Basal renal O2 consumption and the efficiency of O2 utilization for Na$^+$ reabsorption

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Submitted 20 August 2013; accepted in final form 8 January 2014

Evans RG, Harrop GK, Ngo JP, Ow CP, O’Connor PM. Basal renal O2 consumption and the efficiency of O2 utilization for Na$^+$ reabsorption. Am J Physiol Renal Physiol 306:F551–F560, 2014. First published January 15, 2014; doi:10.1152/ajprenal.00473.2013.—We examined how the presence of a fixed level of basal renal O2 consumption (O2$^{\text{basal}}$) is used for processes independent of Na$^+$ transport) confounds the utility of the ratio of Na$^+$ reabsorption (TNa$_{\text{a}}$) to total renal O2 (V$_{O2}^{\text{total}}$) as an index of the efficiency of O2 utilization for TNa$_{\text{a}}$. We performed a systematic review and additional experiments in anesthetized rabbits to obtain the best possible estimate of the fractional contribution of O2$^{\text{basal}}$ to O2$^{\text{total}}$ under physiological conditions (basal percent renal V$_{O2}$). Estimates of basal percent renal V$_{O2}$ from 24 studies varied from 0% to 81.5%. Basal percent renal V$_{O2}$ varied with the fractional excretion of Na$^+$ (FE$_{\text{Na}}$) in the 14 studies in which FE$_{\text{Na}}$ was measured under control conditions. Linear regression analysis predicted a basal percent renal V$_{O2}$ of 12.7–16.5% when FE$_{\text{Na}}$ = 1% (r$^2$ = 0.48, P = 0.001). Experimentally induced changes in TNa$_{\text{a}}$, altered TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ in a manner consistent with theoretical predictions. We conclude that, because V$_{O2}^{\text{basal}}$ represents a significant proportion of V$_{O2}^{\text{total}}$, TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ can change markedly when TNa$_{\text{a}}$ itself changes. Therefore, caution should be taken when TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ is interpreted as a measure of the efficiency of O2 utilization for TNa$_{\text{a}}$, particularly under experimental conditions where TNa$_{\text{a}}$ or V$_{O2}^{\text{total}}$ changes.

THE KIDNEY DERIVES CHEMICAL ENERGY FROM O2, WHICH IT THEN USES TO REABSORB Na$^+$ AND TO PERFORM FUNCTIONS THAT ARE INDEPENDENT OF Na$^+$ REABSORPTION (TNa$_{\text{a}}$). THE RELATIONSHIP BETWEEN TOTAL RENAL O2 CONSUMPTION (O2$^{\text{total}}$) AND TNa$_{\text{a}}$ IS QUASILINEAR. IT IS OFTEN DEPICTED BY A STRAIGHT LINE THAT INTERSECTS THE ORDINAL (V$_{O2}$) AXIS AT A POINT REPRESENTING THE COST OF "BASAL METABOLISM" (O2$^{\text{basal}}$). O2$^{\text{basal}}$ CAN BE DEFINED AS THE SUM OF ALL OF O2$^{\text{total}}$ THAT REMAINS AFTER ACCOUNTING FOR THAT USED FOR (TNa$_{\text{a}}$) (19). THERE IS GENERAL AGREEMENT THAT, UNDER PHYSIOLOGICAL CONDITIONS, O2$^{\text{total}}$ COMPRISSES <20% OF O2$^{\text{total}}$. THIS QUANTITY (100 × O2$^{\text{basal}}$/O2$^{\text{total}}$) CAN BE USED TO ESTIMATE THE EXPENDITURE OF O2$^{\text{total}}$. HOWEVER, THESE ESTIMATES HAVE VARIED WIDELY (TABLE 1), INDICATING THAT THIS PARAMETER IS HIGHLY SUSCEPTIBLE TO EXPERIMENTAL CONDITIONS.

