THE RELATIONSHIP OF RENAL OXYGEN CONSUMPTION TO
RENAL FUNCTION AND WEIGHT IN INDIVIDUALS WITH
NORMAL AND DISEASED KIDNEYS *

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In previous studies of renal oxygen consumption in man the results have been expressed in the following terms: a) the total oxygen consumed per two kidneys per minute (TQO2) (1); b) the quantity of oxygen utilized per 100 g per minute based on the measurement of TQo2 and an assumed weight of 300 g per two kidneys (1); c) the TQO2 as related to total renal blood flow (TRBF) and glomerular filtration rate (GFR) (2). In the latter instance Cargill and Hickam (2) concluded that TQO2 was best correlated with the GFR. Bradley and Halperin (3), on the other hand, suggested that the TQO2 of the kidney was probably related to the "tubular functional mass" as determined by the tubular maximal secretory capacity for sodium para-aminohippurate (TmPAH). However, as noted by Smith (4), no data have been forthcoming with regard to the latter relationship.

Therefore, the present paper is an attempt: 1) to provide data in which the relationship between the total renal oxygen consumption and the TmPAH is defined in normal subjects and in patients with kidney disease; 2) to demonstrate the limitations of such a ratio (TQO2/TmPAH); and 3) to suggest that in future studies TQO2 be considered alone and/or that oxygen consumption be determined as QO2 per 100 g per minute.

MATERIAL AND METHODS

Five "normal" subjects, 5 patients with essential hypertension (grade 2-3), 5 with diabetic nephropathy, 5 with chronic pyelonephritis, and 5 with chronic glomerulonephritis were selected from the wards of the University Hospitals between 1952 and 1958. In addition, one each of the following types of patients was studied as a "control": "juvenile" diabetes mellitus without clinical evidence of retinopathy or nephropathy; essential hypertension before and after the administration of oral glucose and intravenous insulin. In all cases the diagnoses were made on clinical rather than morphological grounds.

All patients, with the exception of those with diabetes mellitus, were studied in a fasting state. The exceptions were given their breakfast as a liquid glucose equivalent along with their daily dose of insulin 1 hour prior to the start of the test. Evidence that such a procedure did not appear to influence the results is presented in the Discussion.

Simultaneous determinations of glomerular filtration rate, total renal plasma flow (TRPF), TRBF, arterio-renal venous oxygen difference (A-RV02), TQ02, renal blood flow per 100 g per minute (RBF), renal oxygen consumption per 100 g per minute (QO2), and in vivo renal weight (Rw) were made, utilizing right renal vein catheterization and techniques previously described for this laboratory (5, 6).

The results, contained in the tables, represent the average of three 15-minute periods. They are uncorrected for surface area since the relationships to be discussed did not lend themselves to correction and/or resulted in cancellation of this correction by virtue of being present in both the numerator and the denominator. Furthermore, the mean values for surface area of the 5 groups did not differ significantly from one another per meter ("normals," 1.80; essential hypertension, 1.81; chronic glomerulonephritis, 1.80; diabetic nephropathy, 1.77; chronic pyelonephritis, 1.82).

Statistical analyses were performed, utilizing the standard t test (7).

RESULTS

The results are presented in Tables I–III. Table I contains the individual data. Table II represents the mean values for each function of

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"Normal" subjects were individuals diagnosed as having "psychoneurotic reaction" (000-X0Y).

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2 The liquid glucose equivalent was calculated as 100 per cent of the carbohydrate, 58 per cent of the protein, and 10 per cent of the fat which would have been consumed at breakfast.
any given group, the standard errors of such means, as well as the level of statistical significance (p) when the mean of a given function in a particular disease group is compared with the mean of the corresponding function of the “normal” individuals. The material contained in Table III has been reserved for the Discussion.

