Sensitivity and Specificity of 3-phase Bone Scintigraphy in the Diagnosis of Complex Regional Pain Syndrome of the Upper Extremity

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Objectives: Joint and bone alterations are seldom mentioned in the diagnostic criteria for complex regional pain syndrome (CRPS) even though they are important for long-term outcome. Altered periarticular bone metabolism can be detected by 3-phase bone scintigraphy (TPBS). Although frequently examining the diagnostic efficacy of TPBS is debatable.

Methods: In all, 78 TPBS (45 CRPS/33 control group) were evaluated qualitatively and quantitatively. Sensitivity and specificity of the qualitative blinded reviewer analysis (n = 57) compared with quantitative region of interest (ROI)-based analysis over the metacarpophalangeal, proximal, and distal interphalangeal joints (n = 74) were evaluated. Patients' sex, age, duration of CRPS, inciting event, extent of joint alteration, and handedness were included as covariables.

Results: Qualitative blinded reviewer TPBS analysis had a high specificity (83%-100%). However, sensitivity was 31% to 50%. Interrater reliability was moderate (κ score 0.56). Using the ROI-based evaluation, the highest sensitivity (69%) and specificity (75%) (ROI score ≥ 1.32) was shown for phase 3, whereas sensitivity of phases 1 and 2 rapidly declined to 50%. Duration of CRPS until TPBS was the only variable with significant impact on ROI scores of phase 3 ($F = 23.7$; $P = 0.000$; $R^2 = 0.42$). ROI scores declined with increasing duration of CRPS.

Discussion: In conclusion, TPBS is a highly specific tool for diagnosing CRPS of the upper limb. ROI evaluation of phase 3 within the first 5 months after onset of CRPS is an appropriate additional diagnostic tool to confirm or exclude CRPS of the upper extremity.

Key Words: complex regional pain syndrome, 3-phase bone scintigraphy, sensitivity, specificity, ROI, duration of CRPS

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Current established diagnostic criteria for complex regional pain syndrome (CRPS) comprise continuing pain, sensory, autonomic, and motor changes.[1,2] Although important for long-term outcome, the alterations of joints, periarticular bone, and deep somatic tissues, which are clinically detectable as joint pain and decreased range of motion are seldom or not mentioned at all in these criteria.[3–7] Furthermore, the increased bone metabolism as shown by increased periarticular tracer uptake using 3-phase bone scintigraphy (TPBS)[8] is not included in the diagnostic criteria. The diagnostic efficacy of TPBS, although frequently examined has been widely debated.[9–12] One reason is the methodologic differences between studies reporting diagnostic sensitivity ranging between 19% and 97% and specificity ranging between 56% and 97% for phase 3 of TPBS.[9,12–17] Moreover, there exists no consensus concerning the usefulness of phases 1 and 2. TPBS shows tracer uptake at 3 different time points after tracer injection. Phases 1 and 2 are obtained directly after tracer injection and represent the perfusion and blood pooling in the limb, whereas phase 3 (obtained 2 to 3 hours after injection) represents the tracer uptake in the bone.

TPBS can be evaluated qualitatively, using description of asymmetry in tracer uptake, or quantitatively, using the region of interest (ROI) technique to quantify tracer uptake in specific limb regions. In general, qualitative evaluation has been performed to date.[8,9,12–22] Some studies used additional or sole ROI evaluation.[16,20,21,23–26] ROIs were usually localized over the entire hand, but not over single joints.[16,20,21,23,26] Proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints have not been examined to date, although clinical signs and symptoms often include these joints.[5] Furthermore, the influence of CRPS duration at the time of assessment on the diagnostic value of TPBS has not previously been evaluated.[9,10,23–25,27]

The aim of the present study was to determine the sensitivity and specificity of TBPS in the diagnosis of CRPS of the upper extremity. Emphasis was placed on examination of interrater reliability and standardization of the ROI analysis in CRPS patients and a control group (CG). Age, sex, duration of CRPS, inciting event, extent of joint alteration, and handedness were included as covariables. To assess differences between qualitative and quantitative evaluation, we compared additionally blinded reviewer and ROI-based analysis of TPBS.

