Three-Phase Bone Scanning in Reflex Sympathetic Dystrophy of the Hand

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Three-phase bone scanning was performed in 181 patients suffering from reflex sympathetic dystrophy (RSD) of the hand. Four quantitative parameters were defined as follows: (a) hemovelocity and (b) blood pool (determined from the Fourier processing of angiographic data); (c) early (3–5 min) and (d) delayed (2–3 hr) bone fixation. Three significant stages of RSD were demonstrated scintigraphically. Stage I (0–20 wk from onset) demonstrated increases in velocity, blood pool, and early and delayed fixations. At stage II (20–60 wk) blood velocity and blood pool were normalized, but early and delayed hyperfixation persisted. During stage III (60–100 wk) blood velocity and blood pool were reduced on the affected hand, and early and delayed fixations were normalized. Such abnormality of decreased hemodynamic parameters may become associated with bone hypofixation in stage III. Early treatment of RSD (as compared with delayed treatment) has been demonstrated to induce normalization of hemovelocity ($p < 0.05$), blood pool ($p < 0.02$), and joint stiffness ($p < 0.001$) without any change in the bone fixation; therefore, three-phase bone scanning may provide useful information regarding the pathophysiologic and clinical evolution of RSD.

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Radioisotopic investigation of the hand affected by reflex sympathetic dystrophy (RSD) using standard static scintigraphy has been used since 1975 (*1,2*) to obtain a detailed picture of the osteoarticular damage. This information has been supplemented in recent years by angiographic data obtained from the three-phase bone scanning (TPBS) technique. Applied to the study of the hemodynamic disturbances that occur in RSD, the utilization of TPBS has led to a fuller and more discriminating scintigraphic description of this disease (*3–13*). There is still some disagreement, however, regarding, in particular, the interpretative criteria during the angiographic phase and their usefulness for the diagnosis of RSD. Makinon and Holder (*8*) found that the sensitivity of the first two phases of TPBS is poor and that only the third phase (which is extremely sensitive) is necessary for the diagnosis. We believe that the divergences of opinion among the published reports can be explained, if one takes into account the exact period of the illness when the TPBS examination is performed. We have investigated 181 patients with unilateral post-trauma or postoperative RSD of the hand over a period of more than 100 wk. The various quantitative parameters measured in TPBS have been correlated with the time lapse between triggering trauma and examination and with the date on which a specific treatment was initiated, since this can affect the TPBS status.

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MATERIAL AND METHODS

Patients

One hundred eighty-one (90 M, 91 F) patients suffering or recovering from RSD of the hand were investigated over a period of more than 100 wk. The average age was 53.6 yr. RSD had been triggered by surgery in 77 cases and by accidents in 98; six cases could not be classified. RSD at the acute stage was defined by the usual clinical syndrome combining pain, joint stiffness, and swelling and/or vasomotor instability. Patients in later RSD stages were selected by the knowledge of a persistent or recovered clinical syndrome and/or radiologic evidence of demineralization initiated by a trauma. The date on which the triggering trauma occurred was used as reference point. Patients with previous trauma or RSD on the contralateral member were excluded. Two hundred thirty examinations were carried out: 133 in the first 20 wk after the trauma, 76 between the 20th and the 60th wk and 21 after

the 60th wk. Thirty-five patients were reexamined once, and seven were reexamined twice.

The patients examined after the acute phase (i.e., after the 20th wk) were separated into two groups in order to study the influence of treatment on the evolution of the scintigraphic parameters. Group A consisted of 30 patients suffering from postoperative RSD, who received some type of the following specific treatment very early: fitting of a flexion splint to the hand associated with (a) pharmacologic (Guanethidin) segmental Bier's block, or (b) transcutaneous electrical nerve stimulation, or (c) calcitonin, or (d) nifedipin. Treatment took place between the 8th day and the 4th wk after surgery. Group B consisted of 35 patients with post-trauma RSD; that was diagnosed and specifically treated only at a later stage, i.e., between the 8th and the 36th wk (mean 24.2 wk). Their treatment consisted of a flexion splint and rehabilitation associated either with calcitonin, nifedipin, and analgesic, or anti-inflammatory drugs.

