Properties Permitting the Renal Cortex to Be the Oxygen Sensor for the Release of Erythropoietin: Clinical Implications

Mitchell L. Halperin,* Surinder Cheema-Dhadli,* Shih-Hua Lin,† and Kamel S. Kamel*

*Division of Nephrology, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada; and †Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense National Center, Taipei, Republic of China

The Po2 at this site where erythropoietin release is regulated should vary only when the hemoglobin concentration changes in capillary blood. The kidney cortex is an ideal location for this O2 sensor for four reasons. First, it extracts a small proportion of the oxygen that is delivered in each liter of blood; this makes the Po2 signal easier to recognize. Second, there is a constant ratio of the work performed (consumption of O2) to the renal blood flow rate (delivery of O2). Third, the high renal blood flow rate improves diffusion of O2 from capillaries to this O2 receptor. Fourth, a high renal cortical PCO2 prevents an additional shift of the O2:hemoglobin dissociation curve by other factors from being a confounding variable. This suggests that the GFR and the renal blood flow rate should be examined in patients with unexplained anemia or erythrocytosis.


The site where the release of erythropoietin is regulated should be exposed to a Po2 that is influenced solely by the concentration of hemoglobin in blood. Our objective is to describe why this control system must be located in the renal cortex. Because of space considerations, we do not discuss other factors that may influence the release of erythropoietin (e.g., the activity of the renin-angiotensin axis [1]) or those that may influence the erythropoietin signal detection in the bone marrow (e.g., androgens, angiotensin II, insulin-like growth factors [for review, see references (2,3)]).

The primary features that permit this control system to function properly can be deduced (Table 1). First, because of the sigmoid shape of the O2:hemoglobin dissociation curve, the quantity of O2 that is extracted per liter of blood flow must be small to have a sensitive and specific signal. Second, because O2 is consumed when biologic work is performed, the amount of this work must be directly proportional to the rate of delivery of O2 for the signal to be influenced solely by the concentration of hemoglobin in blood. Third, the slow step of diffusion of O2 from capillaries to the sensor for O2 must be accelerated to ensure that diffusion does not diminish the sensitivity of this signal system. Fourth, a high renal cortical PCO2 prevents a shift of the O2:hemoglobin dissociation curve by factors other than the concentration of hemoglobin in blood. One additional point merits emphasis. Because red blood cells have a very long life span (approximately 4 mo, or 120 d), this control system may have fluctuations in the minute-hour-day range, but these will have small absolute effects over a much longer time. In the following paragraphs, these features are described in more detail.

Fall in the Po2 in the Renal Cortex Induced by a Small Reduction in the Concentration of Hemoglobin in Blood Must be Large Enough to Be Recognized Easily

The key to understanding the sensitivity to a small change in the concentration of hemoglobin is revealed by examining the O2:hemoglobin dissociation curve (Figure 1). Two hypothetical organs with the same rate of O2 consumption are depicted in this figure. The one on the left has a lower blood flow rate and therefore it extracts more O2 from each liter of blood, and both the flat and the steep portions of the curve are in use. Accordingly, when there is a lower concentration of hemoglobin in blood, only a small reduction in Po2 would be needed to extract the same amount of O2 because the steep portion of the curve is involved. In contrast, the organ on the right has a higher blood flow rate. Hence it extracts less O2 from each liter of blood, and events occur only on the flat portion of the curve. Therefore when there is a lower concentration of hemoglobin in blood, a large reduction in Po2 would be needed to extract the same amount of O2 because events occur on the flat portion of the curve. There are two ways to extract a small amount of O2 per liter of blood flow: Do less work, or have a very high blood flow rate. The kidneys, in fact, have a high rate of blood flow; why this is so important to achieving a better control system is considered later.

Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Dr. Mitchell L. Halperin, Department of Medicine, University of Toronto, St. Michael’s Hospital Annex, Lab #1, Research Wing, 38 Shuter Street, Toronto, Ontario, M5B 1A6, Canada. Phone: 416-864-5292; Fax: 416-864-5943; E-mail: mitchell.halperin@utoronto.ca

Copyright © 2006 by the American Society of Nephrology

ISSN: 1555-9041/105-1049
Table 1. Components that make the signal system to release erythropoietin sensitive only to the concentration of hemoglobin in blood

<table>
<thead>
<tr>
<th>Component</th>
<th>Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to be in most sensitive part of O₂:hemoglobin dissociation curve</td>
<td>Need P₀₂ of 60 to 70 mmHg in capillaries deep in the renal cortex, a high renal blood flow rate, and less O₂ extraction per liter of blood</td>
</tr>
<tr>
<td>Ratio of renal O₂ consumption/delivery of O₂ must be constant</td>
<td>Bulk of renal work is to reabsorb filtered Na⁺; therefore, the filtration fraction must be constant</td>
</tr>
<tr>
<td>Need fast diffusion of O₂ from capillaries to cells in the renal cortex</td>
<td>Diffusion can be fast if the distance is small and blood flow is rapid; the kidney has a high blood flow rate</td>
</tr>
<tr>
<td>There must not be a shift in the O₂:hemoglobin dissociation curve</td>
<td>The O₂:hemoglobin dissociation curve must be rightward shifted (done by a high P⁰ᵧ₂)</td>
</tr>
</tbody>
</table>

Figure 1. O₂:hemoglobin dissociation curve in 1 L of blood. The quantity of O₂ in each liter of blood has a sigmoid relationship to the arterial P₀₂ (shown on x axis). The upper, open rectangle represents the quantity of O₂ extracted from each liter of blood, whereas the lower, shaded rectangle represents the lower P₀₂ needed to extract the same amount of O₂ extracted per liter when there is a small reduction in the concentration of hemoglobin in blood. The dashed lines indicate the change in arterial P₀₂ as a result of this extra extraction of O₂ per liter of blood. In the left portion of the figure, there is a very small change in the capillary P₀₂ for this increment in O₂ extraction, whereas, in the right portion of the figure, there is a much larger fall in the capillary P₀₂ and a much more sensitive signal when much less O₂ is extracted per liter of blood.

Ratio of the Consumption of O₂ to the Delivery of O₂ to the Renal Cortex Must Be Constant to Have a Signal to Release Erythropoietin Related Only to an Abnormal Concentration of Hemoglobin in Blood

O₂ is consumed when work is performed. The vast majority of renal work is to reabsorb approximately 99.5% of filtered sodium (Na⁺) (4). The amount of filtered Na⁺ is the product of the GFR and the plasma Na⁺ concentration in molar terms. Because there is little variation in the plasma Na⁺ concentration in healthy individuals, renal work (or O₂ consumption) is related directly to the GFR.

The ratio between the GFR (O₂ consumption) and renal plasma flow rate (O₂ delivery) is called the filtration fraction, which does not vary appreciably in humans (see equation 1) (5,6). This is achieved because the glomerulus lies between two arterial systems, each with different modulators of vessel constriction. If the filtration fraction does not vary appreciably from day to day, then the sensor for O₂ should be exposed to a near-constant P₀₂ unless the blood has a lower hemoglobin concentration.

Filtration fraction = GFR/renal blood flow (O₂ consumption/O₂ delivery) (1)

Slow Step of Diffusion of O₂ from Renal Cortical Capillaries to the Sensor for O₂ in the Renal Cortex Must Not Interfere with the Ability of a Small Fall in the Concentration of Hemoglobin in Blood to Cause the Release of Erythropoietin

The point to emphasize here is that a high renal cortical blood flow rate speeds up the diffusion of O₂ from its capillaries to the receptor for O₂ deep in the renal cortex. This eliminates another variable and makes the signal to release erythropoietin be related only to an abnormal concentration of hemoglobin in blood.

