BLOOD FLOW RESTRICTION: Scoping Review

Michael Jeanfavre PT, DPT, OCS, CSCS



Safety & Side Effects





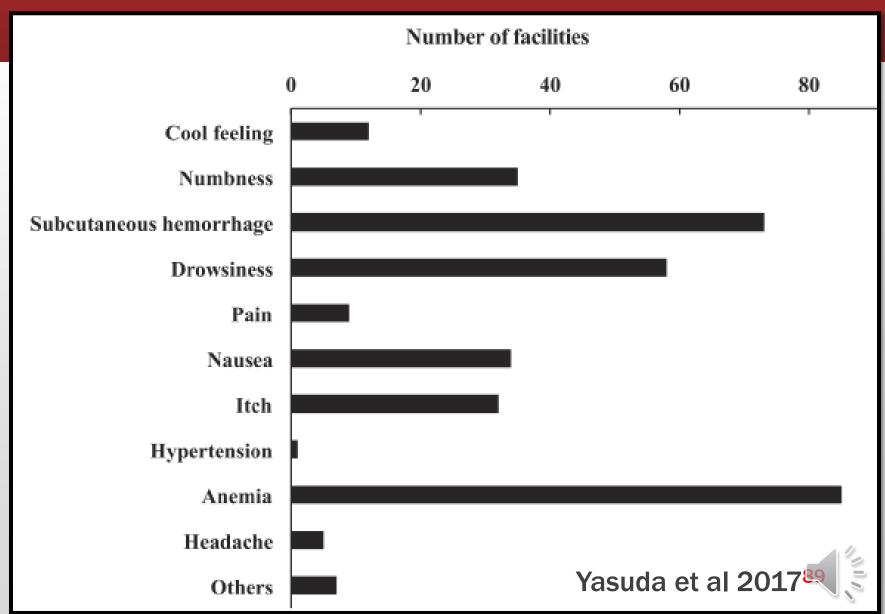
Safety & Side Effects

- 1. Systematic Reviews
- 2. Proposed Screening Processes
- 3. Study Example



Safety & Side Effects - Most Common

- 232 Facilities in Japan
- 12,827 Subjects
- Nov Dec 2016
- Male: 30.1%
- Female 69.9%



Safety & Side Effects – Rare Adverse Events

- 2006 KAATSU Training Survey sent out to 106 facilities across Japan
- Authors –3500 Subjects (2007-2011)⁸⁸

Adverse Events	N =	Comments	
Brain Hemorrhage	1	 Comparable to sudden death during athletic participation <35 y/o: hypertrophic cardiomyopathy, cardiomegaly, coronary artery malformation aortic rupture, brain hemorrhaging >35 y/o: Brain hemorrhaging & coronary artery disease 	
Venous Thrombosis	1	 BFR induces a fibinolytic state (aids in restricting thrombus formation) Healthy: 1-3/10,000 Pregnancy: 3-11/10,000 Post-partum: 30-40/10,000 	
Transient Numbness	NR	- Subjective reports (no paper; lasts days)	
Rhabdomyolysis	1	 Risk Factors: poor hydration, heat & humidity environment Rare in BFR due to low intensity & minimal muscle damage 	
Venous Injury and Induration	NR	 F, 30-50 y/o, spontaneous resolution 1-2 mo. Post Repeat Pressurization & depressurization (get vessels accustom to training) If sedentary lifestyle, more time needed to acclimate Adhere to KAATSU training time (15 – 20 min) 	

Safety & Side Effects – Adverse Events

Case Report

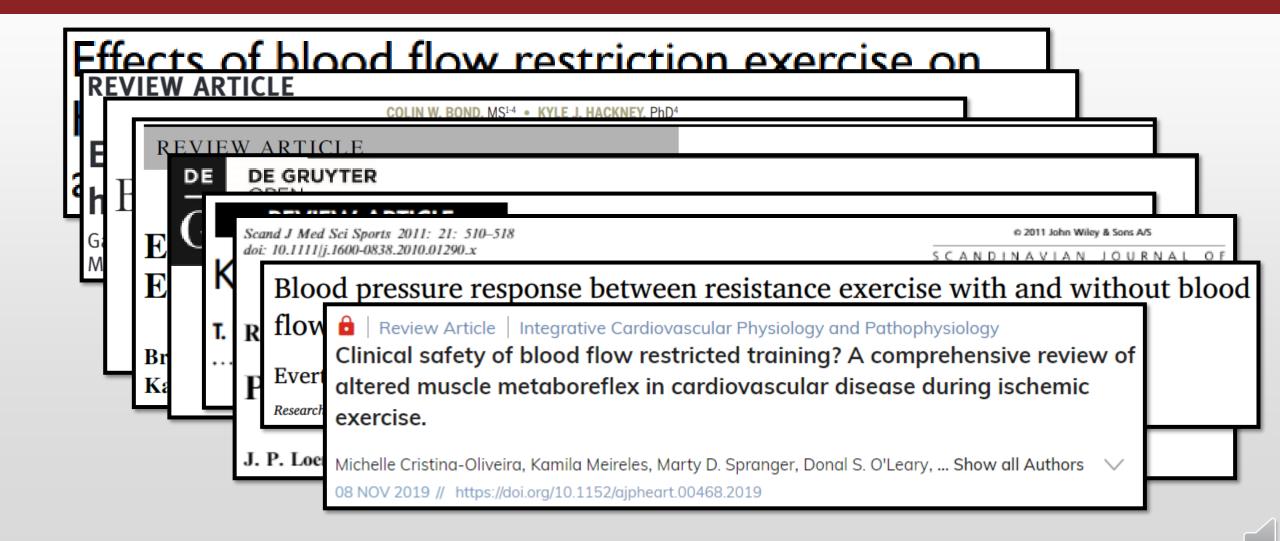
Syncope Episodes and Blood Flow Restriction Training

Juan Martín-Hernández, PhD,* Alejandro Santos-Lozano, PhD,*† Carl Foster, PhD,‡ and Alejandro Lucia, MD, PhD†§

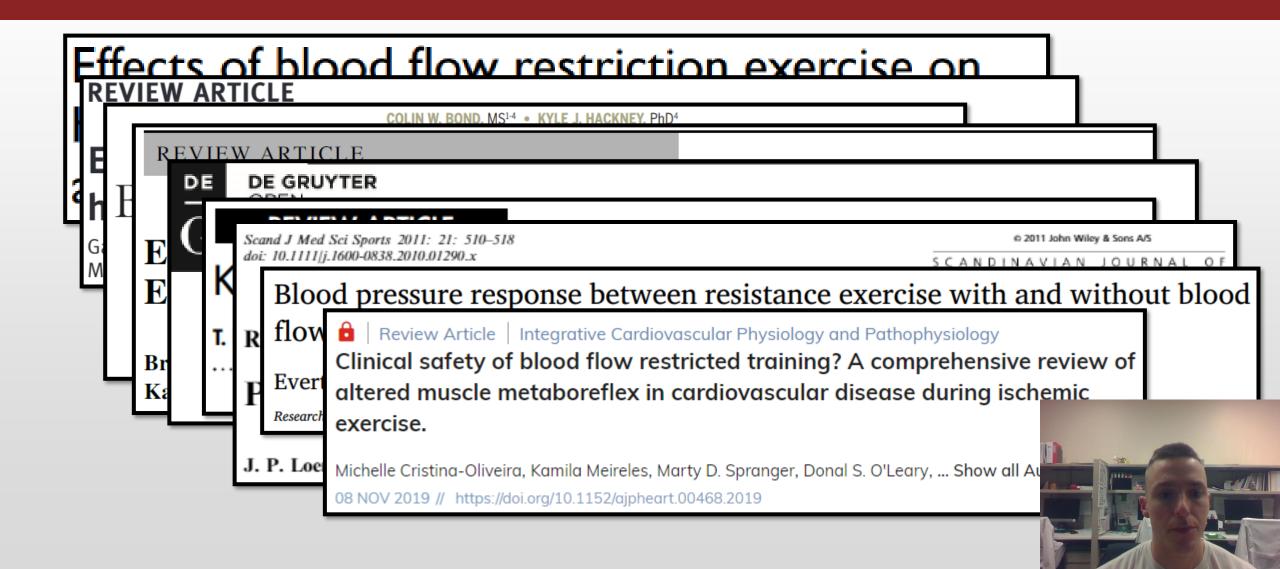
n = 3

- Scientific data indicate the overall safety of BFR, at least in healthy young people.
- Caution is thus needed in the application of BFR, and gentle familiarization with this training modality is also recommended.

