The key innovation of trachea allowed insect to evolve terrestriality from aquatic, crustacean-like ancestors by providing low costs of gas exchange and low respiratory water loss. Tracheal systems also enable the highest mass-specific rates of gas exchange amongst all animals and a “Lazarus-like” ability to recovery from anoxia. However, does the tracheal respiratory system limit insects to small body sizes? Even the largest insects appear to balance O₂ supply and demand, but the preservation of O₂ safety margins seems to require hypermetry of tracheal structures, especially the spiracles and the tracheae of the legs. Insects exhibit fast behavioral and physiological responses to hypoxia, and longer-term, neuro-endocrine-mediated processes that suppress growth, feeding and metabolism, while causing compensatory growth of the trachea and up-regulation of anaerobic pathways. Hypoxia “programs” body size of insects; at least in Drosophila, this can occur partly via HIF-signaling in the endocrine glands that control growth.