Contrast-Enhanced Ultrasound (CEUS) as Predictor for Early Retear and Functional Outcome After Supraspinatus Tendon Repair

Pierre Kunz,1,2 Paul Mick,1 Sascha Gross,1 Gerhard Schmidmaier,1 Felix Zeifang,3 Marc-André Weber,4 Christian Fischer 5

1Center for Orthopedics, Trauma Surgery and Spinal Cord Injury, Ultrasound Center, HTRG—Heidelberg Trauma Research Group, Heidelberg University Hospital, Schlierbacher Landstraße 200a, 69118, Heidelberg, Germany, 2Clinic for Shoulder and Elbow Surgery, Catholic Hospital Mainz, An der Goldgrube 11, 55131, Mainz, Germany, 3Ethianum Klinik Heidelberg, Voßstraße 6, 69115, Heidelberg, Germany, 4Institute of Diagnostic and Interventional Radiology, University Medical Center Rostock, Ernst-Heydemann-Straße 6, 18057, Rostock, Germany

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ABSTRACT: Supraspinatus (SSP) tendon tears represent a common indication for shoulder surgery. Yet, prediction of postoperative function and tendon retear remains challenging and primarily relies on morphologic magnetic resonance imaging (MRI)-based parameters, supported by patients’ demographic data like age, gender, and comorbidities. Considering continuously high retear rates, especially in patients with larger tears and negative prognostic factors, improved outcome prediction could be of high clinical value. Contrast-enhanced ultrasound (CEUS) enables an assessment of dynamic perfusion of the SSP muscle. As a potential surrogate for muscle vitality, CEUS might reflect functional properties of the SSP and support improved outcome prediction after tendon repair. Fifty patients with isolated SSP tendon tears were prospectively enrolled. Preoperatively, SSP muscle perfusion was quantified by CEUS and conventional morphologic parameters like tear size, fatty infiltration, and tendon retraction were assessed by MRI. At six months follow-up, shoulder function, tendon integrity, and muscle perfusion were reassessed. The predictive value of preoperative CEUS for postoperative shoulder function and tendon integrity was evaluated. 35 patients entered the statistical analysis. Preoperative CEUS-based assessment of SSP perfusion significantly correlated with early postoperative shoulder function (Constant, r = 0.48, p < 0.018) and tendon retear (r = 0.67, p < 0.001). CEUS-based subgroup analysis identified patients with exceptionally high, respectively low risk for tendon retear. CEUS-based assessment of the SSP seemed to predict early shoulder function and tendon retear after SSP repair and allowed to identify patient subgroups with exceptionally high or low risk for tendon retear. © 2019 The Authors. Journal of Orthopaedic Research® published by Wiley Periodicals, Inc. on behalf of Orthopaedic Research Society. J Orthop Res 38:1150–1158, 2020

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Tranisc Small or degenerative damage to the rotator cuff is one of the most common indications for shoulder surgery, with an estimated prevalence of 20–25%.1

Besides the primary tendon repair, therapeutic options include prolonged conservative treatment and other surgical procedures like subacromial decompression, bursectomy, or debridement, especially in degenerative tears.2,3 Despite the high incidence and socioeconomic burden of rotator cuff-related shoulder impairment, prediction of tendon healing and functional outcome is still challenging, especially in patients with assumable degenerative aspects to their tear. For such patients, alternative non-reconstructive surgical procedures like subacromial decompression might yield comparable results regarding pain and functional outcome.4,5 With frequently reported high retear rates of 25–45% after tendon repair, a careful selection of patients achieving a sustained benefit due to successful tendon healing appears paramount.5,6

Goutallier et al.6 proposed fatty muscle infiltration assessed by computed tomography as one of the first commonly applied predictors for successful tendon healing. Being adapted for the use in MRI, fatty infiltration and other MRI-based markers such as tear size or tendon retraction represent morphologic parameters, which seem to only partially reflect functional properties and regenerative potential of the musculotendinous SSP system.5,9–11

Although these parameters are widely translated into the clinical routine of cuff tear treatment, their reported predictive strengths are moderate-to-weak and, therefore, still controversially discussed in the current literature. Due to the in part controversial results in terms of tendon integration and functional outcome after tendon repair,6,7,12–15 there is an ongoing demand for improved and stronger outcome predictors after cuff repair to further assist the surgeon in a better prediction of tendon integration in case of a planned tendon repair.

