Effects of Varied Versus Constant Loading Zones on Muscular Adaptations in Trained Men

Authors
B. J. Schoenfeld1, B. Contreras2, D. Ogborn3, A. Galpin4, J. Krieger5, G. T. Sonmez1

Affiliations
Affiliation addresses are listed at the end of the article

Abstract
The purpose of this study was to compare the effects of a protocol employing a combination of loading zones vs. one employing a constant medium-repetition loading zone on muscular adaptations in resistance-trained men. 19 trained men (height = 176.9 ± 7.0 cm; body mass = 83.1 ± 11.8 kg; age = 23.3 ± 2.9 years) were randomly assigned to 1 of 2 experimental groups: a constant-rep resistance training (RT) routine (CONSTANT) that trained using 8–12 RM per set, or a varied-rep RT routine (VARIED) that trained with 2–4 RM per set on Day 1, 8–12 RM per set on Day 2, and 20–30 RM on Day 3 for 8 weeks. Results showed that both groups significantly increased markers of muscle strength, muscle thickness, and local muscular endurance, with no differences noted between groups. Effect sizes favored VARIED over CONSTANT condition for elbow flexor thickness (0.72 vs. 0.57), elbow extensor thickness (0.77 vs. 0.48), maximal bench press strength (0.80 vs. 0.57), and upper body muscle endurance (1.91 vs. 1.28). In conclusion, findings indicate that both varied and constant loading approaches can promote significant improvements in muscular adaptations in trained young men.

Introduction
Adaptations of resistance training (RT) are thought to be optimized by proper manipulation of program variables [1]. Of these variables, intensity of load – defined as the percentage of 1 repetition maximum (RM) – is perhaps the most studied. Resistance training guidelines have used the concept of intensity of load to create distinct “loading zones” that correspond to the optimization of a given fitness outcome: a loading zone of 1–5 RM (low repetition range) is purported to maximize muscle strength; a loading zone of 6–12 RM (medium repetition range) is proposed to maximize muscle hypertrophy; and, a loading of 15+RM (high repetition range) is claimed to maximize local muscular endurance [2].

While these guidelines are generally accepted as tenets, their application to program design remains somewhat equivocal. The preponderance of evidence does seem to suggest the presence of a strength-endurance continuum, whereby low repetition training with heavy loads induce maximal strength increases while light-load, high repetition training promotes greater increases in muscle endurance [3–5]. With respect to skeletal muscle growth, however, the preponderance of evidence fails to show a hypertrophic superiority of one loading zone vs. another in untrained subjects across an array of populations [6]. Moreover, recent work from our lab reveals similar long-term increases in muscle size between resistance trainings sets involving ~3RM and ~10RM [5], and ~10RM and ~30 RM in trained men [4]. It is conceivable that there may be an advantage to combining low, medium, and high repetitions in a long-term training routine. Thus, the purpose of this study was to compare the effects of a protocol employing a combination of loading zones vs. one employing a constant medium-repetition loading zone on muscular adaptations in resistance-trained men. We hypothesized that greater muscular adaptations would be seen when combining loading zones.

Materials and Methods
Subjects
Subjects were 30 trained, male volunteers (height = 176.9 ± 7.0 cm; body mass = 83.1 ± 11.8 kg; age = 23.3 ± 2.9 years) recruited from a university population with a minimum of 1 year of resist-
ance training experience training at least 3 days-per-week and an average experience of 4.7 ± 3.2 years. All subjects reported performing a combination of free weights and resistance machines as part of their regular programs. This sample size was justified by a priori power analysis based on previous work from our lab with a target effect size difference of 0.6, alpha of 0.05 and beta of 0.80, while taking into account the probability of dropouts. Moreover, all subjects regularly performed the barbell back squat and bench press exercises for at least 1 year prior to entering the study. Subjects were free from any existing musculoskeletal disorders and stated they had not taken anabolic steroids or any other illegal agents known to increase muscle size for the previous year.

A total of 19 subjects completed the study; 9 subjects in CONSTANT and 10 subjects in VARIED. 11 subjects dropped out prior to completion: 1 subject experienced a minor joint-related injury during training that precluded adequate participation and the other 10 subjects abandoned participation for various personal reasons. Descriptive data for subjects who completed the study are shown in Table 1.

