Renal and Systemic Oxygen Consumption in Patients With Normal and Abnormal Renal Function[1]

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ABSTRACT

Systemic and renal oxygen consumption and hemodynamics were studied in patients with normal renal function (NI; serum creatinine concentration (S_{creat}), 1.0 ± 0.04 mg/dL) and those with moderate chronic renal failure with diabetes mellitus S_{creat}, 2.7 ± 0.2 mg/dL) or without diabetes mellitus (S_{creat}, 2.4 ± 0.1 mg/dL). Patients with chronic renal failure were anemic and had normal systemic oxygen consumption (NI, 10,564 ± 277; chronic renal failure, 9,669 ± 362 μmol of O_2/min) and elevated systemic oxygen extraction (NI, 22.9 ± 1; chronic renal failure, 30.9 ± 1.2%) ($P < 0.02$). Cardiac output and index and arterial oxygen saturation were equivalent in normal patients and in patients with chronic renal failure. Patients with chronic renal failure had higher renal oxygen extraction (NI, 7.3 ± 0.8; chronic renal failure, 13.9 ± 1%), lower RBF (NI, 572 ± 146; chronic renal failure, 197 ± 20 mL/min/kidney), and lower renal oxygen consumption per kidney (NI, 391 ± 101; chronic renal failure, 177 ± 20 μmol of O_2/min/kidney) than did normal patients ($P < 0.02$). There was a linear relationship between hemoglobin and RBF ($r = 0.47$, $P < 0.02$). Patients with chronic renal failure and diabetes had lower RBF (diabetes mellitus, 146 ± 23; without diabetes, 242 ± 28 mL/min/kidney) and renal oxygen consumption per kidney (diabetes mellitus, 131 ± 21; without diabetes, 218 ± 29 μmol of O_2/min/kidney ($P < 0.03$) but equivalent renal oxygen extraction when compared with patients without diabetes. Patients with chronic renal failure without diabetes mellitus had higher renal oxygen consumption when expressed per 100 mL of creatinine clearance (diabetes mellitus, 1,016 ± 150; without diabetes mellitus, 1,453 ± 175 μmol of O_2/min/100 mL of creatinine clearance; $P < 0.03$). There was a significant linear relationship ($P < 0.005$, $r = 0.38$) between calculated creatinine clearance and renal oxygen consumption with a y intercept representing basal renal oxygen consumption (115 μmol of O_2/min/kidney) and a slope of 2.3 μmol of O_2/mL. Patients with moderate chronic renal failure have normal systemic oxygen consumption but reduced RBF and renal oxygen consumption. The latter parameters are even lower in patients with chronic renal failure and diabetes. Renal hypermetabolism is more likely to exist in nondiabetic than diabetic renal disease. Basic human renal physiology and pathophysiology are described by the relationships between renal oxygen consumption, blood flow, oxygen extraction, and creatinine clearance in patients with normal and abnormal renal function of varied cause.

Key Words: *Chronic renal failure, RBF, renal hemodynamics, diabetes mellitus*

A number of studies have examined systemic oxygen consumption ($S\dot{V}O_2$) in uremic animals (1,2) or people (3–6). However, few studies have investigated the effects of moderate chronic renal failure (CRF) (4,7) on these parameters. Studies of renal oxygen consumption ($R\dot{V}O_2$) in either normal people (8–11) or patients with CRF are even rarer (10). The basic renal physiology describing the relationships between RBF, $R\dot{V}O_2$, renal oxygen extraction $R(a\text{-}v)O_2$, GFR, and renal sodium reabsorption (T_{Na}) has been derived from studies of animals with normal renal function (12–16). The most quoted of these studies used four dogs who were acutely bled in order to alter their RBF and measure the other parameters (16). There is scant literature on these relationships in animals with abnormal renal function (17–23). Two studies with human subjects (8,24) have questioned the existence of similar relationships in people with normal renal function. Thus, the physiology in people with normal renal function may differ from that in animals with normal or abnormal renal function. Recent studies suggest that hypermetabolism,

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defined as increased $R\dot{V}O_2$ per functional unit, may play a role in both the recovery from acute renal failure (21) and the pathogenesis of CRF in rats (19,20,22) but not dogs (23). The only study of $R\dot{V}O_2$ in patients with moderate CRF (10) did not address renal hypermetabolism, did not explore possible differences according to the cause of the CRF, and did not include any diabetic patients.

This study was performed (*1*) to examine the effects of moderate renal dysfunction on systemic oxygen consumption ($S\dot{V}O_2$), $R\dot{V}O_2$, and hemodynamics in people; (*2*) to define the basic relationships between $R\dot{V}O_2$, $R(a\text{-}v)O_2$, RBF, and GFR for people with normal and abnormal renal function; (*3*) to compare these relationships in patients with CRF with or without DM (DM, with diabetes mellitus, NDM, without diabetes mellitus); and (*4*) to investigate whether hypermetabolism exists in human CRF.