A group of 16 informed and consenting subjects (8 M, 8 F, mean age 41.5 yr) without any history of hand trauma or hand disease was similarly investigated in order to constitute a reference population. These subjects were selected from patients undergoing bone scanning for various pathologies.

Radionuclide Examination

For radionuclide angiography (phase I), the patient was seated in front of a wide-angle gamma camera with his hand palms down on the surface of a high-sensitivity, parallel hole collimator. A bolus of 0.2 μCi/kg (7.4 MBq/kg) of technetium-99m (^{99m}Tc) methylene diphosphonate was made through a contralateral antecubital vein, using a catheter to prevent reactive hyperemia following removal of a tourniquet (*14*). Forty 2-sec, 128 × 128 pixel frames were acquired starting at the time of injection. When this dynamic series of frames had been recorded, a high-resolution collimator was rapidly substituted and a static 256 × 256 5-min image was recorded. This early static image (phase II) was usually started within 3–5 min after injection. A delayed, high-resolution 256 × 256 image (phase III) was then obtained 2–3 hr later.

Processing of the Data

Phase I of TPBS. The angiographic data were processed using an original method for the determination of quantitative indexes of the vascular transit and of the blood pool as well as their pixel by pixel distribution over the field examined. This procedure, easy to perform with most available data processing systems, has been described in detail elsewhere (*15–17*). Briefly, 8–12 successive 2-sec frames were first selected from the recorded 40 frame series to describe the early perfusion (i.e., from the tracer's arrival in the camera field to the beginning of the venous return). This selected series was filtered over time (3 points) and space (9 points) and subjected to a pixel by pixel Fourier analysis, limited to the first harmonic. Two functional images were then produced (Fig. 1).

1. The *phase image* is a parametric image of the tracer's arrival times at the pixels throughout the field examined. The tracer's arrival times are represented by angle values; low and high angle values reflect early and late perfusion, respectively, and the maximum of the phase angle histogram is representative of the mean transit time of the tracer. This image demonstrates perfusion asymmetry between the affected and healthy hand.

2. The *average image* is a parametric image of the blood-pool distribution throughout the field. It demonstrates blood-pool asymmetry as well as focal vascular anomalies between the affected and healthy sides.

These functional images yield quantitative indexes which describe the discrepancies between the affected and the healthy sides. Symmetric, rectangular regions of interest (ROIs) were selected, covering the affected and the healthy wrist-hand complexes. Separate phase-angle histograms were generated from the phase image of each of these two ROIs and displayed (Fig. 1A, B). A relative (affected/healthy) index of hemovelocity, R, was defined as the ratio of the histogram areas up to the abscissa of the first maximum encountered (Fig. 1C). This ratio, therefore, was near to unity when the histograms were close (i.e., when the transit times were similar); it was higher or lower than unity, depending on whether perfusion was faster or slower in the affected hand.