Safety & Side Effects – Reviews



Safety & Side Effects – Reviews



Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis

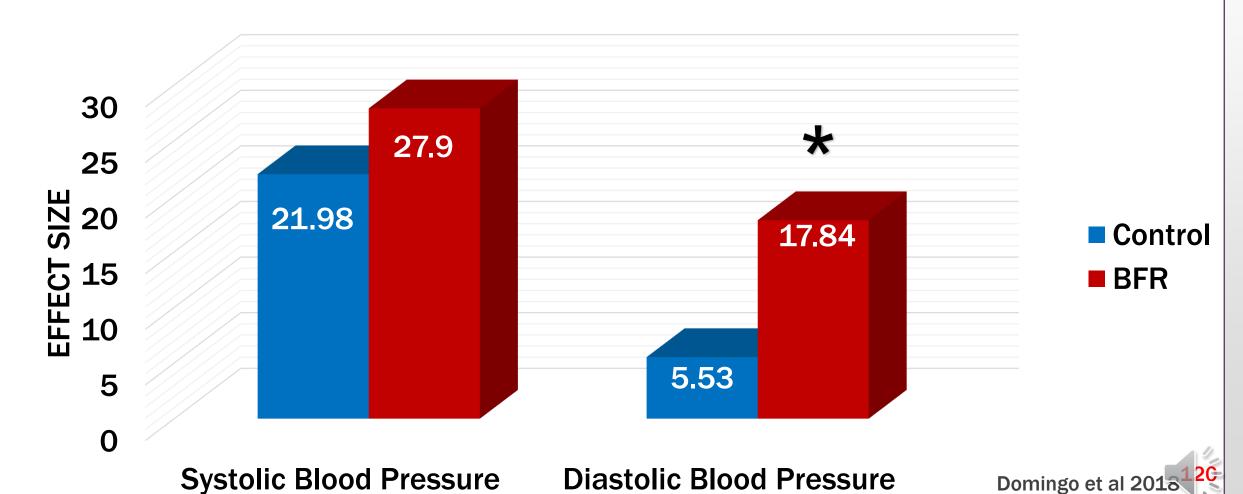
Everton Domingos, Marcos D. Polito*

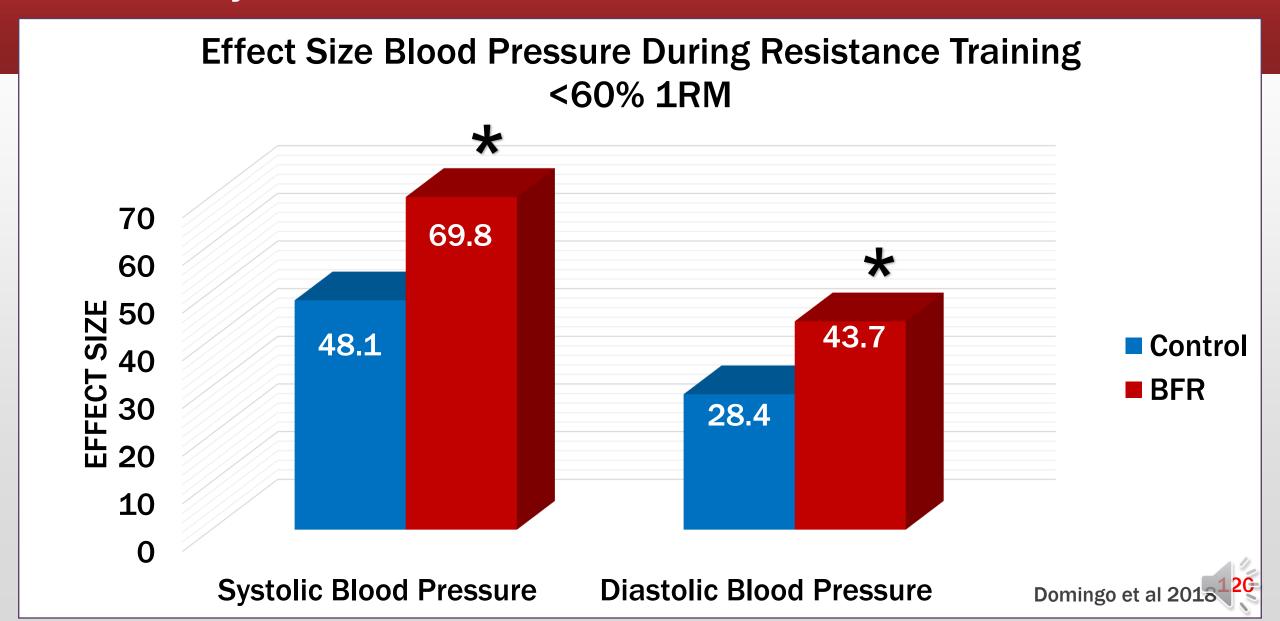
Research Group of Cardiovascular Response and Exercise, Londrina State University, Londrina, Paraná, PR, Brazil

17 Included Studies

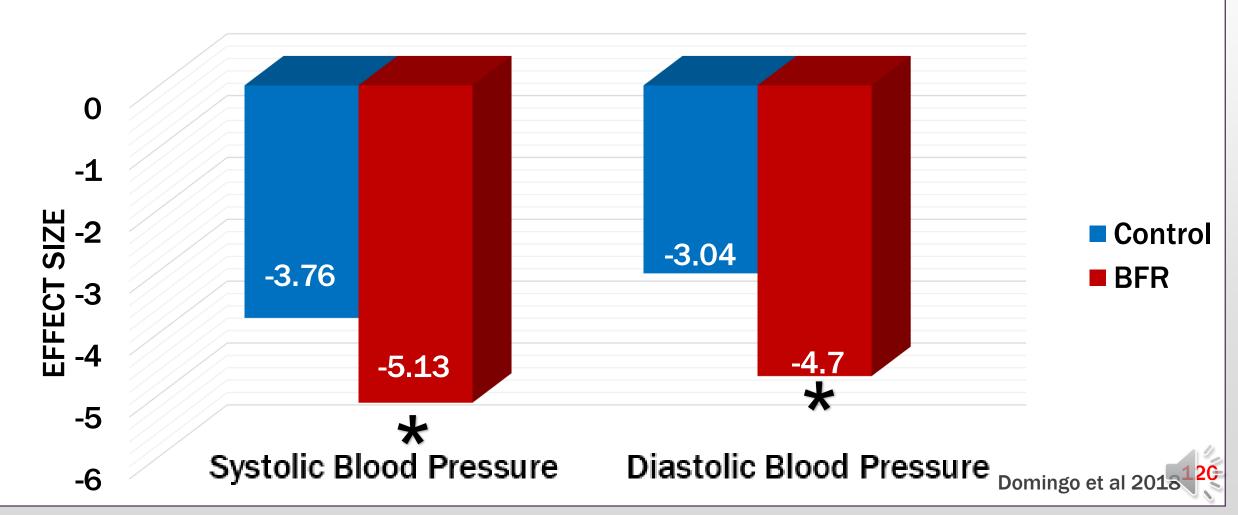


Effect Size Blood Pressure During Resistance Training >60% 1RM









Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis

Everton Domingos, Marcos D. Polito*

Research Group of Cardiovascular Response and Exercise, Londrina State University, Londrina, Paraná, PR, Brazil

- 1. BFR @ >60% 1 RM will result \tau DBP vs Traditional Resistance Training
- 2. BFR @ <60% 1 RM will result ↑ SBP & DBP vs Traditional Resistance Training
- 3. BFR will result in greater \ SBP & DBP in HTN & Healthy BP patients 60 min post exercise vs Traditional Resistance Training

Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis

Everton Domingos, Marcos D. Polito*

Research Group of Cardiovascular Response and Exercise, Londrina State University, Londrina, Paraná, PR, Brazil

"Resistance exercise with BFR should be prescribed with caution, especially when BP control during exercise is necessary."

Effects of blood flow restriction exercise on hemostasis: a systematic review of randomized and non-randomized trials

Nascimento et al 2019130

4 RCT 5 Non-RCT

Blood Factor	Definition	Normal Range
Tissue plasminogen activation (tPA)	protein involved in the breakdown of blood clots	5-40 μg/I
Fibrinogen	soluble protein in blood plasma	150-400 mg/dL
fibrinogen degradation product (FDP)	commonly used to diagnose disseminated intravascular coagulation (DIC)	10 mg/L
Prothrombin Time	how quickly your blood clots	INR < 1.1
D-Dimer	a blood test that can be used to help rule out the presence of a serious blood clot	208-318 ng/ml

Effects of blood flow restriction exercise on hemostasis: a systematic review of randomized and non-randomized trials

Nascimento et al 2019130

SHORT TERM:

- intervention of BFR exercise INCREASED the FIBRINOLYTIC ACTIVITY assessed by tPA measures.
- [The] data effectively support the SAFETY of BFR implementation for: young, middle-aged with stable ischemic heart disease individuals, OR apparently healthy older subjects.

Effects of blood flow restriction exercise on hemostasis: a systematic review of randomized and non-randomized trials

Nascimento et al 2019130

LONG TERM:

- no longstanding sig effects, indicating that blood CLOTTING FUNCTION REMAINED UNCHANGED in healthy subjects
- findings were supported in another investigation reporting no adverse effects of BFR with low-load RT (BFR with elastic band) on FDP or D-dimmer in OLDER, HEALTHY ADULTS.

Safety & Side Effects – BFR & Hemodynamics

REVIEW ARTICLE

Effects of resistance training with blood flow restriction on haemodynamics: a systematic review

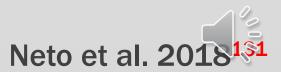
Gabriel R. Neto^{1,2,3}, Jefferson S. Novaes², Ingrid Dias⁴, Amanda Brown², Jeferson Vianna⁵ and Maria S. Cirilo-Sousa^{1,3}

21 Articles

Blood Pressure: n=16

Heart Rate: n=19

Rate of Perceived Exertion: n=4



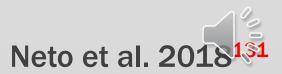
Safety & Side Effects – BFR & Hemodynamics

Effects of resistance training with blood flow restriction on haemodynamics: a systematic review

Gabriel R. Neto^{1,2,3}, Jefferson S. Novaes², Ingrid Dias⁴, Amanda Brown², Jeferson Vianna⁵ and Maria S. Cirilo-Sousa^{1,3}

"Hemodynamic changes (HR, SBP, DBP, MBP, RPP) promoted by LIRT-BFR do NOT seem to differ between ages and body segments (upper or lower)...

These changes are within the normal range.