For illustrating how a large renal blood flow rate may increase the rate of diffusion of O₂ in the renal cortex, events in
skeletal muscle at rest and during exercise are described in quantitative terms.

Quantitative Analysis
When the cardiac output at rest is 5 L/min and the blood volume is 5 L, the circulation time is 60 s; much of this time is spent while red blood cells traverse capillaries. In contrast, the rate of O₂ consumption during vigorous exercise can rise by 20-fold, whereas the cardiac output increases by only four- to five-fold (8). As a result, the circulation time decreases to 12 to 15 s. Therefore, the rate of diffusion of O₂ must be faster in this setting, but both the time available and the driving force (the O₂ concentration difference) are unfavorable for faster rates of diffusion of O₂. We speculate that the much faster blood flow rate during vigorous exercise may increase the speed of diffusion by accelerating mixing of fluid within the interstitial compartment, or, by opening more capillaries, this could shorten the distance for diffusion.

If a similar process occurred in the renal cortex, then the high blood flow rate may accelerate the diffusion of O₂ so that slow diffusion rates would be avoided in the control system for erythropoietin release. This high renal blood flow rate must be accompanied by high GFR, independent of other demands of renal physiology.

A Shift in the O₂:Hemoglobin Dissociation Curve Must Not Interfere with the Sensitivity of This System to Release Erythropoietin
If the O₂:hemoglobin dissociation curve in capillaries of the renal cortex were always shifted to the right (e.g., as a result of a high renal cortical Pco₂), then the Po₂ signal would not be influenced by other factors that may influence this shift (7). One might think that the renal cortical capillary Pco₂ should be only a few mmHg higher than the arterial Pco₂ because a small quantity of O₂ is extracted and thereby little CO₂ would be produced by renal metabolism per liter of blood flow (9). This, however, is not the case because the Pco₂ in the efferent arteriolar or stellate blood vessels deep in the renal cortex—as well as in the luminal fluid in the early and late proximal and distal convoluted tubules—all were approximately 65 mmHg (10). Therefore, it seems that the Pco₂ deep in the renal cortex is higher than expected, probably because these small blood vessels have a countercurrent exchange system. This effect of Pco₂ to shift the O₂:hemoglobin dissociation curve to the right ensures that this is not a major variable in the control system for erythropoietin release in vivo.

Implications of Our Hypothesis for Disease States
Disorders of erythrocytosis may occur if this ratio of O₂ consumption (GFR) to O₂ delivery (renal blood flow) were altered because the hemoglobin concentration would not be the only variable that determines the Po₂ near the sensor for the release of erythropoietin. We stress that it is not the GFR per se that alters the signal to cause the release of erythropoietin; rather, it is the ratio of renal O₂ consumption (GFR) to O₂ delivery. We envision two classes of diseases that may affect erythrocytosis: Those with a high and others with a low filtration fraction (equation 1) and those with a change in the renal blood flow rate.

Disorders with a High Filtration Fraction
A high ratio of GFR (O₂ consumption) to renal blood flow (O₂ delivery) means that more O₂ will be extracted per liter of renal blood flow. This will lower the renal interstitial Po₂; hence, more erythropoietin will be released, which will cause a rise in the red blood cell mass. One important way to achieve this high filtration fraction is to induce efferent arteriolar vasoconstriction, for example, by high levels of intrarenal angiotensin II. As shown in the Appendix, our index case had a high hemoglobin level in blood, a very high plasma renin activity, and a high filtration fraction.

One possible strategy to reduce the hemoglobin concentration, with its increased risk for venous thrombosis, is to lower the GFR by diminishing efferent renal artery vasoconstriction with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers. Although these drugs were effective in treating posttransplantation erythrocytosis (11), they might pose a risk for inducing hemodynamic instability for patients with a low extracellular fluid volume (see the Appendix). Moreover, if one wished to know the lowest dosage of drug that likely would be effective, then one could measure his filtration fraction early because this change should be prompt, whereas the change in reticulocyte count or hemoglobin concentration in blood should occur much later.

