

ACUTE CREATINE MONOHYDRATE SUPPLEMENTATION: A DESCRIPTIVE PHYSIOLOGICAL PROFILE OF RESPONDERS VS. NONRESPONDERS

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ABSTRACT. Syrotuik, D.G., and G.J. Bell. Acute creatine monohydrate supplementation: a descriptive physiological profile of responders vs. nonresponders. *J. Strength Cond. Res.* 18(3):610–617. 2004.—The purpose of this study was to describe the physiological profile of responders (>20 mmol·kg⁻¹ dry weight [dw] increase in total intramuscular creatine monohydrate [Cr] + phosphorylated creatine [PCr]) versus nonresponders (<10 mmol·kg⁻¹ dw increase) to a 5-day Cr load (0.3 g·kg⁻¹·d⁻¹) in 11 healthy men (mean age = 22.7 years). Pre-post 5-day cellular measures included total resting Cr content (Cr + PCr), fiber type composition, and fiber type cross-sectional area (CSA) determined from muscle biopsies of the vastus lateralis. Body mass, daily dietary intake, 24-hour urine outputs, urinary Cr and creatinine (CrN), and strength performance measures (1 repetition maximum [1RM] bench and leg press) were also assessed before and after the 5-day loading period. Results indicated that there were 3 levels of response to the 5-day supplementation: responders (R), quasi responders (QR), and nonresponders (NR) with mean changes in resting Cr + PCr of 29.5 mmol·kg⁻¹ dw ($n = 3$), 14.9 mmol·kg⁻¹ dw ($n = 5$), and 5.1 mmol·kg⁻¹ dw ($n = 3$), respectively. The results support a person-by-treatment interaction to acute Cr supplementation with R possessing a biological profile of lowest initial levels of Cr + PCr, greatest percentage of type II fibers, and greatest preload muscle fiber CSA and fat-free mass. Responders also showed improvement in 1RM leg press scores following the 5-day loading period. NR had higher preload levels of Cr + PCr, less type II muscle fibers, small preload muscle CSA, and lower fat-free mass and displayed no improvements in 1RM strength scores. The results suggest that to be considered a responder to acute oral supplementation, a favorable preexisting biological profile may determine the final extent to which an individual responds to supplementation. Physiologic profiles of nonresponders appear to be different and may limit their ability to uptake Cr. This may help partially explain the reported equivocal performance findings in the Cr supplementation literature.

KEY WORDS. ergogenic, person-by-treatment, phosphocreatine, creatine, strength, muscle fiber type, fiber area

INTRODUCTION

Support scientists have recognized for decades that there are large variances in the response to certain interventions. The literature supports the notion of nonresponders to a particular treatment, suggesting that there are interindividual differences in response to certain stimuli, such as chronic training programs (5, 6). Williams (29) suggests that the same may be said for the response to nutritional ergogenic aids. Although all humans have similar anatomical and physiological characteristics, biological variability due to hereditary differences may also account for the efficacy of nutritional agents. Therefore, the likelihood that there may be some underlying biolog-

ical determining factors that may determine those who are responders and those who do not respond to acute oral creatine monohydrate (Cr) ingestion is quite possible and thus helps partially explain the dichotomy of published performance results.

A brief survey of published literature on the effects of Cr loading and its ergogenic effect on performance suggests that there are some equivocal findings. The preponderance of research indicates that Cr supplementation leads to improved performance in high-intensity, short-duration, repeated bouts of sprint cycling (1, 4, 9, 24) and resistance training (17, 18, 28), while some studies have shown no effect with similar exercise protocols (2, 10, 15, 21, 26, 27). Aside from methodological, procedural, and/or experimental design differences that might account for such contrary results, Greenhaff et al. (17) have suggested that the ergogenic potential of Cr supplementation may depend on the extent of elevation of intracellular muscle Cr that occurs in each individual. Accordingly, they suggest that it may be necessary to increase total muscle creatine (TCr) by close to 20 mmol·kg⁻¹ dry weight (dw) to obtain substantial improvements in exercise performance as a result of ingesting Cr. Kilduff et al. (21) support this speculation, noting that their failure to observe significant improvements in peak force or total work during repeated isometric contractions may have been a function of 4 nonresponders (≤ 21 mmol·kg⁻¹ dw) who masked the overall group changes in an experimental sample of 32.

Based on Greenhaff et al. (17), approximately 20–30% of individuals “do not respond” to Cr supplementation, which is defined as those subjects with less than a 10 mmol·kg⁻¹ dw increase in resting total muscle creatine following 5 days of Cr ingestion at 20 g·d⁻¹. The failure to increase resting cellular Cr concentrations seems to occur in some subjects despite the widely accepted and recommended acute dose protocol of 20–30 g·d⁻¹ for a 5–7-day period (19, 20). Given the possibility of nonresponders within a small experimental sample and the variability of performance measures reported in the research, it is not surprising that some studies do not report significant findings.

