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Effects of Contrast Phases on Automated Measurements of Muscle Quantity and Quality Using CT

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Objective: Muscle quantity and quality can be measured with an automated system on CT. However, the effects of contrast phases on the muscle measurements have not been established, which we aimed to investigate in this study.
Materials and Methods: Muscle quantity was measured according to the skeletal muscle area (SMA) measured by a convolutional neural network-based automated system at the L3 level in 89 subjects undergoing multiphasic abdominal CT comprising unenhanced phase, arterial phase, portal venous phase (PVP), or delayed phase imaging. Muscle quality was analyzed using the mean muscle density and the muscle quality map, which comprises normal and low-attenuation muscle areas (NAMA and LAMA, respectively) based on the muscle attenuation threshold. The SMA, mean muscle density, NAMA, and LAMA were compared between PVP and other phases using paired *t* tests. Bland-Altman analysis was used to evaluate the inter-phase variability between PVP and other phases. Based on the cutoffs for low muscle quantity and quality, the counts of individuals who scored lower than the cutoff values were compared between PVP and other phases.
Results: All indices showed significant differences between PVP and other phases ($p < 0.001$ for all). The SMA, mean muscle density, and NAMA increased during the later phases, whereas LAMA decreased during the later phases. Bland-Altman analysis showed that the mean differences between PVP and other phases ranged -2.1 to 0.3 cm^2 for SMA, -12.0 to 2.6 cm^2 for NAMA, and -2.2 to 9.9 cm^2 for LAMA.The number of patients who were categorized as low muscle quantity did not significant differ between PVP and other phases ($p \geq 0.5$), whereas the number of patients with low muscle quality significantly differed ($p \leq 0.002$).
Conclusion: SMA was less affected by the contrast phases. However, the muscle quality measurements changed with the contrast phases to greater extents and would require a standardization of the contrast phase for reliable measurement.
Keywords: *Body composition; Contrast phase; Imaging; Muscle; Sarcopenia*

INTRODUCTION

Sarcopenia, characterized by a significant loss of muscle quantity and function [1,2], is a skeletal muscle disorder associated with reduced physical wellness, morbidity, and mortality [3-6]. In addition, the consensus of the European Working Group on Sarcopenia in Older People (EWGSOP) 2018 highlighted that muscle quality is as important as muscle quantity [1]. Myosteatosis, a term referring to excessive fat infiltration in skeletal muscles, represents low muscle quality [7]. Myosteatosis, or low muscle quality, is considered a distinct disease from sarcopenia, as it does

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not always accompany the loss of muscle quantity and is related to poor independent survival [8-11].

CT is considered to be the standard noninvasive tool for assessing muscle quantity [12] based on differences in radiodensity (measured in Hounsfield unit [HU]) between the muscle compartment and other tissues (e.g., adipose tissue, bone, and visceral organs) [13,14]. It is advantageous to evaluate muscles because this can be done using existing CT images obtained as part of routine patient care without additional costs or examinations [15,16]. In addition, muscle quality assessment on CT is of growing interest because CT enables the quantitative measurement of fat deposition within muscles because the amount of fat has an inverse linear relationship with CT radiodensity [17]. The mean radiodensity of the muscle area is conventionally used to evaluate the muscle quality. Recently, a muscle quality map was introduced. It further segments the muscle into low- and high-quality parts with low and high radiodensities, respectively. It enables the precise evaluation of the amount and distribution of fatty tissue in muscles [7].

Most clinically acquired abdominal CT scans use contrast agents for good soft-tissue contrast, and measurements of muscle quantity and quality are generally conducted using contrast-enhanced CT [18]. Contrast agent administration elevates the mean radiodensity of the muscles [19]. However, the effects of contrast enhancement on muscle measurements have not been established, and scan timing after contrast administration varies across studies [7,15,20]. Therefore, it is questionable whether contrast administration or the scan phase after contrast administration clinically affects the reliability of muscle quantity and quality measurements. Among contrast phases, the portal venous phase (PVP) may be optimal because it is the most widely used, and it generally has a fixed scan timing.

In this regard, we aimed to investigate the effect of contrast phases on the muscle quantity and quality measured with an automated system on multiphase CT by comparing the results of PVP with those of the unenhanced phase (UP) and other phases after contrast administration. We also investigated whether the standardization of the scan phase after contrast administration is necessary for the evaluation of muscle quantity and quality.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board (Asan Medical Center, IRB No. 2018-0382), and the requirement for informed consent was waived.