THE ACTUAL MAGNITUDE OF BASAL PERCENT RENAL V$_{O2}$ HAS IMPORTANT IMPLICATIONS FOR OUR UNDERSTANDING OF THE MECHANISMS UNDERLYING RENAL HYPOXIA IN ACUTE AND CHRONIC KIDNEY DISEASE. IT HAS BECOME WIDELY ACCEPTED THAT THE QUOTIENT OF TNa$_{\text{a}}$ TO RENAL V$_{O2}^{\text{total}}$ (OR ITS RECIPROCAL) REPRESENTS AN INDEX OF THE EFFICIENCY (OR INEFFECTIVENESS) OF O2 UTILIZATION FOR TNa$_{\text{a}}$ (6, 7, 35, 55). TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ IS REDUCED IN ACUTE KIDNEY INJURY (6, 7, 35, 55), CHRONIC KIDNEY DISEASE (8), DIABETES (51), AND HYPERTENSION (8). THESE OBSERVATIONS HAVE BEEN INTERPRETED AS EVIDENCE THAT INEFFECTIVE UTILIZATION OF O2 FOR TNa$_{\text{a}}$ CONTRIBUTES TO THE RENAL TISSUE HYPOXIA CHARACTERISTIC OF THESE PATHOLOGICAL STATES. FURTHERMORE, LAYCOCK AND COLELAGUES SHOULDED THAT BLOCKADE OF NITRIC OXIDE SYNTHASE REduced THE GLomerular filtration rate (GFR) AND TNa$_{\text{a}}$ BUT INCREASED RENAL V$_{O2}^{\text{total}}$, SO THAT TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ WAS MORE THAN HALVED (35). THESE OBSERVATIONS WERE INTERPRETED AS EVIDENCE THAT NITRIC OXIDE NORMALLY ACTS TO ENHANCE THE "RENAL EFFICIENCY FOR TRANSPORTATION OF SODIUM." CHANGES IN TRANSPORT EFFICIENCY, WHICH CAN BE DEFINED AS THE RATE OF CHANGE IN TNa$_{\text{a}}$ PER UNIT CHANGE IN V$_{O2}^{\text{total}}$ (dTNa$_{\text{a}}$/dV$_{O2}^{\text{total}}$) COULD RESULT FROM CHANGES IN MITOCHONDRIAL FUNCTION, SHIFTS IN TNa$_{\text{a}}$ ALONG THE NEPHRON TO SITES OF DIFFERING EFFICIENCY FOR O2 UTILIZATION, ALTERED Na$^+$ BACKLEAK THROUGH PARACELLULAR PATHWAYS, OR CHANGES IN THE FUNCTION OF MECHANISMS OF SECONDARY ACTIVE TRANSPORT (19). HOWEVER, THE DENOMINATOR OF TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ IS COMPOSED OF A COMPONENT DEPENDENT ON TNa$_{\text{a}}$ (V$_{O2}^{\text{Na}}$) AS WELL AS A COMPONENT INDEPENDENT OF TNa$_{\text{a}}$ (V$_{O2}^{\text{basal}}$). CONSEQUENTLY, THE USE OF TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ AS AN INDEX OF THE EFFICIENCY OF TNa$_{\text{a}}$ (TRANSPORT EFFICIENCY = dTNa$_{\text{a}}$/dV$_{O2}^{\text{total}}$) RESTS ON THE ASSUMPTION THAT V$_{O2}^{\text{basal}}$ IS NEGligible AND DOES NOT VARY MUCH UNDER PHYSIOLOGICAL OR PATHOPHYSIOLOGICAL CONDITIONS. THEREFORE, IN THE PRESENT STUDY, WE SET OUT TO TEST THE HYPOTHESES THAT 1) UNDER PHYSIOLOGICAL CONDITIONS, V$_{O2}^{\text{basal}}$ MAKES UP A SUBSTANTIAL PROPORTION OF V$_{O2}^{\text{total}}$ AND TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ DEPEND ON THE Natriuretic state of the kidney and, thus, vary with the fractional excretion of Na$^+$ (FE$_{\text{Na}}$) AND TNa$_{\text{a}}$. TO ASSESS BASAL PERCENT RENAL V$_{O2}$, WE FIRST PERFORMED A SYSTEMATIC REVIEW OF PUBLISHED REPORTS OF STUDIES OF INTACT ANIMALS IN WHICH BASAL PERCENT RENAL V$_{O2}$ WAS ESTIMATED OR THAT CONTAINED DATA FROM WHICH IT COULD BE ESTIMATED. WE ALSO PERFORMED AN EXPERIMENT TO ASSESS THE EFFECTS OF URERETAL LIGATION ON RENAL V$_{O2}$, SINCE THIS APPROACH HAS BEEN LITTLE USED (TABLE 1). WE THEN REVIEWED PUBLISHED REPORTS IN WHICH TNa$_{\text{a}}$/V$_{O2}^{\text{total}}$ WAS MEASURED OR THAT CONTAINED DATA FROM WHICH IT COULD BE CALCULATED TO DETERMINE WHETHER IT VARIES WITH FE$_{\text{Na}}$ AND/OR TNa$_{\text{a}}$. PATTERNS ARISING IN THESE DATA WERE THEN COMPARRED WITH THEORETICAL RELATIONSHIPS BETWEEN THESE VARIABLES, GENERATED FOR VARYING LEVELS OF V$_{O2}^{\text{basal}}$.

METHODS

Systematic Review: Search Criteria

In a Medline search, we used as Medical Subject Headings (MeSH) and keywords "oxygen consumption" (105,389 results) AND "kidney" (652,799 results) AND either "glomerular filtration rate" (38,655 results) OR the MeSH "sodium" OR the keyword "sodium reabsorption" (127,115 results), giving a combined return of 553...
### Basal Renal O₂ Consumption

#### Table 1. Available estimates of $\dot{V}_O^2_{basal}$ as a percentage of $\dot{V}_O^2_{total}$ (basal percent renal $\dot{V}_O^2$)

