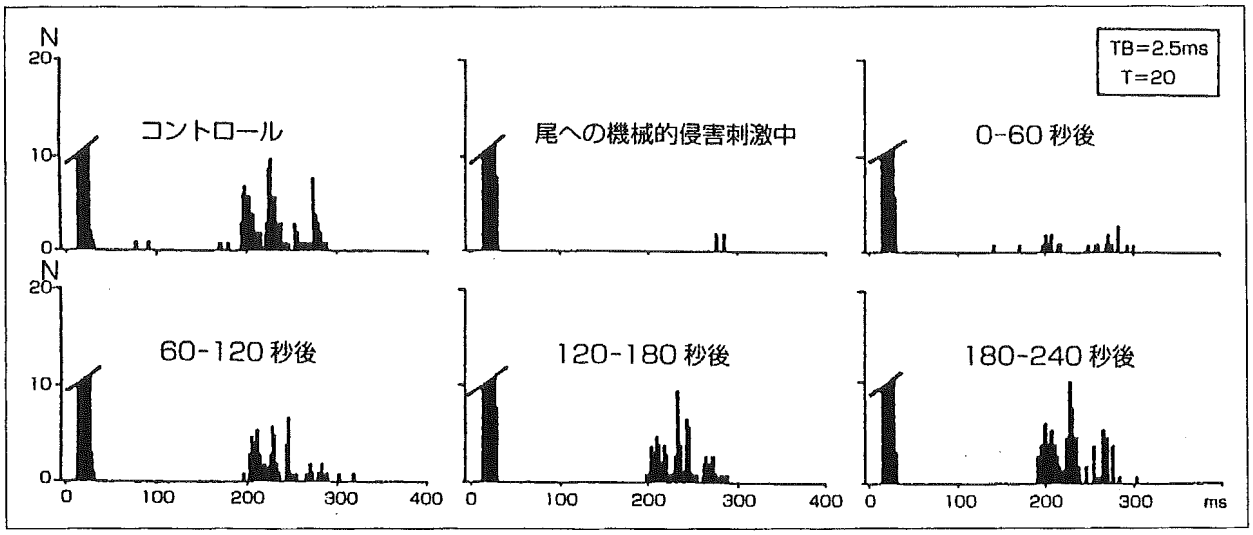


図7　広汎性侵害抑制調節(DNIC)

各図の縦軸は神経線維の発射頻度，横軸は時間経過を示す．各図は潜時の短いA線維の放電と遅れて現れるC線維の放電を表している．ラットの後肢足部に強い電気刺激を与えると脊髄後角広作動域ニューロンにおけるC線維活動が増強している(上段左)．ピンセットで強力にラットの尾を挟みつけると，C線維活動が完全に抑制されている(上段中)．その効果は1分間継続し，3～4分後に元の活動に戻っている(下段右)．　(文献[18]を改変)

が，その受容野以外の場所に与えた侵害的な刺激によって抑制されることを発見し，これをDNICと名づけた(図7)．受容野以外の部位の検討もなされ，ラットの手足や鼻部でも同様の効果[19]が報告されている．すなわち，選手の訴える痛みがその部位以外の手足などの軟部組織に与えた痛み刺激により，抑制されるというものである．このことは，痛み刺激を利用した慢性的な疼痛に対する方法の生理学的な基礎を提示したものであり，この調節機構にポリモーダル受容器の関与が考えられている．また，DNICメカニズムとして脳幹部からのネガティブフィードバック機構の関与[20]が報告されており，脊髄分節性の疼痛抑制などは否定されている．

### 3．内因性オピオイド鎮痛系

生体には強烈な痛みから生体を保護する内因性鎮痛物質(オピオイド物質)が中枢神経系に存在する．その物質にはβ-エンドルフィン，エンケファリン，ダイノルフィンなどがあり，脊髄後角をはじめ，中脳中心灰白質，視床下部，視床内側部，尾状核などにこれら麻薬性鎮痛薬の受容体が存在することがわかっている[21]．したがって，末梢組織でひき起こされた侵害受容性のインパルスは，大脳で痛みとして知覚するまで，中枢のいくつかの部位で抑制される可能性を示している．また，炎症時にはこれらの鎮痛効果が正常時に比べ大きい[22]ことが知られている．さらに，オピオイド物質は前述の下行性疼痛抑制系におけるエンケファリンのように，下行性鎮痛にも作用する．これらの物質は疼痛時に作用するだけでなく，ランニングなどのストレスにも働きかけ，毎日ランニングすることで爽快感が生じ，逆に走らないとイライラするなどの感覚をひき起こす，いわゆる“ランニング・ハイ”現象を生み出す．

### 4．非侵害刺激抑制

1965年MelzackとWall[23]は痛みの抑制に関し，ゲートコントロール説(gate control theory)を提唱した．彼らの説は痛みの特異性説(specificity theory)と痛みの強度説またはパターン説(intensity or pattern theory)からなる．すなわち，痛覚伝導系は末梢から中枢まで存在するが，触刺激などに関与する速い伝導速度をもった太い有髄神経線維(たとえばAβ線維)の興奮が，脊髄後角膠様質細胞(SG細胞)を脱分極させ，痛み信号を伝達する細い神経線維に対して門を閉じるようにSG細胞を過分極させる結果，第Ⅴ層に存在する伝達細胞とシナプスを形成する前に抑制をかけるとするものである．しかしながら，細い神経がSG細胞の過分極を起こし，シナプス前抑制を脱抑制するという考えは多くの神経生理学者に

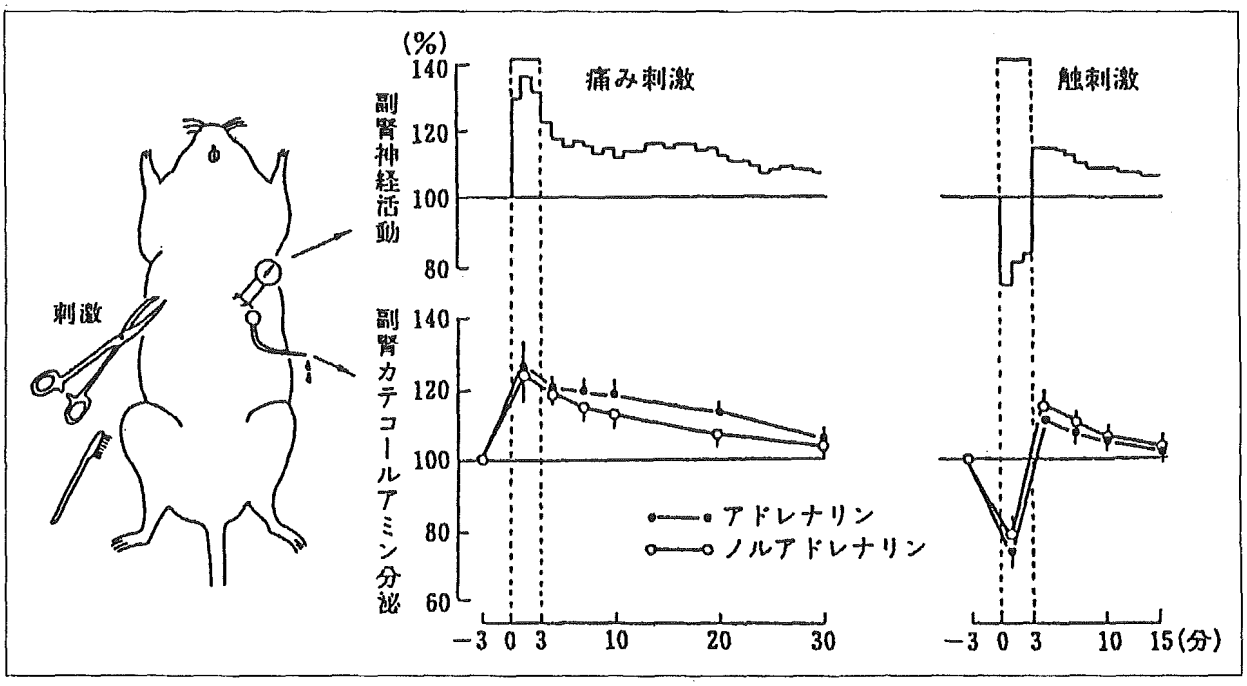


図8　非侵害刺激によるカテコールアミンの分泌
ラットに侵害刺激を与えると副腎からのカテコールアミンの分泌は増強するが，非侵害刺激を与えると，逆の生体反応が出現する．（文献[24]を改変）

よって否定された．その後，ゲートコントロール説の理論上の欠陥は修正され今日に至っているが，この説の痛みに関する新しい概念の臨床的な意義は現在でも高く評価されている．

非侵害刺激による痛みの抑制法はTENSなどに代表される電気刺激，ホットパックや渦流浴などの温熱刺激，テーピングやマッサージなど圧受容器や触受容器を興奮させる各種テクニックなどが含まれる．非侵害刺激である触圧刺激がカテコールアミンの分泌を指標とした実験で侵害刺激による反応とはまったく逆に，局所の交感神経系活動を抑制することが報告[24)25)]されており，その結果，血流増加，筋緊張低下をひき起こすことなどが考えられる（図8）．

