Deafferentation of the Affected Arm

A Method to Improve Rehabilitation?

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Background and Purpose—Reduced somatosensation is a common impairment after stroke. This somatosensory deficit is known to be a reliable predictor of poor rehabilitation outcome. Several methods of physical therapy have addressed this problem, but with only moderate success. Here, we used a new neural plasticity-based approach, ie, a simple, inexpensive, pharmacologically induced temporary functional deafferentation (TFD) of the forearm to investigate whether TFD might result in beneficial effects on the somatosensory sensibility and motor capacity of the stroke-affected hand.

Methods—Examination was performed over 2 consecutive days of an efficient rehabilitation program for stroke patients referred to as constraint-induced movement therapy. Patients were deafferented on one of these days but not on the other (placebo session). The order of deafferentation and nondeafferentation was counterbalanced across patients. TFD of the stroke-affected forearm was realized using an anesthetic cream. Somatosensory abilities were assessed by a Grating orienting task, and a shape-sorter drum task was used to test motor performance. Both tests were performed each day before and after the constraint-induced movement therapy training session.

Results—We found significantly better outcomes for Grating orienting task and shape-sorter drum task after TFD on the forearm as compared to placebo, indicating increased somatosensory abilities and motor performance in stroke patients using the simple TFD procedure.

Conclusions—The improvement was achieved during the course of one of the best established poststroke rehabilitation programs, suggesting that TFD on the more affected forearm might become an efficient additional tool in stroke rehabilitation. (Stroke. 2011;42:1363-1370.)

Key Words: rehabilitation • temporary functional deafferentation • treatment

The global burden of stroke is immense.1–3 Stroke rates are increasing rapidly worldwide, with strongest increases in low- to middle-income countries.2,3 Early stroke case fatality is decreasing,1 highlighting the importance of efficient rehabilitation for stroke survivors.

Today, there exist several evidence-based rehabilitation programs.4–6 One approach that has become prominent as an effective treatment for chronic hemiparesis of upper and lower limbs after stroke is constraint-induced movement therapy (CIMT).4,5,7–9 Furthermore, CIMT is also effective during acute stroke rehabilitation.10,11 CIMT has been shown to significantly increase the use and quality of movement of the stroke-affected limbs of patients during normal day-to-day activity. This was achieved by exposing the more affected arm of chronic stroke patients to an intensive regime of functionally related tasks for 4 to 6 hours per day over a period of 2 to 3 weeks while simultaneously constraining the use of the less affected arm for >90% of waking hours.7,8,12–16

The outcome of CIMT varies across patients and seems not to depend on characteristics such as infarct location, side of stroke, time since stroke, hand dominance, or gender.17,18 However, somatosensory hemihypesthesia, ie, the reduced sensitivity (as a common impairment after stroke) to somatosensory stimuli, such as touch on the affected side, represents one of the best predictors of poor rehabilitation outcome in stroke patients.19–22 Several methods of physical therapy have addressed this problem;22–24 however, the outcome of these approaches has only been of moderate success.22 Experimental studies on temporary functional deafferentation (TFD) on the forearm have shown effects on somatosensory sensitivity,
motor performance, and cortical reorganization. For example, Werhahn et al\textsuperscript{25} showed an increase in tactile spatial acuity and changes in cortical processing for the left hand during cutaneous anesthesia of the right hand in healthy subjects. This site-specific improvement in tactile spatial acuity was hypothesized to represent a behavioral compensatory gain. Furthermore, TFD of the right hand by tourniquet-induced anesthesia resulted in rapid and significant improvement of grip strength, tactile discrimination, sensibility in the left hand, and increased functional MRI activation in the right primary motor cortex.\textsuperscript{26} Tourniquet-induced anesthesia of the less affected hand in stroke patients has been shown to improve somatosensory sensibility\textsuperscript{27} and motor performance\textsuperscript{28} of the affected arm. Muellbacher et al\textsuperscript{29} demonstrated an improved hand motor function in stroke patients produced by a technique of regional pharmacologically induced anesthesia. Moreover, TFD of radial and median nerves in healthy subjects resulted in significant improvements of the discrimination ability around the ipsilateral lip, accompanied by a significant increase in the size of the cortical representation of the ulnar skin area and the lip and a significant decrease of intracortical inhibition within the muscle representation of the abductor digiti minimi muscle.\textsuperscript{30} Finally, increased right hand sensitivity and a rapid expansion of the primary somatosensory cortical hand representation at the expense of the anesthetized forearm’s representation was reported after TFD of the right forearm in healthy subjects by a local anesthetic cream.\textsuperscript{31} Taken together, TFD seems able to induce an increase in somatosensory sensitivity of either neighboring body parts or of homonymous contralateral skin areas. As such, TFD on the forearm seems to be a way to overcome, at least partially, the hemihypesthesia and, thereby, to improve rehabilitation.