Subjects were pair-matched according to baseline squat strength and then randomly assigned to 1 of 2 experimental groups: a constant-rep RT routine (CONSTANT) that trained using 8–12 RM per set (n = 15) or a varied-rep RT routine (VARIED) that trained with 2–4 RM per set on Day 1, 8–12 RM per set on Day 2, and 20–30 RM on Day 3 (n = 15). Approval for the study was obtained from the University Institutional Review Board. Written informed consent was obtained from all subjects prior to beginning the study. The authors acknowledge having read and understood IJSM’s ethical standards document [7] and confirm that the study meets the ethical standards of the journal.

Resistance training procedures
The RT protocol consisted of 7 exercises per session targeting all major muscle groups of the body. The exercises performed were: flat barbell press, barbell military press, wide grip lat pulldown, seated cable row, barbell back squat, machine leg press, and machine knee extension. These exercises were chosen based on their common inclusion in bodybuilding- and strength-type RT programs [13, 14]. Subjects were instructed to refrain from performing any additional resistance-type or high-intensity anaerobic training for the duration of the study. Training for both routines was performed 3 times per week on non-consecutive days for 8 weeks. 3 sets were performed for each exercise. Sets were carried out to the point of momentary concentric muscular failure, operationally defined as the inability to perform another concentric repetition with proper form. Cadence of repetitions was carried out in a controlled fashion, with a concentric action of approximately 1 s and an eccentric action of approximately 2 s. Subjects were afforded 2 min rest between sets. The load was adjusted for each exercise as needed on successive sets to ensure that subjects achieved failure in the target repetition range. All routines were directly supervised by the research team, which included a National Strength and Conditioning Association Certified Strength and Conditioning Specialist and certified personal trainers, to ensure proper performance of the respective routines. Attempts were made to progressively increase the loads lifted each week by approximately 2–5%; if the subject was unable to perform the given lift within the confines of the target repetition range, the load was then adjusted to ensure maintenance of the desired loading zone. Prior to training, the CONSTANT group underwent 10 RM testing and the VARIED group underwent 3RM, 10RM, and 25RM testing to determine individual initial training loads for each exercise. Repetition maximum testing was consistent with recognized guidelines as established by the National Strength and Conditioning Association [13].

Dietary intake
To avoid potential dietary confounding of results, subjects were advised to maintain their customary nutritional regimen and to avoid taking any supplements other than that provided in the course of the study. To maximize anabolism, subjects were supplied with a protein supplement on training days containing 24 g protein and 1 g carbohydrate (Iso100 Hydrolyzed Whey Protein Isolate, Dymatize Nutrition, Dallas, TX). The supplement was consumed within 1 h post-exercise, as this time frame has been purported to help potentiate increases in muscle protein synthesis following a bout of RT [15].

Measurements
Muscle thickness
Ultrasound imaging was used to obtain measurements of muscle thickness (MT). A trained technician performed all testing using a B-mode ultrasound imaging unit (ECO3, Chison Medical Imaging, Ltd, Jiang Su Province, China). The technician applied a water-soluble transmission gel (Aquasonic 100 Ultrasound Transmission gel, Parker Laboratories Inc., Fairfield, NJ) to each measurement site, and a 5 MHz ultrasound probe was placed perpendicular to the tissue interface without depressing the skin. When the quality of the image was deemed to be satisfactory, the technician saved the image to a hard drive and obtained MT dimensions by measuring the distance from the subcutaneous adipose tissue-muscle interface to the muscle-bone interface as per previously established protocol [8]. Measurements were taken on the right side of the body at 3 sites: (1) the elbow flexors, (2) elbow extensors, and (3) vastus lateralis. For the anterior and posterior upper arm, measurements were taken 60% distal between the lateral epicondyle of the humerus and the acromion process of the scapula; for the vastus lateralis, measurements were taken 50% between the lateral condyle of the femur and greater trochanter for the quadriceps femoris. Ultrasound has been validated as a good measurement of muscle volume in these muscles [20, 21], and has been used in numerous studies to evaluate hypertrophic changes [19, 22–25]. In an effort to ensure that swelling in the muscles from training did not obscure results, images were obtained 48–72 h before commencement of the study, as well as after the final training session. This is consistent with research showing that acute increases in muscle thickness return to baseline within 48 h following a RT session [26]. To further ensure accuracy of measurements, at least 2 images were obtained for each site. If measurements were within 10% of one another, the figures were averaged to obtain a final value. If measurements were more than 10% of one another, a third image was obtained and the closest of the measures was then averaged. The test-retest intra-
class correlation coefficient (ICC) for our lab for thickness measurement of the forearm flexors, forearm extensors, and vastus lateralis are 0.986, 0.981, and 0.997, respectively. The standard error of the measurement (SEM) for these measures are 0.16, 0.50, and 0.25 mms, respectively.

