

The effect of 5-HT depletion may be attributed to the specific vasodilating effect of 5-HT on the vessels supplying oxygen and nutrients to tumors. This hypothesis is supported by intravital microscopic evidence [6]. Moreover, by investigating eNOS expression in *5-HTT*^{-/-} tumors, we examined the underlying mechanism of why the physiological level of 5-HT is important for the maintenance of blood vessels supplying the blood flow to tumors. We found that eNOS protein was reduced in the tumors of *5-HTT*^{-/-} mice. Furthermore, we confirmed the importance of 5-HT in eNOS protein expression and phosphorylation in endothelial cells. Under the physiological level of 5-HT, 5-HT induced eNOS protein and phosphorylation of eNOS in a concentration-dependent manner, suggesting that constitutive eNOS is regulated in the presence of 5-HT in tumors.

It has been reported that 5-HT stimulates phosphorylation of ERK1/2 in bovine endothelial cells [26,46], and the 5-HT_{2B} receptor

was reported to play a role in the activation of eNOS in human endothelial cells [21]. Therefore, we focused on the 5-HT receptor 2 family, especially the 5-HT_{2B} receptor. Our results indicate that the 5-HT_{2B} receptor plays a pivotal role in the phosphorylation of both ERK1/2 and eNOS in HUVEC. The 5-HT_{2B} receptor antagonists have been found to inhibit colon cancer [19], and our results suggest that 5-HT_{2B} receptor antagonists reduce tumor growth by inhibiting angiogenesis through phosphorylation of ERK1/2 and eNOS.

There are no differences in MVD between tumor-bearing *5-HTT*^{+/+} and *5-HTT*^{-/-} mice, whereas SB204741 treatment decrease MVD. Because the level of 5-HT in the tumor of *5-HTT*^{-/-} mice was reduced to half of that in *5-HTT*^{+/+} mice (Figure 1C), 5-HT_{2B} receptor in the tumor of *5-HTT*^{-/-} mice was stimulated to a certain extent. However, because SB204741 is specific and strong antagonist of 5-HT_{2B} receptor, 5-HT_{2B} receptor in the tumor of SB204741-treated mice was

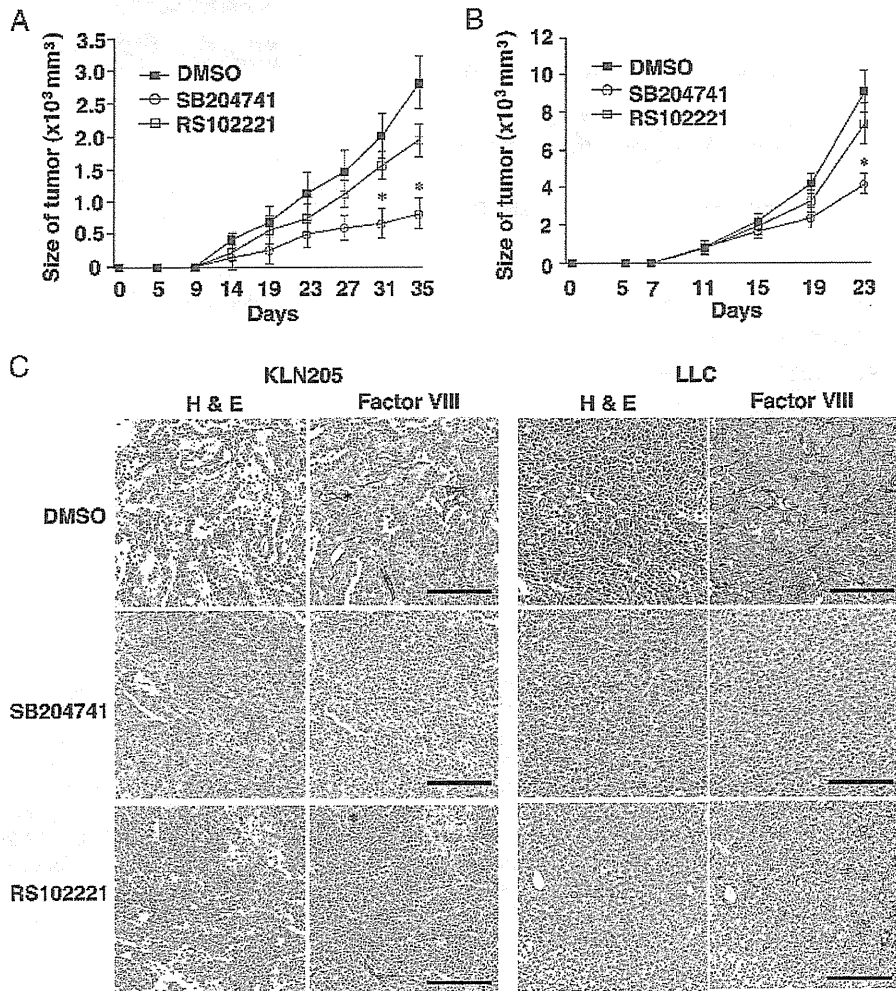


Figure 5. SB204741 reduced tumor growth. (A) Mice were injected s.c. with KLN205 on day 0 and were treated with saline (closed squares), SB204741 (circles), or RS102221 (open squares) from day 6, every 2 days. (B) Mice were injected s.c. with LLC on day 0 and were treated with saline (closed squares), SB204741 (circles), or RS102221 (open squares) from day 6, every 2 days. Tumor volumes were calculated from tumor measurement scores on the indicated day. Results are presented as the mean tumor volume \pm SD. ($n = 8$ per group). *Statistically significant ($P < .05$) compared with saline-treated mice. (C) When the diameter of the tumors reached 1 cm, mice were killed. Bars, 100 μ m. Hematoxylin and eosin–stained sections of KLN205 or LLC tumors (left). Representative sections of tumors stained for factor VIII as a vascular endothelial marker (right; original magnification, $\times 200$).

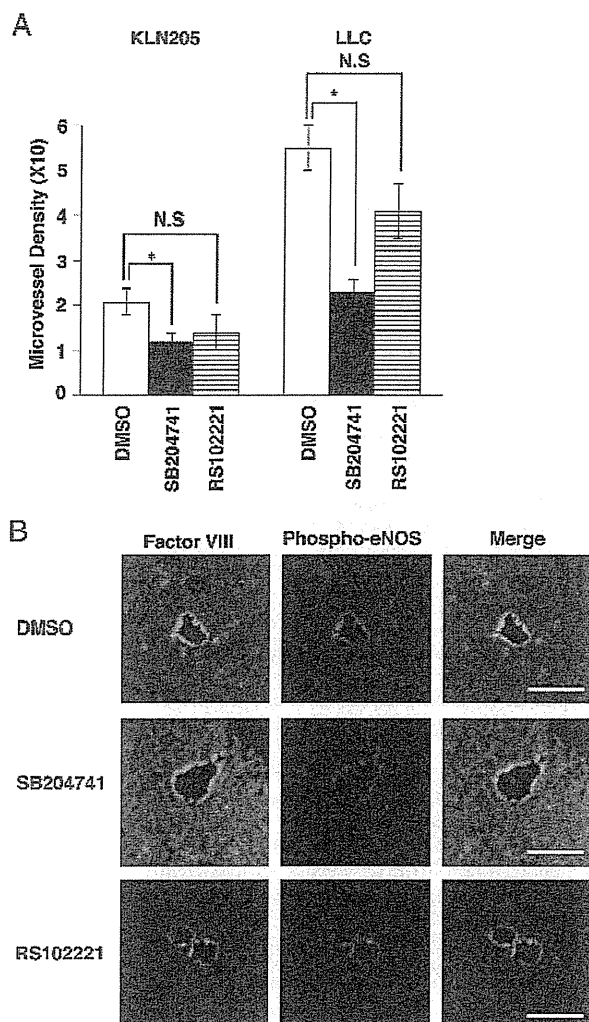


Figure 6. SB204741 treatment induced a decrease in vessel density in tumor tissues. (A) Microvessel densities were calculated. Results are indicated as the mean \pm SD of eight mice in each group. The difference in MVD between control and SB204741 treatment mice was statistically significant ($*P < .05$). N.S.: not significant by one-way ANOVA with Fisher's least significant difference test. (B) Location of phospho-eNOS in the endothelial cells. The LLC tumor tissues were stained with anti-factor VIII-related Ag (green) and anti-phospho-eNOS (red). The images were merged. Bars, 50 μ m.

strongly blocked. Our data might suggest that less 5-HT_{2B} receptor stimulation could not decrease MVD, but completely blocking the 5-HT_{2B} receptor could decrease MVD.

