Table 3. Changes in pre-treatment scores of health-related quality of life during pulmonary rehabilitation with ghrelin or placebo

	At Week 3			At Week 7		
	Ghrelin, n = 14	Placebo, n = 15	Treatment effect (95% CI; p value)	Ghrelin, n = 14	Placebo, n = 13	Treatment effect (95% CI; p value)
SGRQ						
Total	−5.0 (3.2)	−3.9 (3.5)	−1.1 (−10.9 to 8.7; 0.83)	−6.0 (2.7)*	0.8 (2.4)	−6.8 (−14.4 to 0.7; 0.072)
Symptoms	−1.7 (3.0)	0.3 (5.9)	−1.9 (−16.2 to 12.3; 0.77)	−9.4 (4.0)*	6.4 (5.4)	−15.8 (−29.5 to −2.1; 0.026)
Activity	−4.5 (3.5)	−5.0 (3.9)	0.4 (−10.5 to 11.4; 0.94)	0.1 (2.2)	1.3 (2.7)	−1.2 (−8.3 to 5.9; 0.73)
Impacts	−6.3 (4.1)	−4.1 (3.1)	−2.2 (−12.6 to 8.2; 0.67)	−8.9 (3.7)*	−1.9 (3.0)	−7.0 (−16.9 to 2.9; 0.16)
SF-36						
Physical functioning	4.6 (6.1)	0.3 (3.9)	4.3 (−10.0 to 18.5; 0.55)	3.1 (4.7)	−6.9 (4.9)	10.0 (−3.9 to 23.9; 0.15)
Role physical	−8.3 (6.9)	−4.6 (5.4)	−3.7 (−21.6 to 14.1; 0.67)	−12.0 (4.1)*	−22.6 (7.3)**	10.6 (−6.8 to 27.9; 0.22)
Bodily pain	−6.8 (5.3)	8.4 (6.4)	−15.2 (−33.0 to 2.6; 0.090)	−7.6 (6.5)	−3.8 (6.8)	−3.8 (−23.2 to 15.7; 0.69)
General health	−0.6 (4.5)	2.9 (5.2)	−3.5 (−17.9 to 11.0; 0.63)	0.5 (3.4)	5.8 (5.4)	−5.3 (−18.5 to 7.9; 0.41)
Vitality	5.7 (5.5)	7.8 (4.4)	−2.0 (−16.3 to 12.3; 0.77)	3.4 (4.8)	−2.9 (3.4)	6.2 (−5.9 to 18.4; 0.30)
Social functioning	−3.1 (9.5)	3.3 (7.2)	−6.5 (−30.5 to 17.6; 0.59)	−12.5 (8.1)	−2.9 (6.0)	−9.6 (−30.5 to 11.3; 0.35)
Role emotional	−13.9 (5.2)*	−9.5 (9.2)	−4.4 (−27.7 to 18.8; 0.68)	−19.9 (6.6)*	−16.0 (10.4)	−3.9 (−29.3 to 21.5; 0.76)
Mental health	0.4 (6.0)	3.7 (4.2)	−3.3 (−18.0 to 11.5; 0.65)	3.5 (3.3)	−8.2 (4.6)	11.7 (0.0 to 23.4; 0.050)

Data are means (SE), or mean effect (95% CI; p value) unless otherwise indicated. SGRQ = St. George Respiratory Questionnaire; SF 36 = short-Form 36.
*p<0.05,
**p<0.01: change between pre-treatment and post-treatment within-group difference.
doi:10.1371/journal.pone.0035708.t003

improvement in 6-MWD was reduced at Week 7 (mean difference: ghrelin group within group +47 m, p = 0.017 versus placebo group +18 m, within group p = 0.14) (Table 2 and Figure 2A). To assess the time course efficacy of ghrelin versus placebo in 6-MWD, a repeated-measures ANOVA was performed. There was no significant time course effect of ghrelin versus placebo in 6-MWD (F (2, 51) = 1.10, p = 0.34).

Table 4. Adverse events.

Event	Ghrelin, n = 18	Placebo, n = 15
Patients with at least 1 adverse event	12 (67)	5 (33)
Adverse events not considered study therapy-related		
Pneumonia	1 (6)	0 (0)
Depression	1 (6)	0 (0)
Infective enteritis	1 (6)	0 (0)
Lung cancer*	1 (6)	0 (0)
Hypercalcemia	0 (0)	1 (7)
Adverse events considered study therapy-related		
Stomach rumbling	3 (17)	2 (13)
Feeling of being warm	4 (22)	0 (0)
Feeling of hunger	2 (11)	2 (13)
Thirst	2 (11)	0 (0)
Slight liver dysfunction	1 (6)	0 (0)
Hypercholesterolemia	1 (6)	0 (0)
Hypoproteinemia	1 (6)	2 (13)

Values are presented as n (% of group). * One patient developed lung cancer 2 years and 9 months after study treatment.
doi:10.1371/journal.pone.0035708.t004

In the ghrelin group, the peak $\dot{V}o_2$ and $\dot{V}o_2$/HR were significantly increased by 1.2 ml/kg/min and 0.5 ml/beats, respectively, from pre-treatment (within-group p = 0.021, p = 0.019, respectively) (Table 2). However, there was no significant difference between the two groups in the peak $\dot{V}o_2$ and $\dot{V}o_2$/HR. In the ghrelin group, the ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}o_2$) was relatively improved by −3.9 from pre-treatment (within group p = 0.060).

HRQoL and MRC Measures

In both groups, there was no significant difference in each SGRQ score and MRC score between pre-treatment and at Week 3. At Week 7, there was a significant treatment effect between the two groups in SGRQ symptoms (between-group: p = 0.026, Table 3 and Figure 3B), and in the MRC score (between-group p = 0.030, Table 2 and Figure 2B). At Week 7, in the ghrelin group, SGRQ total was decreased by 6.0 from pre-treatment (within-group p = 0.046, between-group p = 0.072) (Table 3 and Figure 3A). Furthermore, there was a significant time course effect of ghrelin versus placebo in SGRQ symptoms (repeated-measures ANOVA, F (2, 51) = 3.19, p = 0.049, Figure 3B).

Body Weight and Food Intake

In the ghrelin group, at Week 1, the relative increase in body weight was+0.42 kg (within group p = 0.092), which was reduced by Week 3 and followed by a re-increase at Week 7 (+0.8 kg, within group: p = 0.054). However there was no significant difference in body weight between the groups at each Week (Table 2). No affect on whole lean body mass from ghrelin was seen at Week 3 (Table 2). No significant increase from baseline in food intake was observed at Week 3 in both groups (Table 2).

Respiratory and Peripheral Muscle Strength

In the ghrelin group, at Week 3, the post-treatment increase in respiratory muscle strength, as indicated by MEP and MIP, was not significantly different from that in the placebo group, but at Week 7, the mean increase from pre-treatment in MEP (+15.6 cmH_2O) was significantly different from that in the placebo group (between group $p=0.015$) (Table 2). Furthermore, there was a significant time course effect of ghrelin versus placebo in MEP (repeated-measures ANOVA, $F\ (2,\ 51)=4.17$, $p=0.021$, Figure 2C).

At Week 3 and Week 7, there was no significant treatment effect between the two groups in grip strength (Table 2).

Pulmonary Function, Plasma Norepinephrine, and Other Hormone Levels

Ghrelin treatment did not significantly change any parameters of the pulmonary function tests, serum TNF-α, serum IL-6, or plasma norepinephrine at rest (Table 2).

Safety

Throughout this trial, 67% of patients in the ghrelin group and 33% of patients in the placebo group reported 12 and 5 adverse events, respectively, but there was no significant difference between the groups (Table 4). In the ghrelin group, alanine aminotransferase increased to 41 IU/L in one patient (6%), and total cholesterol increased to 270 mg/dl in one patient (6%); both increases disappeared at Week 7. Two patients randomized to ghrelin discontinued as a result of adverse events: one because of bacterial pneumonia, and one because of depression, both of which were not considered related to ghrelin treatment. One patient randomized to ghrelin developed lung cancer 2 years and 9 months after the end of ghrelin administration, but this was judged by the efficacy and safety committee as not causally related to ghrelin treatment, considering the period of disease development and the incidence rate of lung cancer [19].