Muscle strength
Upper and lower body strength was assessed by 1RM testing in the bench press (1RMBP) followed by the parallel back squat (1RMSQUAT) exercises. Subjects reported to the lab having refrained from any exercise other than activities of daily living for at least 48h prior to baseline testing and at least 48h prior to testing at the conclusion of the study. Repetition maximum testing was consistent with recognized guidelines as established by the National Strength and Conditioning Association [2]. In brief, subjects performed a general warm-up prior to testing that consisted of light cardiovascular exercise lasting approximately 5–10 min. A specific warm-up set of the given exercise of 5 repetitions was performed at ~50% 1RM followed by one to 2 sets of 2–3 repetitions at a load corresponding to ~60–80% 1RM. Subjects then performed sets of 1 repetition of increasing weight for 1RM determination. 3–5 min rest was provided between each successive attempt. All 1RM determinations were made within 5 attempts. Successful 1RMBP was achieved if the subject displayed a 5-point body contact position (head, upper back and buttocks firmly on the bench with both feet flat on the floor) and executed a full lock-out. Subjects were required to reach parallel in the 1RMSQUAT for the attempt to be considered successful as determined by the trainer. 1RMBP testing was conducted prior to 1RMSQUAT with a 5-min rest period separating tests. Strength testing took place using free weights. 2 research assistants supervised all testing sessions and an attempt was only deemed successful when a consensus was reached between the 2. The test-retest ICC for the 1RMBP and 1RMSQUAT from our lab are 0.995 and 0.998, respectively. The SEM for these measures are 1.03 and 1.04 kg, respectively.

Muscle endurance
Upper body muscular endurance was assessed by performing bench press using 50% of the subjects’ initial 1RM in the bench press (50%BP) for as many repetitions as possible to muscular failure with proper form. Successful performance was achieved if the subject displayed a 5-point body contact position (head, upper back and buttocks firmly on the bench with both feet flat on the floor) and executed a full lock-out. Muscular endurance testing was carried out after assessment of muscular strength to minimize the effects of metabolic stress on performance of the latter.

Statistical analyses
Subject demographic, attendance, and volume load data were assessed for normality using the Shapiro-Wilk test. Differences in demographics, attendance, and volume load between groups were assessed using independent 2-sided t-tests for unequal variances. In cases of non-normally distributed data, differences were assessed using the Wilcoxon signed rank test. Pre/post-intervention data were modeled using a linear mixed model for repeated measures, estimated by a restricted maximum likelihood algorithm. Training intervention (CONSTANT or VARIED) was included as the between-subject factor, time was included as the repeated within-subjects factor, time×intervention was included as the interaction, and subject was included as a random effect. Normality of residuals assumptions were examined using graphical plots; all pre/post-intervention data were found to meet normality of residuals assumptions. Effect sizes were calculated as the mean pre-post change divided by the pooled pretest standard deviation [9]. All analyses were performed using R version 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria). Effects were considered significant at P<0.05, and trends were declared at 0.05<P<0.10. Data are reported as x±SD unless otherwise specified. The scale proposed by Hopkins et al. [10] was used to further qualify probabilities that reflect the uncertainty in the true p-values as follows: 0.5%, most unlikely or almost certainly not; 0.5–5%, very unlikely; 5–25%, unlikely or probably not; 25–75%, possibly; 75–95%, likely or probably; 95–99.5%, very likely; 99.5%, most likely or almost certainly.

Results
Overall attendance for those who completed the study was 93% (92.5% vs. 93.9% for the VARIED and CONSTANT groups, respectively). No significant differences were noted between groups in any baseline measure. Table 2 summarizes results for all outcome variables.

