Reliability of four experimental mechanical pain tests in children

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Purpose: In order to study pain in children, it is necessary to determine whether pain measurement tools used in adults are reliable measurements in children. The aim of this study was to explore the intrasession reliability of pressure pain thresholds (PPT) in healthy children. Furthermore, the aim was also to study the intersession reliability of the following four tests: (1) Total Tenderness Score; (2) PPT; (3) Visual Analog Scale score at suprapressure pain threshold; and (4) area under the curve (stimulus–response functions for pressure versus pain).

Participants and methods: Twenty-five healthy school children, 8–14 years of age, participated. Test 2, PPT, was repeated three times at 2 minute intervals on the same day to estimate PPT intrasession reliability using Cronbach’s alpha. Tests 1–4 were repeated after median 21 (interquartile range 10.5–22) days, and Pearson’s correlation coefficient was used to describe the intersession reliability.

Results: The PPT test was precise and reliable (Cronbach’s alpha ≥ 0.92). All tests showed a good to excellent correlation between days (intersessions r = 0.66–0.81). There were no indications of significant systematic differences found in any of the four tests between days.

Conclusion: All tests seemed to be reliable measurements in pain evaluation in healthy children aged 8–14 years. Given the small sample size, this conclusion needs to be confirmed in future studies.

Keywords: repeatability, intraindividual reliability, pressure pain threshold, pain measurement, algometer

Introduction

Background

Chronic pain, which is often associated with mood disorders, lost social relations, and decreased school attendance, might have profound consequences for the child in every aspect of their daily lives.1,2 Consequently, further investigation of the mechanisms of pain perception in children is needed. Better knowledge might prevent chronification and ensure optimal treatment. In order to study pain perception in children, it is necessary to determine whether the pain measurement tools used in adults are reliable measurements in children.

Tension-type headache (TTH) causes pain and is one of the two most frequent primary headache disorders in children.3 The prevalence of TTH in schoolchildren and adolescents is reported to be 10%–25%; however, 0.1%–5.9% of children suffer from chronic TTH (≥15 days/month).4,5 In adults suffering from frequent TTH, different pain measurement tools have been used to hypothesize about the changes noted in varying levels along the sensory pathway.6 Adult studies of TTH have demonstrated that
increased tenderness in response to the palpation of pericranial myofascial tissues is the most apparent abnormality.6

Until now, very few studies worldwide have focused on pain perception in children and adolescents suffering from TTH, and they primarily concentrated on the Total Tenderness Score (TTS) in pericranial tissue,7–9 as well as pressure pain thresholds (PPT).7,8,11 TTS is a sum score of tenderness evaluated through the standardized palpation of different pericranial muscles and tendons.12 Evaluated using an algometer, PPT is defined as the minimum intensity of a stimulus that is perceived as painful.13

Another way of evaluating pain perception in children could include the rating of stimuli at an individual PPT-adjusted suprathreshold (SupraPPT) by a Visual Analog Scale (VAS) score. This might allow a corrected comparison between children. Furthermore, a test that evaluates the child’s VAS scores after applying increasingly mechanical pressures to a particular muscle could provide a total measure of the child’s pain perception while covering a broad range of pressure intensities. The total measure would be represented by the area under the curve (AUC) of the child’s various VAS scores. The latter tool has previously been used in research in adults.14

Used in children and adolescents in general, the validity and reliability of self-rating scales like the VAS have previously been well described.15 However, research on the reliability of experimental pain measurement tests has been quite limited. The preliminary conclusion of method studies of PPT is that PPT is a reliable pain measurement tool in children.16–18 The reliability of TTS, VAS score at SupraPPT, or the AUC has not yet been assessed.

Influenced by many factors such as demographics (age, sex, ethnicity), genetics, and psychosocial (cognitive processes, psychosocial history, social learning, personality) factors, the experience of pain is highly unique and idiosyncratic across individuals.19 Pain perception studies may nonetheless also be influenced by the measurement error, which refers to the degree to which the pain measurements obtained fail to reflect the actual pain experienced.

One issue, especially with regard to children, is whether or not respondents are cognitively capable of understanding the instructions given, and whether they can reproduce their own results. To test this question, our goal with this study was to determine the intraindividual variability. Intraindividual variability can be tested both in the same session (intrasession) or within a period of days in between testing (intersessions). In the present study, we focused on pain measurement tools used in the craniocephalic region to provide a basis for later research in children with or without frequent TTH.