Study Population and CT Techniques

From January 2012 to December 2012, consecutive participants who had undergone multiphasic abdominal CT for routine screening at a single tertiary institution were retrospectively included. For most participants, multiphasic abdominal CT was indicated for focal hepatic lesions detected on abdominal ultrasonography. Multiphasic abdominal CT was performed with 16-channel or higher CT scanners (Somatom Sensation 16, Siemens Medical Solution; LightSpeed 16, LightSpeed VCT, and Discovery CT 750 HD, GE Healthcare) using the following parameters: tube voltage, 120 kVp; effective tube current, 200 reference mAs (care dose 4D; Siemens Medical Solution) or 100–400 mA (AutomA or SmartmA; GE Healthcare); field of view, 30–40 cm; collimation, 0.31–0.75; and pitch, 0.98–1.00. Using the intravenous administration of a contrast agent at a rate of 3–4 mL/s, images obtained during the following four phases were obtained: UP, arterial phase (AP; scan delay of 20–25 seconds from the 100-HU threshold in the abdominal aorta), PVP (65–72 seconds after injection of the contrast agent), and delayed phase (DP; 3 minutes after injection of the contrast agent). Images were reconstructed using the filtered back-projection technique with the soft tissue reconstruction algorithm (B30f kernel; Siemens Medical Solution; Standard kernel, GE Healthcare) at a section thickness of 5 mm with no interslice gap.

Image Preparation and Generation of the Muscle Quality Map

Axial images at the inferior endplate level of the L3 vertebra were thoroughly selected and matched between the four phases of multiphasic abdominal CT [15] by board-certified radiologists and an experienced image analyst in consensus.

All muscles on the selected images (including the psoas, paraspinal, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, and internal and external oblique muscles) were segmented using a convolutional neural network-based automated segmentation system with a mean Dice similarity coefficient of 0.96–0.97 [21]. The skeletal muscle area (SMA), which is defined as muscle density from -29 to 150 HU with the segmented muscle area, is considered to be the index for muscle quantity [7,15].

Muscle quality was assessed using the two methods. First,

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the mean muscle density of the segmented muscle area was calculated for the four different-phase images. Second, a muscle quality map was generated using the HU of each pixel in the segmented muscle area (Fig. 1). They were categorized into either of the following components based on the HU threshold [7,15]: 1) normal attenuation muscle area (NAMA; threshold, from 30 to 150 HU) and 2) low attenuation muscle area (LAMA; threshold, from -29 to 29 HU).

Outcome and Statistical Analysis

The main outcomes were 1) muscle quantity using SMA and 2) muscle quality using the mean muscle density and muscle quality map (i.e., NAMA and LAMA). SMA, mean muscle density, NAMA, and LAMA obtained during the PVP and other phases (UP, AP, and DP) were compared. Pairwise comparisons between two phases (PVP vs. UP, AP, and DP) were conducted using a paired *t* test. To adjust the body compositions, adjusted indices [22,23], including the area (SMA, NAMA, and LAMA) divided by the height squared, weight, and body mass index (BMI), were compared in the same manner. Bland-Altman plots were used to investigate the agreement between the phases [24].

To explore the clinical impact of the contrast phase on the measurement of muscle quantity, we used the diagnostic cutoff of sarcopenia (representing low muscle quantity) devised by Kim et al. [25]. In brief, they determined the cutoffs for SMA and body composition-adjusted indices (SMA, SMA/m^2, SMA/kg, SMA/BMI) at -2 standard deviations from the mean reference value (i.e., T-scores of -2.0) using approximately 12000 healthy Korean subjects [25], in compliance with the recommendations of the EWGSOP consensus [1]. Individuals with SMA or a body composition-adjusted T-score of < -2.0 were considered to have low muscle quantity, which indicates sarcopenia. The number of individuals with low muscle quality (i.e., those with myosteatosis) was also calculated using the mean muscle density based on cutoffs devised by Martin et al. [9]: mean radiodensity of < 41 for individuals with BMI of < 25.0 and < 33 for individuals with BMI of ≥ 25. The counts of the individuals diagnosed with low muscle quantity and quality during the PVP and other phases (UP, AP, and DP) were compared using McNemar's test. No