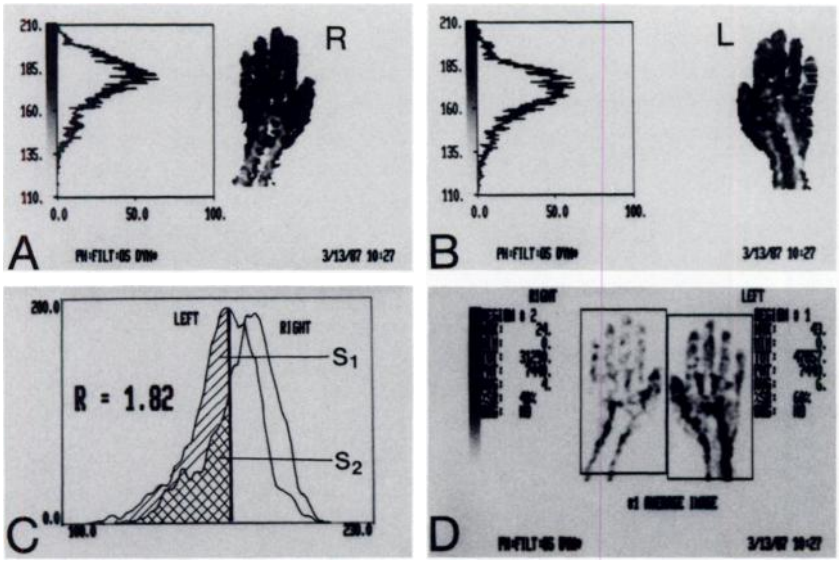

FIGURE 1
Quantification of the radionuclide angiographic phase of TPBS (phase I) in a typical case of left hand RSD. A–B: Separate right and left hand phase images and phase histograms obtained from the Fourier processing of the dynamic acquisition. Early perfusion is represented by low angle values on the y-axis of the histogram and by light gray on the phase image. C: Hemovelocity ratio (R) quantifying the perfusion asymmetry: ratio of the left/right histogram surfaces up to the abscissa of the first histogram maximum encountered (R = S1/S2 = 1.82). D: Average functional image from the Fourier analysis representing the blood pool. The index of blood-pool asymmetry (M) is defined as the count ratio in the two displayed regions of interest (left/right hand M ratio = 1.53).

Similarly a relative (affected/healthy) index of blood pool, m, pool was defined from the "average image" as the count ratio in the two selected ROIs (Fig. 1D). This index, representative of the ratio of the surfaces under the corresponding time-activity curves, was higher or lower than unity, depending on whether the blood pool in the affected hand was increased or reduced.

Normal limits of these indexes were set at two standard deviations (defined from the reference group—Table 1).

Phase II and III of TPBS. Phase II (early image) and phase III (delayed image) represent extracellular activity and bone fixation. The images were quantified by the count ratio (affected/healthy hand) in the two ROIs identical to those used for Figure 1C and D. Normal limits were also set at twice the standard deviation of the reference group.

RESULTS

Evolution of the Four Quantitative TPBS Parameters

Usual evolution: evidence of three scintigraphic stages. The analysis of the mean values of the four TPBS parameters (R, M, early and delayed fixation) allowed the identification of three significant stages during the scintigraphic evolution of RSD (Fig. 2).

1. *Stage I (0–20 wk, 133 examinations).* Increased blood velocity and blood pool; early and delayed hyperfixation.

2. *Stage II (20–60 wk, 76 examinations).* Normalization of blood velocity and blood pool; persistence of early and delayed hyperfixation.

3. *Stage III (60–100 wk, 21 examinations).* Reduced blood velocity and blood pool; normalization of early and delayed fixation.

Individual scintigraphic pattern. The above findings, concerning the whole group of patients, established an average developmental pattern and did not reflect the way in which individual cases actually developed. Figure 3 shows the affected/healthy side distribution of TPBS anomalies in the three evolutive stages in terms of frequencies.

1. *Stage I.* Parameters on the affected side usually increased, although in 4 to 21% of the cases they remained normal and in 1 to 8% of the cases perfusional delay and hypovascularisation occurred unexpectedly on the affected side.

2. *Stage II.* Early and delayed fixation levels remained high; normalization occurred in less than half

TABLE 1
TPBS Parameters in the Normal Group (N = 16)*

Hemovelocity index	R = 0.99 ± 0.13 (s.d.)
Blood pool index	M = 0.99 ± 0.10 (s.d.)
Early fixation	1.00 ± 0.06 (s.d.)
Delayed fixation	1.01 ± 0.05 (s.d.)

* Randomly distributed right/left hand or left/right hand ratios were used for calculation.