Based on the encouraging observations cited, the present study was aimed at demonstrating the benefits to the somatosensory sensibility and motor capacity of the hand of pharmacologically induced TFD of the forearm of poststroke patients by a simple manipulation, namely TFD with an anesthetic cream during CIMT therapy.

### Subjects and Methods

#### Subjects and Standard Course of CIMT

Sixteen chronic stroke patients (8 females, 8 males) who took part in CIMT at our treatment center at the Friedrich Schiller University...
participated in this study. Patients’ characteristics (age, sex, lesion site, National Institutes of Health Stroke Scale, Wolf Motor Function Test, Motor Activity Log, Supplemental Methods, http://stroke.ahajournals.org) are shown in Table 1. The patients had each experienced their first stroke. All patients but 2 were right-hand-dominant before stroke according to the Edinburgh handedness inventory. All patients met a minimum motor criterion of at least 20-degree extensions of the affected wrist and 10-degree extensions of each finger. Other inclusion criteria were: no serious aphasia; sufficient knowledge of German language for communication; no serious uncontrolled medical problems; limited spasticity (modified Ashworth scale score <4); and limited pain (Visual Analog Scale [0–100 mm] <40). However, impaired hand sensitivity was not an inclusion criterion. Before being exposed to the treatment, patients were familiarized with CIMT, including the massive training of the more affected hand and the request to wear a constraining device on their less affected arm throughout 90% of their waking hours for the whole treatment period. While wearing the constraining device, patients received extensive motor training of the more affected arm for ~3.5 hours per day by a procedure termed “shaping” and another 3.5 hours per day with uncontrolled homework. A battery of tasks was used, from which a subset of 15 to 20 was selected for 3.5 hours per day with uncontrolled homework. A battery of tasks was used, from which a subset of 15 to 20 was selected for

**Procedure**

The procedure of the experiment was described to subjects who were then requested to provide written informed consent before their participation. The procedure was approved by the ethics committee of the Friedrich-Schiller University.

On days 3 and 4 or days 7 and 8 of the standard CIMT, subjects participated in an additional test. Each received 2 separate treatments on their more-affected forearm, a placebo plaster (not affecting somatosensory sensitivity) on 1 day, and a local anesthetic cream (Emla; AstraZeneca) to achieve TFD on the other. The order in which the 2 treatments were applied was counterbalanced across patients according to the order of admission (even number, placebo first; odd number, TFD first); 20 grams of Emla (an eutectic emulsion preparation containing 2.5% each of lidocaine/prilocaine) was used per subject. The creams (Emla, placebo) were applied to the volar side of the more affected forearm in a 50-mm wide and 150-mm long area starting parallel with and 10-mm proximal to the wrist (Supplemental Figure I, http://stroke.ahajournals.org). Creams were applied before the standard CIMT was started and they remained under an occlusive bandage for the whole period of examination (3.5 hours). Subjects were told that they would receive 2 types of local anesthetic to enhance training efficiency, and that efficiency would be tested the same day with several additional short tests, including the shape-sorter drum task (SSDT), von Frey hair testing (VFHT), and the Grating orienting task (GOT). SSDT, VFHT, and GOT were applied before and after training, ie, immediately after applying cream to the patients and immediately after the last exercise of the morning training session in the course of standard CIMT, CIMT (U.T.), assessment (E.S., T.W.), and TFD procedure (a study nurse) were performed by different persons; thus, patients and investigators were blinded concerning the actual treatment. However, it should be noticed that the behavioral consequences of the TFD on the forearm often invalidate the blinding.

