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

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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.


T he 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.
The ratio of the consumption of O\textsubscript{2} to the delivery of O\textsubscript{2} to the renal cortex must be constant to have a signal to release erythropoietin related only to an abnormal concentration of hemoglobin in blood.

O\textsubscript{2} is consumed when work is performed. The vast majority of renal work is to reabsorb approximately 99.5\% of filtered sodium (Na\textsuperscript{+}) (4). The amount of filtered Na\textsuperscript{+} is the product of the GFR and the plasma Na\textsuperscript{+} concentration in molar terms. Because there is little variation in the plasma Na\textsuperscript{+} concentration in healthy individuals, renal work (or O\textsubscript{2} consumption) is related directly to the GFR.

The ratio between the GFR (O\textsubscript{2} consumption) and renal plasma flow rate (O\textsubscript{2} delivery) 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 O\textsubscript{2} should be exposed to a near-constant P\textsubscript{o\textsubscript{2}} unless the blood has a lower hemoglobin concentration.

Filtration fraction

\[ \text{Filtration fraction} = \frac{\text{GFR}}{\text{renal blood flow}} \]  

Slow step of diffusion of O\textsubscript{2} from renal cortical capillaries to the sensor for O\textsubscript{2} 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 O\textsubscript{2} from its capillaries to the receptor for O\textsubscript{2} 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 O\textsubscript{2} 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 arterial 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
Figure 2. Possible independent role of the renal blood flow rate on the $P_o$ near the receptor for O$_2$ deep in the renal cortex. The graph depicts the $P_o$ in mmHg that are likely to be present in the capillary blood deep in the renal cortex (points to the left of the line depict diffusion) and its fall during diffusion to the site of the receptor for O$_2$ near the corticomedullary junction (points to its right). The O’s represent the normal control subjects and the X’s represent the patients who have type 1 diabetes with hyperfiltration and a higher filtration fraction. We speculate that although the capillary $P_o$ is lower in this group with diabetes, the higher renal blood flow rate may accelerate the slow diffusion step and thereby diminish the fall in $P_o$ during diffusion. As a result, the $P_o$ near the receptor may not be appreciably different in these two populations.

Concentration of Hemoglobin

renal blood flow rate to deduce what the $P_o$ 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 $P_o$ 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 $P_o$ 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 $^{99m}$Technetium-labeled diethylene triaminopentaacetic acid [16,17]), his renal plasma flow was less reduced (204 ml/min measured by $^{131}$I-orthodiodhippurate [16,17]). Accordingly, his filtration fraction was 31.5%, whereas this ratio was 22 ± 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).

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References

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