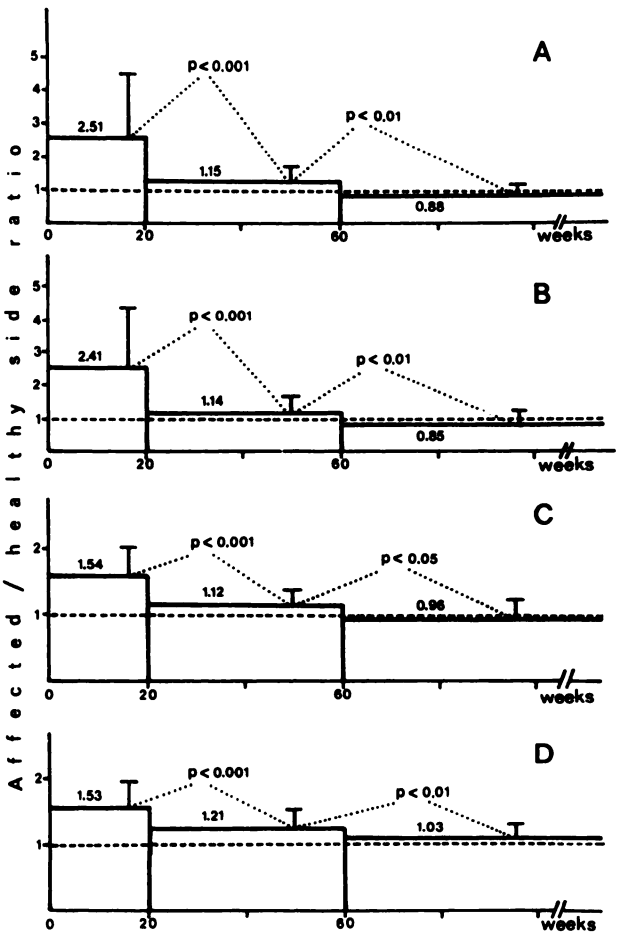

FIGURE 2
Average evolution of TPBS parameters. Parameters, expressed in terms of affected/healthy hand ratio, are the average of 133 examinations for stage I (0–20 wk), 76 for stage II (20–60 wk), 21 for stage III (60–100 wk). A: Hemovelocity (R); B: blood pool (M); C: early fixation; D: delayed fixation.

of the cases (32–51%). However, the angiographic parameters (hemovelocity and blood pool) developed in one of three ways: 1) normalization, 2) persistence of high levels, 3) shift towards delayed perfusion and reduced blood pool on the affected side. These developmental trends, because of nearly equal divergence in opposite directions, averaged out to give a pseudo normal appearance to the hemodynamic parameters for the whole group. Note that R and M did not evolve in a strictly parallel way, since they reflected different physiologic phenomena; the hemovelocity (R) normalized slightly more rapidly than the blood pool (M). Differences in hemovelocity and blood pool behavior are illustrated in Figure 4.

3. *Stage III.* Reduced hemovelocity and blood pool were predominant; R was reduced in 33% of the patients and M in 37%. Regarding early and delayed fixations, it was deduced that many patients also developed towards hypofixation; besides, all cases of delayed

