Anders Lassen Nielsen, MD; Henrik Ærenlund Jensen, MD

Oxygen Status: A Standard Evaluation in Uremic Patients?

Since Johnson et al reported the occurrence of hypoxia during hemodialysis in 1971,[1] many investigations have confirmed occurrence of hypoxia during hemodialysis (HD) in a large number of clinical settings. Much conflicting data and confusion have arisen from these reports. Further difficulty stems from the great inconsistency and inaccuracy of terms used to describe the data and results. The goal of this article is to clarify some of the terminology and present some of our arguments for devoting more attention to monitoring oxygen status of patients in the daily routine.

One difficulty with investigations confirming occurrence of hypoxia during hemodialysis is that in practically all studies, the number of patients involved is relatively small.[2] Based on two larger studies, we recently concluded that severe hypoxia and hypoxemia do indeed occur during HD. The first study involved 56 patients each monitored once;[3] the second involved 20 patients each monitored during all HD sessions during a 6-week period.[4] We also found a significant biovariability that might explain some of the conflicting data reported so far.

Over the years, many mechanisms have been proposed to explain the causes of hypoxia, among them pulmonary microembolism, bioincompatibility, hypoventilation due to CO_2 loss, and the Bohr effect. At present the cause is still not established, but it seems widely accepted that we are dealing with a multifactorial complex.

Although more than 200 papers have been published on occurrence of hypoxia/hypoxemia during HD, only a few have looked into the consequences and therapeutic possibilities.

Hypoxemia. Hypoxemia is traditionally defined as "a relative deficiency of oxygen in the blood." The primary tool for clinical evaluation of oxygen status in blood, however, is measurement of arterial oxygen tension ($pO_2(a)$). Wide clinical misuse of the term hypoxemia to mean a relative deficiency of oxygen tension in the arterial blood has become an everyday offense. This practice not only complicates the terminology of various pathological situations, but also interpretation and comparison of various published results. Since evaluation of oxygen content involves more than oxygen tension, one should return to the traditional definition of the term: *Hypoxemia is a reduction in oxygen content of the blood*.[5]

Hypoxia. The term hypoxia should be defined as *a decrease in $pO_2(a)$*, which is a more suitable definition, is completely compatible with current medical literature, and lends itself most readily to clinical

From the Department of Nephrology, University of Copenhagen, Hvidovre Hospital, Copenhagen,Denmark.

care of patients. Since $pO_2(a)$ above 80 mmHg seldom affects therapeutic clinical judgment, a practical limit below which hypoxia is assumed to exist is 80 mmHg.[6] Arterial oxygen tensions between 80 and 60 mmHg have been described as "mild hypoxia," between 60 and 40 mmHg as "moderate hypoxia," and below 40 mmHg as "severe hypoxia."[7]

Hypoxygenation. Wide use of monitoring oxygen saturation (sO_2) has also contributed to the confusion, since many investigators mislabel a low sO_2 as either hypoxemia or hypoxia, but it is neither. The correct term should be hypoxygenation, since *a decline in sO_2 is defined as hypoxygenation*. For sO_2, a value of 90% can be considered the facultative therapeutic threshold value for hypoxygenation and a value of 75% as the obligatory therapeutic threshold.[8] It has been shown that short-term hypoxygenation with a $sO_2(a)$ about 80% has significant impact on some cognitive processes in normal subjects.[9]

If there is anemia, a patient might well have a high oxygen saturation in the few erythrocytes that are available, which by no means indicates that oxygen-carrying capacity is sufficient.

Oxygen Concentration. If one needs to refer to *total oxygen content in blood*, the term oxygen concentration (ctO_2 expressed in mmol/dL or ml/dL) should be used. It is essential to realize which parameters are involved in estimating ctO_2, and they can be easily identified by looking at the equation used to calculate ctO_2: Concentration of total oxygen is equal to the concentration of active hemoglobin (ceHb) times oxygen saturation (sO_2) plus oxygen tension (pO_2) times the solubility coefficient for oxygen (aO_2). This simply states that oxygen is transported in two ways, bound to hemoglobin and physically dissolved in plasma, and neither oxygen tension nor saturation alone determines ctO_2. Normal values are approximately 20 ml/dl for men and 18 ml/dl for women. A definite minimum therapeutic threshold value of 10 ml/dl at rest can be calculated with the assumption that the myocardium is the limiting organ.[10]

Tissue Hypoxia. Tissue hypoxia exists when inadequate oxygen is available at the cellular level.

