Aubry et al., *Cogent Medicine* (2018), 5: 1512352
https://doi.org/10.1080/2331205X.2018.1512352

cogent medicine

SPORTS & EXERCISE | RESEARCH ARTICLE

The effect of creatine supplementation on the response of central and peripheral pulse wave velocity to high-intensity resistance exercise

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Received: 06 July 2018
Accepted: 13 August 2018
First Published: 17 August 2018

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Reviewing editor:
Andrew Thomas Del Pozzi, Kinesiology, Ball State University, USA

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Abstract: Following a bout of high-intensity resistance exercise, a transient increase in arterial stiffness, as measured through central pulse wave velocity has been shown to occur. Preliminary creatine supplementation research has demonstrated the potential for creatine to alter select measures of arterial stiffness. This study examines whether creatine supplementation independently influences the resistance exercise response of both central and peripheral pulse wave velocity. Forty healthy participants completed a high-intensity knee extension protocol demonstrated to cause increases in pulse wave velocity, both before and after 7 days of supplementing with creatine (n = 21) or placebo (n = 19) at 21 g/day. Resting and post-exercise measures of blood pressure, central (immediately and 20 min post) and peripheral (25 min post) pulse wave velocity were collected. No significant difference in the response of central pulse wave velocity was observed between creatine or placebo supplementation ($p < 0.05$) following high-intensity resistance exercise, as both groups revealed increases from pre-exercise to immediately post-exercise ($p < 0.01$). Similarly, no differences between groups were apparent for the peripheral pulse wave velocity response to exercise ($p = 0.4$). The

ABOUT THE AUTHOR

The Human Performance and Health Research Lab (HPL) at the University of Guelph focuses their research on human performance, exercise physiology and the prevention and management of chronic disease, particularly as it relates to cardiovascular health. Much of the research in the HPL focuses on understanding the effect of exercise on vascular properties such as the cause, effect and clinical significance of exercise induced alterations of arterial stiffness on health. This study conducted in the HPL focuses on the effect of high intensity exercise on arterial stiffening and whether creatine supplementation could be a potential intervention for influencing the demonstrated stiffening effect.

PUBLIC INTEREST STATEMENT

Creatine is a widely used supplement known to improve high-intensity exercise performance over short bouts. High-intensity exercise is associated with a temporary stiffening of the large arteries that transport blood through the body, and the added cardiovascular stress of stiffer arteries could increase the risk of cardiovascular events in those with underlying disease. This study investigated whether a creatine supplement could reduce artery stiffening after high-intensity exercise, in addition to improving muscular strength. To test this concept, young healthy adults had the stiffness of their arteries measured before engaging in intense strength-training exercise. Following exercise on two occasions, the stiffness of their arteries was measured again after identical workouts, one with and one without having taken creatine. The results did not show that creatine reduced arterial stiffening, as was expected. As such, creatine is not supported as a way to decrease cardiovascular risk while participating in intense exercise.

current evidence does not support creatine supplementation as an effective intervention for reductions in arterial stiffness occurring with resistance exercise.

Subjects: Nutrition; Physiology; Clinical Nutrition

Keywords: Arterial stiffness; cardiovascular; blood pressure; hemodynamics; health; isokinetics

1. Introduction

A loss of central arterial distensibility is a recognized risk factor for cardiovascular disease (Laurent et al., 2006; Vlachopoulos, Aznaouridis, & Stefanadis, 2010), and can be measured via pulse wave velocity (PWV), the current gold standard assessment for arterial stiffness (Laurent et al., 2006). An increase in central (aortic) PWV of 1 m/s, occurring with age and disease, has shown to be associated with a 15% increased risk of cardiovascular disease (Vlachopoulos et al., 2010). A single bout of resistance exercise has demonstrated to transiently increase central PWV up to 20 min after exercise (Fahs, Heffernan, & Fernhall, 2009; Heffernan, Collier, Kelly, Jae, & Fernhall, 2007; Nitzsche et al., 2016), and it has been suggested that with repeated exposure to transient increases in PWV, more chronic modulations to the vasculature may occur (Miyachi, 2013). In contrast, the propagation of a pulse wave through the limbs of the body, or peripheral PWV (pPWV), has demonstrated to decrease following a bout of acute exercise—possibly as a result of flow mediated dilation (Heffernan et al., 2006).