A descriptive profile of preexisting biological conditions and/or determining factors may help describe responders and nonresponders within an experimental sample and thus partially explain variability in subject performance measures after oral supplementation. Therefore, the purpose of this study is to document the physiological profile of responders (>20 mmol·kg⁻¹ dw increase in total intramuscular Cr + phosphorylated creatine

[PCr]) versus nonresponders ($<10 \text{ mmol}\cdot\text{kg}^{-1} \text{ dw}$ increase) to a 5-day Cr load ($0.3\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) in 11 healthy men. It was hypothesized that responders and nonresponders can be categorized and grouped by differences in pre-post 5-day measures of total resting muscle Cr content. In addition, it was hypothesized that certain pre-existing biological and physiological determining factors, such as fiber type composition, fiber type cross-sectional area, body mass, daily dietary intake, 24-hour urine outputs and urinary creatine, and creatinine concentrations, would differ between responders and nonresponders and would, in part, determine the loading capability of the muscle.

METHODS

Experimental Approach to the Problem

Using the proposed threshold loading criteria suggested by Greenhaff et al. (17) as a guideline, responders (R) to the 5-day Cr supplementation were defined as subjects who increased their resting total muscle Cr concentrations (both Cr and PCr forms) by $20 \text{ mmol}\cdot\text{kg}^{-1} \text{ dw}$ or greater from preload levels. Nonresponders (NR) were defined as those subjects who did not exceed $10 \text{ mmol}\cdot\text{kg}^{-1} \text{ dw}$ of total resting Cr concentration following the 5-day supplementation phase and “quasi responders” (QR) as those who fell between the 2 criteria measures.

To help establish a biological profile of each of the responder subgroups, muscle biopsies of the vastus lateralis were taken before and after the 5-day acute supplementation period. Biochemical and histochemical analysis was performed in order to help determine total resting Cr content (Cr + PCr), fiber type composition, and fiber type cross-sectional area (CSA). Body mass, daily dietary intake, 24-hour urine outputs, urinary Cr and creatinine (CrN), and strength performance measures (1 repetition maximum [1RM] bench and leg press) were also assessed before and after the 5-day loading period to help build a profile of responders and nonresponders. These dependent variables are the most commonly reported determining factors often cited in the literature and may be linked to an individual's response to acute Cr loading.

To determine the overall extent of Cr loading, a 2-group design (Cr supplement group [CrS] vs. placebo group [Pl]) was initially employed, and inferential statistics were used to determine if there was a statistically significant increase in resting cellular Cr + PCr following the 5-day acute supplementation period. The Cr supplementation group was then analyzed on an individual basis to categorize responders versus nonresponders and their associated biological profile. Because of the small subgroups formed, data analysis for this part of the study was limited to descriptive statistics.

Subjects

Eighteen recreationally weight-trained men from the University of Alberta were recruited from the student population. To be included in the study, it was requested that all subjects have no prior history with creatine monohydrate supplementation. Subjects signed informed consent, and all procedures were approved by the University's Ethic Review Committee for use of human subjects in research. The mean age, height, and weight for all subjects were 22.7 years, 178.1 cm, and 76.2 kg, respectively.

Creatine Supplementation

Following random assignment to either Cr supplementation ($n = 11$) or placebo supplement group (Pl) ($n = 7$), the experiment was conducted over a 5-day loading period. The CrS received $0.3 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ following all pretest measures (19). This Cr loading protocol has been shown to elevate muscle total Cr and PCr by 10–25% (9, 17, 19). The inclusion of a placebo group was to verify that a true group treatment response did occur with the proposed Cr loading protocol. Subsequent descriptive profiling of the Pl subjects was not performed, as the focus of this experiment was to delve into the interindividual characteristics of the CrS subjects.

All creatine doses were measured individually using an electronically calibrated scale (Sartorius L220S, Inc., Göttingen, Germany) and dissolved in 1 L of a heated, flavored drink containing $80 \text{ g}\cdot\text{L}^{-1}$ of simple sugar. The drink was cooled to room temperature and then distributed to subjects with instructions to consume the entire 1-L Cr solution in 4 equal portions throughout the day, separated by 3–4 hours. The Pl group received the flavored drink only and consumed the solution in a similar manner as the CrS. This supplementation schedule was repeated for 5 days.

Physiological Measures

Muscle biopsies from the lateral aspect of the vastus lateralis of the right leg using the suction method described by Evans et al. (14) were obtained before (T1) and after (T2) the 5-day loading period on both groups. Two tissue samples were extracted from each biopsy incision. The first sample was quickly snap frozen within 3 to 5 seconds in liquid nitrogen and stored at -80°C for later biochemical analysis of Cr and PCr creatine concentrations, using the methods outlined by Bernt et al. (3). All samples for this part of the analysis were freeze-dried first. Muscle metabolite concentrations are expressed in $\text{mmol}\cdot\text{kg}^{-1} \text{ dw}$.