## DNICアプローチ

生体に存在する鎮痛の機序のうち，著者が軟部組織由来の疼痛に対して，DNICと非侵害刺激である圧刺激とを利用した抑制法について説明する．DNICアプローチ[26)]はDNICにより疼痛部位の疼痛閾値を高めた後，同部位への圧刺激による交感神経系活動の抑制と脊髄後角レベルでの侵害受容インパルスの抑制を目的とした方法である．以下に，具体的な方法を述べる．

①患者が訴える疼痛部位と疼痛閾値を問診，運動検査，触診により明らかにした後，治療肢位で再確認する（図9-A）．

②疼痛部位に軽く指を当てておき，DNICを利用するため他方の手指において異なる部位（たとえば，僧帽筋，棘下筋，上腕二頭筋，長橈側手根伸筋，外側広筋，腓腹筋など）に比較的強い圧迫による侵害刺激を与える（図9-B）．

③異なる部位に侵害刺激を与えている状態で，元々の疼痛部位に対し，①で疼痛閾値を確認した時と同じ方向，深さ，力で再度圧迫し，疼痛が消失あるいは減少していることを確認する（図9-C）．

④疼痛抑制のために利用した筋に対し，軽く指腹でマッサージし，痛みの感覚を消失させる．

⑤疼痛部位に対し，より多くの圧受容器を興奮させる目的で，筋線維が判別できる程度の軽い圧刺激を手指指腹で約10～20秒施行する（図9-D）．

⑥再度，元々の疼痛部位の閾値を評価し，患者の主観とともに疼痛が抑制されたことを確認する（図9-E）．

⑦疼痛発現動作を再度行わせ，疼痛の軽減とともに動作が改善されたことを確認する．

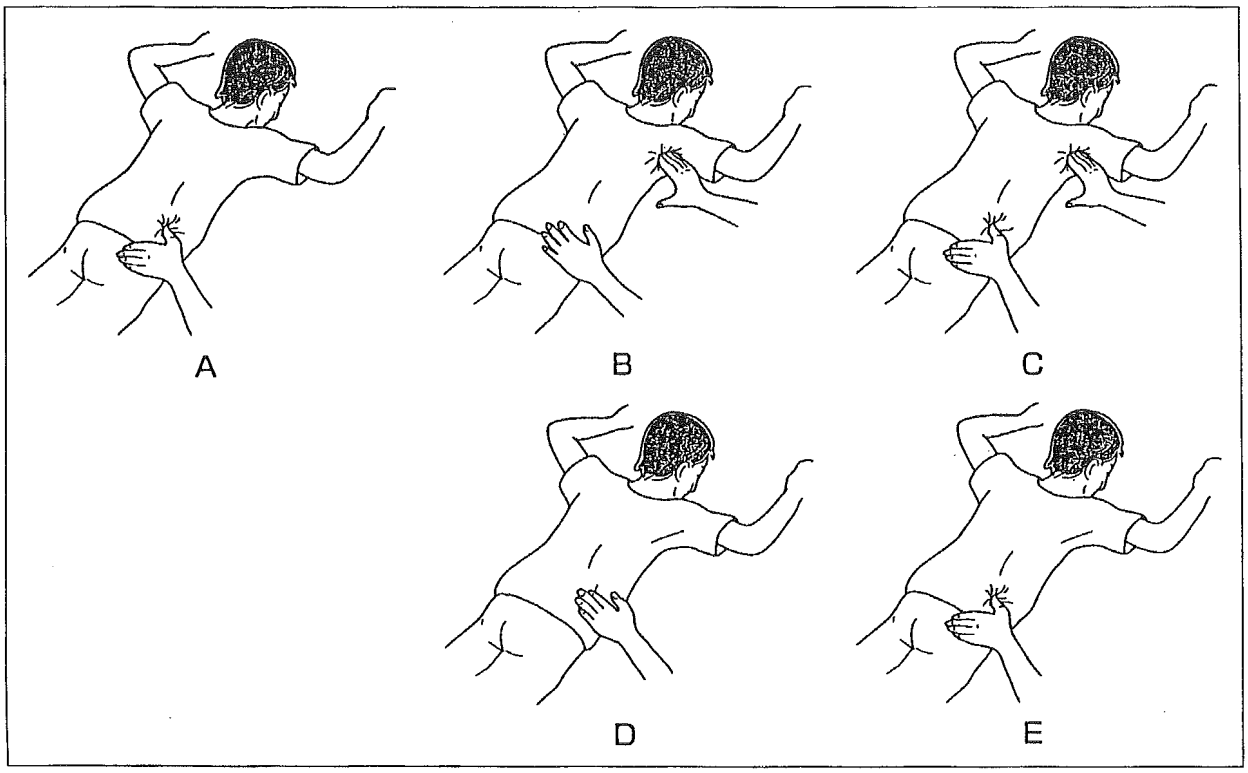


図9 DNICアプローチ
A：治療肢位で疼痛部位を再確認する，B：ほかの部位に侵害刺激を与える，C：ほかの部位に侵害刺激を与えている時に，元々の部位の疼痛が抑制されているかを患者に聞いて確認する，D：疼痛部位を中心に圧刺激を10～20秒加える，E：Aで与えた同じ圧迫力で元々の部位の疼痛が抑制されていることを再確認する．
（文献[26]より引用）

## IDストレッチング

IDストレッチング(individual muscle stretching, 個別的筋伸張法)[27)~30)]とは，痛みの持続などにより伸張性の低下した個々の筋を対象として，関節の動きや柔軟性の改善などを目的として，個々の筋線維の走行や筋同士のつながりを意識したスタティック・ストレッチング法で，神経生理学的にⅠb抑制を利用した方法で，その効果として筋緊張を低下させ血液循環の改善を促す．

ストレッチングが筋緊張低下に効果的であることは，安静時放電の著明な低下[31)]，運動時の異常放電の減少[32)]，関節可動域の増大[33)34)]やモアレ像の正常化[35)]などによって裏づけられている．

また，激しい運動後に発生するいわゆる遅発性筋痛(delayed onset muscle soreness)の筋電図所見[36)]では，運動前に比較すると異常な筋放電が認められているので，DNICアプローチ後に，当該筋に対してIDストレッチングを施行することより，一層疼痛が抑制されるとともに，筋の伸張性，柔軟性が向上し，結果的に可動域の改善とパフォーマンスの改善が期待できると考える．