METHODS

Study Population

Two groups of patients scheduled for elective cardiac catheterization, and thus requiring vascular access, were enrolled in this protocol. The first group consisted of 44 patients with stable CRF, defined as two serum creatinine concentration (S_{creat}) measurements ≥1.8 mg/dL. The second group was composed of 16 patients with normal renal function, defined as a S_{creat} ≤1.4 mg/dL. Exclusion criteria included evidence of New York Heart Association Class IV congestive heart failure, a myocardial infarction within the 2 wk before cardiac catheterization, pregnancy, unstable renal function, or "medical instability" as judged by the cardiologist. A medical history was obtained, and a physical examination was performed with particular emphasis on the pathogenesis of the patient's CRF, the extent of cardiovascular disease, the state of hydration, and current medications. Although patients were placed on a 2-g sodium diet when admitted, the majority of patients were on this diet for ≤24 h; thus, sodium intake was variable. This research protocol was approved by the Institutional Human Experimentation Committee and follows the principles of the Declaration of Helsinki. Informed consent was obtained for all enrollees.

Clinical Measurements

All patients had a complete blood count, serum glucose concentration (S_{glu}), and S_{creat} determined before cardiac catheterization. Those with CRF had two determinations of S_{creat} within 24 h of cardiac catheterization to confirm stable renal function. S_{creat} and S_{glu} were determined on a Beckman Astra (Beckman Inc., Brea, CA), and complete blood counts were performed on a Coulter Counter (Coulter Electronics Mfg., Hialeah, FL). All patients with CRF also had a urinalysis before the protocol. The first 20 patients enrolled with CRF had 12-h, overnight urine collections before cardiac catheterization that were analyzed for volume, sodium, and creatinine. Those results were used to calculate creatinine clearance (CrCl), fractional reabsorption of sodium (FR_{Na}), and T_{Na} by the following formulae (25):

$$CrCl = \frac{(U_{creat})(V)}{S_{creat}}$$

$$FR_{Na} = 100 - \frac{U_{Na}S_{creat}}{S_{Na}U_{creat}}$$

$$T_{Na} = (CrCl)(S_{Na}) - (U_{Na})(V)$$

where V = 12-h urine volume/720 min; U_{creat} is the urinary creatinine concentration; S_{Na} is serum sodium; and U_{Na} is urine sodium. CrCl was also estimated on all the patients by the method of Cockcroft and Gault (26):

$$CrCl \approx \frac{(140 - age)(body\ weight\ in\ kg) \times 0.85\ (women)}{72\ (S_{creat})}$$

Filtration fraction (FF) was calculated as CrCl divided by 2 × single kidney RBF (assuming equal RBF to both kidneys). The CrCl used to calculate FF was that estimated by the method of Cockcroft and Gault in order to maintain uniformity.

Vascular Access

One arterial and two venous sheaths were placed, and 5,000 U of heparin was administered. Catheterization of right side of the heart was performed with a thermodilution Swan-Ganz catheter (Baxter Health-Care Corp., Irving, CA) for the measurement of cardiac output (CO) and right atrial pressure. The tip was placed in the pulmonary artery, and a blood sample was removed for the measurement of hemoglobin oxygen saturation (Pa_{O_2}). A dual thermistor catheter was then placed in the left renal vein for measurement of RBF (see below) and blood sampling for hemoglobin oxygen saturation (Rv_{O_2}). A pigtail catheter was placed in the left ventricle in preparation for ventriculography. Blood was drawn from the femoral artery for measurement of arterial hemoglobin oxygen saturation (a_{O_2}).

Measurement of RBF

RBF was measured with a thermodilution catheter placed in the left renal vein. The method used was a continuous thermodilution technique (27) with a 7 French dual thermistor catheter (Webster Laboratories, Baldwin Park, CA). The catheter was introduced through the femoral vein via an in-dwelling introducer and fluoroscopically guided into the left renal

vein. The position was confirmed by the determination of the oxygen saturation of the blood withdrawn from the catheter. A saturation significantly greater than that of the pulmonary artery and roughly 10 to 15% lower than arterial saturation was considered appropriate (25,28,29). For each determination of RBF, room temperature 5% dextrose was infused through the catheter with a Harvard pump (Harvard Apparatus Co., Millis, MA) at a constant rate of 50 mL/min until the resistance deflections of both thermistors consequent to the thermodilution temperature changes were stable. The measurement of RBF was performed in triplicate and was averaged for each time point. Our replicate measurements had a mean coefficient of variation of 7.8%.

Hemodynamic Measurements and Calculations

All measurements and samples were collected before any radiocontrast administration. Blood was withdrawn from the pulmonary artery, femoral artery, and renal vein for the determination of hemoglobin oxygen saturation by oximetry (Corning 2500 Co-Oximeter; Ciba-Corning Corp., Medfield, MA). The $R(a\text{-}v)O_2$ was calculated as the difference between the saturation of the blood in the femoral artery and that of the renal vein. The systemic arteriovenous oxygen difference $[S(a\text{-}v)O_2]$ was calculated as the difference between the femoral artery and pulmonary artery oxygen saturations. Mean arterial pressure (MAP) was measured with an in-dwelling arterial line. Thermodilution cardiac output was measured and expressed in liters per minute. Cardiac index (CI) was expressed as liters per minute per square meter and was calculated as CO divided by the body surface area. Systemic vascular resistance (SVR) was calculated as 80 × (MAP − right atrial pressure)/CO and expressed in dyne per second per centimeter^{-5}. RBF was measured as detailed above. $R\dot{V}O_2$ and $S\dot{V}O_2$ were calculated by the Fick principle by the following formulae:

$$R\dot{V}O_2 = \frac{(Hgb)(1.34)R(a\text{-}v)O_2(RBF)(44.6)}{10{,}000}\ \frac{\mu mol\ O_2}{min}$$

$$S\dot{V}O_2 = \frac{(Hgb)(1.34)S(a\text{-}v)O_2(CO)(44.6)}{10{,}000}\ \frac{\mu mol\ O_2}{min}$$