| Author(s)          | Reference | Species and Number of Animals Studied | Anesthetic | FE_Na₂⁺, %  | TNa⁺/V₂O₆₅⁺ | Basal Percent Renal $\dot{V}_O^2$
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<tbody>
<tr>
<td>Lassen et al.</td>
<td>34</td>
<td>Dog ($n = 14$)</td>
<td>Pentobarbital</td>
<td>1.51 ± 0.42</td>
<td>23.0 ± 0.6</td>
<td>11.6% by extrapolation$^b$; 18.6% when GFR = 0 (hemorrhage)</td>
</tr>
<tr>
<td>Thaysen et al.</td>
<td>69</td>
<td>Dog ($n = 10$)</td>
<td>NR</td>
<td>NR</td>
<td>23.0 ± 0.6</td>
<td>18.0% when GFR = 0 (hemorrhage); note the likely overlap of data with Lassen et al. (34)</td>
</tr>
<tr>
<td>Thurau</td>
<td>72</td>
<td>Dog ($n = 12$)</td>
<td>Pentobarbital or thiobutabarbital</td>
<td>1.19</td>
<td>NR</td>
<td>17.9% by extrapolation$^b$</td>
</tr>
<tr>
<td>Fujimoto et al.</td>
<td>16</td>
<td>Dog ($n = 21$)</td>
<td>Pentobarbital</td>
<td>Control: $2.40 ± 0.52$; mannitol diuresis: $8.8 ± 0.3$</td>
<td>21.5 ± 2.3$^a$</td>
<td>0% by extrapolation$^b$</td>
</tr>
<tr>
<td>Knox et al.</td>
<td>30</td>
<td>Dog ($n = 42$)</td>
<td>Chloralose or pentobarbital</td>
<td>Control: $26.4 ± 3.8$; mannitol diuresis: $15.6 ± 1.7$</td>
<td>3.7% by extrapolation$^b$; $T_{Na}^+$ reduced by hemorrhage and increased ureteral pressure and infusion of Ringer solution or mannitol solution; 15% by extrapolation$^b$ during ethacrynic acid-induced diuresis if total $\dot{V}_O^2$ is considered the value before ethacrynic acid administration; 20% by extrapolation$^b$ during ethacrynic acid-induced diuresis if total $\dot{V}_O^2$ is considered the value after ethacrynic acid administration.</td>
<td></td>
</tr>
<tr>
<td>Wolf et al.</td>
<td>81</td>
<td>Dog ($n = 15$)</td>
<td>Chlorpromazine/ pentobarbital/ chloralose</td>
<td>Control: $−4$; after ethacrynic acid: $−29$</td>
<td>Control: $−33$; after ethacrynic acid: $−21$</td>
<td>30.5% by extrapolation$^b$</td>
</tr>
<tr>
<td>Sadowski and Torun</td>
<td>58</td>
<td>Dog ($n = 16$)</td>
<td>N-methyl-β-bromoallylisopropyl barbiturate</td>
<td>NR</td>
<td>NR</td>
<td>30.6% by extrapolation$^b$; 63.9% when GFR = 0 (hypertonic mannitol infusion); 81.5% when GFR = 0 (tubular blockade with oil)</td>
</tr>
<tr>
<td>Sejersted et al.</td>
<td>60</td>
<td>Dog ($n = 7$)</td>
<td>Pentobarbital</td>
<td>20.8 during mannitol-Ringer infusion</td>
<td>16.5</td>
<td>33.6% by extrapolation$^b$ before ouabain treatment; $T_{Na}^+$ reduced by aortic constriction; 28.4% by extrapolation$^a$ after ouabain treatment</td>
</tr>
<tr>
<td>Stecker et al.</td>
<td>65</td>
<td>Dog ($n = 8$)</td>
<td>Pentobarbital</td>
<td>NR</td>
<td>NR</td>
<td>35.6% 3 h after complete ureteral obstruction</td>
</tr>
<tr>
<td>Theye and Maher</td>
<td>70</td>
<td>Dog ($n = 13$)</td>
<td>Lightly anesthetized with 0.1% (vol/vol) halothane (plus neuromuscular blockade)</td>
<td>NR</td>
<td>19.4</td>
<td>35.0% by extrapolation$^b$; $T_{Na}^+$ reduced by 1% (vol/vol) expired halothane; 38.1% when GFR = 0 [3% (vol/vol) expired halothane]</td>
</tr>
<tr>
<td>Melchiorri et al.</td>
<td>45</td>
<td>Dog ($n = 6$)</td>
<td>Pentobarbital and phenobarbital</td>
<td>NR</td>
<td>NR</td>
<td>~10% when GFR = 0 (intravenous bombesin)</td>
</tr>
<tr>
<td>Dies et al.</td>
<td>9</td>
<td>Dog ($n = 19$)</td>
<td>Pentobarbital</td>
<td>$−10 (7–13)$</td>
<td>33.9</td>
<td>30.4% by extrapolation$^a$; $T_{Na}^+$ reduced by ouabain, acetazolamine, ethacrynic acid, and furosemide</td>
</tr>
<tr>
<td>Steen et al.</td>
<td>66</td>
<td>Dog ($n = 6$)</td>
<td>Pentobarbital</td>
<td>16.6</td>
<td>21.0</td>
<td>39.0% by extrapolation$^a$; $T_{Na}^+$ reduced by graded doses of ethacrynic acid</td>
</tr>
<tr>
<td>Rosenbaum and DiScala</td>
<td>57</td>
<td>Dog ($n = 5$)</td>
<td>Pentobarbital</td>
<td>NR</td>
<td>23.2 ± 2.2</td>
<td>24% by extrapolation$^a$; $T_{Na}^+$ reduced by intravenous infusion of Ringer solution</td>
</tr>
<tr>
<td>Ostensen and Stokke</td>
<td>49</td>
<td>Dog ($n = 10$)</td>
<td>Pentobarbital</td>
<td>NR</td>
<td>NR</td>
<td>All dogs were pretreated with acetazolamide; 15.1% by extrapolation$^a$; $T_{Na}^+$ reduced by bumetanide and ouabain</td>
</tr>
<tr>
<td>Torelli et al.</td>
<td>73</td>
<td>Rabbit ($n = 24$)</td>
<td>Pentobarbital and urethane</td>
<td>NR</td>
<td>8.8 ± 1.1</td>
<td>64.6% by extrapolation$^a$; 40.5% when GFR = 0 (hemorrhage)</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>13</td>
<td>Rabbit ($n = 6$)</td>
<td>Pentobarbital</td>
<td>12.1 ± 1.6</td>
<td>13.0 ± 0.7$^c$</td>
<td>47.2 ± 5.5% when GFR = 0 (reduced renal artery pressure)</td>
</tr>
<tr>
<td>Present study</td>
<td></td>
<td>Rabbit ($n = 6$)</td>
<td>Pentobarbital</td>
<td>14.8 ± 4.0</td>
<td>11.3 ± 1.1</td>
<td>60 ± 8% when GFR = 0 (90 min after ligation of the ureter)</td>
</tr>
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Continued
Basal Percent Renal $V_O^2$

Overview of available methods for estimating basal percent renal $V_O^2$. Basal renal metabolism can be assessed in vivo in a number of ways. One approach might be pharmacologically to inhibit Na$^+$/K$^+$-ATPase using an agent such as ouabain. However, not all isoforms of Na$^+$/K$^+$-ATPase are ouabain sensitive, particularly in rodents (39), and ouabain is arrhythmogenic. Consequently, caution must be applied to the interpretation of data derived from such studies. Another approach is to plot the relationship between $T_{Na^-}$ and renal $V_O^{2\text{total}}$ observed under relatively normal physiological conditions or in response to maneuvers that alter $T_{Na^-}$ and then calculate the ordinal intercept, where $T_{Na^-} = 0$ (or GFR = 0). This approach has been used widely (Table 1). Nevertheless, this does require the assumption that the relationship between $T_{Na^-}$ and renal $V_O^{2\text{total}}$ is linear [or log linear (58)] and could be confounded by changes in renal metabolism, independent of $T_{Na^-}$, that might occur in response to experimental maneuvers used to alter $T_{Na^-}$. Another approach, which has also been used widely, is to lower arterial pressure below the point at which glomerular filtration ceases. This approach is, of course, limited by the potential for neurohumoral activation, particularly if arterial pressure is lowered by hemorrhage, to alter $V_O^{2\text{total}}$ or the efficiency of $O_2$ utilization for Na$^+$ transport (d$T_{Na^-}$/d$V_O^{2\text{total}}$). Finally, ureteric obstruction will also abolish Na$^+$ excretion, but it has not been definitively established that ureteric obstruction abolishes Na$^+$ transport.