Functional biomarkers might reflect the biological properties and regenerative potential of the musculotendinous SSP system more accurately than a conventional morphologic assessment by MRI. Contrast-enhanced ultrasound (CEUS) allows for a dynamic quantification of perfusion in muscle tissue. Being closely linked to the responsiveness and recruitment of muscle fibers and the muscle metabolism, CEUS has been suggested as functional real-time biomarker for muscle
vitality and function beyond morphologic aspects.\textsuperscript{16–19} Originally implemented for assistive diagnostics of liver and kidney tumors in 2004, CEUS has nowadays been translated into the clinical routine of numerous pathologies and was lately evaluated for various musculoskeletal indications, including shoulder pathologies.\textsuperscript{20–25} In reverse shoulder arthroplasty, CEUS-based quantification of deltoid properties was significantly associated with shoulder function after reverse shoulder arthroplasty.\textsuperscript{25} In a recent retrospective study including patients after SSP tendon repair, CEUS-based supraspinatus muscle perfusion significantly correlated with postoperative tendon healing and shoulder function, with a low postoperative SSP muscle perfusion being associated with tendon retear and inferior shoulder function.\textsuperscript{24}

Within this prospective cohort study, we assessed the SSP muscle perfusion by CEUS in patients receiving an SSP repair. We hypothesized, that preoperative SSP muscle perfusion quantified by CEUS is predictive for early postoperative tendon integration and functional outcome after rotator cuff repair.

\textbf{MATERIALS AND METHODS}

\textbf{Study Cohort}

50 patients with unilateral rotator cuff tear of the SSP tendon were prospectively enrolled. The study has been approved by the local ethics committee (S-153/2015), conducted in accordance to the Helsinki convention in its most recent form and is registered at the German clinical trials register (DRKS00010736). Informed consent was obtained from all individual participants included in the study. Patients exclusion criteria are shown in detail referring to a consolidated standard of reporting trials (CONSORT) and standards for reporting of diagnostic accuracy (STARD) flow diagram (Fig. 1).\textsuperscript{26,27}

\textbf{Study Protocol}

Patients were examined preoperatively and six months after SSP tendon repair, receiving functional, MRI-based, and ultrasonographic assessment of both shoulders. CEUS perfusion examination included dynamic perfusion quantification of the supraspinatus and trapezius muscle by peak enhancement in arbitrary units (PE in a.u.). Exclusion criteria were prior surgery of the affected shoulder, severe impairment of the contralateral shoulder, as well as contraindications to the contrast agent SonoVue® (Bracco Imaging, Milan, Italy).

Pre- and postoperative shoulder function was assessed applying the normalized Constant Murley score (CS), the American Shoulder and elbow score (ASES), and the Disabilities of the arm, shoulder, and hand score (DASH).

MRI-based fatty infiltration of the SSP muscle was assessed according to the Goutallier classification in a T1-weighted Y-plane view of the scapula. Tendon retraction was assessed according to the Patte classification in a proton-density weighted coronal sequence.\textsuperscript{8,28} Antero-posterior extent of tears was measured in millimeters using a proton-density weighted sagittal Y-plane view. Postoperative tendon integrity was classified as intact, partial or full retear in coronary T2, and proton-density weighted

\begin{figure}[h]
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\includegraphics[width=\textwidth]{patients_flow_chart.png}
\caption{Patients flow chart. [Color figure can be viewed at wileyonlinelibrary.com]}
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\textbf{Figure 1.} Patients flow chart. [Color figure can be viewed at wileyonlinelibrary.com]
sequences. Immediately after surgery, the patient’s arm was immobilized in an abduction brace for six weeks, during which physiotherapy focused on passive mobilization followed by active mobilization for another six months.

Quantification of SSP Muscle Perfusion by CEUS
All sonographic examinations, including CEUS, were performed by the same DEGUM (German Society of Ultrasound in Medicine) III certified consultant orthopedic and trauma surgeon at our institution. The examinations were performed preoperatively and at 6 months follow-up using an ACUSON S3000 device (Siemens Healthineers, Erlangen, Germany).

With the patients sitting, their arms hanging relaxed in neutral position and their palms facing inwards as previously described, a 9L4 probe was used to create a sagittal Y-plane section of the SSP muscle within the suprascapular fossa as described earlier (Fig. 2).

Each patient then performed lateral arm raises in a 30° antverted and pronated position of the arm for 120 s at a frequency of 1 Hz to saturate SSP muscle perfusion. A 90 s videoclip was then recorded in line with the most recent recommendations of the EFSUMB, followed by an immediate application of a 4.8 ml bolus of the contrast agent SonoVue®, injected via an antecubital arm vein and flushed by 10 ml of 0.9% saline solution. Muscle perfusion quantification was conducted with a standardized parameter preset (depth of field 4.5 cm, focal point 4 cm, mechanical index 0.09, gain 3 dB) using the Cadence™ contrast mode (Siemens Medical Solutions Inc., Malvern, PA). Videoclips were further analyzed using the VueBox® quantification software V7.1 (Bracco Imaging, Milan, Italy), applying a standardized region of interest (ROI, a circle with a diameter of 1 cm) for all perfusion quantifications, positioned within the best perfused muscle tissue area of the SSP and trapezius (“HotSpot” Fig. 2). In case of a trapezius diameter below 1 cm, the ROI size was adjusted accordingly. To avoid perfusion distortion, any prominent vessels and fasciae were excluded. Time-intensity curves (TIC) were generated and derived parameters were calculated. For statistical analysis, we used the PE in a.u., as this parameter independently reflects the highest quantifiable blood volume within the selected muscular HotSpot.