Discussion

The present study is the first multicenter, randomized, double-blind, placebo-controlled study to assess the effect and safety of repeated ghrelin administration to very severe cachectic patients with COPD. The main results of this study can be summarized as follows. In the ghrelin group, single administration of ghrelin was accompanied by a significant increase in serum GH levels during 3-week treatment, and there was no significant difference in 6-MWD between ghrelin and placebo at Week 3 and at Week 7. With ghrelin, symptomatic improvements in SGRQ symptoms and MRC score were not obtained at Week 3, but significant differences between ghrelin and placebo were seen at Week 7. In the ghrelin group, no significant within-group improvement from pre-treatment was seen in respiratory muscle strength, as indicated by MEP and MIP, at Week 3, but there was a significant difference in MEP between ghrelin and placebo at Week 7. Repeated-measures ANOVA showed significant time course effects of ghrelin versus placebo in SGRQ symptoms and MEP. Finally, ghrelin treatment was well tolerated.

Ghrelin treatment may have beneficial, continuing effects after treatment on HRQoL and MRC measures in this population. Though this study was conducted to determine the effectiveness of ghrelin in cachectic COPD patients, considering a synergistic interaction between ghrelin and PR, the data of this study need to be interpreted with caution, because, especially in advanced stage patients, excessive exercise training may partially worsen the anabolic and catabolic balance [1,20]. In the present study, which included patients with a lower exercise capacity and pulmonary function than those in the pilot study [13] and more cachectic patients than those in other studies on PR [21], the 6-MWD after 3-week PR in the placebo group was decreased in 3 (20%) of the 15 patients. Since 5 patients (33%) in the placebo group found the initial training work rate intolerable, the initial training work rate remained at its initial setting. In addition, at Week 3, outcome measurements showed no improvements with ghrelin compared with placebo. These findings may represent patients' variable responses to PR, which might have an influence on the effects of ghrelin. Of note, however, there were significant treatment effects of ghrelin in both SGRQ symptoms and MRC score. In addition, the treatment tended to improve the total SGRQ score by more than 4 points; a clinically meaningful improvement. These effects were not observed soon after the 3 week-treatment, but were seen 4 weeks after treatment, maintaining the improvement obtained in 6-MWD at Week 3. Similarly, 4 weeks after treatment, the effect of ghrelin on respiratory muscle strength was confirmed, though it has been reported that GH alone does not increase strength in healthy elderly [22,23,24]. Furthermore, repeated-measures ANOVA indicated significant time course effects of ghrelin versus placebo in SGRQ symptoms and MEP. Our data suggest that improving of the respiratory muscle strength, the O_2 pulse, and the ventilatory equivalents for oxygen may serve as a mechanism by which ghrelin-PR combination treatment improved symptoms, though further examination is needed to understand the precise mechanism. These findings suggest that repeated ghrelin administration may have beneficial, sustained effects after administration on symptoms through GH-dependent and/or -independent mechanisms.

Cachectic elderly patients with COPD who were given intravenous ghrelin showed a continuous increase of pulsatile GH secretion in the present study. There is evidence that insufficiency of sarcopenia-related hormones, such as GH and IGF-1, may contribute to cachexia [25,26]. Observational studies in cachectic COPD patients have found decreased levels of these hormones [27,28]. In the present study, despite significant increases in GH secretion levels throughout the 3-week treatment and respiratory muscle strength, ghrelin provided only a significant within-group increase in exercise performance, and a relative within-group increase in IGF-1 levels and body weight. Furthermore, ghrelin did not affect food intake, grip strength or plasma norepinephrine levels at rest in the present study. Although DEXA should be performed a greater number of times during the trial, at Week 3 ghrelin did not show any effects on whole lean body mass. Meanwhile, previous studies showed that ghrelin administration induced a positive energy balance and weight gain [8], increased food intake [9,13], and decreased sympathetic nervous activity [10,11,13]. The discrepancy may be explained by the fact that the intensity of exercise training for some cachectic participants counteracted the effects of ghrelin, though lower extremity exercise training at higher intensity produces greater benefits than lower intensity training [4]. As one of the reasons, the patients treated with both ghrelin and exercise training gained at Week 1, which was not seen in the placebo group. However, this weight gain reduced by Week 3. At Week 7, the weight was regained (Table 2). The days of attending PR in the ghrelin group was negatively correlated with the increase in body weight from Week 3 to Week 7 ($r=-0.710$, $p=0.003$). We speculate that the unintended excessive exercise permitted by ghrelin administration with antidepressant-like effects [29] might prevent the obtained results. Nevertheless, these findings suggest that clinical interventions with ghrelin may help cachectic COPD patients via inhibiting somatopause and regulating metabolic balance.

The participants in the present study tolerated daily administration of ghrelin for 3 weeks (Table 4); the most frequent ghrelin-related side effects were mild and similar to those of previous reports [13,30,31], as well as with those of GH administration by injection [22]. However, given that the previous studies of the responses of ghrelin in proliferation, including tumor development, have demonstrated conflicting findings [32,33,34,35], more studies of the safety of ghrelin treatment are necessary before clinical application.

This study had some limitations. First, the number of participants was small, and few females were included in this trial. Second, the duration of the study was short. A more effective exercise training program, considering its intensity and frequencies, should have been conducted. Additional studies are needed to evaluate a more suitable regimen of ghrelin-PR.

In conclusion, ghrelin administration provided sustained improvements in symptoms and respiratory strength in cachectic COPD patients. Development of ghrelin administration methods may offer potential advantages over the currently approved treatment options for COPD. The lack of a significant between-group difference in exercise tolerance may result from the exercise training program conducted as the combination therapy. Careful examination is needed to develop more effective administration methods of ghrelin and combination therapy with ghrelin.

Supporting Information

Methods S1
(DOC)

Protocol S1
(DOC)

Checklist S1
(DOC)

Acknowledgments

The authors are particularly grateful to the patients who agreed to participate. The authors would also like to thank Dr. **Yoshihiro Onishi** (Institute for Health Outcomes and Process Evaluation Research, Japan) for his help in calculating sample size, Mr. **Kazunori Tsuguchi** (Nihon Ultmarc Inc. Japan) for performing the statistical analysis, and other members of Ghrelin Study Group as follows:

Junichi Ashitani, (Faculty of Medicine, University of Miyazaki, Department of Neurology, Respirology, Endocrinology and Metabolism, Internal Medicine); **Atsuhiko Fukuoka**, (Nara Medical University, Second Department of Internal Medicine); **Yukio Fujita** (Nara Medical University, Second Department of Internal Medicine);**Yoshifumi Yamamoto**, (Nara Medical University, Second Department of Internal Medicine); **Hisako Hashimoto**, (National Hospital Organization (NHO), Toneyama National Hospital, Department of Internal Medicine); **Motone Masaharu** (NHO, Toneyama National Hospital, Department of Internal Medicine); **Norifumi Nakanishi**, (National Cerebral and Cardiovascular Center (NCVC), Department of Cardiovascular Medicine); **Hideo Oya**, (NCVC, Department of Cardiovascular Medicine); **Kohichi Tanaka**, (NCVC, Research Institute, Department of Regenerative Medicine & Tissue Engineering); **Hiroaki Naito**, (NCVC, Department of Radiology and Nuclear Medicine); **Sakashita Yoshiharu** (NCVC, Department of Radiology and Nuclear Medicine); **Takeshi Kotake**, (NCVC, Department of Pharmacy); **Hideki Morishita**, (NCVC, Department of Pharmacy); **Mitsuyoshi Nakashima**, (Hamamatsu University School of Medicine); **Hitonobu Tomoike**, (NCVC); **Kentaro Kimura**, (NHO Kinki-Chuo Chest Medical Center, Clinical Research Center); **Naotsugu Kurihara**, (Ikuwakai Memorial Hospital, Department of Respiratory Medicine); **Yukio Nagasaka**, (Sakai Hospital Kinki University Faculty of Medicine, Department of Respiratory Medicine); **Hisayuki Matsuo**, (NCVC, Research Institute).

Author Contributions

Conceived and designed the experiments: NN KK MN HK RM MY KM SM SO NM K. Yamahara. Performed the experiments: RM KM HK MN NN TH MM SK K. Yoshimura YT MY SM YA NM SO. Analyzed the data: KM RM HK MN NN TH MM SK K. Yoshimura YT MY SM YA NM SO K. Yamahara KK. Wrote the paper: KM.

