Mechanism of Blood Flow Restriction

OBJECTIVE #4

Mechanisms of BFR – Hypertrophy: Primary Factors

Mechanical Tension - formed by active (cross bridge) muscle elements & exerted via passive elastic components, such as fascia & tendon, both in series and in parallel[19]

↑ External Force/Intensity

↓

↑ Active/Passive Contraction

↓

↑ Force Production

↓

↑Mechanical Tension

(Goldberg 1975, Spangenberg 2008, Vandenburgh 1979)

Metabolic Stress - physiological process that occurs during exercise in response to low energy that leads to metabolite accumulation [lactate, phosphate inorganic (Pi) and **ions of hydrogen (H^+)] in muscle cells**[20]

High Volume Training
(4-5 sets with 6-12 reps per set)

↓

More Metabolic Stress

↓

Accumulation of Metabolites like lactate, hydrogen ion, etc

↓

More Anabolic hormones and other growth factors

Mechanisms of BFR – Hypertrophy: Primary Factors

Mechanical Tension

Leads to hypertrophy via:

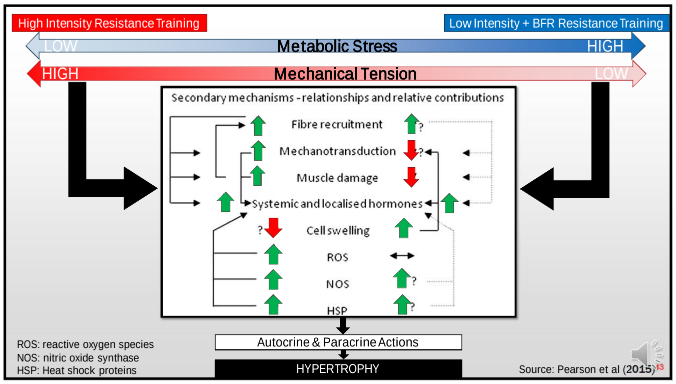
- Mechanotrasduction[27, 29, 30]
- ↑ localized hormone production[31]
- Muscle damage[32]
- ROS production[32, 33]
- ↑ fast twitch fiber recruitment[24-26]

Metabolic Stress

Leads to hypertrophy via:

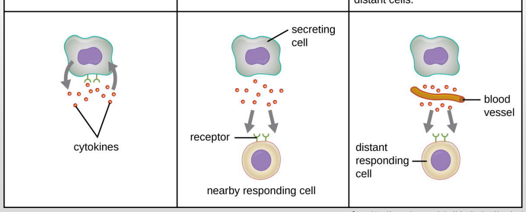
- ↑ systemic hormone production[34]
- ↑ fast-twitch fiber recruitment[35, 36]
- Cell swelling [37]
- Muscle damage[27, 38]
- ↑production of ROS[27, 39-41]

Mechanical Tension + Metabolic Stress = Muscle Hypertrophy



Reminder – Molecular Messengers

CYTOKINES: Molecular Messengers		
Autocrine	**Paracrine**	**Endocrine**
Same cell secretes and receives cytokine signal.	Cytokine signal secreted to a nearby cell.	Cytokine signal secreted to circulatory system; travels to distant cells.



Mechanisms of BFR – Hypertrophy: Muscle Damage

- Available evidence does NOT support the hypothesis that BFR in combination with low-intensity exercise ↑ incidence of muscle damage.[84]
- Evidence suggests minimal to NO muscle damage is occurring with this type of exercise.[84]
- Supporting Factors:
  1. no prolonged
  2. decrements in muscle function
  3. no prolonged muscle swelling
  4. muscle soreness ratings similar to a submaximal low load control
  5. no elevation in blood biomarkers of muscle damage.[84]

Source: Loenneke 2012[1]

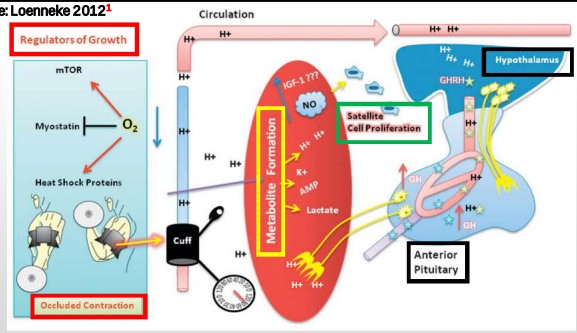
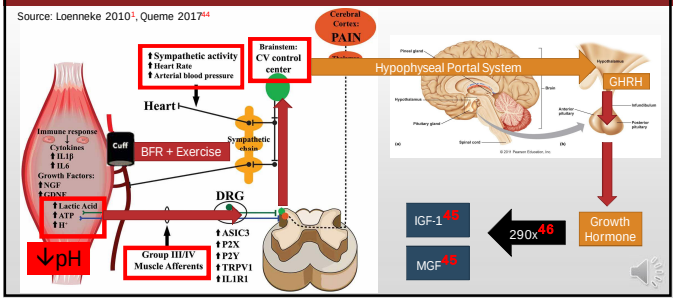


Fig. 1 Mechanisms by which blood occlusion training increases strength and muscular Hypertrophy. Arrows indicate stimulation, and blocked lines indicate inhibition. HSP = Heat shock proteins, GH = Growth Hormone, NO = Nitric oxide, IGF-1 = Insulin like growth factor, GHRH = Growth Hormone Releasing Hormone.