Safety & Side Effects – BFR & Hemodynamics

Effects of resistance training with blood flow restriction on haemodynamics: a systematic review

Gabriel R. Neto^{1,2,3}, Jefferson S. Novaes², Ingrid Dias⁴, Amanda Brown², Jeferson Vianna⁵ and Maria S. Cirilo-Sousa^{1,3}

"[LIRT-BFR] may be considered SAFE & VIABLE for special populations, such as the ELDERLY & CARDIAC patients, among others, because it promotes STRENGTH & HYPTERTROPHY without NEGATIVELY CHANGING HAEMODYNAMIC measurements."

Safety & Side Effects – Exercise Pressor Reflex

Review Article | Integrative Cardiovascular Physiology and Pathophysiology

Clinical safety of blood flow restricted training? A comprehensive review of altered muscle metaboreflex in cardiovascular disease during ischemic exercise.

Michelle Cristina-Oliveira, Kamila Meireles, Marty D. Spranger, Donal S. O'Leary, ... Show all Authors 08 NOV 2019 // https://doi.org/10.1152/ajpheart.00468.2019

Blood flow restriction training and the exercise pressor reflex: a call for concern

Marty D. Spranger, 1,2,4 Abhinav C. Krishnan, 2,4 Phillip D. Levy, 2,3 Donal S. O'Leary, 2,4 and Scott A. Smith 5,6

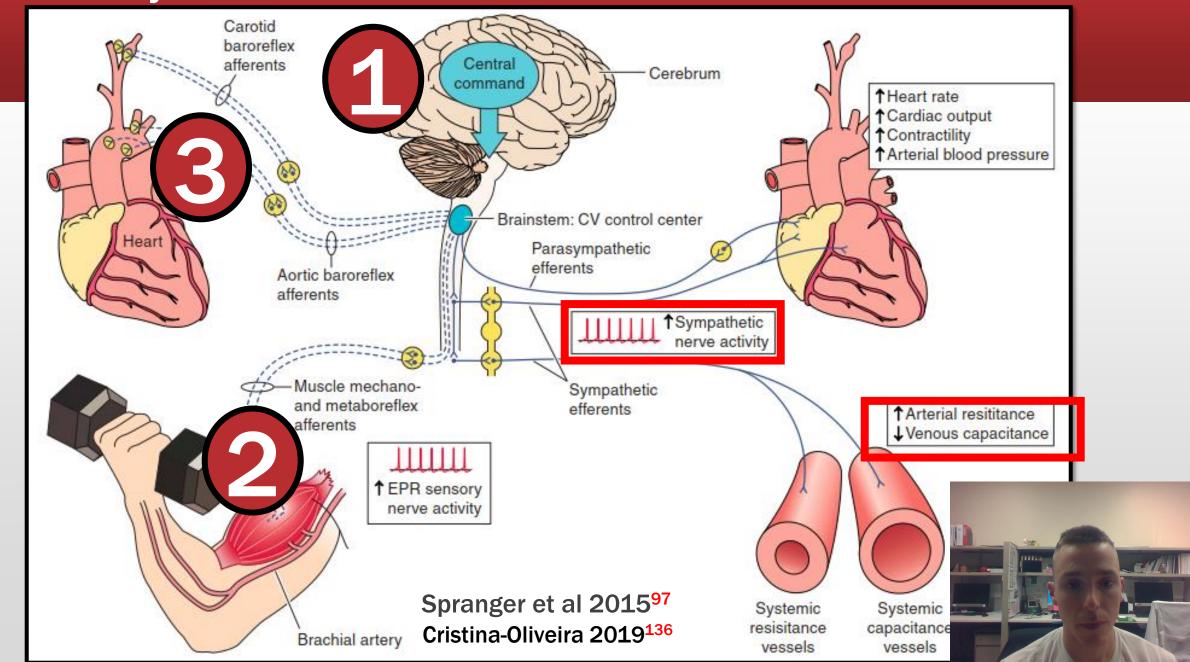
¹Department of Physiology, Michigan State University, East Lansing, Michigan; ²Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan; ³Department of Emergency Medicine, Wayne State University School of Medicine, Detroit, Michigan; ⁴Cardiovascular Research Institute, Wayne State University School of Medicine, Detroit,

Michigan; ⁵Department of Health Care Sciences, University of Texas Southwestern Medical Center, Dallas,

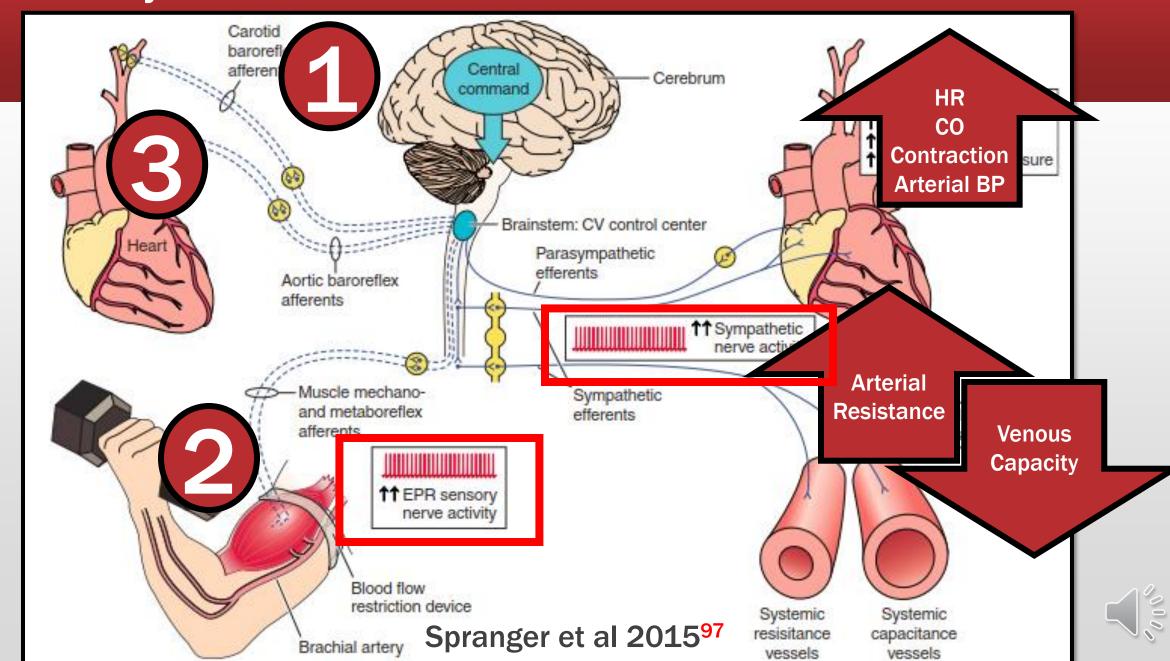
⁶Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

Submitted 20 March 2015; accepted in final form 31 August 2015

Safety & Side Effects – Exercise Pressor Reflex



Safety & Side Effects – Exercise Pressor Reflex



Safety & Side Effects – Exercises Pressor Reflex

- Individuals with CVD (HTN, HF, PAD) are especially at risk of deleterious CV events when performing BFR
- Healthy Individuals Resistance Training
 - Systolic AND Diastolic: >300 mmHg⁹⁹
 - Young Healthy Bodybuilders on Leg Press: 320/240 mmHg (max 480/350 mmHg)⁹⁹
- ↑ Venous Compression → ↑ Venous Pressure → Valve Damage → Chronic Venous Insufficiency
- Spikes in Arterial Pressure (+BFR) = $\uparrow(\uparrow)$ Risk of CV event
- ↑ Pain response w/ BFR → (may) ↑ Central Command & EPR funx →
- **↑SNA**, **↑MAP** in healthy individuals



Safety & Side Effects – Exercises Pressor Reflex

- Arterial waveforms show that vascular changes appear to be localized within the involved musculature
- NO negative effects on:
 - Large Vessel Stiffness
 - Augmentation Index
 - Central Aortic Blood Pressure
- Correlations between BFR-induced Spikes in arterial pressure & risk of Cardiovascular events is unknown
- Further research is needed before BFR can be fully endorsed

Safety & Side Effects – Adverse Events

COLIN W. BOND, MS¹⁻⁴ • KYLE J. HACKNEY, PhD⁴ SCOTT L. BROWN, DPT, OCS, SCS³ • BENJAMIN C. NOONAN, MD, MS¹⁻³

Blood Flow Restriction Resistance Exercise as a Rehabilitation Modality Following Orthopaedic Surgery: A Review of Venous Thromboembolism Risk

Safety & Side Effects - Adverse Events

COLIN W. BOND, MS¹⁴ • KYLE J. HACKNEY, PhD⁴ SCOTT L. BROWN, DPT, OCS, SCS³ • BENJAMIN C. NOONAN, MD, MS¹³

Blood Flow Restriction Resistance Exercise as a Rehabilitation Modality Following Orthopaedic Surgery: A Review of Venous Thromboembolism Risk

Bond et al. 2019¹³²

- "studies have demonstrated that intermittent pneumatic compression (IPC) REDUCES COAGULATION and ENCHANCE FIBRINOLYSIS.^{2,10,12,16,40,41,45,49,81,82,89,108,113,116,123}"
- "several studies have investigated IPC as an alternative or adjunct to prophylaxis and demonstrated SUCCESS results for a number of postsurgical orthopaedic paincluding those withtotal joint replacements.^{26,47,95}

Safety & Side Effects – Adverse Events

SCOTT L

Blood Flow R as a Rehabi Orthopa Venous

"colled BFR in risk of "clinic sympt factor

HYPERCOAGULABLE STATE

- Malignancy
- Pregnancy and peri-partum period
- Oestrogen therapy
- Trauma or surgery of lower extremity, hip, abdomen or pelvis
- Inflammatory bowel disease
- Nephrotic syndrome
- Sepsis
- Thrombophilia

VASCULAR WALL INJURY

- Trauma or surgery
- Venepuncture
- Chemical irritation
- Heart valve disease or replacement
- Atherosclerosis
- Indwelling catheters

CIRCULATORY STASIS

- Atrial fibrillation
- Left ventricular dysfunction
- Immobility or paralysis
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy

on of en the

s and



Safety & Side Effects – Venous Compliance

Not yet included: lida, H., Nakajima, T., Kurano, M., Yasuda, T., Sakamaki, M., Sato, Y., ... & Abe, T. (2011). Effects of walking with blood flow restriction on limb venous compliance in elderly subjects. Clinical physiology and functional imaging, 31(6), 472-476. (https://www.ncbi.nlm.nih.gov/pubmed/21981459)

Safety & Side Effects – Summary

In conclusion, the current research on blood flow restriction training with respect to safety outcomes confirms earlier reports that blood flow restriction exercise, when used in a controlled environment by trained and experienced personnel, provides a safe training alternative for most individuals regardless of age and training status.