Volume load
Volume load data was calculated as load×reps×sets for all sets performed during the study. Volume load in upper body pushing movements was significantly greater for CONSTANT compared to VARIED (p=0.02; CI = 4632, 50335). No significant differences were seen with respect to volume load in either upper body pulling movements (p=0.40; CI = −18700, 62485) nor in lower body exercises (p=0.36; CI = −61604, 157707). Total volume load across all exercises was not different between conditions (p=0.14; CI = −37632, 232487), although the Hopkins et al. [10] scale suggests a likelihood that volume load was greater in CONSTANT. Fig. 1 depicts volume load data across the duration of the study.

Muscle thickness
Ultrasound imaging of the elbow flexors showed that both VARIED and CONSTANT increased muscle thickness from baseline to post-study by 6.6% (p<0.001; ES = 0.72) and 5.0% (p<0.001; ES = 0.48) respectively. No significant differences were seen between groups in upper body exercises (p=0.36; CI = −37632, 232487), although the Hopkins et al. [10] scale suggests a likelihood that volume load was greater in CONSTANT. Table 2 depicts volume load data across the duration of the study.

<table>
<thead>
<tr>
<th>Measure</th>
<th>VARIED-Pre</th>
<th>VARIED-Post</th>
<th>ES</th>
<th>CONSTANT-Pre</th>
<th>CONSTANT-Post</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>elbow flexor thickness (cm)</td>
<td>44.1±3.0</td>
<td>47.0±2.4*</td>
<td>0.72</td>
<td>46.1±4.9</td>
<td>48.4±4.8*</td>
<td>0.57</td>
</tr>
<tr>
<td>triceps brachii thickness (cm)</td>
<td>50.2±4.1</td>
<td>53.4±3.6*</td>
<td>0.77</td>
<td>50.5±4.7</td>
<td>52.6±4.6*</td>
<td>0.48</td>
</tr>
<tr>
<td>vastus lateralis thickness (cm)</td>
<td>58.9±3.6</td>
<td>63.4±4.3*</td>
<td>1.04</td>
<td>55.9±4.6</td>
<td>60.7±4.5*</td>
<td>1.12</td>
</tr>
<tr>
<td>1RM bench press (kg)</td>
<td>98.6±17.2</td>
<td>110.2±19.4*</td>
<td>0.80</td>
<td>110.1±8.0</td>
<td>118.5±8.1*</td>
<td>0.57</td>
</tr>
<tr>
<td>1RM back squat (kg)</td>
<td>125.5±20.0</td>
<td>150.7±23.5*</td>
<td>1.47</td>
<td>116.2±12.6</td>
<td>140.1±14.2*</td>
<td>1.40</td>
</tr>
<tr>
<td>50% bench press (repetitions)</td>
<td>29.0±3.8</td>
<td>38.1±3.4*</td>
<td>1.91</td>
<td>30.2±5.8</td>
<td>36.3±4.2*</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Data are reported as x±SD. An asterisk (*) indicates a significant effect from baseline values. ES = effect size.
Schoenfeld BJ et al. Effects of Varied Versus Constant Loading: A Randomized Controlled Trial of Muscle Hypertrophy and Strength Gains

Discussion

The present study sought to directly investigate muscular adaptations between resistance training protocols using different loading zones vs. a constant "hypertrophy-type" loading zone in trained individuals. Emerging research indicates that there is a fiber type-specific hypertrophic response to training in different loading zones: light-load training promotes superior increases in type I fiber cross-sectional area, while using heavier loads has a greater effect on Type II growth [11–13]. Moreover, disparate responses in intracellular anabolic signalling and myogenic gene expression have been noted following heavy- vs. light-load resistance training, conceivably related to variances in mechanical and metabolic stress between loading zones [14]. These findings raise the possibility that there may be an advantage to combining low, medium, and high repetitions in a long-term training routine. However, our results show no significant differences between the 2 conditions, indicating that both strategies are equally suitable for increases in muscle hypertrophy, strength, and endurance. These findings refute our initial hypothesis that the VARIED approach would elicit superior muscular gains.