**Objectives**

The aim of this study was to explore the intrasession reliability of PPT in healthy children. Furthermore, the aim was also to study the intersession reliability of the following four tests: (1) TTS; (2) PPT; (3) VAS score at SupraPPT; and (4) AUC (stimulus–response functions for pressure versus pain).

**Methods**

**Study design**

This is a test–retest study. An overview of the tests is found in Table 1.

**Participants**

Healthy children were recruited from two schools in the Copenhagen area. The enrolment and examinations took place from May 2009 to November 2010. The age of 7 years was assumed to be the limit of the cognitive capability required to perform the tests. The VAS score has previously been tested as being reliable and valid in children over 5–6 years of age.15 In total, 28 classes with around 20 pupils in each (aged 7–15 years) were told face-to-face about the study by a pediatrician in the classroom. Children who were interested in participating received a letter with written information to take home to their parents. The parents were asked to respond by email, and responding parents were subsequently contacted by telephone by the same pediatrician, and informed oral consent was given. Written informed consent was provided later.

The present study is part of a larger case-control study of the pathophysiological mechanisms involved in children with TTH. The participation of 60 healthy children was initially planned; some of these children are the participants of this study as well.

Sixty children responded; 57 children performed the tests, whereas three children were absent at the day of examination. The school boarders engaged in practical planning of the days to retest; 25 of the 57 children were randomly selected from the initial sample, and each child was tested twice. All of the children asked agreed to be retested. The exact same procedure, test room, rater, and assistant were used at the second test day. A priori, we planned to repeat the test
after 14 days. This time interval should ensure that the child could not remember their last answers, which might introduce bias. The examination of the 25 children who attended the test twice is described in the following section.

Children were excluded if they had more than 12 headache days per year, or if they had any kind of chronic illness. The exclusion criteria were determined by the assumption that infrequent TTH is a very common disease among children, making it difficult to recruit children with no headache at all. They were also determined by the assumption that the presence of eventual infrequent headache disease (<1 day per month) would not affect the test–retest reliability of pain measurements in children.3,5

### Setting

The children were not permitted to take pain medication 12 hours prior to the tests so that the medication did not interfere with eventual pain perception in the myofascial tissues. The examination took place in a familiar room in the child’s own school during the school day.

During the tests, all children were examined by the same physiotherapist with pediatric experience, and each child was assisted by the same pediatrician. The physiotherapist was blinded to the child’s answers. The tests lasted 30 minutes in total, and were performed in the order outlined below. Children performed the examination alone. Parents were invited to participate, but they all felt that that their child was secure. A comfortable environment was established by means of conversation. In order to prevent anxiety, the researchers did their best to inform the child about what to expect during the tests.

The child was placed in a vertical position in an adjustable chair with head- and armrests. The chair was individually adjusted to encourage relaxed muscles during the test. The child was examined while dressed, but was asked to uncover the shoulder and neck area. None of the children reported experiencing a headache during the tests.

### Variables

The following variables were used: TTS, PPT, VAS score at SupraPPT, and AUC (stimulus–response functions for pressure versus pain).

#### Test 1 TTS

Tenderness in the pericranial structures was assessed by the TTS system,12 which was previously proven to be reliable in adults.20 The investigator was positioned in front of the child. Seven myofascial structures were palpated bilaterally: m. masseter, m. temporalis, m. frontalis, processus mastoideus, the neck muscle insertions on basis cranii, m. trapezius, and m. sternocleidomastoidoideus. Each structure was palpated with the pulpa of the second and third fingers using a palpometer.