Renal and systemic O_2 delivery (RO_2del and SO_2del) were calculated as follows:

$$RO_2del = \frac{(Hgb)(1.34)(aO_2)(RBF)(44.6)}{10{,}000}\ \frac{\mu mol\ O_2}{min}$$

$$SO_2del = \frac{(Hgb)(1.34)(aO_2)(CO)(44.6)}{10{,}000}\ \frac{\mu mol\ O_2}{min}$$

Where Hgb = hemoglobin (grams per day), and the constants are: 1.34 mL of O_2 per gram of Hgb, 44.6 μmol of O_2 per mL. The oxygen content of the arterial blood was calculated as (1.34) × (Hgb) × (aO_2) and was expressed in milliliters per 100 mL of blood. The Pao_2 was substituted to calculate a mixed venous oxygen content, and the renal vein saturation (RvO_2) was used to estimate a renal vein oxygen content. The last calculation assumes equivalent arterial and renal vein Hgb levels, which is a reasonable assumption (9). The Hgb used in these calculations was obtained from a peripherally drawn venous sample.

Statistical Analysis

Independent t tests were used to compare mean values between groups. Regression analyses were performed according to standard procedures with first or third order regressions. Differences were considered significant at the level of $P < 0.05$.

RESULTS

Clinical Characteristics

Baseline clinical characteristics for the two groups of patients are shown in Table 1. The 44 patients with CRF included 20 women and 24 men with an age range of 34 to 80 yr (mean, 64.9 ± 1.7). Those with DM were significantly younger than those with NDM. The cause of the CRF was presumed secondary to long-standing DM in 21 patients. Of the 21 patients with DM, 15 were taking insulin and the other 6 were taking oral hypoglycemic agents. S_{glu} was higher in patients with DM the morning of study. Eighteen of the 21 patients had 2+ or greater urinary protein. The other 23 patients did not have DM, and their CRF was presumed secondary to hypertension, interstitial nephritis, lead nephropathy (one case biopsy proven), focal glomerulosclerosis (one case biopsy proven), polycystic kidney disease, or glomerulonephritis, although these diagnoses were not documented by biopsy in the majority of the patients. Thirty of the 44 patients with CRF were taking calcium channel blockers on a long-term basis. These drugs were distributed evenly between patients with or without DM (DM, 16; NDM, 14). Ten of the 44 patients were on β-blocking agents (DM, 3; NDM, 7) and 35 (DM, 18; NDM, 17) were also taking diuretics. Thirty-one of the patients with CRF had hypertension (DM, 14; NDM, 17). Thirty-nine of the 44 patients had severe two-vessel or three-vessel coronary artery disease demonstrated subsequently by cardiac catheterization. The patients with CRF were mildly anemic. The mean baseline S_{creat} of 2.5 ± 0.11 mg/dL and mean estimated CrCl of 32 ± 2 mL/min were equivalent in patients with DM or NDM. CrCl estimated by the method of Cockcroft and Gault correlated strongly with that calculated from the 12-h urine collections performed in the first 20 patients

($r = 0.84$; $P < 0.0001$). FR_{Na}, but not T_{Na}, was significantly higher in patients with NDM than DM.

The 16 patients with normal renal function were all men and were significantly younger with an age range of 39 to 72 yr (mean, 52.8 ± 2.3). None of these patients were taking calcium channel blockers. Cardiac catheterization demonstrated 4 of the 16 patients to have two-vessel or three-vessel coronary artery disease. Two patients in this group had DM. These patients had normal Hgb, S_{creat}, and estimated CrCl values that were all significantly different than the group of patients with CRF.

Systemic Hemodynamics and $S\dot{V}O_2$

The results of systemic hemodynamic measurements and $S\dot{V}O_2$ are shown in Table 2 for both groups of patients. MAP and SVR were higher in patients with CRF than in the control group. CO and CI were comparable and within normal limits in all groups of patients. There were not differences in aO_2. Patients with CRF had a significantly lower Pao_2 and therefore higher $S(a\text{-}v)O_2$. The $S(a\text{-}v)O_2$, expressed as oxygen content (milliliters of 100 mL of blood), was calculated to be 4.52 in normal patients and 4.7 in patients with CRF (not significantly different). $S\dot{V}O_2$ was also similar in the normal group and those with CRF. SO_2del was higher in normal patients than in patients with CRF.

There was a significant linear correlation between $S\dot{V}O_2$ and CO in both normal patients ($P < 0.007$; $r = 0.67$) and patients with CRF ($P < 0.0001$; $r = 0.66$).