Each raw SSP muscle PE was referenced to the corresponding healthy trapezius perfusion PE to account for inter-individual, physiologic differences of contrast-agent inflow. Therefore, the statistically utilized perfusion parameter represents the SSP muscle PE, relative to the trapezius muscle perfusion (PErel, in percent).

Data Analysis
Statistical analysis was performed using SPSS V25 software (SPSS, Chicago, IL). An unpaired t test was applied to assess differences between groups of fatty infiltration and perfusion regarding tendon integration and functional outcome. A paired t test was applied to assess the overall differences of pre- and postoperative function, perfusion, and fatty infiltration. \( \chi^2 \) test was applied to assess the predictive value of preoperative PErel perfusion and fatty infiltration for tendon retear. The Spearman correlation (\( \tau \)) was applied to assess the correlations between preoperative perfusion or fatty infiltration with postoperative functional outcome. \( p \)-Values \(< 0.05\) were considered statistically significant.

To evaluate whether individual preoperative SSP perfusion allows for discrimination in regards of tendon integration and postoperative shoulder function, patients were assigned into four subgroups, based on the natural distribution of preoperative SSP perfusion (PE\text{rel}), with the quartiles serving as cut-off values. A Kruskal–Wallis test was applied for the comparison of functional outcome between more than two patient subgroups. Outliers were defined as mean value ± 2 standard deviations. Reported p-values are two-sided.

RESULTS
Patient Characteristics, Functional Outcome, and Tendon Integrity
Out of 50 enrolled patients, nine patients refused to receive contrast agent for the follow-up and in two patients the surgeon intraoperatively decided against tendon repair in favor of subacromial decompression. Four patients had to be excluded for other reasons.

Figure 2. Contrast-enhanced ultrasound examination setup with the probe positioning medial to the scapular notch. Left top rectangle: B-Mode of the sectional plane with anatomical landmarks, as indicated in the left bottom rectangle. Right top rectangle shows the Siemens-specific Cadence™ contrast pulse sequencing mode after inflow of the contrast agent (green circle = HotSpot region of interest). The bottom right rectangle indicates the dynamic time–intensity curve of the contrast agent, representing the peak enhancements of the trapezius and the supraspinatus. [Color figure can be viewed at wileyonlinelibrary.com]
In preoperative MRI, fatty infiltration was distributed as follows: grade 0 = 6 patients; grade 1 = 13 patients; grade 2 = 9 patients; grade 3 = 7 patients; grade 4 = no patients. With 15 patients demonstrating a progression at follow-up, the mean fatty infiltration increased from 1.5 ± 1 to 2 ± 0.9 (p < 0.001). Preoperative grade of tendon retraction was grade 1 in 14 patients, grade 2 in 14 patients, and grade 3 in 7 patients. The mean preoperative antero-posterior tear size was 13.6 mm (range: 5.5–22.8 mm). Seven patients had a Bateman type 1, 28 patients a type 2, and no patient a type 3 tear.

The mean preoperative SSP muscle perfusion ratio (PE_rel) was 27.5 ± 24.8%. Interestingly, CEUS-based SSP muscle perfusion (PE_rel) significantly increased six months after tendon repair to a mean postoperative PE_rel of 44.8 ± 35.6% (p = 0.015, Fig. 3) within the whole study cohort. Patients suffering from a retear at follow-up showed an increase from a PE_rel of 14.2 ± 16.1% to 23.8 ± 20.3% (p = 0.003), whereas patients with intact tendons at follow-up increased from a PE_rel of 39.1 ± 26.41% to 61.4 ± 37.5% (p = 0.069, Fig. 3).

Higher CEUS-based muscle perfusion values (PE_rel) significantly correlated with lower grades of fatty infiltration in MRI—both pre- and postoperative (preOP: r = −0.42, p = 0.019; postOP: r = 0.39, p = 0.033), whereas no correlations were observed between CEUS-based muscle perfusion and MRI-based tendon retraction or tendon tear width. CEUS-based SSP muscle perfusion ratio (PE_rel) did not significantly vary according to smoking habits, age, gender, or BMI in our study cohort.

