Correction of anaemia on dialysis: did we forget physiology?

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A frequent complication in patients with kidney diseases, chronic anaemia is commonly treated with erythropoietin-stimulating agents (ESA). At present, the optimal target for haemoglobin (Hb) concentration is, however, unknown. The purpose of this communication is to plead for a less aggressive correction of nephrogenic anaemia, fully justified by the adaptive mechanisms that patients on dialysis are prompt to set off in order to increase their tolerance to anaemia. First, their delivery of oxygen from Hb is opportune facilitated. Second, beyond a certain threshold, rising Hb concentration with ESA does not mean increasing tissue oxygenation. Although the physiological adaptation in patients with kidney failure has been known for decades, it has been constantly and startlingly ignored in the design of studies aiming at a full correction of anaemia and an ‘irrational’ normalization of Hb with the use of ESA. Flawed in essence, these studies also demonstrate the dangerousness of a generic approach.

Historically, the food and drug administration (FDA) approved the prescription of recombinant erythropoietin (rHuEPO) in 1989 on the basis of a signal study published 2 years earlier showing that rHuEPO could eliminate the need for transfusions in patients with end-stage renal disease (ESRD), and thereby protect them from immunologic sensitization, infection and iron overload [1]. Twenty years later, on 16 February 2010, the same FDA announced that ESA should actually be prescribed under a ‘risk management programme’, known as the Risk Evaluation and Mitigation Strategy: data collected in longitudinal clinical studies had indeed repeatedly shown that in patients with renal disease or with solid tumours, complete correction of anaemia with ESA had increased the risk of death, nonfatal myocardial infarction [2–4], fatal or nonfatal stroke and blood clots [4]. In retrospect, thus, excessive normalization of Hb levels with ESA may have improved the quality of life of patients with ESRD [5, 6] but at the expense of a decrease in their ‘quantity’ of life [3]. The reasons to avoid blood transfusion still prevail, though, and a low Hb will increase the risk for cardiovascular events in these patients [7], as well. Since experimental findings have strongly suggested that the side effects of ESA are essentially related to a rise in haematocrit and not to some off-target properties of the drugs [8], it is now time to revise our target downwards [9].

The major function of the central circulation is to transport oxygen from the lungs to the peripheral tissues at a rate that satisfies overall oxygen consumption. There is no storage system for oxygen (O₂). In the blood, O₂ is carried attached to Hb with only a small amount (<2%) dissolved in plasma [10]. Oxygen content of blood (CaO₂) is derived from Hb saturation (SaO₂), Hb content and K, the coefficient for Hb–oxygen-binding capacity. Thus, the equation for CaO₂ is: Hb × SaO₂ × K [10]. Importantly, the mutual affinity of Hb for O₂ is not constant (Figure 1A) but affected by at least three biological parameters that are modified by severe renal failure: 2,3-diphosphoglycerate (2,3-DPG) concentration inside the erythrocytes, blood pH and uraemia.

2,3-DPG is a phosphate ester that binds to deoxygenated Hb. By doing so, it impedes O₂ binding and hence facilitates O₂ delivery. P₅₀, the oxygen concentration at which 50% of Hb is saturated (i.e. an affinity index), correlates very well with 2,3-DPG in dialysis patients (r² = 0.76) [11]. In 1972, Blumberg et al. [11] had shown that when compared to healthy subjects, ESRD patients had a significant increase (+52%, P < 0.001) in the concentration of 2,3-DPG in erythrocytes. This explains why their O₂–Hb dissociation curve is opportunistically shifted to the right (Figure 1A) [11,12]. Of note, even though dialysis reduces phosphataemia, it does not affect the concentration of inorganic phosphate inside red blood cells [13], and therefore, the increase in ester 2,3-DPG is not affected either [13,14].

