Changes in atmospheric oxygen over geological time scales are hypothesized to be a major force of natural selection in the evolution of modern air-breathing vertebrates. Evidence for this is based primarily on fossil data but it can be tested using modern experimental approaches such as physiological modeling, experimental comparative physiology, phylogenetic independent contrasts, modeling the rates of genetic adaptation and experimental. Other new approaches may be useful also, such as adding environmental history to phylogenetic analyses or modeling interactions between environmental stresses and biological responses with different time constants. Collectively, results support the hypothesis, assuming the physiological sensitivity to oxygen is similar in ancestral and modern animals. Moreover, recent studies on the physiological genomics of different human populations living at high altitude indicate oxygen is one of the most efficient forces in natural selection studied to date. This latter approach has the potential to improve health care for patients with hypoxia, as well as understanding how animals have evolved with environmental change.