Predictive Value of MRI-Based Parameters
In the analysis of predictive value of the conventional MRI-based parameters fatty infiltration, tear size and tendon retraction, none of these parameters revealed significant correlations with postoperative shoulder function with the given limited sample size of our study cohort. Although a trend toward higher retear rates with higher grades of fatty infiltration could be observed, it did not reach the level of significance in our study cohort (retear rate grade 0: 0%, retear rate grade 1: 30%, grade 2: 44%, grade 3: 42%; χ² for all subgroups: p = 0.232; χ² for grade 0 vs. grade 3: p = 0.07). Likewise, correlation of preoperative grade of tendon retraction with postoperative tendon retear revealed a trend, yet did not reach the level of significance, with 29% of patients with grade 1, 21% of patients with grade 2, and 57% of patients with grade 3 retraction demonstrating a full retear at 6 months follow-up (χ² for all subgroups: p = 0.33; χ² for grade 1 vs. grade 3: p = 0.39).

Patients demonstrating a retorn versus intact tendon at follow-up did not significantly vary regarding preoperative tear size, neither for absolute values in mm, nor according to the Bateman classification (p = 0.421, Kruskal–Wallis, respectively, p = 0.386, χ²).

Predictive Value of CEUS-Based SSP Perfusion
Preoperative CEUS-based SSP perfusion significantly correlated with postoperative shoulder function in our study cohort (CS: r = 0.48, p = 0.004; ASES: r = 0.42, p = 0.013; DASH score: r = 0.47, p = 0.004; Fig. 4). Furthermore, preoperative SSP perfusion strongly correlated with postoperative shoulder function (r = 0.48, p = 0.004).
differed between patients with an intact, respectively fully retorn SSP tendon at follow-up ($p = 0.002$; Fig. 5).

As the clinical value of a potential novel outcome predictor largely depends on its discriminatory power, we evaluated whether preoperative SSP perfusion could clearly discriminate between patients achieving a good or poor postoperative shoulder function, respectively postoperative tendon healing.

We, therefore, assigned all patients into four subgroups, with the quartiles of CEUS-based SSP perfusion ($\text{PE}_{\text{rel}}$) serving as cut-off values (1st quartile: <$9.55\%$; 2nd quartile: <$20.77\%$; 3rd quartile: <$56.39\%$; 4th quartile: >56.39\%, Fig. 6).

The four subgroups significantly differed in regards of mean postoperative CS (patients within the 1st quartile: $52 \pm 27$, within the 2nd quartile: $73 \pm 20$, within the 3rd quartile: $62 \pm 26$, within the 4th quartile: $89 \pm 10$; $p = 0.005$, Kruskal–Wallis), with the strongest distinction between patients with weak (1st quartile) and very strong perfusion (4th quartile) (mean CS: $52 \pm 27$ vs. $89 \pm 10$, $p = 0.003$; mean ASES: $54 \pm 26$ vs. $88 \pm 9$, $p = 0.004$; mean DASH: $59 \pm 25$ vs. $92 \pm 5$, $p = 0.004$).

**Figure 4.** Correlation of preoperative supraspinatus (SSP) perfusion ($\text{PE}_{\text{rel}}$ [%]) with postoperative shoulder function (Constant score); $r = 0.48$, $p = 0.004$. $r$ = correlation coefficient, $p$ = level of significance, $\text{PE}_{\text{rel}}$ = relative peak enhancement.

**Figure 5.** Distribution of preoperative supraspinatus (SSP) perfusion of patients presenting either intact or fully retorn tendons at follow-up (median $\text{PE}_{\text{rel}} = 35\%$, interquartile range = 48\%, respectively, median $\text{PE}_{\text{rel}} = 10\%$, interquartile range = 15\%, $p = 0.002$). Gray boxes indicate first and third quartile and interquartile range. Median is indicated by black line within the boxes. Whiskers represent the 1.5-fold interquartile distance above the upper quartile and the minimum parameter below the lower quartile. $p$ indicates the level of significance, $\text{PE}_{\text{rel}}$ = relative peak enhancement.

**Figure 6.** Preoperative $\text{PE}_{\text{rel}}$ for each study patient and corresponding tendon integrity at follow-up. Green bars indicate intact tendons at follow-up, yellow bars partially retorn, and red bars fully retorn tendons. Patients were assigned into four subgroups, based on the natural distribution of preoperative SSP perfusion ($\text{PE}_{\text{rel}}$), with the quartiles serving as cut-off values (very strong: $\text{PE}_{\text{rel}} > 56.39\%$, strong: $\text{PE}_{\text{rel}}$ between 20.77\% and 56.39\%, moderate: $\text{PE}_{\text{rel}}$ between 9.55\% and 20.77\%, and weak: $\text{PE}_{\text{rel}} < 9.55\%$). $\text{PE}_{\text{rel}}$ = relative peak enhancement. [Color figure can be viewed at wileyonlinelibrary.com]
We then assessed the percentage of patients achieving an above or below median postoperative shoulder function (median CS: 71.5) within each subgroup. Nearly, all patients (88%) with very high preoperative SSP perfusion (PErel within 4th quartile) showed an intact tendon at follow-up, 89% of patients with weak preoperative SSP perfusion (PErel within 1st quartile) presented a shoulder function below the median CS ($p = 0.039, \chi^2$).