Mechanisms of BFR – Hypertrophy: Metabolic Stress

Source: Loenneke 2010[1], Queme 2017[44]



Mechanisms of BFR – Hypertrophy: IGF-1

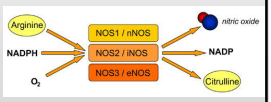
Insulin Like Growth Factor 1 (IGF-1)

- unclear if IGF-1 activity is directly ↑ in response to occlusion training.
- - **Takano et al.**[48] found a significant ↑, whereas two other studies[15, 47] found no ↑(Possibly due to the low intensity of the exercise).
- it is postulate that IGF-1 may NOT be necessary for muscle hypertrophy when other factors such as:
  - Myostatin
  - Heat Shock Protein 72 (HSP-72)
  - Nitric oxide synthase-1 (NOS-1)

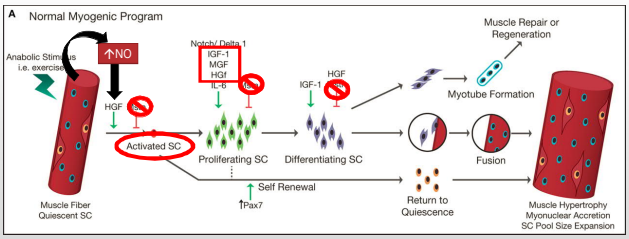
are changed in favor of muscle growth.[47]

Mechanisms of BFR – Hypertrophy: Metabolic Stress

- **Nitric oxide synthase:** enzyme responsible for converting L-arginine into nitric oxide (NO)
- **Nitric Oxide:** electrically neutral molecule capable of moving with ease through tissues[49]
- **Neuronal NOS (nNOS):** found in the transmembrane / dystrophin protein complex of skeletal muscle.[51]
  - **@Rest:** nNOS → produces → low levels of NO → maintain satellite cell quiescence
  - **During exercise-induced contraction:** mechanical shear forces &/or ↑ in intracellular Ca^{2+} concentrations → nNOS activation[50]
  - **Occlusion + Exercise:** ↑ Ca2+ ions &/or reperfusion[47] → ↑nNOS activation



Mechanisms of BFR – Hypertrophy: Metabolic Stress



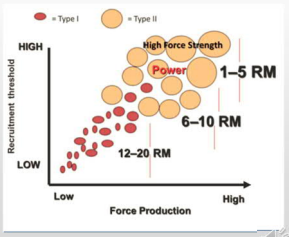
HGF: Hepatocyte growth factor; SC: satellite cell; Msn: myostatin

Anderson 2000[53], 2004[47]; Snijders 2015[52]

Mechanism of BFR – Fiber Recruitment

1. BFR + Exercise = ↓↓O_2
2. ↓ Force Production
3. progressive recruitment of additional motor units (MU) may take place to compensate[55]

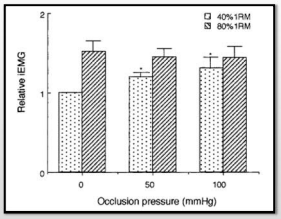
- ↑↑ in MU firing rate & MU spike amplitude associated with **arterial occlusion** suggesting that the recruitment of **high threshold MU (Fast Twitch Fibers)**[97] is affected by:
  1. force and speed of contraction AND
  2. **availability of oxygen**



Kraemer 2012[54]

Mechanism of BFR – Fiber Recruitment

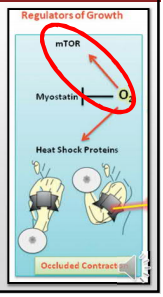
- Subjects: Males 25-40 y.o.
- Exercise: Bicep Curls
- Intensity: 40% & 80% 1 RM
- Occlusion: 0, 50, 100 mmHg
- Type of Occlusion: Pneumatic
- Cuff: 90 mm W, 700 L



- **integrated electromyography (iEMG)** demonstrating NO difference in iEMG activity between **low intensity occlusion** VS **high intensity non-occlusion**
- training suggesting that a greater number of FT fibers are activated at low intensities[59-61]

Mechanism of BFR – Regulators of Growth (mTOR)

