歩行による測定値への
影響を改善

3軸加速度計内蔵
精密歩数計として使用

時間経過
脈拍
酸素飽和度（SpO$_2$）
歩数，単位時間歩数

パルスオキシメータ測定値
（Anypal Walk®）
→
タブレット

新しい
パルスオキシメータシステムの開発と
単位時間歩数の導入による
６分間歩行試験の改良

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6分間歩行試験(6-minute walk test: 6MWT)は慢性呼吸器疾患、慢性心疾患などに罹患した患者の労作時における病態生理学的状態や薬物、リハビリテーションの効果を評価するための重要な臨床検査である[1)]。2012年度の診療報酬改定で在宅酸素療法の導入を検討している患者または施行している患者に対して保険適応となっている。6MWTから得られる6分間歩行距離(6-minute walking distance: 6MWD)は慢性閉塞性肺疾患(chronic obstructive pulmonary disease: COPD)患者の予後予測に有用である[2-4)]。

通常、歩行試験中の安全性を確保するため携帯型パルスオキシメータを用いて動脈血酸素飽和度に良く相関する指尖からの酸素飽和度(oxygen saturation of arterial blood measured by pulse oximeter: SpO_2)と脈拍数を測定する。この際、験者が測定値を目視するため被験者と並んで歩くことで、被験者自身の歩行ペースに影響を及ぼす可能性が指摘されていた。また、COPD患者に6MWTを行うと、息切れ、呼吸困難のため中途で歩行停止･休憩･再歩行を繰り返すことが多い。被験者が歩行停止すると呼吸困難の程度を表すBorg scaleやSpO_2に影響を及ぼす。したがって、試験中の歩行停止の時間帯、合計休憩時間やSpO_2の休憩中の変動に関して記録に残す必要がある。

SpO_2の時間経過と6MWD測定を中心とした従来の評価では、歩行ペース、停止、休憩などを含めた歩行パターンの把握は困難であった。歩行パターンを簡便に描写するため、単位時間歩数(number of steps per second : NSPS)を考案して臨床検討した[5)]。さらに、単位時間歩数を自動測定するためパルスオキシメータに3軸加速度計を組み込み歩行中に歩数検知し、SpO_2、脈拍数、歩数をタブレット型端末に表示するシステムを開発した。単位時間歩数を含めた新しいパルスオキシメータシステム、Anypal Walk®について解説する。

1 単位時間歩数

6MWTは6分間の歩行距離(6MWD)を主に考えていたが、慢性肺疾患患者の重症度によっては途中で歩行速度が変化したり、立ち止まったりすることが少なくなかった。歩行パターンを含めて評価するためには、平均あるいは瞬時歩行速度測定が有用であるが計測は煩雑であった。この問題点を解決するため歩数を単位時間ごとに測定する単位時間歩数の概念を新規考案した。単位時間歩数の定義は以下のようになる[5)]。

単位時間歩数(歩/秒)＝[A秒間の歩数] ÷ A(秒)、Aは360の約数。

[**A秒間の歩数**]の[ ]はガウス記号である。これはA秒間の区間ごとの歩数を計測して整数として求める操作を意味する。統計計算に利用するため、平均単位時間歩数、単位時間歩数の変動係数を定義した。

$$\text{平均単位時間歩数} = \{ \sum_{k=1}^{C} NSPS(\mathrm{A}k) \} \div \mathrm{c},\ \mathrm{c} = 360 \div \mathrm{A},$$

$NSPS(\mathrm{A}k)$は Ak秒(k= 1,2,3,...,c)時点の単位時間歩数。

変動係数＝{c区間の単位時間歩数の標準偏差÷平均単位時間歩数}×100%。

したがって、5秒ごと(A= 5)の区間を考える場合、72区間の平均単位時間歩数は以下のようになる。

$\text{平均単位時間歩数} = \{ \sum_{k=1}^{72} NSPS(5k) \} \div 72$、$NSPS(5k)$は 5$k$秒($k$= 1,2,3,...,72)時点の単位時間歩数。

10秒ごと(A = 10)の区間を考える場合、36区間の平均単位時間歩数は以下のようになる。

$\text{平均単位時間歩数} = \{ \sum_{k=1}^{36} NSPS(10k) \} \div 36$、$NSPS(10k)$は10$k$ 秒(k= 1,2,3,...,36)時点の単位時間歩数。

一般的に、平均･歩行速度(m／秒)＝平均･一歩の距離(m／歩)×単位時間歩数(歩／秒)の関係が成り立つ。この式から、歩行速度∝単位時間歩数が成り立ち、歩数を単位時間ごとに測定し単位時間歩数を計算すると歩行のパターンや停止した時間帯などが明らかになる。直接、歩行速度を測定するためには経過時刻と移動距離が必要であるが、今回考案した単位時間歩数は単位時間の歩数のみ測定すれば計算できる。例えば単位時間のA秒間を5秒間とすると6分間では360(秒)÷5(秒)=72区間に分割して、時間経過による変化を考えることになる[5)]。単位時間歩数の概念を導入すれば短い単位時間ごとの歩行速度から歩行パターンを分離して具体的に図示し新しい臨床評価が可能になる。

2 単位時間歩数の臨床応用

6MWTに単位時間歩数を導入して有用性を検討した。6MWTは米国胸部疾患学会の標準プロトコール[1)]を使用した。6MWTを繰り返し行うと歩行距離の増大がみられ、6MWTの学習効果(learning effect)として知られている[6,7)]。学習効果の影響を小さくするため、実際の試験前に最低2回の予行練習が望ましいとされる。今回、健常者は予行練習として6分間歩行試験を2回行い、3回目を測定した。COPD患者は予行練習で息切れ、疲労を認めたため、別個の日に歩行の予行練習を2回行った。

測定方法は、①被験者に6分間、病棟の廊下を速く歩き、できるだけ遠くまで歩行するようにと説明した。被験者は直線歩行し、廊下の所定地点に着くと折り返し歩行する。疲れたり、呼吸困難を自覚したら準備した椅子に座って休憩してもらう。検査中は安全のため自動記録機能のあるパルスオキシメータでSpO_2と脈拍数を記録した。②デジタルビデオで対象者の歩行を記録する。③6分間経過後、歩行距離(6MWD)を測定した。④後ほど記録されたビデオ映像を直接確認しながら5秒ごとの歩数を数えて単位時間歩数を72区間計算する。単位時間歩数(歩／秒)=[5秒間の区間歩数]÷5秒とした。⑤縦軸に単位時間歩数、横軸に時間のグラフを作成する。速度が低下すれば単位時間歩数も低下する。歩行停止したら単位時間歩数は0になる。また、ビデオ記録された映像から患者の歩行停止時間も正確に計測できる[5)]。

図1は健常高齢者とCOPD患者(気流閉塞の重症度III期)の単位時間歩数を指標にした6MWTの1例である。6MWDは各々、505m、225mであったが、単位時間歩数を導入するとCOPD患者が歩行試験中に歩行停止して休憩している状況、歩行ペースが遅い状態が直感的に把握できる。表1は単位時間歩数を6MWTから計測した11例の健常高齢者群、7例のCOPD患者群の臨床的背景と測定結果である。COPD患者の気流閉塞の重症度はI期1例、II期3例、III期2例、IV期1例であり、7例中4例が息切れ、呼吸困難のため歩行停止･休憩した。 健常高齢者は1秒間に平均2歩程度進むがCOPD患者では有意に低値であった。変動係数も有意差を認めた。これは、COPD患者の歩行ペースが遅いことに加えて、歩行停止･休憩を反映している。単位時間歩数を利用した指標は、従来の方法では評価できなかった現象を明確に表せる。