Disorders with a Low Filtration Fraction
When less O₂ is extracted per liter of renal blood flow, the Po₂ in the interstitial compartment near the O₂ sensor will be higher and less erythropoietin will be released. The result could be the development of chronic anemia. Perhaps one example of this pathophysiology is the chronic anemia that is associated with the use of the ACE inhibitor enalapril (1,12). For identification of which patient with chronic anemia has this functional form of erythropoietin deficiency, the GFR and renal plasma flow could be measured to reveal the low filtration fraction.

Influence of the Renal Blood Flow Rate
The hyperfiltration that occurs early in patients with diabetes does not lead to erythrocytosis. For example, Sochett et al. (13) found that patients who had type 1 diabetes had significantly higher GFR values than did control subjects (179 versus 111 ml/min); they also had significantly higher filtration fractions (0.24 versus 0.17). Although the Po₂ in renal cortical capillaries should be lower in these patients with diabetes, they did not lead to an appreciably higher hemoglobin concentration. To explain this inconsistency, it is noteworthy that this population with diabetes had higher renal plasma flow rates (771 versus 659 ml/min). If, as postulated above for vigorous exercise, a higher blood flow rate may minimize the fall in Po₂ in the slow diffusion step between capillaries and the receptor for O₂ deep in the renal cortex, then there may not be a lower Po₂ near its receptor to signal the release of more erythropoietin (Figure 2). Therefore, one must examine both the filtration fraction and the
renal blood flow rate to deduce what the $P_{O_2}$ may be deep in the renal cortex. Patients with chronic renal insufficiency have a lower number of cells capable of producing erythropoietin. Hence they would need a lower cortical $P_{O_2}$ to have a stronger stimulus to release erythropoietin and thereby avoid anemia. This may be the case because they also have a lower blood flow rate, and perhaps interstitial abnormalities, which may slow the rate of diffusion of $O_2$ from capillaries to the site where the $P_{O_2}$ is recognized by the erythropoietin-producing cells. Therefore, a given patient can have a high, normal, or low red blood cell mass depending on which of these factors is the dominant one.

Conclusion

The hypothesis presented should permit physicians to understand why erythropoietin is synthesized in the kidney cortex and why having both a high GFR and a very large renal blood flow rate are components of an efficient control system (filtration fraction and the renal blood flow rate). Three pathophysiologic entities that might affect the red blood cell mass can be recognized and tested easily on the basis of this theoretical foundation.

Appendix: Case Study

A young man with an established diagnosis of Gitelman’s syndrome (equivalent to having a thiazide diuretic acting 24 h/d [14]) had an extremely high hemoglobin concentration in blood in steady state (19.0 g/dL, or 190 g/L) (15). Although one could attribute this high hemoglobin concentration simply to a low plasma volume, this facile explanation was discarded after a simple quantitative analysis: He would have needed a 40 to 45% reduction in his plasma volume to explain his high hemoglobin concentration without a rise in his red blood cell mass. In additional studies, his erythrocytosis was due in large part to a high content of hemoglobin. Although his GFR was somewhat reduced (64 ml/min measured by the clearance of $^{125}$I-iodohippurate [16,17]), his renal plasma flow was less reduced (204 ml/min measured by $^{131}$I-orthoiodohippurate [16,17]). Accordingly, his filtration fraction was 31.5%, whereas this ratio was $22 \pm 3\%$ in other patients ($n = 30$) whom we studied and who had a wide range of GFR values; this is similar to values reported by others (5,6).

Acknowledgments

All sources of funding were from the Canadian Institutes of Health Research (grant MT 15485).

References

13. Sochett EB, Cherney DZI, Curtis JR, Dekker MG, Scholey JW, Miller JA: Impact of renin angiotensin system modul-