IDストレッチングでは以下の点に留意して施行する．

①ストレッチング前に疼痛を軽減させておく．DNICアプローチあるいは各種物理療法により疼痛閾値を高め，ストレッチングがより容易に行えるようにする．

②可動域の制限が存在している場合は，安易に拮抗筋を責任筋としない．逆に，主動筋が可動域制限の責任筋である場合が多い．

③筋連結を意識し，筋連結を利用しながらストレッチングするように心がける．

④筋走行を常に思い浮かべながら行う．

⑤ストレッチングを施行する順序は，原則として表在筋から深部筋，近位筋から遠位筋へと進める．

⑥伸張反射の防止のため，急速にストレッチングしない．

⑦疼痛が発生しないように，ストレッチング

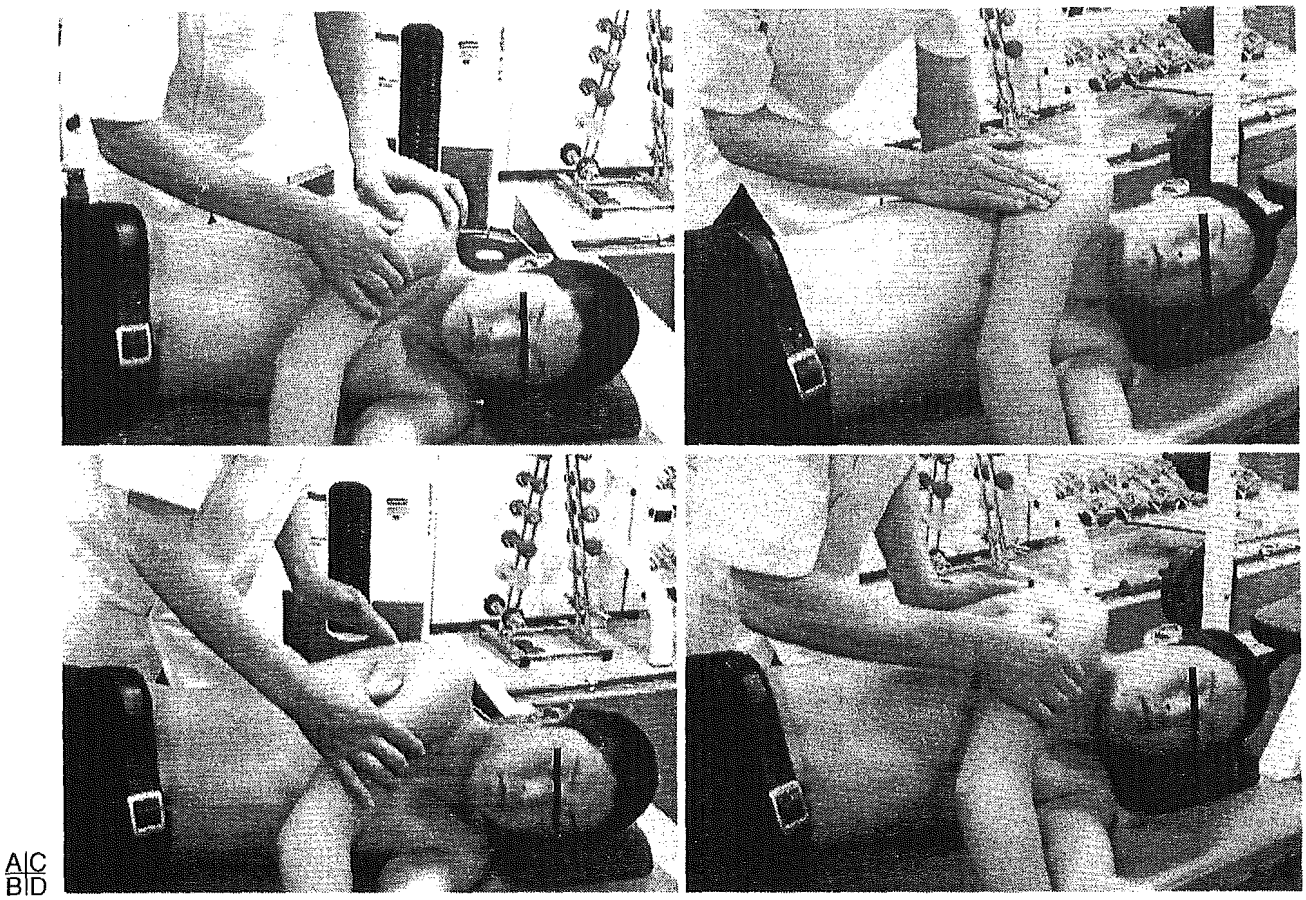


図10　三角筋後部線維へのDNICアプローチ
A：疼痛を発生させる筋硬結部をみつけ，疼痛閾値を確認する．B：ほかの部位(ここでは棘下筋)に侵害刺激を加える．C：筋硬結部の疼痛閾値が上昇したことを確認後，圧刺激を加える．D：再度，疼痛閾値の変化を確認する．

強度を調節する．

⑧一定した呼吸パターンを持続させる．

⑨関節面をひき離すように牽引をかけながら行う．

⑩自身の体重移動を利用してストレッチングする．

⑪ベッドの高さを調節する．

⑫なるべく当該筋を圧迫しない．

⑬自身の肢位や固定位置に注意する．

## 症例紹介

〔症例1〕17歳，男子．高校野球部．2003年3月，右肩関節内インピンジメントの診断を受ける．関節可動域は右肩屈曲180°，外旋30°(外転90°)であった．理学的所見はHAWKINS's impingement test(＋)，NEER's impingement test(－)，Relocation test(＋)，Clunk test(＋)，Sulcus sign(－)であり，肩関節周囲筋群にはオーバーユースによる拘縮，圧痛を認め，保存療法で経過を追うこととなった．整形外科初診3週間後においても強い投球動作で右肩に疼痛が残存していた．運動痛および圧痛の訴えは，三角筋後部線維および三角筋付着部近傍に存在した．三角筋後部線維の中でも，とくに圧痛の強い筋硬結部に対し，疼痛抑制を目的としてDNICアプローチを施行した(図10)．当該部の疼痛閾値が改善したことを患者の主観とpush-pull gauge(AIKOH社製，model-9505A)で確認した．続いて，三角筋後部線維に対し，筋走向を考慮して筋硬結部が存在していた筋線維を意識して，もっとも効率よく伸長できる方向，すなわち肩関節屈曲，内転方向に伸張し，最終域で軽度内旋方向にIDストレッチングを施行した(図11)．

IDストレッチング後，投球動作において確認したところ，投球時に発生していた三角筋後部線維の運動痛はほぼ消失したが，今度は上腕三

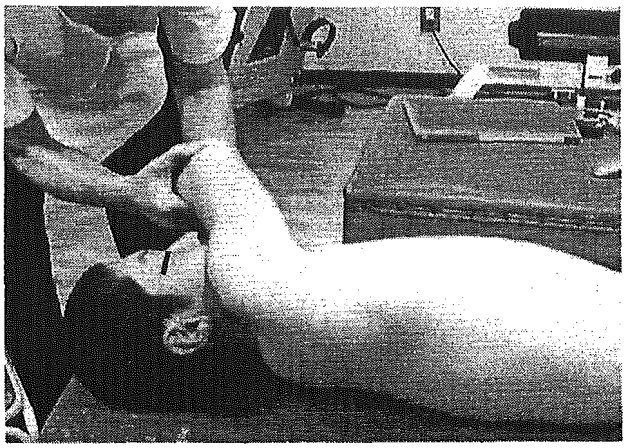

図11　右三角筋後部線維のIDストレッチング
背臥位で頸椎を左回旋後，筋線維の方向を意識しながら，肩関節を牽引後，内転・屈曲方向に動かし，最終域で軽度内旋し，筋線維にテンションがかかったところで保持する．

頭筋外側部線維に運動痛を訴えたので，同様に疼痛部位を確定し，DNICアプローチとIDストレッチングを施行した．上腕三頭筋外側頭のIDストレッチングでは同筋長頭の伸長方向と比較して，手関節以下をより体幹中央部に固定し肩関節を屈曲した後，より内転方向に伸張した(図12)．その結果，三角筋後部線維と上腕三頭筋外側部線維の疼痛閾値の上昇とともに圧痛が軽減した(図13)．投球動作では肩関節外旋と水平外転の可動域が増加し，投球時の運動痛も消失した．この効果を持続させるため，自宅や学校でできるアクティブIDストレッチングを指導した．部活動を継続した1週間後に再受診したが，三角筋後部線維と上腕三頭筋の運動痛の再発もなく，初診時に比較し右肘関節が投球時に上がるようになり効果は持続していた(図14)．

〔症例2〕16歳，男子．高校野球部．2003年3月，部活練習中，手押し車肢位で両下肢保持者が前方に転倒したため，右肩を地面にぶつけ受傷．診断は右肩関節唇損傷，肩板断裂であった．理学的所見はHAWKINS's impingement test(−)，NEER's impingement test(−)，Relocation test(−)，Clunk test (+)，Sulcus sign(−)で肩関節周囲筋群の拘縮，圧痛を認めた．関節可動域は右肩関節内旋に制限がみられた(図15-A)．運動痛および圧痛は右三角筋中部線維の中でも後部線維に近い筋硬結部位に存在していた．肩板断裂の診断名であったが，筋硬結部位に対し，症例1と同様に右三角筋中部線維に対し，DNICアプローチとIDストレッチングを施行した．三角筋中部線維の中でも後方の線維であったため，IDストレッチングは肩関節を牽引した後，軽度屈曲，軽度水平内転方向に施行した．三角筋中部線維のアプローチ後，肩関節内旋可動域と投球動作が改善した(図15-B)．1週間後の再受診時には部活動を継続していたにもかかわらず，三角筋中部線維の運動痛は消失していたが，内旋最終域で棘下筋に痛みを訴えたため，棘下筋の疼痛痛部位に対し，再度，同様のアプローチを施行した．棘下筋のIDストレッチングは，頸椎を