Classically, tissue hypoxia is divided into four main types (see

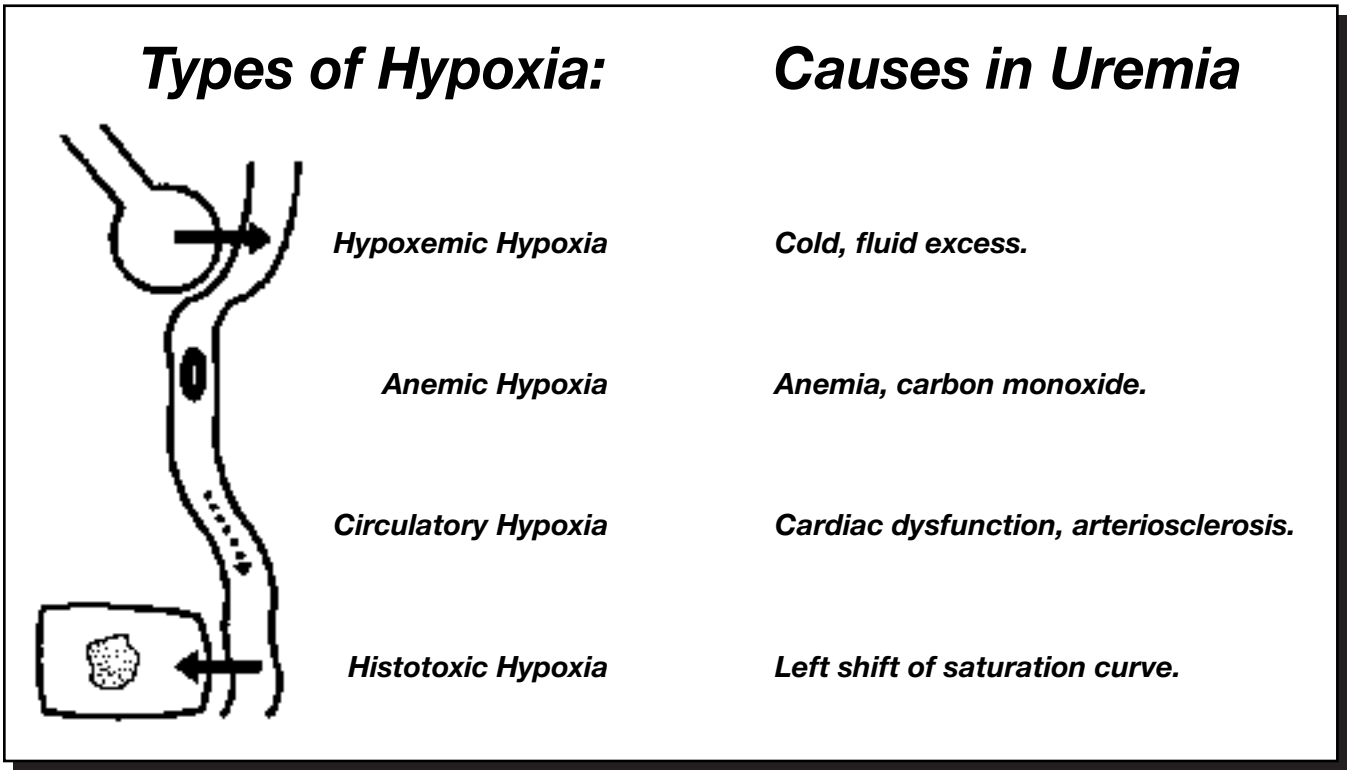

Figure 1: Main types of tissue hypoxia.

Figure 1), but various subdivisions are used relative to different medical specialties. The four main types of tissue hypoxia are:

1. *Hypoxemic tissue hypoxia*. In essence, this is tissue hypoxia due to hypoxia; however, the presence of arterial hypoxia does not automatically indicate the presence of tissue hypoxia. In fact, the cardiovascular system may adequately compensate by increasing cardiac output so less oxygen has to be removed from each quantity of blood presented to the tissue. This mechanism frequently allows tissue oxygen requirements to be met.