Blood pH is also of profound influence. Acidosis should actually decrease the O₂–Hb affinity through the Bohr effect (described in 1904). Similarly, acidification of the intra-erythrocytic medium increases the relaxation rate of 2,3-DPG phosphorus atoms [15], which should make the binding of 2,3-DPG to Hb stronger. Together, O₂ delivery is expected to be facilitated by acidosis. However, acidosis also blunts the adaptive increase in 2,3-DPG. Eventually, acidic (pH ≤ 7.3) patients on dialysis exhibit a regrettable normal O₂ dissociation curve [11]. Dialysis will correct acidosis, but on the other hand, long sessions (≥6 h) have been reported to induce even a drop in P₅₀ [14,16]. A zealous alkalaemia should therefore be avoided, and a ‘neutral’ pH (7.4) is the proper aim.

Uraemia determines the strength with which 2,3-DPG binds to Hb. 2,3-DPG binding is, thus, reinforced by the
presence of urea at concentrations ordinarily observed in patients on dialysis (~30 mM) [17]. This beneficial effect, presumably related to urea-induced direct modifications of the structure of Hb, is lost for very high concentrations of urea in the blood because excessive amounts of isocyanic acid (that originates from the dissociation of urea) will, on the contrary, induce the carbamylation of Hb and compete with 2,3-DPG binding [17]. In sum, to some extent, uraemic patients have an advantage from an increase in both the concentration and in the binding capacity of 2,3-DPG and will deliver O2 relatively easier when compared to healthy subjects. Last, whatever the (unknown) mechanisms at stake, it is noteworthy that P50 increases with the duration (in months) of dialysis [18].

What is the influence of a prescription of rHuEPO in this context? Young red blood cells contain more 2,3-DPG than old ones [19], which is why the increase in the reticulocyte count that follows the introduction of rHuEPO is associated with an increase in P50 [20]. This is, however, transient and in adult uraemic patients, the correction of anaemia overrides this effect, so that no significant variation of P50 is seen in the long-term [20,21].

These old studies, performed before the era of rHuEPO, help us to understand why dialysis patients are able to tolerate anaemia at a higher degree than what would be expected. The increase in 2,3-DPG in the erythrocytes, mild uraemia and other dialysis-related factors (not all identified) make the a delivery of O2 to the tissues easier. Aiming at a ‘normal’ haematocrit is therefore not only unsafe (which we know in retrospect) but also irrational. We should also keep in mind that even though increasing the concentration of Hb will mathematically increase the rate of O2 delivery (DO2, the product of cardiac output, Hb concentration, O2 saturation and the constant K), the relationship between the global O2 consumption and the rate of O2 delivery is not linear but reaches a plateau so that at some point (Figure 1B), tissue oxygenation is independent from O2 delivery [10]. No clinical benefit in terms of tissue oxygenation can, therefore, be expected from a rise in Hb concentration beyond a certain threshold. Of note, because O2 delivery is influenced by the intercapillary distance [10], excessive fluid is detrimental and extra care should be paid to optimize fluid balance in dialysis patients.

What now? The FDA, as well as the scientific committees of the K/DOQI [22] (Kidney Disease Outcome Quality Initiative) and KDIGO [23] (Kidney Disease: Improving Global Outcome) organizations issuing the guidelines for the treatment of anaemia in patients with chronic kidney disease, have unanimously called for new studies, aiming at defining the ideal target for Hb concentration in this population. Meanwhile, the 9–11 g/dL window is a reasonable option [24]. But we should be careful not to repeat history again and again. Hb is nothing but a surrogate, and the spectrum of kidney patients is broad. It is trivial to write that an elderly dialysis patient with limited physical activity and a severe heart condition or a cancer may have a different need for oxygen delivery than a young athletic one literally dying for a transplant. In view of the severe side effects observed in the longitudinal studies that all aimed at reaching a ‘magic’ and universal number of Hb concentration, irrespective of the patient’s comorbidities, functional status or well-being, it may be time for us to adapt and consider a more tailored, less automatic approach to avoiding transfusion (the primary objective). This is also very basic – but who knows? It might be safe.

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References
Diuretics and secondary hyperparathyroidism in chronic kidney disease

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Secondary hyperparathyroidism (SHPT), one of the salient features of chronic kidney disease (CKD), has received substantial attention based on observational studies that indicate its association with increased mortality in both patients with end-stage renal disease (ESRD) \cite{1} and with non-dialysis-dependent (NDD)-CKD \cite{2}. As shown in Table 1, diverse conditions including medications are associated with relatively high or low serum PTH levels in...