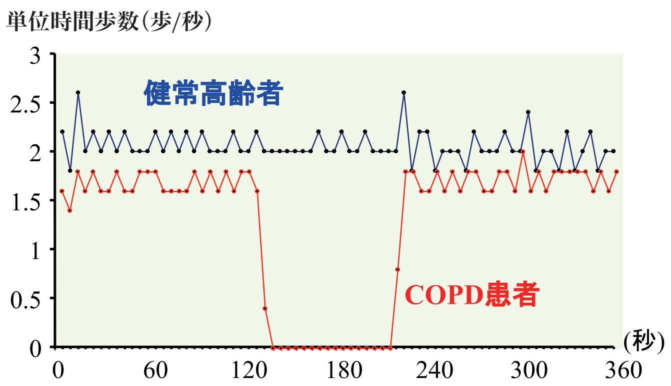


図1. 健常高齢者とCOPD患者の単位時間歩数の例

健常高齢者(66歳女性)に比べてCOPD患者(64歳男性)は歩行停止の時間帯があり、単位時間歩数は全体として低値だった。

表1. 健常高齢者群とCOPD患者群の臨床的背景と測定結果（文献5から改変引用）

	健常高齢者	COPD患者	p-value *
n	11	7	
年齢	68.6 ± 5.4	70.7 ± 4.8	0.316
身長 (m)	1.58 ± 0.07	1.60 ± 0.06	0.934
体重 (kg)	61.0 ± 8.3	48.7 ± 7.9	0.012
FVC (L)	2.98 ± 0.72	2.78 ± 0.92	0.696
FEV_1 (L)	2.48 ± 0.62	1.34 ± 0.75	0.008
FEV_1, % predicted (%)	103.2 ± 14.2	55.2 ± 27.1	0.003
6分間歩行距離 (m)	486.9 ± 35.0	289.5 ± 123.7	0.005
平均単位時間歩数(歩/秒)	1.98 ± 0.13	1.42 ± 0.43	0.0009
単位時間歩数の変動係数 (%)	7.4 ± 1.3	44.7 ± 45.3	0.0097
歩行停止回数	0	1.0 ± 1.2	0.005
合計休憩時間 (秒)	0	65.6 ± 83.8	0.0062
最低 SpO_2 (%)	94.4 ± 1.2	88.0 ± 5.7	0.0052
平均 SpO_2 (%)	95.5 ± 0.9	90.9 ± 4.1	0.0043

平均 ± 標準偏差. * : Mann-Whitney U test.
FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 second.

3 Anypal Walk® による単位時間歩数の自動記録

Anypal Walk®の特徴は、歩行中の測定データを同時に携帯型端末のタブレットに表示する点である。6MWT中に験者が被験者の横でパルスオキシメータの監視のため歩行すると被験者本来の歩行ペースを乱す要因になっていた。離れて監視できれば客観的な6MWTが実行できる。あわせて、3軸加速度計を組み込んであり、自動で歩数をカウントできる。測定データはパルスオキシメータ、タブレット両者に保存され、測定データを試験後ダウンロードしてエクセルで読み出し、任意の図を作成可能である。従来、パルスオキシメータを歩行試験に使用する際、腕振運動でSpO_2の測定値が不正確な場合があった。Anypal Walk®には歩行運動によるSpO_2測定においてセンサの工夫を行うことでぶれを少なくし、運動時に実用的な測定値が得られるように最適化されている。

図2はAnypal Walk®による単位時間歩数の自動測定例である。IV期COPD患者に対してプロカテロール吸入前後で6MWTを行い、Anypal Walk® を用いて10秒ごとの単位時間歩数を計36区間自動測定した。6MWDはプロカテロール吸入によって吸入前227 m、歩行停止時間は88秒だったが、吸入後は歩行停止無しで299mに延長した。休憩時間はタブレット画面上の休憩･再開ボタンを使用することで自動的に計測される。

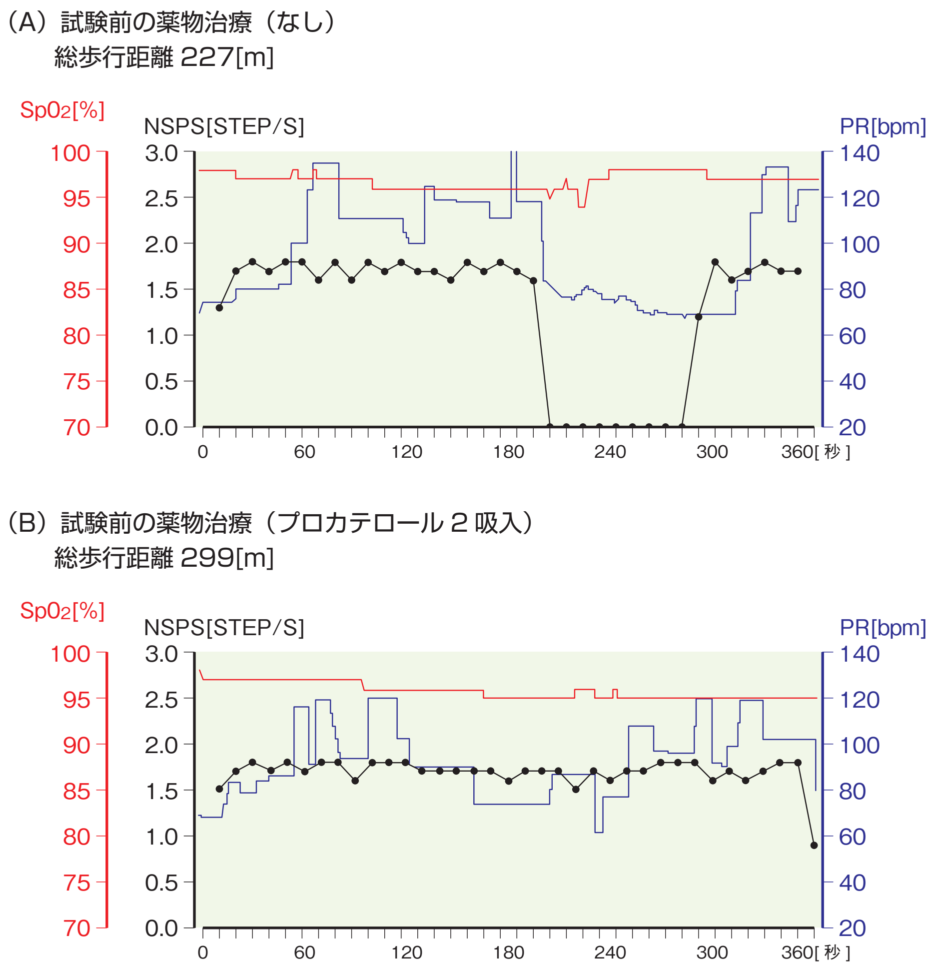


図2.Anypal Walk® による単位時間歩数の自動測定例(75 歳、男性、Ⅳ期 COPD)

酸素1.5L/分吸入しながら6分間歩行試験を行った。Anypal Walk®のレポート表示でプロカテロール吸入前後のNSPS(単位時間歩数、黒丸)、PR(脈拍数、青線)、SpO_2(赤線)の時間推移を示す。
6分間歩行距離は吸入前(A)が227m、歩行停止時間は88秒だったが、吸入後(B)は歩行停止無しで299mに延長した.単位時間歩数は吸入前、歩行停止で0になっている。
平均単位時間歩数は吸入前が1.28(歩/秒)、吸入後は1.69(歩/秒)に改善した。
Anypal Walk®のレポート表示は試験の全記録を残せる利点がある。

短時間作用性β_2刺激薬のプロカテロール（メプチンエアー™）は、吸入で強力に気道平滑筋を拡張する。プロカテロールは気管支喘息患者やCOPD患者に広く臨床応用されている。COPD患者に対して、労作前のプロカテロール吸入は歩行時の換気増加による動的肺過膨張（dynamic lung hyperinflation）を抑制し、息切れを軽減して歩行距離を延長させると報告されている[8,9]。一方、臨床的に有意な最小の変化量はminimal clinical important difference (MCID)と定義されている。COPD患者の6MWTに関して、介入による有意なMCIDは54m以上であると報告された。その後、54m[10]は大きすぎるとされ35m以上[11]あるいは25m以上[12]と修正されている。

本症例の単位時間歩数の時間経過は吸入前の歩行停止を除いて吸入前後でほぼ同様であった（図2）。したがって、「速く、できるだけ遠くまで歩く」という指示は忠実に守られていたと考えられた。プロカテロール吸入で6MWDが72m延長した理由は、図2の脈拍数、SpO_2の経時的変動からプロカテロール吸入が肺の動的過膨張を抑制して歩行停止がなくなり歩行距離が有意に延長したと推測される。単位時間歩数と脈拍数、SpO_2を同時に図示すると距離だけの評価では得られない情報が得られる。単位時間歩数はCOPD患者に対する気管支拡張薬の効果判定にも有用と思われる。

Anypal Walk® は自動で歩数を記録して経過時間と累積歩数の関係を確認できる（図3）。吸入前後で傾きが同一であれば同じ歩行ペースであることを意味する。歩行停止の時間帯以外は、傾きがほぼ同一であり、試験の妥当性が確認できた。6MWTは簡便で有用な運動負荷試験である。歩行距離だけでなく新規考案した単位時間歩数を考慮して新しい観点から慢性呼吸器疾患患者の病態生理を解析できる。