Accordingly, we analyzed tendon integrity at follow-up within these patient subgroups. Tendon integrity significantly varied among the subgroups. Whereas all patients with a very strong preoperative SSP perfusion (PErel within 4th quartile) showed an intact tendon at follow-up, 89% of patients with weak preoperative SSP perfusion (PErel within 1st quartile) presented a tendon retear (all groups: $p = 0.002$; very strong vs. weak: $p = 0.001$; strong vs. moderate: $p = 0.270$, $\chi^2$). The discriminatory power was also evident between the intermediate subgroups (very strong vs. moderate, $p = 0.016$; strong vs. weak, $p = 0.006$) and indicated a continuous effect throughout all subgroups (Fig. 7). These findings were independent from patient characteristics like BMI, age, and gender, and also from MRI-based parameters. Figure 8 shows exemplary CEUS measurements of patients with strong (a/b), respectively, weak (c/d) SSP perfusion.

**DISCUSSION**

In this prospective study, we assessed the preoperative SSP muscle perfusion by CEUS in patients with SSP tears and detected a predictive value for postoperative tendon integrity and shoulder function. In view of the large body of literature on rotator cuff tears and outcome predictors, frequently reported retear rates around 25–45% seem noteworthy and indicate a potential for improvement in this field.1,2 Despite the establishment of morphological MRI-based and patient-related outcome predictors, a valid prediction of tendon healing often appears challenging due to a weak to moderate predictive strength of these parameters. Patient stratification according to their individual SSP tendon/muscle properties currently relies on such MRI-based morphological and patient-related parameters. Whereas these without doubt support the treatment decision,33–35 their predictive value, especially for functional outcome remains controversially discussed.7,33,36 Accordingly, a relevant number of patients at risk for poor functional outcome or failed tendon healing remains undetected. Novel outcome predictors allowing a better discrimination regarding tendon healing and shoulder function after cuff repair might therefore be of high clinical value.

Functional biomarkers like muscle perfusion by CEUS might better reflect the regenerative potential of the SSP muscle/tendon system than morphologic parameters assessed by MRI, and might, therefore, more accurately identify patients being predisposed for an early tendon retear. Assessing microcirculation as surrogate parameter for tissue vitality and metabolism,18,37 CEUS offers insight into muscle tissue properties beyond morphologic aspects by conventional imaging modalities. Accordingly, CEUS-based SSP perfusion has already been described to directly correlate with shoulder function in a retrospective study including 67 patients after cuff repair.24

In this prospective study, CEUS-based preoperative SSP muscle perfusion revealed a correlation with postoperative tendon integrity and functional outcome and enabled the identification of patient subgroups with exceptionally high, respectively, low risk for tendon retear in our study cohort. The predictive value of SSP perfusion (PErel) for tendon healing was superior to MRI-based fatty infiltration, tendon retraction, and tear size—both within our study cohort and compared with previous studies assessing MRI-based predictors.14,38,39

Considering muscle perfusion being associated with intramuscular metabolic characteristics and the amount of recruited muscle fibers,18,20,37,40 the altered preoperative SSP perfusion may directly reflect its regenerative potential and muscle physiology.41–43
In line with this, it appears plausible that the SSP muscle undergoes physiological changes after tendon repair. Such changes have yet not been detected by MRI-based parameters, with an irreversibility or even progress of fatty infiltration after tendon repair,\textsuperscript{9,44} despite an improvement of shoulder function. Accordingly, with 15 patients presenting a progression, we detected an increased average fatty infiltration at follow-up within our whole study cohort. In contrast, CEUS revealed a significant increase of the average SSP muscle perfusion six months after tendon repair within the study cohort, correlating with shoulder function and being well-compatible with increased postoperative muscle demands. This might be explained by remaining healthy muscle fibers adapting to the repair, resulting in better muscular utilization of these muscle portions. Whereas the detection of such adaptation processes seems noteworthy, we do not know yet, whether they are of clinical relevance and how they proceed in a longer follow-up.

As CEUS-based perfusion quantification represents a novel and yet not established potential outcome predictor for patients with rotator cuff tears and since this is the first prospective study investigating its predictive value, it is difficult to compare our data with other studies. Accordingly, we carefully analyzed our study cohort for potential confounders’ being either associated with individual muscle perfusion or possibly represent a selective patient cohort bias.