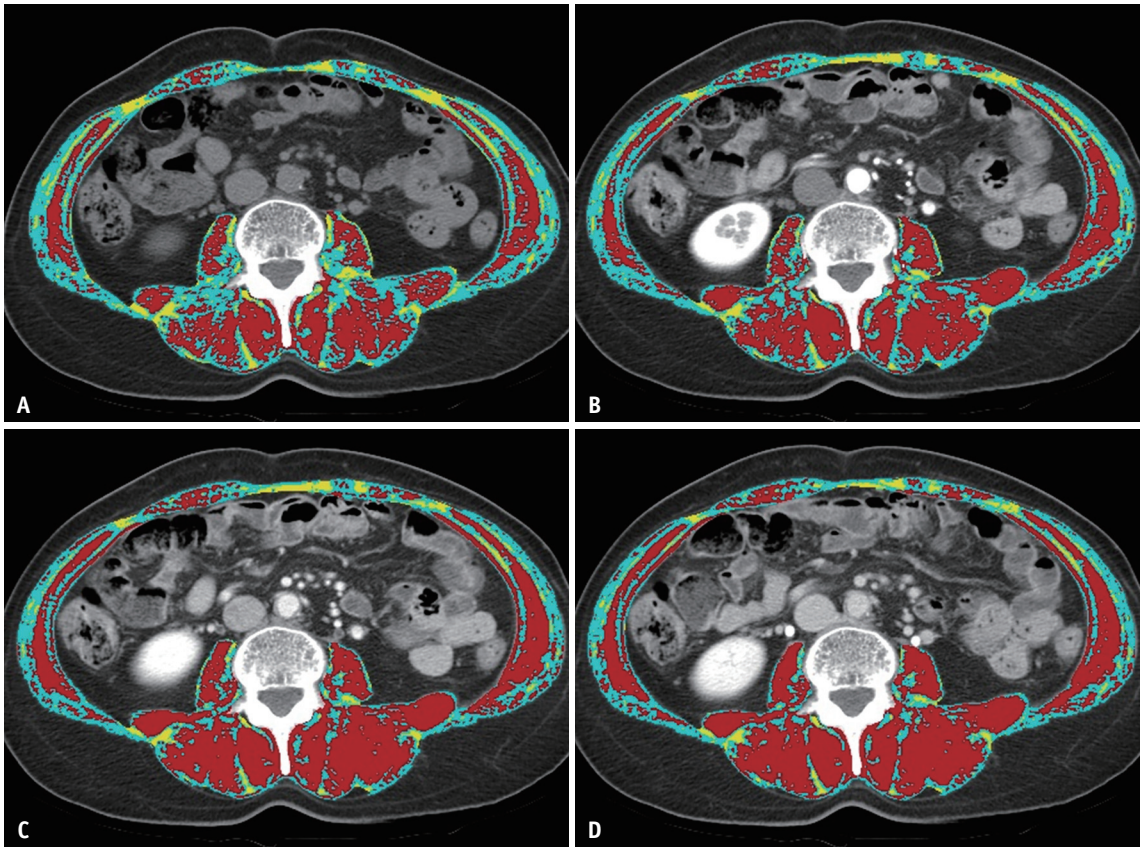

Fig. 1. Muscle quality maps for the unenhanced phase (A), arterial phase (B), portal phase (C), and delayed phase (D) CT images.
Areas in red represent the normal attenuation muscle area (threshold: from 30 to 150 HU) and those in cyan represent the low attenuation muscle area (threshold: from -29 to 29 HU). HU = Hounsfield unit

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investigation was conducted using the muscle quality map because there are no established cutoffs for the diagnosis of low muscle quality based on NAMA or LAMA.

The statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc.), IBM SPSS Statistics for Windows version 23.0 (IBM Corp.), and MedCalc version 18.2.1 (MedCalc). Differences were considered statistically significant at a p value of < 0.05, and correction for multiple comparisons was not considered because all the analyses performed were head-to-head comparisons between PVP and one of the other phases.

RESULTS

Study Population

Among 94 participants undergoing multiphasic abdominal CT, five were excluded from the analysis because of unmatched CT slices for the comparison of the four phases (n = 4) and lack of pre-contrast phase images (n = 1). Finally, the CT scans from 89 participants (mean age [range], 52.2 years [28–79 years]; 52 male and 37 female) were included in the analysis. The mean height and weight of the participants were 166.8 ± 8.6 cm and 65.6 ± 11.4 kg, respectively. Regarding BMI (mean, 23.4 ± 2.7 kg/m^2), 9 participants were underweight (BMI < 20 kg/m^2), 52 participants had normal weight (BMI, 20–24.9 kg/m^2), and 28 participants were overweight (BMI, 25–29.9 kg/m^2).