Creatine supplementation is broadly supported as an ergogenic aid to increase performance in high-intensity and intermittent exercise such as resistance training (Izquierdo, Ibañez, González-Badillo, & Gorostiaga, 2002; Kreider, Ferreira, & Almada, 1998; Volek et al., 1997). Additionally, creatine supplementation has been purported to influence the cardiovascular system, by attenuating elevations in PWV and blood pressure with exercise (Sanchez-Gonzalez, Wieder, Kim, Vicil, & Figueroa, 2011). It is suggested that this may occur as a result of a reduced metabolite accumulation with exercise following creatine supplementation (Balsom, Soderlund, Sjodin, & Ekblom, 1995), and thus blunting of the metaboreflex response and the associated increase in sympathetic activation (Davies, Frenneaux, Campbell, & White, 2007), which in turn alters vasoconstriction and blood pressure.

To date, evidence demonstrating an attenuation of PWV elevation following resistance exercise with creatine has focused on brachial-ankle PWV (baPWV) (Sanchez-Gonzalez et al., 2011). Assessment of baPWV encompasses both central and peripheral vasculature, as it measures PWV using pulse transit times collected at distal portions of both the upper and lower limbs, thus including an effect of the central vasculature (descending aorta) (Sugawara et al., 2005; Tanaka et al., 2009), but not measuring it specifically or directly. Elevations in central PWV are demonstrably correlated with increased cardiovascular disease (Vlachopoulos et al., 2010); whereas pPWV, appears to have little prognostic value (Heffernan et al., 2006). As such, it is possible that the demonstrated ability of creatine supplementation to attenuate elevations in PWV with resistance exercise (Sanchez-Gonzalez et al., 2011) is being influenced by changes in peripheral vasculature, giving creatine supplementation limited value for meaningfully affecting cardiovascular event risk, acutely or chronically. Carotid-femoral PWV (cfPWV) is best representative of central aortic arterial stiffness (Weber et al., 2009), and unlike baPWV does not consider peripheral vasculature.

The purpose of this study is to investigate the independent effects of creatine supplementation on cfPWV following resistance exercise. Peripheral PWV was also measured independently. We hypothesized that creatine supplementation would attenuate the well characterized acute increase in cfPWV and blood pressure which occurs following resistance exercise. Reductions in

this cardiovascular stress could have meaningful implications for persons who would benefit from exercise training but are at an elevated risk for an exercise-related adverse cardiovascular event.

2. Methods

A total of 45 participants were recruited for this study, with 40 participants completing all components and 5 withdrawing for non-study related reasons. All subjects were aware of experimental procedures and risks and gave written informed consent in accord with the experimental protocol and the declaration of Helsinki. All procedures were approved prior to study onset by the University of Guelph institutional research ethics board.

The study used a randomized, double blind, placebo-controlled design. Participants visited the lab on three occasions consisting of 1) eligibility screening, 2) baseline testing and 3) experimental testing. During the screening visit, participants were asked to disclose their health history, current medications and previous creatine supplement use, and were familiarized to the exercise protocol and cardiovascular measurements. Participant inclusion criteria required participants to be: between the ages of 18–45 years, ostensibly healthy (as confirmed using a PAR-Q^{+}), with a BMI < 30; while exclusion criteria called for the removal of participants who were: pregnant, had significant medical disorders, currently used any pharmaceutical or performance enhancing drugs/supplements, or any participant who used creatine supplementation within 3 months of recruitment. During both the baseline and experimental visit, participants completed identical testing sessions consisting of a high-intensity resistance exercise protocol and pre- and post-exercise cardiovascular measurements of blood pressure, cfPWV and pPWV of the leg (Figure 1). Participants were instructed to abstain from intense exercise for 48 h, coffee and alcohol for 12 h, and heavy meals for 3 h prior to testing and to maintain their regular exercise regime between visits. Participants rested supine for 10 min prior to blood pressure and central and pPWV measurements. Blood pressure and central PWV measures were collected immediately and 20 min following the exercise protocol while pPWV of the leg was measured 25 min following the protocol, to accommodate for time required to collect each measure (Figure 1).

