Skeletal muscle represents one of the most abundant tissues in our body that primarily acts as a protein reservoir as well as maintains the structural framework of the body regulating important life processes. Similar to other muscle tissues, skeletal muscle maintains its mass and functionality by balancing the rate of muscle synthesis and degradation. However, disruption of this intricate balance results in debilitating wasting conditions such as myopathies and dystrophies that not only adversely affects skeletal muscle but also promotes whole body catabolism during various pathological and physiological conditions. Exposure to high altitude hypoxia also results in sustained muscle wasting which eventually might culminates in decreased physical activity, increased fatigue and in severe cases increased mortality with no available therapeutic interventions.

With the objective of preventing muscle mass loss incurred on hypobaric hypoxia exposure, the present study aimed at identifying the hind limb skeletal muscle more susceptible to hypobaric hypoxia and focused on understanding the molecular mechanisms that regulate skeletal muscle mass loss therein and finally to attenuate this muscle mass loss using suitable therapeutic intervention.

Male Sprague Dawley rats were exposed to hypobaric hypoxia for different durations and the relative vulnerability of soleus and gastrocnemius muscle was assessed in terms of oxidative stress and decrease in total protein content. This study not only showed the differential response of the gastrocnemius and soleus muscle to different durations of hypobaric hypoxia but also
brought to light the substantive differences in the temporal responses of each of these muscles. The gastrocnemius muscle was found to be more susceptible to hypobaric hypoxia induced oxidative stress as reflected by increased levels of lipid peroxidation, free radical generation, protein carbonyl formation and nitric oxide levels. Gastrocnemius muscle also showed a significant depletion in the antioxidant status in addition to the increased oxidative stress. Further investigations were then done in gastrocnemius muscle to assess the effects of acute and chronic hypobaric hypoxia on protein metabolism. The results of this part of study explained that 1) acute and chronic hypobaric hypoxia alters protein metabolism through different mechanisms. Acute exposure decreases protein synthesis rate with a concomitant increase in the protein degradation rate. However, chronic hypobaric hypoxia leads to elevated skeletal muscle protein synthesis rate along with increased muscle proteolysis. It proves that synthesis rate is not a factor responsible for loss of skeletal muscle mass under chronic exposure, 2) fold increase in protein degradation is much higher than fold increase in protein synthesis leading to overall decreased protein turnover following chronic exposure and 3) upregulation of ubiquitin- proteasome and calpains are responsible for the enhanced protein degradation after exposure to both acute and chronic hypobaric hypoxia. Various factors (such as enzymes, hormones and oxidative stress) which can alter muscle protein metabolism were also studied. It was also evident by the results that hormones have a significant role in maintaining muscle protein balance in acute hypoxic conditions whereas under chronic hypoxia, protein turnover is not driven by changes in hormones. An increase in glutaminase enzyme activity supports the observed increase in protein degradation rate as glutaminase catalyzes the breakdown of glutamine residue resulted from proteolysis of skeletal muscle proteins. Similarly, glutamine synthetase enzyme activity may be a factor responsible for the altered protein synthesis rates as observed under acute and chronic
hypoxia conditions. Chronic hypobaric hypoxia also resulted in loss of skeletal muscle integrity which was evident by decreased creatine phosphokinase activity in skeletal muscle homogenates. Histopathological studies provided significant evidence of skeletal muscle atrophy following different durations of exposure to chronic hypobaric hypoxia.

Further experiments were done in rat L6 myoblasts to evaluate the molecular mechanism by which hypoxia upregulates ubiquitin–proteasome pathway and calpain pathway. Various biochemical and expression studies validated that the transcription factor NF-KB, is the key regulator muscle mass under hypoxic conditions. Increased oxidative stress leads to activation of NF-KB which leads to increased activities of proteolytic pathways and consequent increased muscle protein degradation. The major protein affected during hypoxia is myosin heavy chain which constitutes the significant portion of myofibrillar proteins. Myofibrillar proteins constitute 55 to 60% of total protein in muscle tissue by weight. The myofibrillar proteins are not only the largest class of skeletal muscle proteins but also are responsible for the contractile properties of muscle and for most of the functional and properties of muscle therefore any loss in these proteins alter the functional ability of skeletal muscle. Since, NF-κB has found to be playing a significant role in muscle proteolysis, the present study has opened a new area for developing therapeutic strategies for prevention of muscle protein loss.

Finally to attenuate the skeletal muscle mass loss, curcumin was daily administered *in-vivo* to rats which were exposed to 14 days of hypobaric hypoxia. Curcumin inhibited hypobaric hypoxia mediated muscle mass loss by decreasing muscle proteolysis which is attributed to the decreased activities of the ubiquitin–proteasome pathway and calpains. The declined proteolytic activities of these pathways were mediated through decrease in hypobaric hypoxia induced
oxidative stress and decreased expression of NF-KB, both of which play significant role in regulation of various proteolytic pathways. This study thus explored the dual role of curcumin as an anti-oxidant as well as inhibitor of NF-KB in preventing skeletal muscle mass loss following hypobaric hypoxia exposure. Since, curcumin is easily accessible, inexpensive, and non-toxic even at high doses, it may therefore offer an important treatment modality in muscle wasting under various pathological and physiological conditions.