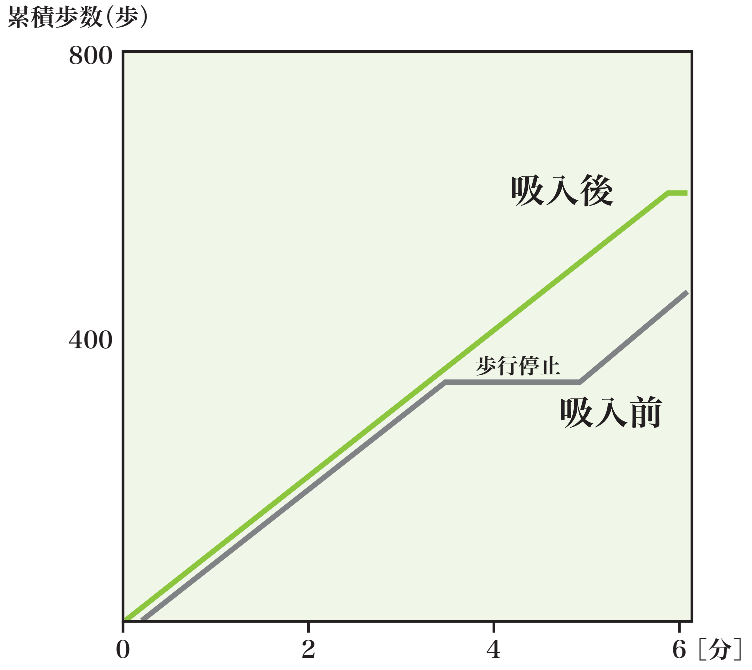


図3．6分間歩行試験の時間経過と累積歩数の関係

歩行停止の時間帯以外はプロカテロール吸入前後で傾きがほぼ同一であり、歩行ペースが同等であったと思われる。

結　語

臨床的見地から6MWT実施時に有用と思われる改良点をAnypal Walk® に複数導入した。最も大きな特徴は、歩行中の測定データをタブレット端末上のソフトで確認できる点である。被験者と離れて脈拍数、SpO_2を閲覧できるので6MWTだけでなく慢性呼吸器疾患や心疾患罹患者に対するリハビリテーション実行時にも安全に利用可能である。さらに、Anypal Walk® に3軸加速度計を組み込み精密歩数計として歩数を経時的に自動記録できるようにした。その結果、自動で単位時間歩数の時間経過を描写して歩行パターンや6MWTの歩行停止を含めた経過を直感的に把握可能とした。単位時間歩数は歩行パターンを把握するための新しい指標である。薬物投与やリハビリテーションなどの臨床介入前後においても応用可能である。

Anypal Walk® は表示装置としてタブレットを導入することで修正Borg scaleをタッチパネルから被験者自身が他者から影響を受けずに入力できる特徴もある。このパルスオキシメータは脈拍数、SpO_2を16時間記録可能なため、夜間睡眠中の低酸素血症の有無にも使用できる。今後、6MWTだけでなく日常臨床を含めた種々の局面でAnypal Walk®の臨床応用が期待される。

参考文献

1. ATS Committee on proficiency standards for clinical pulmonary function laboratories. Am J Respir Crit Care Med 166:111-7, 2002.
2. Casanova C et al. Chest 134:746-52, 2008.
3. Golpe R, et al. Respir Care 58:1329-1334, 2013.
4. Pinto-Plata VM, et al. Eur Respir J 23:28-33, 2004.
5. Burioka N, et al. Yonago Acta medica 57: 61-63, 2014.
6. Solway S, et al. Chest 119: 256-270, 2001.
7. Sciurba F, et al. Am J Respir Crit Care Med 167:1522-1527, 2003.
8. Fujimoto K, et al. Respirology 12:93-99, 2007.
9. Satake M, et al. Arzneimittelforschung 61:8-13, 2011.
10. Redelmeier DA, et al. Am J Respir Crit Care Med 155:1278-82, 1997.
11. Puhan MA, M et al. Eur Respir J 32:637-43, 2008.
12. Holland AE, et al. Arch Phys Med Rehabil 91:221-5, 2010.

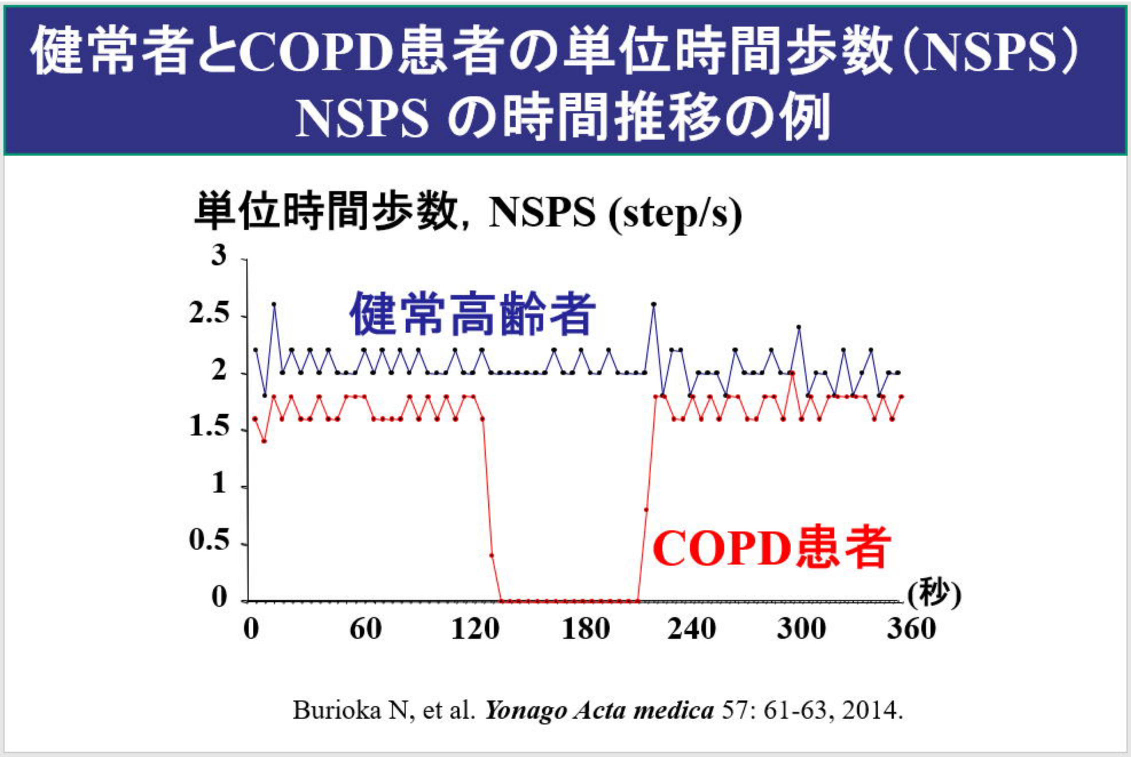
単位時間歩数の臨床応用例

時間内歩行試験が呼吸器疾患や循環器疾患患者などの運動耐容能を調べるために，広く臨床適用されている．時間内歩行試験は６分間歩行試験が一般的である．しかし，６分間歩行試験時に酸素飽和度を同時測定・確認するために，験者が被験者の横でパルスオキシメータを視認する必要があった．併歩行すると被験者の歩行ペースが験者の歩行ペースに影響されることがあった．この問題点を解決するため，短距離通信（Bluetooth）を用いてパルスオキシメータの情報を市販のタブレットに表示させるシステムを開発した．それが，「Anypal Walk」である．