Normal. The results obtained in such individuals were in accord with those previously reported from this (5, 6) and other laboratories (4). The values for GFR may be questioned as being normal. However, “normal” mean values given by other investigators, using the inulin clearance technique, with PAH at low plasma levels, have ranged between 114 and 140 ml per minute with standard deviations of ±4.4 to ±40 ml per minute (4). Also, the GFR’s presented in Table I were obtained at the same time as the determinations of TmPAH. The latter procedure, based on 30 different investigations in as many patients, produced a decrease in GFR of 19 per cent (8) over those obtained before PAH saturation. This is in accord with previous observations (4).

Essential hypertension. A comparison of the data of these patients with those obtained in “normal” subjects shows that GFR (p < 0.05), TRBF (p < 0.02), and the TQ02 (p < 0.05) were significantly reduced. In contrast, the A-RV02 (p > 0.2), the RBF per 100 g per minute (p > 0.7), as well as the renal Q02 per 100 g per minute (p > 0.3) were not significantly different from normal. The decline in TRBF and TQ02, as compared with the lack of change in these functions when expressed on a unit weight basis, is probably related to the significant reduction in renal weight (p < 0.05). The mean value for TmPAH was 11 mg per minute less than the mean value for this function in normal subjects, but this difference was not statistically significant (p > 0.12).

The ratio of the TQ02 to the TmPAH or to the GFR remained unaltered (p > 0.3 in both instances). The significant decrease in TRBF/
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*SE = standard error of the mean.
†p = Level of statistical significance when mean of group is compared with mean of "normals." For other abbreviations see text.
RENAL OXYGEN CONSUMPTION

TABLE III
Control studies

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<th>Patient no.</th>
<th>GFR</th>
<th>TRBF</th>
<th>TmPAH</th>
<th>GFR</th>
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<th>A-RV01</th>
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<td></td>
<td>ml/min</td>
<td>ml/min</td>
<td>mg/min</td>
<td>ml/min</td>
<td>ml/min</td>
<td>vol%</td>
<td>ml/min</td>
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<td>1. Diabetes mellitus without nephropathy</td>
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<td>865</td>
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<td>0.90</td>
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<td>1.8</td>
<td>15.6</td>
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<td>740</td>
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<td>1.14</td>
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<td>9.8</td>
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* Control, fasting.
† Thirty to 60 minutes after 0.1 U insulin/kg i.v., plus 100 g glucose p.o.

TmPAH (p < 0.05) and the constancy of the GFR/ Rwt (p > 0.7) were expected, in view of the fact that the pathological changes in such kidneys are primarily of a vascular nature. In contrast, the significant reduction in GFR/TmPAH (p < 0.05), and the increase in TmPAH/Rwt (p < 0.05), were unexpected findings. A possible explanation for these observations is presented in a later section.

Chronic glomerulonephritis. As in patients with essential hypertension, the GFR (p < 0.02) and TRBF (p < 0.02) were significantly decreased. However, when these functions were related to the TmPAH, a significant reduction was noted in GFR/TmPAH (p < 0.05), while TRBF/ TmPAH remained unchanged (p > 0.3). Furthermore, there was a fall in GFR/Rwt (p < 0.05). Such findings indicated the primary glomerular involvement in this entity. The absence of a change in TRBF/TmPAH (p > 0.3), despite significant reductions in TRBF (p < 0.02) as well as RBF per 100 g per minute (p < 0.05), is interpreted to mean that the fall in renal blood flow was proportionate to the progressive renal damage in this disease.

TmPAH/Rwt remained unchanged (p > 0.1) while all of the other estimations were similar to those found in the individuals with essential hypertension.

Diabetic nephropathy. The features which distinguished this group of patients from “normal,” as compared with the groups with essential hypertension and glomerulonephritis, were the significant reductions noted in TmPAH (p < 0.001), TmPAH/Rwt (p < 0.01), QO2 per 100 g per minute (p < 0.02) and the significant increases in TQO2/TmPAH (p < 0.01) and TQO2/GFR (p < 0.05). Furthermore, GFR/TmPAH and TRBF/ TmPAH, which heretofore, either alone or in combination were significantly altered, remained unchanged in these individuals.