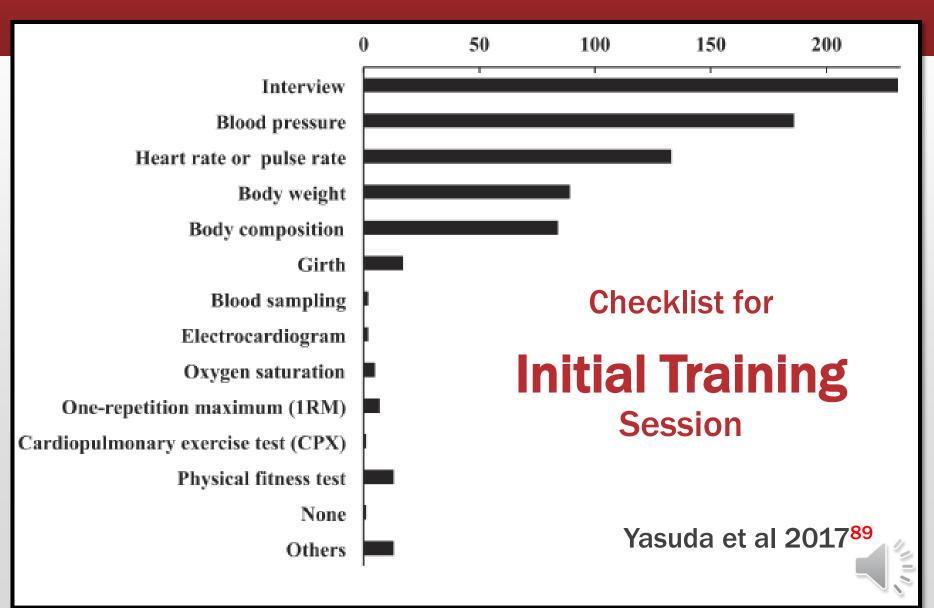


Safety & Side Effects

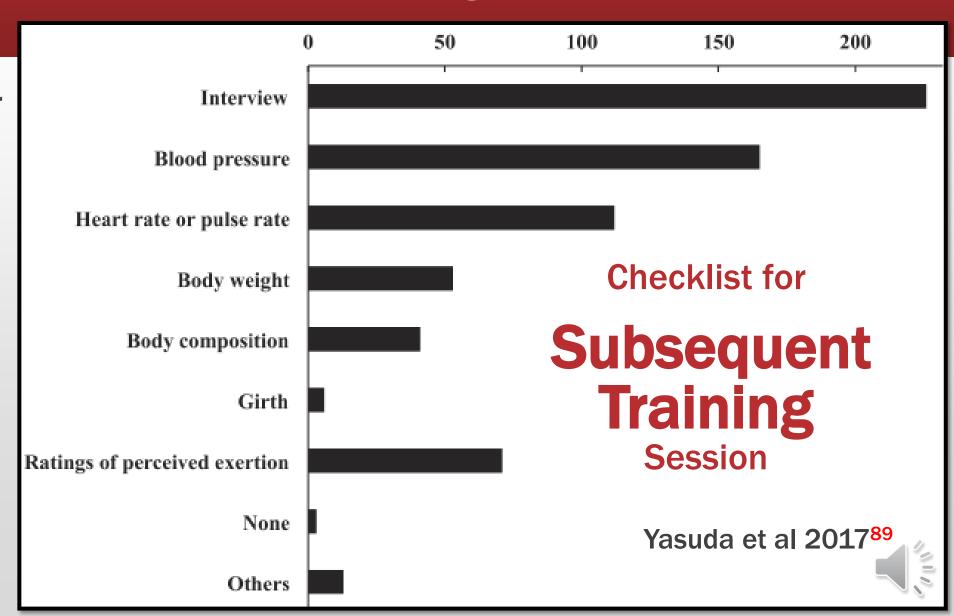
- 1. Systematic Reviews
- 2. Proposed Screening Processes
- 3. Study Example

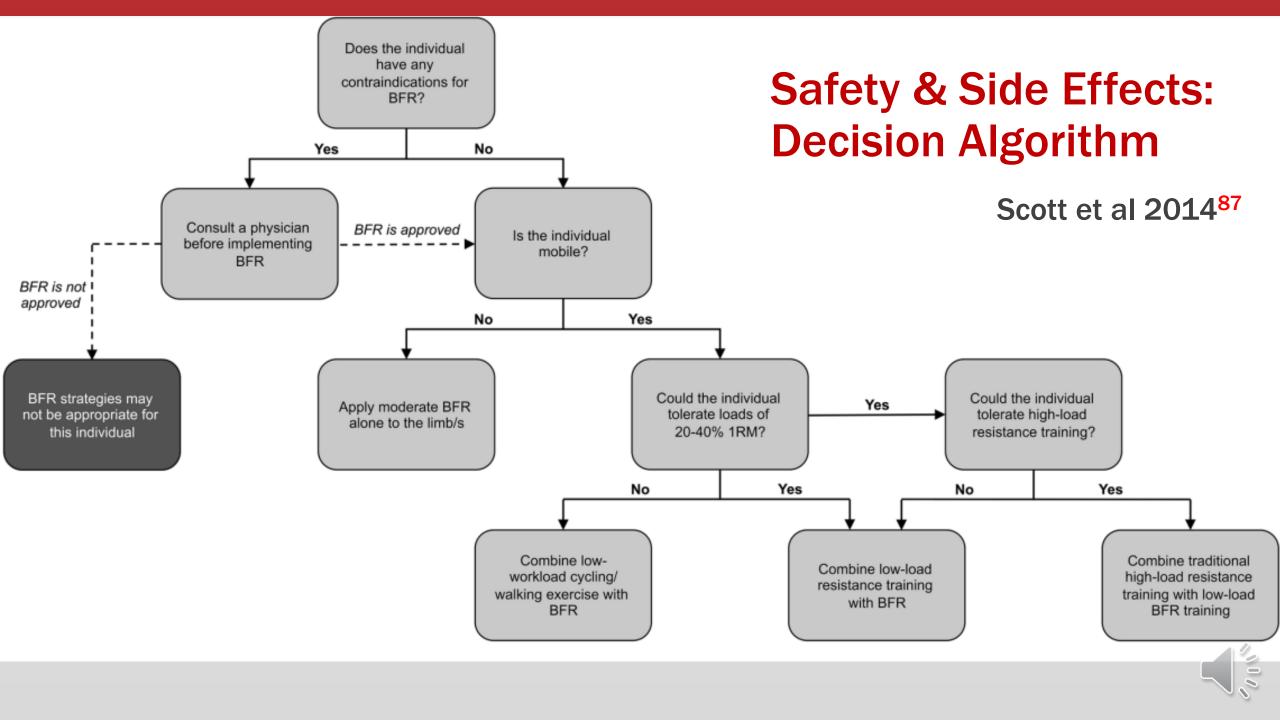


- Adherence to proper screening & testing
- 232 Facilities in Japan
- 12,827 Subjects
- Nov Dec 2016

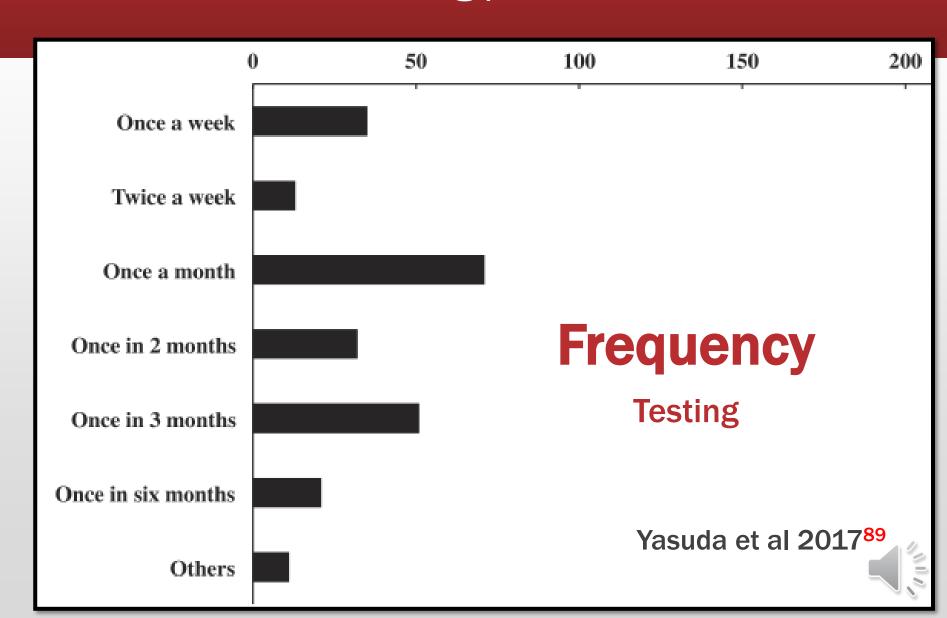


- Adherence to proper screening & testing
- 232 Facilities in Japan
- 12,827 Subjects
- Nov Dec 2016