From the standpoint of therapeutic applications, there is an increasing evidence that the 5-HT_{2B} receptor located on endothelial cells of meningeal blood may be implicated in the pathophysiology of migraine through the NO pathway [47]. In addition, recent studies have shown that the 5-HT_{2B} receptor mediates the excitatory effects of 5-HT in the human colon [48], indicating that antagonists of this receptor might be valuable for treatment of irritable bowel syndrome [49]. We found that selective blockade of the 5-HT_{2B} receptor resulted in the inhibition of tumor angiogenesis and growth through the inhibition effect of ERK1/2 and eNOS.

Recently, 5-HT-related medicines have been extensively used in many clinical settings such as psychiatric and coagulation disorders. In addition to the possibility of the 5-HT_{2B} receptor as a molecular target, our study suggests that we should be cautious in the use of 5-HT-related medicines in patients with solid tumors or with a risk of cancer.

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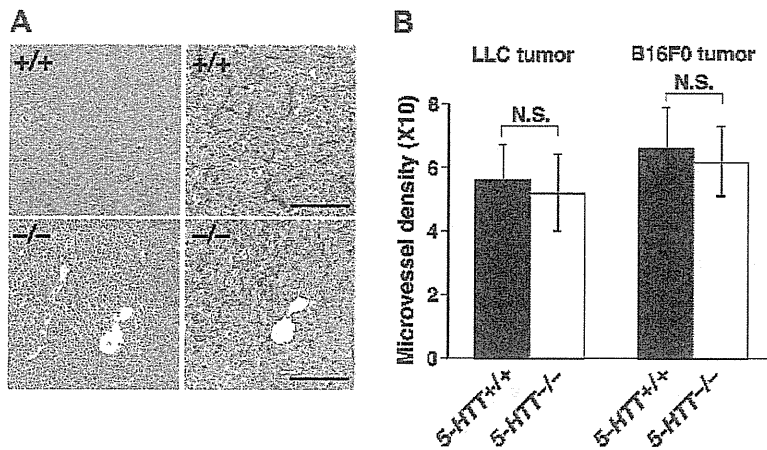


Figure W1. (A) Bars, 100 μm . Hematoxylin and eosin-stained sections of LLC tumors (left). Representative sections of tumors stained for factor VIII as a vascular endothelial marker (right; original magnification, $\times 200$). (B) Microvessel densities were calculated. Results are indicated as the mean \pm SD of six mice in each group. N.S.: not significant by one-way ANOVA with Fisher's least significant difference test.

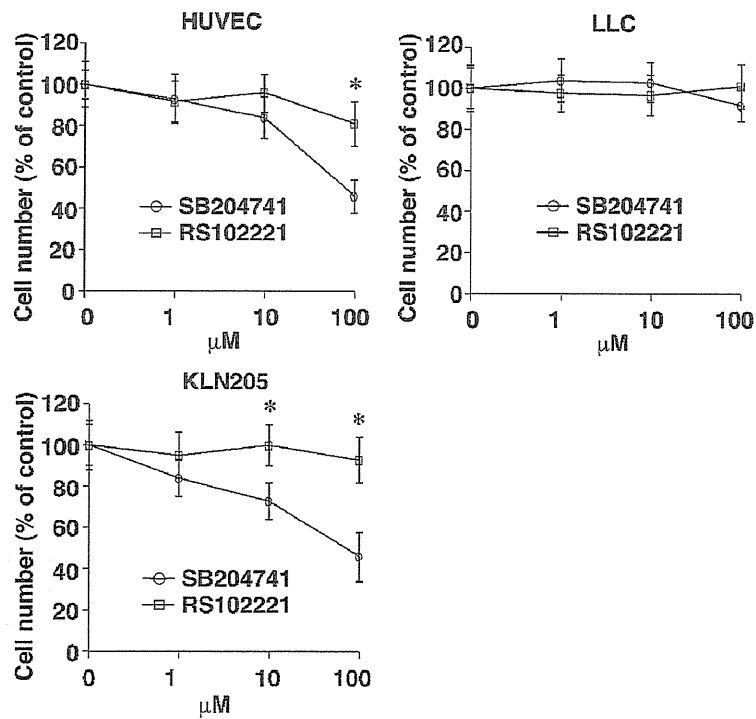


Figure W2. Human umbilical vein endothelial cells, LLCs, and KLN205 cells (5.0×10^3 cells) were cultured with the indicated amounts of SB204741 or RS102221. Each cell was cultured for 48 hours. Cell numbers were determined by water-soluble tetrazolium assay. Data are shown as the mean \pm SD of triplicate samples. The values were considered significant ($*P < .05$) versus controls. Similar results were obtained from three independent experiments.

特集

各論

KEY WORD

転倒危険者の早期発見から予防まで
—最新のエビデンスから—

●toe clearance ●前脛骨筋 ●重心動揺
●アロマセラピー

2. 予防戦略

5) 転倒のバイオメカニクスとそれに基づく予防アパラスの開発

SUMMARY

われわれは転倒者のバイオメカニクスを検討した。そしてそれに基づいて、新たな転倒予防法を考案した。まず、高齢者の toe clearance は低下しており、その機序は前脛骨筋の筋力が低下して起こるものと考えられることに基づき、前脛骨筋トレーニングスリッパを開発した。これの使用は高齢者の負担が少なく、持続可能でコンプライアンスのいい転倒予防法になると思われる。次に、転倒者の歩行時の体幹中心が動揺しているということは、重心が動揺しているということであり、高齢者の重心の動揺をアロマセラピーにより安定化させることを探索した。すると、精油による匂い刺激で高齢者の重心が安定化することを見出した。

海老原 覚

はじめに

一般的な体操や運動などの転倒の予防法はそれを行うのに、持続的な努力を要する。持続的に努力できる高齢者はいいが、認知症高齢者や超高齢者などの持続的努力ができない高齢者においては無力である。そこで考えなければならないのは、できるだけ高齢者あるいはその介護者や家族の努力が少なく済む、あるいは努力のいらぬ転倒予防法の開発である。そのためには、今一度転倒が起こるメカニズム、とりわけ生物物理的メカニズムについて探求することが普遍的で、かつ持続可能な転倒予防法に不可欠と考えられる。そこでわれわれは、転倒者のバイオメカニクスを検討した。そしてそれに基づいて、新たな転倒予防法を考案した。本稿では、そのわれわれの研究を紹介する。

高齢転倒者の歩行の軌跡

われわれは三次元モーションキャプショニング(VICON)を駆使して、高齢転倒者の歩行の軌跡を解析した。まず高齢者歩行時のつま先の

軌跡を解析すると、その toe clearance は転倒者において有意に低下していることが判明した(図1)¹⁾。また、歩行中の体幹中心の軌跡を解析すると、転倒者の方が有意に左右に動揺しながら歩いていることがわかった(図2)。そこで、この2つの軌跡の変化に対する介入法を考案した。