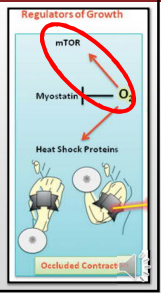
- ↑ rates of protein synthesis ➔ skeletal muscle hypertrophy response[62]
- **mammalian target of rapamycin (mTOR) pathway** regulates numerous components involved in:
  1. **protein synthesis** (initiation & elongation factors)
  2. **biogenesis of ribosomes themselves**[63]
- **S6K1 Phosphorylation** - a critical regulator of exercise-induced muscle protein synthesis & product of mTOR Pathway[62-63]
  - has been demonstrated to ↑ 3x immediately post exercise with occlusion training, and remained elevated relative to control at 3 hours post exercise.[63]



Mechanism of BFR – Regulators of Growth (mTOR)

mammalian target of rapamycin (mTOR) pathway

- **REDD1 (regulated in development and DNA damage responses)** - which is normally expressed in states of hypoxia, is **NOT** ↑ in response to occlusion training
- REDD1 ➔ ↓ protein synthesis through inhibition of the mTOR, responsible for the regulation of translation initiation[63]
- NO ↑ **REDD1** ➔ **↑(mTOR) pathway**



Mechanism of BFR – Regulators of Growth (Myostatin)

Myostatin: a myokine, a protein produced & released by myocytes that acts on muscle cells' autocrine function to inhibit myogenesis

- mutations of this gene result in overgrowth of musculature in mice, cattle, and humans[65-67]
- inhibit satellite cell proliferation[67-69]
- Myostatin is expressed in adult satellite cells ➔ regulates satellite cell quiescence & self-renewal, showing it does play a role in adult myogenesis.[69]

[Mechanical Overloading] OR **[Low Intensity Exercise + BFR]**[40]

↓Muscle Myostatin gene expression

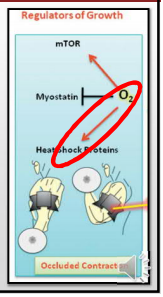
BFR ➔ favorable hypertrophic changes in Myostatin as a result of hypoxia &/or the ↑metabolic sub-products.

Mechanism of BFR – Regulators of Growth (HSP)

Heat Shock Proteins (HSPs) - induced by stressors such as heat, ischemia, hypoxia, free radicals

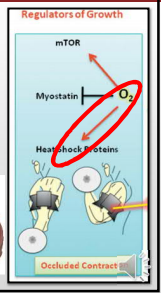
HSP Purpose:
1. chaperones to prevent misfolding or aggregation of proteins.
2. useful to slowing atrophy,[40] as HSP-72 plays a protective role in preventing protein degradation during periods of reduced contractile activity,[72] by inhibiting key atrophy signaling pathways[71,72]

- primary pathway involved in mediating protein degradation is the **ubiquitin proteasome pathway**



Mechanism of BFR – Regulators of Growth (HSP)

- **In Vivo Study: ↑ levels of HSP-70 is sufficient to prevent skeletal muscle disuse atrophy**
  - HSP-70 inhibits:
    1. the promoter activation of atrogin-1 / muscle atrophy F-box (MAFbx)
    2. Muscle specific RING finger 1 (MuRF1)
    3. transcription factors which regulate their expression, forkhead box O (Foxo) and nuclear factor of P + NF-P +[71]
- **occlusion training ➔↑ HSP-72 in a rat model**[71]
  - postulated to be a potential mechanism...



Mechanisms of Blood Flow Restriction: Absence Exercise

BFR – Exercises =

- Takarada et al. (2000a)[2]
  - BFR (238 mmHg, 9 cm wide cuff) to patients post ACLR → ↓ post operation disuse atrophy (measured by MRI) of the knee extensors
- Kubota et al. (2008)[13]
  - BFR (200 mmHg, 7.7 cm wide cuff) to a cast immobilized limb → attenuates ↓ muscle size (measured by leg circumference) & muscle strength.
- Kubota et al. (2011)[71]
  - lower pressure of 50 mmHg → ↓ muscular weakness induced by chronic unloading (BUT NO EFFECT on attenuating changes in leg size)

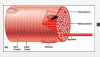
Mechanisms of Blood Flow Restriction

BFR – Exercises =

- acute ↑ in real-time ultrasound measured muscle thickness
  - changes were maintained following the removal of the cuff → acute changes in muscle thickness were actual acute ↑ in muscle size (i.e., muscle swelling) and NOT attributed to venous pooling
  - **Fry 2010**[10]
    - observed greater acute ↑ in muscle size (measured by circumference) with BFR resistance exercise vs resistance exercise alone
- **Abe 2006**[10], **Ozaki 2011**[5]: swelling may also help explain the ↑ in muscle size & strength previously observed from slow walking + BFR

Mechanisms of Blood Flow Restriction

BFR – Exercises =

- BFR → ↑ H_2O →  → stimulation of mTOR pathway.
- **Swelling Hypothesis:** dependent on research completed on **hepatocytes**[8]
  - unknown how well this mechanism may translate over to human skeletal muscle.
- Future cellular research should attempt to determine whether or not muscle swelling plays a significant role in the muscle hypertrophic signaling response in humans, which would have important clinical implications for populations contraindicated to exercise