Renal Hemodynamics and $R\dot{V}O_2$

Measurements of renal hemodynamics and $R\dot{V}O_2$ are shown in Table 3 for both groups of patients. Patients with CRF had a significantly lower $R\dot{V}O_2$

TABLE 1. Clinical and laboratory characteristics[a]

	Normal	CRF (DM + NDM)	CRF (DM)	CRF (NDM)
N	16	44	21	23
Age (yr)	52.8 ± 2.3	64.9 ± 1.7[b]	60.4 ± 2.6	69 ± 1.8[b,c]
Wt (kg)	88.4 ± 3.6	76 ± 2.3[b]	76 ± 3.1[b]	76 ± 3.5[b]
Hgb (g/dL)				
Women		10.2 ± 0.2	9.9 ± 0.3	10.6 ± 0.2
Men	14.6 ± 0.4	12.6 ± 0.4[b]	13 ± 0.8[b]	12.5 ± 0.4[b]
S_{glu} (mg/dL)	123 ± 10	129 ± 9	154 ± 31[b]	105 ± 21[c]
S_{creat} (mg/dL)	1.0 ± 0.04	2.5 ± 0.11[b]	2.7 ± 0.2[b]	2.4 ± 0.1[b]
CrCl (mL/min)	108 ± 9.0	32 ± 2.0[b]	33 ± 4.0[b]	33 ± 3.0[b]
FR_{Na} (%)[d]	NA	98.1 ± 0.3	97.6 ± 0.5	98.7 ± 0.2[c]
T_{Na} (mEq/min)[d]	NA	5.4 ± 0.8	4.6 ± 0.0	6.2 ± 1.0

[a] Values are means ± SE.

[b] Normal versus CRF, CRF (DM), or CRF (NDM); $P < 0.01$ by *t* test.

[c] CRF (DM) versus CRF (NDM); $P < 0.05$ by *t* test.

[d] $N = 20$; DM, 10; NDM, 10.

TABLE 2. Systemic hemodynamics and $S\dot{V}O_2$[a]

	Normal	CRF (DM + NDM)	CRF (DM)	CRF (NDM)
N	16	44	21	23
MAP (mm Hg)	99 ± 3.0	108 ± 2.0[b]	110 ± 3.0[b]	106 ± 3.0[b]
aO_2 (%)	94 ± 0.6	93 ± 0.4	92 ± 0.6	94 ± 0.6
Pao_2 (%)	71 ± 1.0	62 ± 1.0[b]	61 ± 2.0[b]	63 ± 2.0[b]
$S(a\text{-}v)O_2$ (%)	22.9 ± 1.0	30.9 ± 1.2[b]	31.4 ± 1.6[b]	30.5 ± 1.7[b]
CO (L/min)	5.6 ± 3.0	4.8 ± 0.2	5.2 ± 0.3	4.6 ± 0.3
CI (L/min/m^2)	2.7 ± 0.1	2.6 ± 0.1	2.8 ± 0.1	2.4 ± 0.1
SVR (dyne/s/cm^5)	1,382 ± 77	1,821 ± 84[b]	1,682 ± 99[b]	1,947 ± 128[b]
$S\dot{V}O_2$ (μmol of O_2/min)	10,564 ± 277	9,669 ± 362	10,263 ± 584	9,127 ± 424
SO_2del (μmol of O_2/min)	45,266 ± 3,166	30,898 ± 1,658[b]	31,916 ± 2,470[b]	29,968 ± 2,267[b]

[a] Values are means ± SE.

[b] Normal versus CRF, CRF (DM), or CRF (NDM); $P < 0.02$ by *t* test.

TABLE 3. Renal hemodynamics and $R\dot{V}O_2$[a]

	Normal	CRF (DM + NDM)	CRF (DM)	CRF (NDM)
N	16	44	21	23
RvO_2 (%)	87 ± 0.7	79 ± 1.0[b]	78 ± 2.0[b]	80 ± 2.0[b]
$R(a\text{-}v)O_2$ (%)	7.3 ± 0.8	13.9 ± 1.0[b]	14.4 ± 2.0[b]	13.4 ± 1.0[b]
RBF (mL/min/kidney)	572 ± 146	197 ± 20[b]	146 ± 23[b,c]	242 ± 28[b]
$R\dot{V}O_2$ (μmol of O_2/min/kidney)	391 ± 101	177 ± 20[b]	131 ± 21[b,c]	218 ± 29[b]
$R\dot{V}O_2$ (μmol of O_2/min/100 mL of CrCl)	781 ± 219	1,244 ± 120	1,016 ± 150	1,453 ± 175[b]
RO_2del (μmol of O_2/min/kidney)	5,081 ± 1,400	1,327 ± 154[b]	942 ± 181[b,c]	1,660 ± 221[b]
FF	0.15 ± 0.02	0.12 ± 0.02	0.17 ± 0.03	0.08 ± 0.01[c]

[a] Values are means ± SE.

[b] Normal versus CRF, CRF (DM) or CRF (NDM); $P < 0.02$ by *t* test.

[c] CRF (DM) versus CRF (NDM); $P < 0.03$ by *t* test.

and thus higher $R(a\text{-}v)O_2$ than normal controls. The $R(a\text{-}v)O_2$ calculated as oxygen content was 1.43 mL/100 mL in normal patients and 2.1 mL/100 mL in patients with CRF ($P < 0.05$).