前脛骨筋トレーニングスリッパ

高齢者の toe clearance の低下は、その機序から前脛骨筋の筋力が低下して起こるものと考えられる。そこで高齢者のこの toe clearance の低下を、前脛骨筋の筋力を改善する道具としてのサンダル(スリッパ)を開発して改善する方法を試みた。そこでわれわれは、被験者が重いと感じない程度の重さのおもりをはがれないように、足の甲の部分に付着させることができる前脛骨筋リハビリテーション用スリッパを開発した(図3)。スリッパでおもりのないスリッパをプラセボスリッパとし、12人の高齢者に前脛骨筋トレーニングスリッパを、13人の高齢者にプラセボスリッパを配布し、それぞれ週のうち

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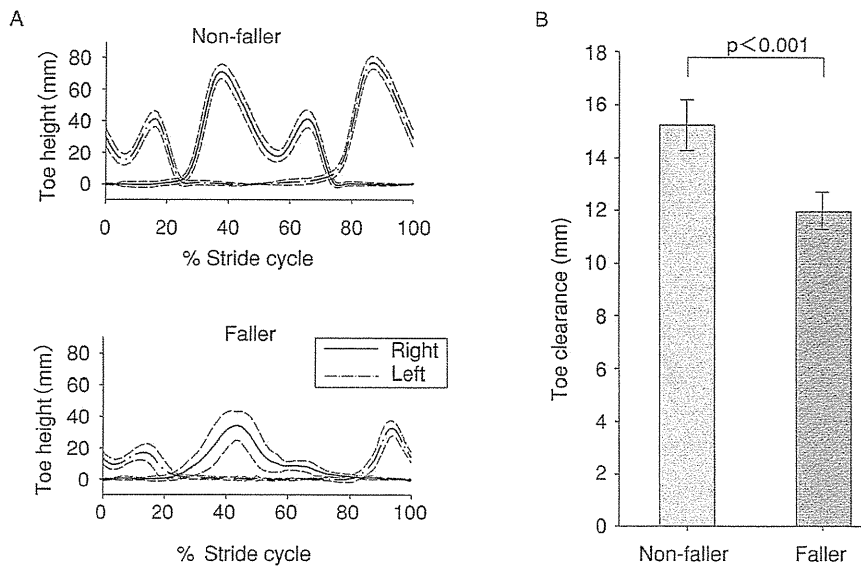


図1 高齢者歩行時のつま先の軌跡
 A：上図：非転倒者のつま先の軌跡。遊脚期の極小値がtoe clearanceである。下図：転倒者のつま先の軌跡。B：転倒者と非転倒者のtoe clearanceの比較。

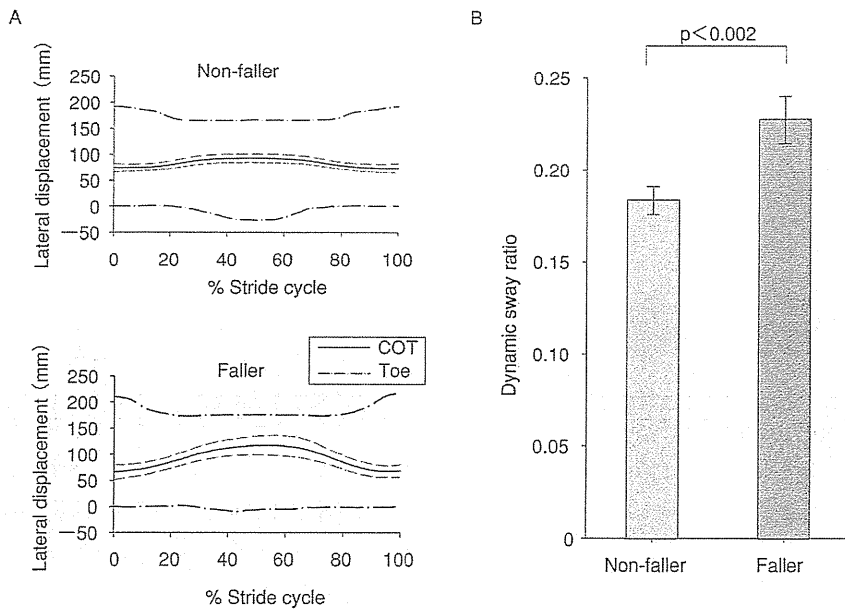


図2 高齢者歩行時の体幹中心の軌跡
 A：上図：非転倒者の体幹中心の軌跡。下図：転倒者の体幹中心の軌跡。B：体幹中心の動揺の転倒者と非転倒者の比較。体幹中心の動揺はスタンスに対する体幹中心左右振れ幅の比として表した。

前脛骨筋トレーニングスリッパ
=つま先を上げる力の訓練

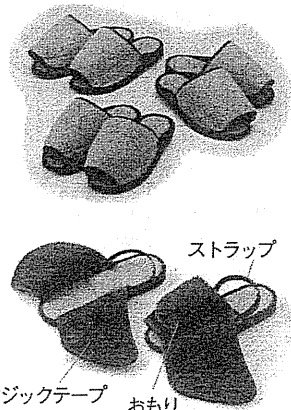


図3 前脛骨筋トレーニングスリッパ

1日だけ10分ずつ2回履いてもらった。スリッパを履いているときは、その人の最も快適なスピードで歩いていただいた。そして3カ月後間の介入の前後でTimed up & go testを行い、時間を測定した。すると、われわれが開発した前脛骨筋リハビリテーションスリッパは、Timed up & go testを改善し高齢者の歩行能力を改善することがわかった(図4)²⁾。このことを通して、この器具の使用は高齢者の負担が少なく、持続可能でコンプライアンスのいい転倒予防法となることが示唆された。

アロマセラピーによる 重心動揺の安定化

転倒者の歩行時の体幹中心が動揺しているということは、重心が動揺しているということである。われわれは、高齢者の重心動揺が匂い刺激にて安定化することを発見した³⁾。黒コショウ精油、ラベンダー精油、蒸留水の匂いを嗅がせ重心動揺計にて重心動揺を測定したところ、黒コショウとラベンダーは重心動揺を安定させる効果があったが、蒸留水にはそれがなかった。したがって、これらによる匂い刺激が高齢者の転倒予防に役立つものと思われた。

地域在住高齢者に3日間歩行ラボに来てもらい、重心動揺を測定した。開眼静止立位にて

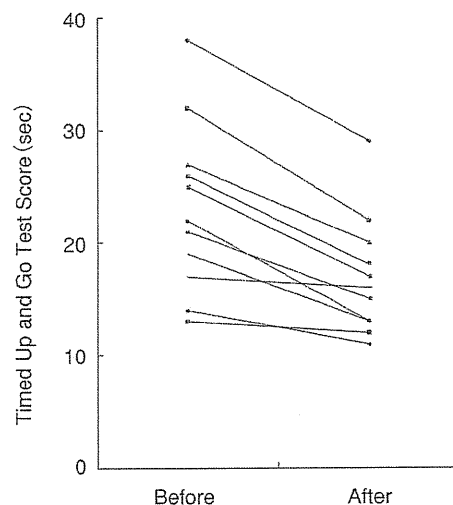


図4 前脛骨筋トレーニングスリッパ使用前後での高齢者のTimed Up & Go testに対する効果

45秒間重心動揺を測定し、その後1分間休み、次に閉眼静止立位にて45秒間重心動揺を測定する。その後2分間匂い刺激を行い、開眼静止立位にて匂い刺激を行いながら45秒間重心動揺を測定し、その後1分間匂い刺激継続しつつ休憩をとり、次に閉眼静止立位にて45秒間重心動揺を測定する。そうして、重心変化をX軸Y軸2方向の座標としてデジタル採取し解析する。3日のうち1日は黒コショウ精油の匂いを嗅がせ、ほかの1日はラベンダー精油の匂いを