Comparison of Measurements according to Multiple CT Phases

Indices representing muscle quantity, including SMA, SMA/height^2, SMA/weight, and SMA/BMI, showed significant differences during the PVP and other phases (p < 0.001 for all comparison pairs) (Table 1). Notably, the mean SMA value during the PVP was slightly higher than that during the UP (138.2 cm^2 vs. 136.1 cm^2; mean difference, 2.1 cm^2).

All indices of muscle quality also showed significant differences during the PVP and other phases (p < 0.001 for all comparison pairs) (Table 1). Notably, the mean muscle density increased with time after the administration of the contrast agent (UP, 40.0 HU; AP, 46.2 HU; PVP, 51.5 HU; and DP, 54.2 HU). The NAMA-related indices also showed higher values during the later phases, whereas the LAMA-related indices reciprocally decreased with delays after the administration of the contrast agent.

Bland-Altman plots for two CT phases (i.e., PVP vs. UP, AP, and DP) showed higher mean area differences in NAMA (from -12.0 to 2.6 cm^2) and LAMA (from -2.2 to 9.9 cm^2) than SMA (from -2.1 to 0.3 cm^2) (Figs. 2-4). The 95% limit of agreement of the Bland-Altman plots also showed

Table 1. SMA, NAMA, and LAMA according to the CT Phase

Index	Portal Venous Phase*	Unenhanced Phase*	$P^\dagger$	Arterial Phase*	$P^\dagger$	Delayed Phase*	$P^\dagger$
Muscle quantity index							
SMA, cm^2	138.15 ± 34.02	136.08 ± 34.21	< 0.001	136.74 ± 33.72	< 0.001	138.48 ± 33.75	< 0.001
SMA/height^2, cm^2/m^2	49.15 ± 9.20	48.40 ± 9.27	< 0.001	48.64 ± 9.08	< 0.001	49.28 ± 9.09	< 0.001
SMA/weight, cm^2/kg	2.09 ± 0.28	2.06 ± 0.29	< 0.001	2.07 ± 0.28	< 0.001	2.10 ± 0.28	< 0.001
SMA/BMI	5.86 ± 1.13	5.78 ± 1.16	< 0.001	5.81 ± 1.13	< 0.001	5.88 ± 1.12	< 0.001
Muscle quality index							
Mean radiodensity, HU	51.50 ± 6.84	40.00 ± 5.85	< 0.001	46.23 ± 6.36	< 0.001	54.17 ± 6.74	< 0.001
NAMA-related index							
NAMA, cm^2	112.06 ± 31.13	100.10 ± 32.08	< 0.001	106.49 ± 31.10	< 0.001	114.64 ± 31.31	< 0.001
NAMA/height^2, cm^2/m^2	39.81 ± 8.84	35.43 ± 9.36	< 0.001	37.78 ± 8.93	< 0.001	40.73 ± 8.78	< 0.001
NAMA/weight, cm^2/kg	1.70 ± 0.33	1.51 ± 0.36	< 0.001	1.61 ± 0.34	< 0.001	1.74 ± 0.33	< 0.001
NAMA/BMI	4.77 ± 1.17	4.26 ± 1.24	< 0.001	4.53 ± 1.18	< 0.001	4.88 ± 1.17	< 0.001
LAMA-related index							
LAMA, cm^2	26.09 ± 10.43	35.98 ± 11.25	< 0.001	30.25 ± 11.13	< 0.001	23.84 ± 9.30	< 0.001
LAMA/height^2, cm^2/m^2	9.35 ± 3.62	12.97 ± 4.12	< 0.001	10.86 ± 3.94	< 0.001	8.55 ± 3.28	< 0.001
LAMA/weight, cm^2/kg	0.39 ± 0.13	0.55 ± 0.15	< 0.001	0.46 ± 0.14	< 0.001	0.36 ± 0.11	< 0.001
LAMA/BMI	1.09 ± 0.36	1.52 ± 0.38	< 0.001	1.27 ± 0.38	< 0.001	1.00 ± 0.31	< 0.001

*All data are mean ± standard deviation, †For pairwise comparison with portal venous phase using paired t test without adjustment for multiple comparison. BMI = body mass index, HU = Hounsfield unit, LAMA = low attenuation muscle area, NAMA = normal attenuation muscle area, SMA = skeletal muscle area

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that inter-phase variability was higher for muscle quality measurements (NAMA and LAMA) than for muscle quantity (SMA) measurements.