References

1. Wagner PD (2008) Possible mechanisms underlying the development of cachexia in COPD. Eur Respir J 31: 492–501.
2. Wilson DO, Rogers RM, Wright EC, Anthonisen NR (1989) Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis 139: 1435–1438.
3. Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting JW (1997) Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. Am J Respir Crit Care Med 156: 1800–1806.
4. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, et al. (2007) Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest 131: 4S–42S.
5. Zinna EM, Yarasheski KE (2003) Exercise treatment to counteract protein wasting of chronic diseases. Curr Opin Clin Nutr Metab Care 6: 87–93.
6. Zaloga GP (2005) Ghrelin, diet, and pulmonary function. Chest 128: 1084–1086.
7. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, et al. (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402: 656–660.
8. Tschop M, Smiley DL, Heiman ML (2000) Ghrelin induces adiposity in rodents. Nature 407: 908–913.
9. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, et al. (2001) A role for ghrelin in the central regulation of feeding. Nature 409: 194–198.
10. Matsumura K, Tsuchihashi T, Fujii K, Abe I, Iida M (2002) Central ghrelin modulates sympathetic activity in conscious rabbits. Hypertension 40: 694–699.
11. Nagaya N, Kojima M, Uematsu M, Yamagishi M, Hosoda H, et al. (2001) Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. Am J Physiol Regul Integr Comp Physiol 280: R1483–1487.
12. Itoh T, Nagaya N, Yoshikawa M, Fukuoka A, Takenaka H, et al. (2004) Elevated plasma ghrelin level in underweight patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170: 879–882.
13. Nagaya N, Itoh T, Murakami S, Oya H, Uematsu M, et al. (2005) Treatment of cachexia with ghrelin in patients with COPD. Chest 128: 1187–1193.
14. Jones PW, Quirk FH, Baveystock CM, Littlejohns P (1992) A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 145: 1321–1327.
15. Ware JE, Jr., Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30: 473–483.
16. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K (1998) Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol 51: 1037–1044.
17. Fukuhara S, Ware JE, Jr., Kosinski M, Wada S, Gandek B (1998) Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. J Clin Epidemiol 51: 1045–1053.
18. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH (1959) The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 2: 257–266.
19. Calverley PM, Spencer S, Willits L, Burge PS, Jones PW (2003) Withdrawal from treatment as an outcome in the ISOLDE study of COPD. Chest 124: 1350–1356.
20. Rabinovich RA, Ardite E, Mayer AM, Polo MF, Vilaro J, et al. (2006) Training depletes muscle glutathione in patients with chronic obstructive pulmonary disease and low body mass index. Respiration 73: 757–761.
21. Puhan MA, Schunemann HJ, Frey M, Scharplatz M, Bachmann LM (2005) How should COPD patients exercise during respiratory rehabilitation? Comparison of exercise modalities and intensities to treat skeletal muscle dysfunction. Thorax 60: 367–375.
22. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, et al. (2007) Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 146: 104–115.
23. Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GA, et al. (1996) Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann Intern Med 124: 708–716.
24. Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, et al. (2002) Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA 288: 2282–2292.

25. Anawalt BD, Merriam GR (2001) Neuroendocrine aging in men. Andropause and somatopause. Endocrinol Metab Clin North Am 30: 647–669.
26. Lamberts SW, van den Beld AW, van der Lely AJ (1997) The endocrinology of aging. Science 278: 419–424.
27. Creutzberg EC, Wouters EF, Mostert R, Pluymers RJ, Schols AM (2003) A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest 124: 1733–1742.
28. Koehler F, Doehner W, Hoernig S, Witt C, Anker SD, et al. (2007) Anorexia in chronic obstructive pulmonary disease–association to cachexia and hormonal derangement. Int J Cardiol 119: 83–89.
29. Lutter M, Elmquist J (2009) Depression and metabolism: linking changes in leptin and ghrelin to mood. F1000 Biol Rep 1.
30. Akamizu T, Takaya K, Irako T, Hosoda H, Teramukai S, et al. (2004) Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. Eur J Endocrinol 150: 447–455.
31. Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, et al. (2004) Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation 110: 3674–3679.
32. Cassoni P, Allia E, Marrocco T, Ghe C, Ghigo E, et al. (2006) Ghrelin and cortistatin in lung cancer: expression of peptides and related receptors in human primary tumors and in vitro effect on the H345 small cell carcinoma cell line. J Endocrinol Invest 29: 781–790.
33. Belloni AS, Macchi C, Rebuffat P, Conconi MT, Malendowicz LK, et al. (2004) Effect of ghrelin on the apoptotic deletion rate of different types of cells cultured in vitro. Int J Mol Med 14: 165–167.
34. Ghe C, Cassoni P, Catapano F, Marrocco T, Deghenghi R, et al. (2002) The antiproliferative effect of synthetic peptidyl GH secretagogues in human CALU-1 lung carcinoma cells. Endocrinology 143: 484–491.
35. Murata M, Okimura Y, Iida K, Matsumoto M, Sowa H, et al. (2002) Ghrelin modulates the downstream molecules of insulin signaling in hepatoma cells. J Biol Chem 277: 5667–5674.

Sleep Breath
DOI 10.1007/s11325-012-0775-2

ORIGINAL ARTICLE

Breathing irregularity during wakefulness associates with CPAP acceptance in sleep apnea

Motoo Yamauchi · Frank J. Jacono · Yukio Fujita · Masanori Yoshikawa · Yoshinobu Ohnishi · Hiroshi Nakano · Cara K. Campanaro · Kenneth A. Loparo · Kingman P. Strohl · Hiroshi Kimura

Received: 12 March 2012 / Revised: 29 August 2012 / Accepted: 8 October 2012

Abstract
Purpose Individuals have different breathing patterns at rest, during wakefulness, and during sleep, and patients with sleep apnea are no different. The hypothesis for this study was that breathing irregularity during wakefulness associates with CPAP acceptance in obstructive sleep apnea (OSA).
Methods From a 2007–2010-database of patients with a diagnostic polysomnography (PSG) and prescribed CPAP (n=380), retrospectively, 66 patients who quit CPAP treatment at 6 months were identified. Among them, 27 OSA patients quit despite having no side effects for discontinuing CPAP (Group A) and were compared to a matched group (age, body mass index, and apnea–hypopnea index) with good 6-month CPAP adherence (Group B; n=21). Five minutes of respiratory signal during wakefulness at the initial PSG were extracted from respiratory inductance plethysmography recordings, and measured in a blinded fashion. The coefficients of variation (CV) for the breath-to-breath inspiration time (T_i), expiration time (T_e), T_i+T_e (T_{tot}), and relative tidal volume, as well as an independent information theory-based metric of signal pattern variability (mutual information) were compared between groups.

M. Yamauchi (✉) · Y. Fujita · M. Yoshikawa · H. Kimura
Second Department of Internal Medicine (Department of Respiratory Medicine), Nara Medical University,
840 Shijo-cho, Kashihara,
Nara 634-8522, Japan
e-mail: mountain@pastel.ocn.ne.jp

Y. Fujita
e-mail: yukio08090314@dune.ocn.ne.jp

M. Yoshikawa
e-mail: noriy@naramed-u.ac.jp

H. Kimura
e-mail: kimura@nmu-gw.naramed-u.ac.jp

F. J. Jacono · C. K. Campanaro · K. P. Strohl
Division of Pulmonary, Critical Care and Sleep Medicine,
Case Western Reserve University,
Cleveland, OH, USA

F. J. Jacono
e-mail: frankjacono@gmail.com

C. K. Campanaro
e-mail: cara.campanaro@case.edu

K. P. Strohl
e-mail: kpstrohl@aol.com

F. J. Jacono · C. K. Campanaro · K. P. Strohl
Louis Stokes Cleveland VA Medical Center,
Cleveland, OH, USA

Y. Ohnishi
Department of Internal Medicine, Tenri City Hospital,
Tenri, Japan
e-mail: 194kousuke@ares.eonet.ne.jp

H. Nakano
Department of Pulmonology, Fukuoka National Hospital,
Fukuoka, Japan
e-mail: nakano_h@palette.plala.or.jp

K. A. Loparo
Department of Electrical Engineering and Computer Science,
Case Western Reserve University,
Cleveland, OH, USA
e-mail: kenneth.loparo@case.edu

Published online: 19 October 2012

Results The CV for tidal volume was significantly greater (p=0.001), and mutual information was significantly lower (p=0.041) in Group A as compared to Group B.
Conclusions Differences in two independent measures of breathing irregularity correlated with CPAP rejection in OSA patients without nasal symptoms or comorbidity. Prospective studies of adherence should examine traits of breathing stability.