Table 1.—Continued

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Reference</th>
<th>Species and Number of Animals/Patients Studied</th>
<th>Anesthetic</th>
<th>$F_{E_{Na^-}}$,%</th>
<th>$T_{Na^-}/V_O^{2\text{total}}$</th>
<th>Basal Percent Renal $V_O^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juillard et al.</td>
<td>27</td>
<td>Pig ($n = 8$)</td>
<td>Ketamine and xylazine</td>
<td>8.1 ± 2.7</td>
<td>19.6</td>
<td>15% when GFR = 0 (reduced renal artery pressure)$^f$</td>
</tr>
<tr>
<td>Parekh and Veith</td>
<td>52</td>
<td>Rat ($n = 22$)</td>
<td>Thiobutabarbital</td>
<td>0.66 ± 0.19</td>
<td>25.8</td>
<td>19.9% by extrapolation$^c$; $T_{Na^-}$ reduced by subjecting some rats to ischemia-reperfusion injury 40 days before the experiment</td>
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<tr>
<td>Elinder and Aperia</td>
<td>12</td>
<td>Rat ($n = 24$)</td>
<td>Thiobutabarbital</td>
<td>1.05</td>
<td>14.9</td>
<td>12.3% by extrapolation$^c$; $T_{Na^-}$ reduced by intravenous infusion of isotonic saline</td>
</tr>
<tr>
<td>Welch et al.</td>
<td>80</td>
<td>Rat ($n = 10$ Wistar-Kyoto rats + n = 10 spontaneously hypertensive rats)</td>
<td>Thiobutabarbital</td>
<td>NR</td>
<td>15.1 ± 1.6</td>
<td>Wistar-Kyoto rats: 43.4% by extrapolation$^c$; spontaneously hypertensive rats: 21.1% by extrapolation$^b$</td>
</tr>
<tr>
<td>Brodwall; Brodwall and Laake</td>
<td>2, 3</td>
<td>Human ($n = 24$)</td>
<td>Unanesthetized</td>
<td>NR</td>
<td>43.4</td>
<td>19.8% by extrapolation$^{b,c}$</td>
</tr>
<tr>
<td>Ofstad et al.</td>
<td>48</td>
<td>Human ($n = 10$)</td>
<td>Unanesthetized</td>
<td>Control: 1.96; after furosemide: 14.4</td>
<td>Control: 13.7; after furosemide: 12.1</td>
<td>0.1% by extrapolation$^b$ before furosemide treatment; 30.8% by extrapolation$^b$ after furosemide treatment</td>
</tr>
<tr>
<td>Kurnik et al.</td>
<td>33</td>
<td>Human ($n = 60$)</td>
<td>Unanesthetized</td>
<td>1.9 ± 0.3$^i$</td>
<td>NR</td>
<td>29.4% by extrapolation$^{b,c}$</td>
</tr>
</tbody>
</table>

$V_O^{2\text{total}}$, basal renal $O_2$ consumption; $V_O^{2\text{total}}$, total renal $V_O^2$; $F_{E_{Na^-}}$, fractional excretion of Na$^+$ under control conditions; $T_{Na^-}$, Na$^+$ reabsorption; GFR, glomerular filtration rate; NR, not reported; $T_{Na^-}/V_O^{2\text{total}}$ results, including $V_O^{2\text{total}}$. *Extrapolation* refers to the estimation of $V_O^2$ when either GFR or $T_{Na^-} = 0$ from regression analysis of the relationships between $V_O^2$ and $T_{Na^-}$ or GFR. $^b$From the relationship between GFR or $T_{Na^-}$ and $V_O^2$ determined in the absence of any specific interventions to alter these variables. $^c$From the relationship between GFR or $T_{Na^-}$ and $V_O^2$ determined using specific interventions to alter these variables. $^d$This is the slope of the line of best fit between $T_{Na^-}$ and $V_O^2$ and can be used in this case because the line of best fit passed through the origin. $^e$Due to a calculation error, the values of $T_{Na^-}/V_O^{2\text{total}}$ presented in this study (13) were twice the true value, which is presented here. $^f$Approximated by reading off Fig. 3 in their study. $^g$Patients with normal renal function or chronic kidney disease were studied before cardiac catheterization. $^h$The ordinal intercept of the relationship between $T_{Na^-}$ and $V_O^2$ was estimated by inspection. $^i$No measure of $F_{E_{Na^-}}$ was available for normal subjects, so values for patients with chronic renal failure (with and without diabetes) are presented.

results (from 1946 to November 1, 2013). Two authors (G. K. Harrop and R. G. Evans) then performed an initial screen and excluded 478 articles that lacked data from which basal percent renal $V_O^2$ or $T_{Na^-}/V_O^{2\text{total}}$ might be estimated. The remaining 75 articles formed the basis of the literature search. Additional articles were sourced from the references of articles obtained from the search and from an examination of articles that cited the papers identified in our search. The final analysis included only original studies with at least an examination of the effects of maneuvers that reduced $T_{Na^-}$ or $V_O^2$ determined in the absence of any specific interventions to alter these variables. From the relationship between GFR or $T_{Na^-}$ and $V_O^2$ determined using specific interventions to alter these variables. This is the slope of the line of best fit between $T_{Na^-}$ and $V_O^2$ and can be used in this case because the line of best fit passed through the origin. Due to a calculation error, the values of $T_{Na^-}/V_O^{2\text{total}}$ presented in this study (13) were twice the true value, which is presented here. Approximated by reading off Fig. 3 in their study. Patients with normal renal function or chronic kidney disease were studied before cardiac catheterization. The ordinal intercept of the relationship between $T_{Na^-}$ and $V_O^2$ was estimated by inspection. No measure of $F_{E_{Na^-}}$ was available for normal subjects, so values for patients with chronic renal failure (with and without diabetes) are presented.