PATIENTS AND METHODS

Patients

The Ethics Committee of the Ruhr-University of Bochum (registry number 2173) approved this study. In all, 78 patients attending the pain clinic with pain in the upper limb were enrolled (Fig. 1). These patients underwent TPBS in the department of nuclear medicine as a diagnostic procedure. At the same time, the patients were clinically examined in the department of pain management.

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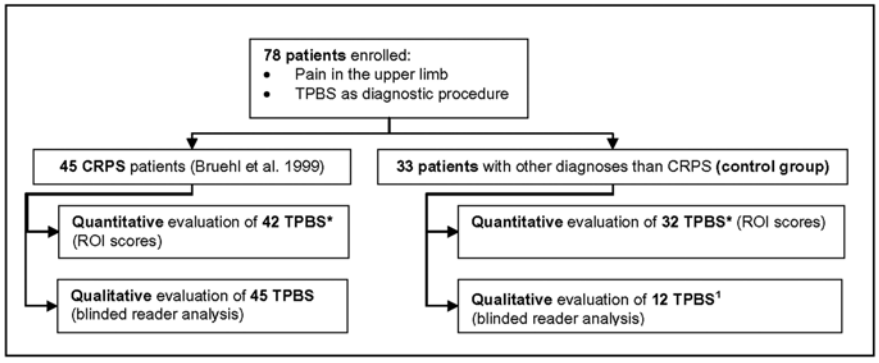

* Difference: Quantitative evaluation not possible due to contractures and malpositions of the fingers (CRPS n=3; CG n=1)

1 Difference: After the first qualitative and quantitative evaluation authors decided to increase the control group from 12 to 33 TPBS to have a comparable sample sizes in both groups.

FIGURE 1. Flow chart illustrating the enrollment and investigation of patients.

Forty-five patients (20 female/44%) fulfilled the research diagnostic criteria for CRPS proposed by Bruehl et al,[28] which is used as the diagnostic gold standard. All CRPS patients (100%) had persistent limb pain spreading to the affected distal extremity. At the time of evaluation, 100% decreased range of motion, 76% temperature asymmetry, 70% hyperhidrosis, 70% tremor, 58% edema, 38% of the patients showed dynamic mechanical allodynia, 29% skin color changes, 15% trophic changes and 4% dystonia. Six of 45 CRPS patients had a nerve injury (radial nerve = 1; median nerve = 4; ulnar nerve = 1) and therefore were classified as CRPS II.

In all, 33 patients (18 females/55%), who underwent TPBS for suspected CRPS in the surgical department served as CG. After the clinical, neurologic, and radiologic evaluation, the following diagnoses were made: posttraumatic nerve injury of the forearm (15/45%; injured nerves: radial = 4, median = 1, ulnar = 5, combined injuries = 5), posttraumatic wrist osteoarthrosis (10/30%), postoperative or posttraumatic pain due to long-term disuse of the forearm or hand with rapid improvement after onset of adequate exercise program (5/16%), factitious disorders (2/6%, proved by psychologic exploration followed by patient report), and polyneuropathy (1/3%). All of these patients had ongoing pain and in addition 71% decreased range of motion, 19% localized edema, 19% demonstrated allodynia, 14% temperature asymmetry, 14% skin color changes, 10% trophic changes and 5% hyperhidrosis.

The mean ages in the CRPS and CGs were 50.7 years (SD ± 11.5, range 26-76) and 48.9 years (SD ± 15.8, range 16-81), respectively ($F = 0.35$; $P = 0.558$). The average time from onset of symptoms to TPBS was 9.8 months for the CRPS group (SD ± 21.5, range 0.8-146 mo) and 18.6 months for the CG (SD ± 41.8, range 1.1-233) ($F = 1.38$; $P = 0.244$). Additional clinical data concerning covariables included in evaluation of CRPS patients are presented in Table 1.

TPBS Protocol and Evaluation

All TPBS were performed using ^{99m}Technetium-labeled methylene diphosphonate (^{99m}Tc-MDP) and a Siemens E.CAM 180 dual-head γ camera equipped with a low-energy high resolution collimator. All bone scans showed hands and distal forearms from the palmar side.