**VFHT**

The VFHT was used to characterize the efficiency of TFD on mechanical thresholds of the more affected forearm and possible correlations between VFHT and the other parameter. Thresholds for touch were tested at a point marked for VFHT assessment in the middle on the occlusive bandage of the treated forearm before and after training. A von Frey hair set VF2 OptiHair 2 (Marstock Nervtest) was used for assessment. According to Rolke et al, a method of limits, ie, 5 ascending and descending series of VFHT, was used to determine tactile detection thresholds. The force of the first von Frey hair in increasing order that was perceived by the patient was noticed as the first suprathreshold value. Beginning with this force, von Frey hairs were then applied in decreasing order until the patient did not perceive the force any more. This force was noticed as the first infrathreshold value. The procedure was repeated 5 times. VFHT was defined as the geometric mean of all 10 values, ie, of 5 suprathreshold and 5 infrathreshold values.

**SSDT**

SSDT was used to measure movement performance with a substantial amount of visual and somatosensory requirements. Subjects were required to take 20 objects with their more affected hand from a standard position and put them into a drum. Objects had to be put into separate slots according to their size and shape. Objects and slots were adapted to the abilities of subjects but were the same for a given subject on all measurements. The dependent variable, performance time, was measured from the start of movements to the instant the last object was put into the drum, so shorter times represent better performance. SSDT requires visual–motor as well as somatosensory–motor coordination to fulfill the task. A specified description of the SSDT is given in the Supplemental Methods.

**GOT**

GOT was used to measure limits of tactile resolution, using a modified technique similar to that of Van Boven et al. We used a set of 14 hemispherical plastic domes with gratings cut into their surfaces, resulting in parallel bars and grooves of equal widths (0.5–10 mm) on each dome. Before measurement, patients familiarized themselves with the task by inspecting the gratings. During the task, a cardboard screen was placed over the patient’s arm to shield the view of the hand. Gratings were applied with the ridges and grooves randomly oriented in 1 of 2 orthogonal directions (perpendicular or parallel to the axis of the finger). Patients were asked to identify the alignment. We determined GOT thresholds, defined as the groove width at which responses were 75% correct. A specified description of the procedure is given in the Supplemental Methods. GOT is unique among psychophysical tests in providing a valid measure of spatial resolution that corresponds consistently with patient self-assessment of sensory status. Other advantages of the GOT are the low day-to-day variability, an important prerequisite for longitudinal measures, as used in our study, as well as the significantly higher sensitivity than other tests of tactile function when evaluating peripheral nerve injury or deafferentation, as in our study.

**Time Schedule**

The overall time schedule consisted of the application of a cream, baseline evaluation (t1) using the tests mentioned, the usual course of
Table 2. Raw Data of the Dependent Variables von Frey Hair Testing, Shape-Sorter Drum Task, and Grating Orienting Task for the Treatments Temporary Functional Deafferentation and Placebo

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<th>VFHT Placebo Before, mN</th>
<th>VFHT Placebo After, mN</th>
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<th>SSDT TFD After, s</th>
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<th>GOT TFD Before, mm</th>
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Mean±SD: 135.4±226.62 498.6±233.23 145.2±217.54 450.9±352.39 399.4±360.89 440.8±366.89 5.1±3.62 4.5±3.90 5.0±3.59 4.8±3.70

Sensory deficit is the quotient of GOT performance on the index finger for paretic hand/GOT performance on the index finger for control hand. GOT indicates Grating orienting task; TFD, temporary functional deafferentation; SSDT, shape-sorter drum task; VFHT, von Frey hair testing.

*Patients received TFD as the first treatment and placebo as the second treatment. All other patients received placebo treatment first.
CIMT for 3.5 hours, and treatment evaluation (t2) using the tests described (Figure 1).