Our study cohort was comparable with larger previous studies investigating functional outcome prediction after tendon repair regarding patients’ age, gender, pre- and postoperative function detected by CS, ASES, and DASH, as well as the cause of the SSP tear.\textsuperscript{45,46} Distribution of the MRI-based morphologic parameters fatty infiltration, tendon retraction, and tear size were also comparable with previously reported studies.\textsuperscript{9,47,48} A relatively small tendon tear size within our study cohort is partially explained by our study protocol with selective inclusion of isolated supraspinatus tears. In line with other previous studies, preoperative MRI-based parameters did not significantly predict postoperative shoulder function and tendon retear within our cohort.\textsuperscript{9,14,15,49} However, since it was not a main aspect of our study to evaluate the previously reported conventional MRI-based predictors, we cannot rule out that we missed predictive effects due to our small cohort size and herefrom resulting low statistical power for the expected moderate-to-weak effects of these parameters. The tendon retear rate within our cohort was relatively high, yet still well in the range of previous reports.\textsuperscript{11,34,44}

Muscle perfusion might possibly be biased by patient-specific attributes like smoking, BMI, or diabetes mellitus, yet we could not detect significant effects on the predictive value of CEUS-based preoperative muscle perfusion for either one of them. This might be explained by the circumstance that we applied perfusion ratios with the patients’ healthy trapezius used as reference, therefore, neutralizing possible patient-specific alterations. In a previous retrospective study applying CEUS in patients with rotator cuff tears, no significant correlations could be detected for smoking, yet patients with a high BMI demonstrated slightly lower relative perfusion values comparable with our findings.\textsuperscript{24}

Several limitations apply to this preliminary prospective study. First, our study cohort is small, and approximately 30% of enrolled patients could not be followed-up, limiting the statistical power of our results. Next, despite a dedicated software-assisted quantification, CEUS remains semi-objective and might be error prone due to the necessity of manual positioning of the...
ROIs. To reduce thereby arising effects, we standardized ROI selection applying a circular, predefined HotSpot ROI, according to a routinely applied micro-vessel quantification method in tumor research. Yet, it remains unproven, whether perfusion quantification within HotSpots always reflects the true regenerative potential of the SSP muscle. Another unknown bias might lie within an SSP repair induced lateralization of the muscle belly, bringing higher perfused muscle tissue into the CEUS sectional plane, thus enlarging perfusion differences to those muscles with failed repair. Furthermore, our postoperative assessment was rather early, and eventual functional outcome may further improve within the first two years after SSP tendon repair. Accordingly, the presented results need to be validated by longer follow-up and independent validation studies.

Despite these limitations, the presented results to our understanding suggest preoperative SSP muscle assessment by CEUS as an interesting diagnostic modality with the potential to contribute to a further improved prediction of functional outcome and tendon integration in patients facing a cuff repair.

**CONCLUSION**

CEUS-based preoperative SSP muscle perfusion seems to reflect muscle vitality and the regenerative potential of the supraspinatus system. Individual assessment of muscle perfusion by CEUS further seems to be predictive for early shoulder function and tendon healing after tendon repair and appears to support an identification of patient subgroups with exceptionally high, respectively low risk for tendon retear and therefore a preoperative risk-stratification.

**AUTHORS’ CONTRIBUTION**

P. K.: research design, acquisition, analysis and interpretation of data, drafting the paper; P. M.: acquisition, analysis and interpretation of data, drafting the paper; S. G.: research design, drafting the paper or revising it critically; G. S.: drafting the paper or revising it critically; F. Z.: drafting the paper or revising it critically; M.-A. W.: research design, drafting the paper or revising it critically; C. F.: research design, acquisition, analysis and interpretation of data, drafting the paper. The manuscript has been read and approved by all authors, and all authors are convinced that the manuscript represents honest work.