Chronic pyelonephritis. Patients in this group, with two exceptions, were similar from both functional and metabolic standpoints to the patients with diabetic nephropathy. First, although the mean value for TQO2/TmPAH was increased to an even greater extent (0.300 ml per mg) than that observed in the patients with diabetic nephropathy (0.271 ml per mg) it was nevertheless not found to be statistically different from normal, due to the variability of the individuals within the group. Secondly, TQO2/GFR was significantly increased (p < 0.01).

DISCUSSION

It is obvious that the renal TQO2 represents the sum of the oxygen consumed by the individual parts of the kidney. However, in the past, efforts have been made to relate the former quantity of oxygen to one functional measurement [e.g., TRBF (9, 10), GFR (2)]. Therefore, since it was conceivable that TQO2 might be primarily related to TRBF, to the “tubular functional mass” or to glomerular function and, since all of these functions have not heretofore been measured simultaneously in patients with “normal” and diseased kidneys (4), the present study was undertaken in an effort to test whether such a primary relationship existed.

Total renal blood flow. Van Slyke, Rhoads, Hiller and Alving (9), as well as others (10),
initially concluded that the total renal oxygen consumption was related to the total renal blood flow. Subsequent studies by Clark and Barker (1) and Barker and Crosley and co-workers (11-13), utilizing measures which alter total renal blood flow, showed that such was not the case in normal human subjects or in patients with renal disease. Thus the arterio-renal venous oxygen difference could indeed narrow or widen in response to change in blood flow, thereby maintaining an unchanged oxygen consumption. Furthermore, since \( T_{\text{Qo}_2} \) is derived as the product of TRBF and the arterio-renal venous oxygen difference, one would predict a high correlation between TRBF and \( T_{\text{Qo}_2} \) on a purely mathematical basis. In addition, it follows that the narrower the range of the arterio-renal venous oxygen differences the higher the correlation. In the present study this range was so narrow that there was no significant difference between the arterio-renal venous oxygen differences of the diseased groups and those of the "normals"; hence a correlation between TRBF and \( T_{\text{Qo}_2} \) was not considered applicable.

"Tubular functional mass." Although it had been suggested by Bradley and Halperin (3) that the most likely relationship between the \( T_{\text{Qo}_2} \) and the renal functional elements was between \( T_{\text{Qo}_2} \) and the "tubular functional mass" (\( T_{\text{Qo}_2}/T_{\text{mPAH}} \)), no data on this ratio have been forthcoming until the present study (4). Support for such a relationship is the finding here that the correlation between these two factors is highly significant (\( R = +0.923, p < 0.001 \)).

Glomerular filtration rate. As previously noted, Cargill and Hickam (2) reported a positive correlation between the total oxygen consumption of the kidney and the glomerular filtration rate. On the surface, such findings pose the problem as to why oxygen consumption should be related to a function whose primary energy source is that of the net hydrostatic pressure of the blood. However, recent evidence by Dubach and Recant (14) lend support to such a relationship, since their in vitro investigations of individual glomeruli attribute important oxidative functions to this structure. The present data are also in accord with the concept that total oxygen consumption is related to glomerular activity, since the correlation coefficient between these two functions, utilizing all of the patients in the five groups, was \( R = +0.955 \) (\( p < 0.001 \)).

In view of the highly significant correlation coefficients for both GFR and \( T_{\text{mPAH}} \) as related to \( T_{\text{Qo}_2} \) it appears that one explanation for such data is that, in renal disease, there is a symmetrical destruction of both glomeruli and tubules and that associated with the loss of such nephrons there is a proportionate reduction in \( T_{\text{Qo}_2} \). Such a statement would be in agreement with the findings of Bricker, Morrin and Kime in unilaterally induced renal disease in dogs, which appear to demonstrate proportionate declines in glomeruli and tubules (15). An alternative explanation would be that suggested by Cargill and Hickam (2), that tubular activity is largely governed by the quantity of glomerular filtrate and thus a close correlation between GFR, \( T_{\text{mPAH}} \) and \( T_{\text{Qo}_2} \) might be expected.