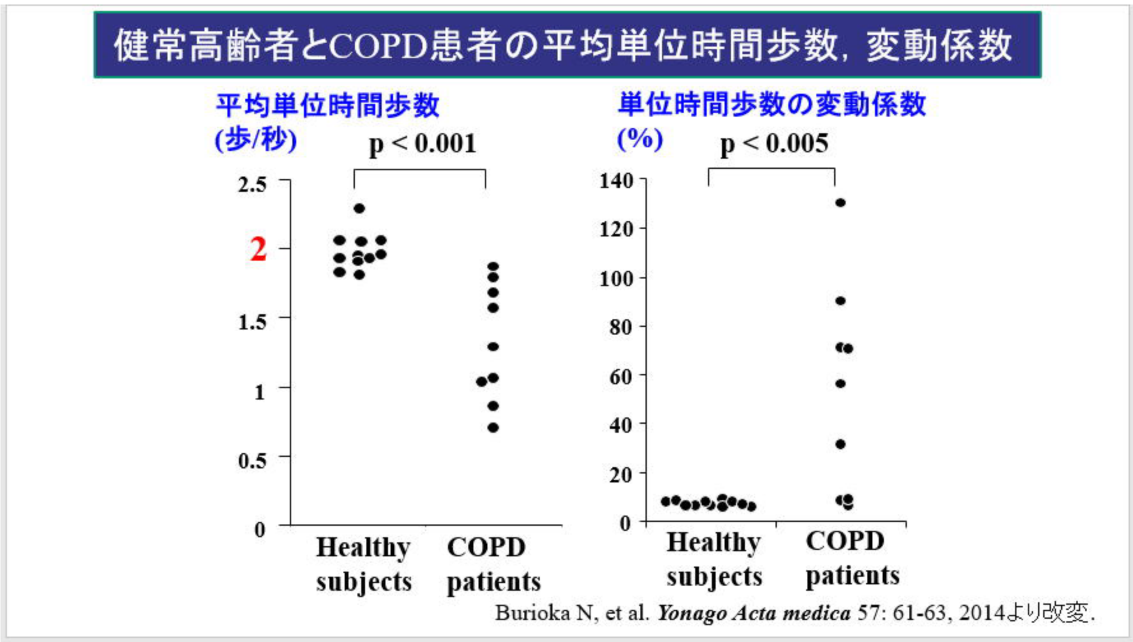
これに加えて，COPD 患者は６分間歩行試験時に息切れによって歩行停止することがある．歩行停止に関して評価法が少なかった．臨床的課題を解決するために，単位時間歩数を考案した．以下に応用例を説明する．(「Anypal Walk」は酸素飽和度，脈拍数だけではなく，３軸加速度計を内蔵しているので歩数，単位時間歩数を表示可能である）

単位時間歩数を利用すると，
・被験者の歩行パターン・歩行ペースが直感的に把握できる
・歩行試験中の停止が分かる
・歩行試験の歩行停止を含めた歩行状況，酸素飽和度の変化などをいわゆる「魚拓」のように記録を残せる．

１．健常高齢者と COPD 患者の違い

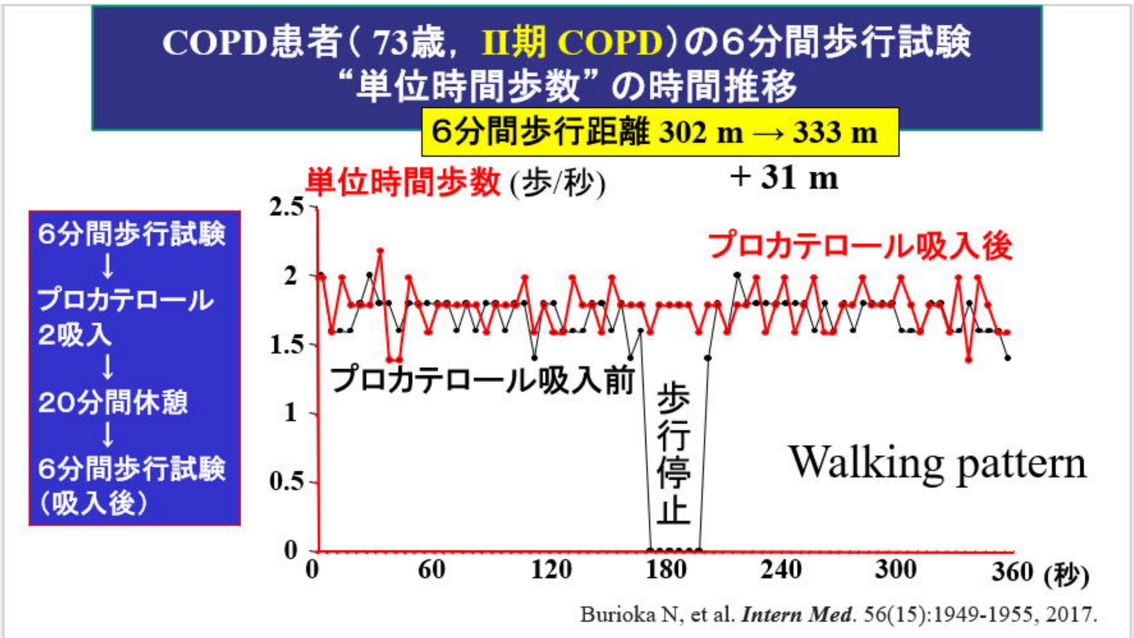


縦軸に単位時間歩数，横軸に時間をとって時間推移を描写する．
健常高齢者は，平均１秒間に２歩進む．一方 COPD 患者は１秒間の歩数が小さく，中途で息切れのため休憩して単位時間歩数が０になっている時間帯があるのが分かる．



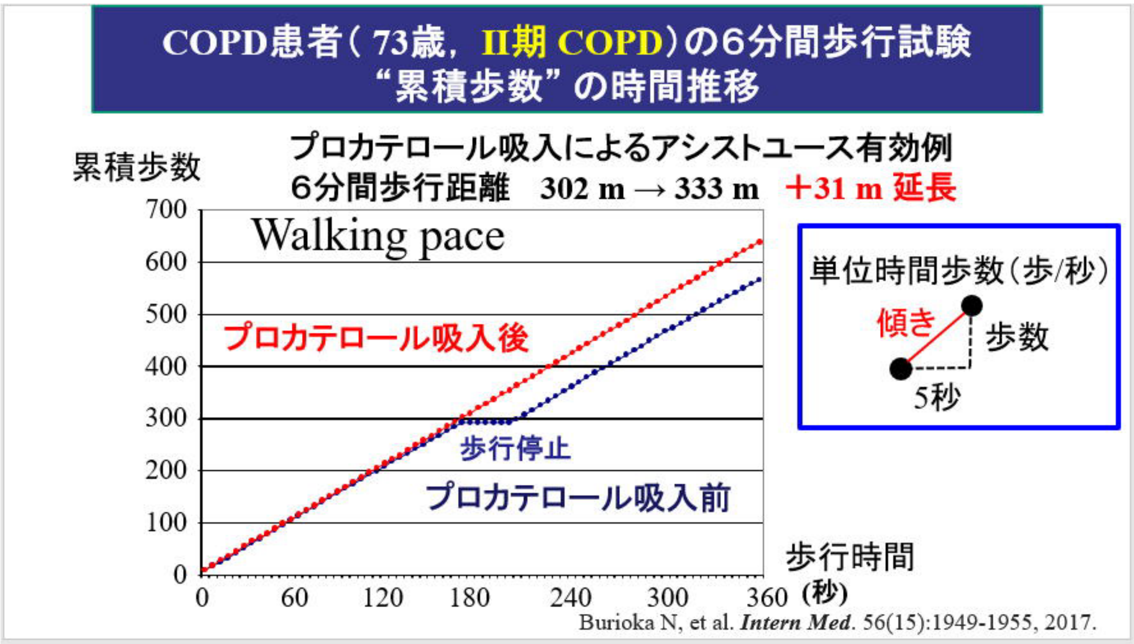
歩行停止すると単位時間歩数の変動係数が大きくなる．

２．短時間作用性気管支拡張薬，プロカテロールの吸入前後の歩行パターン，歩行ペースの違い



歩行パターンの違いが直感的に分かる．

上記症例では，プロカテロール吸入によって動的肺過膨張が改善し，歩行停止がなくなり６分間歩行距離が延びたと思われる．



縦軸を累積歩数にすると歩行ペースが客観的に分かる．歩行停止以外では傾きが吸入前後でほぼ同じであり，客観的に６分間歩行試験が行われたと推測される．

歩行停止以外の「累積歩数－時間」の傾きが吸入前後で大きく異なっている場合，６分間歩行試験に何らかの外的要因が加わった可能性も疑うべきである．

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

A Modified Method for Examining the Walking Pattern and Pace of COPD Patients in a 6-min Walk Test Before and After the Inhalation of Procaterol

Naoto Burioka[1], Sachiko Nakamoto[1], Takashi Amisaki[2], Takuya Horie[1] and Eiji Shimizu[3]

Abstract

Objective The 6-min walk test (6MWT) is a simple test that is used to examine the exercise tolerance and outcomes in patients with chronic obstructive pulmonary disease (COPD). Although the 6MWT is useful for assessing exercise tolerance, it is difficult to evaluate time-dependent parameters such as the walking pattern. A modified 6MWT has been devised to assess the walking pattern by calculating the number of steps per second (NSPS). This study was performed to investigate walking pattern of COPD patients in the modified 6MWT before and after a single inhalation of the short-acting β_2-agonist procaterol.