The second biopsy sample was oriented cross sectionally and mounted in an embedding medium (OCT) on a piece of cork, frozen in isopentane cooled to near freezing with liquid nitrogen, and stored at -80°C for later histochemical analysis. Samples were subsequently serial sectioned ($8 \mu\text{m}$ thick) in a cryostat at -20°C , placed on a glass coverslip, and assayed for myofibrillar ATPase activity using the technique of Brooke and Kaiser (8). Pre-incubation solutions were set at a pH of 10.4, 4.3, and 4.45 in order to determine type I, IIa, IIb, and IIc fibers, respectively. Determination of muscle fiber cross-sectional areas was performed with the assistance of a PSI computer assisted image analysis system (Perceptive Systems Inc., League City, TX). Fiber type determination and cross-sectional area measures were based on a mean of 99 fibers per biopsy across sampling times.

To help profile the CrS, anthropometric measures of height, weight, and 4 skinfold sites (triceps, biceps, and subscapular and suprailiac crest) were obtained before and after the 5-day supplementation period. The sum of all 4 sites was determined from the mean of the 2 measures that were within 0.5 mm of each other. Percent body fat was calculated using the formula by Durnin and Womersley (12).

To help monitor daily fluid and protein intake, each subject completed a 3-day dietary log during 3 consecutive days immediately prior to and after the 5-day Cr

loading period. Macronutrients, including fluid ingestion, were analyzed using a nutritional software program (Food Processor, ESHA Research, Salem, OR).

Pre-post 5-day, 24-hour urine samples were collected, beginning after the first urination of the day and ending with the first urination on the morning of the next day. The volumes for the 24-hour samples were recorded and provided an indirect measure of water retention that might occur during the supplementation phase. A sample of the urine was also used to determine pre-post urinary Cr and CrN concentrations using the modified reverse-phase high-performance liquid chromatography (HPLC) method of Dunnnett et al. (11).

To determine upper- and lower-body strength performance changes over the 5-day Cr supplementation period, 1RM bench and incline leg press tests were performed. Both pre-post 1RM strength performance measures were conducted prior to the biopsy procedures. The incline leg strength test was completed before the bench press measure on both occasions with each test separated by a 10-minute recovery period. The testing protocol followed that outlined in Syrotuik et al. (27). Briefly, following a 5-minute warm-up on a cycle ergometer and static stretching, each subject performed 3 submaximal warm-up sets of 10, 6, and 3 repetitions with progressively higher loads. A 1RM was established in the next 2–3 sets. Once 1RM was obtained, subjects were urged to complete a second repetition in order to validate that 1RM had been achieved. Incline leg press and bench press scores were reported to the nearest 2.5 and 1 kg, respectively. A 2–3-minute rest was provided between testing sets. This protocol has been used in our lab before and has produced intraclass correlations (ICC) for test-retest reliability above 0.98.

Statistical Analyses

To compare effects of the 5-day Cr load on resting levels of Cr + PCr, data were initially analyzed by a 2-way analysis of variance with repeated measures that involved a comparison between groups CrS and PL over time. Alpha was preset at $p \leq 0.05$. The categorizing of responders, nonresponders, and quasi responders was based on the absolute criteria of increases that occurred in total muscle resting Cr concentrations of ≥ 20 , ≤ 10 , and in between 10 and 20 $\text{mmol}\cdot\text{kg}^{-1}\text{ dw}$, respectively. Descriptive statistics were used to describe the physiological characteristics associated with each categorized response group. Because of the small sample size of these categories or subgroups, no inferential statistics were used.

RESULTS

Figure 1 illustrates that there was an interaction in total resting muscle Cr + PCr for those supplementing with creatine monohydrate for the 5-day loading period. The CrS significantly increased their total resting muscle Cr + PCr from $111.12 \pm 8.87 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ (T1) to $127.30 \pm 9.69 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ (T2), while the placebo group remained relatively unchanged ($115.70 \pm 14.99 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ vs. $111.74 \pm 12.95 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ for T1 and T2, respectively). The change in total resting muscle Cr + PCr for the CrS represents a mean increase of 14.5%.

Figure 2 highlights the individual person-by-treatment response to the 5-day Cr load (A) and placebo (B). Figure 2A shows that the individual response to the Cr loading was variable. Based on the operational definitions

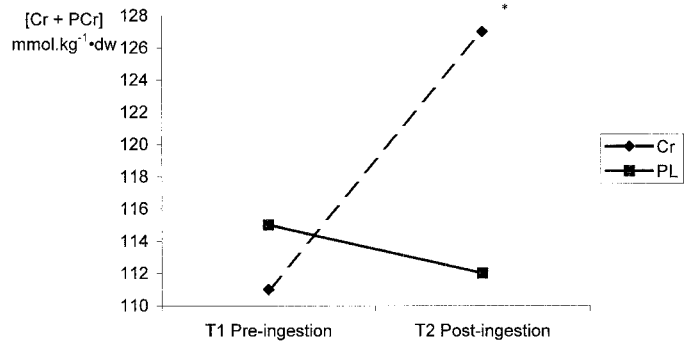


Figure 1. Changes in total resting muscle creatine monohydrate (Cr) + phosphorylated creatine content before and after the 5-day Cr loading period ($0.3 \text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$). * = significantly different between T1 and T2 ($p < 0.05$).