- Adherence to proper screening & testing
- 232 Facilities in Japan
- 12,827 Subjects
- Nov Dec 2016



Intake Information	Criteria		If indicated, action(s) to be taken
Symptoms	☐ Chest Pain/Discomfort☐ Palpitations☐ Shortness of Breath	□ Dizziness□ Fainting□ Intermit. Claudication	☐ Exercise Tolerance Test
History of Disorder	□ Cardiovascular Disease□ Orthopedic or Joint Disor	der	☐ Exercise Tolerance Test☐ Orthopedic Examination
Lifestyle Disorders	☐ High Blood Pressure☐ Diabetes☐ Hyperlipidemia☐ Obesity		☐ Assess Severity of selected criteria
Family History	☐ Myocardial Infarction (He of 1 st degree relatives	art Attack) & sudden death	☐ Exercise Tolerance Test
Lifestyle Habits	□ Sedentary Lifestyle (worl□ Smoking□ Alcohol	kout <3 days/week)	☐ Lifestyle Guidance
Resting EKG	 ☐ Myocardial Infarction ☐ ST-T segment abnormali ☐ Ventricular arrhythmia ☐ Important Observations 	ty	□ Exercise Tolerance Test Nakajima 2011

Safety & Side Effects – Indications, Precautions, Contraindications

Disease	Indications	Precautions	Contraindications
High Blood Pressure	- 140-159/90-94 mmHg	- 160-179/95-99 mmHg*	- >180/>100mmHg - CTR >55% - Life threatening Arhythmia - Uric protein: 100 mg/dl - Hypertension in fundus oculi
Diabetes	- Fasting BG: 110-139 mg/dl	- Fasting BG: 140-249 mg/dl*	 - Fasting BG: ≥250 mg/dl - Urinary ketone body (+) - Diabetic Retinopathy (+)
Hyperlipidemia	- TC: 220-249 mg/dl - TG: 150-299 mg/dl	- TC: 250 mg/dl* - TG: 300 mg/dl*	
Obesity	- BMI: 24.0 – 29.9	- BMI: 24.0 – 29.9 & LE joint damage (ortho exam)	- BMI: >30

TC: Total Cholesterol; TG: total triglycerides; ★: M:>40 y/o or F:>50 y/o require 'Exercise Tolerance Test'

Safety & Side Effects – BFR Risk Stratification

Points	1	2	3	4	5
Criteria	☐ Age 40-58	□ Age > 60	☐ Varicose Veins LE	☐ Pregnancy	☐ Hx of DVT
	☐ Female	☐ Malignancy	☐ Immobility¥		☐ Antiphospholipid
	□ BMI 25-30	□ BMI >30	☐ A-Fib or Heart Failure	Antibody	
		☐ Hyperlipidemia			Syndrome
		☐ Leg Tourniquet			☐ Hx of PE
		☐ Oral Contraceptive			
		☐ Corticosteroid Use			
		☐ Quadriplegia			
		☐ HMG >20g/dL			
Column Score					
Total Score		≤ 1 Low Risk 2 Mild Risk 3 Moderate Risk 5 ≥ 4 High Risk 6 6 6			

HMG: hemoglobin; ¥: incapable of 8 hours thromboprophylaxis rehabilitation

Nakajima 201188



Safety & Side Effects

- 1. Systematic Reviews
- 2. Proposed Screening Processes
- 3. Study Example



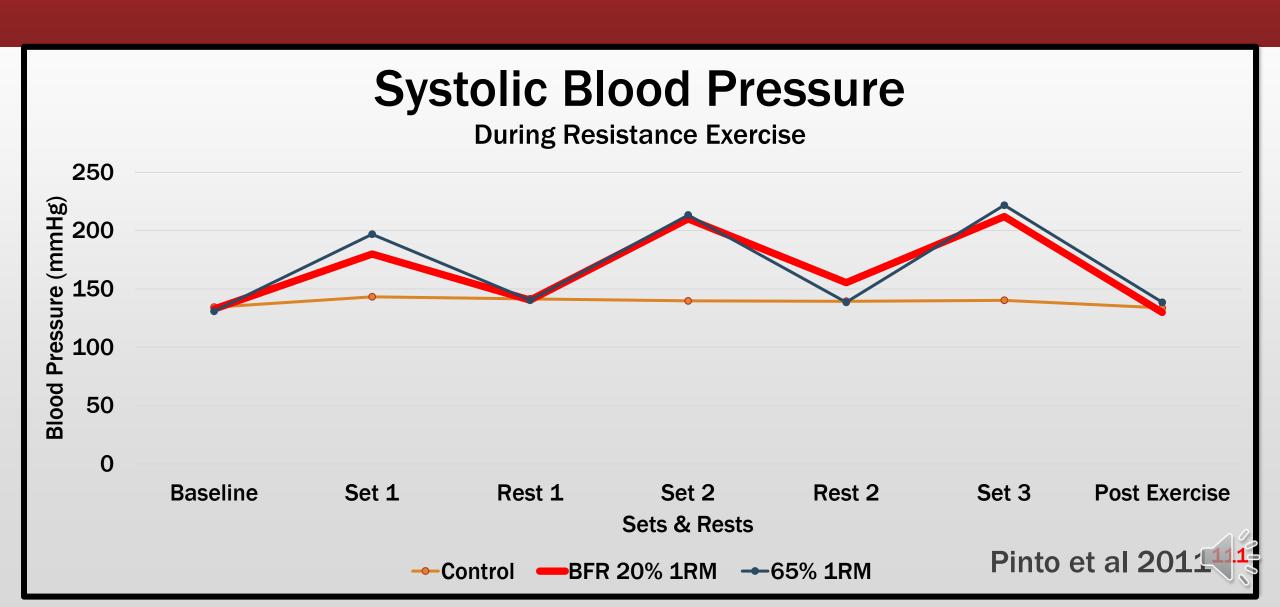
Method Variable	Value		
Study Design	Randomized Cross Over		
Subjects	N = 18, > 60 y/o		
Duration	3 sessions Each Session Randomized: 1. Control: No Exercise 2. BFR: 20% 1 RM 3. Strength: 65% 1 RM		
Cuff	Width: 90 mm		
Туре	Knee Extension		
Volume/Intensity	3x10 (1 min rest) Control: N/A BFR: 20% 1RM Strength: 65% 1 RM		
Tempo	2 sec CON / 2 sec ECC 40 sec/set 4 min/session		