Methods Nine male COPD patients participated in this study. The 6MWT was performed before and after the inhalation of procaterol hydrochloride. A digital video recording of the 6MWT was made. After the 6MWT, the number of steps walked by the subject in each 5-s period was counted manually with a hand counter while viewing the walking test on the video monitor.

Results After the inhalation of procaterol, the 6-min walking distance increased significantly in comparison to baseline ($p<0.01$). The mean NSPS was also significantly increased after the inhalation of procaterol in comparison to baseline ($p<0.01$). The walking pattern was displayed on a graph of time versus NSPS, and the walking pace was shown by a graph of time versus cumulative steps.

Conclusion The analysis of the COPD patients' walking test performance and their walking pattern and pace in the 6MWT may help to evaluate the effects of drug treatment.

Key words: β_2-agonist, chronic obstructive pulmonary disease, 6-min walk test, procaterol, steps

(Intern Med 56: 1949-1955, 2017)
(DOI: 10.2169/internalmedicine.56.7961)

Introduction

The 6-min walk test (6MWT) has been used to evaluate the functional capacity and to predict mortality in patients with chronic respiratory disease (1, 2). This test assesses the maximum distance that a patient can walk during a 6-min period (3). Although the test is simple, it is useful for measuring clinical improvement in response to pulmonary rehabilitation and drug therapy (4).

Chronic obstructive pulmonary disease (COPD) is one of the most important respiratory diseases and is associated with a high mortality rate (5). Physical activity and the number of steps walked per day are strong predictors of all-cause mortality in COPD patients (6, 7). The functional status of COPD patients is examined by performing lung function tests and timed walking tests such as the 6MWT. In COPD patients, exercise causes dynamic lung hyperinflation and an increase in the end-expiratory lung volume (EELV) due to the trapping of air due to decreased elastic recoil, which occurs secondarily to the destruction of the alveoli and the narrowing of the small airways (8-10). The inspiratory capacity (IC) of COPD patients is significantly decreased during the 6MWT (11). The decrease in the IC of

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Received for publication July 7, 2016; Accepted for publication October 4, 2016
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Table 1. Pulmonary Function of Male COPD Patients (n=9).

	before	after procaterol inhalation
FVC (L)	2.56 ± 0.73	2.80 ± 0.77
FEV_1 (L)	1.21 ± 0.52	1.38 ± 0.68
FEV_1/FVC (%)	46.7 ± 12.3	47.5 ± 13.3
FEV_1 %pred. (%)	56.6 ± 25.2	62.0 ± 28.1

Values are the mean ± standard deviation.
FVC: forced vital capacity
FEV_1: forced expiratory volume in one second

COPD patients was significantly attenuated and the 6-min walking distance (6MWD) was increased after the inhalation of the short-acting β_2-agonist procaterol hydrochloride in comparison to patients who inhaled a placebo (11).

However, many COPD patients cannot walk for 6 minutes without stopping and may have to rest several times during the 6MWT due to dyspnea (12). Their walking pace and resting time may influence the results of the 6MWT, because oxygen desaturation can be improved by resting. Although the conventional 6MWT is useful for assessing the general exercise tolerance, it is difficult to evaluate time-dependent parameters such as the instantaneous walking speed. A modified 6MWT has been developed to examine the walking pattern by determining the number of steps per second (NSPS) (12). In the present study, we assessed the effect of a single dose of inhaled procaterol on the improvement of the walking distance, the resting time, and the walking pattern and pace (as NSPS) in COPD patients who performed the 6MWT.

Materials and Methods

Patients

Nine male patients with COPD (72.9±6.0 years) participated in this study. Spirometry was performed before and after the inhalation of 20 μg of procaterol hydrochloride (Meptin™, Otsuka Pharmaceutical, Tokyo, Japan) using a pulmonary function testing system (Chestac-7800, Chest, Tokyo, Japan) on another day (Table 1). The severity of airflow limitation in COPD was classified according to forced expiratory volume in one second (FEV_1) after the inhalation of a bronchodilator (5). Five of the 9 patients inhaled tiotropium, 3 patients inhaled tiotropium and salmeterol, and 1 patient inhaled formoterol with budesonide, regularly. Patients who had experienced unstable angina or myocardial infarction during the previous month, those who had a resting heart rate of more than 120 bpm, a resting systolic blood pressure of more than 180 mmHg or a diastolic pressure of more than 100 mmHg, orthopedic or neurologic conditions were excluded from the study (3). The present study was approved by the ethics boards of Tottori University and Hitachi Memorial Hospital (No. 1845). All of the participants gave their written informed consent.

Study protocol

The baseline 6MWT was performed before the inhalation of procaterol. The subjects performed the baseline 6MWT and then inhaled 20 μg of procaterol using a spacer device. After resting on a chair for 20 minutes, the patients performed the 6MWT again. The 6MWT was performed in a flat corridor of 54 m in length at Tottori University Hospital or Hitachi Memorial Hospital; the other technical aspects of the 6MWT were in accordance with the published guidelines (3). Arterial blood oxygen saturation was measured by pulse oximetry (SpO_2) with a finger sensor (Pulsox 300i, Konica-Minolta, Tokyo, Japan) and was continuously recorded during the test. The pulse oximetry variables were analyzed using the DS-5 Pulsox software program (Konica-Minolta). The severity of dyspnea was subjectively assessed before and after the 6MWT using a modified Borg scale (13). It has been reported that at least 2 practice walks should be performed before the 6MWT since training influences the results of the test (14, 15). The patients performed at least 2 practice walks on another day prior to the actual test because dyspnea and fatigue could have influenced the results of the 6MWT if they had practiced on the same day. The patients were allowed to sit on a chair to rest during the test, if needed, and resumed walking themselves when they had recovered. The duration of each rest was measured with a stopwatch. All of the walking tests were recorded on digital video and the 6MWD was measured.

The calculation of the number of steps per second (NSPS)

The NSPS is a new index (12); it is defined as the steps walked in A-second period divided by A, where A is a divisor of 360. We used A=5 (5-s interval) in the present study. The mean NSPS is calculated using the following formula:

$$\text{Mean NSPS} = \frac{\lfloor total\ steps\ in\ 360\rfloor}{360} = \frac{\lfloor total\ steps\ in\ 360\rfloor \div 5}{360 \div 5}$$

$$= \frac{\{\lfloor steps\ in\ 0 < t \le 5\rfloor + \lfloor steps\ in\ 5 < t \le 10\rfloor + \cdots + \lfloor steps\ in\ 355 < t \le 360\rfloor\} \div 5}{72}$$

$$= \frac{\sum_{k=1}^{72}\{\lfloor steps\ in\ 5(k-1) < t \le 5k\rfloor \div 5\}}{72} = \frac{\sum_{k=1}^{72} NSPS_k}{72},$$

where ⌊ ⌋ is the floor function, and $NSPS_k$ is the value of NSPS at the k-th 5-s interval (k=1,2,3,..., 72). $NSPS_k$ shows the slope of time versus the cumulative steps in 5-s (12).

The number of steps walked by a subject in each 5-s period was counted manually with a hand counter while viewing the walking test on the video monitor. The walking speed (m/s) was considered to be the average step length (m/step) × NSPS (step/s) (12). The NSPS was calculated as the number of steps walked in a 5-s period divided by 5, and this calculation was performed for 72 consecutive periods (360 s ÷ 5 s) in each subject. Because the NSPS is proportional to the walking speed, it usually decreases when a patient walks more slowly and falls to zero if the patient

Table 2. Results of the 6-min Walk Test (6MWT) before and after Inhalation of Procaterol (n=9).