Statistical Analysis
Repeated-measures ANOVA, with within-subject factors time (t1 versus t2) and treatment (placebo versus anesthetic cream), were performed to assess differences in SSDT, VFHT, and GOT performances. Post hoc testing of significant results was performed using paired t tests. Because our primary goal was to improve motor performance, we used performance of SSDT as the primary outcome criterion, whereas GOT and VFHT were secondary criteria. We expected interactions between factors time and treatment because no differences were expected at t1 on either treatment, but significant differences were expected for the 2 types of treatment (placebo versus anesthetic cream) at t2. All statistical tests were performed with SPSS for Windows (version 15.0).

Results
The raw data and mean values of the dependent variables VFHT, SSDT, and GOT for the treatments TFD and placebo are presented in Table 2.

Effectiveness of the TFD on VFHT
We found significant main effects of factors time (F1,15 = 23.95; P < 0.001) and treatment (F1,15 = 25.45; P < 0.001), as well as a significant time × treatment interaction (F1,15 = 30.16; P < 0.001). Main effects of time and treatment resulted from higher thresholds during TFD on the forearm by the anesthetic cream (Table 2). This is substantiated by the time × treatment interaction that revealed no differences in VFHT between t1 and t2 for the placebo cream, but significantly higher VFHT for the analgesic cream at t2 (t = −5.55; P < 0.001; Figure 2). Furthermore, there were no significant differences for t1 of placebo compared to t1 of TFD.

Effectiveness of the TFD on SSDT
ANOVA revealed a significant main effect of factor time (F1,15 = 9.56; P < 0.01) and a significant interaction between factors time and treatment (F1,15 = 5.52; P < 0.05). Although the main effect of time resulted from overall shorter performance times, ie, improvement of performance by the training irrespective of treatment, the analysis of the time × treatment interaction revealed no differences in performance times at t1 compared to t2 when subjects were treated with placebo cream, but significantly shorter performance times at t2 when subjects were treated with the analgesic cream as compared to t1 (t = 2.81; P < 0.05; Figure 3). The outcome data and mean values of VFHT for the treatments TFD and placebo are shown in Table 2. Moreover, there were no significant differences for t1 in placebo compared to t1 in TFD. We also analyzed effects of hand dominance (left versus right) and lesion site (left versus right), but these differences were not significant.

Figure 2. Changes of the von Frey hair test (VFHT) thresholds at the forearm during temporary functional deafferentation (TFD) with anesthetic cream (left) and with the placebo (right). Performance is expressed as percent of pretest value, and higher values indicate higher thresholds, ie, less sensitivity. Single traces show single subjects.

Figure 3. Performance time for the shape-sorter drum test (SSDT) during temporary functional deafferentation (TFD) with anesthetic cream (left) and during placebo (right). Performance is expressed as percent of pretest value. Single traces show single subjects. The inset shows the task structure.
Effectiveness of the TFD on GOT

We analyzed the differences attributable to treatment and also characterized the sensory deficit on the more affected hand as a difference in GOT for the index finger (Table 2). ANOVA revealed a main effect of factor time ($F_{1,15}=7.94; P<0.05$) and a significant interaction between factors time and treatment ($F_{1,15}=5.42; P<0.05$). Analysis of this interaction revealed no differences in tactile resolution between t1 for the 2 treatments and between t1 and t2 when subjects were treated with placebo cream; however, tactile resolution was significantly better at t2 compared to t1 when subjects were treated with analgesic cream ($t=3.76; P<0.01$; Figure 4). Furthermore, the index finger of the more affected hand showed a highly significant sensory deficit in GOT (tactile resolutions, mean ± SD: 5.11±3.61 mm) compared to the less affected index finger (2.64±1.95 mm; $t=-2.97; P=0.01$).

Discussion

In the present study, a simple and inexpensive technique was able to establish TFD of the forearm of the more affected arm in poststroke patients by a standard anesthetic cream. This TFD led to a significant increase in motor performance in poststroke patients by a standard anesthetic cream. This improvement is in line with a previous report of tourniquet-induced deafferentation of the less affected hand in stroke patients.

