

Introduction

REVIEWER #1

REVEIWER #2

Therefore, my central hypothesis is:

Despite the age difference, both COPD and CF, as a result of chronic cellular hypoxia, lead to alterations in both skeletal muscle *oxygen supply* and *demand* parameters, as well as *insulin resistance*.

Accordingly, the primary objective of the current proposal is to compare and contrast skeletal muscle performance, oxygen transport and utilization, morphology, and insulin resistance in two different age groups where chronic hypoxia may contribute to the phenomenon of skeletal muscle dysfunction.

Specific Aim 1 – Effects of COPD and CF on skeletal muscle oxygen demand

I hypothesize that there is a decrease in skeletal muscle oxygen demand in patients with COPD or CF in response to both whole-body and small muscle mass exercise, and this will be related to severity and duration of hypoxia and not age. Under this aim, I will measure single leg oxygen consumption (Vo_2) during both bicycle exercise and single leg knee extensor exercise, and explore the relationships among Vo_2 , muscle structure (*i.e.*, fiber-type distribution, fiber size, % fiber type areas), biochemistry (*i.e.*, oxidative enzyme activity), and muscle performance (*i.e.*, force production, fatigability).

Specific Aim 2 – Effects of COPD and CF on oxygen supply to skeletal muscle

I hypothesize that there is a decrease in skeletal muscle oxygen supply (increased resistance) in patients with COPD or CF in response to both whole-body and small muscle mass exercise, and this will be related to severity and duration of hypoxia and not age. Under this aim, I will measure hemodynamic (*i.e.*, blood flow) and oxygenation (*i.e.*, current and historical Pao_2 , Sao_2 from arterial blood gases) parameters to calculate leg O_2 delivery and extraction, and explore the relationships among these physiological and morphological parameters of oxygen supply (*i.e.*, muscle capillarity).

Specific Aim 3 – Effects of COPD and CF on insulin sensitivity

I hypothesize that there is a decrease in insulin sensitivity in patients with COPD or CF, which is related to decreases in both oxygen supply and peripheral muscle mass.

Under this aim, I will explore relationships among peripheral blood and oxygen supply, body composition (*i.e.*, % lean muscle mass, BMI), glucose metabolism (*i.e.*, insulin sensitivity index and intravenous glucose tolerance test) and skeletal muscle metabolic indicators (*i.e.*, enzymology and GLUT-4 concentration).

BACKGROUND AND SIGNIFICANCE

COPD, CF and hypoxemia

COPD, an umbrella term that primarily refers to emphysema and chronic bronchitis, affects nearly 12 million Americans, is the fourth leading cause of death in the United States,² accounts for 1.7% of ambulatory care visits,³ and costs an estimated \$30.4 billion per year.⁴ While the overall death rate in the past 20 years has decreased 18%, COPD mortality has increased 42%,⁵ this rate is even higher in mountainous (high altitude) states where less oxygen is available.⁶ Long-term oxygen therapy, however, decreases mortality and improves quality of life in patients with hypoxic COPD.⁷

CF, although it affects only 30,000 Americans, has an incidence of 1:2,500 US births and is one of the most common genetically inherited conditions.⁸ Repeated, progressive pulmonary infections and