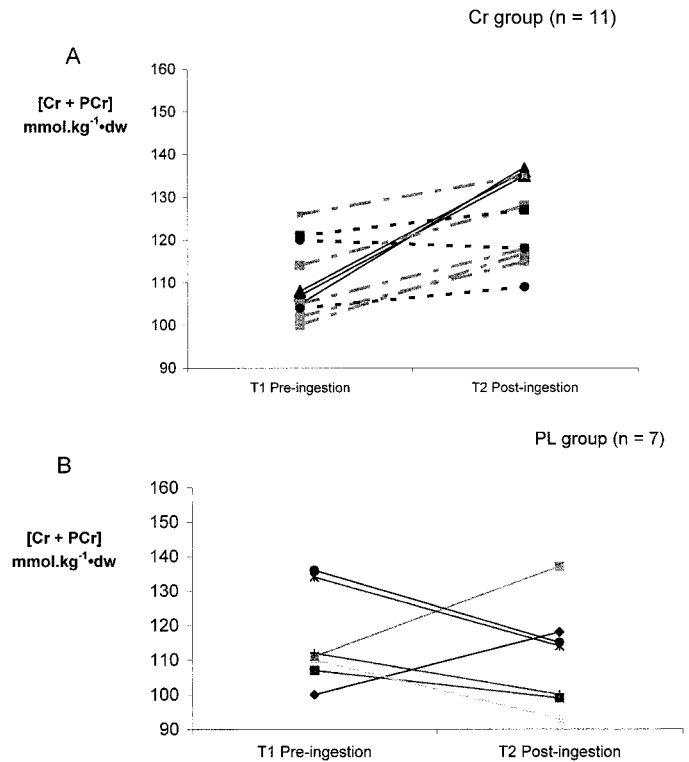


Figure 2. Individual values for muscle creatine monohydrate (Cr) + phosphorylated creatine concentration before and after 5-day Cr (A) or PL (B) loading period. — responders $>20 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ ($n = 3$); - - - quasi responders $10\text{--}20 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ ($n = 5$); . . . nonresponders $<10 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$ ($n = 3$).

that delineate responders ($\geq 20 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$), quasi responders ($10\text{--}20 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$), and nonresponders ($<10 \text{ mmol}\cdot\text{kg}^{-1}\text{ dw}$), the data show 3 responders (R), 5 quasi responders (QR), and 3 nonresponders (NR), with a mean increase in resting Cr + PCr of 29.5, 14.9, and 5.1 $\text{mmol}\cdot\text{kg}^{-1}\text{ dw}$, respectively. The mean percentage change increase in Cr + PCr corresponds to 27.0, 13.6, and 4.8% for the R, QR, and NR, respectively. Figure 2B contains the response to the PL ingestion.

Table 1 contains a summary of the individual estimates for fiber type populations of the 11 Cr-loaded subjects as determined from the muscle biopsies. There was

Table 1. Type I, II, and IIc fiber type population of responders, quasi responders, and nonresponders to a 5-day Cr load.*

	Type I (%)	Type II (%)	Type IIc (%)
Responders (R)			
R1	31.9	63.6	4.4
R2	31.7	65.5	2.7
R3	39.3	60.2	0.5
$\bar{X}$	34.3	63.1	2.5
Quasi responders (QR)			
QR1	35.5	58.0	6.4
QR2	68.2	30.5	1.2
QR3	59.8	36.4	3.7
QR4	36.5	57.4	6.3
QR5	57.1	42.0	0.1
$\bar{X}$	51.4	45.5	3.5
Nonresponders (NR)			
NR1	46.4	52.7	0.8
NR2	59.8	30.8	9.5
NR3	60.0	35.1	4.8
$\bar{X}$	55.4	39.5	5.0

* Cr = creatine monohydrate.

a descending trend between R, QR, and NR individuals in mean percentage fiber type populations, with the R subgroup displaying the highest percentage of type II fibers (63.1%), followed by the QR (45.5%) and NR (39.5%) groups.

Pre- and postload muscle fiber cross-sectional areas are shown in Table 2. The responders and quasi responders to the Cr load exhibit larger initial cross-sectional areas for type I (1,509 and 1,270 μm^2), type IIa (1,807 and 2,238 μm^2), and type IIb (1,695 and 1,740 μm^2) fibers, respectively, than nonresponders (type I = 900 μm^2 , type IIa = 1,377 μm^2 , type IIb = 1,213 μm^2). Responders had a mean fiber area increase of 320, 971, and 840 μm^2 in type I, IIa, and IIb fibers, respectively, with nonresponders having the least mean fiber area increase of 60, 46, and 78 μm^2 for type I, IIa, and IIb fibers, respectively.