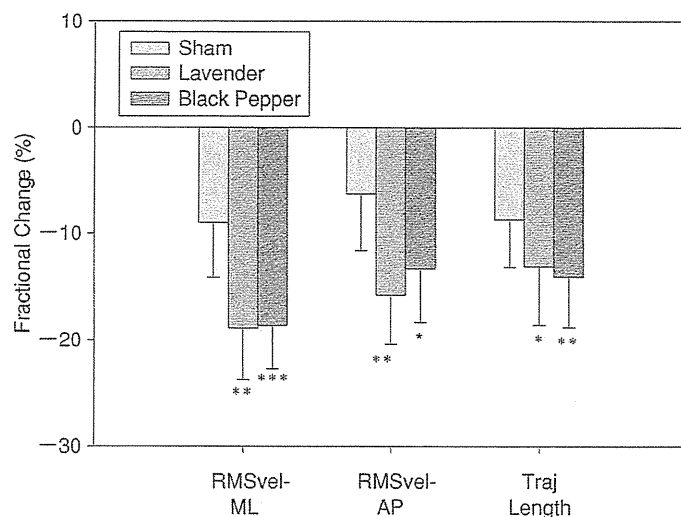


図5 黒コショウやラベンダーによるアロマセラピーの高齢者重心動揺に対する効果

重心速度の前後方向の実効値面積(RMSvel-AP), 左右方向の実効値面積(RMSvel-ML),そして総軌跡長(Traj Length)のアロマセラピー前に対する変化率(Fractional change %)をグラフ化した。マイナス変化は改善されていることを示す。

嗅がせ、さらにもう1日は蒸留水の匂いを嗅がせる。この順番は乱数表により任意に決めることとする。まず重心変移の前後方向の実効値面積(RMSdisp-AP), 左右方向の実効値面積(RMSdis-ML), 重心速度の前後方向の実効値面積(RMSvel-AP), 左右方向の実効値面積(RMSvel-ML), そして総軌跡長(Traj Length)を解析した。それらの介入による RMSvel と Traj Length の変化率は図5のようになった。この結果より黒コショウでもラベンダーでも匂い刺激は、高齢者の閉眼時の重心動揺を改善することがわかった。

おわりに

高齢者の転倒は、その倒れる方向によって3種類に分けることができる。1つは前方向の転倒で、もう1つは横方向の転倒、そして最後に後ろ方向の転倒である。このうち前方向の転倒

はつまずきにより発生し、横方向の転倒は重心バランスを失うことにより起こると考えられる。これまで述べてきたことより、前脛骨筋リハビリテーション用スリッパは前方向の転倒を予防することが期待でき、アロマセラピーは横方向の転倒を予防することが期待できると考えられる。これらの方法が実際にどのような集団で有効であるのかなど検討するのが、今後の課題と思われる。

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1. 高齢者 COPD における呼吸機能検査

SUMMARY

■ 高齢者 COPD において、肺機能検査は診断と病態把握の上で非常に大事である。さらに近年、COPD の早期発見のために肺年齢という概念が提唱され、これは肺機能検査から計算される。しかしながら、加齢肺と気腫肺には違いがあることや、肺年齢の算出値が実年齢より上か下かなど、その値そのものの扱いは実地臨床家として注意をする必要がある。フローボリューム曲線の形などに留意することが肝要である。

海老原 覚

はじめに

生理的な加齢変化によっても肺は気腫化する (senile emphysema)。しかし、senescence-accelerated mouse (SAM) などの解析から、加齢肺は気腫肺と違い、肺胞径の拡大はあるものの肺胞破壊が少なく、また肺胞径は均一に拡大しており、様々な径の肺胞が混在している肺気腫とは違う¹⁾。しかしながら、この違いを明確に区別することは肺機能検査では困難である。加齢によっても残気量は増加し、機能的残気量も増加することとなる。これは高齢者の肺機能を基にした概念で、日本呼吸器学会が中心となり (日本呼吸器学会 肺年齢普及推進事務局)、COPD の早期発見と予防を目的として一般市民向けに提唱されている²⁾。しかしながら、われわれ臨床医がこの肺年齢をとらえるときは、この言葉だけが独り歩きしないように、細心の注意と理解が必要である。

肺年齢とは

潜在患者が多い呼吸器疾患 (主に COPD) に対する予防と自覚を促すための概念である。肺年齢は、日本呼吸器学会・肺生理専門委員会 (2001) が定義している 1 秒量の式を基に³⁾、測

定した身長、年齢、1 秒量を代入することでベースとなる年齢を計算し、1 秒率と 1 秒量から分類したグループごとにコメントを提示することで、肺の健康指導に活用されることを想定している。

具体的にはまず、性別ごとに定義した図 1 に示される算出式を基に算出する。ここで、肺生理委員会の回帰式が 18~95 歳までを対象とした式であるため、この間を超える算出結果には「18 歳未満」または「95 歳以上」とする。COPD の疑いがある 1 秒率 70% 未満の者のうち、1 秒量が 100% 以上になるケースについては実年齢より若く肺年齢が算出されるため、誤解を防ぐ観点から実年齢に補正し、COPD 軽症に準じたコメントを表示することになっている。以上のフローチャートを図 2 にまとめる。

加齢による肺機能変化

生理的な肺の加齢変化は肺胞の膨張と末梢気道の支持組織の喪失によって、ガス交換面の減少、弾性リコイルの減少および残気量・機能的残気量の増加をもたらす。胸郭のコンプライアンスは悪くなり、Work of breathing は若年者に比べ増大する。呼吸筋力も加齢により弱くなる。以上の結果により、年齢とともに肺活量や 1 秒量も低下してくる。そして、閉塞性障害の

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肺年齢の式および算出ロジック

日本呼吸器学会(JRS)肺生理専門委員会(2001)
1秒量の標準回帰式(18~95歳)

男性: $FEV_1(L) = 0.036 \times \text{身長}(cm) - 0.028 \times \text{年齢} - 1.178$
女性: $FEV_1(L) = 0.022 \times \text{身長}(cm) - 0.022 \times \text{年齢} - 0.005$

性別、身長、 $FEV_1(L)$ を基に標準回帰式の逆計算にて肺年齢を算出

肺年齢の計算式(18~95歳)

男性: $\text{肺年齢} = (0.036 \times \text{身長}(cm) - 1.178 - FEV_1(L)) / 0.028$
女性: $\text{肺年齢} = (0.022 \times \text{身長}(cm) - 0.005 - FEV_1(L)) / 0.022$

