Think about Hemoglobinopathies

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Hemoglobin (Hb) is one of the most studied human structures, and numerous point mutations have been discovered in the globin genes. Mutations leading to a decrease in the alpha or beta globin protein levels will result in thalassemia; however, many point mutations induce clinical consequences due to altered hemoglobin function; the most well-known example is sickle cell hemoglobin. Other hemoglobinopathies can be divided into a few types:

- High oxygen affinity hemoglobinopathies causing erythrocytosis
- Low oxygen affinity Hb mutants. These hemoglobinopathies can cause dyspnea or cyanosis, especially when the oxygen dissociation curve is shifted extremely to the right and when the variant hemoglobin is abundant
- M hemoglobins causing pseudocyanosis.

Physiologically, a steady state exists between the oxygenated hemoglobin, also called the R (relaxed binding) state and deoxyhemoglobin, called the T (tight binding) state, as shown in Figure 1A. This steady state is influenced by the levels of 2,3-DPG and CO, pH, and the partial pressure of oxygen. Some point mutations in any of the globin genes can influence this steady state [1].

In this issue of *IMAJ*, Marcus et al. [2] describe the case of a young patient presenting with dyspnea, who was eventually diagnosed with Titusville hemoglobinopathy. Hb Titusville was first described by Schneider et al. in 1975 [3]. An additional two families with Hb Titusville were described almost two decades later [4,5]. The clinical presentation varied between low oxygen saturation that was clinically asymptomatic, dyspnea and peripheral cyanosis. A Scandinavian patient who presented with shortness of breath, low oxygen saturation measured by pulse oximetry, low oxygen saturation in arterial blood, but normal partial pressure of oxygen in arterial blood was later described [6]. Low oxygen affinity hemoglobinopathies can also cause a mild anemia, as was shown in a murine model of Hb Titusville [7]. In the first case described by Schneider et al. [3], no cyanosis was detected, and indeed most cases are asymptomatic. The patient described here by Marcus and colleagues [2] probably had contributing factors, such as heavy smoking, which exacerbated the clinical presentation.

Hb Titusville results from a point mutation causing a G to A change at codon 94 in the alpha globin gene, leading to a change

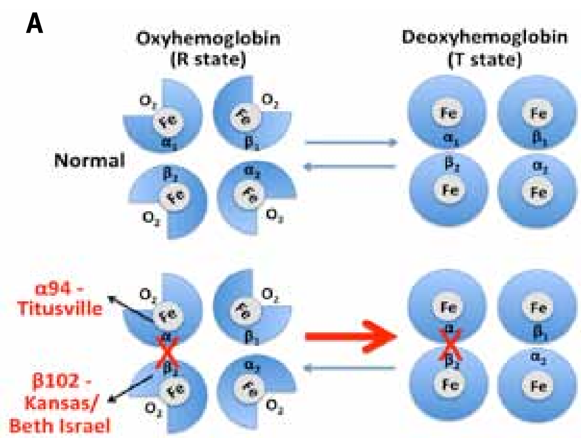
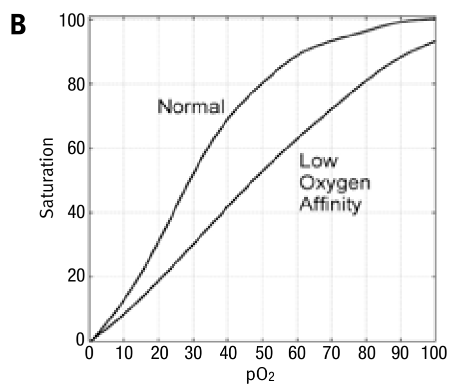


Figure 1.
[A] The hemoglobin molecule is a tetramer of two alpha globin and two beta globin chains. Normally, there is an equilibrium between oxyhemoglobin and deoxyhemoglobin. In Hb Titusville, as well as in Hb Kansas and Hb Beth Israel, the interaction between alpha1 and beta2 is disrupted, and the equilibrium is shifted towards the deoxyhemoglobin state



[B] Oxygen dissociation curves of normal and low oxygen affinity hemoglobin. "Normal" represents the oxygen dissociation curve for normal adult hemoglobin, and "Low Oxygen Affinity" represents the mildly right shifted oxygen dissociation curve found in disorders causing low oxygen affinity, such as Hb Titusville from aspartic acid to aspargine. This site is involved in the contact area between alpha1 and beta2 globins. The effect manifests as a stabilization of the T state and lowering the affinity of the hemoglobin to oxygen [Figure 1A]. Interestingly, mutations in the beta globin, involving the same contact area, have also been described, including Hb Kansas [8] and Hb Beth Israel [9], both involving residue 102 of the beta globin. Asn102, in the beta globin, is connected to asp94 in the alpha globin by a hydrogen bond. Thus, Hb Kansas, Hb Beth Israel and Hb Titusville all cause an interruption to the alpha1-beta2 interface. Similarly, in Hb F-Sarajevo, amino acid 102 of the gamma globin is involved [10], leading to cyanosis appearing early in life and subsiding after the neonatal period. All of the described cases of Hb Titusville are heterozygous to the mutation, and no known homozygotes have been found as this is most likely a lethal defect.

In Hb Titusville, as in other hemoglobinopathies causing low oxygen affinity, the oxygen dissociation curve is shifted to the right [Figure 1B] and the oxygen extraction to the tissues is enhanced [7]. The p50 of Hb Titusville is higher than normal. Oxygen saturation measured by pulse oximetry is low; however, the partial pressure of oxygen in the arterial blood is normal. The diagnosis can be made by hemoglobin electrophoresis and confirmed by DNA sequencing. A bedside test that can rule out the presence of methemoglobin, sulfhemoglobin and hemoglobin M can be performed by exposing the blood of the patient to oxygen. In low oxygen affinity hemoglobinopathies, blood will turn from purple to bright red upon exposure to oxygen, while the color will not change in methemoglobinemia, sulfhemoglobinemia and hemoglobin M disease. This test cannot, however, rule out cardiopulmonary diseases that will give the same effect.

In summary, low affinity hemoglobin variants are usually benign, causing no or mild symptoms. However, they should be considered in the differential diagnosis of any patient with unexplained low oxygen saturation, dyspnea or cyanosis, especially when there is no evidence of cardiopulmonary abnormalities. Correct diagnosis of low oxygen affinity hemoglobinopathies is important, as it can eliminate the need for an expensive and invasive workup and is relatively simple, when these abnormalities are properly considered in the differential diagnosis.

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