RBF was significantly lower in all patients with CRF than in normal patients. Patients with CRF had equivalent RBF whether or not they had hypertension or were taking (221 ± 28 mL/min/kidney) or not taking (212 ± 41 mL/min/kidney) calcium channel blockers. Patients with DM had significantly lower RBF than did those with NDM. There were no differences within DM or NDM groups when analyzed according to hypertension or calcium channel blocker therapy. RO_2del was significantly lower in patients with CRF than in normal patients. Again, patients with DM had a lower RO_2del than did those with NDM. $R\dot{V}O_2$, expressed per kidney, was significantly lower in CRF than in normal controls. In addition, those patients with DM had a significantly lower $R\dot{V}O_2$ than did those with NDM. However, $R\dot{V}O_2$, when expressed per 100 mL of CrCl, was elevated only in patients with CRF without DM when compared with the normal controls ($P < 0.03$). $R\dot{V}O_2$ was not different when analyzed according to the presence of hypertension, or calcium channel blocker therapy (with calcium channel blocker, 199 ± 25 μmol of O_2/min/kidney; without, 168 ± 34 μmol of O_2/min/kidney) in patients with CRF or subsets of DM or NDM. There were no significant correlations between MAP and RBF or $R\dot{V}O_2$ in patients with CRF or subgroups of DM or NDM. There were no significant correlations between S_{glu} and RBF, $R\dot{V}O_2$, CrCl, or FF. FF was not different between normal and all CRF patients; however, NDM patients had a significantly lower FF than did DM patients.

There were significant linear correlations between Hgb and RBF ($r = 0.47$; $P < 0.02$) (Figure 1) and between Hgb and $R\dot{V}O_2$ ($r = 0.31$; $P < 0.04$) in patients with CRF.

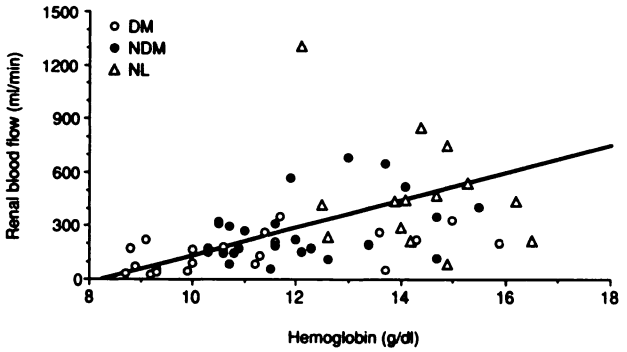

Figure 1. There is a significant linear correlation between Hgb and RBF in all patients with CRF combined ($r = 0.47$; $P < 0.02$).

Figure 2 demonstrates the relationship between $R\dot{V}O_2$ and RBF for all patients combined (third order, $r = 0.91$). $R\dot{V}O_2$ also correlated significantly with RBF in normal controls (third order, $r = 0.98$) and in patients with CRF (third order, $r = 0.74$) when analyzed separately.

Figure 3 demonstrates the significant linear correlation between estimated CrCl and $R\dot{V}O_2$ in all patients combined ($r = 0.38$; $P < 0.005$; *y* intercept, 115; slope, 2.3). This relationship was significant in all patients with CRF ($P < 0.02$; $r = 0.37$; *y* intercept, 65; slope, 3.5) and in patients with NDM alone ($P < 0.04$; $r = 0.45$, *y* intercept, 55; slope, 4.9). However, it was not significant in patients with DM or normal patients when analyzed independently. There were no significant correlations between $R\dot{V}O_2$ and FR_{Na} or T_{Na}.

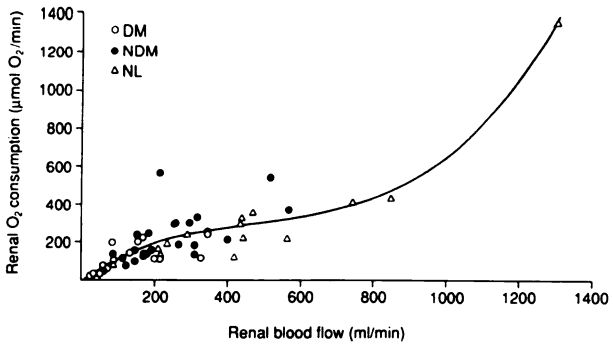

Figure 2. A third-order polynomial fit of $R\dot{V}O_2$ versus RBF for all patients combined ($r = 0.91$).

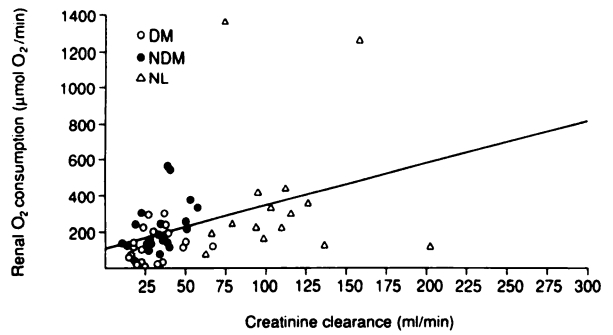

Figure 3. Estimated CrCl by the method of Cockcroft and Gault (26) versus $R\dot{V}O_2$ in all patients combined. There was a significant linear correlation ($P < 0.005$, $r = 0.38$). The y intercept of this plot is 115, and the slope is 2.3.