Total body mass and fat-free mass before and after the

Table 3. Individual and mean values for total body and fat-free mass before and after the 5-day Cr load.*

	Total body mass (kg)			Fat-free mass (kg)		
	T1	T2	Δ	T1	T2	Δ
Responders (R)						
R1	98.4	100.8		82.2	84.2	
R2	88.8	90.8		74.2	77.4	
R3	78.0	90.8		60.6	63.0	
$\bar{X}$	88.4	90.8	2.4	72.3	74.8	2.0
Quasi responders (QR)						
QR1	73.2	74.4		62.7	63.4	
QR2	83.4	85.8		71.1	73.1	
QR3	81.7	84.5		71.1	73.6	
QR4	78.7	81.8		60.5	63.6	
QR5	72.6	73.6		59.7	60.5	
$\bar{X}$	77.9	80.0	2.1	65.0	66.8	1.8
Nonresponders (NR)						
NR1	61.0	62.5		51.0	53.3	
NR2	63.7	66.1		55.4	57.5	
NR3	82.6	84.6		70.4	72.1	
$\bar{X}$	69.1	71.0	1.9	59.2	60.9	1.7

* Cr = creatine monohydrate.

5-day loading period are presented in Table 3. A similar descending response for changes in the mean total body mass and fat-free mass for the R, QR, and NR subgroups was evident, with larger subjects, preload, increasing their mass the most and the lighter subjects the least. Although the subjects with the greatest initial body mass and fat-free tissue appeared to be those that best responded to the Cr loading protocol, one of the nonresponders (NR3) who was the fourth-heaviest and possessed the fifth-highest fat-free mass preload was considered a nonresponder to the Cr treatment.

The individual and mean values for daily dietary protein, fluid intake, 24-hour urine outputs, and the ratio of fluid intake to urine output are displayed in Table 4. The protein intake was variable among individuals, but the NR group appeared to have a slightly higher consumption before and after the 5-day Cr supplementation (1.7 and

Table 2. Individual and mean values for muscle fiber cross-sectional areas (μm^2).

	Type I			Type IIa			Type IIb		
	T1	T2	Δ	T1	T2	Δ	T1	T2	Δ
Responders (R)									
R1	1,024	2,142		1,724	4,197		1,855	3,993	
R2	1,643	1,691		1,767	1,877		1,555	1,910	
R3	1,857	1,651		1,929	2,259		1,676	1,702	
$\bar{X}$	1,509	1,828	320	1,807	2,778	971	1,696	2,535	840
Quasi responders (QR)									
QR1	802	948		1,919	2,085		1,448	—	
QR2	1,152	1,534		2,679	2,626		—	2,898	
QR3	1,521	1,703		2,188	2,485		2,114	2,531	
QR4	1,337	1,758		1,604	2,214		1,401	2,290	
QR5	1,539	1,632		2,800	2,663		1,998	2,075	
$\bar{X}$	1,270	1,515	245	2,238	2,414	176	1,740	2,448	708
Nonresponders (NR)									
NR1	975	1,285		1,342	1,821		1,293	1,580	
NR2	913	636		1,304	1,025		1,140	1,003	
NR3	813	—		1,487	—		1,208	—	
$\bar{X}$	900	960	60	1,377	1,423	46	1,213	1,291	78

Table 4. Individual and mean values for daily dietary protein intake, fluid intake, 24-hour urine output, and fluid intake to urine output ratios before and after the 5-day Cr load.*

	Daily protein intake (g·kgBM ⁻¹ ·d ⁻¹)		Fluid intake (ml/24 h)			Urine output (ml/24 h)			Fluid intake/urine output ratio		
	T1	T2	T1	T2	Δ	T1	T2	Δ	T1	T2	Δ
Responders (R)											
R1	1.3	1.2	3,346	4,434		1,995	3,145		1.65	1.40	
R2	2.5	2.1	3,260	4,253		3,250	2,985		1.00	1.09	
R3	0.9	—	2,025	2,139		1,810	1,095		1.11	1.95	
$\bar{X}$	1.6	1.6	2,877	3,608	731	2,351	2,405	57	1.25	1.45	0.2
Quasi responders (QR)											
QR1	2.5	1.7	4,496	5,787		1,655	1,805		2.71	3.20	
QR2	1.1	1.5	3,141	5,576		3,010	2,235		1.04	2.49	
QR3	1.4	1.6	5,334	7,038		4,975	6,135		1.07	1.14	
QR4	1.3	1.5	2,990	3,997		1,125	2,765		2.65	1.44	
QR5	1.7	1.9	1,425	3,050		1,205	1,045		1.18	2.91	
$\bar{X}$	1.6	1.6	3,477	5,089	1,612	2,395	2,797	401	1.73	2.23	1.29
Nonresponders (NR)											
NR1	2.2	2.3	1,931	3,930		2,095	2,490		0.92	1.57	
NR2	2.2	1.7	3,346	4,260		685	875		4.88	4.86	
NR3	0.7	1.5	2,742	4,480		800	1,445		3.42	3.10	
$\bar{X}$	1.7	1.8	2,673	4,223	1,550	1,193	1,603	410	3.07	3.17	0.1

* Cr = creatine monohydrate.