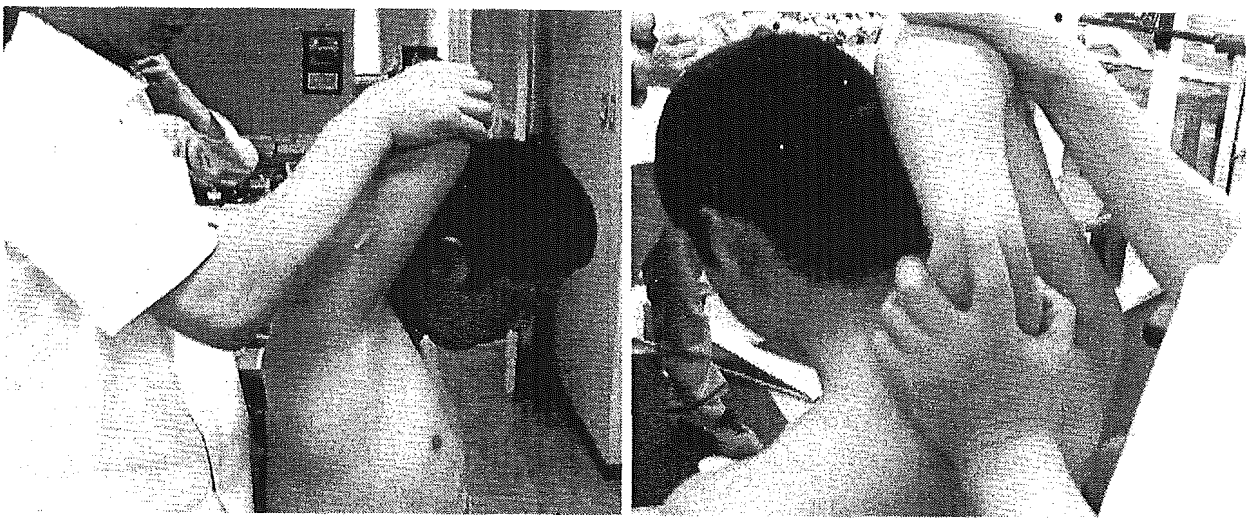

図12　右上腕三頭筋外側頭のIDストレッチング
端坐位で，右手で肘頭部を，左手で手背部を脊柱線上に保持し，肘関節を最大屈曲した後，肩関節を屈曲，内転する．

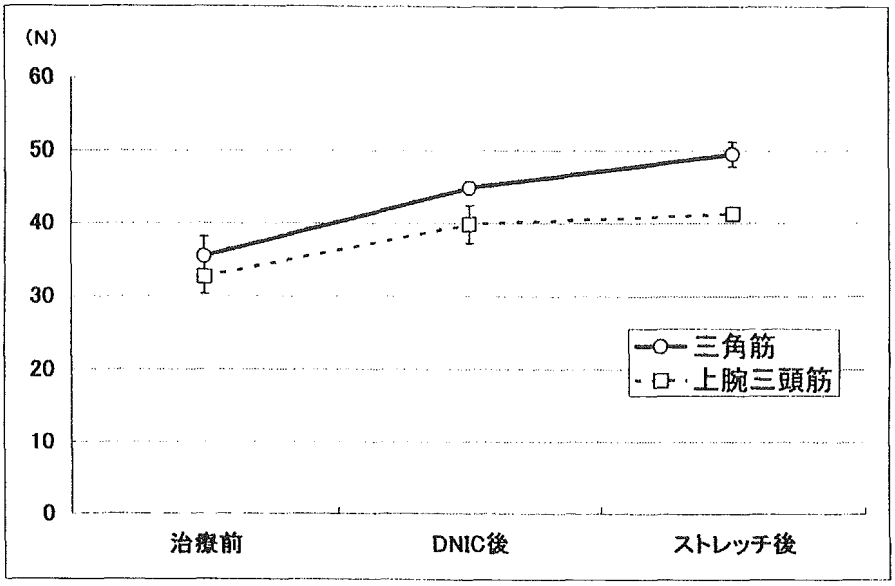


図13　疼痛閾値の変化
三角筋後部線維と上腕三頭筋外側頭の疼痛閾値は，治療前に比較しDNICアプローチ後，IDストレッチング後に上昇し，治療効果を裏づけた．

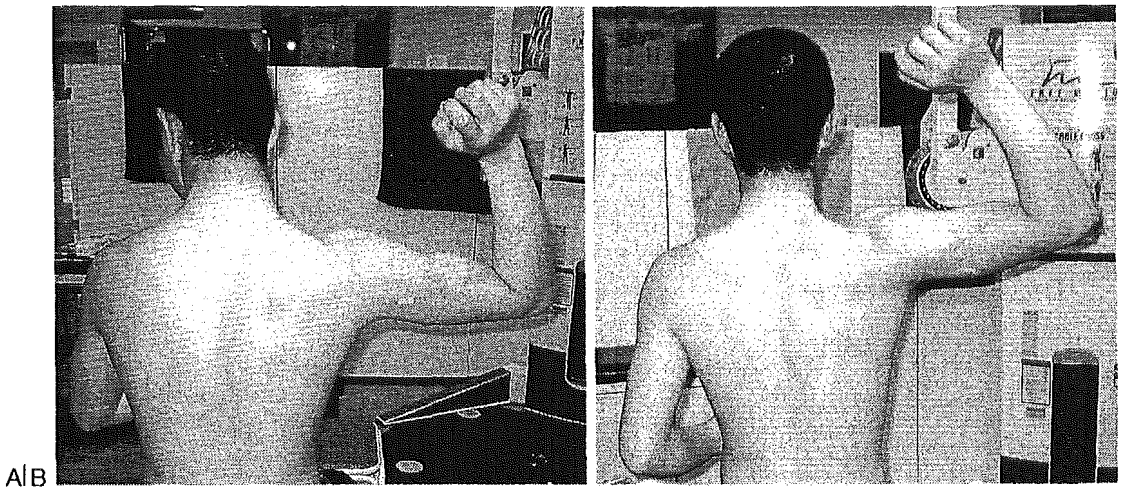


図14　右肩関節外旋の可動域変化
A：初診時は外旋および水平外転の可動域制限とともに，肘関節の下降が目立った．
B：初診1週間後は可動域の改善とともに肘関節が上がり，胸が張れるようになった．

伸展，左回旋に保持した後，三角筋後部線維に比べさらに肩関節の屈曲角度を強めながら内転し，最終域で軽度内旋した．その結果，肩関節内旋可動域はさらに改善し，投球時の疼痛が消失した(図15-C)．本症例にも自宅や学校で行うアクティブIDストレッチングを指導し，部活動終了後のストレッチングの重要性を説明した．

〔症例3〕23歳，女性．小学5年からバレーボールを行う．高校2年の時激しい腰痛があるも放置する．2003年10月腰痛出現．2004年4月再度腰痛出現．第5腰椎分離症の診断を受ける(図16)．左腰部の自発痛および運動時痛(＋)，左腹部の筋緊張(＋)，SLR-T正常，腱反射：正常，知覚：正常．現在，実業団バレー部に所属している．疼痛閾値が低下している左腸肋筋の筋硬結部に対し，DNICアプローチとIDストレッチングを施行した(図17)．その結果，第5腰椎分離症の器質的変化が存在するにもかかわらず，指床間距離，体幹伸展が改善した(図18)．本症例は腰椎分離症の器質的変化と筋緊張亢進による痛みおよび運動制限とが併発した例と考えられ，DNICアプローチとIDストレッチングが後者の機能的