To our knowledge, the present study is the first to assess site-specific changes in muscle size between different loading zones rotated on a weekly basis using resistance-trained subjects. Results did not indicate a significant difference in growth (between training conditions) for any of the muscles assessed. Kraemer et al. [15] compared muscular adaptations in a 3 day-per-week protocol using constant loading (8–10RM) or varied loading (4–6RM on day 1; 8–10RM on day 2; 12–15RM on day 3). Body composition was assessed by the 3-site skinfold technique. After 9 months of training, the absolute change in fat-free mass was significantly greater in the varied- vs. the constant-loading condition (3.3 ± 1.7 kg vs. 1.6 ± 2.4 kg), and there was a statistical trend for an interaction in fat-free mass values favoring varied training over time. Alternatively, Hunter et al. [16] investigated the effects of varied vs. constant loading on body composition changes, as measured by air displacement plethysmography, in a cohort of elderly men and women over the course of 6 months. The protocol was set up so one group trained at 80% 1RM each session while another trained at 50%, 65%, and 80% 1RM across the 3 weekly training days. Increases in fat-free mass were similar between conditions at the end of the study period.

When attempting to reconcile findings between studies, there are notable differences in the subject populations. For one, subjects in Kraemer et al. [15] were young women while those in Hunter et al. [17] were older men and women; in contrast, the present study used healthy young men. Moreover, both Kraemer et al. [15] and Hunter et al. [17] employed untrained subjects whereas subjects in our study were experienced lifters. Both acute exercise and short-term (6–10 weeks) training studies clearly demonstrate that gender, age, and exercise training history influence numerous aspects of the RT-induced anabolic response [18]. While significant hypertrophic differences were not found between training approaches in the present study, the greater effect sizes seen for increases in upper body muscle thickness indicate a potential benefit for VARIED. Given the study’s relatively short duration (8 weeks) and factoring in missed sessions, subjects in VARIED trained in each loading zone for a total of 7–8 sessions over the course of the study period. It is therefore pos-
sible that longer training periods, like those used by Kraemer et al. [15], might be necessary for significant differences to manifest. This hypothesis warrants further investigation. It is also interesting that volume load was consistently lower across all conditions (push, pull, leg, total) in VARIED as compared to CONSTANT; however, only the reduction in push volume load was statistically significant. Nevertheless, this data suggests the possibility that VARIED loading may allow for comparable hypertrophic adaptations with less volume load than training at a constant 8–12 RM repetition range.

With respect to muscular strength, 1RM_{BENCH} and 1RM_{SQUAT} improved equally between the training groups over the study period. These findings are consistent with those of Hunter et al. [17] who found that varied and constant loading approaches produced similar increases in 1RM in the leg press, chest press, elbow flexion, and seated press. In contrast, Kraemer et al. [15] demonstrated significantly greater increases in absolute 1-RM leg press and shoulder press for varied vs. constant loading after 9 months of training. The majority of the existing data regarding the specificity of strength development have tested single repetition ranges against each other. While data on VARIED loading may be mixed, it appears that low repetition (high intensity of load) ranges (approximately 3–5 RM) may be superior for strength development specific to the exercise at which subjects are trained [3, 4, 19, 20]. Campos et al. [3] compared training at low (3–5RM), intermediate (9–11 RM) and high (20–28RM), finding that while all RM zones increased muscular strength, the increase following low repetition training (3–5RM) was approximately double the change that occurred following both the intermediate and high repetition conditions. This data suggests the transition from intermediate (9–11 RM) to low repetitions (3–5 RM) may represent the threshold for which enhanced strength adaptations could be expected. In the present design it is possible that the volume of exercise performed at or above this threshold was insufficient to increase strength beyond that which occurred in the CONSTANT loading in an intermediate, 8–12RM range.