	First 6MWT	Second 6MWT after procaterol inhalation	p value
6-min distance (m)	258.7 ± 124.0	293.4 ± 115.6	p<0.01 *
Total no. of steps	473.6 ± 153.9	526.1 ± 135.6	p<0.02 *
Resting HR before test (min^{-1})	91.5 ± 10.5	92.3 ± 9.1	p>0.43 *
Mean length of a step (m)	0.52 ± 0.09	0.54 ± 0.09	p>0.10 *
Mean NSPS (step/s)	1.32 ± 0.43	1.46 ± 0.38	p<0.01 *
Total resting time (s)	85 (20.3 - 149.8) †	59 (13.3 - 104.8) †	p<0.05 **
Borg scale after 6MWT	3.0 (1.8 - 4.2) †	3.0 (1.9 - 4.1) †	p>0.99 **
Lowest SpO_2 (%)	88.7 ± 5.1	88.2 ± 5.5	p>0.45 *
Mean SpO_2 (%)	91.4 ± 3.7	91.3 ± 3.8	p>0.75 *

HR: heart rate

Values are the mean ± standard deviation or median (interquartile range) †.

*: Paired t-test, **: Wilcoxon matched-pairs signed-rank test

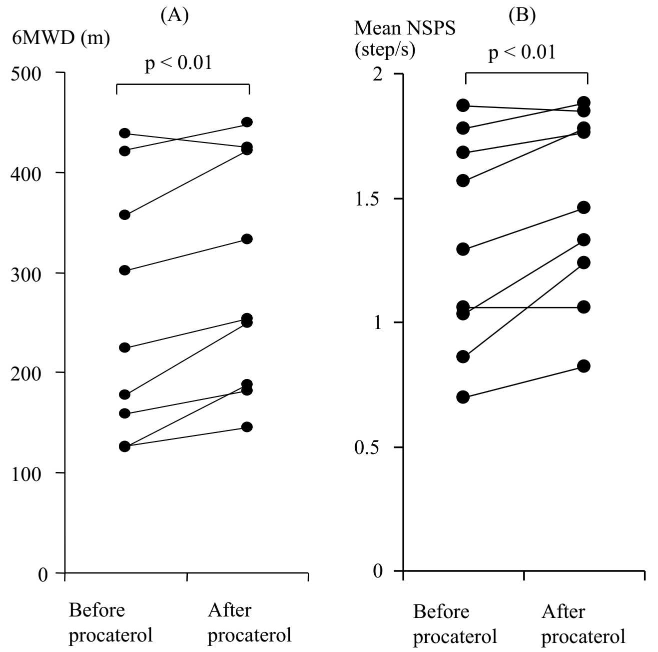

Figure 1. The 6-min walking distance (6MWD) and the mean of number of steps per second (NSPS) before and after the inhalation of procaterol. (A) The inhalation of procaterol significantly increased the mean 6MWD. (B) The mean NSPS was also significantly increased after the inhalation of procaterol.

stops walking (12).

Statistical analysis

The results are presented as the median (interquartile range) or mean ± SD. Comparisons were performed using the Wilcoxon matched-pairs signed-rank test or the paired *t*-test. The StatFlex software program was used to perform the statistical analyses (StatFlex, ViewFlex, Tokyo, Japan). p values of <0.05 were considered to indicate statistical significance.

Results

With regard to the severity of airflow limitation in our COPD patients, 3 patients were classified as Global initiative for chronic Obstructive Lung Disease (GOLD) 1 (predicted FEV_1 (%) ≥80%), 2 patients were classified as GOLD 2 (50% to <80%), 3 patient were GOLD 3 (30% to <50%), and 1 patient was classified as GOLD 4 (<30%) (5). The height, weight and body mass index of the 9 COPD patients were 1.58±0.06 m, 51.6±9.2 kg and 20.7±4.2 kg/m^2, respectively. Table 1 shows the results of a pulmonary function test before and after the inhalation of procaterol on another day. Table 2 shows the results of the 6MWT before and after the inhalation of procaterol. After a single inhalation of procaterol, the 6MWD was significantly longer in comparison to baseline (Fig. 1A). An increase of >30 m in the 6MWD is considered to be the minimal clinical important difference (MCID) for the patients with chronic respiratory disease (1, 2). After the inhalation of procaterol, the 6MWD changed by more than 30 m in 4 of the 9 COPD patients. The resting heart rate was not significantly changed in comparison to that before the 6MWT. The total number of steps in 6 minutes was significantly increased by the inhalation of procaterol, but the mean step length did not change (Table 2). Six of the 9 patients had to rest on a chair during the baseline 6MWT. The median (range) number of rests before and after the inhalation of procaterol was 1 (0-3) and 1 (0-3), respectively. Although the number of rests was almost same, the total resting time was significantly shorter after the inhalation of procaterol (Table 2). The mean NSPS showed a significant increase after the inhalation of procaterol in comparison to the baseline value (Fig. 1B). On the other hand, the lowest SpO_2 and mean SpO_2 values were not significantly different after the inhalation of procaterol. There was no significant difference in the modified Borg scale values after the 6MWT before and after the inhalation of procaterol (Table 2).

Fig. 2A shows an example of the walking pattern and

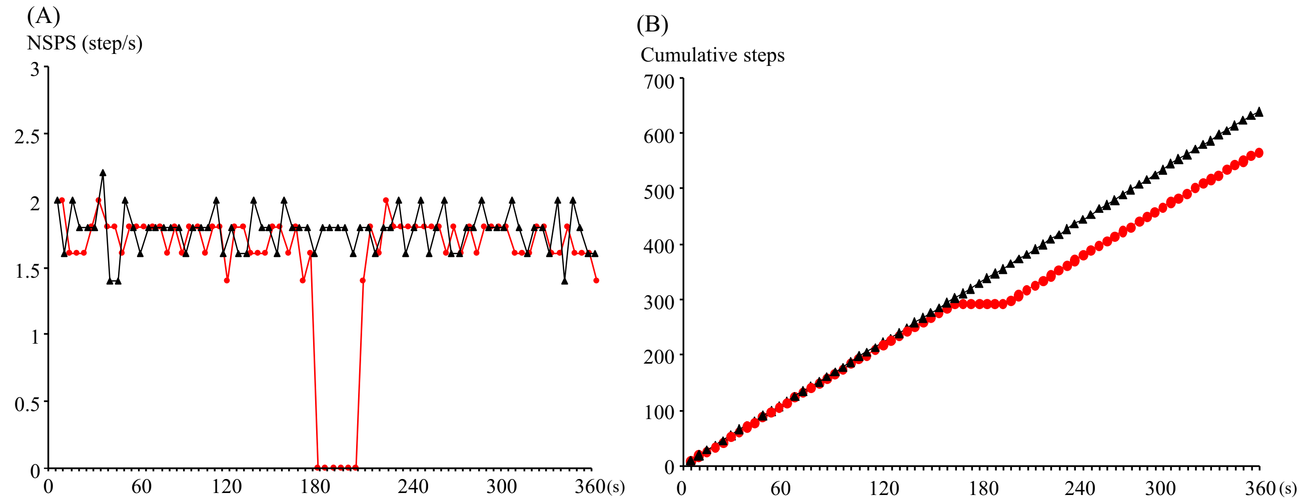

Figure 2. Determining the walking pattern and pace from the number of steps per second (NSPS) and the cumulative steps before and after the inhalation of procaterol. The patient was a 73-year-old man with COPD. Although the patient walked 302 m in the 6-min walk test (6MWT) with 32 s of rest before the inhalation of procaterol (closed circle), he could walk 332.5 m without a rest after the inhalation of procaterol (closed triangle). The walking pattern is clearly displayed on this graph of time versus NSPS (A). During the 6MWT, the NSPS falls to zero each time the patient stops walking. The cumulative number of steps is shown as a function of time for each test (B). The slope indicates the walking pace. This patient walked at the same pace before and after the inhalation of procaterol, except for during rest periods.

pace (as the NSPS) in a 73-year-old patient with moderate COPD. The 6MWD improved by 30.5 m following the inhalation of procaterol. Note that NSPS falls to zero when the patient stops walking. The patient rested for a total of 32-s before the inhalation of procaterol (Fig. 2A). After the inhalation of procaterol, this patient could walk for 6 minutes without rest. Fig. 2B shows the numbers of the cumulative steps during the 6MWT for the same patient. The results of the two tests (before and after the inhalation of procaterol) shared a common slope (except for during the rest periods), and the slope was constant (Fig. 2B), which suggested that, with the exception of the rest periods, the walking pace was almost the same during the 6MWT. The mean NSPS before and after the inhalation of procaterol in the 6MWT was 1.57 and 1.78 (step/s), respectively. The mean NSPS is increased by a decrease in the rest time and/or an increase in the walking pace. In this case, the inhalation of procaterol led to a decrease in the rest time, resulting in an increase in the mean NSPS. Figs. 3 and 4 show that when the resting time was decreased by the inhalation of procaterol, the 6MWD was improved by more than 30 m after the inhalation of procaterol.