Ten seconds after the injection of approximately 10 MBq/kg bodyweight ^{99m}Tc-MDP (totally, 500-700 MBq) into the cubital vein of the unaffected side 60 dynamic frames were acquired with patient's hands palm side down on the γ camera (phase 1: 1 s/frame, 64 × 64 matrix). Phase 1 immediately faded to the blood pool phase. A dynamic sequence of 18 frames was subsequently recorded (phase 2: 10 s/frame, 64 × 64 matrix). The static picture of the mineralization phase was taken 2 to 3 hours after injection (phase 3: 5 min, 128 × 128 matrix).

Except for 4 of 78 TPBS, all TPBS were evaluated quantitatively (see Results). A subgroup of 57 TPBS (45 CRPS/12 CG) was evaluated qualitatively. Twenty-one TPBS of the CG were evaluated only quantitatively because after the first quantitative and qualitative evaluation, authors decided to increase the small sample size of the CG from 12 to 33 TPBS to have comparable sample sizes in both groups (Fig. 1).

The qualitative evaluation was undertaken by 1 experienced resident and 3 consultants for radiology,

TABLE 1. Clinical Characteristics of CRPS Patients (n = 45)

Inciting event (%)	
Surgically treated fractures	19 (42.2)
Conservatively treated fractures	10 (22.2)
Soft tissue injuries	8 (17.8)
Combined injuries	6 (13.3)
No inciting event reported	2 (4.4)
Joint alterations*(%)	
Slight	15 (33.3)
Severe	27 (60.0)
Missing data	3 (6.7)
Handedness (%)	
Dominant hand affected	22 (48.9)
Nondominant hand affected	12 (26.7)
Ambidexterity	5 (11.1)
Missing data	6 (13.3)

*Joint alterations: slight = finger tip-to-palm-distance < 3 cm, no contractures, slightly decreased range of motion or reduced mobility < 20 degrees of several joints.

Severe = finger tip-to-palm-distance ≥ 3 cm, decreased range of motion because of contractures in > 3 joints.

CRPS indicates complex regional pain syndrome.

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recording asymmetries in the tracer uptake of the carpus, metacarpophalangeal joints (MCP), PIP, and DIP of all 4 fingers in each of the 3 phases. TPBS data were anonymized except for the inciting event, affected side, and time of onset of symptoms, information which was required by radiologists for clinical evaluation. Sites of fracture were not evaluated. Results of the quantitative ROI-based evaluation and the qualitative evaluation of the others were unknown to the investigator. The criterion for a CRPS-positive TPBS, assembled by the 4 raters, was increased tracer uptake in each reviewed region in all 3 phases in the affected hand. These criteria were used in the routine diagnostic service in our department.

Regions of interest (ROIs) were used to quantify tracer uptake in different areas of the affected and unaffected hand. ROIs were localized over the MCP, PIP, and DIP of all 4 fingers in each of the 3 phases (Fig. 2). We chose ROI localization because of the predominance of signs and symptoms in the distal part of the limb and the typical periarticular accentuation of bone changes in CRPS.[2,29,30] The carpus was excluded from ROI evaluation because of the presence of fractures and osseous injury in the distal forearm or wrist in about 60% of CRPS patients. The thumb was not considered during scintigraphic evaluation because of its rare involvement in CRPS.[5] A comparable ROI evaluation as presented here has not been described to date. Average tracer uptake, measured as counts per pixel, was recorded for each ROI and phase. Uptake ratios (ROI score) between the affected and unaffected side were computed for each ROI from average tracer uptake of the affected side divided by average tracer uptake of the unaffected side. A ROI score of 1 indicated similar tracer uptake in the ROIs of both sides. A mean ROI score per phase was computed from ROI scores of the MCPs, PIPs, and DIPs.

Statistical Analysis

Sensitivity and specificity of the qualitative evaluation were determined for each of the 4 reviewers and of the ROI-based evaluation for each phase and ascending ROI scores using square tables. To analyze interrater reliability, κ score was computed and interpreted as suggested by Viera and Garrett.[31] Pearson linear correlation coefficient was applied to examine correlation between ROI scores. Analysis of variance was performed to compare age, duration of disease, and mean ROI scores of CRPS patients and the CG. A P value ≤ 0.05 was considered significant. The impact of covariables on ROI scores of phase 3 was examined using multiple regression analysis with "mean ROI score of phase 3" as dependent variable and the covariables as independent variables. Using the procedure stepwise, only variables with significant impact on ROI scores of phase 3 ($P \leq 0.05$) were included. Variables were excluded for $P \geq 0.1$.