Basal Percent Renal $V_O^2$

Overview of available methods for estimating basal percent renal $V_O^2$. Basal renal metabolism can be assessed in vivo in a number of ways. One approach might be pharmacologically to inhibit Na$^+$/K$^+$-ATPase using an agent such as ouabain. However, not all isoforms of Na$^+$/K$^+$-ATPase are ouabain sensitive, particularly in rodents (39), and ouabain is arrhythmogenic. Consequently, caution must be applied to the interpretation of data derived from such studies. Another approach is to plot the relationship between $T_{Na^-}$ and renal $V_O^{2\text{total}}$ observed under relatively normal physiological conditions or in response to maneuvers that alter $T_{Na^-}$ and then calculate the ordinal intercept, where $T_{Na^-} = 0$ (or GFR = 0). This approach has been used widely (Table 1). Nevertheless, this does require the assumption that the relationship between $T_{Na^-}$ and renal $V_O^{2\text{total}}$ is linear [or log linear (58)] and could be confounded by changes in renal metabolism, independent of $T_{Na^-}$, that might occur in response to experimental maneuvers used to alter $T_{Na^-}$. Another approach, which has also been used widely, is to lower arterial pressure below the point at which glomerular filtration ceases. This approach is, of course, limited by the potential for neurohumoral activation, particularly if arterial pressure is lowered by hemorrhage, to alter $V_O^{2\text{base}}$ or the efficiency of $O_2$ utilization for Na$^+$ transport (d$T_{Na^-}$/d$V_O^{2\text{total}}$). Finally, ureteric obstruction will also abolish Na$^+$ excretion, but it has not been definitively established that ureteric obstruction abolishes Na$^+$ transport.

Inclusion and exclusion criteria for published data. Some studies of the effects of maneuvers that reduced $T_{Na^-}$ [e.g., reduced arterial pressure and/or renal blood flow (RBF) or the administration of diuretics] were excluded because of the unavailability of information on GFR and/or $T_{Na^-}$ (10, 11, 18, 20, 26, 32, 36, 37, 59, 75, 78). Others were excluded because GFR was not reduced to zero and $T_{Na^-}$ was not measured or because there was no analysis of the relationship between GFR or $T_{Na^-}$ and $V_O^{2\text{total}}$ from which basal percent renal $V_O^2$ could be derived (1, 21, 22, 25, 28, 46, 50, 53, 56, 63, 64, 67, 76, 77) or because no significant correlation was observed between $T_{Na^-}$ and $V_O^{2\text{total}}$ (47). We also excluded studies in which both renal $V_O^{2\text{total}}$ and $T_{Na^-}$ were measured, but the latter were not varied sufficiently to allow the ordinal intercept of the relationship(s) between $V_O^{2\text{total}}$ and $T_{Na^-}$ or GFR to be determined (7, 38), or because the data were not presented in a form to allow this relationship to be extracted (29, 42, 54). Studies in which $T_{Na^-}$ and $V_O^{2\text{total}}$ were varied by the induction of acute renal failure (23, 24) or clinical studies in patients with acute kidney injury (55) were excluded on the basis that these pathophysiological conditions might be associated with increased renal $V_O^{2\text{total}}$. Studies in which agents were administered that are known to alter the efficiency of $O_2$ utilization for $T_{Na^-}$ were also excluded (6, 35). Studies in isolated perfused kidneys (44, 62, 68, 74) were excluded, in part because of the nonphysiological nature of these experimental conditions but also because of the difficulty in defining an appropriate denominator for the calculation of basal percent renal $V_O^2$ under what might be considered “physiological” conditions. Thus, we restricted our analysis to in vivo studies in which renal $V_O^{2\text{total}}$ was measured under relatively normal physiological conditions as well as under conditions in which it was established that glomerular filtration had...
Basal Renal O₂ Consumption

From the published reports identified in our systematic review, we identified studies in which both \( \text{Fe}_{\text{Na}} \) and \( \text{T}_{\text{Na}}/\text{V}_{\text{O}2}^{\text{total}} \) were reported, both \( \text{T}_{\text{Na}} \) and \( \text{T}_{\text{Na}}/\text{V}_{\text{O}2}^{\text{total}} \) were reported, or that provided data from which these variables could be calculated. For the most part, we confined our analysis to reports in which \( \text{T}_{\text{Na}}/\text{V}_{\text{O}2}^{\text{total}} \) was or could be calculated from \( \text{T}_{\text{Na}} \) and \( \text{V}_{\text{O}2}^{\text{total}} \) measured in individual animals or humans. However, in seven cases, we calculated \( \text{T}_{\text{Na}}/\text{V}_{\text{O}2}^{\text{total}} \) from between-animal mean values of \( \text{T}_{\text{Na}}^{\text{basal}} \) and \( \text{V}_{\text{O}2}^{\text{total}} \) (9, 27, 33, 50, 52, 61, 66).

Theoretical Predictions for the Rat Kidney

We assumed that 28 mol of Na⁺ are reabsorbed for every 1 mol of O₂ consumed (43), as follows:

\[
\frac{dT_{\text{Na}}}{dV_{\text{O}2}^{\text{total}}} = \frac{T_{\text{Na}}^+}{\text{V}_{\text{O}2}^{\text{total}}} = \beta = 28
\]  

(1)

We also assumed a linear relationship between \( \text{V}_{\text{O}2}^{\text{total}} \) and \( T_{\text{Na}}^+ \), as follows:

\[
\text{V}_{\text{O}2}^{\text{total}} = \text{V}_{\text{O}2}^{\text{basal}} + \text{V}_{\text{O}2}^{\text{Na}^+} = \text{V}_{\text{O}2}^{\text{total}} + \frac{T_{\text{Na}}^+}{\beta}
\]  

(2)

In addition, we assumed that a rat kidney reabsorbs 100 μmol of Na⁺ each minute under normal physiological conditions (\( \alpha = 100 \mu\text{mol/min} \)), based on a value of \( T_{\text{Na}} \) of 115 μmol·min⁻¹·g kidney wt⁻¹ in Wistar-Kyoto rats whose kidneys weighed ~1.1 g (80). \( \text{V}_{\text{O}2}^{\text{total}} \) was set as a constant (i.e., independent of the actual rate of \( T_{\text{Na}} \)), defined as a proportion (\( \gamma \)) of the O₂ required to reabsorb 100 μmol/min of Na⁺, as follows:

\[
\text{V}_{\text{O}2}^{\text{total}} = \gamma \times \frac{\alpha}{\beta}
\]  

(3)