**REFERENCES**

1. Minagawa H, Yamamoto N, Abe H, et al. 2013. Prevalence of symptomatic and asymptomatic rotator cuff tears in the general population: from mass-screening in one village. J Orthop 10:8–12.
2. Matsen FA 3rd. 2008. Clinical practice. Rotator-cuff failure. N Engl J Med 358:2138–2147.
3. Pedowitz RA, Yamaguchi K, Ahmad CS, et al. 2011. Optimizing the management of rotator cuff problems. J Am Acad Orthop Surg 19:368–379.
4. Flurin PH, Hardy P, Abadie P, et al. 2013. Rotator cuff tears after 70 years of age: a prospective, randomized, comparative study between decompression and arthroscopic repair in 154 patients. Orthop Traumatol Surg Res 99:S371–S378.
5. Kukkonen J, Joukainen A, Lehtinen J, et al. 2015. Treatment of nontraumatic rotator cuff tears: a randomized controlled trial with two years of clinical and imaging follow-up. J Bone Joint Surg Am 97:1729–1737.
6. Mall NA, Tanaka MJ, Choi LS, et al. 2014. Factors affecting rotator cuff healing. J Bone Joint Surg Am 96:778–788.
7. McElvaney MD, McGoldrick E, Gee AO, et al. 2015. Rotator cuff repair: published evidence on factors associated with repair integrity and clinical outcome. Am J Sports Med 43:491–500.
8. Goutallier D, Postel JM, Bernageau J, et al. 1994. Fatty muscle degeneration in cuff ruptures. Pre- and postoperative evaluation by CT scan. Clin Orthop Relat Res 78–83.
9. Gladstone JN, Bishop JY, Lo IKY, Flatow EL. 2007. Fatty infiltration and atrophy of the rotator cuff do not improve after rotator cuff repair and correlate with poor functional outcome. Am J Sports Med 35:719–728.
10. Choi S, Kim MK, Kim GM, et al. 2014. Factors associated with clinical and structural outcomes after arthroscopic rotator cuff repair with a suture bridge technique in medium, large, and massive tears. J Shoulder Elbow Surg 23:1675–1681.
11. Elia F, Azoulay V, Lebon J, et al. 2017. Clinical and anatomic results of surgical repair of chronic rotator cuff tears at ten-year minimum follow-up. Int Orthop 41:1219–1226.
12. Chaudhury S, Dines JS, Delos D, et al. 2012. Role of fatty infiltration in the pathophysiology and outcomes of rotator cuff tears. Arthritis Care Res (Hoboken) 64:76–82.
13. Fermont AJM, Wolterbeek N, Wessel RN, et al. 2014. Prognostic factors for successful recovery after arthroscopic rotator cuff repair: a systematic literature review. J Orthop Sports Phys Ther 44:153–163.
14. Khair MM, Lehman J, Tsouris N, et al. 2016. A systematic review of preoperative fatty infiltration and rotator cuff outcomes. HSS J 12:170–176.
15. Kim IB, Kim MW. 2016. Risk factors for retear after arthroscopic repair of full-thickness rotator cuff tears using the suture bridge technique: classification system. Arthroscopy 32:2191–2200.
16. Hildebrandt W, Schwarzbach H, Pardun A, et al. 2017. Age-related differences in skeletal muscle microvascular response to exercise as detected by contrast-enhanced ultrasound (CEUS). PlOS One 12:e0172771.
17. Amarteifio E, Wormsbecher S, Krix M, et al. 2012. Dynamic contrast-enhanced ultrasound and transient arterial occlusion for quantification of arterial perfusion reserve in peripheral arterial disease. Eur J Radiol 81:3332–3338.
18. Weber MA, Krakowski-Rosen H, Hildebrandt W, et al. 2007. Assessment of metabolism and microcirculation of healthy skeletal muscles by magnetic resonance and ultrasound techniques, J Neuroimaging 17:323–331.
19. Murrant CL, Sarelius IH. 2000. Coupling of muscle metabolism and muscle blood flow in capillary units during contraction. Acta Physiol Scand 168:531–541.
20. Krix M, Weber MA, Krakowski-Rosen H, et al. 2005. Assessment of skeletal muscle perfusion using contrast-enhanced ultrasonography. J Ultrasound Med 24:431–441.
21. Piscaglia F, Nolaece C, Dietrich C, et al. 2012. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschall Med 33:33–59.
22. Doll J, Gross S, Weber MA, et al. 2019. The AMANDUS project—advanced microperfusion assessed non-union diagnostics with contrast-enhanced ultrasound (CEUS) for the
detection of infected lower extremity non-unions. Ultrasound Med Biol 45:2281–2288.
23. Fischer C, Frank M, Kunz P, et al. 2016. Dynamic contrast-enhanced ultrasound (CEUS) after open and minimally invasive locked plating of proximal humerus fractures. Injury 47:1725–1731.
24. Fischer C, Gross S, Zeifang F, et al. 2018. Contrast-enhanced ultrasound determines supraspinatus muscle atrophy after cuff repair and correlates to functional shoulder outcome. Am J Sports Med 46:2735–2742.
25. Fischer C, Krammer D, Hug A, et al. 2017. Dynamic contrast-enhanced ultrasound and elastography assess deltoid muscle integrity after reverse shoulder arthroplasty. J Shoulder Elbow Surg 26:108–117.