Following baseline testing, participants were randomized to either an oral creatine group (n = 21) or an oral placebo group (n = 19). Both the creatine monohydrate (GNC, Pittsburgh PA) and dextrose placebo (Sports Supplements Ltd., UK) were taken as an oral powder mixed with water at a dose of 21 g/day (3 doses of 7 g) for 7 days. Participants reported compliance and returned all supplement containers for confirmation.

The exercise protocol consisted of single leg maximal knee extension exercise at an angular velocity of 180°/second on a custom-made isokinetic dynamometer, validated in our lab to a HUMAC NORM Dynamometer (CSMi Medical Solutions, Stoughton, MA) (data in press). Participants were positioned on the dynamometer with identical settings for each visit, including a 90° angle at the knee joint with shoulders and waist restricted using straps. The exercise protocol consisted of 5 sets of 15 maximal repetitions with 1-minute rest between sets.

Supine brachial blood pressure was measured in triplicate using an automated oscillometric blood pressure device (bpTRU, Coquitlam, British Columbia), with the first measure discarded and

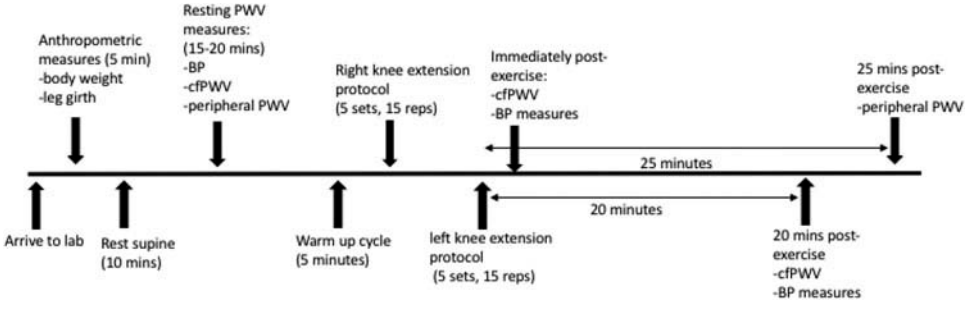

Figure 1. Procedural timeline of both baseline and experimental testing days investigating the effect of 7 days of creatine supplementation on the cardiovascular and hemodynamic response to intense single-leg resistance exercise.

the average of the last two used for analysis. PWV was calculated as the path length distance of the pulse wave over transit time. Measurement was accomplished with a validated semi-automated system (SphygmoCor CPVH, Atcor Medical, Sydney Australia), using techniques in accordance with Clinical Applications on Arterial Stiffness, Task Force III (Van Bortel et al., 2002). Pressure waveforms were obtained 1) from the common carotid artery and femoral artery, for central PWV and 2) from the femoral and posterior tibialis artery, for pPWV. A 10 sample of waveforms was captured consecutively at each site, using ECG gating to track the transit time across cardiac cycles. Pulse wave arrival was defined by the initial systolic upstroke of each pulse wave using the intersecting tangents method. Path length was measured as the straight-line distance from the carotid artery to the sternal notch, subtracted from the distance from the sternal notch to the femoral site, as this best represents the travel length of the pulse wave across the central vasculature (Weber et al., 2009). The pPWV path length was measured as the direct distance from the femoral artery measurement site to that of the posterior tibialis artery.

Unpaired Student's t-tests were used to compare baseline physical characteristics (age, height, weight, BMI, leg girth) between the creatine and placebo groups.

A Paired t-test was used to compare (without supplementation) pPWV of the leg, before and after the exercise protocol, as well as to compare pre to post supplementation of resting body mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and cfPWV in the creatine and placebo groups separately.

To understand the expected effect of the resistance exercise protocol across time before supplementation (baseline testing; on SBP, DBP, MAP, cfPWV) repeated measures ANOVA was used across the 3 time points (pre-, immediately post, 20 min post). To control the potential influence of changes in blood pressure, cfPWV measures were examined both with and without correcting for MAP (cfPWV/MAP) (Townsend et al., 2015).

The effect of creatine supplementation compared to placebo across time on SBP, DBP, MAP, cfPWV and cfPWV/MAP following the resistance exercise protocol was analyzed using a repeated measure 3 (time) x 2 (group) ANOVA.

The effect of supplementation on the resistance exercise response of pPWV of the leg was analyzed using a 2 (time) x 2 (group) ANOVA. All values are reported as mean ± SD. A priori significance was set at < 0.05.

