</td>
<td>M</td>
<td>33</td>
<td>57.1</td>
<td>101.0</td>
<td>228</td>
<td>.44</td>
<td>103.0</td>
<td>—</td>
</tr>
<tr>
<td>G. R.</td>
<td>F</td>
<td>36</td>
<td>56.8</td>
<td>110.0</td>
<td>257</td>
<td>.43</td>
<td>81.4</td>
<td>—</td>
</tr>
<tr>
<td>A. P.</td>
<td>M</td>
<td>32</td>
<td>65.3</td>
<td>91.2</td>
<td>207</td>
<td>.44</td>
<td>64.2</td>
<td>—</td>
</tr>
<tr>
<td>M. H.</td>
<td>F</td>
<td>28</td>
<td>48.7</td>
<td>90.7</td>
<td>243</td>
<td>.37</td>
<td>—</td>
<td>322</td>
</tr>
<tr>
<td>J. F.</td>
<td>M</td>
<td>56</td>
<td>76.0</td>
<td>59.0</td>
<td>132</td>
<td>.45</td>
<td>81.4</td>
<td>—</td>
</tr>
<tr>
<td>A. McD.</td>
<td>F</td>
<td>24</td>
<td>55.8</td>
<td>106.0</td>
<td>325</td>
<td>.33</td>
<td>77.0</td>
<td>—</td>
</tr>
<tr>
<td>E. K.</td>
<td>F</td>
<td>37</td>
<td>45.4</td>
<td>76.9</td>
<td>273</td>
<td>.28</td>
<td>33.5</td>
<td>189</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84.5</td>
<td>328</td>
</tr>
<tr>
<td>Normal</td>
<td>Males</td>
<td></td>
<td>127.0</td>
<td>655</td>
<td>.19</td>
<td>77.2</td>
<td>375</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Females</td>
<td></td>
<td>118.0</td>
<td>600</td>
<td>.20</td>
<td>77.2</td>
<td>375</td>
<td></td>
</tr>
</tbody>
</table>
analyzed, in order to be certain that there was no interference from glucose.

Preliminary studies established that there was no effect of either glucose or thiosulfate on the determination of the other substance. However, during $T_m$ determinations with thiosulfate, it was found advisable to administer the glucose from a separate flask and into a separate vein.

RESULTS

The pertinent data on each patient are presented in Table II.

The glomerular filtration rate (mean = 88.5 ml. per min. per 1.73 M$^2$; $\sigma = 14.0$) in these patients was reduced to 46.4 to 93.2 per cent of corresponding average normal values for the respective sexes (16). Because of the greater reduction in renal plasma flow (mean = 277 ml. per min. per 1.73 M$^2$; $\sigma = 74.0$), which ranged from 20.2 to 72 per cent of the normal average values, the filtration fraction was increased from the normal average of 0.19-0.20 to a mean value of 0.34.

There was no significant relationship between the intensity of clinical signs of congestive failure, venous pressures, circulation times, etc. and the absolute value of GFR in individual patients. With intensification of failure in five patients by the addition of salt to the diet, there was an increase in filtration fraction which reflected largely the further decrease in renal plasma flow (Table II).

Tubular maximal capacity for excreting para-aminohippurate ($T_{mPAH}$) was within normal limits in 12 of the 13 subjects (mean = 74.5 mg. per min. per 1.73 M$^2$; $\sigma = 14.6$). In one patient, E. K., who had been receiving almost daily mercurials at another hospital including an injection 20 hours before the $T_m$ determinations, $T_{mPAH}$ was decreased to 43.5 per cent of normal.

As indicated in Figure 1, there was no demonstrable relationship between either the GFR or RPF and $T_{mPAH}$, plotted as per cent of average normal values. Because of the decrease in GFR and RPF, the ratios of GFR/$T_{mPAH}$ and RPF/$T_{mPAH}$ decreased.