Keywords Obstructive sleep apnea · CPAP adherence · Respiratory control · Nonlinear analysis

Introduction

Individuals breathe in different ways under strictly defined conditions during quiet wakefulness. There are also significant effects of different cognitive events such as thought, attention, and emotion on the basic breathing pattern, presumably through forebrain influences. Although forebrain activity is depressed during slow-wave sleep (non-REM), breathing individuality persists [1]. Moreover, identical twins breathe with a similar pattern [2, 3]. Thus, genetic background affects breathing pattern, and accounts for variation across individuals.

Breathing variability is measured not only through physiologic extractions of respiratory frequency and tidal volume but also using analyses of the breathing signal unrelated to the physiologic extractions. The latter includes methods such as sample entropy and mutual information that deconstruct the signal, and disclose features and patterns that reveal structural underpinnings and complexity. Such complexity occurs in expression of and differs among apnea types [4]. Previously, we reported a difference in an information theory-based metric of signal pattern variability (sample entropy) among patients with obstructive sleep apnea syndrome (OSAS) comparing those with many mixed apneas (>30 % of events being mixed apneas) to those with predominant obstructive apnea. Secondary observations in this data set suggested that breathing variability during wakefulness could be a predictor of acceptance of CPAP as a therapy [5]. While studies indicate that age, sex, severity of disease, symptoms of sleepiness, socioeconomic status, nasal symptoms, and psychological factors relate to CPAP adherence in OSAS [6–15], none have considered an individual's inherent features of respiratory control as quantified in terms of measures of variability.

Using a case–control design, we tested the hypothesis that the regularity of resting breathing during wakefulness might be a predictive feature of subsequent CPAP acceptance. Patients with nasal symptoms and comorbidity known to affect adherence were excluded, and our analysis focused on the breathing pattern during wakefulness prior to the diagnostic polysomnography (PSG). Ventilatory pattern variability was quantified using conventional (linear) statistical analysis (coefficient of variation (CV)) of breath-to-breath tidal volume and frequency from noninvasive measures, as well as an information-based analysis of the respiratory signal using mutual information, an approach that uses the raw respiratory waveform data that does not depend on either breath depth or frequency identification.

Methods

Subjects

There was an initial exclusion of patients with an apnea–hypopnea index (AHI) <20 who had medical history of arrhythmia, cerebral infarction, and psychosomatic/psychogenic diseases or who used opioid, hypnotic medications, or antidepressant; all of which might have an influence on breathing irregularity. Figure 1 shows the ascertainment profile of the study that resulted in the final comparison

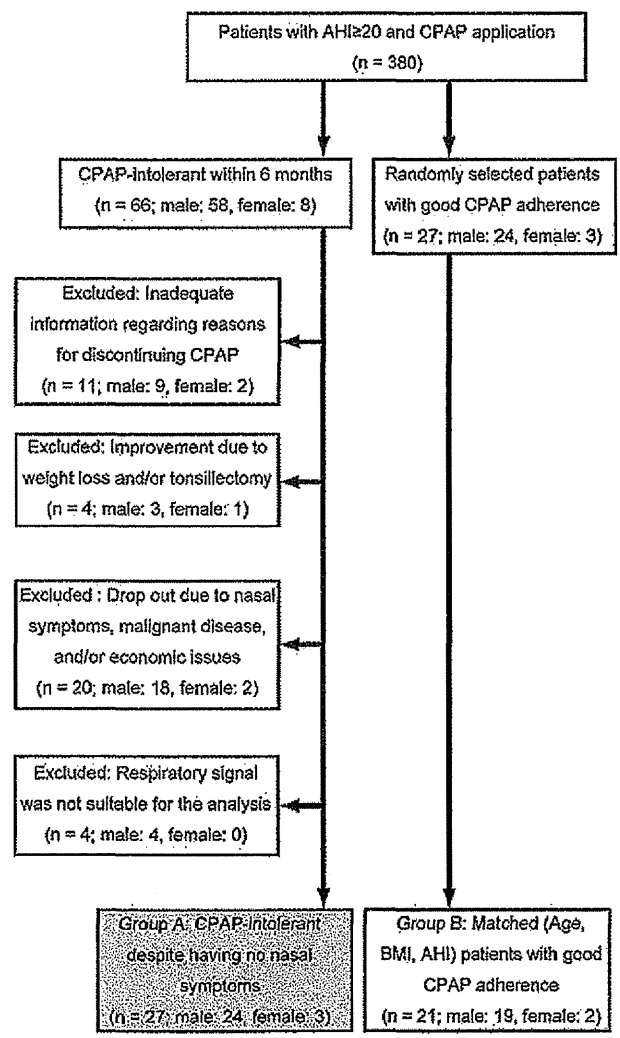

Fig. 1 Diagram for the comparison groups enrollment

groups. Among 380 patients with obstructive sleep apnea (OSA) who had a diagnostic PSG and then who were prescribed CPAP from 2007 to 2010, 66 patients quit CPAP treatment at 6 months. Among these 66 patients, 11 patients were excluded from further analysis due to loss of the information regarding reasons for CPAP dropout, 4 patients quit CPAP because sleep disordered breathing was improved by weight loss and/or tonsillectomy, 20 patients were CPAP-intolerant because of nasal symptoms, malignant diseases, and/or economic issues, and 4 patients were excluded as an adequate respiratory signal could not be obtained during wakefulness. Eventually, 27 patients were enrolled to this study analysis (Group A). We also randomly extracted 27 patients with good CPAP adherence from the same database. Fairly good adherence to CPAP was defined at a high threshold, i.e., more than 90 % of days with more than 5 h usage each night. A final group of 21 patients that were matched for age, body mass index (BMI), and AHI within the mean and standard deviation values for Group A were designated as Group B. Data were collected on the Epworth sleepiness scale (ESS) and current medications. Written informed consent was obtained from all patients, and the Human Subjects Ethics Committee of Nara Medical University approved the study.

Diagnostic PSG

Data acquisition started from 9 p.m. and continued until 6 a.m. on the following morning. Subjects were not informed that the respiratory signal before sleep onset was extracted and used for analysis. When sensors were applied and data acquisition could be initiated, subjects were instructed to close their eyes and the recording started.

The PSG was performed using a polygraph system (EEG7414; Nihon Kohden, Tokyo, Japan). electroencephalogram (EEG; C3-A2, C4-A1), bilateral EOG, submental electromyogram (EMG), ECG, and bilateral anterior tibial EMG were recorded. Airflow was monitored using an oronasal thermal sensor and/or nasal air pressure transducer. Thoracic and abdominal respiratory movements were monitored using respiratory inductance plethysmography (RIP) (Respitrace; Ambulatory Monitoring Inc., Ardsley, NY, USA). Oxyhemoglobin saturation and pulse rate were monitored using pulse oximetry with a finger probe (OLV-3100; Nihon Kohden, Tokyo, Japan). All the signals were digitized and stored on a personal computer. Apneas were defined as an episode of complete airflow cessation measured from the thermal sensor lasting more than 10 s. Hypopnea was defined by≥30 % reduction in amplitude of the RIP-sum signal lasting more than 10 s with≥3 % oxygen desaturation. AHI was calculated as the average number of apnea–hypopnea events per hour over the total sleep period.

CPAP

All patients were initiated on nasal CPAP (REMstar Auto; Respironics; Pittsburgh, PA, USA or GoodKnight 420E; Tyco Mallinckrodt Plaisir, France) with auto titrating mode. All patients under CPAP treatment visited our sleep laboratory every month, which is mandatory in the Japanese healthcare insurance system, and CPAP adherence was monitored every month using data extracted from the memory of the CPAP equipment. If necessary, CPAP settings including pressure range or CPAP mode (auto or fixed mode) were modified by an expert physician at the monthly visit to our laboratory. Eventually, most of the patients used CPAP with auto titrating mode during the follow up period.

Analysis of the respiratory signal

An investigator blinded to the groups chose approximately 5 min of artifact-free respiratory signal data before sleep onset, without a change in body position and scored as wakefulness, from the diagnostic polysomnography. Respiratory signals were generated by the sum of chest and abdominal signals using RIP. The sum was not calibrated to volume but adjusted to have a similar tidal displacement among subjects. The respiratory signal was identified, and the EMG (chin and limb) signal was used to detect body movements. When the amplitude of the EMG signal was high, that part of the respiratory signal was considered to be during movement and inappropriate for analysis. The part of respiratory signal in which eye movements without alpha rhythm in epochs not scored as sleep was also excluded from analysis. In the analytic phase of the study, investigators were also blinded to the group assignment, and each 5-min record of the respiratory signal during EEG-staged periods of wakefulness was analyzed for breath-to-breath inspiration time (T_i), expiration time (T_e), T_i+T_e (T_{tot}), and relative tidal volume. To avoid the fluctuation of breathing due to drowsiness, we extracted 5 min of respiratory signal if EEG were considered to be fully awake for each epoch (30 s) over a 5-min period. To assess breathing irregularity, the CV ([standard deviation / mean]×100) for each parameter was calculated.