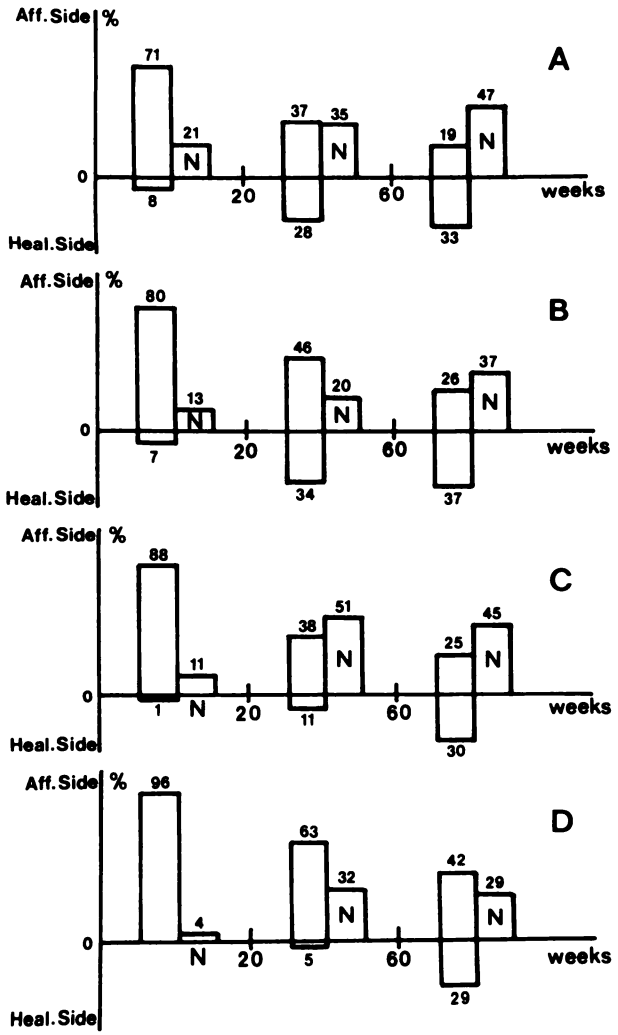

FIGURE 3
Frequency histogram of TPBS anomalies in the three stages of RSD. Data are plotted on the positive y-axis when the affected/healthy hand ratio is significantly greater than unity (i.e., when the increase in hemovelocity, blood pool, early or delayed fixation concerns the affected hand). They are plotted on the negative y-axis in the opposite case of reduced blood velocity and blood pool or hypofixation on the affected hand. N represents the normal cases where the affected/healthy hand ratio lies in the normal limits (set at two s.d.s defined from the normal group—Table 1). A: Hemovelocity (R); B: blood pool (M); C: early fixation; D: delayed fixation.

bone hypofixation exhibited delayed perfusion and a reduced blood pool in the affected hand. No increase in the normalization rate of early and delayed fixation was observed between stage II and III, contrary to the angiographic parameters.

Our data showed that hemodynamic and bone fixation disorders can persist over a long time after the triggering trauma; especially, 42% of the patients investigated during stage III displayed persistence of bone hyperfixation. Among the four TPBS parameters, delayed bone fixation was the most sensitive at stage I (96%) for diagnosing acute RSD and at stage III for assessing the persistence of the disease. The hemodynamic parameters were less sensitive at stage I, but exhibited the highest rate of reversal at stage III, thus justifying their analysis from a pathophysiologic point of view.

Influence of Early Treatment on the Scintigraphic Development Pattern

Among the patients examined after the 20th week, we made a distinction between those who had received a specific treatment very early (Group A) and those for whom RSD had been diagnosed and treated only at a later stage (Group B). Both clinical and scintigraphic data are summarized in Table 2. A very favorable effect on joint stiffness due to early treatment has been observed ($p < 0.001$), whereas pain was not affected. Regarding the TPBS data, a higher normalization rate in hemovelocity ($p < 0.05$) and blood pool ($p < 0.02$) parameters occurred in Group A as compared with Group B. Very strikingly, this normalization of angiographic parameters in response to early treatment did not affect early and delayed fixations at all. Such a discrepancy between hemodynamic and bone evolution is illustrated in Figure 4.

The detailed analysis of the angioscintigraphic data also revealed a higher incidence of a reversal of hemodynamic parameters (hemovelocity as well as blood pool) in Group B than in Group A (Table 2); this may reflect the natural (and certainly unfavorable) pathophysiologic development of the disease in Group B.

DISCUSSION

Our methodology for the quantitative processing of TPBS data has been described and explained in earlier papers (*15–17*). Unlike the usual methods, based on the computer generation of time-activity curves for anatomical regions of interest (*5,12,13,18–20*), functional images allow the combination of temporal and spatial data into one picture. This means that the analysis of the angiographic phase of TPBS is not restricted to focal regions assumed to be pathologic and selected as such as areas of interest. Indeed, very often, this method reveals vascular focal anomalies, which are not suspected when the sequential images are viewed cineangiographically. Since scintigraphic anomalies, characteristic of reflex sympathetic dystrophy, are diffuse or multifocal (*1,2,4,9*), quantitative analysis of the functional images was carried out for regions of interest covering the whole of the wrist-hand complex. Later, these regions were used again to evaluate early and delayed fixations.