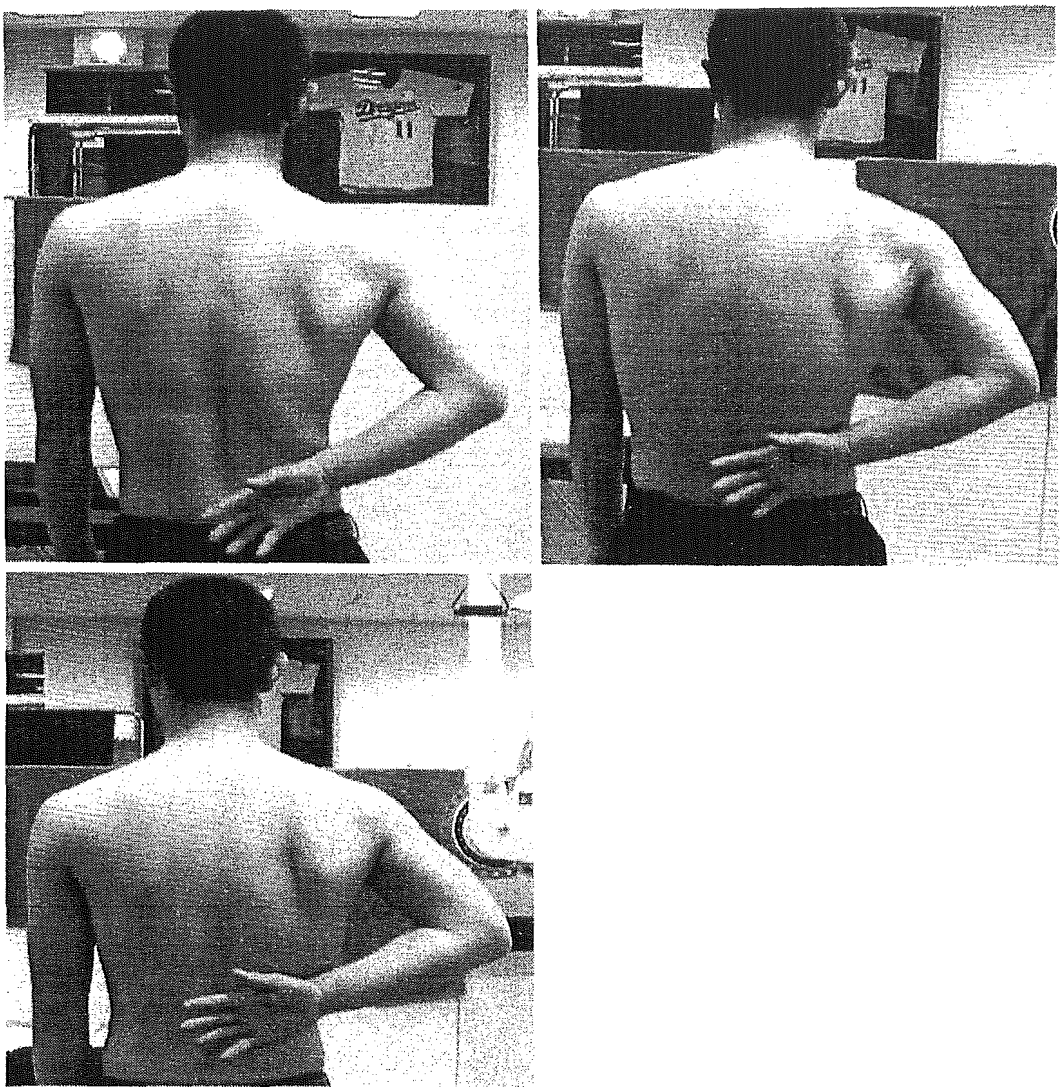

図15　右肩関節内旋の可動域変化

A：治療前は内旋の可動域制限が著明であった．

B：治療後は可動域の改善がみられた．

C：治療効果は1週間後持続し，投球時の疼痛が消失するとともに，棘下筋へのアプローチ後は肩関節内旋の可動域が増大した．

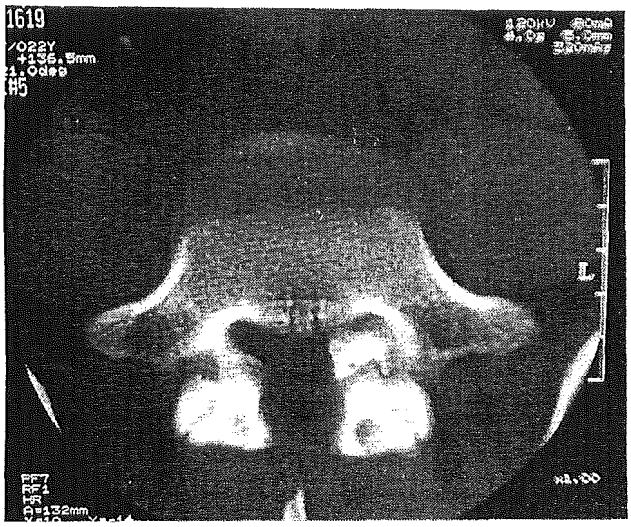

図16　CT画像

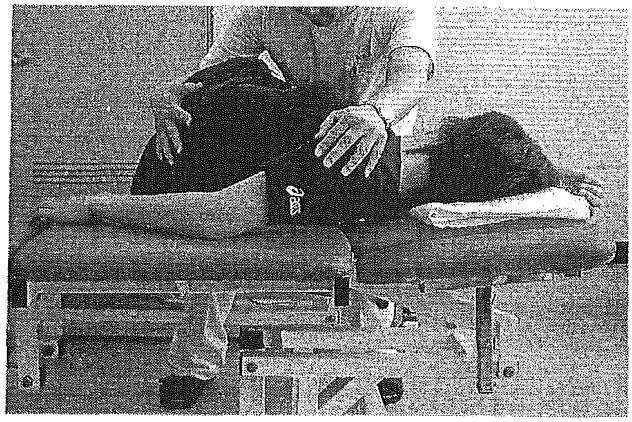

図17　左腸肋筋・最長筋に対するIDストレッチング

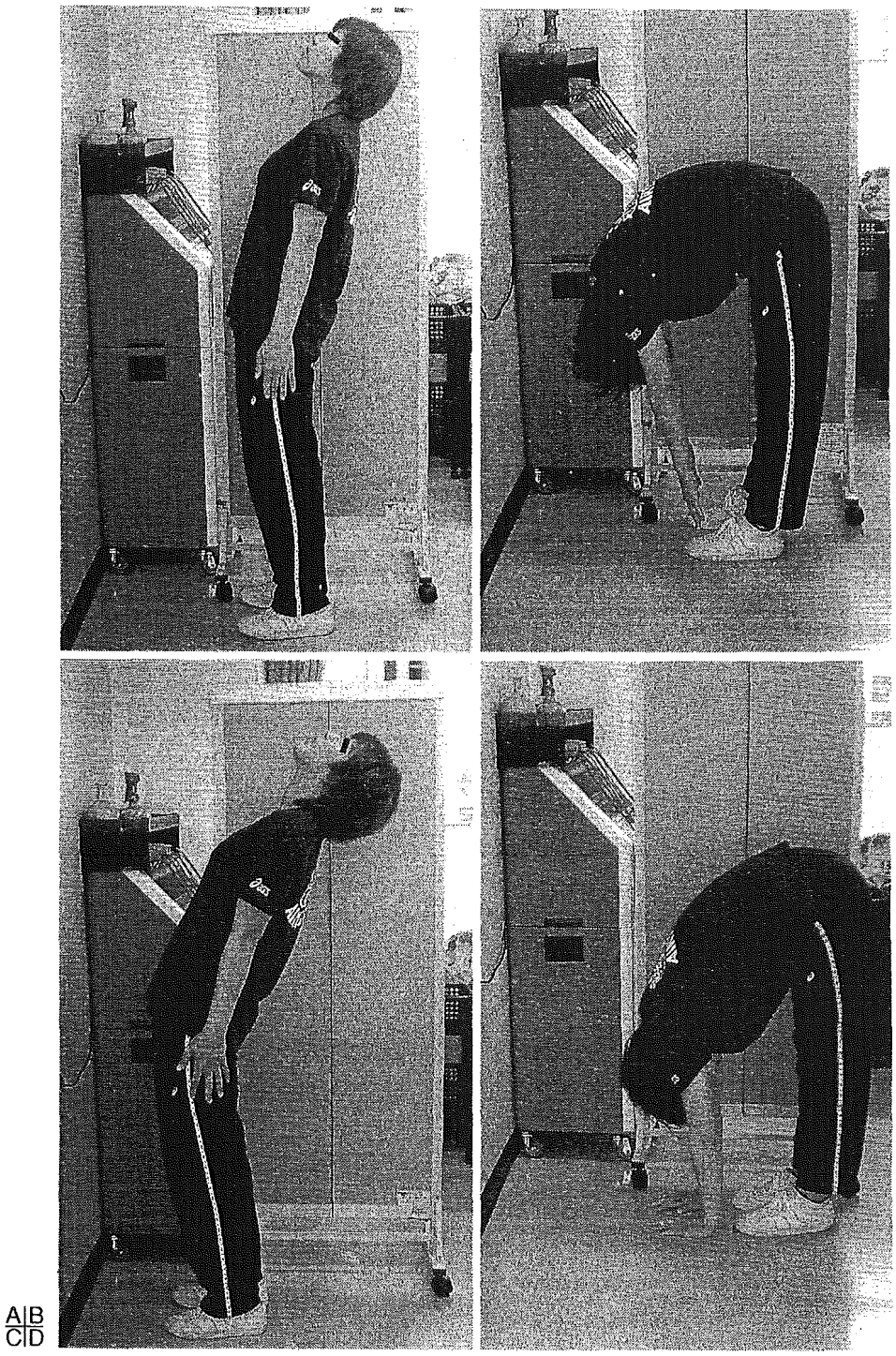


図18　治療前後の比較
A：治療前体幹伸展，B：治療前体幹屈曲，
C：治療後体幹伸展，D：治療後体幹屈曲．

変化に対して効果をもたらしたと考える．

## おわりに

スポーツ傷害の中でも軟部組織を中心とする疼痛のメカニズムおよび著者が提唱している疼痛抑制法である広汎性侵害抑制調節(diffuse noxious inhibitory controls；DNIC)アプローチおよび疼痛抑制後のストレッチング法としてIDストレッチング(individual muscle stretching，個別的筋伸張法)について述べた．単純X線やMRIなどで観察できる器質的な変化が存在する場合においても，軟部組織の機能的な変化により疼痛

や関節可動域の低下をひき起こすことが少なからず存在する．したがって，スポーツ傷害の保存療法では積極的に軟部組織の疼痛抑制および当該筋のストレッチングを施行することが重要であると考える．

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# A proposal for a simple and useful research design for evaluating the efficacy of acupuncture: multiple, randomized n-of-1 trials

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**Abstract**

*[Aim] To develop an experimental design suitable for clinical acupuncture research.*

*[Design] Long-term n-of-1 trials (B-A-B-A design)*

*[Setting] University Hospital of Meiji University of Oriental Medicine*

*[Patient] A chronic bronchial asthma patient*

*[Intervention] Weekly acupuncture treatments for 10min with de-qi were given. The initial 10 treatments (period B1) were followed by 9 weeks baseline (A1), a second period of 12 treatments (B2.), and a further baseline period (A2).*

*[Main outcome measure] Asthma symptom score by diary*

*[Results] The patient's symptoms were clearly reduced during the treatment period but returned during the baseline period. These changes in asthma score were highly reproducible in this patient.*

*[Conclusion] The value of long-term n-of-1 trials in acupuncture research was clearly demonstrated, and it is suggested that the n-of-1 trial enables demonstration of the mi-byo-chi of acupuncture treatment. To increase the external validity of n-of-1 data, multiple, randomized n-of-1 trials is proposed as an appropriate design for clinical research into acupuncture.*

## Introduction

It is well recognized that the randomized controlled trial (RCT) is the most powerful experimental design for generating strong evidence (1). However, using the RCT to evaluate the clinical usefulness of acupuncture raises various issues that need to be resolved (2). One of the major problems is that the acupuncture treatment procedure is not fixed according to the disease or the patient's condition. Acupuncturists carefully select points for needle insertion that are individualized for each patient. This traditional approach to acupuncture treatment is very popular and has spread widely. The majority of acupuncturists who are clinically well trained reject the use of fixed points or a predetermined set of points when treating patients, as they believe that acupuncture with an incorrect choice

of points or inadequate procedures is ineffective. Their belief is usually based on clinical experience, not on evidence. They need to provide evidence to support their concept that the selection of points and other aspects of the process of acupuncture must be individualized in order to be effective. To evaluate the efficacy of acupuncture, various designs and types of control can be used, depending on the research question of the investigator (3).