Although hypoxia does not necessarily imply tissue hypoxia, it should certainly be suspected. At a $pO_2(v)$ of 40 mmHg, the pressure gradient between capillaries and mitochondria is severely compromised,[7] thus signifying severe tissue hypoxia.

2. *Anemic tissue hypoxia*. This represents defective tissue oxygenation due to a reduction in the oxygen-carrying capacity of the blood or a decreased willingness to release oxygen to the tissues.

A reduction in oxygen-carrying capacity may be caused by either a lack of hemoglobin or inability of the hemoglobin to carry oxygen (methemoglobinemia, carbon monoxide poisoning, and others). The willingness of the hemoglobin to release oxygen is a function of the oxygen saturation curve. If the curve is shifted to the left, a smaller amount of oxygen is released to the tissues at the capillary level.

These reasons stress the importance for clinicians to realize the differences between sO_2, pO_2 and ctO_2.

Also in this condition, the main compensatory mechanism is an increase in cardiac output.

3. *Circulatory tissue hypoxia*. In this situation, circulation is inadequate to meet the cellular requirement of oxygen. This can be thought of as either blood stagnation in the capillaries or failure of the capillaries to allow a flow of oxygenated blood to the tissues (arteriovenous shunting). Stagnant hypoxia is a result of sluggish peripheral capillary blood flow, which is most often caused by decreased cardiac output, but may also be due to vascular insufficiency and neurochemical abnormalities.

4. *Histotoxic hypoxia*. This represents tissue oxygen deficiency due to failure of oxygen utilization at the cellular level.

We verified, as have others, that the most significant hypoxia occurs during the first 30 to 60 minutes of hemodialysis.

IS HYPOXIA DURING HD OF CONSEQUENCE?

Because oxygen is necessary to all living tissue, lack of oxygen may impose severe damages to the vital organs, jeopardizing patient survival. There are several indications more or less evident suggesting that hypoxia during HD is of serious consequence to patients.

A. Silent ischemia with frequency between 25%[11] and 40%[12] has been reported during HD. A relative constant 16- to 19-fold increase in mortality exists in HD patients compared with the general population, and approximately 50% die of cardiovascular causes. Findings from a 1991 EDTA report show that 14% of patients die of myocardial infarct and 13% die of cardiac arrest.[13] Mazin et al reported that "introduction of hyperbaric oxygenation diminished lethality by 29%" in acute kidney failure.[14]

B. Investigation of cardiovascular diseases showed that oxygen deficiency causes many changes in the cardiovascular system, acute as well as chronic. Changes such as impairment of cardiac function,[15] changes of the vascular smooth muscles and changes of the endothelium accelerate the arteriosclerotic processes.

C. Some symptoms following dialysis have a close resemblance to symptoms of high altitude sickness, and Hartitzsch et al suggested that they are caused by the induced hypoxia during HD.[16] Some symptoms also bear resemblance to those found in patients suffering from sleep apnea. Furthermore, patients who suffer from sleep apnea have similar long-term complications as those seen in long-term HD treatment, e.g., dementia, accelerated arteriosclerosis and preterm death.

D. If we all look more closely at our patients as they relate to the four main types of "classical tissue hypoxia," we shall most certainly find that most patients have some and a few have many conditions hinting at possible tissue hypoxia (see *Figure 1*).

Some of the conditions follow:

1. Impaired lung function and HD-induced hypoxia. Hemodialysis-induced chronic lung disease,[17] interstitial fibrosis, calcification of the alveolar walls and overloading are common in patients with chronic renal failure. All conditions that jeopardize oxygenation in the lungs re-

present hypoxemic tissue hypoxia.

We are positive that HD-induced hypoxia does occur frequently. In our first study[3] using continuous monitoring of blood gases in the arterial line during HD, we found pO_2(al) values below 70 mmHg in 38 patients 4% of the total time recorded during 56 HDs (180 hours of continuous monitoring). This means that hypoxia was present roughly one-third of the time monitored. Values below 60 mmHg were recorded 14.2% of the time, with the lowest recorded value at 42 mmHg. We were able to verify, as have others, that the most significant hypoxia occurs during the first 30 to 60 minutes of hemodialysis.