図1 肺年齢の計算式

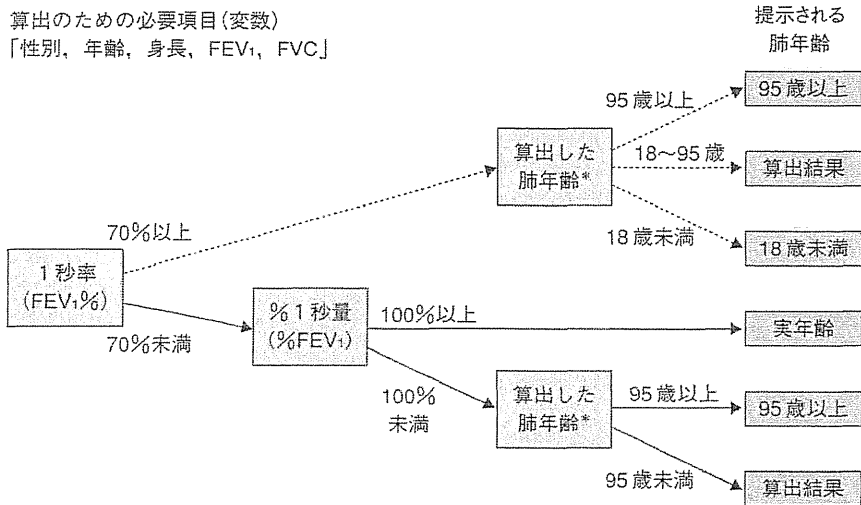


図2 肺年齢のフローチャート

指標であるゲンスラーの1秒率($FEV_1/FVC\%$)はどうであろうか。日本呼吸器学会肺生理専門委員会の回帰式によると³⁾、年齢とともに身長を固定した場合、男性の場合-0.190、女性の場合-0.240の係数で低下する。したがって、年齢とともに閉塞性障害は強まることとなるが、血液ガスをみても動脈血酸素分圧も二酸化炭素分圧もほとんど変化なく、年齢との有意な相関は見出せない。つまり、生理的加齢変化だけでは血液ガスに変化をもたらすことができないのである。この点がCOPDによる肺の変化

と大きく異なる。

COPDのス파이ロメトリー

ス파이ロメトリーがCOPDの診断および重症度判定に必須なのは周知の事実である。努力呼出した際の1秒量(FEV_1)を努力性肺活量(FVC)で除した FEV_1/FVC をゲンスラーの1秒率($FEV_1\%$)と呼び、閉塞性換気障害の指標となる。COPDでは気管支拡張薬および吸入ステロイドを含む治療においても、1秒率が70%

以上になることはない。重症度は1秒量を予測値で割った $\%FEV_1$ で評価され、 $\%FEV_1 > 80\%$ 、 $80\% \geq \%FEV_1 > 50\%$ 、 $50\% \geq \%FEV_1 > 30\%$ 、 $\%FEV_1 \leq 30\%$ をそれぞれ、軽症、中等症、重症、最重症としている。また、努力呼気曲線を縦軸に流速、横軸に肺気量で置き換えると、フローボリューム曲線が得られる。閉塞性換気障害の場合は、曲線の下降脚が下向きに凸の形を示す。肺気腫が顕著な重症 COPD では、呼気の流速が急速に低下し、下降脚が屈曲した形を呈し、安静換気時の呼気流速を下回る。これは、強制呼気時に気道が虚脱し、急速に呼気流速が低下する結果であり、ダイナミックコンプレッションと呼ばれる。

スパイロメトリーと肺年齢の例

筆者が大学病院で診察している症例のスパイロメトリーを紹介する。図3Aは66歳、男性であり、CT上も肺気腫である。FVC 3.26 L (101.2%予測値)、 FEV_1 1.15 L (50.2%予測値)、ゲンスラーの1秒率は35.3%であった。フローボリューム曲線のパターンはダイナミックコンプレッションパターンであり、この症例の肺年齢を計算すると95歳以上となった。

図3Bは、心房細動にてワルファリン服用中の88歳の高齢女性である。呼吸機能は健常であり、FVC 1.93 L (101%予測値)、 FEV_1 1.64 L (157.7%予測値)、ゲンスラーの1秒率は85.0%であった。この症例の肺年齢は計算すると73歳である。

図3CはEx-smokerで息切れがあり、COPDの治療をしている64歳の男性症例である。FVC 4.62 L (133%予測値)、 FEV_1 2.86 L (106%予測値)、ゲンスラーの1秒率は61.9%であった。この症例の肺年齢は、図3Bの症例と同じ73歳である。しかし、フローボリューム曲線の形は先ほどのより下降脚の下に凸である。同じ肺年齢でも、実年齢より若い場合と老けている場合で、フローボリューム曲線の形が異なってくる。

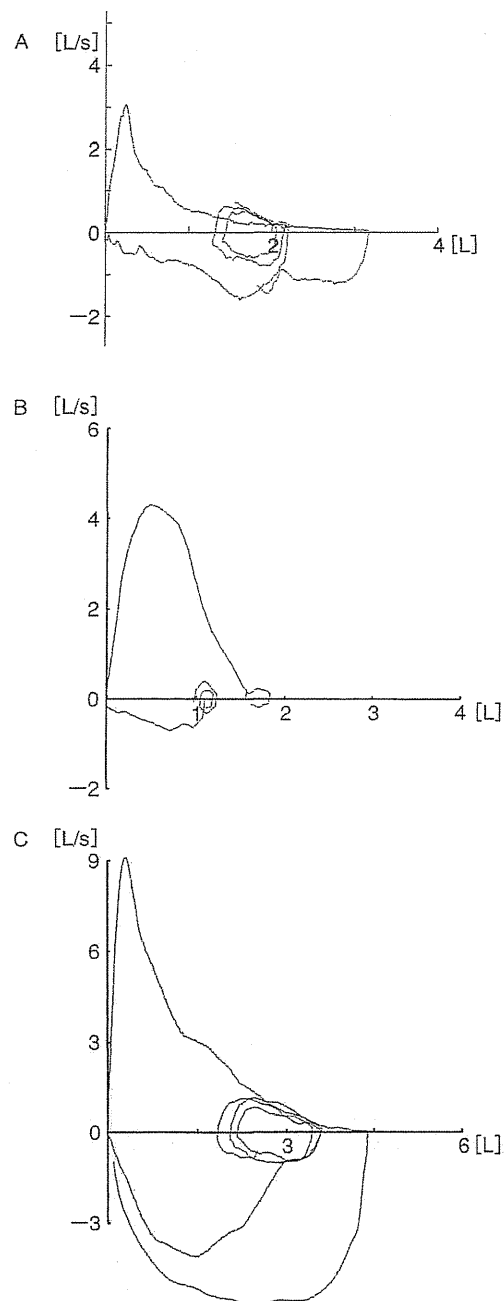


図3 フローボリューム曲線の例

COPDの肺気量分画、気道抵抗、肺拡散能

COPDでは、安静呼吸下におけるエアートラ

ツピングと、肺胞の破壊に伴う肺弾性収縮圧の低下により肺が過剰に膨張し、機能的残気量、残気量(RV)、残気率(RV/TLC)は過膨張とともに増加する。気道抵抗(Raw)は比較的中枢側の気道の狭窄を反映しやすいが、末梢気道病変によって末梢気道がびまん性に狭小化すると上昇する。肺拡散能(DLco)はガス交換能の指標であり、肺気腫タイプでは肺胞の破壊に伴い、有効換気面積の減少と喚起血流比不均等によって低下を示し、肺胞気量で補正した DLco/VA (Permeability) はさらに低値を示す。気腫病変

が明らかでない気道病変タイプの COPD では DLco の低下がないか、あるいは軽度である。

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herd effect of PCV7 would be similar in nonbacteremic cases and IPD, the results of the current study suggest a possible combined effect of PPV23 (direct) and PCV7 (indirect) against NBPCAP in older adults. Further studies are needed to elucidate the direct and indirect benefits of pneumococcal vaccinations against NBPCAP in older adults.

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INTENSIVE STEPWISE METHOD FOR ORAL INTAKE USING A COMBINATION OF TRANSIENT RECEPTOR POTENTIAL STIMULATION AND OLFACTORY STIMULATION INHIBITS THE INCIDENCE OF PNEUMONIA IN DYSPHAGIC OLDER ADULTS

To the Editor: Dysphagia in older adults is an important cause of pneumonia, which causes high morbidity and mortality.¹ The incidence of aspiration as a cause of community- and hospital-acquired pneumonia in older adults has been reported to be 67%.² Rehospitalization after inpatient treatment of pneumonia occurs in one-tenth of all hospitalizations.³ A vicious spiral in which aspiration predisposes patients to pneumonia is generated and hard to avoid. In the course of treatment and care of aspiration pneumonia, one of the most critical and challenging questions is when and how such patients should start to eat.