DISCUSSION

Clinical Characteristics

Our "normal" control patients were younger than those with CRF and generally healthier, as is indicated by the lower prevalence of DM and significant coronary artery disease. Those patients with CRF had moderate renal dysfunction and were mildly anemic. CrCl, as estimated by the method of Cockcroft and Gault, has been demonstrated to be a reasonable approximation of GFR in patients with diabetic nephropathy (30), and our results also showed a strong correlation between estimated CrCl and 12-h, overnight CrCl. However, both methods have significant associated errors. In the case of the timed CrCl, this error is due to variations in creatinine excretion, inaccuracy of urine collections, and significant tubular secretion of creatinine, particularly in CRF (25). In the absence of a control for diuretic therapy or sodium intake, it is impossible to draw meaningful conclusions regarding sodium balance. However, it is still reasonable to relate sodium transport to renal oxygen consumption. Unfortunately, the very narrow range in sodium excretion may be responsible for a lack of correlation.

Systemic Hemodynamics and Oxygen Consumption

Our patients with normal renal function had normal MAP, CO, CI, and SVR (31). Patients with CRF had an elevated MAP due to a higher SVR, because their CO and CI were not different from those of the normal group. There were no significant differences in CO, CI, SVR, or MAP between patients with DM or NDM. Elevated MAP and SVR have been previously described in CRF (3,25,28,32,33).

All of our patients had normal aO_2. Because aO_2 and CO were normal in CRF, the reduced oxygen delivery was predominantly a function of their anemia. Despite the lower oxygen delivery in patients with CRF, normal $S\dot{V}O_2$ (31) was accomplished through their elevated extraction.

Studies in azotemic rats have demonstrated either normal (1) or reduced (2) $S\dot{V}O_2$. Fewer studies address $S\dot{V}O_2$ in human CRF, and the majority of these are in patients with severe CRF with or without uremia (3–6). Both normal (4–6) and reduced (3) $S\dot{V}O_2$ have been reported. However, these studies did not differentiate according to the cause of the renal disease. Our results demonstrate a normal $S\dot{V}O_2$ in patients with moderate CRF irrespective of underlying disease (DM versus NDM). $S\dot{V}O_2$ in DM is normal during insulin therapy (34), according to a study in which renal function was not addressed. The diabetic state is associated with higher than normal 2,3-diphosphoglycerate (DPG) levels, which shift the oxyhemoglobin dissociation curve to the right. At the same time, patients with DM have higher levels of hemoglobin A_1C, which has a high affinity for oxygen. These two factors balance one another to result in normal P_{50} (35,36).

Our study is unique in describing SVO_2 in patients with moderate CRF with or without DM. We demonstrate that neither the presence of DM and CRF nor moderate CRF regardless of cause alters $S\dot{V}O_2$. Patients with moderate CRF compensate for their anemia through increased $S(a\text{-}v)O_2$, perhaps facilitated by elevated 2,3-DPG, causing a rightward shift of the oxyhemoglobin oxygen disassociation curve (37).

Renal Hemodynamics and $R\dot{V}O_2$

Most authoritative physiology and nephrology sources (25,28,31,32,38) only briefly address $R\dot{V}O_2$. This may be in part because of the difficulty in measuring $R\dot{V}O_2$ and RBF, which require invasive procedures. The relationships between RBF, $R\dot{V}O_2$, GFR, and $R(a\text{-}v)O_2$ have been studied predominantly in normal animals (12–16). Recent literature suggests a role for hypermetabolism in both the recovery from an acute ischemic insult (21) and the pathogenesis of CRF in rats (19,20,22) but not in dogs (23). In the study presented here, we describe these relationships in both normal controls and in patients with

CRF, segregating the latter according to the presence of DM.

Our measurements of RBF, FF, RvO_2, $R\dot{V}O_2$, and $R(a\text{-}v)O_2$ in normal patients are comparable to those of prior human studies (8–11,29). Our data demonstrate that patients with CRF have lower RBF than do those with normal renal function, consistent with the available literature (10,39,40). Our data suggest that chronic calcium channel blocker therapy had no effect on RBF, although a larger group would be required to definitively address this issue.

Prior studies measuring RBF in patients with CRF have not compared the data according to the presence or absence of DM. Our patients with CRF and DM had even lower RBF than did those with comparable renal function without DM. The FF was higher in the patients with DM than in those with NDM and was equivalent to the FF in our normal controls. Both normal (41,42) and reduced (43,44) FF have been reported in patients with DM and CRF. Of note, these prior studies used *p*-aminohippuric acid clearance for the measurement of RBF, a technique that may be inaccurate in CRF (25,42). Unlike early DM where the elevated FF is a function of a high GFR (25,28), in the presence of CRF, the normal FF is a function of the lower RBF. The pathogenesis of the lower RBF and normal FF in CRF and DM is unknown. It has been suggested that these changes may have both functional and structural components (44).