In our second study,[4] we monitored 20 patients for 6 weeks (total of 258 HD sessions), and found the following significant patient inter- and intravariability: Three patients never reached values below 80 mmHg; 7 patients reached values below 80 mmHg for very short periods; 3 patients reached values below 80 mmHg frequently; 3 patients dropped to values below 80 mmHg during most of their dialysis; and 4 patients dropped to values below 80 mmHg during the entire session.

2. Reduced carrying and release of oxygen. (a) Administration of erythropoietin has partly rectified anemia in patients.

(b) A left-shifted oxygen saturation curve implies reluctance of hemoglobin to release oxygen at tissue level. A shift toward left does occur during HD as a result of the pH shift from acidosis toward alkalosis.

(c) Elevated carbon monoxide content (COHb), partially caused by increased hemolysis, is frequent in patients on HD. In a study of 69 patients, we found COHb values as high as 2.3% in nonsmokers;[18] a normal upper limit is 1%. Carbon monoxide competes with binding of oxygen to hemoglobin; consequently, a COHb of 2.3% means that 2.3% of oxygen-binding capacity is blocked by CO. In addition, increased hemolysis is probably seen during HD because of the direct physical impact of HD on the erythrocytes.[19] All of these examples represent anemic tissue hypoxia.

3. Cardiovascular impairment. Cardiac dysfunction makes the necessary compensatory increase in cardiac output impossible. Arteriosclerosis jeopardizes capillary circulation. Cardiac dysfunction and arteriosclerosis obviously represent circulatory tissue hypoxia.

ART OF MONITORING

To accomplish assessment of oxygen status of tissue one must clinically assess: respiratory status, cardiac status, peripheral perfusion status and oxygen status of the blood (see *Figure 2*). The problem of how to perform oxygen status measurement has not been completely solved, and all available types of measurement have limitations and drawbacks.

Arterial Puncture. So far, arterial puncture yields the most information, especially if the sample is analyzed on equipment combining blood gas analysis with acid-base and hemoximetry measurements. We have performed extensive investigations comparing blood gas values—sO_2(a), pO_2(a) and ctO_2(a)—on blood drawn from the radial artery with that of gas measurements—sO_2(al), pO_2(al) and ctO_2(al)—on blood drawn from the arterial line of dialyzers of patients who have a well-functioning fistula. Our results show that blood drawn from the arterial line represents arterial blood and, as such, mirrors systemic blood gas values. These findings eliminate, on the whole, the need for puncturing arteries in heparinized patients.

Unfortunately, measuring by blood samples drawn from the arterial bloodline may present problems. First, the number of measurements must, for natural reasons (time and blood consump-

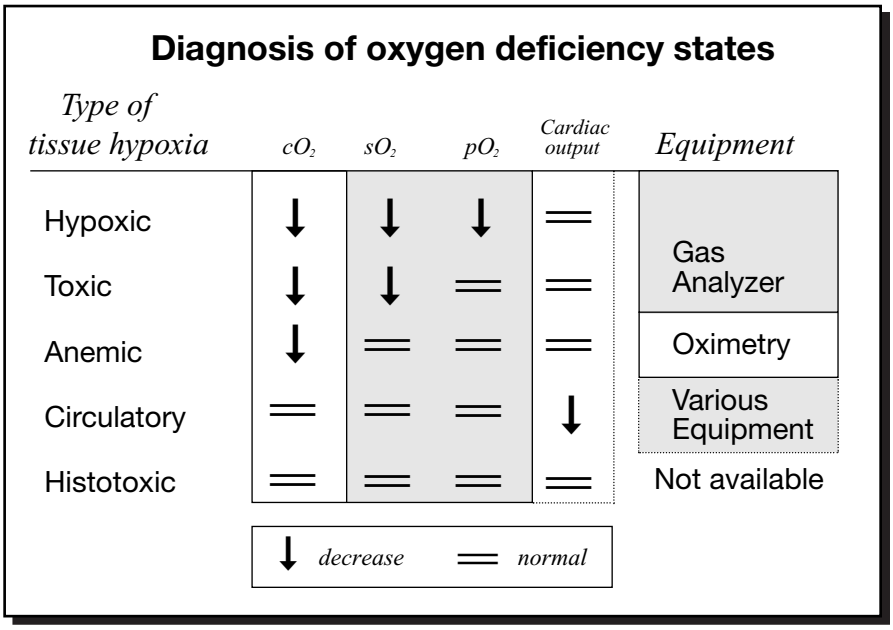

Figure 2: Diagnosis of oxygen deficiency states.