26. Bossuyt PM. 2004. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Fam Pract 21:4–10.
27. Schulz KF, Altman DG, Moher D. 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother 1:100–107.
28. Lippe J, Spang JT, Leger RR, et al. 2012. Inter-rater agreement of the Goutallier, Patte, and Warner classification scores using preoperative magnetic resonance imaging in patients with rotator cuff tears. Arthroscopy 28:154–159.
29. Sidhu P, Cantisani V, Dietrich C, et al. 2018. The EFSUMB guidelines and recommendations for the clinical practice of contrast-enhanced ultrasound (CEUS) in non-hepatic applications: update 2017 (long version). Ultraschall Med 39:e2–e44.
30. Tang MX, Mulvana H, Gauthier T, et al. 2011. Quantitative contrast-enhanced ultrasound imaging: a review of sources of variability. Interface Focus 1:520–539.
31. Namdari S, Donegan RP, Chamberlain AM, et al. 2014. Factors affecting outcome after structural failure of repaired rotator cuff tears. J Bone Joint Surg Am 96:99–105.
32. Willinger L, Lacheta L, Beitzel K, et al. 2018. Clinical outcomes, tendon integrity, and shoulder strength after revision rotator cuff reconstruction: a minimum 2 years’ follow-up. Am J Sports Med 46:2700–2706.
33. Saccomanno MF, Sircana G, Cazzato G, et al. 2015. Prognostic factors influencing the outcome of rotator cuff repair: a systematic review. Knee Surg Sports Traumatol Arthrosc 24:3809–3819.
34. Osti L, Buda M, Del Buono A. 2013. Fatty infiltration of the shoulder: diagnosis and reversibility. Muscles Ligaments Tendons J 3:351–354.
35. Sahni V, Narang AM. 2016. Review article: risk factors for poor outcome following surgical treatment for rotator cuff tear. J Orthop Surg (Hong Kong) 24:265–268.
36. Lambers Heerspink FO, Dorrestijn O, van Raay JJAM, Diercks RL. 2014. Specific patient-related prognostic factors for rotator cuff repair: a systematic review. J Shoulder Elbow Surg 23:1073–1080.
37. Weber MA, Krakowski-Roosen H, Delorme S, et al. 2006. Relationship of skeletal muscle perfusion measured by contrast-enhanced ultrasonography to histologic microvascular density. J Ultrasound Med 25:583–591.
38. Jeong HY, Kim HJ, Jeon YS, et al. 2018. Factors predictive of healing in large rotator cuff tears: is it possible to predict retear preoperatively? Am J Sports Med 46:1693–1700.
39. Chung SW, Kim JY, Kim MH, et al. 2013. Arthroscopic repair of massive rotator cuff tears: outcome and analysis of factors associated with healing failure or poor postoperative function. Am J Sports Med 41:1674–1683.
40. Womack L, Peters D, Barrett EJ, et al. 2009. Abnormal skeletal muscle capillary recruitment during exercise in patients with type 2 diabetes mellitus and microvascular complications. J Am Coll Cardiol 53:2175–2183.
41. Mendias CL, Roche SM, Harning JA, et al. 2015. Reduced muscle fiber force production and disrupted myofibril architecture in patients with chronic rotator cuff tears. J Shoulder Elbow Surg 24:111–119.
42. Steinbacher P, Tauber M, Kogler S, et al. 2010. Effects of rotator cuff ruptures on the cellular and intracellular composition of the human supraspinatus muscle. Tissue Cell 42:37–41.
43. Laron D, Samagh SP, Liu X, et al. 2012. Muscle degeneration in rotator cuff tears. J Shoulder Elbow Surg 21:164–174.
44. Deniz G, Kose O, Tugay A, et al. 2014. Fatty degeneration and atrophy of the rotator cuff muscles after arthroscopic repair: does it improve, halt or deteriorate? Arch Orthop Trauma Surg 134:985–990.
45. Aagaard KE, Abu-Zidan F, Lunøe K. 2015. High incidence of acute full-thickness rotator cuff tears. Acta Orthop 86:558–562.
46. Goutallier D, Postel JM, Radier C, et al. 2009. Long-term functional and structural outcome in patients with intact repairs 1 year after open transosseous rotator cuff repair. J Shoulder Elbow Surg 18:521–528.
47. Kim JY, Park JS, Rhee YG. 2017. Can preoperative magnetic resonance imaging predict the reparability of massive rotator cuff tears? Am J Sports Med 45:1654–1663.
48. Namdari S, Donegan RP, Dahiya N, et al. 2014. Characteristics of small to medium-sized rotator cuff tears with and without disruption of the anterior supraspinatus tendon. J Shoulder Elbow Surg 23:20–27.
49. Chung SW, Kim JY, Yoon JP, et al. 2015. Arthroscopic repair of partial-thickness and small full-thickness rotator cuff tears: tendon quality as a prognostic factor for repair integrity. Am J Sports Med 43:588–596.
50. Weidner N, Semple JP, Welch WR, et al. 1991. Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma. N Engl J Med 324:1–8.
51. Gulotta LV, Nho SJ, Dodson CC, et al. 2011. Prospective evaluation of arthroscopic rotator cuff repairs at 5 years: part I—functional outcomes and radiographic healing rates. J Shoulder Elbow Surg 20:934–940.