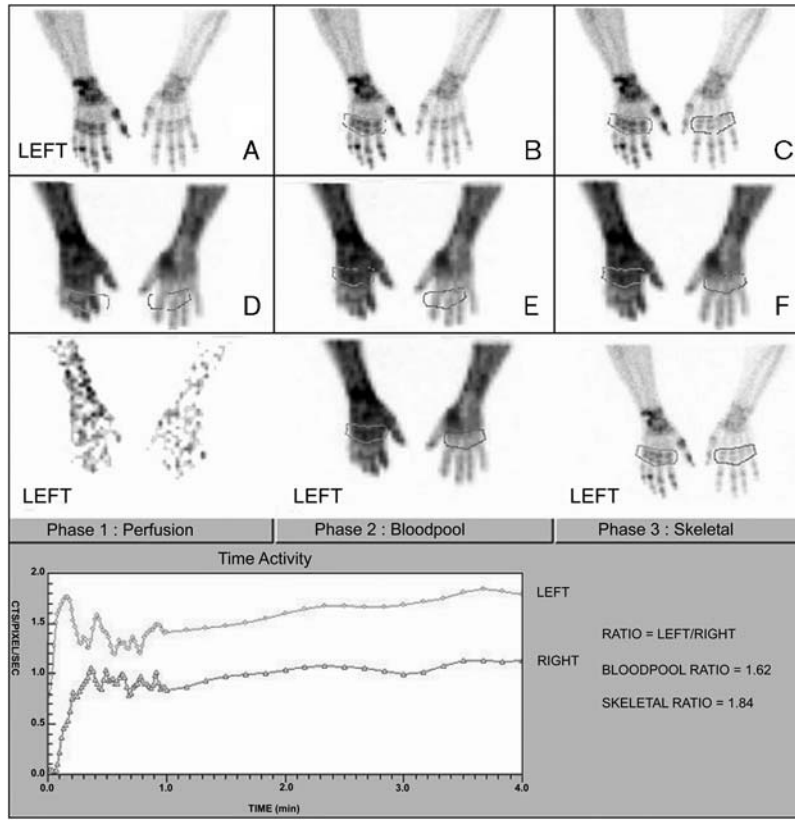

FIGURE 2. ROI-based evaluation. A to C, Process of ROI localization over the MCPs in phase 3. D to F, Process of ROI localization over the MCPs in phase 2. Bottom, Time-activity curves of phases 1 and 2 and ROI scores of phases 2 and 3. [ROI score of phase 1 = counts/pixel/sec of the first peak (upper curve)/counts/pixel/sec of the first peak (lower curve)]. MCP indicates metacarpophalangeal joints; ROI, region of interest.

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TABLE 2. Sensitivity and Specificity of the Qualitative 4 Rater Evaluation (57 TPBS)

	Rater					Rater			
CRPS (n = 45)	**1**	**2**	**3**	**4**	**CG (n = 12)**	**1**	**2**	**3**	**4**
True positive	14	22	15	20	True negative	11	10	10	10
False negative	31	22	30	25	False positive	0	1	2	2
Not evaluated	0	1	0	0	Not evaluated	1	1	0	0
Sensitivity (in %)	31.1	50.0	33.3	44.4	Specificity (in %)	100	90.9	83.3	83.3

CG indicates control group; CRPS, complex regional pain syndrome; TPBS, 3-phase bone scintigraphy.

RESULTS

Qualitative evaluation by independent investigators revealed sensitivity between 31% and 50% due to a high rate of false-negative CRPS diagnoses. In contrast, few bone scans were rated as false positive for CRPS, resulting in a high specificity between 83% and 100% (Table 2). Interrater reliability yielded a median κ score of 0.56, indicating a moderate reliability (Table 3).

In 4 of the 78 TPBS (3 CRPS/1 CG), marked contractures and malposition of the fingers did not allow correct ROI localization. These TPBS were excluded from ROI-based evaluation. For the following analysis, the computed mean ROI score per phase was used (see 2.2). This was accurate due to the high correlation within the 3 ROI scores of 1 phase ($r = 0.78$-0.95). Correlation was moderate between ROI scores of MCPs and DIPs of phases 1 and 2 ($r = 0.60$-0.66).