Basal percent \( \text{V}_{\text{O}2} \) was then defined as follows:

\[
\text{Basal percent } \text{V}_{\text{O}2} = 100 \times \frac{\text{V}_{\text{O}2}^{\text{total}}}{\text{V}_{\text{O}2}^{\text{basal}}}
\]  

(4)

First, we set the filtered load of Na⁺ at 100 μmol/min and at various levels of \( \gamma (0–0.6) \); we then calculated how changes in \( \text{Fe}_{\text{Na}} \) would affect basal percent \( \text{V}_{\text{O}2} \) and \( \text{T}_{\text{Na}}/\text{V}_{\text{O}2}^{\text{total}} \). We then examined the effects of changes in \( \gamma \) on the way \( \text{T}_{\text{Na}}/\text{V}_{\text{O}2}^{\text{total}} \) varies with \( \text{T}_{\text{Na}} \) within the range from 0 to 200 μmol/min. Finally, we examined the effects on estimates of basal percent \( \text{V}_{\text{O}2} \) of the presence of an additional source of renal \( \text{V}_{\text{O}2} \) for functions other than \( \text{T}_{\text{Na}} \), but that nevertheless varies in proportion to \( \text{T}_{\text{Na}} \). We defined this additional source of \( \text{V}_{\text{O}2} \), distinct from both \( \text{V}_{\text{O}2}^{\text{basal}} \) and \( \text{V}_{\text{O}2}^{\text{Na}^+} \), as \( \gamma \times \text{V}_{\text{O}2}^{\text{Na}^+} \), so that:

\[
\text{V}_{\text{O}2}^{\text{total}} = \text{V}_{\text{O}2}^{\text{basal}} + \text{V}_{\text{O}2}^{\text{Na}^+} + \gamma \times \text{V}_{\text{O}2}^{\text{Na}^+}
\]  

(5)

RESULTS

Basal Percent Renal \( \text{V}_{\text{O}2} \)

Systematic review. The text below summarizes the experimental procedures and major findings of the 23 published studies included in our final analysis (Table 1).

We identified 10 publications that presented estimates of basal percent renal \( \text{V}_{\text{O}2} \) determined by extrapolation to the ordinal intercept of the relationship between GFR or \( \text{T}_{\text{Na}} \) and \( \text{V}_{\text{O}2}^{\text{total}} \) (i.e., when GFR or \( \text{T}_{\text{Na}} = 0 \)) in experiments in which no specific interventions were applied to alter GFR or \( \text{T}_{\text{Na}} \). In anesthetized dogs (16, 34, 58, 72, 81) and rats (80) and unanesthetized humans (2, 3, 33, 48), estimates of basal percent \( \text{V}_{\text{O}2} \) ranged from 0% to 43.4% (Table 1).

We identified 12 publications reporting estimates of basal percent renal \( \text{V}_{\text{O}2} \) derived from an extrapolation of the relationship between GFR or \( \text{T}_{\text{Na}} \) and \( \text{V}_{\text{O}2}^{\text{total}} \) from experiments in which specific treatments were applied to alter GFR or \( \text{T}_{\text{Na}} \). These treatments included progressive hemorrhage (30, 73), suprarenal aortic constriction (60), administration of diuretic agents (9, 30, 49, 79, 81), expansion of extracellular fluid volume (12, 57), inhibition of ouabain-sensitive Na⁺-K⁺-ATPase (9), halothane inhalation (70), and chronic recovery from ischemia-reperfusion injury (52). These estimates of basal percent renal \( \text{V}_{\text{O}2} \) from studies in anesthetized dogs, rabbits, and rats, ranged from 15% to 64.6% (Table 1).

We identified nine published reports including estimates of basal percent renal \( \text{V}_{\text{O}2} \) determined by comparison of \( \text{V}_{\text{O}2}^{\text{total}} \) under control conditions with \( \text{V}_{\text{O}2} \) when glomerular filtration was abolished. The specific interventions included hemorrhage (27, 34, 69, 73), suprarenal aortic constriction (13), high-dose halothane (70), administration of bombesin (45), administra-
ation of hypertonic mannitol (58), blockade of tubular flow by retrograde filling of the lower urinary tract with oil (58), or complete ureteral occlusion (65). These estimates of basal percent renal $\dot{V}O_2$, from studies in anesthetized dogs, pigs, and rabbits, ranged from 10% to 51.5% (Table 1).

New experimental studies. Baseline levels of MAP (73 ± 1 mmHg), heart rate (256 ± 6 beats/min), RBF (23.0 ± 2.3 ml/min), arterial blood Po$_2$ (107 ± 4 mmHg) and hemoglobin saturation (99.5 ± 0.2%), renal venous blood Po$_2$ (60 ± 3 mmHg) and hemoglobin saturation (77.2 ± 2.0%), renal Do$_2$ (183 ± 17 $\mu$mol/min) and Vo$_2$ (42 ± 5 $\mu$mol/min), fractional $O_2$ extraction (22.8 ± 1.9%), and FENa$^+$ (14.8 ± 4.0%) were similar to those we have observed in previous studies using this experimental preparation (13–15).

Ureteral ligation did not significantly alter MAP, RBF, arterial blood Po$_2$ or saturation, or renal Do$_2$, but renal venous Po$_2$ was increased by 11 ± 4% and hemoglobin saturation increased to 84.6 ± 2.2%. Consequently, fractional $O_2$ extraction was reduced to 15.6 ± 2.2% and renal Vo$_2^{\text{total}}$ was reduced by 40 ± 8%. Thus, this experiment provided an estimate of basal percent renal Vo$_2$ of 60 ± 8%.

**Patterns in the data.** Published estimates of basal percent renal Vo$_2$ have been highly variable. In general, calculated basal percent Vo$_2$ appears to be greater when estimated using treatments that abolish glomerular filtration by blockade of tubular flow (Refs. 58 and 65 and the present study) than by methods that abolish glomerular filtration by lowering renal perfusion pressure (Refs. 27, 34, 69, and 73). Linear regression analysis established a positive relationship between FE$_{\text{Na}^+}$ and the estimate of basal percent renal Vo$_2$ ($P = 0.001$; Fig. 1).