Fig. 5A shows an example of the increase in the walking pace after the inhalation of procaterol. This 68-year-old patient could walk in 6-minute without a rest. Fig. 5B shows a graph of time versus the cumulative steps during the 6MWT. The slope increased after the inhalation of procaterol (Fig. 5B), which suggests that the walking pace increased during the 6MWT. The mean NSPS before and after the inhalation of procaterol in the 6MWT was 1.78 and 1.88 (step/s), respectively. In this case, the increase in the walking pace following the inhalation of procaterol might have resulted in an increase in the mean NSPS; however, a placebo study will be necessary. The results in 5 participants in whom the improvement in the 6MWD was <30 m after the inhalation of procaterol are not shown.

Discussion

The present study demonstrated that a single inhalation of procaterol significantly prolonged the 6MWD, and shortened the total resting time or increased the walking pace during the 6MWT, suggesting that the inhalation of procaterol may be useful for improving the exercise performance of COPD patients undertaking this test. In addition, the steps per second and the cumulative steps were effective measures for analyzing the changes in the walking pattern and pace after the inhalation of procaterol in COPD patients. Determining the number of steps walked per unit time and the consideration of the total resting time during the 6MWT may be important when assessing the functional status before and after drug treatment because some COPD patients cannot walk continuously for 6-minute without resting.

In COPD patients, exercise causes an increase in the EELV along with an increase of ventilation, which is known as dynamic lung hyperinflation (8-10). A significant relationship has been reported between dynamic lung hyperinflation and dyspnea during exercise in COPD patients (8). Several reports have also shown that the pretreatment of COPD patients with inhaled procaterol improves dynamic

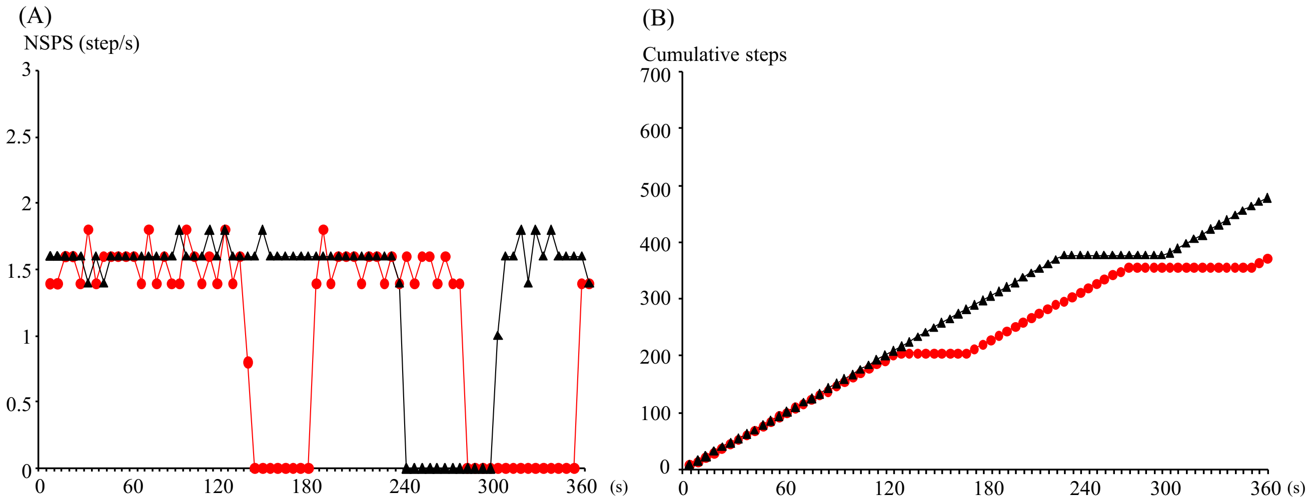

Figure 3. Determining the walking pattern and pace from the number of steps per second (NSPS) and the cumulative steps before and after the inhalation of procaterol. The patient was an 80-year-old man with COPD. Although the patient walked 177 m in the 6-min walk test (6MWT) with 114 s of rest before the inhalation of procaterol (closed circle), he could walk 249.5 m with 62 s of rest after the inhalation of procaterol (closed triangle) (A). The cumulative number of steps is shown as a function of time for each test (B). The slope indicates the walking pace. This patient walked at the same pace before and after the inhalation of procaterol, except for during rest periods.

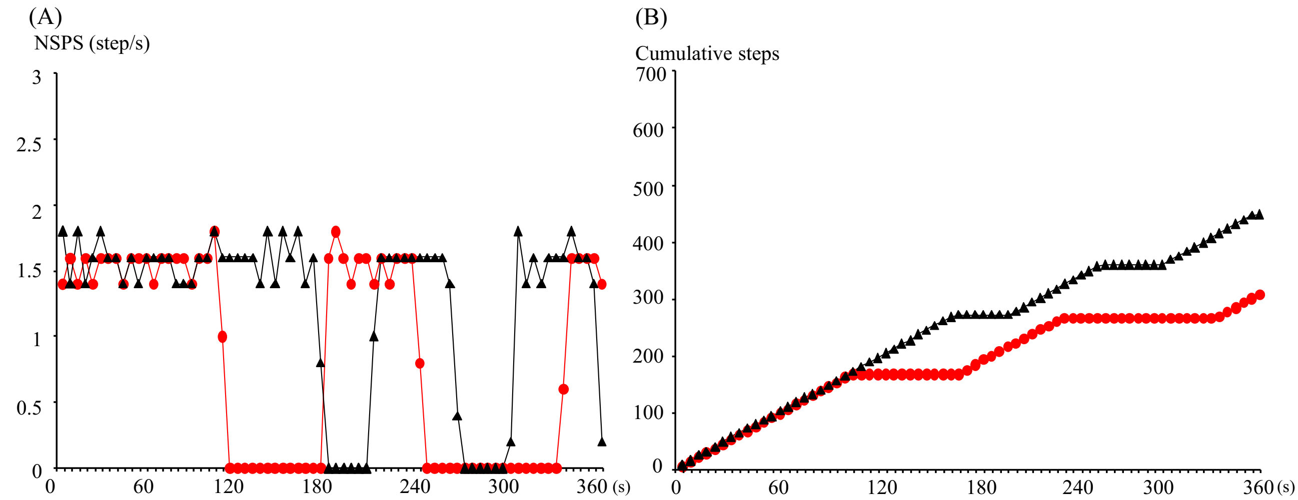

Figure 4. Determining the walking pattern and pace from the number of steps per second (NSPS) and the cumulative steps before and after the inhalation of procaterol. The patient was an 81-year-old man with COPD. Although the patient walked 125 m in the 6-min walk test (6MWT) with 158 s of rest before the inhalation of procaterol (closed circle), he could walk 188 m with 77 s of rest after the inhalation of procaterol (closed triangle) (A). The cumulative number of steps is shown as a function of time for each test (B). The slope indicates the walking pace. This patient walked at the same pace before and after the inhalation of procaterol, except for during rest periods.

lung hyperinflation and exercise tolerance (10, 11, 16-18). A previous report also indicated that the inhalation of formoterol increased the 6MWD (19). In addition, Fujimoto et al. reported that dynamic lung hyperinflation secondary to hyperventilation reduced the IC in COPD patients, while the IC was increased by the inhalation of procaterol (10). Moreover, the use of procaterol has been shown to improve both the exercise tolerance and health-related quality of life (16).