To further quantify breathing pattern variability, the mutual information of the raw respiratory signal (RIP-sum signals) sampled at 10 Hz was quantified. Mutual information is a measure of statistical dependence in a data set [16, 17]. This information theory-based metric reflects the decrease in uncertainty associated with a time-shifted data point $x(t+\tau)$ that results from knowledge of the coordinate $x(t)$. Mutual information (measured in bits) was computed as described previously [18, 19], and additional details are provided in an appendix. Due to the periodic nature of the respiratory pattern, mutual information was calculated over

multiple time delays (τ's) from unity to one cycle length. Values were averaged across time lags excluding those with high linear correlations as defined by the first minimum of the mutual information function. Average mutual information (excluding small lags) was reported for each group. In practice, higher values of mutual information suggest increased statistical dependence (decreased variability and greater predictability) in the signal, while lower mutual information is associated with more variable (less predictable) patterns [20].

Statistical analysis

Comparison of continuous variables between the groups was done by the unpaired t test, and categorical variables were compared by the chi-squared test. Differences with $p<0.05$ were considered significant. All results were expressed as means±standard deviation (SD). Statistical analysis was done with IBM SPSS Statistics 19 for Windows software (SPSS Inc., Chicago, IL).

Results

Subject characteristics

Table 1 shows subject characteristics for each group. There were no significant differences in ESS and the use of medications for hypertension, hyperlipidemia, and diabetes mellitus between groups. In Group A, the main reasons for poor CPAP acceptance were an uncomfortable feeling with CPAP or a sensation of it being hard to breathe and fall asleep. Some reported removing CPAP without awareness during sleep. Also, those who refused or could not tolerate CPAP treatment generally felt no significant improvement in presenting symptoms such as excessive daytime sleepiness, morning headache, and sleep quality. Regarding the 39 patients with poor CPAP acceptance excluded from the analysis, the AHI, age, and ESS were similar to 27 patients that were analyzed in Group A (data not shown).

Table 1 Subject characteristics

	Group A (n=27)	Group B (n=21)	p value
Age, year	51.6±10.1	51.3±10.0	N.S.
Sex, (male/female)	24/3	19/2	N.S.
AHI, /h	46.4±18.3	53.6±23.7	N.S.
ESS	10.4±5.7	11.4±6.0	N.S.
BMI, kg/m^2	25.2±3.2	26.8±2.4	N.S.
Hypertension	6/27 (22.2 %)	8/21 (38.1 %)	N.S.
Dyslipidemia	4/27 (14.8 %)	4/21 (19.0 %)	N.S.
Diabetes mellitus	3/27 (11.1 %)	0/21 (0.0 %)	N.S.

Data are shown as mean±SD or no. (%). Group A are the patients who dropped out of CPAP therapy; Group B are the patients with good CPAP adherence

AHI apnea–hypopnea index, *ESS* Epworth sleepiness scale, *BMI* body mass index, *N.S.* not significant

Breathing irregularity during rest before sleep onset

Figure 2 shows examples of RIP-sum signals during wakefulness for two subjects with poor CPAP acceptance (Group A) and two subjects with good CPAP adherence (Group B). These tracings highlight the more irregular breathing pattern, especially in amplitude rather than respiratory frequency, prior to sleep onset in Group A as compared to Group B. Although the CV values for T_i were significantly higher in Group A (22.6±10.2 vs. 15.9±7.8 %; $p<0.05$), the CV values for T_e and T_{tot} were similar between groups (T_e, 24.0±11.3 vs. 19.5±8.5 %; T_{tot}, 18.7±8.9 vs. 15.2±6.7 %, $p>0.05$). The CV values for tidal volume in Group A were significantly greater than in Group B (30.7±7.8 vs. 22.1±9.0 %; $p<0.01$) (Fig. 3). The independent analyses of the respiratory waveform also identified differences in breathing pattern. The mutual information was significantly lower in Group A as compared to Group B (0.94±0.16 vs. 1.16±0.52 bits, respectively, $p<0.05$) (Fig. 4). Mutual information is a measure of statistical dependence between points, so the lower value in Group A suggests a greater variability of the breathing pattern during wakefulness in subjects with poor CPAP acceptance. There were no correlations between severity of OSA (AHI) and parameters for breathing irregularity including CVs and the mutual information (data not shown).

Discussion

The present study supports the hypothesis of an association of breathing irregularity during wakefulness prior to the diagnostic sleep study, as quantified by two independent measures, to CPAP adherence. We observed that breathing irregularity is greater in the patients with OSA who could not tolerate CPAP therapy than in age-, AHI-, and BMI-matched patients with good CPAP adherence. While highly selected for the absence of nasal symptoms and confounding medical conditions, these findings suggest that during wakefulness, a pattern of individual resting breathing irregularity could be a predictive marker for CPAP acceptance.

Breathing irregularity during wakefulness is associated with genetic diseases such as RETT syndrome [21, 22], with certain environments such as high altitude [23, 24], with treatment with opioid medications [25, 26], and with medical conditions including heart failure [27–29] and cerebral infarction [30, 31]. These phenomena reflect particular features of the respiratory control system that involve respiratory rhythm generation and/or central and peripheral

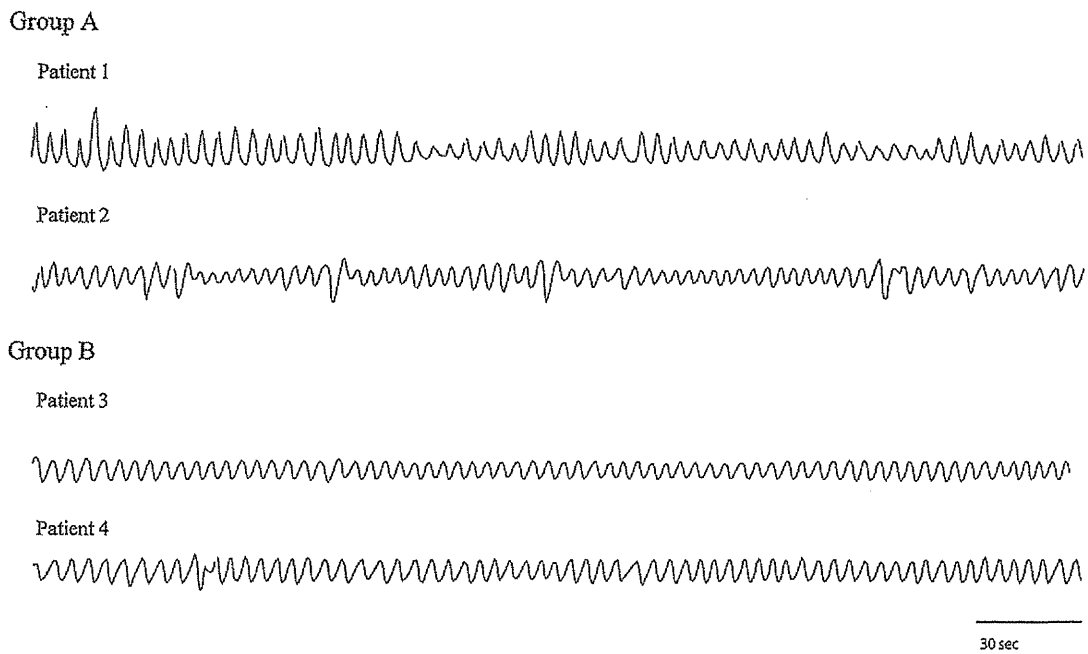

Fig. 2 Examples of RIP-sum tracings before sleep onset. Tracings of each two patients from Group A and B were presented, showing the breath-to-breath greater irregularity in tidal volume rather than respiratory frequency in Group A. *Group A* is composed of the patients who dropped out of CPAP therapy. *Group B* is composed of the patients with good CPAP adherence

chemoreception. Breathing "stability" or "instability" is operationally defined from the output of the respiratory controller. We previously reported that breathing behavior during wakefulness even in room air and in the phase of post acute hypoxic exposure as well were different between mouse strains [32–35], thus we think that the patterning of breaths over time (periodic, chaotic, etc.) around eupnea is an important feature to begin to define not only operationally but mechanistically. In a previous study, findings suggested that the central respiratory control system in mixed apnea dominant OSAS is different from obstructive apnea dominant OSAS and closer to patterning in central apnea syndrome [5]. These results taken together with the present study indicate that patients with OSA who cannot tolerate CPAP and showed irregular breathing may have somewhat of a different respiratory control system from patients with good adherence to CPAP.