Indeed, this linear relationship accounted for 48.3% of the variance in estimates of basal percent renal Vo$_2$. The theoretical relationships we constructed (Fig. 2A) were a family of curves that deviated only slightly from linearity within the range of FE$_{\text{Na}^+}$ = 0–70%. The relationships predict that basal percent renal Vo$_2$ increases with increasing FE$_{\text{Na}^+}$. The slope of the relationship increases as FE$_{\text{Na}^+}$ or Vo$_2^{\text{basal}}$ increase.

The experimental data and theoretical relationships shown in Figs. 1 and 2A indicate that estimates of basal percent renal Vo$_2$ from studies performed in animals in a natriuretic state likely overestimate basal percent renal Vo$_2$ under truly physiologic conditions. This likely includes estimates of basal percent Vo$_2$ from studies in pentobarbital-anesthetized rabbits (Refs. 13 and 73 and the present study), since our experience is that this anesthetic tends to inhibit $T_{\text{Na}^+}$. Estimates of basal percent renal Vo$_2$ derived from studies of dogs in a natriuretic state are also likely to be overestimates (9, 60, 66, 81). If we
versely with FENa deviated only slightly from linearity within the range of FENa in Fig. 1 provide an estimate of basal percent renal V˙O2 of the line of best fit was determined by the ordinary least-squares regression. When linear regression analysis across the entire data set failed to detect a significant relationship between the two variables (r² = 0.12, P = 0.07). Numbers in parentheses refer to specific references.

assumed a physiological value of FENa+ of 1%, the data shown in Fig. 1 provide an estimate of basal percent renal V˙O2 of 16.5% under physiological conditions according to the line of best fit determined by ordinary least-squares regression. When the line of best fit was determined by the ordinary least-products method (40, 41), basal percent renal V˙O2 was predicted to be 12.7%.

TNa+/V˙O2total

The theoretical relationships we constructed (Fig. 2B) between FENa+ and TNa+/V˙O2total were a family of curves that deviated only slightly from linearity within the range of FENa+ = 0–70%. They predict that TNa+/V˙O2total decreases with increasing FENa+. The slope of the relationship increases as FENa+ or V˙O2total increase.

We identified 13 published reports, of studies in anesthetized dogs, rats, rabbits, and pigs in which TNa+ was manipulated, from which we could retrieve paired values of TNa+ and TNa+/V˙O2total. TNa+ was manipulated by reducing renal perfusion pressure, altering renal vascular tone by electrical stimulation of the renal nerves or renal arterial infusion of vasoactive agents, by increasing ureteral pressure, or by administration of a range of diuretic agents. In some reports, the effects of more than one maneuver and/or of graded stimuli were presented. These data were normalized by expressing both variables as percent changes from their control level (Fig. 4). We observed a strong positive relationship between percent changes in TNa+ (x) and TNa+/V˙O2total (y), which was consistent across species exposed to similar stimuli. For example, the observations of Warner et al. (76) of the effects of progressively reduced renal artery pressure in anesthetized pigs were virtually superimposable on those of Evans et al. (13) of the effects of this maneuver in anesthetized rabbits. There was also remarkably little variation in this relationship between maneuvers that altered TNa+, chiefly by altering GFR through effects on renal hemodynamics, and those in which TNa+ was more directly manipulated by administration of diuretic agents.

The theoretical relationships we constructed between TNa+ (or the percent change in TNa+) and TNa+/V˙O2total (or the percent change in TNa+/V˙O2total) were curvilinear (Fig. 5). They predicted that TNa+/V˙O2 in the rat kidney falls steeply as TNa+ is reduced below the physiological level of 100 μmol/min and increases in a less steep manner when TNa+ is increased above
Theoretical Impact of TNa

A proportion (V˙O2/total) was set at a proportion (γ = 0, 0.01, 0.02, 0.05, 0.1, 0.2, 0.4, and 0.6) of the O2 required to reabsorb 100 µmol of Na+ per minute, assuming 28 mol of Na+ are reabsorbed for every 1 mol of O2 consumed. Note that B, which shows the relationships between percent changes in these variables, is essentially a logarithmic transformation of the data in A.

The range of variations increased with increasing V˙O2total. Importantly, the experimental data (Fig. 4) followed a similar trend to the theoretical relationships between percent changes in TNa+ and TNa+/V˙O2total (Fig. 5B).

**Theoretical Impact of TNa+ - Dependent Changes in V˙O2 for Processes Other Than TNa+**

As would be expected, the imposition of an additional source of V˙O2 used for functions other than TNa+, but nevertheless linearly dependent on TNa+, increases the slope of the relationship between TNa+ and V˙O2total. As a result, estimates of basal percent renal V˙O2 that would be predicted to arise from experimental studies are reduced (Fig. 6).

**DISCUSSION**

Why is it important to know what basal percent V˙O2 is? Primarily, its importance lies in the interpretation of TNa+/V˙O2total as a measure of the efficiency of O2 utilization for TNa+.

The denominator of this ratio comprises at least two components: a “variable” cost of O2 utilization for Na+ transport (V˙O2Na+) and a presumed “fixed” cost of V˙O2basal. To make things even more complicated, it is possible that O2 utilization for functions other than TNa+ may vary with TNa+ (see below and Refs. 4, 62, and 68). To better understand how V˙O2basal confounds the use of TNa+/V˙O2total as an index of the efficiency of O2 utilization for TNa+, we analyzed the available data regarding the magnitude of V˙O2basal as a percentage of V˙O2total (basal percent renal V˙O2). We also examined how estimates of basal percent renal V˙O2 and TNa+/V˙O2total vary with the physiological state of the kidney.

We are able to draw two important conclusions. First, although available estimates of basal percent renal V˙O2 vary widely, ranging from 0% to 81.5%, nearly half of this variation can be accounted for by variations in FENa+. Consequently, regression analysis of available experimental data provided a “consensus” estimate of basal percent renal V˙O2 of 12.7–16.5% when FENa+ is 1%, depending on the method used to perform linear regression (40, 41). Our analysis of these experimental observations is in accordance with the results of our theoretical analysis, which predicted a positive curvilinear relationship between FENa+ and basal percent renal V˙O2.

