

# Impaired Aerobic Performance with Low-Affinity Hemoglobinopathy

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## Abstract

A patient of Asian extraction was found to have 16% Hemoglobin Titusville, which has decreased affinity for oxygen. The patient underwent a maximal exercise test revealing impaired aerobic performance which can be explained by adverse effects on oxygen uptake in the lungs, reduced arterial oxygen content and impaired oxygen delivery to tissues.

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## Clinical History

A 51 year-old Chinese woman born in Shanghai was referred for abnormally low oxygen saturation. She was healthy, physically active on no chronic medications. During screening colonoscopy, finger oximetry on room air revealed an oxygen saturation of 86%. The patient endorsed no significant dyspnea, wheezing, or other respiratory symptoms. Family history was non-contributory.

Her initial workup revealed a normal physical examination, chest x-ray and pulmonary function tests. Total hemoglobin was 13 gm/dL. Echocardiogram with bubble study, CT angiogram of the chest, and a lung/liver perfusion scan showed no evidence of intracardiac or intrapulmonary shunting. Oxygen saturation rose to 92% with six L/min supplemental oxygen. Hemoglobin (Hb) electrophoresis revealed 16% of an abnormal variant, identified as Hemoglobin Titusville and a normal amount of Hemoglobin F.

The patient underwent a maximal incremental cycle ergometry exercise test with breath-by-breath measurement of oxygen uptake ( $\text{VO}_2$ ) and carbon dioxide output ( $\text{VCO}_2$ ). A graphical representation of the results of this test are shown in Figure 1. She achieved a maximum heart rate of 142 bpm (80% of age-related reference value). Her  $\text{VO}_2$  at maximum exercise was 1.27 L/min (21 ml/kg-min), which was 89% of the reference value for the patient. The metabolic threshold (anaerobic threshold) was decreased, implying impaired aerobic performance. While this could be attributed to deconditioning, the reduced oxygen-carrying capacity of her abnormal hemoglobin could also be a contributing factor. Arterial blood gases showed  $\text{PaO}_2$  93 mmHg at rest and 99 mmHg at maximum exercise with

normal  $\text{PaCO}_2$  values throughout the test. Oxygen saturation by pulse oximetry ( $\text{SpO}_2$ ) was 86% both at rest and during exercise. At maximum exercise the blood lactate was normal at 8 mM.