Recent evidence suggests (45,46) that the anemia of CRF is beneficial in preventing glomerular hypertension and the progression of CRF. In a rat model of uninephrectomy and streptozotocin-induced DM, glomerular hypertension was prevented through the direct effect of anemia to cause constriction of the afferent arteriole (46). Our data support a relationship between anemia and RBF. The low RBF of CRF could be due in part to the anemia and could be a protective mechanism to prevent the progression of CRF.

The concepts and relationships regarding energy metabolism in animals with normal or abnormal renal function may not apply to the human diseased kidney. Animal studies of $R\dot{V}O_2$ have demonstrated either normal (17) or reduced (18) $R\dot{V}O_2$ in dogs with acute renal failure and increased $R\dot{V}O_2$ in rats after acute ischemia (21) and in a rat remnant kidney model when expressed per nephron number (19,20,22). The latter was termed "hypermetabolism" and was suggested to contribute to the progression of chronic renal disease. However, $R\dot{V}O_2$, when expressed per kidney or per gram of kidney tissue, was either reduced or normal in those studies. Similarly, in a dog remnant kidney model, $R\dot{V}O_2$ was elevated, compared with normal kidneys, only when expressed per 100 mL of GFR (23) but was reduced when expressed per kidney weight. Our data demonstrate that patients with CRF have a reduced $R\dot{V}O_2$ of 44% that of normal patients when expressed per kidney. In addition, our patients with DM had even lower $R\dot{V}O_2$. Because we cannot count nephron number in our patients, we are unable to draw conclusions regarding the presence of "hypermetabolism" defined as such. Although kidney weights are also not available, it is well documented that patients with DM and CRF have normal or enlarged kidneys as compared with those of patients with an equivalent degree of CRF without DM (25,47,48). Thus, the $R\dot{V}O_2$ corrected for kidney weight would likely be even lower in patients with DM. Because patients with NDM presumably have lower kidney weights than do normal patients, in addition to their reduced $R\dot{V}O_2$, it is impossible to predict what the $R\dot{V}O_2$ would be when corrected for kidney weight when compared with normal kidneys. On the basis of this analysis, the CRF of DM does not appear to be characterized by hypermetabolism, defined as an elevated $R\dot{V}O_2$ corrected for kidney weight. Corroborating this speculation, if $R\dot{V}O_2$ is expressed per 100 mL of glomerular filtrate (using our estimated CrCl), only the NDM patients with CRF demonstrate renal hypermetabolism. Patients with CRF and DM show no difference in $R\dot{V}O_2$ from normal. It is likely that the remnant kidney model of neither the rat nor dog is completely analogous to human CRF where the disease process is functionally and pathologically heterogeneous. If renal hypermetabolism plays a role in the progression of human renal disease, it may be limited to patients without DM.

Verapamil has been shown to reduce $R\dot{V}O_2$ in the remnant kidney model in rats, thus potentially slowing the progression of CRF (20). Chronic calcium channel blocker therapy did not alter the $R\dot{V}O_2$ in our patients with CRF or subgroups of DM or NDM. It is possible that these agents may not alter $R\dot{V}O_2$ in people, that different classes of calcium channel blockers have different effects and need to be evaluated separately, or that we have an insufficient number of patients in each group to draw meaningful conclusions.

Similarly, the relationships between $R\dot{V}O_2$, RBF, GFR, and $R(a\text{-}v)O_2$ may differ between animals and people or according to the level of renal function. Those relationships presented in modern nephrology and physiology texts (25,28,31,38) are based largely on an animal study by Lassen *et al.* (16), which included 12 normal dogs, 4 of which were bled acutely to achieve lower RBF. Our data define the relationship between RBF and $R\dot{V}O_2$ in people with normal and abnormal renal function. With some overlap, our three groups of patients tended to fall along different segments of the RBF-$R\dot{V}O_2$ curve (Figure 2). Those patients with normal renal function had higher RBF and $R\dot{V}O_2$; patients with CRF segre-