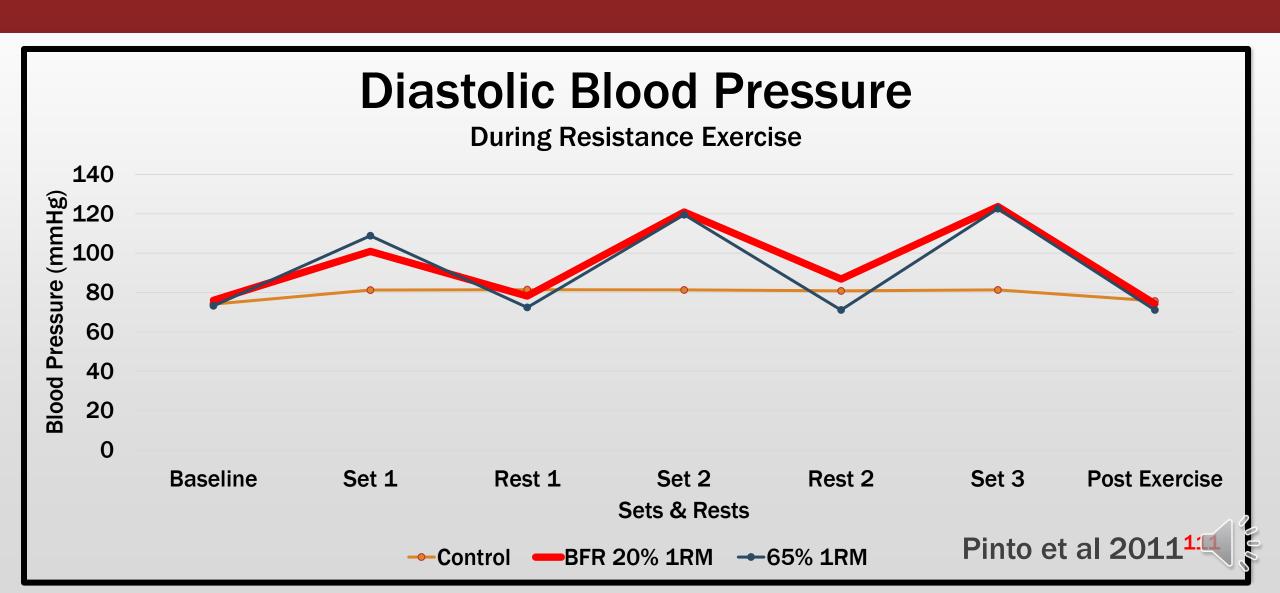


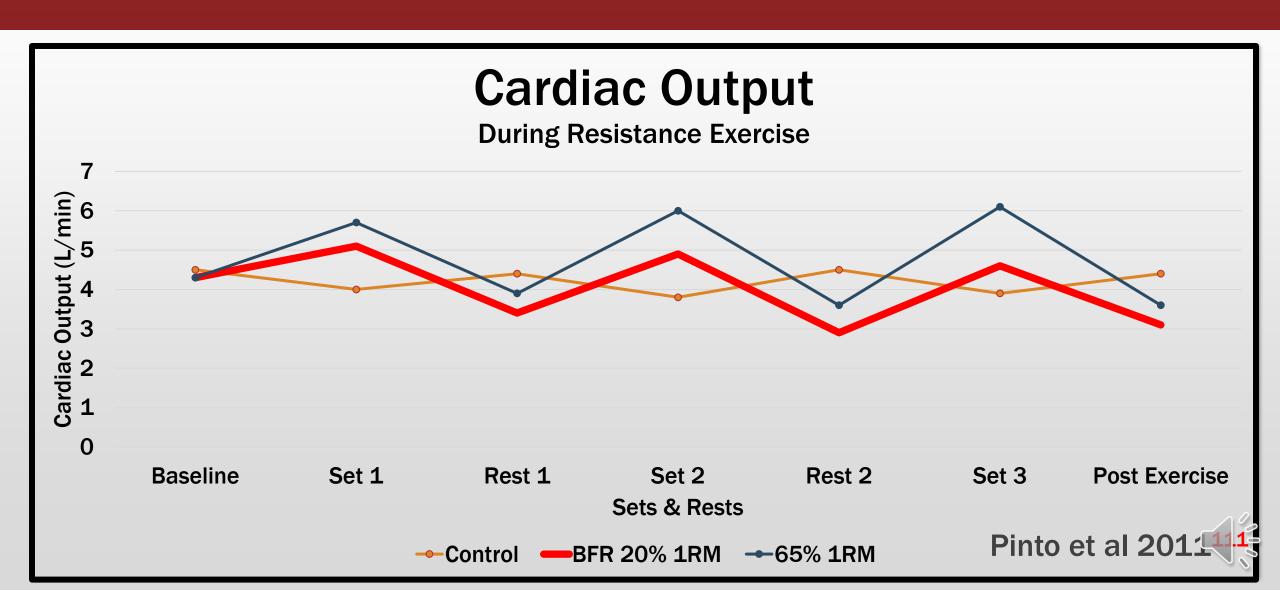
Pinto et al 2011¹¹¹











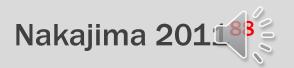
Conclusion & Summary



Safety & Side Effects – Follow Basic Principles

- 1. Confirm No Contraindications
- 2. Hemodynamically Unstable Patients should NOT partake
- 3. Thrombotic Diseased Patients are Contraindicated
- Explain **Petechial Hemorrhage Risk**
- 5. Individualize training

- 7. Pay Attention to faintness, dizziness, or light-headedness
- 8. Caution: Older (>65), Bedridden, Postoperative Patients (DVT risk)
- 9. AED Available
- **10.SHORT Term and LOW intensity Loads**
- 11. CONTRAINDICATION: Patient is sick
- 6. Build Relationship & Trust with Patient 12. If unsure about medical condition seek specialist consult



Questions, Comments, Feedback, Discussion...





- 1. Loenneke, Jeremy P., et al. "Blood flow restriction: how does it work?." Frontiers in physiology 3 (2012): 392.
- 2. Takarada, Y., Takazawa, H., and Ishii, N. (2000a). Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. *Med. Sci. Sports Exerc.* 32, 2035–2039.
- 3. Takarada, Y., Takazawa, H., Sato, Y., Takebayashi, S., Tanaka, Y., and Ishii, N. (2000b). Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J. Appl. Physiol.* 88, 2097–2106.
- 4. Yasuda, T., Brechue, W. F., Fujita, T., Shirakawa, J., Sato, Y., and Abe, T. (2009). Muscle activation during low- intensity muscle contractions with restricted blood flow. *J. Sports Sci.* 27, 479–489.
- 5. Ozaki, H., Sakamaki, M., Yasuda, T., Fujita, S., Ogasawara, R., Sugaya, M., et al. (2011). Increases in thigh muscle volume and strength by walk training with leg blood flow reduction in older participants. *J. Gerontol. A Biol. Sci. Med. Sci.* 66, 257–263.
- 6. Schliess, F., Richter, L., Vom Dahl, S., and Haussinger, D. (2006). Cell hydration and mTOR-dependent signal- ling. *Acta Physiol. (Oxf.)* 187, 223–229.
- 7. Suga, T., Okita, K., Morita, N., Yokota, T., Hirabayashi, K., Horiuchi, M., et al. (2010). Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J. Appl. Physiol.* 108, 1563–1567.
- 8. Loenneke, J. P., Fahs, C. A., Rossow, L. M., Abe, T., and Bemben, M. G. (2012a). The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med. Hypotheses* 78, 151–154.
- 9. Loenneke, J. P., Wilson, J. M., Marin, P. J., Zourdos, M. C., and Bemben, M. G. (2012b). Low intensity blood flow restriction training: a meta-analysis. *Eur. J. Appl. Physiol.* 112, 1849–1859.
- 10. Fry, C. S., Glynn, E. L., Drummond, M. J., Timmerman, K. L., Fujita, S., Abe, T., et al. (2010). Blood flow restriction exercise stimulates mTOR signaling and muscle protein synthesis in older men. *J. Appl. Physiol.* 108, 1199–1209.

- 11. Manini, T. M., Vincent, K. R., Leeuwenburgh, C. L., Lees, H. A., Kavazis, A. N., Borst, S. E., et al. (2011). Myogenic and proteolytic mRNA expression follow-ing blood flow restricted exercise. *Acta Physiol. (Oxf.)* 201, 255–263
- 12. Kubota, A., Sakuraba, K., Koh, S., Ogura, Y., and Tamura, Y. (2011). Blood flow restriction by low compressive force prevents disuse muscular weakness. *J. Sci. Med. Sport.* 14, 95–99.
- 13. Kubota, A., Sakuraba, K., Sawaki, K., Sumide, T., and Tamura, Y. (2008). Prevention of disuse muscular weakness by restriction of blood flow. *Med. Sci. Sports Exerc.* 40, 529–534.
- 14. Laurentino, G. C., Ugrinowitsch, C., Roschel, H., Aoki, M. S., Soares, A. G., Neves, M. Jr. et al. (2012). Strength training with blood flow restriction diminishes myostatin gene expression. *Med. Sci. Sports Exerc.* 44, 406–412.
- 15. Abe, T., Kearns, C. F., and Sato, Y. (2006). Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J. Appl. Physiol.* 100, 1460–1466.
- 16. VanWye, William R., Alyssa M. Weatherholt, and Alan E. Mikesky. "Blood Flow Restriction Training: Implementation into Clinical Practice." International journal of exercise science 10.5 (2017): 649.
- 17. Martín-Hernández, Juan, et al. "Adaptation of Perceptual Responses to Low-Load Blood Flow Restriction Training." Journal of strength and conditioning research 31.3 (2017): 765-772.
- 18. Kumagai, K., et al. "Cardiovascular drift during low intensity exercise with leg blood flow restriction." Acta Physiologica Hungarica 99.4 (2012): 392-399.
- 19. Kaufman, Kenton R., et al. "Physiological prediction of muscle forces—I. Theoretical formulation." Neuroscience 40.3 (1991): 781-792.
- 20. de Freitas, Marcelo Conrado, et al. "Role of metabolic stress for enhancing muscle adaptations: practical applications." World journal of methodology (2017): 46.

- 21. Goldberg AL, Etlinger JD, Goldspink DF, et al. Mechanism of work-induced hypertrophy of skeletal muscle. Med Sci Sports. 1975;7(3):185–98.
- 22. Spangenburg EE, Le Roith D, Ward CW, et al. A functional insulin-like growth factor receptor is not necessary for loadinduced skeletal muscle hypertrophy. J Physiol. 2008;586(1): 283–91. 38.
- 23. Vandenburgh H, Kaufman S. In vitro model for stretch-induced hypertrophy of skeletal muscle. Science. 1979;203(4377):265–8.
- 24. Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. Exerc Sports Sci Rev. 2009;37(2):78–85.
- 25. Suga T, Okita K, Morita N, et al. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. J Appl Physiol. 2009;106(4):1119–24.
- 26. Cook SB, Murphy BG, Labarbera KE. Neuromuscular function after a bout of low-load blood flow-restricted exercise. Med Sci Sports Exerc. 2013;45(1):67–74.
- 27. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. Sports Med. 2013;43(3):179–94.
- 28. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24(10):2857–72.
- 29. Goldspink G. Cellular and molecular aspects of muscle growth, adaptation and ageing. Gerodontology. 1998;15(1):35–43.
- 30. Zou K, Meador BM, Johnson B, et al. The a7b1-integrin increases muscle hypertrophy following multiple bouts of eccentric exercise. J Appl Physiol. 2011;111(4):1134–41.
- 31. Adams GR. Invited review: autocrine/paracrine IGF-I and skeletal muscle adaptation. J Appl Physiol. 2002;93(3):1159-67.
- 32. Tatsumi R, Liu X, Pulido A, et al. Satellite cell activation in stretched skeletal muscle and the role of nitric oxide and hepatocyte growth factor. Am J Physiol. 2006;290(6):C1487-94.