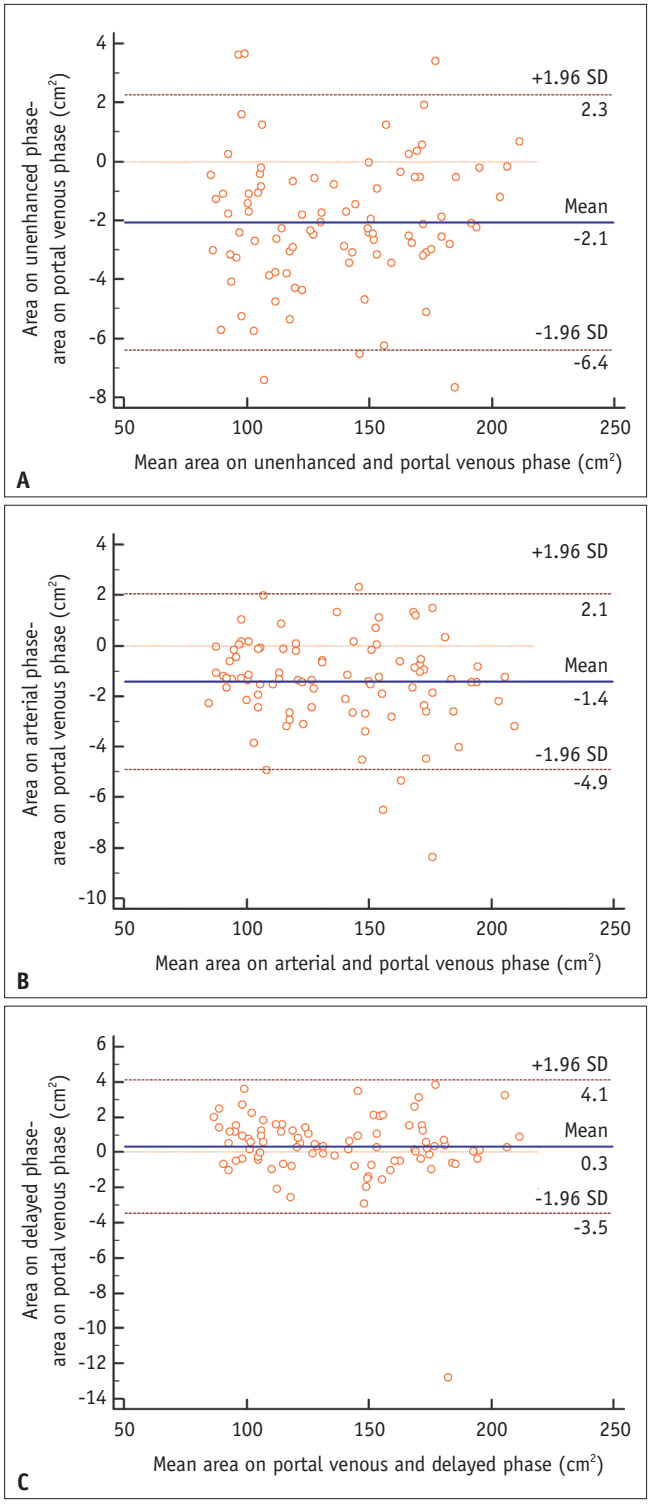

Fig. 2. Bland-Altman plots of the skeletal muscle area for the portal venous phase and unenhanced phase (A), arterial phase (B), and delayed phase (C). SD = standard deviation

Clinical Impact of the Contrast Phase on the Muscle Quantity and Quality

The demographic characteristics of the participants with and without low muscle quantity (i.e., sarcopenia) are