**N-of-1 trial as a useful design for acupuncture research**

In the WHO guidelines on clinical research on acupuncture, single subject experimental designs (single case design, or n-of-1 trial) are introduced (4). N-of-1 trials (this term will be adopted in this paper) developed in the field of psychology, and have recently been adapted for clinical research (5-9). The statistical issues concerning the evaluation of the results have been clarified (10,11).

The simplest design of an n-of-1 trial is a reversal design. Baseline data are collected repeatedly during period "A" and their stability is confirmed, without treatment. Then a specific intervention is applied during period "B". The changes in outcome data are evaluated by visual inspection of a graphical figure or by the usual non-parametric test for two groups (12). Repeating the two stages of the trial (A-B-A-B-A-B- -) strengthens the plausibility of the results. The order BA instead of AB can be used when treatment is required urgently before the baseline period.

N-of-1 trials can evaluate the effectiveness of various specialized interventions in a number of patients who differ in several ways. They are easy to adopt for an exploratory study. The characteristics of the n-of-1 trial seem to be suitable for acupuncture research and the use of n-of-1 trials in acupuncture has been recommended (4, 13). However, the n-of-1 trial is not appropriate in cases where acupuncture treatments have long-lasting or irreversible effects. Moreover it has been pointed out that the results of n-of-1 trials cannot be easily generalized (14). Here we propose a unique protocol of n-of-1 trials that allows generalization from the results obtained from each patient attending an acupuncture clinic.

**Long-term n-of-1 trials: a research design applied in an acupuncture clinic**

In general, the majority of patients at acupuncture clinics seem to be regular attenders who visit the clinic each time their chronic illness deteriorates. Their complaints are treated successfully by acupuncture but will reappear after several weeks, months or years. Based on such a course of acupuncture treatment over time, we propose a new design for clinical research in acupuncture.

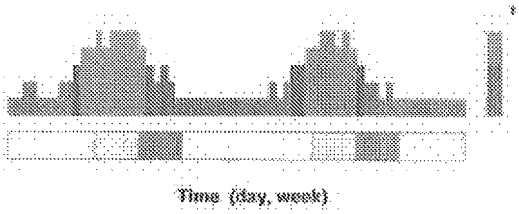


*Figure 1: Hypothetical example of a long-term n-of-1 trial*
*A1, A2: baseline, B1, B2: intervention*
*Criteria for the onset of baseline data measurement should be determined in the protocol*

Figure 1 shows a hypothetical illustration of a long-term n-of-1 trial (ABAB design). The upper figure shows the severity of symptoms and the lower bar shows the baseline (A1, 2) and

intervention (B1, 2) phases. In cases where patients' complaints are severe, the active intervention can be used first (BABA design). Another n-of-1 experimental design such as alternation may also be applicable. If the symptomatic changes produced by the intervention are very long lasting or permanent, a simple group comparison design should be used.

**An example of a long-term n-of-1 trial in an asthma patient**

The effects of acupuncture on chronic bronchial asthma were examined by n-of-1 trials (BABA design) in one patient. The patient, who was receiving care from a medical doctor but was resistant to steroid treatment (oral and by inhalation), was recruited to the study. The patient received acupuncture treatment (once a week, 10 times, repeated for a second course). Acupuncture needles (0.16mm in diameter, 40mm in length) were inserted and retained for 10 minutes at the following meridian points bilaterally: LI1, CV12, LI5, CV4, and B13. The severity of asthma was recorded by a dairy of asthma symptoms, a VAS of dyspnea, and Hugh-Jones classification. During the experiment the patient continued to receive steroids regularly.

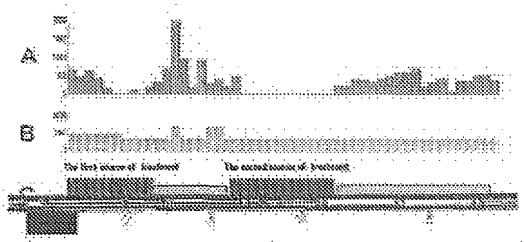


*Figure 2: Example of a long-term n-of-1 trial of acupuncture for an asthma patient*

*A: score of the symptoms from asthma diary, B: dose of drug used, C: periods of treatment with acupuncture (B) and non-treatment baseline (A)*

Figure 2 clearly shows that every symptom measure gradually improved, almost completely disappearing after the initial 10 weekly acupuncture treatments, and then rapidly returned to the pre-treatment level 9 weeks after cessation of treatment (initial BA session). The second treatment course of 12 weeks produced more rapid and sustained improvement during the treatment, but the symptoms again returned after treatment had stopped. Changes in the measures before and after the second treatment were as follows: Symptomatic scores: 66 to 0, VAS of dyspnea: 87 to 0, H-J classification: IV to I.

These results show that a long-term n-of-1 trial may be useful for demonstrating the effects of acupuncture on patients over a long treatment period. This kind of situation, with repeated treatments for chronic conditions, may be very common in acupuncture clinics. So, we propose a unique protocol to allow generalization from the results obtained from long-term n-of-1 trials.

**N-of-1 RCT (randomized controlled trial)**

The clinical usefulness of n-of-1 trial has become widely recognised, but, in respect of evidence based medicine (EBM) overall, its lack

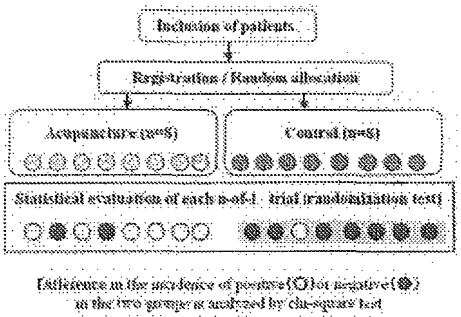


*Figure 3. A block diagram of the protocol of multiple randomized n-of-1 trials*

of external validity reduces the strength of evidence that it can contribute. In a recent EBM textbook, the n-of-1 RCT was ranked as the strongest evidence for making treatment decisions

(15). This high ranking of the n-of-1 RCT is mainly based on its high internal validity, that is, the n-of 1 RCT can make it possible to decide whether an intervention is suitable for a particular subject.

Patients are randomly allocated to each group then the effect of acupuncture or control intervention in each patient is evaluated by an n-of-1 trial (the randomization test can be used). Incidence of positive or negative results are analyzed statistically. (using chi-square test ). In this case, chi square=6.3349 and p=0.0117. However, small samples require Yates' continuity correction, with which the results become, chi-square=4.063, p=0.0438. This result indicates the external validity of n-of-1 trials.

*Table I:. A hierarchy of the strength of evidence for treatment decisions (Modified from ref #15)*

| | |
|---|---|
| 1 | N-of-1 RCT (randomized controlled trial) |
| 2 | SR of randomized trials |
| 3 | Single randomized trial |
| 4 | SR of observational studies addressing patient-important outcomes |
| 5 | Single observational study addressing patient-important outcomes |
| 6 | Physiologic studies (studies of blood pressure, cardiac output, exercise capacity, bone density, and so forth) |
| 7 | Unsystematic clinical observations |

The simplest n-of-1 RCT is as follows: the patient is randomly allocated to two periods of interventions, either A/B or B/A. The efficacies of interventions A and B are evaluated by the use of appropriate outcome measures, and these alternating interventions continue until a significant difference is detected between their effects. If intervention A is superior to B, then A will selected as better treatment for the subject.
Regarding the analysis of n-of-1 data, various methodological issues have been identified. Time series analysis was strongly recommended instead of conventional group comparison tests (6,10). Other statistical tests such as C-statistics have also been proposed as an indicator for an n-of-1 trial (11). Recent developments in computer technology make it possible to use the randomization test to analyse the data from n-of-1 trials (16).