In all the 3 phases, mean ROI scores of CRPS patients were higher than scores of the CG. Phases 2 and 3 ROI scores differed significantly between the 2 groups (Table 4). Fifteen CRPS patients (35.7%) had decreased tracer accumulation of the affected hand in phases 1 and 2 (ROI score < 1), whereas in phase 3 four CRPS patients (9.5%) showed decreased tracer uptake of the affected hand (ROI score < 1).

Sensitivity and specificity were analyzed for ascending ROI scores between 1.0 and 2.0 (Table 5). In phases 1 and 2, sensitivity declined to 50% (ROI score ≥ 1.2) whereas specificity increased continuously to 94% to 100%. Phase 3 (ROI score ≥ 1.32) showed both high sensitivity and specificity of 69% and 75%, respectively.

Duration of CRPS until TPBS was the only independent variable that influenced significantly the mean ROI scores in phase 3 ($F = 23.7$; $P = 0.000$; $R^2 = 0.42$) as proven by multiple linear regression analysis. ROI scores declined with increasing duration of CRPS (Figs. 3, 4). In cases where CRPS lasted less than 5 months, the mean ROI score of phase 3 was significantly higher (mean ROI score = 2.04) than the score of patients that exceeded the 5-month threshold (mean ROI score = 1.27; $F = 25.7$; $P = 0.000$). In the subgroup with duration of CRPS of less than 5 months sensitivity of the ROI-based evaluation increased to 91% (ROI score = 1.4, specificity 71.4%). For phase 2, duration also had a significant impact on ROI scores ($F = 13.01$; $P = 0.001$). Age ($P = 0.863$), sex ($P = 0.269$), inciting event ($P = 0.220$), extent of joint alteration ($P = 0.596$), and handedness ($P = 0.931$) did not influence the mean ROI scores of phase 3 significantly.

TABLE 3. Interrater Reliability (κ Scores)

Rater	1	2	3	4
1	—	0.53 n = 55	0.71 n = 56	0.56 n = 56
2	0.53 n = 55	—	0.54 n = 55	0.66 n = 55
3	0.71 n = 56	0.54 n = 55	—	0.55 n = 57
4	0.56 n = 56	0.66 n = 55	0.55 n = 57	—

Median of κ = 0.56.

DISCUSSION

This study shows that TPBS is a highly specific tool for diagnosing CRPS of the upper limb. Quantitative ROI evaluation of phase 3 within the first 5 months after onset of CRPS is an appropriate additional diagnostic tool to confirm or exclude CRPS of the upper extremity. We propose ROI localization over the MCP in phase 3, acquired 2 to 3 hours after tracer infections. Using these criteria, an ROI score of ≥ 1.32 produces the highest sensitivity and specificity. Regions of fracture or joint trauma should be excluded from evaluation. The applied criteria for qualitative evaluation used in our study should be adapted.

The results of our study reinforce TPBS as a valuable diagnostic tool with high specificity for patients with CRPS of the upper limb (specificity, 75%-100%). This is in accordance with all quoted studies performed to date (specificity, 60%-100%). Particularly the specificity of the late phase of TPBS seems to be at least as high as reported for the use of the most rigorous clinical criteria as suggested by Harden et al[32] (for discussion see Refs. 33, 34). Earlier evaluations of the specificity of CRPS criteria were calculated by comparison only with patients with postherpetic neuralgia or diabetic polyneuropathy.[28] Patients with CRPS-mimicking diseases such as posttraumatic osteoarthrosis or self-induced disorders were not enrolled. However, patients with these diseases are frequently referred to pain clinics with suspected CRPS.[35] TPBS reduces the risk of an incorrect CRPS diagnosis in those patients. In our study, the qualitative evaluation of TPBS lead to no false-positive diagnoses whereas 1 of 2 patients with self-induced disorder and 2 of 10 patients with posttraumatic osteoarthrosis had mean ROI scores ≥ 1.32 in phase 3.