This improvement of motor performance reported here were shown only using a single training session, but we found a hint of long-term effects testing the assessment of SSDT for the subgroup of patients who receives TFD first. There was a trend for SSDT comparing both pretest values in this group (Supplemental Results). This is in line with Muellbacher et al, who demonstrated an improved hand motor function in stroke patients produced by a pharmacologically induced anesthesia 2 weeks after treatment. From a pharmacological point, it seems possible to repeat TFD on a daily basis in clinical practice, eg, CIMT. However, long-term effects and the clinical relevance of these improvements in everyday life should be demonstrated in separate trials using TFD on the more affected forearm for the whole training period of CIMT.

TFD on the more affected forearm significantly improved somatosensory sensitivity as measured by GOT. This result is in accordance with improvements from other kinds of TFD found in healthy subjects or ischemic TFD in stroke patients. Animal and human experiments have demonstrated a reorganization of somatosensory receptive fields at different levels of the somatosensory system starting minutes after a pharmacological deafferentation. The changes in receptive fields might underlie the observed improvement of sensitivity. Moreover, pharmacological TFD on the right hand of healthy subjects was found to increase the central processing of the somatosensory system, as demonstrated by increased somatosensory-evoked potentials. These data together with the observed improvement in GOT show promise for the enhancement of somatosensory abilities in poststroke patients.

There are several elements of the motor test (SSDT) that could affect the overall performance. These include visual elements, such as the discrimination of objects and the assessment of distance to the drum, somatosensory elements, such as during the grasping of an object, and aspects of motor control, such as muscle synergies, and so on. Although some of these elements might be affected by TFD of the more affected forearm, other aspects are less likely to be changed. As stated, somatosensory abilities are improved by TFD. Therefore, it is likely that the improved somatosensory sensibility contributes to the improvement of SSDT by TFD on the forearm. However, there was no significant correlation between changes in GOT and changes in SSDT (Supplemental Results). Alternatively, the somatosensory and the motor...
system work independently or there might be a possible competition between somatosensory and motor systems. We found a trend for a negative correlation between SSDDT and VFHT (Supplemental Results) supporting this hypothesis. Furthermore, TFD has been shown to change motor excitability as well as organization of receptive fields in the primary motor cortex. Therefore, our results indicate that some aspects of motor control have been improved by TFD on the forearm. Other motor aspects, eg, muscle synergies, are less likely to be affected. Finally, there are some hints that intermodal plasticity could potentially contribute to the improvement of GOT performance. Nevertheless, it seems unlikely that TFD would affect any of these elements of the task, especially the visual, in a way that would be able to account for our results.

Taken together, our data show that a simple, inexpensive, pharmacologically induced TFD on the more affected forearm by an anesthetic cream results in improvements of motor performance and somatosensory discrimination. After testing its long-term efficiency, this technique might become an additional tool in the improvement of motor rehabilitation in poststroke patients, as has been shown in single-subject studies.

Acknowledgments
T.W. participated in the study design and implementation, data analysis, and helped write the report. E.S. participated in the study design, data analysis, had full access to data, and helped write the report. U.T. was the clinical investigator, participated in the examination, and helped write the report. W.M. and O.W.W. participated in the study design and helped write the report. C.P. participated in data analysis and helped write the report. W.H.R.M. participated in the study design and implementation, data analysis, and helped write the report.

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Disclosure
None.

References
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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/05/11/STROKEAHA.110.601138.DC1
SUPPLEMENTAL MATERIAL
Supplemental Methods

*Application of the Emla cream.* Supplemental figure S1 demonstrates the application of the Emla cream.

*Shape-sorter-drum task SSDT.* SSDT belongs to the battery of tasks used in the CIMT. Subjects were required to take 20 objects only with their more affected hand from a standard position marked on the table and put them into a drum. The objects were wooden building bricks which had different shapes (see supplemental figure S2). Objects had to be put into separate slots according to their size and shape. Objects and slots were adapted to the abilities of subjects based on the suggestion of the CIMT examiner. However, for a given subject the task was identically on all measurements and included at least 14 objects. The dependent variable, performance time, was measured from the start of movements to the instant the last object was put into the drum. The test was stopped when the subject was not able to put in all objects with the more-affected hand within 900 seconds.