3. Results

Descriptive participant characteristics can be found in Table 1. No group differences existed at baseline in subject characteristics. Participant compliance was > 98% for both creatine and placebo supplements.

Table 1. Baseline Characteristics of participants in the oral creatine group (n = 21) and the oral placebo group (n = 19)

	Oral Creatine (n = 21)	Oral Placebo (n = 19)
Sex (M/F)	10/11	10/9
Age (years)	21.8 ± 2.3	22.5 ± 3.2
Height (cm)	170.2 ± 9.7	171.8 ± 8.2
Weight (kg)	68.3 ± 11.0	70.3 ± 9.6
BMI	23.4 ± 2.0	23.7 ± 2.7
Leg Girth Right (cm)	49.0 ± 3.9	49.9 ± 3.9
Leg Girth Left (cm)	48.6 ± 4.1	50.0 ± 3.8

Prior to any supplementation, an expected baseline time effect was apparent in all participants following the high-intensity resistance exercise protocol for SBP, MAP and cfPWV ($p < 0.001$), such that there was a significant increase in these variables from pre-exercise to immediately post-exercise, followed by decreases back to baseline immediately post-exercise to 20 min post-exercise (Table 2). Notably, this temporal effect disappears when correcting for MAP (cfPWV/MAP). Prior to supplementation, no change was observed for pPWV of the leg from pre- to post-exercise ($p = 0.2$) (Table 2).

Resting body mass, BP, and cfPWV did not change significantly from pre to post supplementation in either the creatine group *(body mass: 0.41 ± 0.95 kg, p = 0.07; SBP: −1.23 ± 5.4, p = 0.3; DBP: −0.33 ± 4.5 mmHg, p = 0.7; MAP: 0.63 ± 3.2 mmHg,p = 0.4; cfPWV: 0.0 ± 0.7 m/s p = 0.9)* or the placebo group *(body mass: 0.35 ± 2.1 kg, p = 0.07; SBP: 0.11 ± 6.6 mmHg, p = 0.3; DBP: −1.5 ± 6.0 mmHg, p = 0.7; MAP: −0.95 ± 5.6 mmHg,p = 0.4; cfPWV: −0.28 ± 0.58 m/s p = 0.05)*

Following 7 days of creatine or placebo supplementation, the temporal response to high-intensity resistance exercise was not altered from baseline for cfPWV, MAP or cfPWV/MAP (Figure 2, inset A-C). No group effect (between creatine and placebo; $p = 0.5$) or group by time interaction ($p = 0.1$) was found for any outcome.

No significant time, group or group by time interaction (all $p > 0.4$) was found for pPWV of the leg (Figure 2, inset D).

4. Discussion

The major novel finding of the current study was that increases in cfPWV and blood pressure were not attenuated following a high-intensity resistance exercise protocol, after 7 days of creatine supplementation. This result is contrary to the findings of Sanchez-Gonzalez et al., (2011), which demonstrate an attenuation in the increase of baPWV, and SBP, following a similar maximal single-leg knee extension protocol in participants having supplemented with creatine for 3 weeks.

The discrepancy of the current results with those of Sanchez-Gonzalez et al. may be attributed, at least in part, to the methodological difference for measuring PWV. In the current study cfPWV and pPWV were measured and interpreted independently, as they have different prognostic values and respond differentially to exercise. In contrast, Sanchez-Gonzalez et al. used baPWV (Sanchez-Gonzalez et al., 2011), which uses both the upper and lower limbs as well as the descending aortic portion simultaneously (Sugawara et al., 2005). Both cfPWV and baPWV have been validated for clinical use and have shown to be broadly correlated with cardiovascular disease (Ohkuma et al., 2017); however, there are major differences between these two measurements, which could

Table 2. Vascular stiffness and pressure measures prior, immediately following and 20 min following a high-intensity resistance exercise protocol in the absence of creatine supplementation (n = 40)