In our study, the highest sensitivity (69%) was achieved using the ROI-based evaluation of phase 3 (ROI score 1.32). According to Zyluk,[25] ROI evaluation of metacarpal bones and MCP in phase 3 had greatest

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TABLE 4. ROI Scores of CRPS Patients and the Control Group

		CRPS (n = 42)	CG (n = 32)	Comparison Between Groups* F (*P*)
Phase 1	Mean SD (R)	1.63 ± 1.47 (0.47-9.10)	1.14 ± 0.45 (0.33-2.71)	3.259 (0.075)
Phase 2	Mean SD (R)	1.36 ± 0.59 (0.68-3.40)	1.07 ± 0.30 (0.46-1.91)	6.120 (0.016)
Phase 3	Mean SD (R)	1.67 ± 0.63 (0.63-3.55)	1.24 ± 0.28 (0.86-2.00)	13.436 (0.000)

*Univariate analysis of varience.
CG indicates control group; CRPS, complex regional pain syndrome; R, range; ROI, region of interest; SD, standard deviation.

diagnostic value with 80% sensitivity and 67% specificity for the ROI over the metacarpal bones (ROI score 1.3) and 64% sensitivity and 80% specificity for the ROI over the MCPs (ROI score 1.8). Sensitivity and ROI scores were higher in the cited study compared with our results. But ROI localization differed in both evaluations. The very short duration of CRPS (4 mo) might explain the higher values in the former evaluation.[25] The elevated sensitivity of the ROI over the metacarpal bones compared with the MCPs does not correspond to the typical periarticular accentuation of tracer uptake with CRPS.[30] Also Zyluk's results for phase 2 cannot be supported by our data. He proposed a supplementary evaluation of the metacarpal bones in phase 2 for diagnosing CRPS. Phases 1 and 2 represent the perfusion and blood pooling in the hands resulting in clinically detectable alterations in skin temperature and color. These are dynamic parameters that obviously depend on the environmental temperature, emotional stress, and physical exercise,[36] all of which change during the course of CRPS.[3,36–38] Therefore, phases 1 and 2 are less specific and we propose in contrast to Schuermann et al[12] that both early phases of TRBS should not be used for the diagnostic algorithm of CRPS.

In contrast to these promising results using a ROI-based evaluation and also to the former published literature (sensitivity 19%-100%) our qualitative evaluation produced a lower sensitivity of 31% to 50%. The criterion for a CRPS-positive TPBS in our study was increased tracer uptake in each reviewed region in all 3 phases in the affected hand. This criterion has been used for routine diagnostic service in our radiologic department and was evaluated in this study. Several studies used the same criterion.[12,13,15,21] In the study of Todorovic-Tirnanic et al,[15] 36/37 TPBS were rated as true CRPS positive with this criterion. Steinert and Hahn,[21] reached a sensitivity of 96% and a specificity of 100%. In contrast, only 8/22 TPBS fulfilled the criterion in the study of Holder and Mackinnon.[13] The sensitivity in the evaluation of the study of Schuermann et al[12] was 14% (16 wk after trauma) and 19% (8 wk after trauma), respectively. Additionally, results of our ROI-based evaluation, where average tracer accumulation is increased in the affected hand in all 3 phases, highest in phase 3 (mean ROI score > 1) underline the use of this criterion. In contrast, in phases 1 and 2, 36% of CRPS patients showed decreased tracer accumulation (ROI score < 1).

In our study, the 4 investigators reviewed all 3 phases simultaneously. Having considered the results of the ROI-based evaluation, we propose to review only phase 3 qualitatively to increase sensitivity. Criterion for a CRPS-positive TPBS is increased periarticular tracer uptake in phase 3. Rater training is also likely to increase interrater reliability and sensitivity. Additional quantitative evaluation of TPBS should always be performed.

The high sensitivity mentioned in the previous published studies should be critically examined as the diagnosis of CRPS is based on nonstandardized criteria.[13–15,17,19,21] Standardized criteria for CRPS were established after the date of publication of some of the quoted studies, but even subsequent clinical studies do not apply these criteria.[1,39] Moreover, there are no comments pertaining to TPBS

TABLE 5. Sensitivity and Specificity of the Quantitative ROI-based Evaluation (74 TPBS)