An interaction of respiratory output with the upper airway and diaphragm may determine the expression of apnea types, such as central and obstructive [4]. The relative proportion of these components would depend on individual factors, which may be genetic or secondary to a medical condition. We speculate that patients with poor CPAP acceptance may have a relatively high central gain rather than peripheral chemoreceptor component as compared to patients with good adherence to CPAP, and this difference may be reflected by the breath-to-breath variability in tidal volume. Previously, we had compared mixed apnea predominant to obstructive apnea dominant, and in that comparison, the differences were in the variability in respiratory frequency and, to a lesser extent, tidal volume [5]. In the present study, we focused on obstructive apnea dominant patients; and, while variability was different in tidal volume, breath-by-breath variability in respiratory frequency was similar between groups. In both studies, however, analysis of the raw signal provided insight in the direction of difference, being lower in groups will less adherence.

Although the augmented breath, sigh, is considered an important component of normal breathing [36], Baldwin et al. concluded that sighs indicate maturity and functional integrity of the neurorespiratory feedback control and proposed sighs as being important for the regulation and resetting of the neurorespiratory controller [37]. Moreover, in general, sigh could occur both during stress and negative emotions, such as panic and pain, and during positive emotions, such as relaxation and relief [38–40]. In the current study, we did not exclude sighs from the 5-min segment of respiratory data. The number of sighs might affect the CV values for tidal volume. Thus, sigh was not discarded in the analysis, because it could contribute to greater tidal volume variability and poor CPAP acceptance. This is supported by previous reports that psychological factors may relate to adherence to CPAP [15]. Therefore, differences in the respiratory control system such as a high central component or an intrinsic psychological status can explain our results; however, exploring the exact mechanism for this variability

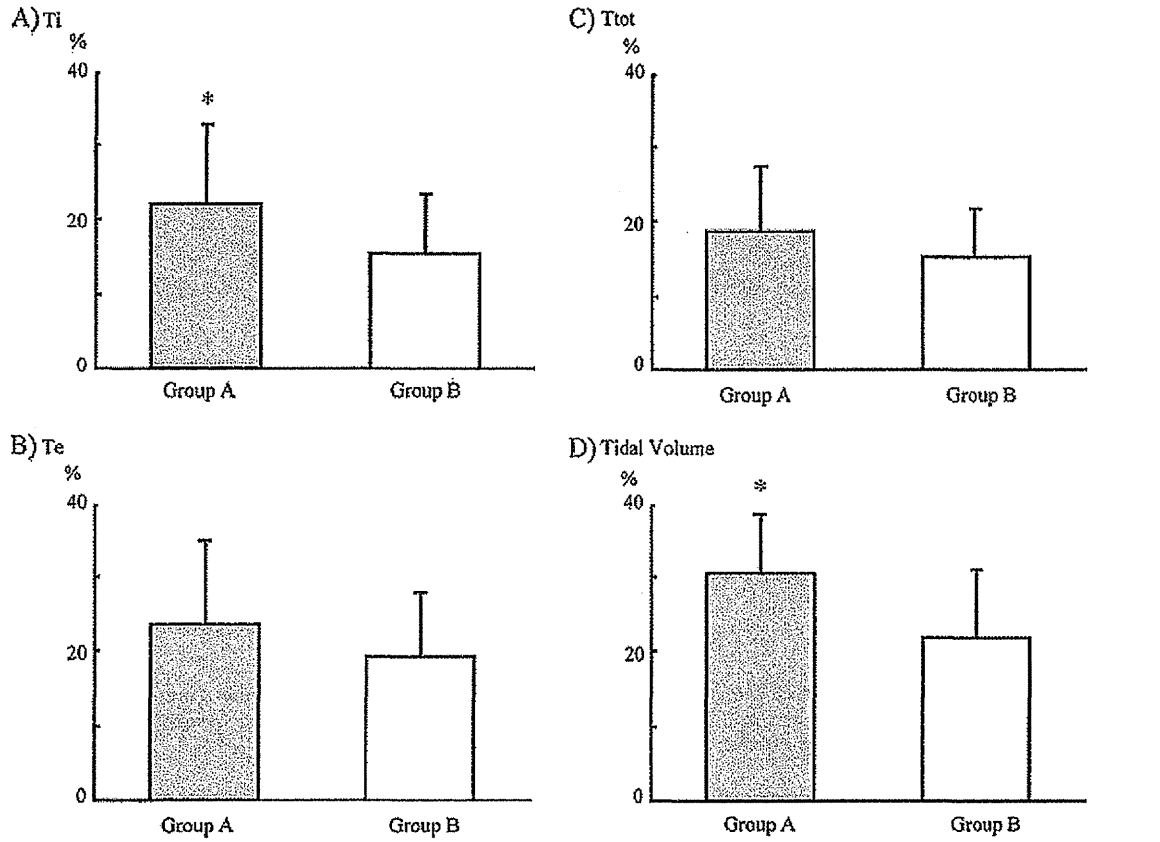

Fig. 3 Coefficients of variation for breath-to-breath respiratory variables during resting breathing before sleep onset. Values are mean±SD. **a** *Ti*, inspiration time; **b** *Te*, expiration time; **c** T_{tot}, T_i+T_e, **d** Tidal volume. *Group A* is composed of the patients who dropped out of CPAP therapy. *Group B* is composed of the patients with good CPAP adherence. The *asterisk* indicates significant difference between groups

is beyond the scope of this study. In addition, it has been recently demonstrated that arousability is one of the physiological traits that contribute to the pathogenesis of OSA [41]. Arousal due to positive airway pressure and/or CPAP discomfort may worsen CPAP adherence, thus the difference in individual arousal threshold may have contributed to our results, but further study would be needed to elucidate this issue.

A strength of the study was an ability to select a sufficient number of patients to match highly successful CPAP users to an extremely intolerant group and in both excluding known factors (stroke, opioid use, etc.) that might confound the comparisons. There are limitations in the present work. First, we cannot exclude a possible effect of hypocapnia in the poor CPAP acceptance group; however, if this were the case, then the differences between the groups would be based on a respiratory control factor such as hypercapnic responsiveness and/or apneic threshold of carbon dioxide. Second, although the statistics reveal that the CV values for tidal volume in the patients with OSAS who can not tolerate CPAP were significantly higher than in patients with good adherence, the average difference in CV values between the groups was less than 10; however, the fact that the independent measure of mutual

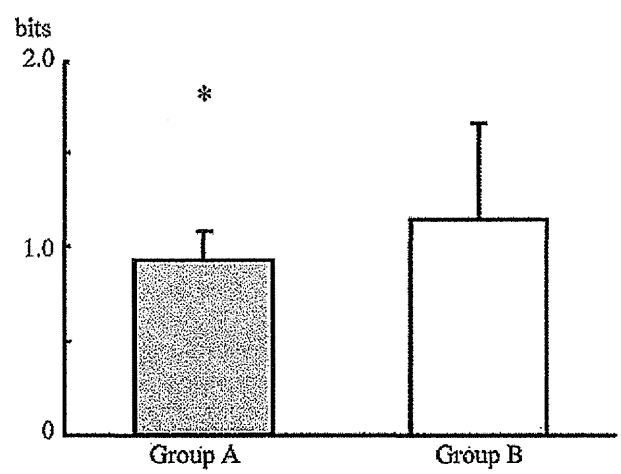

Fig. 4 The mutual information of the raw respiratory signal (RIP-sum signals). The mutual information was significantly lower in Group A as compared to Group B, suggesting a greater variability of the breathing pattern in Group A. *Group A* is composed of the patients who dropped out of CPAP therapy. *Group B* is composed of the patients with good CPAP adherence. The *asterisk* indicates significant difference between groups

information also showed such differences suggests that even small absolute differences could be important to consider. Third, although we successfully demonstrated a significant association between breathing irregularity during wakefulness and CPAP acceptance, this was a retrospective study. Thus, a prospective study will be needed to confirm that breathing irregularity predicts CPAP adherence. Lastly, the prescription of different commercial-based CPAP devices might be a confounding factor for CPAP adherence, but dropout rate was not different between these CPAP devises users.