	Pre-Exercise (Rest)	Post-exercise (0–5 min)	Post-exercise (20 mins)
cfPWV (m/s)	5.7 ± .80	6.1 ± .80*	5.7 ± .70†
SBP (mmHg)	107 ± 9.4	120 ± 11.7*	109 ± 9.5†
DBP (mmHg)	68 ± 7.6	69 ± 6.6	69 ± 6.9†
MAP (mmHg)	81 ± 7.2	86 ± 7.4*	82 ± 6.7†
cfPWV/MAP (AU)	0.07 ± .009	0.07 ± 0.007	0.07 ± .008
pPWV (m/s)	9.0 ± 1.1	-	8.7 ± 1.5

*Significance from pre-exercise ($p < 0.05$)

† Significance from immediately post-exercise ($p < 0.05$)
Note: leg PWV was measured 25 min post-exercise

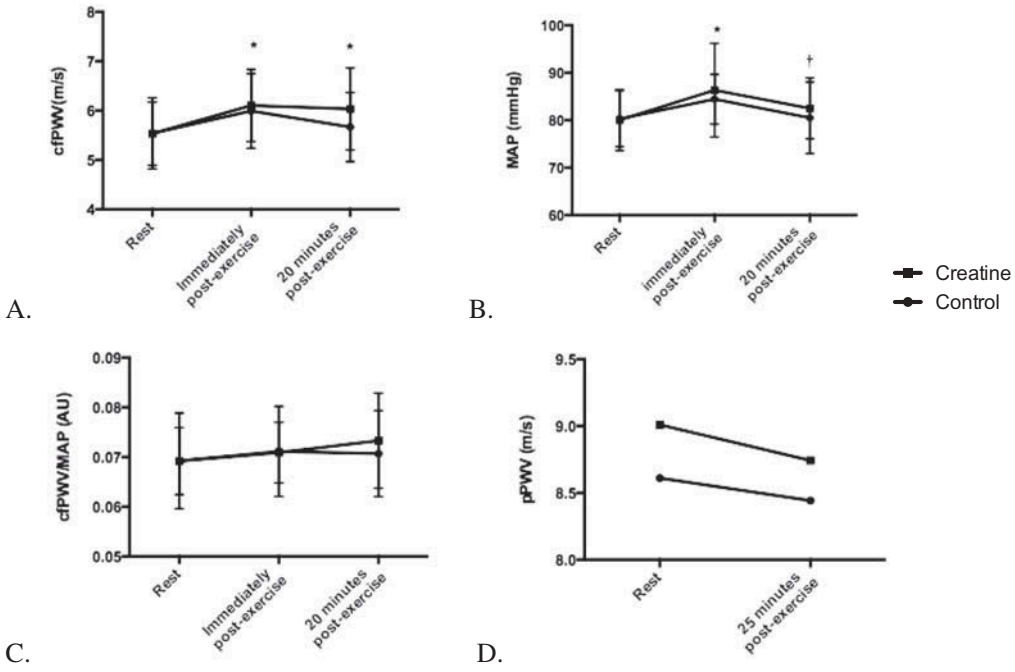

Figure 2. Comparison of creatine (squares) and placebo (circles) supplementation groups across time, at rest, immediately post-exercise and 20 min post-exercise. In set A) carotid-femoral pulse wave velocity (cfPWV), B) Mean arterial pressure (MAP) and across time and C) carotid-femoral pulse wave velocity (cfPWV)/ mean arterial pressure (MAP). Comparison at rest and 25 min post-exercise in D) peripheral PWV (pPWV) *Time effect; significantly difference from Rest. † significantly different from Rest. No differences occurred at any time point between groups.

contribute to demonstrated differences in the results found between these two indices with regard to the effects of creatine supplementation on vascular properties. Measurement of baPWV appears to overestimate central PWV by approximately 20% when compared to cfPWV (Tanaka et al., 2009) and Sugawara et al. have shown that 23% of the variance in baPWV was explained by leg PWV, demonstrating the significant contribution of peripheral arterial stiffness in the baPWV calculation (Sugawara et al., 2005; Sugawara & Tanaka, 2015). As such, it is highly likely that changes occurring in the peripheral vasculature would influence the results measured with baPWV. However, we did not observe a difference in the influence of creatine and placebo supplementation on peripheral leg PWV changes specifically with resistance exercise, therefore, it appears unlikely that creatine affects cfPWV differently from baPWV.