In the present study, the 6MWD was significantly increased after the inhalation of procaterol. It is reported that a >30-m increase in the 6MWD represents the minimal clinically important difference (MCID) for COPD patients (1, 2). The 6MWD changed by >30 m following the inhalation of procaterol in 4 of the 9 COPD patients. In a graph of time versus cumulative steps, 3 of the 4 patients who showed an improvement of >30 m after the inhalation of procaterol

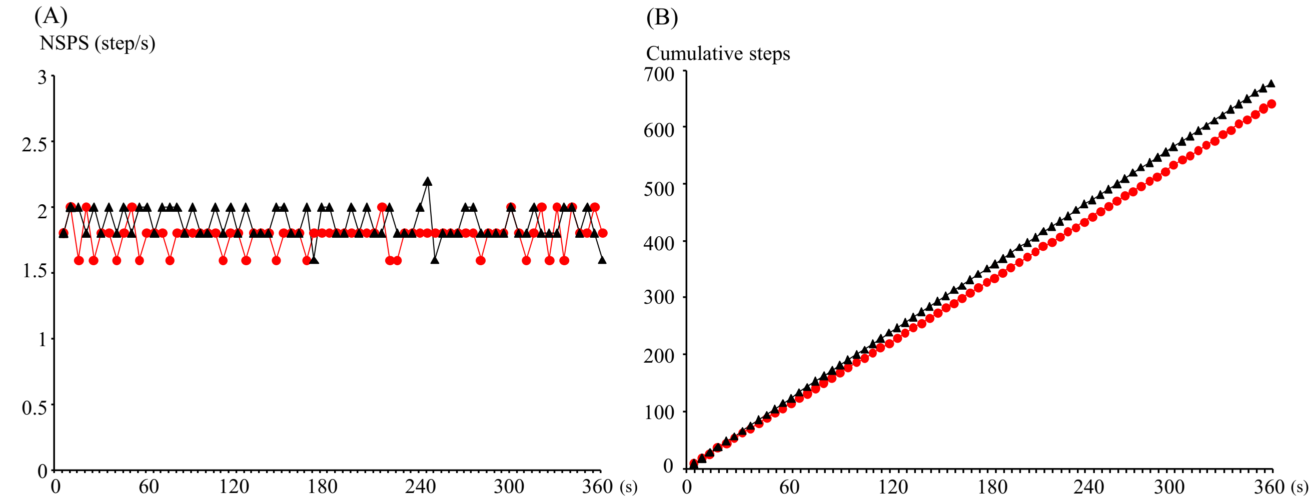

Figure 5. **Determining the walking pattern and pace from the number of steps per second (NSPS) and the cumulative steps before and after the inhalation of procaterol. The patient was a 68-year-old man with COPD. Although the patient walked 356.5 m in a 6-min walk test (6MWT) without a rest before the inhalation of procaterol (closed circle), he could walk 422 m after the inhalation of procaterol (closed triangle) (A). The cumulative number of steps is shown as a function of time for each test (B). The slope indicates that the walking pace was increased by the inhalation of procaterol.**

showed a shorter total rest time, and the walking pace of one patient increased during the 6MWT. Thus, the increase in the 6MWD after the inhalation of procaterol might be a clinically relevant effect in 4 patients.

Although Golpe et al. found that exercise-related oxygen desaturation during the test was not an independent predictor in a multivariate analysis (20), the 6MWT has been reported to predict mortality in COPD patients (20-22). However, patients with moderate or severe COPD frequently rest during the 6MWT, as was noted in the present study, and exercise-related oxygen desaturation could improve after resting. In this study, the modified Borg scale after the 6MWT, the lowest SpO_2, and the mean SpO_2 were not significantly changed by the inhalation of procaterol. This suggests that our COPD patients walked as far as possible until they needed to rest during both tests, and recovered SpO_2, resulting in no significant change in dyspnea or in the lowest or mean SpO_2 values. Thus, it is important to take the rest time during the 6MWT into consideration when assessing the changes in SpO_2 and desaturation during exercise. The previous reports did not clarify importance of a number of points, including the number of rests and the total resting time. The NSPS value, which decreases with rest during the 6MWT, can be used to evaluate the impact of resting in the 6MWT. An analysis of the walking pattern and pace during the 6MWT would be useful in clinical studies on COPD medications.

The total steps walked during the 6MWT is reported to be useful for assessing the exercise capacity of patients with chronic heart disease (23, 24). We have developed a modified 6MWT, in which the walking pattern is examined by counting steps (12), allowing the walking pattern of COPD patients to be displayed on a graph of time versus NSPS. In addition, the walking pace could be displayed by a graph of time versus cumulative steps because $NSPS_k$ (k=1,2,3,..., 72) shows a slope in 5-s (12). Moreover, it has been reported that a 3-dimensional accelerometer can accurately detect steps while a subject is walking (23, 24), and evaluate daily physical activity (25). If a pulse oximetry system that incorporates a 3-dimensional accelerometer that can accurately count steps is developed, the device could record SpO_2 continuously, compute the NSPS, and plot a graph of time versus NSPS automatically to display the walking pattern during the 6MWT.

The present study is associated with several limitations, with the most obvious being its relatively small sample size. Furthermore, we did not investigate a random sample of COPD patients who showed a spectrum of disease severity or use a placebo. Further studies that include a placebo group will be needed to clarify the effects of pretreatment with inhaled procaterol on the exercise performance of COPD patients (26) and the usefulness of our new modified 6MWT with NSPS in assessing the response to drug treatment and the efficacy of pulmonary rehabilitation.

The authors state that they have no Conflict of Interest (COI).

References

1. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J **44**: 1447-1478, 2014.
2. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J **44**: 1428-1446, 2014.

3. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med **166**: 111-117, 2002.
4. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J **39**: 495-501, 2009.
5. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med **187**: 347-365, 2013.
6. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest **140**: 331-342, 2011.
7. Waschki B, Spruit MA, Watz H, et al. Physical activity monitoring in COPD: compliance and associations with clinical characteristics in a multicenter study. Respir Med **106**: 522-530, 2012.
8. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med **164**: 770-777, 2001.
9. Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. Am J Respir Crit Care Med **184**: 1367-1373, 2011.
10. Fujimoto K, Yoshiike F, Yasuo M, et al. Effects of bronchodilators on dynamic hyperinflation following hyperventilation in patients with COPD. Respirology **12**: 93-99, 2007.
11. Satake M, Takahashi H, Sugawara K, et al. Inhibitory effect of procaterol on exercise dynamic lung hyperinflation during the 6-min walk test in stable patients with chronic obstructive pulmonary disease. Arzneimittelforschung **61**: 8-13, 2011.
12. Burioka N, Imada A, Kiyohiro A, et al. Modified six-minute walk test: number of steps per second. Yonago Acta Medica **57**: 61-63, 2014.
13. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scand J Work Environ Health **16** (Suppl 1): 55-58, 1990.
14. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest **119**: 256-270, 2001.
15. Sciurba F, Criner GJ, Lee SM, et al. Six-minute walk distance in chronic obstructive pulmonary disease: reproducibility and effect of walking course layout and length. Am J Respir Crit Care Med **167**: 1522-1527, 2003.
16. Hasegawa M, Dobashi K, Horie T, Wada N, Shirakura K. Influence of inhaled procaterol on pulmonary rehabilitation in chronic obstructive pulmonary disease. Respir Investig **50**: 135-139, 2012.
17. Ohbayashi H, Adachi M. Pretreatment with inhaled procaterol improves symptoms of dyspnea and quality of life in patients with severe COPD. Int J Gen Med **5**: 517-524, 2012.
18. Sukisaki T, Senjyu H, Oishi K, Rikitomi N, Ariyoshi K. Single dose of inhaled procaterol has a prolonged effect on exercise performance of patients with COPD. Physiother Theory Pract **24**: 255-263, 2008.
19. Cazzola M, Biscione GL, Pasqua F, et al. Use of 6-min and 12-min walking test for assessing the efficacy of formoterol in COPD. Respir Med **102**: 1425-1430, 2008.
20. Golpe R, Pérez-de-Llano LA, Méndez-Marote L, Veres-Racamonde A. Prognostic value of walk distance, work, oxygen saturation, and dyspnea during 6-minute walk test in COPD patients. Respir Care **58**: 1329-1334, 2013.
21. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J **23**: 28-33, 2004.
22. Casanova C, Cote C, Marin JM, et al. Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. Chest **134**: 746-752, 2008.
23. Jehn M, Schmidt-Trucksäess A, Schuster T, et al. Accelerometer-based quantification of 6-minute walk test performance in patients with chronic heart failure: applicability in telemedicine. J Card Fail **15**: 334-340, 2009.
24. Jehn M, Prescher S, Koehler K, et al. Tele-accelerometry as a novel technique for assessing functional status in patients with heart failure: feasibility, reliability and patient safety. Int J Cardiol **168**: 4723-4728, 2013.
25. Hataji O, Naito M, Ito K, Watanabe F, Gabazza EC, Taguchi O. Indacaterol improves daily physical activity in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis **8**: 1-5, 2013.
26. Aguilaniu B. Impact of bronchodilator therapy on exercise tolerance in COPD. Int J Chron Obstruct Pulmon Dis **5**: 57-71, 2010.