1.8 g·kg BM⁻¹·d⁻¹, respectively) than the R subgroup (1.6 and 1.6 g·kg BM⁻¹·d⁻¹, respectively). The 3-day dietary logs reported mean fluid intakes that increased considerably in all subgroups following the 5-day load (R = 713 ml; QR = 1,612 ml; NR = 1,550 ml), with the QR group showing the greatest absolute change. There was no discernable trend between subgroups in 24-hour urine outputs other than expected increases in all groups with the increased consumption of fluids noted at the end of the 5-day supplementation schedule. The ratio of fluid intake to urine output was calculated to indirectly examine any water retention that might occur with subjects while loading with Cr. The ratios for all subgroups did increase following the 5 days of Cr ingestion, with the NR subgroup exhibiting the least change from T1 to T2.

Table 5 contains the individual and mean urinary Cr and CrN concentrations. The responders showed the lowest mean preload urinary Cr (R = 0.0452 mmol/L; QR = 0.2153 mmol/L; NR = 0.0687 mmol/L) and had the greatest absolute increases after 5 days of loading, compared to the other subgroups (R = 0.6635 mmol/L; QR = 0.3295 mmol/L; NR = 0.4866 mmol/L). The urinary CrN data were variable with no distinguishing trends between subgroups of responders.

Figure 3 represents the mean absolute strength changes for 1RM bench and incline leg press scores for the 3 levels of response. There was little or no change in bench press for all groups; however, the R group increased their 1RM incline leg press by 25.8 kg, while the QR and NR subgroups had little change (2.5 and 2.0 kg, respectively). The NR group exhibited considerably less maximal strength for both the bench and the incline leg press 1RM scores than either of the R or QR groups.

DISCUSSION

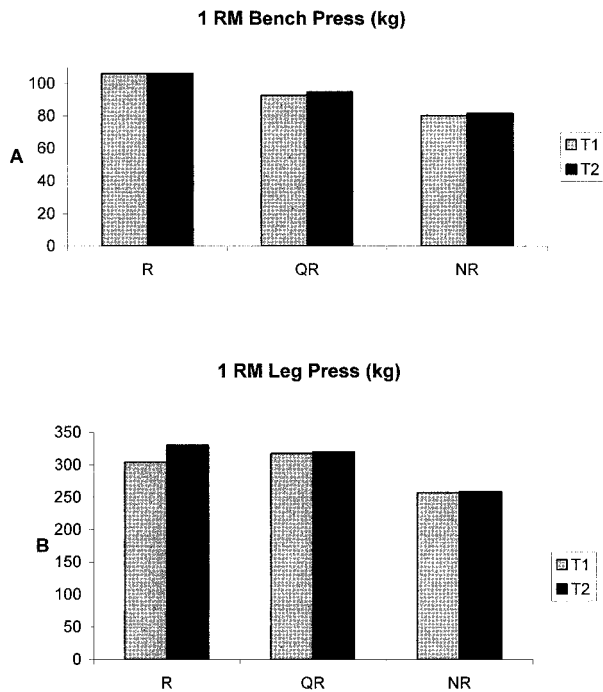
The response of individuals to the 5-day creatine monohydrate loading period (0.3 g·kg⁻¹·d⁻¹) appears to have been variable and supports a person-by-treatment re-

sponse. Using the suggested criterion Greenhaff et al. (17) of a 20 mmol·kg⁻¹ dw increase in total resting muscle Cr + PCr following an acute loading period, only 3 of the 11 subjects could be considered true responders. Similarly, using the same authors' criterion of an increase of less than 10 mmol·kg⁻¹ dw of resting muscle Cr + PCr, the current results suggest that 3 individuals (~30% of the sample) could be classified as true nonresponders. This occurred despite a loading protocol that has been shown to elevate resting Cr + PCr levels by approximately 20% (9, 17, 19). Five of the 11 subjects did not reach the true responder criterion of 20 mmol·kg⁻¹ dw but did exceed the nonresponder level of 10 mmol·kg⁻¹ dw. These QR had absolute increases in total cellular Cr + PCr ranging from 10.2 to 18.3 mmol·kg⁻¹ dw or from 8.0 to 13.2% over initial preload levels.

A closer examination of the individual data shows that the responders had initial Cr + PCr that were below the initial group mean concentration of 111.12 ± 8.87 mmol·kg⁻¹ dw. This lower initial level of cellular Cr + PCr, in part, may help explain the large increases of 27.4, 32.0, and 28.5 mmol·kg⁻¹ dw for subjects R1, R2, and R3, respectively. Eklom (13) concluded that those subjects who begin with low creatine levels benefit more from supplementation than those who have high levels when supplementation begins. Harris et al. (19) reported that supplementation response was greatest in subjects with low initial Cr + PCr content and also supports this observation. This observation is further supported by the quasi-responder group data. Changes within the QR group followed a similar trend with those exhibiting the lowest initial levels of Cr + PCr content (QR2 = 101.5 mmol·kg⁻¹ dw) increasing their resting levels the most (18.3 mmol·kg⁻¹ dw or 18%) and those with the highest preload content (QR5 = 126.8 mmol·kg⁻¹ dw) responding the least (10.2 mmol·kg⁻¹ dw or 8%). The nonresponder group, of which 2 subjects had some of the highest initial levels of Cr + PCr (NR1 = 120.7 mmol·kg⁻¹ dw, NR2 = 120.8

Table 5. Individual and mean values for urinary creatine [Cr] and creatinine [CrN] concentrations before and after the 5-day load.