Finally, the unexpected findings of the increased \( T_{\text{Qo}_2}/T_{\text{mPAH}} \) and \( T_{\text{Qo}_2}/\text{GFR} \) and the significant decreases in \( T_{\text{mPAH}}/\text{R}_{\text{wt}} \) in patients with diabetic nephropathy and chronic pyelonephritis, as well as the decreased GFR/\( T_{\text{mPAH}} \) in essential hypertension, must be considered. No definitive explanation is forthcoming for any of these results.

However, in the case of the increased \( T_{\text{Qo}_2}/T_{\text{mPAH}} \) and \( T_{\text{Qo}_2}/\text{GFR} \) in patients with diabetic nephropathy and chronic pyelonephritis, these changes do not appear to be due to: a) the diabetic state per se, since they occurred in patients without diabetes (e.g., chronic pyelonephritis and Patient P.M. with glomerulonephritis); b) the presence of insulin and/or the glucose-equivalent breakfast, since a control diabetic patient (Table III, no. 1) and a nondiabetic patient (no. 2) given a "glucose-insulin" tolerance test did not show elevations of these ratios; c) the oxygen consumption of nonexcretory renal tissue (e.g., scar tissue), since the \( Q_{\text{o}_2} \) of such tissue is lower than that of excretory renal tissue (16). In view of the significant decreases in \( Q_{\text{o}_2} \) per 100 g per minute associated with the increased \( T_{\text{Qo}_2}/T_{\text{mPAH}} \) and \( T_{\text{Qo}_2}/\text{GFR} \), one can only speculate that the latter findings may be related to the fact that a total quantity (oxygen) was related to only a part (\( T_{\text{mPAH}} \) and/or GFR) of the total metabolizing tissue of the kidney (\( T_{\text{mPAH}} \) and/or GFR plus scar and exudative tissue). In a similar
fashion, one can only hypothesize that the significant depression in TmPAH/Rw in these cases, may be due to the fact that a significant portion of the kidney weight was composed of nonexcretory renal tissue (scar tissue). If so, the ratio TmPAH/Rw may serve as an index of renal "scarring."

The observation of a significant decrease in GFR/TmPAH in patients with essential hypertension has not been the usual finding in other series (4). Such data may be fortuitous, since the number of patients was small and the significance was borderline (p < 0.05). However, a recent report by Baldwin and associates (17) in patients with essential hypertension revealed a decline in the GFR/TmPAH in the majority of the cases. Furthermore, White, Sambhi and Grollman have reported such findings in experimentally induced hypertension in rats (18).

SUMMARY AND CONCLUSIONS

1. A number of observations was made in individuals with "normal" and diseased kidneys in an effort to determine whether any single functional component [total renal blood flow (TRBF), glomerular filtration rate (GFR), "tubular functional mass" (TmPAH)] was a primary contributor to the total oxygen consumed per two kidneys per minute (TQO2). None could be found.

2. Since in certain disease categories (diabetic nephropathy and chronic pyelonephritis) TQO2/TmPAH or TQO2/GFR was increased, while at the same time TQO2 and renal oxygen consumption per 100 g per minute (QO2) were decreased, it is suggested that in future studies TQO2 be considered alone or, if a base reference is desired, that renal oxygen consumption be determined in terms of QO2 per 100 g per minute.

3. TmPAH/Rw was significantly reduced in patients with chronic pyelonephritis and diabetic nephropathy, while the GFR/TmPAH was reduced in essential hypertension. No definitive explanation is forthcoming for such findings.

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