In a real clinical setting, when a patient is unable to receive a nutritionally adequate diet orally and the need for nutritional support is expected to last for more than 2 weeks, gastrostomy may be the route of choice for enteral feeding.⁴ Another report has shown that early tube feeding reduces care fatalities, whereas the use of enteral tube feeding has been found to increase the risk of death.⁵ We often vacillate in the choice of enteral feeding in a clinical setting.

It was recently reported that the thermal and pharmacological stimulation of the transient receptor potential (TRP) V1 or TRPM8 can improve the latency of the swallowing reflex in older adults with dysphagia.⁶⁻⁹ Moreover, it was recently reported that nasal inhalation of volatile black pepper oil can activate the insular or orbitofrontal cortex, resulting in improvement of the reflexive swallowing movement.¹⁰

Therefore, a 2-year historical cohort study was conducted to determine the effect of an intensive stepwise method for starting oral intake in older adults with dysphagia that combines TRP superfamily stimulation of the swallowing reflex with the effect of aromatherapy using black pepper oil in 17 hospitalized patients with pneumonia, who had a past history of recurrent pneumonia in a 3-year period and were physically handicapped, mainly because of cerebrovascular disease. The incidence of pneumonia and febrile days were assessed with or without the intensive stepwise method (Table 1).

Table 1. Patient Characteristics and Effect of the Intensive Stepwise Method on Older Adults with Dysphagia

Characteristic	Control Phase	Intervention Phase	P-Value
Age, mean \pm SD	80.3 \pm 7.2	81.2 \pm 7.0	.80
Male, n	14	14	1.00
Charlson Comorbidity Index, mean \pm SD	3.3 \pm 1.3	4.3 \pm 0.9	<.01*
Mental and physical state			
Mini-Mental State Examination score, mean \pm SD	5.2 \pm 4.8	4.8 \pm 4.2	.82
Barthel Index, mean \pm SD	24.3 \pm 20.6	20.5 \pm 19.3	.52
Dysphagia evaluation			
Latency of swallowing reflex, seconds, mean \pm SD	18.9 \pm 23.4	20.6 \pm 23.9	.84
Cough reflex sensitivity, log mg/mL, mean \pm SD	0.9 \pm 0.8	0.8 \pm 0.6	0.83
Nutrition and immune state			
Body mass index, kg/m ² , mean \pm SD	19.3 \pm 4.8	18.6 \pm 4.5	.73
Serum albumin, g/dL, mean \pm SD	2.9 \pm 0.7	2.9 \pm 0.5	.97
Total cholesterol, mg/dL, mean \pm SD	135 \pm 17.6	135.4 \pm 39.1	.98
Total lymphocyte count/ μ L, mean \pm SD	1,748.1 \pm 785.8	1,224.2 \pm 510.9	<.04 [†]
Medication, patients, n			
Angiotensin-converting inhibitor	4	9	1.7
Dopamine-releasing agent	2	8	1.4
Mosapride	1	3	.43
Percutaneous endoscopic gastrostomy, patients, n	2	5	.30
Cases of pneumonia, n	16	5	<.001*
Number of febrile days, mean \pm SD	6.8 \pm 4.7	1.3 \pm 1.7*	<.007*
Number of febrile days in patients with percutaneous endoscopic gastrostomy, mean \pm SD	2.4 \pm 3.8	2.5 \pm 3.5	.93

*A significant difference between control phase and intervention phase was obtained at the .01 level ($P < .01$).

[†]A significant difference between control phase and intervention phase was obtained at the .05 level.

SD = standard deviation.

The intensive stepwise method for starting oral intake advocated is as follows. Oral feeding of the older adults was postponed until their pneumonia was confirmed to be cured. Soon after patients were judged to be nearly cured of pneumonia based on the return of inflammation markers to the normal range and diminishing shadows of pneumonia on chest X-ray or computerized tomography, aromatherapy with black pepper oil was started as the first step. Aromatherapy was executed using a sheet of white nonwoven fabric (size 6.5 \times 4.5 cm) adhered to the patient's gown near the neck area with volatile black pepper oil adhered to multiple carbon nanoparticles continuously diffused from the fabric. The second step was the additional application

of capsaicin troches (round, 15 mm in diameter with a center hole 7 mm in diameter, capsaicin 1.5 μ g/tablet), three times per day 3 days after the start of aromatherapy with black pepper oil.⁸ The third step was that jelly including a menthol ingredient (menthol gel) was provided as the first meal when eating was resumed 5 days after the addition of the capsaicin troches. The menthol gel (weight 80 g) was made of gelatin with menthol at a concentration of 10⁻³M.⁹ The hardness, cohesion power, and adhesive power of the jelly were 5,700 N/m², 39 J/m³, and 0.49 at 20°C, respectively. These parameters were recognized as being safe for swallowing by people with dysphagia. If patients were able to swallow the menthol jelly safely, they were provided in a step-by-step manner with the proper food texture depending on their ability to swallow such food as paste or pudding or usual meals including liquids and solids. Both phases were executed with usual care for the prevention of aspiration such as specific swallowing exercise by a speech pathologist and oral care by nurses after every meal.

Despite the Charlson Comorbidity Index, oral intake before the intervention phase was greater and the number of total lymphocytes before oral intake in the control phase was less than that in the other phase ($P < .01$ and $P < .05$, respectively), the incidence of pneumonia and the number of febrile days for 1 month from the start of oral intake in the intervention phase were significantly less than that in the control phase ($P < .01$).

The intensive stepwise method for starting oral intake in older adults with dysphagia may be effective in decreasing the incidence of pneumonia presumably induced by aspiration. This method may decrease the number of patients who require enteral tube feeding.

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Takae Ebihara and Satoru Ebihara have a domestic patent in Japan for the effect of volatile black pepper oil on dysphasia (Japan domestic patent number 3762969, Date of registration with the Japan Patent Office: January 27, 2006).

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INTERVENTIONS TO PREVENT PNEUMONIA IN NURSING HOME RESIDENTS

To the Editor: We applaud Quagliarello and colleagues for “Pilot testing of intervention protocols to prevent pneumonia in nursing home residents.”¹ Intervention protocols were directed toward oral hygiene and swallowing dysfunction. We are writing to ask clinicians to consider two additional areas with potential preventive efficacy: medication review and anti-reflux therapy.

Certain medications decrease salivation; impair swallowing, cough, and mobility; facilitate reflux; or promote gastric colonization with oral respiratory pathogens by reducing acidity or contributing to stagnation or paresis.² In addition, inhaled corticosteroids are associated with a greater risk of pneumonia.³

Residents colonized with gram-negative rods (GNRs), *Staphylococcus aureus*, or yeast demonstrated poor pharyngeal clearance of radiolabeled albumin from the oropharynx (stasis).⁴ Salivary flow and swallowing facilitate mechanical clearance of the mouth. Studies have shown that anticholinergic medication decreases salivary production and slows clearance of isotope.⁵ Dry mouth has been associated with coated tongue and halitosis, and in one

study, dry mouth was associated with a greater risk of ventilator-associated pneumonia.^{2,6}

Pulmonary and allergy practice guidelines acknowledge gastroesophageal regurgitation as a possible cause of cough, asthma, and sinusitis.² Although a strong association between gastroesophageal reflux disease (GERD) and pneumonia remains an area of controversy, in one study, 35% of deaths attributed to GERD were from aspiration.⁷ Aspirated gastric contents may contain food, acid, enzymes, or colonizing microbes. Gastric aspiration events may therefore produce chemical pneumonitis or bacterial pneumonia.² Hypochlorhydria and stasis (gastroparesis, bowel obstruction) facilitate gastric bacterial colonization by oral flora (including GNRs and *S. aureus*). In a case-control study, current proton pump inhibitor (PPI) use in outpatients was associated with a risk of pneumonia 1.9 times as great as in those who stopped the PPI.²