Differences in results between the two studies could also be related to dissimilarities in creatine products and supplementation protocols, as Sanchez-Gonzalez et al. used a creatine supplementation protocol of 10g/day for 3 weeks (Sanchez-Gonzalez et al., 2011), while the current study supplemented at 21g/day for 7 days. However, it has been demonstrated in the literature that creatine accumulation in the muscle and plasma with supplementation will be saturated following only 2 days of supplementation, and any additional creatine will not increase total creatine in the muscle (Harris, Soderlund, & Hultman, 1992) and, therefore, it is unlikely the difference in protocols had a major effect on the differing results. Both studies used a demographic of young participants; however, the population in Sanchez-Gonzalez was male participants only (Sanchez-Gonzalez et al., 2011), while the current study consisted of both male and female participants. There does not appear to be sex differences with creatine use on performance (Mesa, Ruiz, González-Gross, Gutiérrez Sáinz, & Castillo Garzón, 2002); however, sex differences in creatine use on vasculature has not yet been studied.

The demonstrated elevations in cfPWV, SBP and MAP that occurred immediately following the high-intensity resistance exercise protocol are consistent with the literature. Multiple studies have reported increases in cfPWV of 0.5–1.0 m/s following exercise (Fahs et al., 2009; Heffernan et al., 2007; Nitzsche et al., 2016), while we report an increase in cfPWV of approximately 0.4 m/s. As blood pressure is known to influence changes in arterial stiffness, and changes in pressure and vessel diameter will inevitably lead to changes in wall stiffness (Kim et al., 2007), cfPWV was

divided by MAP to control for this confounding variable (Townsend et al., 2015). When correcting cfPWV for changes in MAP, there was no longer any significant change in arterial stiffness (cfPWV/MAP) following exercise, confirming the strong influence of blood pressure on transient PWV changes. This also signifies that changes observed are hemodynamic in nature. Much of the literature fails to correct for blood pressure changes with exercise testing (Heffernan et al., 2007; Thiebaud et al., 2016; Yoon et al., 2010), and the conclusions could be misleading as to whether these acute increases in cfPWV are related to alterations in the stiffness of the vessel wall or merely the effect of a change in pressure. Sanchez-Gonzalez et al. also reported a significant attenuation of SBP along with baPWV following resistance exercise with creatine supplementation (Sanchez-Gonzalez et al., 2011), which we did not observe, and this further highlights a potential role of blood pressure on changes in PWV (Kim et al., 2007). Although Sanchez-Gonzalez et al. did not specifically correct for this alteration in BP when analyzing the changes in baPWV (Sanchez-Gonzalez et al., 2011), our own calculations using their reported data shows this to be correct.

As with all research, there are limitations to the current study. Measurements of cfPWV and blood pressure were taken immediately and 20 min following exercise, while pPWV was taken 25 min following exercise. Ideally, such measures would be taken during the exercise of interest; however, current technology does not permit this, thus post-exercise measures are the best surrogate available. Furthermore, the temporal pattern and magnitude of changes in blood pressure, cfPWV and pPWV between these time points are unknown and it is possible that undetected differences in the response were occurring during this time. While supplementation compliance was not perfect, it is unlikely the doses missed had an effect on the results, as the maximum reported dose missed was 4 (27g) over 7 days (98% compliance across all participants), and it has been demonstrated in the literature, that a much lower cumulative creatine supplementation dose is sufficient to increase muscle and plasma creatine stores and have a bioactive effect (Green, Simpson, Littlewood, MacDonald, & Greenhaff, 1996; Harris et al., 1992). Furthermore, our study was well powered with large experimental and placebo groups to overcome the effects of outlying data points.

The present study demonstrates that 7 days of creatine supplementation does not influence the cfPWV, blood pressure or pPWV response to a high-intensity single leg knee extension protocol in young, healthy participants. Therefore, contrary to previous results, we do not find evidence supporting creatine supplementation for the purpose of cardiovascular or hemodynamic alteration in young, healthy adults.

Funding
The authors received no direct funding for this research.

Competing interests
The authors declare no competing interests.

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Citation information
Cite this article as: The effect of creatine supplementation on the response of central and peripheral pulse wave velocity to high-intensity resistance exercise, Rachel L. Aubry, Alanna K. Whinton & Jamie F. Burr, *Cogent Medicine* (2018), 5: 1512352.

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Cogent Medicine **(ISSN: 2331-205X) is published by Cogent OA, part of Taylor & Francis Group.**