To our knowledge, the present study is the first to evaluate changes in local muscular endurance following a varied vs. constant training approach. Although no significant differences were seen between conditions, the relative increases in 50%_{BENCH} markedly favored VARIED and the probability of these results were likely based on the Hopkins et al. [10] scale. Moreover, the effect size was substantially greater for VARIED as well. Studies that have compared differing training intensities in isolation have generally supported the strength-endurance continuum, suggesting that higher repetition training favors the development of muscular endurance [3, 19, 21]. Training with low intensity and high repetitions result in greater time-under-tension [22], and greater time-under-tension is associated with an increased acute mitochondrial protein synthetic response to strength training [23]. Such mitochondrial adaptations, if coincident with muscle fiber phenotypic adaptations towards more oxidative fiber types (Type I, IIA), may confer a distinct advantage to the development of muscular endurance. The present data does not allow for firm conclusion regarding fiber-type specific responses; however, at the functional level the data are consistent with the strength-endurance continuum in that the VARIED condition, which included high repetition training (20–30RM), resulted in superior adaptations in muscular endurance. It is also possible that such adaptations in VARIED were attenuated relative to training exclusively at 20–30RM. We cannot exclude the possibility that there is a degree of offset of the strength adaptations of high-load training with the endurance adaptations promoted with low-load training, such that VARIED provides a subdued response relative to exclusive training in each RM zone. Unfortunately, due to limitations in the experimental design, we cannot determine whether such a response occurred, as a low (2–4RM) and high (20–30RM) repetition experimental group was not included.

The study had several notable limitations. First, muscle thickness measurements were obtained only at the mid-portion of each muscle. While this measure is commonly used as a proxy of whole-muscle growth, research shows that hypertrophy often manifests in a regional-specific manner, with greater protein accretion occurring at the proximal and/or distal aspects of a given muscle [24, 25]. We therefore cannot rule out the possibility that subjects may have experienced differential changes in proximal or distal muscle growth in one condition vs. the other that would not have gone undetected by the testing methods employed. Second, we did not perform muscle biopsies and thus cannot discern whether the conditions studied resulted in different fiber-type specific adaptations. This has potentially important implications both for maximizing whole muscle hypertrophy as well as muscular performance, and hence warrants further study. Third, although subjects were advised to maintain their usual dietary regimen, we were unable to assess compliance. Thus, it remains possible that variances in either energy or macronutrient consumption unduly influenced results. Finally, due to experimental constraints it was not possible to include additional experimental groups that trained exclusively at each of the repetition ranges used in the VARIED protocol. Consequently, the comparisons above are specific to constant loading at an 8–12 RM. We cannot exclude the possibility that a differential response would have occurred regarding both maximal strength and endurance had experimental groups been included that trained at either the higher or lower loading zone.

**Conclusion**

Training with a variety of repetition ranges has been theorized to provide an optimal hypertrophic stimulus to both type I and II fibers, and possibly augment the hypertrophic response as compared to training in fixed repetition ranges in isolation [26]. The present results suggest that comparable hypertrophic, strength, and endurance adaptations occur when a varied training protocol is compared against a fixed loading program at 8–12 RM; however, trends suggest that improved muscular endurance may occur in protocols that employ high repetition ranges. Of interest, VARIED loading schemes may provide comparable adaptations with reduced volume-load, indicating a training stimulus of greater efficiency as compared to training exclusively in a fixed repetition range.

**Acknowledgements**

Acknowledgements: This study was supported by a grant from Dymatize Nutrition. The authors gratefully acknowledge the contributions of Robert Harris, Andrew Alto, Marvin Alba, Romaine Fearon, Fanny Chen, Lucas Campos, Geronimo Brannigan, Gabriel Irizarry and Jason Peters in their indispensable role.
as research assistants in this study. We also would like to express our gratitude to Dymatize Nutrition for providing the protein supplements used in this study.

**Conflict of interest:** The authors have no conflict of interest to declare.

**Affiliations**

1 Department of Health Sciences, CUNY Lehman College, Bronx, United States
2 Sport Performance Research Institute, Aukland University of Technology, Aukland, New Zealand
3 Health Sciences, McMaster University, W. Hamilton, Canada
4 Neuromuscular and Neurometabolic Unit, Cal State Fullerton, Fullerton, United States
5 Weightology.net, Issaquah, United States

**References**

2 Baechle TR, Earle RW. Essentials of strength training and conditioning. 2008
17 Hunter GR, Brock DW, Byrne NM, Chandler-Laney PC, Del Corral P, Gower BA. Exercise training prevents regain of visceral fat for 1 year following weight loss. Obesity (Silver Spring) 2010; 18: 690–695
18 Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res 2010; 24: 2857–2872
26 Ogborn D, Schoenfeld BJ. The role of fiber types in muscle hypertrophy: Implications for loading strategies. Strength Cond J 2014; 36: 20–25