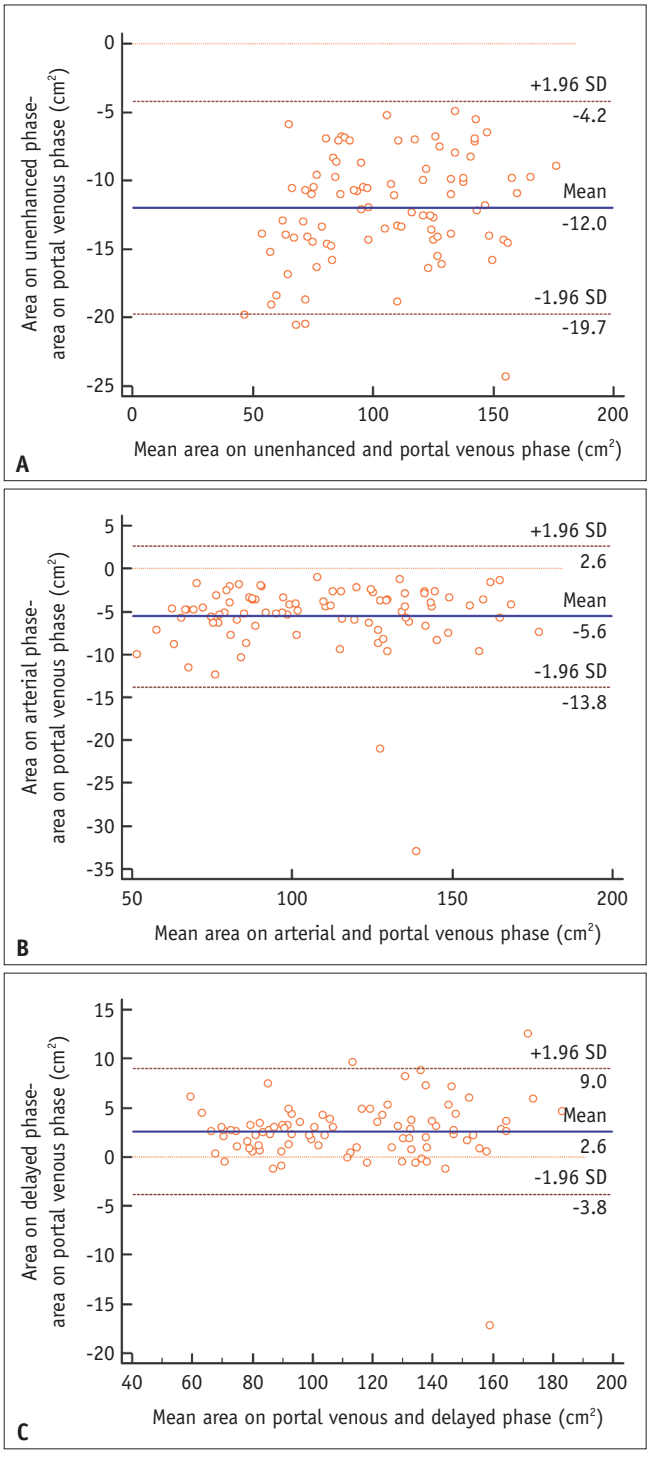

Fig. 3. Bland-Altman plots of the normal attenuation muscle area for the portal venous phase and unenhanced phase (A), arterial phase (B), and delayed phase (C). SD = standard deviation

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described in Supplementary Table 1. As presented in Table 2, based on the SMA, the number of patients with low muscle quantity differed during UP (n = 4) and other CT phases (n = 2 each in AP, PVP, and DP, respectively; Supplementary Table 2); however, these differences were not statistically significant ($p \geq 0.5$). When using other SMA indices (SMA/height2, SMA/weight, and SMA/BMI), there were no inter-phase differences in the number of patients with low muscle quantity.