In summary, we conclude that irregular breathing in terms of respiratory amplitude and temporal variability of the breathing signal during wakefulness may affect CPAP acceptance. This suggests that there are distinct features of respiratory control in patients who accept CPAP or cannot tolerate CPAP.

Acknowledgments The authors would like to thank Kaoru Senzaki, RPSGT, for her help with polysomnogram scoring. This study is partly supported by a Grant-in-Aid for Young Scientists (B) (21790781) from The Ministry of Education, Culture, Sports, Science and Technology, Japan. US investigators were supported in part by the NIH-NHLBI [R33HL087340-01], and the VA Research Service.

Conflicts of interest None of the authors have financial conflicts of interest to declare as it relates to the contents of this manuscript.

Appendix

Mutual Information: Mutual information (MI) is a measure of the statistical dependence between two time series, or two collections of points from a data set, that can arise from both linear and nonlinear sources [42]. The Mutual information between a given time series $x(t)$ and its time-shifted version $x(t+\tau)$ is computed from the joint probability distribution of $x(t)$ and $x(t+\tau)$, where τ represents a time lag. The joint probability distribution is defined as $P[x(t), x(t+\tau)]$, where $P[x(t)]$ and $P[x(t+\tau)]$ are the marginal distributions of the original and time-shifted time series, respectively. The MI can be computed as follows:

$$MI[x(t), x(t+\tau)] = \sum_i \sum_j P[x_i(t), x_j(t+\tau)] \log \left[\frac{P[x_i(t), x_j(t+\tau)]}{P[x_i(t)] \cdot P[x_j(t+\tau)]} \right]$$

Because the breathing pattern over long time periods is strongly periodic, we computed MI for τ values from one sample (adjacent points separated by 100 ms) to one cycle length. MI tends to decrease quickly as τ is increased from a lag of one and then becomes more uniform at higher time lags, and the average MI of a given epoch was quantified excluding small lags as defined by the first minimum of the MI function.

References

1. Shea SA, Guz A (1992) Personnalite ventilatoire—an overview. Respir Physiol 87(3):275–291
2. Shea SA, Benchetrit G, Pham Dinh T, Hamilton RD, Guz A (1989) The breathing patterns of identical twins. Respir Physiol 75 (2):211–223
3. Kawakami Y, Yamamoto H, Yoshikawa T, Shida A (1984) Chemical and behavioral control of breathing in adult twins. Am Rev Respir Dis 129(5):703–707
4. Cherniack NS (1981) Respiratory dysrhythmias during sleep. N Engl J Med 305(6):325–330
5. Yamauchi M, Tamaki S, Yoshikawa M, Ohnishi Y, Nakano H, Jacono FJ, Loparo KA, Strohl KP, Kimura H (2011) Differences in breathing patterning during wakefulness in patients with mixed apnea-dominant vs obstructive-dominant sleep apnea. Chest 140 (1):54–61
6. Basoglu OK, Midilli M, Midilli R, Bilgen C (2011) Adherence to continuous positive airway pressure therapy in obstructive sleep apnea syndrome: effect of visual education. Sleep Breath
7. Shapiro GK, Shapiro CM (2010) Factors that influence CPAP adherence: an overview. Sleep Breath 14(4):323–335
8. Yetkin O, Kunter E, Gunen H (2008) CPAP compliance in patients with obstructive sleep apnea syndrome. Sleep Breath 12(4):365–367
9. Gay P, Weaver T, Loube D, Iber C (2006) Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 29(3):381–401
10. Sin DD, Mayers I, Man GC, Pawluk L (2002) Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: a population-based study. Chest 121(2):430–435
11. Budhiraja R, Parthasarathy S, Drake CL, Roth T, Sharief I, Budhiraja P, Saunders V, Hudgel DW (2007) Early CPAP use identifies subsequent adherence to CPAP therapy. Sleep 30(3):320–324
12. Weaver TE, Grunstein RR (2008) Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 5(2):173–178
13. Simon-Tuval T, Reuveni H, Greenberg-Dotan S, Oksenberg A, Tal A, Tarasiuk A (2009) Low socioeconomic status is a risk factor for CPAP acceptance among adult OSAS patients requiring treatment. Sleep 32(4):545–552
14. Platt AB, Field SH, Asch DA, Chen Z, Patel NP, Gupta R, Roche DF, Gurubhagavatula I, Christie JD, Kuna ST (2009) Neighborhood of residence is associated with daily adherence to CPAP therapy. Sleep 32(6):799–806
15. Wild MR, Engleman HM, Douglas NJ, Espie CA (2004) Can psychological factors help us to determine adherence to CPAP? a prospective study. Eur Respir J 24(3):461–465
16. Shannon CE (1997) The mathematical theory of communication. 1963. MD Comput 14(4):306–317
17. Fraser AM, Swinney HL (1986) Independent coordinates for strange attractors from mutual information. Phys Rev A 33 (2):1134–1140
18. Koo BB, Strohl KP, Gillombardo CB, Jacono FJ (2010) Ventilatory patterning in a mouse model of stroke. Respir Physiol Neurobiol 172 (3):129–135
19. Dhingra RR, Jacono FJ, Fishman M, Loparo KA, Rybak IA, Dick TE (2011) Vagal-dependent nonlinear variability in the respiratory pattern of anesthetized, spontaneously breathing rats. J Appl Physiol 111(1):272–284
20. Jacono FJ, De Georgia MA, Wilson CG, Dick TE, Loparo KA (2010) Data acquisition and complex systems analysis in critical care: developing the intensive care unit of the future. J Healthc Eng 1(3):337–355
21. Kerr AM (1992) A review of the respiratory disorder in the Rett syndrome. Brain Dev 14(Suppl):S43–S45

22. Ogier M, Katz DM (2008) Breathing dysfunction in Rett syndrome: understanding epigenetic regulation of the respiratory network. Respir Physiol Neurobiol 164(1–2):55–63
23. Eckert DJ, Jordan AS, Merchia P, Malhotra A (2007) Central sleep apnea: pathophysiology and treatment. Chest 131(2):595–607
24. Netzer NC, Strohl KP (1999) Sleep and breathing in recreational climbers at an altitude of 4200 and 6400 meters: observational study of sleep and patterning of respiration during sleep in a group of recreational climbers. Sleep Breath 3(3):75–82
25. Pattinson KT (2008) Opioids and the control of respiration. Br J Anaesth 100(6):747–758
26. Teichtahl H, Wang D (2007) Sleep-disordered breathing with chronic opioid use. Expert Opin Drug Saf 6(6):641–649
27. Bradley TD, Floras JS (2003) Sleep apnea and heart failure: Part II: central sleep apnea. Circulation 107(13):1822–1826
28. Caples SM, Garcia-Touchard A, Somers VK (2007) Sleep-disordered breathing and cardiovascular risk. Sleep 30(3):291–303
29. Leung RS, Bradley TD (2001) Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 164(12):2147–2165
30. Cherniack NS, Longobardo G, Evangelista CJ (2005) Causes of Cheyne-Stokes respiration. Neurocrit Care 3(3):271–279
31. Hardavella G, Stefanache F, Ianovici N (2006) Cheyne stokes respiration in stroke patients. Rev Med Chir Soc Med Nat Iasi 110(1):82–87
32. Han F, Subramanian S, Dick TE, Dreshaj IA, Strohl KP (2001) Ventilatory behavior after hypoxia in C57BL/6J and A/J mice. J Appl Physiol 91(5):1962–1970
33. Han F, Subramanian S, Price ER, Nadeau J, Strohl KP (2002) Periodic breathing in the mouse. J Appl Physiol 92(3):1133–1140
34. Yamauchi M, Dostal J, Kimura H, Strohl KP (2008) Effects of buspirone on posthypoxic ventilatory behavior in the C57BL/6J and A/J mouse strains. J Appl Physiol 105(2):518–526
35. Yamauchi M, Ocak H, Dostal J, Jacono FJ, Loparo KA, Strohl KP (2008) Post-sigh breathing behavior and spontaneous pauses in the C57BL/6J (B6) mouse. Respir Physiol Neurobiol 162(2):117–125
36. Perez-Padilla R, West P, Kryger MH (1983) Sighs during sleep in adult humans. Sleep 6(3):234–243
37. Baldwin DN, Suki B, Pillow JJ, Roiha HL, Minocchieri S, Frey U (2004) Effect of sighs on breathing memory and dynamics in healthy infants. J Appl Physiol 97(5):1830–1839
38. Vlemincx E, Taelman J, De Peuter S, Van Diest I, Van den Bergh O (2011) Sigh rate and respiratory variability during mental load and sustained attention. Psychophysiology 48(1):117–120
39. Vlemincx E, Van Diest I, De Peuter S, Bresseleers J, Bogaerts K, Fannes S, Li W, Van Den Bergh O (2009) Why do you sigh? Sigh rate during induced stress and relief. Psychophysiology 46 (5):1005–1013
40. Wuyts R, Vlemincx E, Bogaerts K, Van Diest I, Van den Bergh O (2011) Sigh rate and respiratory variability during normal breathing and the role of negative affectivity. Int J Psychophysiol 82 (2):175–179
41. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, Gautam S, Owens RL, Malhotra A, White DP (2011) A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol 110(6):1627–1637
42. Shannon CE, Weaver W (1949) The mathematical theory of communication. University of Illinois Press, Urbana