From the viewpoint of patient-oriented medicine, the n-of-1 RCT design is valuable and highly recommended. However, it should be noted that an n-of-1 RCT does not provide external validity. In Sackett's standard textbook of EMB, the n-of –1 RCT is not included in his classification of clinical trials and list of recommendations (Table II), but he noted the importance of the design and stated guidelines

*Table II: Levels of evidence and grade of recommendations modified from ref #17)*

| Grade of recommendation | Level of evidence | Design of clinical trials |
|---|---|---|
| A | 1a | SR (with homogeneity) of RCT |
| | 1b | Individual RCT (with narrow confidence interval) |
| | 1c | All or none |
| B | 2a | SR (with homogeneity) of cohort studies |
| | 2b | Individual cohort study (including low-quality RCT) |
| | 2c | "Outcome" research |
| | 3a | SR (with homogeneity) of case-control study |
| | 3b | Individual case-control study |
| C | 4 | Case series (and poor-quality cohort and case control studies) |
| D | 5 | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" |

for limitations on its application (17). Every researcher agrees that a systematic review of homogenous RCTs is the best EBM methodology for providing external validity.

We now propose a method to increase the external validity of n-of-1 trials by adding a randomization procedure in the group comparison.

**Multiple, randomized n-of-1 trials**

We propose that multiple, randomized n-of-1 trials are a suitable design for increasing the external validity of a single n-of-1 study. Figure 3 shows the outline of the protocol. Patients who match the entry criteria are registered and randomly allocated into the acupuncture and control groups. Their condition or symptoms are treated by various acupuncture techniques,

depending on the practitioner's method of diagnosis and treatment, the details of which should be reported in detail following the STRICTA recommendations (18). The effect on each patient is evaluated by a suitable statistical method such as a non-parametric test (12), then the incidence of positive and negative results is compared between the two groups using a chi-square test.

To conduct this protocol successfully, several issues should be considered. The symptom should be stable over a long period and responsive to the intervention. The severity of the major symptom or the overall condition should be recorded daily during the experimental period by simple questionnaire or VAS scale. When the symptom appears to be stable (an essential inclusion criterion), baseline data are collected (period A: days, weeks or months), then the intervention is applied repeatedly (period B: days, weeks or months). Follow-up data are also collected. The interventions should be repeated at least twice to increase the reliability of results. This protocol is easy to conduct if suitable patients can be recruited. If the sample size is large enough to allow a subgroup analysis, the effectiveness of various combinations of symptoms and methods of acupuncture treatment may also be examined by the incidence of positive of negative results.

**The concept of "mi-byo-chi " for the acupuncture treatment**

In general, the majority of patients at acupuncture clinics are regular and they feel that felt individual symptoms getting worse to maintain restore their a good health. If the treatment is performed when the symptom is not so too severe, the results will be better than those obtained those applied when the symptoms getting more severe. Figure 4 schematically illustrates the concept of "mi-byo-chi ".

The borderline between health and disease is not completely clear. In the ancient Chinese literature (the Yellow Emperor's textbook), the concept of mi-byo-chi was introduced. The "Mi-byo" means that the condition is pre-symptomatic, and "chi" means treatment, so the phrase indicates the importance of giving treatment before the symptoms become severe. When the treatment (thick black band) is applied to a condition that is

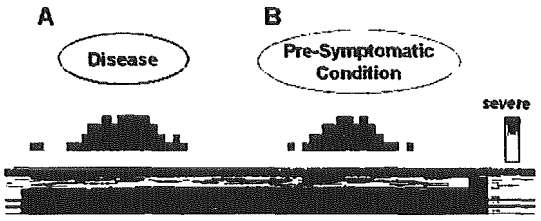


*Figure 4: A schematic illustration of the concept of the "mi-byo-chi"*

*A: treatment of the developed disease takes a long time, B: treatment of the pre-symptomatic condition is rapidly effective.*

less severe (B), the symptoms are abolished more rapidly than when it is applied to a condition that is more severe (A) (Fig. 4).

This concept clearly highlights the importance of the preventive aspect of acupuncture treatment. For evaluating the validity of the concept of "mi-byo-chi", the proposed multiple randomized n-of-1 trial may be applicable and would be worth conducting in a large sample in order to increase both internal and external validity of the clinical trial and provide stronger evidence.

**Acknowledgement**

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Examination in Anma-Massage-Acupressure, Acupuncture And Moxibustion.

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# A proposed experimental model of myofascial trigger points in human muscle after slow eccentric exercise

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***Abstract***

*Background* The purpose of this study was to develop an experimental model of myofascial trigger points to investigate their pathophysiology.

*Methods* Fifteen healthy volunteers who gave informed consent underwent repetitive eccentric exercise of the third finger of one hand (0.1Hz repetitions, three sets at five minute intervals) until exhaustion. Physical examination, pressure pain threshold, and electrical pain threshold of the skin, fascia and muscle were measured immediately afterwards and for seven days. Needle electromyogram (EMG) was also recorded in a subgroup of participants.

*Results* Pressure pain thresholds decreased to a minimum on the second day after the exercise, then gradually returned to baseline values by the seventh day. On the second day, a ropy band was palpated in the exercised forearm muscle and the electrical pain threshold of the fascia at the palpable band was the lowest among the measured loci and tissues. Needle EMG activity accompanied with dull pain sensation was recorded only when the electrode was located on or near the fascia of the palpable band on the second day of exercise.

*Conclusion* These results suggest that eccentric exercise may yield a useful model for the investigation of the myofascial trigger points and/or acupuncture points. The sensitised nociceptors at the fascia of the palpable band might be a possible candidate for the localised tender region.

***Keywords***

*Myofascial trigger point, acupuncture point, eccentric exercise, palpable band, fascia, controlled trial.*

## *Introduction*

The clinical value of the concept of myofascial trigger points has been widely recognised,[1,2] and the close relation between myofascial trigger points and acupuncture points has also been noted.[3,4]

Myofascial trigger points have been characterized by their location on a palpable taut band of skeletal muscle, and by the induction of local twitch responses, jump signs and particular patterns of referred pain.[1,5,6] However, it has been shown to be quite difficult to discriminate trigger points from the tender points found in fibromyalgia patients and spontaneous tender points in normal subjects.[1,7]

The palpable band has long been supposed to be the site of muscle contracture, based on the existence of contraction knots and the lack of electrical activity.[8] However, recent studies have demonstrated that spontaneous electrical activity (SEA) can be recorded from palpable bands in patients with the myofascial pain syndrome. The origin of this SEA is uncertain, and different possibilities such as endplate potential and intrafusal fibre activity in muscle spindles have been proposed.[6,9] Uncertainty also exists in discussion about the acupuncture points: some acupuncture points have been characterized by their tenderness (called '*Ah shi*' points) which are often situated on a palpable band.[10] In addition, electrical activity that has been recorded from acupuncture points has been proposed to originate in spinal reflex activity,[11] or in intrafusal fibre activity in muscle spindles.[12] Thus, myofascial trigger points and acupuncture points seem to have some similarities, although their pathophysiology is still not fully understood.

In the present study, we investigated the localised tenderness of experimentally induced

muscle pain, compared its characteristics with those of myofascial trigger points, and evaluated its usefulness as a model for trigger points and possibly some acupuncture points. We used repetitive eccentric exercise to generate delayed onset muscle soreness (DOMS): eccentric exercise involves a muscle lengthening under load, and is particularly associated with the production of DOMS.

## *Methods*

### *Subjects*

Fifteen healthy volunteers (five male and ten female), ranging in age from 18 to 48 years (mean 22.6 years) who gave informed consent, were involved. All were in good health and not engaged in any training programmes involving exercise of the extensor digitorum muscle. The first group of seven subjects (five male and two female) underwent three sets of investigations in random order (crossover design): 1) a control procedure in which pain thresholds were measured (see below) without exercise; 2) a series of assessments in which pain thresholds of the tender area were measured after exercise; 3) a series of assessments in which the distribution of pain thresholds around the tender area after exercise were measured, again after exercise. Each set of investigations was performed at intervals of six months or more, since the induction of DOMS leads to a resistance to further development of the condition for some time. The second group consisted of the remaining eight subjects (all female) who underwent a single series of EMG recordings daily after exercise.

### *Procedure of eccentric exercise*

The subject was seated, with one forearm supported as far as the wrist on a mat on top of a desk. A moveable 475g weight, consisting of a metal nut threaded on to a long-shaft bolt, was placed on the middle finger of one hand. The position of the weight was adjusted until the subject could retain the finger in a horizontal position for at least 10 seconds. The subject was then asked to hold this position as long as possible, and each time the finger bent 20° downward at the metacarpophalangeal joint, the finger was manually reset to the original horizontal position by the experimenter. This exercise continued repeatedly until exhaustion of the volunteer's extensor muscle. Three sets of this loading exercise were performed, separated by five minute rest periods. During the exercise, the electromyogram (EMG) of the extensor digital muscle was monitored and displayed on an oscilloscope to indicate when other muscles were being recruited to assist the tiring extensor digitorum.

### *Pressure Pain and Electrical Pain Threshold Measures*

Pressure pain threshold (PPT) was determined by pressing the skin over the muscle with a finger pressure algometer (Aikoh Engineering Corp, Model 9500) which has a probe 6mm in diameter.[13] The measurement was repeated three times where a sensation of tenderness was first elicited and the minimum value was employed as the threshold value.