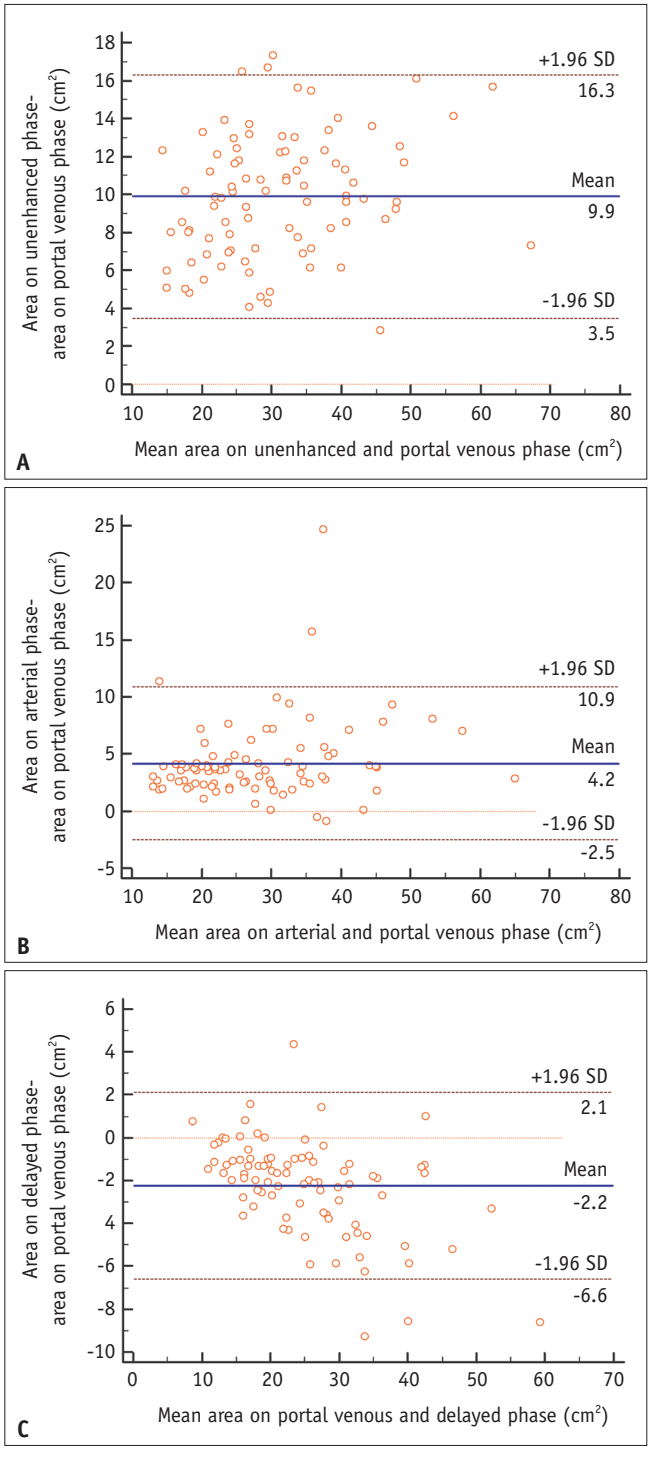

Fig. 4. Bland-Altman plots of the low attenuation muscle area for the portal venous phase and unenhanced phase (A), arterial phase (B), and delayed phase (C). SD = standard deviation

The number of individuals identified with low muscle quality, based on mean density, was 50 (56.2%), 26 (29.2%), 14 (15.7%), and 7 (7.9%) during the UP, AP, PVP, and DP, respectively. Compared with PVP, the number of individuals with low muscle quality significantly differed during the UP ($p < 0.001$), AP ($p < 0.001$), and DP ($p = 0.002$).

DISCUSSION

In this study, we evaluated the effect of the contrast phase on muscle measurement by comparing the indices representing muscle quantity and quality during PVP and the other phases. From a statistical perspective, measurements of both muscle quantity and quality were significantly altered during the UP, AP, and DP compared with the PVP ($p < 0.001$). However, from a clinical perspective, there was no significant change in the number of individuals diagnosed with low muscle quantity during the PVP and other phases, revealing the reliability of the measurement of muscle quantity irrespective of the contrast phase. However, the number of individuals with low muscle quality based on mean muscle density significantly differed during the PVP and the other phases, and the differences in NAMA and LAMA between the PVP and other phases were higher than those in SMA. Thus, the measurement of muscle quality is affected by the contrast phase when used for clinical assessments.

Several studies have investigated the effect of the contrast phase on the measurements of muscle quantity [26-29]; however, their results are conflicting. Some studies [26,27] have reported significant differences in muscle quantity across contrast phases, whereas others [28] reported no such difference. Furthermore, one multiphasic CT study showed a statistically significant difference in muscle quantity only for particular pairs of contrast phases [29]. These conflicting results may be primarily due to subtle (e.g., < 2% of segmented areas) differences in muscle quantity across the contrast phases [26,29]. Another explanation may be the difference in sample size, timing of the contrast phase, and CT parameters across the studies. Irrespective of the statistical significance of the differences, it is important to determine whether certain differences are

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Table 2. Number of Patients with Low Muscle Quantity according to the Different CT Contrast Phases

Index	Cutoff*	Portal Venous Phase†	Unenhanced Phase†	P‡	Arterial Phase†	P‡	Delayed Phase†	P‡
SMA, cm^2	119.3 (male) or 74.2 (female)	2 (2.2)	4 (4.5)	0.5	2 (2.2)	1	2 (2.2)	1
SMA/height^2, cm^2/m^2	39.8 (male) or 28.4 (female)	3 (3.4)	3 (3.4)	1	3 (3.4)	1	3 (3.4)	1
SMA/weight, cm^2/kg	1.65 (male) or 1.38 (female)	2 (2.2)	2 (2.2)	1	2 (2.2)	1	2 (2.2)	1
SMA/BMI	4.97 (male) or 3.46 (female)	3 (3.4)	3 (3.4)	1	3 (3.4)	1	3 (3.4)	1