### Table 1 Overview of tests performed during one session (30 minutes)

| Test               | Sinister/dexter | Test site                                                                 | Apparatus | Pressure intensity | Repeated at 2 minute intervals | Outcome measure          | Sum-score |
|--------------------|----------------|---------------------------------------------------------------------------|-----------|-------------------|-------------------------------|--------------------------|-----------|
| Test 1 TTS         | Bilateral      | m. masseter, m. temporalis, m. frontalis, processus mastoideus, the neck muscle insertions on basis cranii, m. trapezius, m. sternocleidomastoidoideus | Pressure controlled palpation with second and third fingers using a palpometer | 120 AU                      | No                             | Tenderness score 0–3 | TTS 0–42  |
| Test 2 PPT         | Nondominant    | P1 first finger                                                           | Algometer | Increasing ×3      | kPa                           | VAS score                |           |
|                    |                | P2 m. temporalis                                                          |           | ×3 kPa            |                               | VAS score                |           |
|                    |                | P3 m. trapezius                                                          |           | ×3 kPa            |                               | VAS score                |           |
| Test 3 VAS at SupraPPT | Nondominant | P1 second finger                                                           | Algometer | Individually calculated | No                             | VAS score                |           |
|                    |                | P2 m. temporalis                                                          |           | No                |                               | VAS score                |           |
|                    |                | P3 m. trapezius                                                          |           | No                |                               | VAS score                |           |
| Test 4 AUC         | Nondominant    | P2 m. temporalis                                                          | Algometer | 23, 45, 67, 89, and 111 kPa | No                             | VAS score                | AUC       |
|                    |                | P3 m. trapezius                                                          |           | 23, 45, 67, 89, and 111 kPa | No                             | VAS score                | AUC       |

Abbreviations: TTS, Total Tenderness Score; AU, arbitrary units; PPT, pressure pain threshold; VAS, Visual Analog Scale; SupraPPT, pressure pain threshold-adjusted suprathreshold; AUC, area under the curve.
If a difference between the two sides was detected, each side was palpated separately to obtain a score. The palpation pressure was moderate and standardized according to 120 arbitrary units (AU) on a palpometer kindly on loan from the Danish Headache Centre, Glostrup University Hospital, Denmark. The palpometer has previously been described and validated as a useful tool for obtaining a standardized pressure, and 120 AU has been demonstrated to represent a pressure equal to 235 g. Tenderness was evaluated on a four-point scale: 0 = no visible reaction and denial of tenderness; 1 = no visible reaction but verbal report of discomfort or mild pain; 2 = verbal report of painful tenderness, facial expression of discomfort, or no reaction; and 3 = marked grimacing or withdrawal, verbal report of marked painful tenderness, and pain. Values from both sides were summed to a TTS between 0 and 42.

**Test 2 PPT**

The PPT was assessed using a Somedic Algometer type II (SBMEDIC Electronics, Solna, Sweden). The algometer is comprised of a gauge attached to a hard rubber tip, and the gauge is connected to a finger button. Pressure was applied through the rubber surface area of 1 cm² at a rate of 10 kPa per second. The instrument was placed perpendicular to the skin’s surface. Only the nondominant side was tested to avoid any differences in tissue composition and pain perception according to hand dominance. We tested PPT at three different sites: P1, dorsum of the second finger’s interphalanx; P2, the anterior temporal region where palpation revealed the belly of the muscle during contraction; and P3, m. trapezius, the halfway point between C7 and the acromion. The method was demonstrated one time at each site before testing to ensure that the participants were familiar with the test. The participants were asked to indicate when the pressure became painful based on this definition: “When you feel the sensation changes from pressure to the slightest pain press the button immediately.” The electronic display was then read. This procedure was conducted in accordance with the International Association for the Study of Pain’s definition of the pain threshold, which is, “the minimum intensity of a stimulus that is perceived as painful.” Each measure site was tested three times with 2 minutes between each test, but the site was changed at each measure.

**Test 3 VAS score at SupraPPT**

The SupraPPT in each individual child and test site is defined as the mean of the child’s three consecutive PPT measures + 50%. SupraPPT was calculated at the three test sites, P1, P2 and P3. The algometer was placed perpendicular to the skin. The pressure of the calculated SupraPPT was applied to the child for a total of 3–4 seconds at each site. The child was asked to mark the pain level with a pencil on a printed VAS showing a happy face on one end and a crying face in the other end. The child was then told that the happy face represented no pain and the crying face represented the worst pain they could imagine. The VAS score was later measured at 0–10.0 cm.

**Test 4 AUC (stimulus–response functions for pressure versus pain)**

The Somedic Algometer II (SBMEDIC Electronics) was used to apply pressure of five different intensities to the test sites: P2 (m. temporalis) and P3 (m. trapezius). Again, only the nondominant side was tested to avoid any differences in tissue composition and pain perception according to hand dominance. The intensities were: 23 kPa, 45 kPa, 67 kPa, 89 kPa, and 111 kPa. Each pressure was applied for a total of 4 seconds in a randomized order, alternating between the two muscles. The child was asked to score the pain level at a VAS score with the same procedure as explained in Test 3.