tion) be rather limited and can never be continuous. Thus, fluctuations in oxygen status may be missed unless they are of a very low frequency. Handling of sampling material and sampling syringes must be optimized, which stresses the need for proper equipment to avoid escape of oxygen from the syringes and, at the same time, avoid trapping gas bubbles in the syringe. Samples must be chilled and analyzed shortly after they have been obtained, which presents problems to most hospital physicians who don't have analyzing equipment available at patients' bedside. Transport time lags may alter gas composition of samples in an unpredictable way.

Pulse Oximeter. Pulse oximetry equipment is used primarily to obtain samples from the earlobe or fingertip, which are peripheral areas of the circulation and are subject to substantial changes in blood flow induced by cardiovascular homeostatic mechanisms. This may give erroneous results showing decreased local oxygen saturation levels because of impaired blood flow, in spite of normal systemic values. If there is anemia, a patient might well have a high oxygen saturation in the few erythrocytes that are available, which by no means indicates that oxygen-carrying capacity is sufficient. Furthermore, a shift in the oxygen saturation curve to the left may inflict changes in oxygen saturation not paralleled by similar changes in oxygen tension or concentration, thus misleading clinicians in judging a patient's oxygen status. The possibility of an elevated CO content adds further to the unreliability of the pulse oximeter.

Continuous Monitoring of Blood Gases. New equipment that is capable of continuous monitoring of oxygen and carbon dioxide tensions is recently available, but only as a prototype for scientific use. The equipment, which measures inside the arterial blood line during HD, consists of an electrode (Radiometer A/S) placed in a casing (Gambro A/B) in the arterial blood line. A sensor is connected to a monitor (TINA, Radiometer A/S), and the monitor is interfaced to a standard personal computer. Data are sampled at intervals of 10 seconds. Using this equipment, we have found a surprisingly high inter- and intra-patient variability in blood gases, which emphasizes the need for close monitoring. Although oxygen tension is a major component in assessing oxygen status, it is not a sufficient evaluation on its own.

Unfortunately, methods for continuous measurement of pO_2 and sO_2 are not sufficiently reliable as the only means of monitoring. They may be used as guidelines or trends but not as the "absolute truth," implying that whenever they suggest problems, supplementary blood sampling must be done to evaluate oxygen availability (*Figure 2*). These data combined with a clinical examination form the basis for diagnosing tissue hypoxia.

Having diagnosed HD patients with impaired oxygen status, the theoretical countermeasures against tissue hypoxia include:

1. Counteracting hypoxemic tissue hypoxia:
a. Improvement of lung function (such as reducing overload).
b. Administration of supplementary oxygen.
c. Use of more biocompatible membranes.
2. Counteracting anemic tissue hypoxia:
a. Correcting the anemia (increasing EPO, blood transfusions).
b. Reducing hemolysis during HD (such as moderate UF, reduced blood flow).
c. Abandon smoking during HD.
3. Counteracting circulatory tissue hypoxia:
a. Supportive cardiovascular measurements.
4. Counteracting histotoxic tissue hypoxia:
a. General reduction in level of uremia.

SUMMARY

Tissue hypoxia is a condition in which there is inadequate oxygen at the cellular level. We believe this occurs more frequently than normally realized, regrettably with grave consequences for patients. Tissue hypoxia should always be suspected in critical situations during hemodialysis. Direct measurement of this condition is not yet clinically available. In addition, all relevant indirect variables are not yet continuously measurable and profound knowledge of the patient's cardiovascular status is mandatory. Diagnosis, therefore, must continue to be based on supplementary clinical evaluation, and the condition may only be anticipated from skilled interpretation of various clinical and laboratory findings.