	Phase 1		Phase 2		Phase 3	
ROI Score	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**
≥ 1.0	64.3	34.4	64.3	34.4	90.5	18.8
≥ 1.1	64.3	50.0	59.5	56.3	85.7	37.5
≥ 1.2	**52.4**	**65.6**	**50.0**	**68.8**	76.2	56.3
≥ 1.3	42.9	81.3	42.9	84.4	69.0	71.9
≥ 1.32	42.9	81.3	42.9	90.6	**69.0**	**75.0**
≥ 1.34	40.5	81.3	40.5	90.6	66.7	75.0
≥ 1.36	40.5	81.3	35.7	90.6	61.9	75.0
≥ 1.38	40.5	81.3	35.7	90.6	61.9	75.0
≥ 1.4	40.5	81.3	35.7	93.8	59.5	78.1
≥ 1.5	31.0	84.4	33.3	93.8	54.8	87.5
≥ 1.6	23.8	90.6	21.4	93.8	52.4	90.6
≥ 1.7	21.4	93.8	19.0	93.8	47.6	90.6
≥ 1.8	19.0	93.8	14.3	93.8	40.5	93.8
≥ 1.9	16.7	93.8	11.9	96.9	33.3	96.9
≥ 2.0	14.3	93.8	9.5	100	26.2	96.9

The bold entries represent ROI scores with the best ratio between sensitivity and specificity.
ROI indicates region of interest; TPBS, 3-phase bone scintigraphy.

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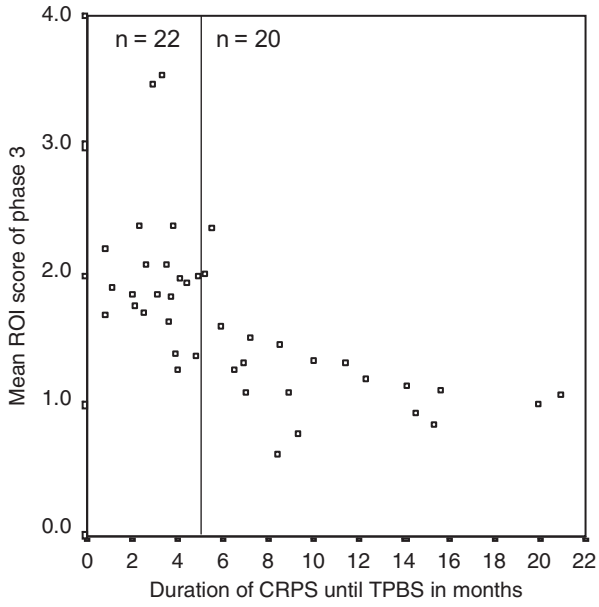

FIGURE 3. Decreasing ROI scores with increasing duration of CRPS. CRPS indicates complex regional pain syndrome; ROI, region of interest.

evaluation, for example by whom they were evaluated and if the evaluation was anonymous.[8,13,15–19] A comparable blinded reviewer analysis was only performed by O'Donoghue et al,[14] Steinert and Hahn,[21] and Schuermann et al.[12] Furthermore, duration of CRPS until TPBS, if mentioned at all by the authors, is quite short (< 6 mo).[12,15,17–19,21]

We also focused on the analysis of interrater reliability revealing an only moderate interrater reliability (κ scores 0.53-0.71). Tondeur et al[40] reported similar results. Observers' interpretations vary, if TPBS differed from classic patterns. O'Donoghue et al[14] presented κ scores between 0.50 and 0.65 for 3 observers, which approximately correspond to our results. Despite the only moderate agreement, sensitivity for all the 3 phases reached 76%, although results are based on a consensus of 2 or more observers. We abstained from using a consensus decision.

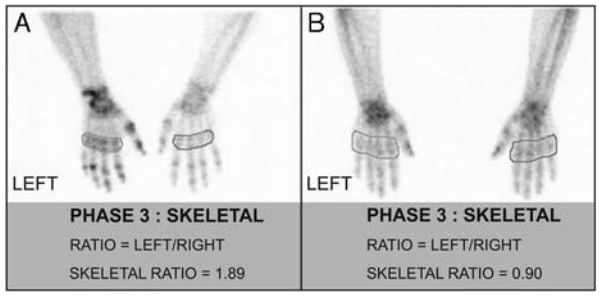

FIGURE 4. Impact of duration of CRPS on the ROI score of phase 3. A, CRPS of the left hand (42 y, male) after surgically treated humeral fracture (TPBS 1.5 mo after onset of CRPS). B, CRPS of the left hand (47 y, male) after conservatively treated scaphoid fracture (TPBS 14 mo after onset of CRPS). CRPS indicates complex regional pain syndrome; ROI, region of interest; TPBS, 3-phase bone scintigraphy.