The aim of this study was to provide additional information about the scintigraphic development pattern of patients suffering from reflex sympathetic dys-

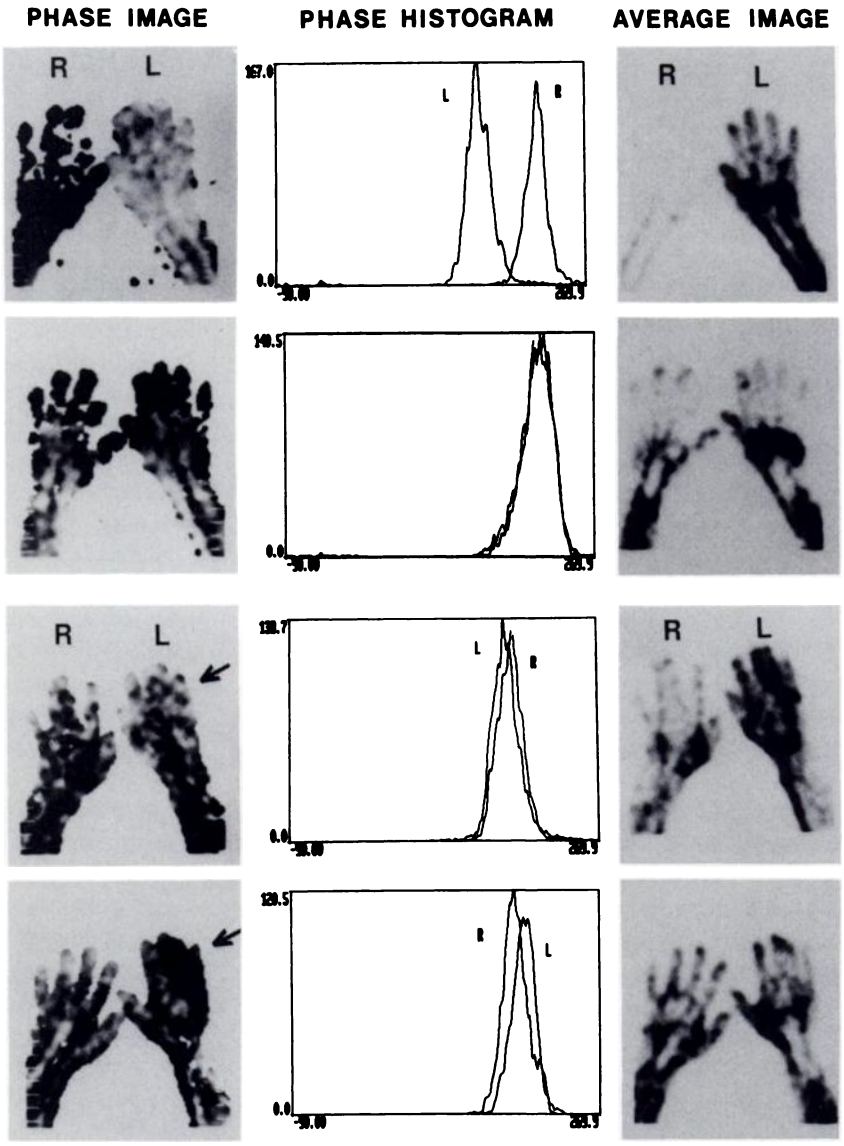

FIGURE 4
Examples of different scintigraphic development patterns after treatment. *Top patient* (left hand RSD). All TPBS parameters during the acute phase are strongly increased on the affected side (Row 1). Hemovelocity (R = 1.12) as well as bone fixation (not represented) are normalized 6 wk after treatment (Row 2); but the blood pool remains significantly elevated (M = 1.56). *Bottom patient* (left hand RSD). All TPBS parameters are increased on the left hand during the acute stage. A clear reversal of hemovelocity can be seen 12 wk after treatment (see especially the cubital side of the left hand) whereas the blood pool is normalized (M = 1.04) and the bone hyperfixation unchanged (not represented). These examples show that the two angiographic parameters, hemovelocity (R) and blood pool (M), do not always evolve in a parallel way and that bone fixation does not reflect the hemodynamic situation.

trophy rather than to establish the diagnostic value of this method. The analysis of the average evolution of the four quantitative TPBS parameters (R, M, early and delayed fixations) allowed the identification of three significant stages: I (0–20 wk), II (20–60 wk), III (60–100 wk). Stage I corresponded to the acute stage with vasomotor disturbances and bone hyperfixation, all parameters being generally increased on the affected side. Some cases of perfusional delay and of a reduced blood pool were, however, observed. Such situations are not uncommon and have been reported, particularly in young patients and hemiplegics (*10,11,20*).