Only one similar study has been conducted assessing stimulus–response functions, but it was conducted on adults using a palpometer/pressure controlled palpation. In order to replicate the area of second finger pulp to produce results comparable to that of the previous study, a 2 cm² tip was used on the algometer. The technique in the present study differs slightly in that an algometer was used instead of pressure-controlled palpation used by Bendtsen et al. Furthermore, in order to compare results we standardized the stimuli on the algometer to the palpometer pressures (80–200 AU). The two highest stimuli equivalents (180 and 200 AU) were withdrawn, as a pilot study showed that stimuli above 111 kPa were too painful for some of the children, and this was ethically unacceptable due to the participants’ ages.

The previous study conducted on adults showed that the relationship between force applied to the palpometer and palpometer output (AU) was linear in the range from 80–200 units, and that the range was equivalent to a force range of 235–1550 g. The Somedic Algometer type II output is kPa (1 kPa = 10.20 g/cm²). The stimulus intensities in our study (23 kPa to 111 kPa) were equivalent to the five lowest palpometer pressure units (80–160 AU), as used in Bendtsen et al’s experiment, whereas 80 palpometer units was equivalent to 23 kPa, and the increase in force for each stimulation was 22 kPa, which equaled 20 AU. In studies of
pain perception in children, using methods that are available, replicable, and reliable is crucial in allowing the comparison of results from different scientific groups and countries. Because the palpometer is not easily available for future studies, the present study uses the Somedic Algometer type II (SOMEDIC Electronics). The same algometer was used for all subjects and was calibrated with a 100 kPa weight before each test day.

**Study size**

The sample size of 25 participants was arbitrarily selected, but was stated in the protocol before inclusion. Power calculations were not possible a priori, as this is the first study of its kind in children.

**Statistical methods**

SPSS version 20 (IBM Corporation, Armonk, NY, USA) computer software was used for data analysis. A statistician was consulted for statistical approval of the methods applied.

Data (TTS, PPT, VAS at SupraPPT, and AUC) are characterized by the mean and standard deviation (SD). AUC was calculated for each of the two test muscles (P2, P3) using the trapezoidal method.

Intrasession reliability in the PPT test from session 1 was assessed by Cronbach’s alpha. Cronbach’s alpha, which provides a lower bound of intrasession reliability and can attend values between 0 (no internal consistency) and 1 (perfect internal consistency), is used as a measure of reliability of a test score for a sample of examinees. In order to improve reliability during the statistical analyses, the mean of the three trials in each PPT site was calculated and used in the further analysis of intersession reliability.

Intersession reliability of the different tests was assessed using the Pearson product-moment correlation coefficient. In general, Pearson’s r below 0.4 is considered to represent poor reliability. Values between 0.4 and 0.75 represent good reliability, and values above 0.75 represent excellent reliability. The difference between sessions 1 and 2 was calculated for each participant in the different tests. The difference mean (SD) represents the mean of the differences for all participants in each test.

In order to analyze the systematic difference between each pair of measurements, a one-sample t-test at the differences between the first and second sessions was calculated for the individual tests. We used the Benjamini–Hochberg method to correct for multiplicity in the one-sample t-tests. According to this correction, $P < 0.0056$ indicates a statistically significant systematic difference in the results. We judged the results in light of this corrected $P$-value.

**Results**

**Participants**

Twenty-five children aged 10.8 years (SD 1.9, range 8–14 years), 16 females and nine males, participated and completed the test–retest sessions. Sessions 1 and 2 were performed with a median of 21 days between them (interquartile range, 10.5–22, range 7–30).

**Outcome data**

Data are presented in Table 2.

**Intrasession reliability**

The PPT test, the only test performed more than once on the same day, was repeated three times at the same site at 2 minute intervals. The test was precise and repeatable as the Cronbach’s alpha (session 1) was $\geq 0.92$ for all three sites (second finger, m. temporalis, m. trapezius) (Table 2).

**Intersession reliability**

All calculated correlation coefficients were highly statistically significant ($P < 0.001$). The Benjamini–Hochberg method to correct for multiplicity in the one-sample t-test did not show any indications of significant systematic differences in any of the tests (Table 2).