Japanese clinicians conducted small studies in nursing home residents to assess the effectiveness of interventions designed to reduce gastric regurgitation and aspiration. Twenty-eight bed-bound residents were placed in a seated position for 2 hours after meals and compared with 34 controls.⁸ The intervention group sustained 13 febrile days per patient over the course of the 100-day study, compared with 18 days in the control group ($P < .05$). In a second study, residents who had experienced a cerebrovascular accident and were being fed using a percutaneous endoscopic gastrostomy tube were studied for 12 months. Thirty-eight received mosapride, a pro-motility agent, versus 37 controls. Forty-seven percent of the intervention group developed pneumonia, compared with 81% in the control group ($P = .004$). Mortality was 26% in the intervention group, compared with 59% in controls ($P = .01$).⁹ Elevating the head of the bed to prevent reflux, regurgitation, and aspiration is a standard of care in the intensive care unit, but this position will increase the pressure applied to the sacral skin.¹⁰

In summary, medication review and anti-reflux therapy may also be the focus of intervention efforts to prevent pneumonia in nursing home residents.

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LETTER TO THE EDITOR

Effects of capsiate on the triggering of the swallowing reflex in elderly patients with aspiration pneumonia

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Dear Editor,

Morbidity and mortality from aspiration pneumonia continue to be major health problems in the elderly.^{1,2} Dysphagia, such as delayed triggering of the swallowing reflex, an important respiratory defense mechanism, predisposes subjects to aspiration pneumonia.^{1,3} Triggering of the swallowing reflex could be accelerated if swallowed material was warmed up, even in dysphagic patients.⁴ Moreover, it has been reported that capsaicin accelerated the swallowing reflex in patients with aspiration pneumonia.⁵ Because the hot sensation is sensitized through transient receptor potential vanilloid 1 (TRPV1),⁶ the results indicate that TRPV1 stimulation together with laryngeal food stimuli accelerate swallowing reflex in the elderly. Although capsaicin is a well-known and efficient TRPV1 agonist, its pungency is sometimes unacceptable to elderly people. Capsiate is obtained from the non-pungent cultivar of red peppers named CH-19 Sweet.⁷ CH-19 Sweet is a fixed cultivar that was selected and cultivated from a pungent cultivar, CH-19, of pepper. Capsiate is known to activate TRPV1,⁸ and, despite non-pungency, increases adrenaline secretion and oxygen consumption like capsaicin.⁹ Hence, capsiate may have a capability to accelerate the swallowing reflex without inducing a pungent sensation in elderly people. Therefore, we examine herein the effect of capsiate in elderly patients with aspiration pneumonia. Twelve elderly patients with aspiration pneumonia were recruited from those referred and admitted to the Geriatric Unit, Tohoku University Hospital for treatment of pneumonia from May 2006 to April 2007. Pneumonia was diagnosed by the presence of pulmonary infiltration on chest radiograph and computed tomography (CT) and according to systemic

inflammation as determined by white blood cell (WBC) count and C-reactive protein (CRP). The criteria for pneumonia were established according to the pneumonia guidelines of the Japanese Respiratory Society.¹⁰ In the current study, aspiration was defined according to the Japanese Study Group on Aspiration Pulmonary Disease as pneumonia in a patient with a predisposition to aspiration because of dysphagia or swallowing disorders.¹¹ We studied the swallowing reflex in 12 patients (seven men and five women) as they recovered from treatment such as antibiotic drip infusion. Informed consent was obtained from all subjects or their families. The patients fed themselves or needed help in eating. Patients had neither feeding tube nor percutaneous endoscopic gastrostomy. The protocol was approved by the Institutional Review Board of the Tohoku University Ethics Committee and it conformed to the provisions of the Declaration of Helsinki. The swallowing reflex was induced by a bolus injection of 1 mL distilled water into the pharynx through a nasal catheter (8-Fr). The subjects were unaware of the actual injection. Swallowing was identified by sub-mental electromyographic (EMG) activity and/or visual observation of characteristic laryngeal movement. EMG activity was recorded from surface electrodes on the chin. The swallowing reflex sensitivity of elderly patients was evaluated as a latent time of swallowing reflex (LTSR), timed from the injection to the onset of swallowing.¹² Capsiate was extracted from CH-19 Sweet (kind gift from Ajinomoto, Kawasaki, Japan). Harvested chili peppers (CH-19 Sweet) were washed and dried. Then, the crude oil was extracted from the dried chili peppers using n-hexane. The crude oil was refined by distillation and column chromatography. Finally, in order to adjust the concentration, the refined oil was diluted with medium-chain

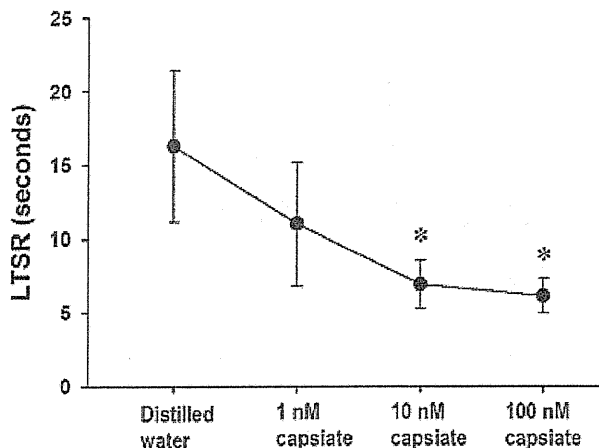


Figure 1 Latent time of swallowing reflex (LTSR) induced by distilled water and 1, 10 and 100 capsiate in patients with aspiration pneumonia ($n = 12$). Each plot indicates mean \pm standard deviation. * $P < 0.05$ vs distilled water by one-way ANOVA with Scheffe as a post-hoc test.

triglyceride. In this original capsiate extract solution, the capsiate content of the sample was approximately 7%. The rest of the extract solution was mainly caprylic acid. Capsiate was dissolved in distilled water using a sonicator. Various concentrations (1–100 nM) of capsiate and distilled water at room temperature were injected in a double-blind and randomized manner at 2-min intervals. Statistical analysis was conducted using SPSS ver. 9.0J. The comparisons among groups were done by one-way ANOVA with post-hoc application of Fisher's least significant difference test. $P < 0.05$ was taken as significant.

For the 12 patients who completed the study, the mean age was 79.8 ± 8.2 years (standard deviation; range, 63–93). The mean LTSR induced by distilled water at room temperature was 16.3 ± 5.1 s. The LTSR was significantly shortened in a concentration-dependent manner of the capsiate (Fig. 1). The mean LTSR induced by 1, 10 and 100 nM capsiate were 11.0 ± 4.2 , 6.9 ± 1.6 and 6.1 ± 1.2 s, respectively. In each subject, after the completion of LTSR measurements, we tested whether they experienced pungency by 100 nM capsiate. A droplet of each 100 nM capsiate solution was added to the filter paper disc (8 mm diameter), and then the disc was placed on the left side of the tongue 2 cm from the tip (i.e. locus for left chorda tympani nerve), for a 1 s. Nobody sensed pungency. There was no harmful effect or unpleasant feelings exhibited by patients during and after the study.