During later stages (20–100 wk) scintigraphic normalization occurred but at a low rate (29–47%), confirming the well-known long-lasting character of this disease. Slightly better normalization rates were reported [50%–55% (*4,21*)] for various localizations of RSD after an average time lapse of more than 1 yr.

A noteworthy result of the present study was the observation of many cases of hemodynamic reversal (delayed perfusion and reduced blood pool on the affected side), occurring during stage II and becoming more frequent during stage III. Moreover, several patients exhibited bone hypofixation on the affected member, especially after the 60th week. In all of these cases perfusion was delayed and the blood pool was reduced. Reduced flow in advanced RSD may be due, in part, to amyotrophia caused by disuse of the member. This is a common feature of the post-hemiplegic RSD (*10–11*), but bone hypofixation is rarely described in the literature. A few cases have been reported for young adults and children (*22–24*) and for hemiplegic patients suffering from severe atrophy (*11*). Hypofixation may be caused by decrease of the blood supply to the member and its bone tissue (because of disuse) or by modification of the bone tissue itself. In advanced stages of the disease, indeed, the remaining and the newly apposed bone tissues have a normal structure, but the

TABLE 2
Clinical and TPBS Status After the 20th Week*

		Early treatment Group A (N = 30)	Delayed treatment Group B (N = 35)	Chi-square test
Pain	Persistent	40%	48%	
	Absent	60%	52%	N.S.
Joint stiffness	Persistent	20%	66%	
	Absent	80%	34%	$p < 0.001$
Hemovelocity (R)	Abnormal	Increased 23%	Increased 25%	
		Decreased 30%	Decreased 55%	$p < 0.05$
	Normal	47%	20%	
Blood pool (M)	Abnormal	Increased 20%	Increased 28%	
		Decreased 33.3%	Decreased 55%	$p < 0.02$
	Normal	46.7%	17%	
Early fixation	Abnormal	57%	60%	
	Normal	43%	40%	N.S.
Delayed fixation	Abnormal	60%	57%	
	Normal	40%	43%	N.S.

* Influence of early treatment on clinical and scintigraphic status after the 20th week, i.e., during stages II and III. Patients of group A received early treatment (2–4 wk after surgery for postoperative RSD) and were examined after an average of 40.8 wk. Patients of group B received delayed treatment for late-diagnosed post-trauma RSD and were investigated after an average of 44.8 wk.

apposition phenomenon cannot compensate for the loss of tissue that occurred in the acute stage; normally structured bone substance may thus remain in an atrophic condition and be quantitatively diminished (*24*).

The early specific treatment of RSD (consisting especially in the fitting of a flexion splint to the hand) was shown to influence the evolution of the disease considerably: joint stiffness disappeared more often than in patients receiving more delayed treatment and this clinical normalization was associated with normalization of the angioscintigraphic parameters, without any change in bone fixation. A clear normalization of the hemodynamic parameters without any decrease in the bone hyperfixation was also found by Renier et al. (*18*) in four patients treated with calcitonin. This shows the pathophysiologic interdependence of blood flow and stiffness on which a symptomatic treatment may act, whereas the bone disease continues to develop.

If the angioscintigraphic phase of TPBS is not essential for the diagnosis of acute reflex sympathetic dystrophy, it may, however, constitute an early evolutive criterion of the disease, especially after treatment, since quite different hemodynamic patterns occur as soon as the 20th wk after onset of the disease, at a time when bone fixation is still high. At late stages, reversal of the hemodynamic situation highlights the frequent observation of bone hypofixation on the affected hand.

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