For test 1 (TTS), the correlation in TTS between the two different test days was excellent ($r = 0.81$).

For test 2 (PPT), the correlation was excellent in two of the three sites tested (second finger, $r = 0.79$; m. temporalis, $r = 0.81$), whereas the correlation was good in m. trapezius ($r = 0.70$).

For test 3 (VAS score at SupraPPT), the correlation was excellent at the second finger ($r = 0.81$), but only moderate in m. temporalis ($r = 0.74$) and m. trapezius ($r = 0.66$).

For test 4 (AUC, stimulus–response functions for pressure versus pain), the correlation of AUC in both m. temporalis ($r = 0.80$) and m. trapezius ($r = 0.76$) was excellent.

**Discussion**

The present study indicates that TTS, PPT, VAS score at SupraPPT, and AUC (stimulus–response functions) are reliable measurements in pain evaluation in healthy children of 8–14 years of age.

**Intrasession reliability examined at 2 minute intervals**

PPT was measured three times at 2 minute intervals at the second finger, m. temporalis, and m. trapezius. The Cronbach’s alpha was $\geq 0.92$ at all three sites, which indicates that the test is precise and repeatable. Children are able to define...
their PPT very precisely and they are also capable of understanding the procedure. However, low intrasession reliability could be expected if the child was confused and pressed the button when they felt it was expected of them, or if they just pressed it randomly when some pressure had been applied. Furthermore, the high Cronbach’s alpha indicates that the test is objective and standardized. Error in the instrument or method would induce bias and low repeatability. The only other study of PPT intrasession reliability in children was conducted by Chaves et al., who found a moderate to excellent intraclass correlation coefficient (0.65–0.81) in three consecutive measures of PPT in different masticatory muscles and in the right thenar region among 16 healthy children aged 7–12 years. The study was, however, smaller than the present study, and the researchers used a manual algometer (Kratos, model DDK-10, Kratos Ltd, Cotia, Sao Paulo, Brazil) with a different measurement technique, which might explain the lower reliability. In the present study, the examination lasted 30 minutes in total, which we assumed to be the upper limit of concentration in the participating children. We had to be selective about the tests used, which is why we did not assess the intrasession reliability of the other three tests.

**Intersession reliability examined on different days**

To our knowledge, this study is the first to evaluate the intersession reliability of TTS, VAS score at SupraPPT, and AUC (stimulus–response function for pressure versus pain) in children. In this study, the children showed excellent intersession reliability both in test 1 (TTS; r = 0.81) and test 4 (AUC; m. temporalis, r = 0.80; m. trapezius, r = 0.76).

In test 2 (PPT) and test 3 (VAS score at SupraPPT), however, the coefficients fell in the high range of the interval between a good correlation and an excellent correlation (r = 0.66–0.81). These results are comparable with the PPT intersession reliability found by Chaves et al. In adults, TTS has proven to be a valid and reliable method for measuring tenderness in pericranial structures. Furthermore, PPT assessments in adults using an algometer were also found to be reliable. Since the body is a complex structure with day-to-day fluctuations in tenderness and biological processes, the total correlation between sessions is beyond the bounds of possibility. We believe that the observed variances seen in our different tests are acceptable and expected.

Systematic differences can be introduced if all of the children are affected in some way at the first examination. Anxiety might induce decreased PPTs and increased VAS scores in the first session, if the children felt insecure and felt that they were not in a friendly environment. We did not find any significant systematic differences in any of the four tests between days.

Rater palpation pressure has previously been shown to be stable from week to week. In order to standardize and objectify the manual palpation pressure in the TTS test, the