- 33. Uchiyama S, Tsukamoto H, Yoshimura S, et al. Relationship between oxidative stress in muscle tissue and weight-liftinginduced muscle damage. Pflugers Arch. 2006;452(1):109–16.
- 34. Takarada Y, Nakamura Y, Aruga S, et al. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. J Appl Physiol. 2000;88(1):61–5.
- 35. Takarada Y, Takazawa H, Sato Y, et al. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. J Appl Physiol. 2000;88(6): 2097–106. 7.
- 36. Takarada Y, Sato Y, Ishii N. Effects of resistance exercise combined with vascular occlusion on muscle function in athletes. Eur J Appl Physiol. 2002;86(4):308–14
- 37. Loenneke JP, Fahs CA, Rossow LM, et al. The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. Med Hypotheses. 2012;78(1):151–4
- 38. Febbraio MA, Pedersen BK. Contraction-induced myokine production and release: is skeletal muscle an endocrine organ? Exerc Sport Sci Rev. 2005;33(3):114–9
- 39. Schiaffino S, Dyar KA, Ciciliot S, et al. Mechanisms regulating skeletal muscle growth and atrophy. FEBS J. 2013;280(17): 4292–314.
- 40. Kawada S, Ishii N. Skeletal muscle hypertrophy after chronic restriction of venous blood flow in rats. Med Sci Sports Exerc. 2005;37(7):1144–50.
- 41. Pope ZK, Willardson JM, Schoenfeld BJ. A brief review: exercise and blood flow restriction. J Strength Cond Res. 2013;27(10):2914-26.



- 43. Pearson, Stephen John, and Syed Robiul Hussain. "A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy." Sports Medicine 45.2 (2015): 187-200.
- 44. Queme, Luis F., Jessica L. Ross, and Michael P. Jankowski. "Peripheral mechanisms of ischemic myalgia." Frontiers in cellular neuroscience 11 (2017): 419.
- 45. Ehrnborg C, Rosen T. Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports. Asian J Androl 2008; 10: 373–383
- 46. Takarada Y, Nakamura Y, Aruga S, Onda T, Miyazaki S, Ishii N. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. J Appl Physiol 2000; 88:61–65
- 47. Kawada S, Ishii N. Skeletal muscle hypertrophy after chronic restriction of venous blood flow in rats. Med Sci Sports Exerc 2005; 37: 1144–1150
- 48. Takano H, Morita T, Iida H, Asada K, Kato M, Uno K, Hirose K, Matsumoto A, Takenaka K, Hirata Y, Eto F, Nagai R, Sato Y, Nakajima T. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. Eur J Appl Physiol 2005; 95: 65–73
- 49. Anderson JE, Wozniak AC. Satellite cell activation on fibers: modeling events in vivo an invited review. Can J Physiol Pharmacol 2004; 82: 300–310.
- 50. Uematsu M, Ohara Y, Navas JP, Nishida K, Murphy TJ, Alexander RW, Nerem RM, Harrison DG. Regulation of endothelial cell nitric oxide synthese mRNA expression by shear stress. Am J Physiol 1995; 269:C1371– C1378

- 51. Reid MB. Role of nitric oxide in skeletal muscle: synthesis, distribution and functional importance. Acta Physiol Scand 1998; 162: 401–409
- 52. Snijders, Tim, et al. "Satellite cells in human skeletal muscle plasticity." Frontiers in physiology 6 (2015): 283.
- 53. Anderson JE. A role for nitric oxide in muscle repair: Nitric oxide-mediated activation of muscle satellite cells. Mol Biol Cell 2000; 11:1859–1874
- 54. Kraemer, William J., and David P. Looney. "Underlying mechanisms and physiology of muscular power." Strength & Conditioning Journal 34.6 (2012): 13-19.
- 55. Moritani T, Sherman WM, Shibata M, Matsumoto T, Shinohara M. Oxygen availability and motor unit activity in humans. Eur J Appl Physiol 1992; 64: 552–556
- 56. Idstrom JP, Subramanian VH, Chance B, Schersten T, Bylund-Fellenius AC. Energy metabolism in relation to oxygen supply in contracting rat skeletal muscle. Fed Proc 1986; 45: 2937–2941
- 57. Katz A, Sahlin K. Effect of decreased oxygen availability on NADH and lactate contents in human skeletal muscle during exercise. Acta Physiol Scand 1987; 131: 119–127
- 58. Moritani T, Muro M, Nagata A. Intramuscular and surface electromyogram changes during muscle fatigue . J Appl Physiol 1986 ; 60:1179–1185
- 59. Takarada Y,Nakamura Y, Aruga S,Onda T, Miyazaki S, Ishii N. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. J Appl Physiol 2000; 88:61–65
- 60. Takarada Y, Takazawa H, Sato Y, Takebayashi S, Tanaka Y, Ishii N. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. J Appl Physiol 2000; 88:2097–2106
- 61. Takarada Y, Takazawa H, Ishii N. Application of vascular occlusion diminsh disuse atrophy of knee extensor muscles. Med Sci Sports Exerc 2000; 32: 2035–2039

- 62. Wang X, Proud CG. The mTOR pathway in the control of protein synthesis. Physiology (Bethesda) 2006; 21: 362–369
- 63. Fujita S, Abe T, Drummond MJ, Cadenas JG, Dreyer HC, Sato Y, Volpi E, Rasmussen BB. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. J Appl Physiol 2007; 103: 903–910
- 64. Drummond MJ, Fujita S, Takashi A, Dreyer HC, Volpi E, Rasmussen BB. Human muscle gene expression following resistance exercise and blood flow restriction. Med Sci Sports Exerc 2008; 40: 691–698
- 65. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997; 387: 83–90
- 66. McPherron AC, Lee SJ. Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci USA 1997; 94: 12457-12461
- 67. Schuelke M, Wagner KR, Stolz LE, Hubner C, Riebel T, Komen W, Braun T, Tobin JF, Lee SJ. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med 2004; 350:2682–2688
- 68. Mesires NT, Doumit ME. Satellite cell proliferation and differentiation during postnatal growth of porcine skeletal muscle. Am J Physiol Cell Physiol 2002; 282: C899–9
- 69. McCroskery S, Thomas M, Maxwell L, Sharma M, Kambadur R. Myostatin negatively regulates satellite cell activation and self-renewal. J Cell Biol 2003; 162: 1135–1147
- 70. Grounds MD, Yablonka-Reuveni Z. Molecular and cell biology of skeletal muscle regeneration. Mol Cell Biol Hum Dis Ser 1993; 3: 210-256

- 71. Dodd S, Hain B, Judge A. Hsp70 prevents disuse muscle atrophy in senescent rats. Biogerontology 2008
- 72. Senf SM, Dodd SL, McClung JM, Judge AR. Hsp70 overexpression inhibits NF-kappaB and Foxo3a transcriptional activities and prevents skeletal muscle atrophy. FASEB J 2008; 22: 3836–3845
- 73. Naito H, Powers SK, Demirel HA, Sugiura T, Dodd SL, Aoki J. Heat stress attenuates skeletal muscle atrophy in hindlimb-unweighted rats. J Appl Physiol 2000; 88: 359 363
- 74. Takarada Y, Takazawa H, Ishii N. Application of vascular occlusion diminsh disuse atrophy of knee extensor muscles. Med Sci Sports Exerc 2000; 32: 2035–2039
- 75. Takarada Y, Tsuruta T, Ishii N. Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion. Jpn J Physiol. 2004;54(6):585–92.
- 76. Takada S, Okita K, Suga T, et al. Low-intensity exercise canincrease muscle mass and strength proportionally to enhancedmetabolic stress under ischemic conditions. J Appl Physiol.2012;113(2):199–205.
- 77. Sumide T, Sakuraba K, Sawaki K, et al. Effect of resistanceexercise training combined with relatively low vascular occlusion. J Sci Med Sport. 2009;12(1):107–12.
- 78. Loenneke JP, Pujol TJ. The use of occlusion training to produce muscle hypertrophy. Strength Cond J. 2009;31(3):77–84.
- 79. Moore DR, Burgomaster KA, Schofield LM, et al. Neuromuscular adaptations in human muscle following low intensity resistance training with vascular occlusion. Eur J Appl Physiol. 2004;92(4–5):399–406.
- 80. Kaijser L, Sundberg CJ, Eiken O, et al. Muscle oxidative capacity and work performance after training under local leg ischemia. J Appl Physiol. 1990;69(2):785–7.



- 81. Shinohara M, Kouzaki M, Yoshihisa T, et al. Efficacy of tourniquet ischemia for strength training with low resistance. Eur JAppl Physiol Occup Physiol. 1998;77(1–2):189–91
- 82. Loenneke JP, Kearney ML, Thrower AD, et al. The acute response of practical occlusion in the knee extensors. J Strength Cond Res. 2010;24(10):2831–4.
- 83. Heitkamp, H. C. "<u>Training with blood flow restriction. Mechanisms, gain in strength and safety</u>." The Journal of sports medicine and physical fitness 55.5 (2015): 446-456.
- 84. Loenneke, J. P., R. S. Thiebaud, and T. Abe. "Does blood flow restriction result in skeletal muscle damage? A critical review of available evidence." Scandinavian journal of medicine & science in sports 24.6 (2014): e415-422.
- 85. Slysz, Joshua, Jack Stultz, and Jamie F. Burr. "The efficacy of blood flow restricted exercise: A systematic review & meta-analysis." Journal of science and medicine in sport 19.8 (2016): 669-675.
- 86. Loenneke, Jeremy P., et al. "Low intensity blood flow restriction training: a meta-analysis." European journal of applied physiology 112.5 (2012): 1849-1859.
- 87. Scott, Brendan R., et al. "Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development." Sports medicine 45.3 (2015): 313-325.
- 88. Nakajima, T., Morita, T., Sato Y. "Key Considerations when conducting KAATSU training." Int. J KAATSU Training Res. 2011; 7:1-6.
- 89. Yasuda, T, Meguro M, Sato, Y, Nakajima T. "Use and safety of KAATSU training: results of national survey in 2016." Int. J KAATSU Training Res. 2017; 13:1-9.