## Discussion

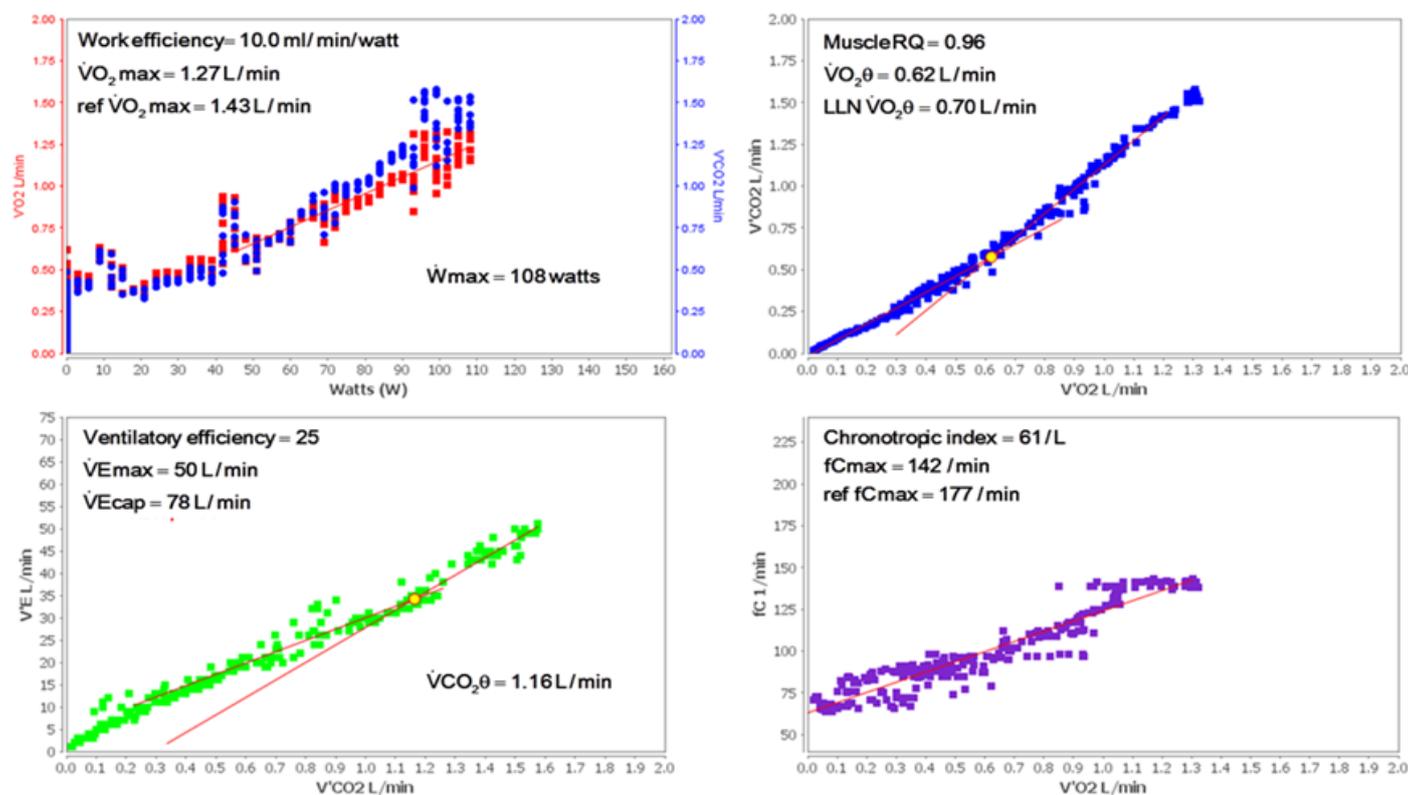
Rarely, hemoglobin variants alter affinity for oxygen. Hemoglobin Titusville was first reported in 1975<sup>[1]</sup> and results from an asparagine substitution for aspartate on the  $\alpha$ -chain. It was identified in an African-American child during a survey of persons at risk for Sickle Cell disease. This variant decreases affinity for oxygen and is unique, as all other reported variants with decreased affinity for oxygen have resulted from abnormal  $\beta$ -chains<sup>[2]</sup>. There have been three subsequent reports of the Titusville variant: three family members of Scandinavian descent<sup>[3]</sup>, a child described as Caucasian<sup>[4]</sup> and a Finnish man<sup>[5]</sup>. This patient is the first ethnic Asian reported with the variant. The percentage of Hb Titusville in the original case was 35%<sup>[1]</sup>, but in subsequent reports, the percentage has been similar to that of the present patient: 16 - 17% (3,4,5). Factors influencing the percentage of abnormal hemoglobin include transcription rates, the ability of the abnormal globin to incorporate into the Hb tetramer and the degradation rates of the normal and abnormal Hb tetramers. With one of four  $\alpha$ -chain genes abnormal, the production of monomers would theoretically be 25% of the total. The abnormal and normal globin chains do not readily hybridize, and this form constituted only 3.4% of the total hemoglobin in the original report<sup>[1]</sup>. The finding of 35% hemoglobin Titusville in the original report, approximately twice that seen in subsequent



reports, including the present patient, suggests the occurrence of more than one abnormal gene, perhaps related to consanguinity.

Following the work of Perutz and others<sup>[2,6]</sup>, it has long been known that the hemoglobin tetramer of subunits, two  $\alpha$ -chains and two  $\beta$ -chains, shows cooperativity, a property which shields the heme groups, inhibiting binding of oxygen. As oxygen molecules become bound, cooperativity decreases and the hemoglobin shifts from the so-called T-form (Tense) to the R-form (Relaxed) in which the heme groups are more exposed and have higher affinity for oxygen. In humans, genes for the  $\alpha$ -chains and  $\beta$ -chains are duplicated. Variants such as hemoglobin Titusville represent spontaneous mutations, presumably affecting only one of the two genes coding for the  $\alpha$ -globin chain.

Physiologically, it has been assumed that any property which limits oxygen uptake by red cells passing through the lung would also enhance oxygen unloading in tissues, thus facilitating oxygen delivery ( $\dot{V}O_2$ ). Consequently oxygen uptake would be normal, otherwise these patients would develop erythrocytosis, which in general they do not. This hypothesis has not been well studied, and certainly not for low affinity hemoglobins such as Hemoglobin Titusville. Based on the results of the cardiopulmonary exercise test, this patient would appear to have impaired aerobic performance. The extent to which this is due to deconditioning would depend on her response to a reconditioning exercise program. Exposure to the hypoxia of altitude could be more problematic. However, a High Altitude Simulation Test (HAST) would be helpful to guide recommendations for supplemental oxygen under such circumstances.



**Figure 1:** Four-panel graphical display of the exercise test data generated by the UCLA automated exercise test application (AXT). Panel A shows aerobic capacity (1.27 L/min) is 89% of the reference value and confirms that there was anaerobiasis. Panel B shows the metabolic (lactate) threshold (0.62 L/min) is detected and lies below the lower limit of normal. Panel C shows absence of ventilatory limitation and normal ventilatory efficiency. Panel D shows absence of cardiovascular limitation but a high chronotropic index.

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