Electrical pain thresholds (EPTs) of skin, fascia and muscle were measured by a pulse algometer (Unique Medical Co Ltd, UPA-100).[14,15] A stainless steel needle electrode insulated with acrylic resin (180μm in diameter, impedance 391±30kΩ at 1kHz; Nishin Medical Institute) was used as a cathodal monopolar stimulating electrode. The needle was inserted manually and held in a guide tube attached to skin with adhesive tape. The needle was inserted progressively in steps of 0.5-1.0mm in order to measure the pain thresholds of the skin, fascia and muscle. The location of the fascia was determined by the needling stiffness (physical resistance to the needle) with the help of ultrasonic echo imaging (LOGIQ™400, GE Medical Systems) to identify the depth of the border between subcutaneous tissue and muscle. A metal, anodal, surface electrode 10mm in diameter was attached to the skin 10mm away from the needle. The subjects were requested to press a button when they felt pain (pain threshold), which automatically triggered a digital display of the stimulus current and terminated the current stimulus pulse.

For the control session without exercise, the location for testing both PPT and EPT was the middle of the extensor digital muscle, where the focal muscle tenderness tended to be produced.

To assess the distribution of the pressure and

electrical pain thresholds, assessments were made at the tender region and at four points 10mm away from the focus (proximal, distal, medial and lateral).

For the three sets of examinations of these seven subjects (see *Subjects* above), the schedules for assessment were as follows: 1) for the control session, pressure and electrical pain thresholds were measured once daily for seven days; 2) for threshold levels, PPTs were measured before, immediately after, and one, two, three, four and seven days after the eccentric exercise. EPTs were measured on the second and seventh day after the exercise; 3) for assessment of pain distribution, measurements were made on the second and seventh day after the exercise.

*Detection of palpable band*

On the second day after the exercise, the forearm extensor muscles were examined for the presence of a palpable band by a well-trained licensed acupuncturist with four years' training and seven years' clinical experience. The subject was again seated with the forearm placed relaxed on a soft mat, while being examined with repeated light pressure with the fingertip. In several cases, but not all, the observer was blinded as to which arm had been exercised: in other cases, he was present during the exercise procedure.

*Recordings of referred pain pattern*

The pattern of the referred pain elicited by finger pressure at the most tender region on the palpable band was drawn on the skin surface then was copied on a clear sheet. When the subject could not recognize any patterns of referred pain, the subject was classified as 'no referred pain'.

*Recordings of needle EMG activity*

In the second group of eight subjects the electrical activity at the skin, fascia and muscle of the focal tender region and non-tender region of palpable band and 10mm away from the band were measured.

An insulated needle, as used for the stimulation above, was used as a recording electrode, together with an indifferent surface electrode. The EMG activity was amplified using a band pass filter of 0.1-10kHz (DAM-80, WPI), displayed on an oscilloscope (V-202F, Hitachi) and recorded on a data recorder (RD-135T, TEAC). Electrical activity was recorded for one minute or more at 1.0mm increments of depth. The unitary discharge that continued for at least 30 seconds with relatively regular intervals (1-60Hz) was classified as EMG(+). At the same time, the surface EMG was recorded from a pair of metal surface electrodes (10mm in diameter) placed on the skin 50mm distal from the needling point.

Measurements were made on the second day after exercise.

***Statistical analysis***

Pressure pain and electrical pain thresholds were shown as mean ± standard deviation (mean±SD). Non parametric multiple test of Tukey and Dunnet's multiple test (Yukms version 5; Yukms Company) were used for the statistical analysis. The level of statistical significance was defined as $P<0.05$.

***Results***

Immediately after the repetitive eccentric exercise, subjects reported warmth and tenderness of the working muscle of the forearm. The region of tenderness was gradually restricted to the muscle in a region about 50mm distal to the elbow, where a ropy taut band could be detected on the first and second days after the exercise. By the seventh day, the palpable bands and local tender regions were hardly detectable.

*Changes in pressure pain threshold*

The PPTs at the centre of the measuring area, where a palpable band was usually formed after the eccentric exercise, are shown in Figure 1. In the control session, the PPT did not change significantly during the experimental periods for seven days (Dunnett's multiple test, P=0.75-0.99). After exercise, on the other hand, the PPTs gradually decreased to a minimum on the second day, then recovered by the seventh day. The mean value for PPT before the exercise was 972±178 arbitrary units (AU; 1AU=1.8g), decreasing significantly to 274±57AU on the second day (Dunnett's multiple test, $P<0.01$).

Spatial distribution of the PPTs on and around the palpable band is demonstrated in Figure 2, and the values (Table 1) show that a significant difference between the tender locus and other

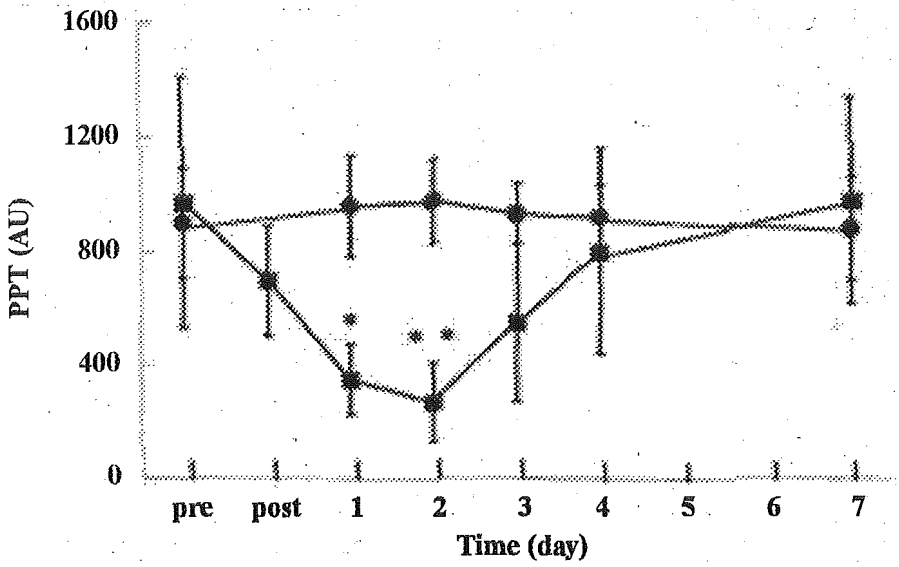


*Figure 1 This figure shows the effects of eccentric exercise of extensor digitorum on the pressure pain threshold (PPT) in seven subjects (mean±SD arbitrary units (AU)). Circles indicate values in the control session without exercise, and squares indicate values in the experimental session with exercise. Asterisks indicate significant difference compared with the baseline threshold (Dunnet's multiple test, *P<0.05, **P<0.01); **pre: pre-exercise; post: post-exercise.***

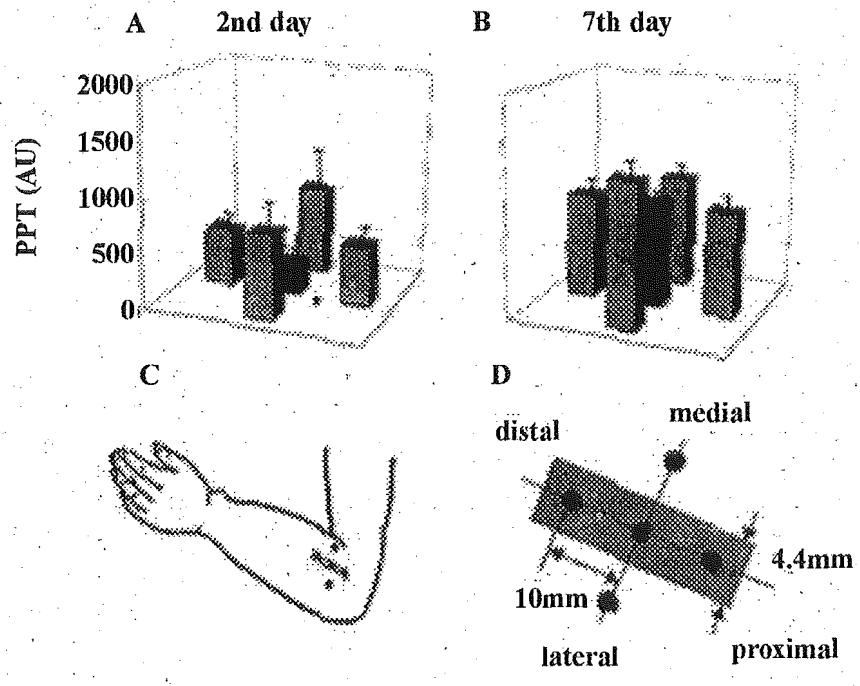


*Figure 2 This figure shows the distribution of pressure pain thresholds on and around the palpable band. A and B show the distribution of pressure pain thresholds (PPTs) on the second and seventh days after the exercise. The distribution of PPTs on the sites of PPT measurement are illustrated schematically in C and D.*