*Grating orienting task GOT.* Subjects were seated comfortably at a table, with their hand in a supine position. The index finger was rested on a wooden wedge and fixated by double-faced adhesive tape. Stimuli were applied with a moderate force (producing about 1-2 mm of skin indentation) on the distal pad of the index finger and held for about 1-2 sec. Each dome was tested in a block of 20 trials (10 trials for each of the two orientations which were presented randomly). Based on the findings of Tremblay et al. the 5-mm dome was applied first. If the subject scored under 65% correct answers (less than 13 domes) with the 5-mm dome, the 10-mm dome was selected as the next grating. Ensuing the examiner proceeded to the next grating dome in a sequence of increasing difficulties. To hold the test short and to avoid undue fatigue, the test was stopped when the number of correct answers for the presented dome was less than 13 (i.e., less than 65 % correct answers). We determined GOT thresholds, approximating as the groove width at which responses were 75% correct. Order of testing: 1. the more-affected index finger; 2. the less-affected index finger.
National Institutes of Health Stroke Scale (NIHSS)

The NIHSS measures impairment and disability of stroke patients on a 6-point ordinal scale. It assesses volitional arm and hand movements, tone, and mobility. The NIHSS was obtained at the initial examination by a neurologist to describe stroke severity, but not used as a screening tool for inclusion. For further information - see Brott et al.²

Wolf Motor Function Test (WMFT)

The WMFT assesses laboratory-based upper-extremity motor function. The test contains 17 items, i.e. 15 timed and 2 strength tasks. The strength-based tasks are measured by weight lifted and grip strength. The timed tasks are rated according to 6-step scales (0 to 5) for functional ability, and the time period patients needed to complete the motor task was measured. Time tasks are ordered from simple to complex, and measure shoulder, elbow, and upper extremity movements. For further information - see Wolf et al.³

Motor Activity Log (MAL)

The MAL assesses real-world outcome by a structured interview that obtains information about 20 common activities of daily living carried out outside the laboratory. The modified MAL in German language consists of 30 items. For each activity patients are asked to rate the quality of movement and the amount of use by using a 6-step scale (0 to 5). The items include areas as feeding, dressing, and cleaning. For further information see Uswatte et al.⁴ and Bauder et al.⁵
Supplemental Results

*Correlations between the dependent variables*

Supplemental Table S3 shows the Pearson correlation coefficients between the dependent variables, i.e., the changes in VFHT, the changes in GOT, and the changes in SSDT for the treatment TFD. As Table S3 indicates, we did not found any significant correlations beside a trend for a negative correlation between the changes in SSDT and VFHT (p=.09). Furthermore, the correlations between the raw data of the dependent variables VFHT, SSDT, and GOT for the treatment TFD were also not significant beside a trend for a negative correlation between the raw data of post-testing for SSDT and the raw data of post-testing for VFHT (r=-.49; p=.06) supporting the trend reported above.

*Effects of treatment order*

We tested the assessments for GOT and SSDT at t1 for the patients who received Emla cream on day 1 by performing paired t-tests. T1 on day 1 and t1 on day 2 did not significantly differ in GOT (t=.26; p=.81) and SSDT for this group (n=7). Interestingly, there was a trend for SSDT (t=2.34; p=.06) that possibly suggest long-term effects of TFD on motor performance. However, long-term effects should be demonstrated in separate trials.
Supplemental Table

Table S3: Pearson Correlation Coefficients and p-values between changes in VFHT, changes in GOT, and changes in SSDT for treatment TFD

<table>
<thead>
<tr>
<th>Changes in VFHT</th>
<th>Changes in GOT</th>
<th>Changes in SSDT</th>
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<tbody>
<tr>
<td></td>
<td>r=-.20</td>
<td>r=-.46</td>
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<tr>
<td></td>
<td>p=.48</td>
<td>p=.09</td>
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<td>Changes in GOT</td>
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<td>r=-.12</td>
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Supplemental Figures

Supplemental Figure S1: Application of the cream to the volar side of the more-affected forearm. VFHT was performed at the point in the middle of the occlusive bandage, i.e. about 1 cm proximal to the wrist.

Supplemental Figure S2: Wooden building bricks showing the different shapes used for SSDT.
Supplemental References


