The impact of metabolic stress on hypertrophic adaptations is exemplified by blood flow restriction (BFR) training studies. BFR training involves restricting venous inflow via the use of a pressure cuff while training (figure 2.5) with light weights (generally equating to <40% of 1RM), thereby heightening ischemia in the muscle as it contracts. The prevailing body of literature shows that BFR training stimulates anabolic signaling and muscle protein synthesis (233) and markedly increases muscle growth (427) despite employing loads often considered too low to promote significant hypertrophy (119, 392).

It has been speculated that metabolic stress is the driving force behind BFR-induced muscle hypertrophy. Significant metabolite buildup has been noted during such training (425), pointing to an association between metabolic stress and muscle growth. In further support of this contention, significant increases in cross-sectional area of the thigh muscle were found in college-aged males after 3 weeks of walking with BFR of the legs (8). Given that healthy young subjects generally do not gain muscle from performing low-intensity aerobic exercise, the study provides strong evidence that factors other than mechanical tension were responsible for hypertrophic adaptations. Indeed, increases in muscle cross-sectional area were found to be significantly correlated with the changes in inorganic phosphate ($r = 0.876$) and intramuscular pH ($r = 0.601$) during BFR training carried out at 20% of 1RM. This indicates that metabolic stress generated during resistance exercise is a key regulator of muscle growth (735).

Studies investigating resistance training under conditions of hypoxia provide further evidence for a correlation between metabolic stress and muscle growth. Kon and colleagues (377) found that breathing 13% oxygen during a multiset, low-load (~50% of 1RM) protocol with fairly short interset rest intervals (~1 min) significantly heightened blood lactate levels compared to the same routine performed under normoxic conditions. Similarly, Nishimura and colleagues (533) reported significantly greater increases in elbow flexor cross-sectional area when 4 sets of 10 repetitions at 70% of 1RM were performed under conditions of acute hypoxia versus normoxia. Mechanistic actions responsible for the enhanced hypertrophic response to hypoxic training have yet to be determined, but increased metabolite accumulation is suspected to play a role in the process (674).

The precise mechanisms whereby metabolic stress augments fast-twitch fiber recruitment are not entirely clear. It has been hypothesized that H+ accumulation plays a substantial role by inhibiting contractility in working fibers and thus promoting the recruitment of additional high-threshold motor units (173, 495, 738). MacDougall and colleagues (443) proposed that fatigue during single-set training to failure is due to a combination of acidosis...