*Based on the cutoffs devised by Kim et al. [25], †All data are presented as number and percentage in the parenthesis, ‡For pairwise comparison with portal venous phase without adjustment for multiple comparison. BMI = body mass index, SMA = skeletal muscle area

clinically meaningful for the determination of individuals with low muscle quantity. In this regard, our study aimed to directly investigate the difference in individuals diagnosed with low muscle quantity based on the established cutoff for sarcopenia [25], and our results indicate that the counts of patients with low muscle quantity were similar across the contrast phases. Our results indicate that such statistically significant but relatively small differences in muscle quantity across the contrast phases are unlikely to affect the determination of individuals with low muscle quantity.

Regarding the measurement of muscle quality, our results were consistent with those of previous studies [26-29], which reported significant differences in mean radiodensity across contrast phases. One [27] study showed substantial differences in the number of patients with low muscle quality based on cutoffs identical to ours. We also attempted to evaluate an emerging measurement tool for muscle quality, namely, the muscle quality map. It enables the visualization of the degree of fat accumulation in the muscle and can help with the precise assessment of muscle quality [7,30]. To the best of our knowledge, this is the first study to investigate the effects of the contrast phase on muscle quality measurements using a muscle quality map. Given the wider differences in NAMA and LAMA compared with SMA, the muscle quality map may be substantially affected in the diagnosis of individuals with low muscle quality. Therefore, it is necessary to determine the contrast phase for the measurement of muscle quality, and PVP may be optimal [27] for the following reasons. First, it is the most widely used, and it is embedded in most CT examinations for abdominal evaluation [31-33]. Unlike PVP, UP is not always included in the examination, particularly for individuals requiring repetitive CT scans to reduce radiation exposure hazards [34], and other contrast-enhanced phases (e.g., AP, DP) are less frequently used [31-33]. Second, the timing of PVP is usually not subject to the hemodynamics of individuals [18,35], and it generally uses fixed timing after contrast administration [18,35]. Finally, the timing of PVP is similar across institutions and for the purposes of the CT examinations.

Our study had several limitations. First, it included only healthy participants. Therefore, in future studies, additional investigations should be conducted on patients with worse health statuses (e.g., patients with malignancy) who are prone to low muscle quantity and quality. Second, since a single CT image with a 5-mm thickness during each phase was used for the comparison, the differences in the level of the CT slice across the contrast phases may, in part, affect muscle measurements. However, we excluded patients with unmatched images for the contrast phases, and the effect on muscle measurements caused by one- or two-slice differences (i.e., a difference of < 10 mm in distance) may be negligible [36]. Third, it may not be appropriate to apply pre-existing cutoffs for low muscle quality [9] because the cutoffs were devised based on the western population diagnosed with malignancy. Approximately half of the participants in our study were diagnosed with low muscle quality, although all were healthy.

In conclusion, CT measurement of muscle quantity was less affected by the contrast phases. However, the muscle quality measurements changed with the contrast phases to greater extents, and it might affect the evaluation of muscle quality and the determination of myosteatosis in clinical practice. Therefore, the CT phase after contrast administration should be standardized for reliable CT measurements of muscle quality, and the PVP may be a candidate.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0105.

Conflicts of Interest

Kim KW, Park T, and Lee J are inventors of the patent issued by the Korean Intellectual Property Office (KR patent

application number: 10-2018-0035284). None of the other authors have conflicts of interest to declare.

Author Contributions

Conceptualization: Kyung Won Kim. Data curation: Dong Wook Kim, Yousun Ko, Taeyong Park. Formal analysis: Jung Bok Lee, Dong Wook Kim. Funding acquisition: Kyung Won Kim. Investigation: Dong Wook Kim, YouSun Ko, Taeyong Park. Methodology: Dong Wook Kim, Kyung Won Kim. Project administration: Yousun Ko, Kyung Won Kim, Jeongjin Lee. Resources: Jiyeon Ha, Hyemin Ahn, Yu Sub Sung. Software: Taeyong Park, Jeongjin Lee. Supervision: Hong-Kyu Kim. Visualization: Yousun Ko, Taeyong Park. Writing—original draft: Dong Wook Kim. Writing—review & editing: Kyung Won Kim, Yousun Ko, Taeyong Park, Jiyeon Ha, Hyemin Ahn, Yu Sub Sung, Hong-Kyu Kim.

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