	[Cr] mmol/L			[CrN] mmol/L		
	T1	T2	Δ	T1	T2	Δ
Responders (R)						
R1	0.1163	0.8821		0.3134	0.4230	
R2	0.0151	0.7317		0.2459	0.0265	
R3	0.0313	0.3864		0.1461	0.0439	
$\bar{X}$	0.0452	0.6667	0.6134	0.2354	0.1644	-0.071
Quasi responders (QR)						
QR1	0.1201	0.5436		0.2990	0.4043	
QR2	0.2838	0.3596		0.2561	0.3342	
QR3	0.5134	1.100		0.2562	0.4840	
QR4	0.1227	0.0849		0.2474	0.2986	
QR5	0.0068	0.6318		0.2339	0.0395	
$\bar{X}$	0.2153	0.5448	0.3295	0.2585	0.3123	0.0538
Nonresponders (NR)						
NR1	0.1826	0.6566		0.1858	0.3306	
NR2	0.1131	0.7228		0.2547	0.1797	
NR3	0.0687	0.2867		0.2346	0.1686	
$\bar{X}$	0.0687	0.5553	0.4866	0.2250	0.2263	0.0013

**Figure 3.** Mean absolute strength changes in a 1 repetition maximum (1RM) bench press (A) and incline leg press (B) following 5 days of creatine monohydrate supplementation for responders (R), quasi responders (QR), and nonresponders (NR).

mmol·kg⁻¹ dw), increased only 8.0 and 0.1 mmol·kg⁻¹ dw, respectively, following the 5-day load. Interestingly, the remaining subject in the NR group (NR3) had one of the lowest initial levels of Cr + PCr (105.0 mmol·kg⁻¹ dw) and increased their cellular content only by 7.2 mmol·kg⁻¹ dw or 6.9% following supplementation.

In terms of preexisting biological conditions that may help identify responders versus nonresponders, the present data appear to reveal 2 principle-dependent variables as possible determining factors: muscle fiber type com-

position and initial cross-sectional area of muscle fibers. The trend in our data shows that the R group exhibited the greatest percentage of type II fibers (63.1%), followed by the QR subjects (51.4%) and finally the NR group (39.5%). As well, the R and QR to the Cr load had larger initial CSA for type I, IIa, and IIb fibers compared to the nonresponders. Furthermore, following the 5-day loading period, the R had a mean fiber area increase of 320, 971, and 840 μm^2 in type I, IIa, and II b, respectively, with NR having the least mean fiber area increase of 60, 46, and 78 μm^2 in type I, IIa, and IIb, respectively (Table 2). It would seem feasible that initial fiber CSA and size would favor a greater potential to increase the storage of creatine within that fiber type. Creatine is a very osmotic substance, and thus postsupplementation increases in cross-sectional area of the muscle fibers may likely be due to an induced influx of water into the cell (28). In addition, since the type II fibers are noticeably larger than type I fibers, particularly in the R and QR groups, this factor may also determine the ultimate response to supplementation. Casey et al. (9) have suggested that performance benefits may be related to increases in creatine within the type II muscle fibers. The larger and greater number of type II fibers reported for the 3 responders may help partially explain the 25.8-kg increase in 1RM leg press scores for that group.

The average preload total body mass and fat-free mass of the R subgroup was higher than either the QR and the NR subjects and showed the greatest postload increases. The increases in Cr + PCr content is directly linked with fat-free mass and particularly muscle, where the vast majority of the body stores of creatine are located (16). Since the R subjects displayed lower initial preload level of Cr + PCr and had the highest percentages of fat-free tissue, it is not surprising that the cellular concentration of Cr + PCr increased so substantively in these individuals. A review of the descending preload body mass and fat-free mass data of the QR and NR groups (Table 3) would seem to support this observation. The exception, however, would be subject NR3, who, despite being heavier than 7

others and possessing the fifth-highest fat-free mass, was categorized as a nonresponder.

In terms of daily dietary protein intakes, there was no obvious trend in daily protein consumption. The NR group reported the highest pre-post load intakes of 1.7 and 1.8 g·kg BM⁻¹·d⁻¹, respectively, while the R subjects averaged 1.6 and 1.6 g·kg BM⁻¹·d⁻¹ for the same time period. To what extent this factor promotes and/or inhibits the absorption of creatine monohydrate is difficult to determine from these data. Since dietary creatine, which is associated with fish and red meat consumption, accounts for approximately one-half of the body's daily need for creatine, one might speculate that lower daily protein intakes might promote a response more than high protein ingestion. Since the preload daily protein consumption for both the R and the NR groups is high, there does not appear to be any identifiable linkage with this response pattern. Perhaps a more detailed analysis of the composition of the protein consumed by each subject (animal or vegetable sources) may be a more important factor than total daily protein intake alone.