There was no detectable reduction in $T_{mPAH}$ in those patients who exhibited gross evidence of pulmonary congestion or peripheral edema. Moreover, when the degree of failure was intensified by adding 8 gm. of NaCl to the daily intake, in three patients (A. P., G. R., and A. McD.) there was no change in $T_{mPAH}$, and in one (J. McM.), there was a 20 per cent decrease in the $T_{mPAH}$, which remained, however, within normal limits.

Tubular maximal capacity for reabsorbing glucose ($T_mG$) also was within the normal limits in all patients (Mean = 328 mg. per min. per 1.73 M$^2$; $\sigma = 70.8$), but one (E. K.), whose $T_{mPAH}$ was also reduced. There was poor correlation between this tubular maximal function and GFR and RPF, when plotted as per cent of the average normal values (16) for the respective sexes (Figure 2).

Since any error in the calculated filtration rate

---

**Figure 1. The Relationship between Glomerular Filtration Rate and $T_mG$ (Open Circles) and $T_{mPAH}$ (Closed Circles) in Congestive Failure**

---

**Figure 2. The Relationship between Renal Plasma Flow and $T_mG$ (Open Circles) and $T_{mPAH}$ (Closed Circles) in Congestive Failure**
will produce variation in the same direction in the calculated TmG, an apparent, but spurious, correlation between the two functions may result. Furthermore this error is also proportional to the plasma concentration of glucose and will be greater in cardiac subjects in whom higher levels are necessary to achieve adequate tubular loads.

**DISCUSSION**

The finding of normal tubular maximal capacities for reabsorbing glucose and excreting paraaminohippurate in this series of patients in chronic congestive failure suggests that there has been a generalized reduction in blood flow to each nephron, and that at least two tubular functions have not been depressed by the marked renal ischemia and hypoxia. Previously, Landowne, Alving, and Adams (17) had found normal diodrast Tm's in two patients in severe congestive failure due to chronic constrictive pericarditis.

Others recently have reported that there may be a reduction in TmpAH in congestive failure. Earle and his associates (18) observed that TmpAH was reduced in two edematous patients in severe congestive failure, but returned to normal after treatment had been started and edema decreased. Heller and Jacobson (19) found that the average TmpAH was normal in partially compensated or edema-free patients in chronic congestive failure, despite the reduction in GFR and RPF. In contrast, in eight patients exhibiting peripheral edema or rales, with elevated venous pressures and more severely reduced RPF's, the average TmpAH was reduced. However, review of their data reveals that five of the eight severely decompensated patients were over 55 years of age, so that renal arteriosclerosis might have contributed to the reduction in TmpAH. Moreover, in the two patients in whom TmpAH's were measured before and after treatment, the observed increase in TmpAH after the disappearance of edema was associated with an apparent decrease in GFR. Such a measured fall, if due to technical errors alone, would result in a higher calculated TmpAH. It is also conceivable that in severely decompensated patients a marked reduction in RPF may occur during the stress of TmpAH determination and reduce the tubular load below the required level, thereby lowering the apparent Tm. Simultaneous right renal vein catheterization, with determination of "true" RPF by the Fick method, is necessary to evaluate this point.

Similarly, Hilden's (20) group of six patients included four patients with arteriosclerotic heart disease, with a fairly proportionate reduction in GFR and TmG. Such findings would be anticipated in renal arteriosclerosis where various functional components of the nephrons tend to "drop out" together (21). It is noteworthy that his two younger patients with luetic heart disease had normal TmD's.

In the present series of severely decompensated but younger patients, presumably free of organic renal disease, there was no relationship between TmpAH and the reduced renal circulation. Although this finding probably excludes the diversion of blood from any significant number of tubules, the possibility remains that the slower blood flow in chronic congestive failure may permit more time for the excretion of PAH or diffusion of PAH to otherwise bypassed tubules, thereby maintaining the Tm at normal levels. However, in other diseases leading to impaired renal hemodynamics, the TmpAH tends to be reduced early and significantly (9, 21).