The study showed that capsiate has an effect similar to capsaicin on triggering the swallowing reflex, confirming the involvement of TRPV1 in the neural afferent of the swallowing reflex. The capsiate dosage used was much lower than that used to increase adrenaline

secretion and oxygen consumption, and induce irritant pungency in mice,^{8,9} but higher than that used to accelerate swallowing reflex by capsaicin.⁵ The dosage used here is close to that used to induce response in the TRPV1-expressed cell line *in vitro*.⁸

Our results suggest that capsiate-stimulation restores sensitivity to the triggering of the swallowing reflex in dysphagic patients without inducing any pungent sensation. The addition of capsiate to liquids or food may stimulate the swallowing reflex and help to prevent aspiration pneumonia in the elderly without changing their taste. We previously showed that a lozenge containing capsaicin could improve the swallowing reflex in the dysphagic elderly.¹³ Hence, there is a possibility that letting a lozenge containing capsiate dissolve in the mouth before meals in the dysphagic elderly may improve the sensitivity of the swallowing reflex without inducing a pungent sensation. Further longitudinal studies are needed to clarify this.

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ORIGINAL ARTICLE: SOCIAL RESEARCH,
PLANNING AND PRACTICE

Understanding the oldest old in northern Japan: An overview of the functional ability and characteristics of centenarians

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Aim: To increase knowledge of the functional ability of centenarians by examining the situation of Japanese centenarians residing in an urban region in northern Japan.

Methods: Questionnaires focused on functional ability, demographics, housing and care needs were received from 56 centenarians and 104 control subjects: 56 aged 80–89 and 48 aged 90–99.

Results: Centenarian physical capabilities, care needs and health history were diversified. Centenarians most commonly resided with family in the community and were likely to utilize informal and insurance care services. Gender differences in functional ability by age groups known as gender cross-over were observed in control subjects but reduced in centenarians. A few who reported physical limitations were not entitled to receive nationally subsidized care services suggesting inaccuracies may have occurred during certification determination.

Conclusion: Centenarians in northern Japan represent a heterogeneous cohort suggesting multiple paths to the attainment of advanced old age. This is the first study designed to provide a solid knowledge base of actual circumstances experienced by centenarians specifically in northern Japan. *Geriatr Gerontol Int* 2010; 10: 78–84.

Keywords: aged, aging, health services for the aged, health status, gender characteristics.

Introduction

Japan, a nation famous for longevity, is one of the fastest graying nations in the world. The Japanese population aged over 65 will rise from 20.1% in 2006 to 26% by 2015 and 30.9% by 2030.¹ The number of centenarians in Japan in 2005 was 25 554, 85.2% being female, and is projected to increase to over 166 000 by 2025.¹ With continuous developments in medical care, people are

expected to live longer while the prevalence of individuals living with disabilities and or diseases requiring care is also anticipated to increase.

Due to the historical stigma towards institutionalized care combined with the lack of adequate long-term care facilities, many elderly people were hospitalized for long periods of time in regular hospitals.² Long-Term Care Insurance (LTCI) introduced in Japan in April 2000 aimed to increase home care services, reduce the number of hospitalizations and unnecessary medical expenses, and increase support to the elderly and their burdened caregivers.

Centenarians represent a heterogeneous cohort and require a diverse range of care from informal and formal care services. By understanding the strengths and weaknesses of LTCI and its utilization by centenarians in

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Japan, other nations may be able to more effectively customize health-care systems to meet the needs of the oldest old.

This paper aims to provide an analysis of centenarians focusing upon functional ability, social situation, and care status. The authors wished to elucidate the effectiveness of the current LTCI system in allocating care and services to the oldest old.

Methods

This is the first study to investigate centenarians in Sendai City, northern Japan. Sendai City reported 1.4 centenarians per 10 000 people,³ double the general rate in the USA of 0.7 per 10 000.⁴ At the time of this study, the sex ratio of centenarians in Sendai City was 6.75 females to one male.

Resident registrars in Sendai City, the second largest city in northern Japan with a population of approximately 1 million people, were manually searched by the principal investigator (S. F.) and all names, addresses, gender and birthdates of the 135 registered centenarians (individuals aged 100 years or older as of 1 January 2007) were selected for the present study. Simultaneously, 135 people aged 90–99 years and 135 people aged 80–89 years were recorded as control subjects. Immediately following each centenarian located in the registrar book, the next 80–89-year-old and 90–99-year-old individuals listed in the subsequent pages were selected as control subjects. Of the 405 questionnaires, 160 (39.5%) were completed by 56, 48 and 56 respondents aged 80–89, 90–99 and 100–107 years, respectively, and included for analysis in this study.

Questionnaires mailed on the same date included questions relating to the respondents demographics, activities of daily living (ADL) and instrumental activities of daily living (IADL) levels, and care situation.

Questionnaire respondents were assessed for problems in carrying out ADL using the Barthel Index (BI), a widely used 10-item ADL scale.⁵ Individuals were divided into six groups according to BI score based upon research by Gondo:⁶ Independent A (score 100); Independent B (score 80–99); Minimal Help (score 60–79); Partially Dependent (score 40–59); Very Dependent (20–39); and Totally Dependent (score <20). Independent (combination of Independent A and B scores) and Dependent (combination of Very Dependent and Totally Dependent scores) were used for analysis.

More complex IADL were evaluated using the IADL scale created by Lawton and Brody.⁷ This scale ranges 0–8 points for women and 0–5 points for men where a score of 8 for women or 5 for men means that no help is needed.

To analyze the levels of care required, the LTCI care needs level designations given to recipients by the Japanese Ministry of Health, Labor and Welfare were used.

Applicants are categorized into one of three categories: self-supporting, support needs levels 1 through 2 (called “yoshien” in Japanese), or care needs levels 1 through 5 (called “yokaigo” in Japanese). Self-supporting individuals are ineligible to receive LTCI assistance. Support needs levels and care needs levels receive eligibility ranging from the fewest amount of community-based services: Support 1, to the maximum allotted amount of care including community as well as institutional services (Care 5). Individuals with LTCI certification choose which services they receive and the company to provide the care.

Care services used by respondents were divided into informal services provided by unpaid family members and formal services comprised of LTCI services and privately paid services.

Informed consent was obtained from all participants. This study was conducted in accordance with the ethical guidelines of Tohoku University School of Medicine.

Statistical analysis was conducted using Microsoft Office Excel 2003 and SPSS ver. 15.0. Analysis was performed using independent samples tests, two-tailed Student's *t*-test for equality of means, Kruskal–Wallis one-way ANOVA, and test of means using ANOVA. $P < 0.05$ was considered significant.

Results

The status of centenarian and control subjects is shown in Table 1. Fifty-six centenarians ranging in age from 100–107 years (mean 102.0 ± 1.3 years; males : females, 10:46) and 104 control subjects including 56 respondents aged 80–89 (mean 83.7 ± 2.2 years) and 48 respondents aged 90–99 (mean 92.4 ± 2.2 years) were included in this study. No significant differences in response rate were observed between gender or age groups (Fig. 1).

Centenarian physical functioning was lower than 80–99-year-old control subjects ($P < 0.001$). Mean BI scores for 90–99-year-old males were higher than 90–99-year-old females ($P < 0.0001$). There were more Independent centenarian males than females (45.5% vs 18.2%). The percentages of 90–99-year-old and centenarian Independent males were both three times larger than females. The prevalence of Dependent centenarians was 20% more than controls. The proportion of Dependent males was higher than females for both 80–89-year-old (14.82% vs 8%) and centenarian (54.6% vs 47.7%) respondents.

IADL scores showed a general decline as respondent age increased ($P < 0.001$). Differing patterns of IADL status by age were shown between males and females. Males aged 90–99 years showed higher IADL levels than both 80–89-year-old and centenarian respondents.

Respondents reported experiencing various comorbidities including hypertension, dementia, swallowing