Reported fluid intakes increased considerably during the loading period in all Cr supplementation subjects, with no apparent trend. The increased fluid intake for all groups was expected, as creatine is an osmotically active substance that likely increases the intracellular water content of the muscle cell (28). Similarly, there was no discernable trend between subgroups in 24-hour urine outputs other than the expected increased output that would occur with the overall increase in fluid consumption. Some authors have reported that a reduction in urine output as a measure of water retention within the body may indirectly indicate the amount of creatine being absorbed by the muscle (20). Since this did not occur in the present study, a ratio of fluid intake to urine output was calculated for each subject to hopefully address this proposed condition. All subgroups slightly increased this ratio following the 5-day loading period, inferring a retention of fluid within the body (Table 4), but there was no convincing trend associated with either the R or the NR data.

An increase in urinary Cr content has been linked with the ingestion of large quantities of Cr monohydrate (19). As the body increases its Cr storage over the first 3 days of supplementation and reaches its upper biological limits for absorbing Cr, urinary excretion rates of Cr increase. The urinary Cr data from this study support this notion, with all subjects increasing their postload concentrations and with the R subgroup displaying the greatest absolute mean increase following the 5-day loading schedule (Table 5). The responders also showed the lowest initial Cr prior to the acute loading phase, compared to either the QR or the NR groups. Based on the current data in this study, perhaps preload measures of urinary Cr could be used as a simple and noninvasive indicator of whether a subject will be a responder to an acute Cr load. Certainly, larger amounts of normative data are required to be able to adequately support or refute this proposed screening tool as well as follow-up assessment of actual loading.

Finally, it has been suggested that in order to see an ergogenic effect in performance from Cr supplementation, a critical threshold increase of 20 mmol·kg⁻¹ dw in resting muscle cell Cr + PCr must occur (17). In spite of the responders reaching this postload level, neither they nor

any other subgroup recorded an increase in 1RM bench press following the 5-day loading period. However, the R subgroup increased their 1RM incline leg press scores by a mean of 25.8 kg, whereas the QR and NR subjects reported small changes of 2.5 and 2.0 kg, respectively. It may be possible that the larger muscle mass and/or fiber type composition of the lower body may better accommodate Cr loading than the upper-body musculature of the chest and arms.

Summary

The purpose of this study was to describe the physiological profile of responders versus nonresponders to a 5-day Cr load (0.3 g·kg⁻¹·d⁻¹). The response of individuals to the Cr loading period appears to have been variable and supports a person-by-treatment response with 3 responder types identified: true responders ($n = 3$, >20 mmol·kg⁻¹ dw from preload levels), quasi responders ($n = 5$, >10 and <20 mmol·kg⁻¹ dw from preload levels), and nonresponders ($n = 3$, <10 mmol·kg⁻¹ dw from preload levels). Although it is difficult to identify any 1 specific biological or determining factor that will predict those who will load (responder) versus those who will not load (nonresponder) to an acute oral supplementation schedule from such a small data set, there appears to be a few related factors. It seems that the initial levels of cellular Cr + PCr are important, with the responders in the current study generally displaying the lowest initial preload concentrations. Responders also possessed the greater percentage of type II muscle fibers and exhibited the greatest preload muscle fiber CSA and fat-free mass. Generally, nonresponders had higher initial levels of cellular Cr + PCr, less type II muscle fibers, smaller muscle fiber CSA, and lower fat-free mass. The only 1RM improvements associated with the 5-day load appeared in the responder group, whose mean 1RM incline leg press score improved by 25.8 kg.

The authors recognize that the generalized conclusions from such a small data set should be viewed with caution. Further confirmation, using a larger sample size, is warranted.

PRACTICAL APPLICATIONS

The results of this descriptive study suggest that a threshold increase of 20 mmol·kg⁻¹ dw in resting total muscle Cr + PCr may be governed by a preexisting biological profile that produces a favorable person-by-treatment response to Cr supplementation. Which singular biological-determining factor controls the extent of acute Cr uptake by the muscle cell is difficult to resolve. The final and ultimate response is probably the result of a complex interaction of many factors. The strength and conditioning specialist, when discussing the use of creatine monohydrate as part of the total training package with a client, should be aware that there may be a preexisting muscle morphological profile that dictates whether the trainee will benefit from supplementation. The laboratory-generated data in this study suggest that there is no easy marker or practical screening tool that will identify these individuals. However, the results clearly show that NRs to an acute oral supplementation protocol do exist. Finally, the individual subject response to Cr loading quite likely accounts for some of the equivocal performance measures reported in Cr supplementation research since

nonresponders could mask the effects of the total experimental group.

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