Table 2  Measurements, intrasession and intersession reliability

| Test | Session 1 mean (SD) | Session 2 mean (SD) | Cronbach’s alpha | Difference mean (SD) | Pearson’s correlation coefficient | One-sample t-test – difference P-value |
|------|---------------------|---------------------|------------------|----------------------|----------------------------------|--------------------------------------|
| Test 1: TTS (0–42) | 6.2 (4.5) | 6.6 (4.4) | 0.4 (2.8) | 0.81\(^{a}\) | \(0.522\) |
| Test 2: PPT | 104.4\(^{a}\) (56.9) | 119.3 (59.3) | 0.931 | 14.9 (37.4) | 0.79\(^{b}\) | \(0.058\) |
| m. temporalis kPa | 104.1\(^{a}\) (48.0) | 118.1 (40.5) | 0.955 | 13.9 (28.2) | 0.81\(^{b}\) | \(0.021\) |
| m. trapezius kPa | 100.6\(^{a}\) (42.4) | 119.6 (50.7) | 0.921 | 19.0 (37.0) | 0.70\(^{b}\) | \(0.017\) |
| Test 3: VAS score at SupraPPT | 2.7 (2.1) | 2.5 (2.0) | –0.19 (1.27) | 0.81\(^{b}\) | \(0.466\) |
| Second finger | 3.3 (2.5) | 3.4 (2.0) | 0.08 (1.72) | 0.74\(^{b}\) | \(0.827\) |
| m. temporalis cm | 3.1 (2.5) | 3.4 (2.5) | 0.30 (2.06) | 0.66\(^{b}\) | \(0.468\) |
| m. trapezius cm | 222.1 (161.4) | 195.3 (149.9) | –26.8 (99.3) | 0.80\(^{b}\) | \(0.190\) |
| Test 4: AUC – (stimulus–response functions) | 191.1 (131.3) | 159.4 (136.1) | –31.7 (93.0) | 0.76\(^{b}\) | \(0.101\) |
| m. temporalis AUC | 16 | 16 | –0.058 | \(0.001\) | \(0.931\) | \(0.81\) |
| m. trapezius AUC | 26.8 (99.3) | 26.8 (99.3) | 0.81\(^{b}\) | \(0.0056\) | \(0.0006\) |

Notes: *The average of the three measurements on each test day; P < 0.001. Results from Tests 1–4 in the first and second session are presented. Calculated in the first session, Cronbach’s alpha is a measurement of the internal reliability of the individual test, ie, of the intrasession reliability. Difference mean (SD) represents the mean of the difference initially calculated for each participant between sessions 1 and 2. Pearson’s correlation coefficient represents the intersession reliability of the different subtests. The one-sample t-test tests the H0: diff = 0. According to the Benjamini–Hochberg correction for multiplicity, P < 0.0056 rejects H0: diff = 0 and indicates a statistically significant systematic difference between sessions 1 and 2.

Abbreviations: SD, standard deviation; TTS, Total Tenderness Score; PPT, pressure pain threshold; VAS, Visual Analog Scale; SupraPPT, pressure pain threshold-adjusted suprathreshold; AUC, area under the curve.
same rater was used throughout the study and trained in applying a pressure of 120 AU using the same palpometer previously used in adult studies. Gender differences have been observed in measurements of PPT; however, we are not aware of data indicating gender differences in PPT reliability. The sample size of 25 children in the present study does not allow us to search for conclusions about gender differences among the four pain measurement tools.

The tests described in the current article may primarily be used for studying pain mechanisms in chronic pain disorders; however, one could imagine that the TTS might be used to determine the general craniocephalic tenderness of a child attending the clinic. The mean of the three trials in each PPT site was calculated and used in the further analysis of intersession reliability. In other studies, a similar procedure would have to be followed in order to achieve similar levels of reliability. At present, only very few studies of experimental pain measurement tests exist in children worldwide. The present study is, to our knowledge, the first for some of the measurement tools. However, the results of the present study are tentative due to the sample size. If the study had been more extensive, it would have been of great interest to determine the interrater reliability of the tests using a second rater on a third test day. Initially, we planned to examine all of the children with 14 days between, but practical difficulties in the available test days resulted in a variation in the number of days between tests. We believe that a longer test period might have decreased the reliability; however, we found moderate to excellent reliability in all tests. Finally, it was only the highly motivated children who participated, but we believe they represented the general population of schoolchildren, aged 8–14 years, in Denmark.

Conclusion
The present study indicates that pain measurement tools such as TTS, PPT, VAS score at SupraPPT, and AUC (stimulus–response functions for pressure versus pain) appear to be reliable measurements in pain evaluation in healthy children aged 8–14 years. However, given the small sample size, the conclusion needs to be confirmed in future studies.

Approval
Written informed consent was obtained from all participants. The study was approved by the local biomedical research ethics committee (H-D-2009-019) and the Danish Data Protection Agency (2009-41-3172).

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Disclosure
The authors report no conflicts of interest in this work.

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