References

■ 1. Johnson NR, Bischel MD, Boylen CT. Hypoxia and hyperventilation in chronic haemodialysis. *Clin Res* 19:145, 1974.

■ 2. Cardoso M, Vinay P, Vinet B, et al. Hypoxemia during hemodialysis: A critical review of the facts. *Am J Kidney Dis* 11(4):281–297, 1988.

■ 3. Nielsen AL, Jensen HAE, Brinkenfeldt H, et al. Hypoxemia during haemodialysis is severe. *JASN* 3(3):382, 1992. (Abstract)

■ 4. Nielsen AL, Brinkenfeldt H, Thunedborg P, et al. Critical oxygen concentration during hemodialysis. *JASN* 4(3):372, 1993. (Abstract)

■ 5. Zander R. The oxygen status of arterial human blood. *Scan J Clin Lab Invest* 50(Suppl 203):187–196, 1990.

■ 6. Shapiro BA, Harrisson RA, Cane RD, et al. *Clinical Application of Blood Gases*. New York: Year Book Medical Publishers Inc. 1989.

■ 7. Ledingham IM, Naguib M. Overview: Evolution of the concept from Fick to the present day. In *Oxygen Transport: Principles and Practice*, eds. JD Edwards, WC Shoemaker, J-L Vincent, pp. 3–20. London: W. B. Saunders Co. Ltd., 1993.

■ 8. Mertzlufft F. Normal and therapeutic threshold values for arterial O2 saturation. In *The Oxygen Status of Arterial Blood*, eds. R. Zander, F. Mertzlufft, pp. 136–143. Basel: Karger, 1991.

■ 9. Noble J, Jones JG, Davids EJ. Cognitive function during moderate hypoxaemia. *Anest Intens Care* 21:180–184, 1993.

■ 10. Zander R. Therapeutic thresholds for acute and chronic alterations in arterial oxygen concentration. In *The Oxygen Status of Arterial Blood*, eds. R. Zander, F. Mertzlufft, pp. 233–237. Basel: Karger, 1991.

■ 11. Zuber M, Steinmann E, Huser B, et al. Incidence of arrhythmias and myocardial ischaemia during haemodialysis and haemofiltration. *Nephrol Dial Transplant* 4:632–634, 1989.

■ 12. Pochmalicki G, Jan F, Fouchard I, et al. Frequence de l'ischemie myocardique indolore au cours de l'hemodialyse de 50 insuffisants renaux chroniques. *Arch Mal Caeur* 83:1671–1675, 1990.

■ 13. Raine AEG, Margreiter R, Brunner FP, et al. Report on management of renal failure in Europe, XXII, 1991. *Nephrol Dial Transplant* 2
(Suppl):7–35, 1992.

■ 14. Mazin VV, Dubrov AI, Zhukov AA. Hyperbaric oxygenation in the combined treatment of acute kidney failure. *Urol Nefrol (Mosk) USSR* 4(6):29–30, 1992.

■ 15. Rostand SG, Rutsky EA. Ischemic heart disease in chronic renal failure: Demography, epidemiology and pathogenesis. In *Cardiac Dysfunction in Chronic Uremia*, eds. PS Parfrey, JD Harnett, pp. 53–66. Dordrecht: Kluwer Academic Publishers, 1992.

■ 16. Von Hartitzsch B, Eaton JW, Buselmeier TJ, et al. Dialysis disequilibrium: A manifestation on impaired tissue oxygenation. *Trans Am Soc Artif Intern Organs* 20:373–376, 1974.

■ 17. Moinard J, Guenard H. Membrane diffusion of the lungs in patients with chronic renal failure. *Eur Respir J* 6(2):225–230, 1993.

■ 18. Thunedborg P, Nielsen AL, Brinkenfeldt H, et al. Carbon monoxide in chronic uremic patients compared with EPO treatment and smoking habits. *Scan J Urol Nephrol*, In press: 1994.

■ 19. Nielsen AL, Thunedborg P, Brinkenfeldt H, et al. Carbon monoxide during hemodialysis. *Blood Purif* 11(3):204, 1993.