If basal percent renal V˙O2 varies with the natriuretic state of the kidney, it follows that TNa+/V˙O2total should too, as demonstrated by our theoretical analysis. Our finding of a positive relationship between experimentally induced changes in TNa+ and TNa+/V˙O2total supports this prediction. Thus, our second conclusion is that the use of TNa+/V˙O2total as an index of the efficiency of O2 utilization for TNa+ is confounded by the presence of V˙O2basal. Consequently, caution should be applied when this variable is used as a quantitative index of the efficiency of O2 utilization for TNa+, especially when experimental manipulations result in changes in TNa+. Our observations reflect the fact that renal V˙O2 includes a component that does not vary with TNa+/V˙O2total as well as a component that does vary with TNa+/V˙O2total. Consequently, TNa+/V˙O2total can change independently of the efficiency of TNa+ (dTNa+/dV˙O2), especially when TNa+ changes.

Three caveats must be applied to our conclusions. The first caveat relates to the assumption that the V˙O2 for functions other
than T_{Na^+} is relatively constant. There is evidence that this quantity, which theoretically could include true \( V_{O_2}^{basal} \) as well as a component of \( V_{O_2} \) for functions other than \( T_{Na^+} \), but that nevertheless varies with \( T_{Na^+} \), is not static (4, 62, 68). For example, Cohen and colleagues (4) provided evidence, using the isolated perfused kidney, that the rate at which lactate enters into \( O_2 \)-dependent biochemical pathways (e.g., glucose production) increases as \( T_{Na^+} \) increases. Our theoretical analysis indicates that the presence of this additional source of \( V_{O_2} \) would lead to an underestimation of the efficiency of direct \( O_2 \) utilization for \( T_{Na^+} \) and reduce basal percent \( V_{O_2} \) when determined experimentally by abolition of \( T_{Na^+} \).

Second, it should be acknowledged that some of the variation in estimates of basal percent \( V_{O_2} \) likely arises from the confounding influence of the maneuvers used to alter \( T_{Na^+} \). For example, the greatest estimates of basal percent \( V_{O_2} \) came from the present study, in which the ureter was ligated (60%), and from an earlier study (58), in which tubular flow was blocked by a retrograde infusion of oil (81.5%). It has been proposed that damage to the tubular epithelium induced by blockade of tubular flow at a downstream site may lead to increased renal \( V_{O_2} \) (58). It is also possible that ligation of the ureter does not cause the complete cessation of \( Na^+ \) transport. Finally, it is also likely that the presence and mode of anesthesia used in these studies could have influenced estimates of basal percent \( V_{O_2} \). For example, pentobarbital is known to influence mitochondrial function by inhibition of complex I (NADH dehydrogenase) of the respiratory chain (71), thus leading to reduced cellular \( ATP \) availability. This action might occur when the bioavailability of nitric oxide is reduced (35), or by factors that inhibit passive \( Na^+ \) transport and/or secondary active transport. For example, Deng et al. (6) provided strong evidence that inhibition of carbonic anhydrase can reduce the efficiency of \( O_2 \) utilization for \( T_{Na^+} \). They showed that the carbonic anhydrase inhibitor benzolamide increased renal \( V_{O_2}^{total} \) by \( \sim 50\% \) despite a concomitant reduction in \( T_{Na^+} \) of \( \sim 25\% \). They proposed that this effect was mediated by increased active \( Cl^- \) transport in the proximal tubule. Similarly, Knox et al. (30) found that the slope of the relationship between \( T_{Na^+} \) and renal \( V_{O_2}^{total} \) was increased during diuresis induced by an infusion of mannitol, implying that the metabolic cost of \( T_{Na^+} \) was increased by mannitol, at least under the conditions of their experiment. However, the fact that the experimental observations shown in Fig. 4 are consistent with the theoretical relationships shown in Fig. 5B, despite the fact that \( T_{Na^+} \) was manipulated by a wide range of maneuvers, suggests that effects of the maneuvers on the efficiency of \( O_2 \) utilization for \( T_{Na^+} \) have not undermined our results. Interestingly, the one obvious outlier shown in Fig. 4 represents the effects of benzolamide observed by Deng et al. The fact that \( T_{Na^+}/V_{O_2}^{total} \) was reduced more by benzolamide that any of the other maneuvers, for a given reduction in \( T_{Na^+} \), provides some level of confidence that the ability of benzolamide to alter the efficiency of \( O_2 \) utilization for \( T_{Na^+} \) is the exception rather than the rule.

In conclusion, renal \( V_{O_2}^{basal} \) accounts for a significant proportion of renal \( V_{O_2}^{total} \). Estimates based on the literature vary from 0% to 81.5% of renal \( V_{O_2}^{total} \). Our best estimate based on linear regression equations relating estimates of \( V_{O_2}^{basal} \) and \( V_{O_2}^{total} \) to the natriuretic state of the experimental preparation is 12.7–16.5% of renal \( V_{O_2}^{total} \) when FE_{Na^+} = 1% (i.e., standard physiological conditions). We also conclude that \( T_{Na^+}\)/\( V_{O_2}^{total} \) should be interpreted cautiously, because \( V_{O_2}^{basal} \) is not negligible and may vary in ways we cannot predict. Consequently, significant changes in \( T_{Na^+}/V_{O_2}^{total} \) can occur when \( T_{Na^+} \) changes, even if the efficiency of \( O_2 \) utilization for \( T_{Na^+} \) remains unaltered. One way to at least partially overcome the limitations of \( T_{Na^+}/V_{O_2}^{total} \) as an index of the efficiency of \( O_2 \) utilization for \( T_{Na^+} \) would be for experimenters to directly determine renal \( V_{O_2}^{basal} \) under the conditions of their experiments. This would allow \( V_{O_2}^{basal} \) to be removed from the denominator of \( T_{Na^+}/V_{O_2}^{total} \).

ACKNOWLEDGMENTS

The authors thank Dr. Prabhleen Singh for providing information regarding relevant publications from her research group, but absolve her of any responsibility for any errors we might have made.

GRANTS

This work was supported by National Health and Medical Research Council of Australia Grants 606601 and 1024575 (to R. G. Evans) and American Heart Association Grant 10SDG4150061 (to P. M. O’Connor).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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