gated into those with NDM or DM, with DM having progressively lower RBF and $R\dot{V}O_2$. Our RBF-$R\dot{V}O_2$ curve is similar to that generated by Lassen *et al.* in dogs. The kidney is unique in that its high blood flow relative to other organs is considered necessary for regulating body composition rather than for providing the kidney with nutrients and oxygen. Thus, it is not surprising that in the presence of normal renal function, changes in RBF are accompanied by parallel changes in $R\dot{V}O_2$, which are felt to be due to changes in GFR and filtered load of sodium. The reabsorption of sodium has been shown in animal studies (12–15) to be the major energy-requiring process in the kidney, consuming between 75 and 85% of total $R\dot{V}O_2$. By analyzing the relationship between GFR and $R\dot{V}O_2$, Lassen *et al.* (16) extrapolated a basal $R\dot{V}O_2$, presumed to be the metabolic requirement of a nonfiltering kidney, of approximately 1 μmol of O_2/min/g of kidney tissue with a slope of the relationship between $R\dot{V}O_2$ and GFR of 5.7 μmol of O_2/mL of filtrate. This is similar to our basal $R\dot{V}O_2$ of 115 μmol of O_2/min/kidney, assuming kidney weights in the range of 100 to 150 g in our patients with CRF or normal function. Our slope was only 2.3, suggesting less oxygen consumption per milliliter of filtrate. The lower slope may represent either more efficient sodium transport or less sodium transport, possibly related to a species difference between dogs and humans, the effects of diuretics (11,13,17), or metabolic differences related to the cause of the renal disease (23). Recent animal studies suggest that sodium transport may not be the major oxygen-consuming process in pathological states (19,21), although a strong correlation was demonstrated in the remnant kidney model in the dog (23). Alternatively, it may not be physiologically valid to combine patients with normal renal function and those with CRF of diverse cause on one plot when examining the relationship between CrCl and $R\dot{V}O_2$. If analyzed separately, patients with CRF had a basal $R\dot{V}O_2$ of 65 μmol of O_2/min/kidney and a slope of 3.5. Patients with CRF and NDM had a basal oxygen consumption of 55 μmol of O_2/min/kidney and a slope of 4.9. However, the data on patients with CRF and DM or normal renal function did not produce a statistically significant regression when analyzed separately. Our inability to correlate $R\dot{V}O_2$ with GFR in normal patients may reflect insufficient data or may be limited by the narrow range of GFR. If the subgroups of DM or normal renal function had generated significant linear relationships, it would have been interesting to compare them with the relationship in NDM patients. The data on $R\dot{V}O_2$ and CrCl in diabetics with CRF tended to look like a scatter plot, although the mean $R\dot{V}O_2$ was lower in DM when expressed per kidney or kidney weight. The absence of a correlation could represent a dissociation between oxygen consumption and sodium transport in diabetics with CRF. The lower mean $R\dot{V}O_2$ in patients with DM but the CrCl comparable to NDM patients could reflect either a lower basal oxygen consumption or lower reabsorption-related oxygen consumption. Patients with DM may have lower basal $R\dot{V}O_2$ and altered relationships between $R\dot{V}O_2$ and CrCl because of metabolic abnormalities. These could include altered gluconeogenesis, or glucose metabolism via the hexose monophosphate shunt or sorbitol pathways (49). The patients with DM and CRF had slightly higher baseline glucose than did normal or NDM groups. Substrate availability has been shown to account for variations in $R\dot{V}O_2$ in the isolated perfused rat kidney (50,51), and glucose may be used preferentially as a metabolic fuel in anaerobic pathways by some renal segments (41). Reduced renal oxygen use in these patients might explain why their R(a-v)O_2 was not higher than that in patients with CRF and NDM, as was demonstrated between patients with CRF and NDM and patients with normal renal function. These speculations are all subject to the criticism that GRF was not measured directly but rather was estimated by a calculated CrCl method that may be less accurate, as discussed above. However, this method has been well correlated with inulin clearance (26,30), and although it is possible that our exact numbers may be slightly inaccurate, the trends are probably the same.

There is little literature on $R\dot{V}O_2$ in humans (8–11,24). Nitter-Hauge and Brodwall (8) studied the relationships between RBF, R(a-v)O_2, and $R\dot{V}O_2$ in a series of patients with rheumatic mitral valve disease, low CO, and normal renal function. They demonstrated low RBF, which reflected the low CO, and elevated R(a-v)O_2 differences. $R\dot{V}O_2$ in their patients was inexplicably increased and was unrelated to RBF. In a second study, Bradley and Halperin (9), demonstrated constant R(a-v)O_2 and decreased $R\dot{V}O_2$ during acute reductions of RBF in humans by abdominal compression. Barker *et al.* (24) demonstrated an inverse relationship between RBF and R(a-v)O_2 in people with normal renal function given salt-poor human albumin i.v. to elevate RBF. Overall, the relationships described for our patients are more similar to those generated in dogs (16) than in prior human studies (8,9). However, the data from those three studies may not be pertinent to our patients who have CRF rather than a low CO state or acute changes in RBF. The only study of patients with CRF was that by Cargill and Hickam (10), who evaluated six patients with CRF and a mean CrCl of 30.5 mL/min. Their patients included four with chronic glomerulonephritis and two with pyelonephritis. They had a reduced mean RBF of 353 mL/min, a mean FF of 0.13, and a low $R\dot{V}O_2$, similar to that of our population. Cargill and Hickam concluded that R(a-v)O_2 remains constant and within a normal range despite

the presence of CRF and low RBF. If the data from these six patients are incorporated into our figures, they fall in the same range as that of our larger group of patients with CRF. Thus, our data extend this limited study.

In conclusion, this study describes systemic and renal hemodynamics and oxygen consumption in patients with normal renal function and those with CRF with or without DM. We demonstrate normal $S\dot{V}O_2$, reduced RBF, and reduced $R\dot{V}O_2$ in patients with moderate CRF, despite elevated $S(a\text{-}v)O_2$ and $R(a\text{-}v)O_2$. Patients with DM and equivalent renal function had even lower RBF and $R\dot{V}O_2$ than did patients without DM, probably representing more pronounced renal hemodynamic and/or metabolic changes. Renal hypermetabolism, defined as $R\dot{V}O_2$ per 100 mL of CrCl, may exist in patients with CRF without DM but not in patients with DM and CRF. Our data were used to define the relationships between RBF, $R\dot{V}O_2$, and CrCl in people with normal and chronically impaired renal function.

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