- 90. Loenneke JP, Fahs CA, Rossow LM, et al. Effects of cuff width on arterial occlusion: implications for blood flow restricted exercise. Eur J Appl Physiol. 2012;112(8):2903–12.
- 91. Cook SB, Clark BC, Ploutz-Snyder LL. Effects of exercise load and blood-flow restriction on skeletal muscle function. Med Sci Sports Exerc. 2007;39(10):1708–13.
- 92. Loenneke JP, Kim D, Fahs CA, et al. Effects of exercise with and without different degrees of blood flow restriction on torque and muscle activation. Muscle Nerve. Epub 2014 Sep 3. doi:10.1002/mus.24448.
- 93. Wilson JM, Lowery RP, Joy JM, et al. Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. J Strength Cond Res. 2013;27(11):3068–75.
- 94. Loenneke JP, Thiebaud RS, Fahs CA, et al. Effect of cuff type on arterial occlusion. Clin Physiol Funct Imaging. 2013;33(4):325-7
- 95. Loenneke JP, Thiebaud RS, Fahs CA, et al. Blood flow restriction: Effects of cuff type on fatigue and perceptual responses to resistance exercise. Acta Physiol Hung. 2014;101(2):158–66.
- 96. Kacin A, Strazar K. Frequent low-load ischemic resistanceexercise to failure enhances muscle oxygen delivery and endur-ance capacity. Scand J Med Sci Sports. 2011;21(6):e231–41.
- 97. Spranger, Marty D., et al. "Blood flow restriction training and the exercise pressor reflex: a call for concern." American Journal of Physiology-Heart and Circulatory Physiology 309.9 (2015): H1440-H1452.
- 98. Patterson, Stephen D., and Richard A. Ferguson. "Increase in calf post-occlusive blood flow and strength following short-term resistance exercise training with blood flow restriction in young women." European journal of applied physiology 108.5 (2010): 1025-1033.

- 99. MacDougall JD, Tuxen D, Sale DG, Moroz JR, Sutton JR. Arterial blood pressure response to heavy resistance exercise. J Appl Physiol 58:785–790, 1985
- 100. Loenneke, J. P., et al. "Potential safety issues with blood flow restriction training." Scandinavian journal of medicine & science in sports 21.4 (2011): 510-518.
- 101. Mattar, Melina Andrade, et al. "Safety and possible effects of low-intensity resistance training associated with partial blood flow restriction in polymyositis and dermatomyositis." Arthritis research & therapy 16.5 (2014): 473.
- 102. Douris, Peter C., et al. <u>"THE EFFECTS OF BLOOD FLOW RESTRICTION TRAINING ON FUNCTIONAL IMPROVEMENTS IN AN ACTIVE SINGLE SUBJECT WITH PARKINSON DISEASE."</u> International Journal of Sports Physical Therapy 13.2 (2018).
- 103. Tennent, David J., et al. "Blood flow restriction training after knee arthroscopy: a randomized controlled pilot study." Clinical Journal of Sport Medicine 27.3 (2017): 245-252.
- 104. Iida, Haruko, et al. "Effects of walking with blood flow restriction on limb venous compliance in elderly subjects." Clinical physiology and functional imaging 31.6 (2011): 472-476.
- 105. Luebbers, Paul E., Emily V. Witte, and Johnathan Q. Oshel. <u>"The Effects Of Practical Blood Flow Restriction Training On Adolescent Lower Body Strength."</u> Journal of strength and conditioning research (2017).
- 106. Ozaki, Hayao, et al. "Increases in thigh muscle volume and strength by walk training with leg blood flow reduction in older participants." Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences 66.3 (2010): 257-263.
- 107. Ozaki, Hayao, et al. "Effects of 10 weeks walk training with leg blood flow reduction on carotid arterial compliance and muscle size in the elderly adults." Angiology 62.1 (2011): 81-86.

- 108. Jørgensen, A. N., et al. "Blood-flow restricted resistance training in patients with sporadic inclusion body myositis: a randomized controlled trial." Scandinavian journal of rheumatology (2018): 1-10.
- 109. Libardi, C. A., et al. "Effect of concurrent training with blood flow restriction in the elderly." International journal of sports medicine (2015).
- 110. Hackney, Kyle J., et al. "Blood flow-restricted exercise in space." Extreme physiology & medicine 1.1 (2012): 12.
- 111. Pinto, Roberta R., et al. "Acute resistance exercise with blood flow restriction in elderly hypertensive women: haemodynamic, rating of perceived exertion and blood lactate." Clinical physiology and functional imaging 38.1 (2018): 17-24.
- 112. Takarada, Yudai, Haruo Takazawa, and Naokata Ishii. "Applications of vascular occlusions diminish disuse atrophy of knee extensor muscles." Medicine and science in sports and exercise 32.12 (2000): 2035-2039.
- 113. Iversen, Erik, Vibeke Røstad, and Arne Larmo. "Intermittent blood flow restriction does not reduce atrophy following anterior cruciate ligament reconstruction." Journal of Sport and Health Science 5.1 (2016): 115-118.
- 114. Ohta, Haruyasu, et al. "Low-load resistance muscular training with moderate restriction of blood flow after anterior cruciate ligament reconstruction." Acta Orthopaedica Scandinavica 74.1 (2003): 62-68.
- 115. Slysz, Joshua T., and Jamie F. Burr. <u>"The effects of blood flow restricted electrostimulation on strength and hypertrophy."</u> Journal of sport rehabilitation 27.3 (2018): 257-262.
- 116. Bittar, S. T., et al. "Effects of blood flow restriction exercises on bone metabolism: a systematic review." Clinical physiology and functional imaging (2018).
- 117. Krieger JW (2010) Single vs. multiple sets of resistance exercise for muscle hypertrophy: a meta-analysis. J Strength Cond Res 24 (4):1150-1159

- 118. Thomas, H. J., B. R. Scott, and J. J. Peiffer. "Acute physiological responses to low-intensity blood flow restriction cycling." Journal of science and medicine in sport 21.9 (2018): 969-974.
- 119. Martín-Hernández, Juan, et al. "Adaptation of perceptual responses to low-load blood flow restriction training." Journal of strength and conditioning research 31.3 (2017): 765-772.
- 120. Domingos, Everton, and Marcos D. Polito. "Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis." Life sciences 209 (2018): 122-131.
- 121. Takarada, Yudai, et al. "Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans." Journal of applied physiology 88.6 (2000): 2097-2106.
- 122. Takarada, Yudai, Tomomi Tsuruta, and Naokata Ishii. "Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion." The Japanese journal of physiology 54.6 (2004): 585-592.
- 123. Kubota, Atsushi, et al. "Prevention of disuse muscular weakness by restriction of blood flow." Medicine and science in sports and exercise 40.3 (2008): 529-534.
- 124. Kubota, Atsushi, et al. "Blood flow restriction by low compressive force prevents disuse muscular weakness." Journal of science and medicine in sport 14.2 (2011): 95-99.
- 125. Centner, Christoph, et al. "Effects of Blood Flow Restriction Training on Muscular Strength and Hypertrophy in Older Individuals: A Systematic Review and Meta-Analysis." Sports Medicine (2018): 1-15.

- 126. Nakajima T, Kurano M, Iida H, Takano H, Oonuma H, Morita T, et al. Use and safety of KAATSU training: results of a national survey. Int J KAATSU Train Res. 2006;2:5–13.
- 127. Bowman, Eric N., et al. "Proximal, Distal, and Contralateral Effects of Blood Flow Restriction Training on the Lower Extremities: A Randomized Controlled Trial." Sports health (2019): 1941738118821929.
- 128. Bennett, Hunter, and Flynn Slattery. "Effects of Blood Flow Restriction Training on Aerobic Capacity and Performance: A Systematic Review." The Journal of Strength & Conditioning Research 33.2 (2019): 572-583.
- 129. Martín-Hernández, Juan, et al. "Syncope Episodes and Blood Flow Restriction Training." Clinical Journal of Sport Medicine 28.6 (2018): e89-e91.
- 130. da Cunha Nascimento, Dahan, et al. "Effects of blood flow restriction exercise on hemostasis: a systematic review of randomized and non-randomized trials." International Journal of General Medicine 12 (2019): 91.
- 131. Neto, Gabriel R., et al. "Effects of resistance training with blood flow restriction on haemodynamics: a systematic review." Clinical physiology and functional imaging 37.6 (2017): 567-574.
- 132. Bond, Colin W., et al. "Blood Flow Restriction Resistance Exercise as a Rehabilitation Modality Following Orthopaedic Surgery: A Review of Venous Thromboembolism Risk." journal of orthopaedic & sports physical therapy 49.1 (2019): 17-27.
- 133. Lixandrao, Manoel E., et al. "Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance training associated with blood-flow restriction: a systematic review and meta-analysis." Sports medicine 48.2 (2018): 361-378.
- 134. Törpel, Alexander, et al. "Strengthening the Brain—Is Resistance Training with Blood Flow Restriction an Effective Strategy for Cognitive Improvement?." Journal of clinical medicine 7.10 (2018): 337.
- 135. May, Anthony K., Aaron P. Russell, and Stuart A. Warmington. "Lower body blood flow restriction training may induce remote muscle strength adaptations in an active unrestricted arm." European journal of applied physiology 118.3 (2018): 617-627.

136. Cristina-Oliveira, M., Meireles, K., Spranger, M. D., Oleary, D. S., Roschel, H., & Peçanha, T. (2019). <u>Clinical safety of blood flow restricted training?</u>

<u>A comprehensive review of altered muscle metaboreflex in cardiovascular disease during ischemic exercise</u>. American Journal of Physiology-Heart and Circulatory Physiology. doi: 10.1152/ajpheart.00468.2019