More important, the glucose Tm, which is a measure of the functional integrity of both glomeruli and their attached tubules—or of the number of functioning whole nephrons—is normal in the present series of patients. If, for example, the reduced GFR in congestive failure were due to the absence of filtration in some glomeruli due to intrarenal redistribution of blood, a corresponding reduction in TmG would result. Similarly, since each tubule can receive the glucose it reabsors only from the attached glomerulus, any functional exclusion of tubules also would depress the TmG. The normal TmG encountered, therefore, is irrefutable evidence against any extensive intrarenal shunting mechanism.

It is possible that the very severe, persistent renal ischemia and hypoxia present in intractable congestive failure may lead ultimately to parenchymal metabolic depression. Under these circumstances, TmpAH or TmG conceivably might be reduced.\(^6\) However, there was no such depres-

\(^6\)At this stage of so markedly reduced GFR and RPF, it is highly questionable whether plasma levels of PAH and glucose adequate for Tm measurements can be achieved safely. Moreover, the deleterious hemodynamic
sion in the present series of patients in classical congestive failure, many of whom accumulated salt and water even on a low salt cardiac diet.

The renal circulatory abnormality in chronic congestive failure evidently consists of generalized renal ischemia with decrease in filtration in the glomerulus of each nephron but without reduction in the tubular mass perfused. Moreover, the finding of normal $T_{m}$'s and $T_{m\text{PaH}}$'s establishes the fact that at least two functions of the tubule are not impaired by the renal ischemia and hypoxia. Thus, there is a functional glomerulotubular imbalance which may greatly influence renal excretion of salt and water (4).

Recently, Selkurt, Hall and Spencer (22), and Pitts and Duggan (23), have demonstrated in dogs that acutely decreasing the filtration rate by 25 to 50 per cent results in the virtual disappearance of sodium from the urine. Regardless of whether one accepts or rejects the existence of a distal tubule $T_{m}$ for sodium (4), these data suggest that a moderate reduction infiltration rate without change in tubular function can result in salt and water retention. Although the renal mechanism for excreting sodium in the dog may differ from that in man (24), this pattern of renal dysfunction, per se, could furnish a simple explanation for the more complete tubular reabsorption of sodium occurring in congestive failure and other conditions in which glomerular filtration is diminished more than is tubular function (5, 21, 25).

It should be re-emphasized, however, that one of the body's responses to the inadequate output of the failing heart is to conserve salt and water (25, 26). That not one but several mechanisms probably are activated for this purpose is not surprising. Many factors—excessive accumulation of anti-diuretic substances, adrenal cortical steroids or hepatic VDM, increased renal or systemic venous pressure, exercise, reduced renal blood flow, etc. (6, 25, 27-32)—may promote salt and water retention in congestive failure. However, whenever the filtration rate is reduced without arteriosclerotic or hypertensive renal tubular involvement, as in younger patients in chronic congestive failure, the influence of the resulting glomerulo-tubular imbalance on salt and water excretion should not be underestimated.

SUMMARY AND CONCLUSIONS

1. In a series of patients in well-established congestive heart failure, with characteristically reduced glomerular filtration rates and renal plasma flows, the maximal tubular capacities for the excretion of para-aminohippurate and the reabsorption of glucose were normal.

2. These findings exclude the possibility of any significant intrarenal redistribution of blood.

3. The significance of the resulting glomerulotubular imbalance in relation to the retention of sodium and water in chronic congestive failure, uncomplicated by organic renal disease, is discussed.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Mr. Morris Wolfman, Mrs. Lila Wolfman, and Mrs. Madie Ross for their technical assistance, and to Doctors D. J. W. Escher and T. D. Ullmann for their aid in some of the studies.

BIBLIOGRAPHY

1. Smith, H. W., Lectures on the Kidney. University Extension Division, University of Kansas, Lawrence, Kansas, 1943.


7. Stead, E. A., Jr., Myers, J. D., Scheinberg, P., Cargill, W. H., Hickam, J. B., and Levitan, B. A.,