The diagnostic value of TPBS is limited mainly by the duration of CRPS before performing TPBS. In our study duration, CRPS is obviously shorter than disease duration in the CG. Due to our specialization in management of CRPS patients, these patients are referred to our department at an earlier stage. In our patient subgroup with a duration of CRPS of less than 5 months, the ROI score of phase 3 was significantly higher (ROI score 2.04) and sensitivity reached 91% (ROI score 1.4). Similar data can be found in the literature.[9,10,23–25] The optimum time to use TPBS in the diagnosis of CRPS is within the first 5 months after symptom onset. This aspect must be considered when interpreting the low sensitivity of our qualitative reviewer evaluation. CRPS patients who underwent TPBS evaluation in which all blinded raters felt that there was a significant change in TPBS in agreement with the clinical diagnosis had a shorter duration of CRPS (3.2 mo). In contrast, TPBS from CRPS-positive patients rated as CRPS negative by one or more of the radiologists were obtained after a longer duration of CRPS (false-negative evaluation by all radiologists: 21.7 mo; false-negative evaluation by at least 1 radiologist: 5 mo).

Further examined variables had no significant impact on ROI scores of phase 3. We expected a significant impact from the inciting event as presented by Zyluk,[25] but we have various types of inciting event among our CRPS patients (Table 1). Zyluk reported a significantly higher tracer uptake in each phase and ROI after fracture than after soft tissue injuries in CRPS patients. Even though 53 CRPS patients with a fracture and only 17 CRPS patients with a soft tissue injury were analyzed, the effect was significant.

The usefulness of CRPS affecting the lower extremity has not been as fully evaluated. Steinert and Hahn reported that they were not able to distinguish between CRPS and non-CRPS patients by ROI scores. In a follow-up study (23 TPBS: 11 CRPS/12 CG; data not shown), we saw several technical limitations of TPBS at the feet, for example tracer uptake in phase 3 was less high than in the hands, leading to a weaker demarcation of the joints. Furthermore, ROIs could be localized only over the metatarsophalangeal joints. Therefore, the technique needs to be modified to improve the diagnostic sensitivity of TPBS in patients with CRPS involving the feet.

The underlying mechanisms of bone alterations in CRPS are still unknown as are so many aspects of CRPS. Increased tracer uptake indicates high bone metabolism resulting in demineralization.[41,42] Immobilization alone cannot explain the localization and the extent of bone loss.[41] Presumably the decreased sympathetic activity during the early stages of CRPS[36,43] or abolished sympathetic activity[27,44,45] may enhance bone metabolism resulting in increased tracer uptake as well. A further mechanism for increased bone metabolism could be neurogenic inflammation (for instance because of the enhanced release of calcitonin gene-related peptide).[46,47]

One limitation to our study is that data relating to covariables in CRPS patients were collected retrospectively from the patients' records and a computerized documentation system. Usage of standardized questionnaires and examination tools ensured complete and exact data. Further analysis regarding the impact of covariables in the CG was not performed due to the heterogeneity of the diagnoses in this group. We did not include any patients after sympathectomy, which may mimic the TPBS pattern observed in acute CRPS.[27] Nevertheless, from the clinical point of view,

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due to the high specificity of the late phase of TPBS, TPBS is of important value to discriminate patients with CRPS from those with pseudo-CRPS mimicking CRPS symptoms, particularly from patients with self-induced disorder or other psychosomatic.[35]

In conclusion, TPBS is a highly specific tool for diagnosing CRPS of the upper limb in contrast to most clinical criteria. The high correlation between ROI scores of each phase suggests that it is sufficient to analyze only 1 ROI per phase. Regions in which the tracer uptake is enhanced due to the former trauma or fracture should not be used for ROI analysis to avoid false-positive results. The highest sensitivity can be reached using ROI evaluation of phase 3 within the first 5 months after onset of CRPS. After this time, a negative TPBS does not exclude the diagnosis of CRPS. Therefore, ROI-based evaluation of phase 3 TPBS may be considered for inclusion in diagnostic guidelines for early CRPS.

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