1968

呼吸器疾患に伴う肺高血圧症

Pulmonary hypertension due to lung diseases

熊本牧子(写真)　木村　弘
Makiko KUMAMOTO and Hiroshi KIMURA
奈良県立医科大学内科学第二講座

◎これまで呼吸器疾患に伴う肺高血圧症として，COPDを代表とする閉塞性肺疾患，肺線維症や結核後遺症などの拘束性肺疾患があげられていたが，2008年2月にアメリカ・ダナポイントで開催された第4回肺高血圧症ワールドシンポジウムでの討議を経て，あらたに拘束性および閉塞性の混合型パターンをとる呼吸器疾患が追加された．この新しいサブグループには気管支拡張症，嚢胞性肺線維症に加えて，上肺野優位の肺気腫に下肺野優位の肺線維症を合併した症例(CPFE)が含まれる．CPFEは予後が悪く，予後不良因子として約半数に肺高血圧症(PH)が関与していると報告されている．また，COPD患者において肺の機能的障害が軽度～中等度であるにもかかわらず顕著な呼吸困難と肺動脈圧の上昇を示す“out of proportion”な予後不良である一群の存在が認識されつつある．従来，呼吸器疾患に合併するPHは比較的軽度であることより，酸素療法以外の特異的治療法は行われてこなかった．しかし，肺動脈性肺高血圧症で用いられる肺血管拡張薬が適応となる可能性も考えられ，前向きに検討すべきである．シルデナフィルの有用性を示唆する報告もあり，さらなるデータの集積は今後の重要な課題である．

Key word：呼吸器疾患，肺高血圧症(PH)，換気/血流バランス，out of proportion，気腫合併肺線維症(CPFE)

慢性閉塞性肺疾患(chronic obstructive pulmonary disease：COPD)，間質性肺疾患などの呼吸器疾患において肺高血圧(pulmonary hypertension：PH)をきたすことは以前から知られていたが，呼吸器疾患に合併するPHはおおむね軽症～中等症であり，現時点では確立された治療は酸素療法や右心不全に対する薬剤療法が主体である．しかし近年，肺のフローボリウム曲線や画像所見に比べて高度のPHを有する症例が存在することも報告されており，このような病態に対するあらたな治療戦略の確立が必要となってきている．

呼吸器疾患の疫学

軽症のCOPDも含めた多数の症例に右心カテーテルを行うことは倫理上難しい．また，心エコーのみによる診断は正確さを欠くため，COPDにおけるPHの有病率については患者の全体像を表すデータはない．しかし，入院患者におけるCOPDにおけるPHの有病率についてはいくつかの報告がある．一秒率の平均値が40%である175人のCOPD患者において，平均肺動脈圧(mean pulmonary arterial pressure：mPAP)　>20 mmHgのPHの有病率は35%であった[1]．重症のCOPDにおいてはPH有病率が50%以上と高いもののおおむね軽症であった[2,3]．間質性肺疾患ではPHの有病率は32～39%と報告されており[4]，肺線維症に肺気腫が合併した病態(combined pulmonary fibrosis and emphysema：CPFE)ではPH有病率は約50%程度とさらに高くなる[5]．

COPDにおいては，PHの合併は生存期間の短縮[3](図1)および急性増悪の頻度の増加[6]と関連する．肺線維症やCPFEにおいてもPHは予後不良因子である[4,7]．

発症要因

呼吸器疾患に併発するPHの要因としてはさま

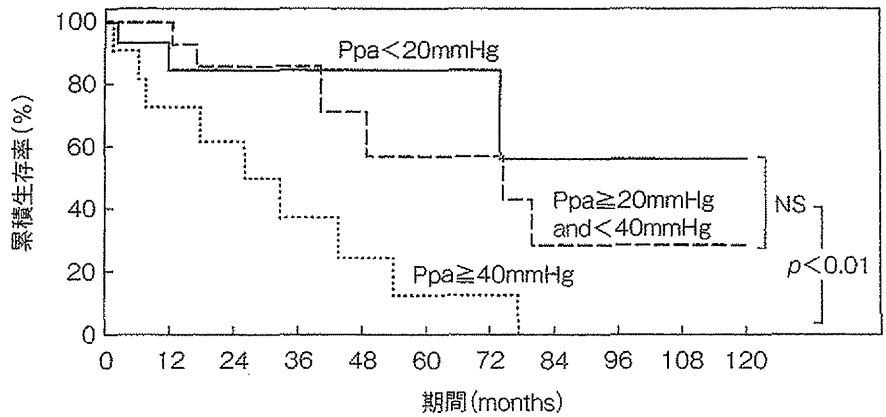

図 1　COPD患者におけるPHの重症度別の生存率[3]
NS：not significant(有意差なし).

表 1　COPDにおいて肺血管抵抗を増強させる因子[19]

COPD における PH を起こす因子	肺血管への作用
気流の制限	血管への圧変動
気腫性病変	血管床の減少
肺胞低酸素	血管攣縮，リモデリング
高炭酸ガスによるアシドーシス	血管攣縮
赤血球増多	血液の粘性増加
肺および全身の炎症	リモデリング，線維化

サイドメモ

気腫合併肺線維症(CPFE)

2005 年に Cottin らが，気腫病変と線維化病変が合併している 61 例を気腫合併肺線維症(combined pulmonary fibrosis and emphysema：CPFE)という病名で報告したのを契機に，その存在が注目されるようになった[5]．しかし，この病態はすでにわが国ではよく認知されており，1991 年の特発性間質性肺炎の臨床的診断基準(第三次改訂案)において「特発性間質性肺炎本来の縮小性変化に気腫性変化が加わるもの」を「B 群(非定型例)」として記載されている疾患群と同じであると考えられる[20]．CPFE の有病率は 0.2～0.96%で，肺気腫症例の約 6%と報告されている[21]．①重喫煙者の男性，②肺活量や一秒率の低下は軽度であるにもかかわらず，高度の肺拡散能低下があり，労作時に著しい低酸素血症を生じる，③上肺野に小葉中心性肺気腫病変，下肺野に線維化病変の存在，④肺高血圧症の合併が約半数にあり，予後不良因子となる，⑤肺癌(とくに扁平上皮癌)の合併が多い，といった特徴がある．気腫病変と線維化病変という異なる病態が一個体に併存するのは，肺の炎症や損傷に対する修復過程においてアポトーシスの誘導，蛋白分解，線維化が生じるが，肺のそれぞれの部位で何らかの因子によって主体となる修復機転が異なることが原因ではないかと考えられている[22]．CPFE は肺気腫のみや肺線維症のみとは異なった臨床的特徴を有しており，予後不良因子となる肺高血圧や肺癌の合併にはとくに注意が必要である．

ざまな見解があるが，もっとも重要な因子のひとつとして低酸素性肺血管攣縮(hypoxic pulmonary vasoconstriction：HPV)があげられる．HPV とは肺胞気の酸素分圧が低下するとその領域を走行する血管が限局的に収縮するという現象である．HPV は本来，低換気の肺胞領域の血流を下げて換気血流比の不均等分布による低酸素血症を予防するという生理的な反応であるが，重症の COPD などでは肺胞気酸素分圧が低い領域が著しく拡大し，広範な領域で肺血管収縮が起こり，肺動脈圧の上昇をきたす．

また，気腫性変化や線維性変化に伴う肺血管の破壊・閉塞・狭小化による肺血管床の減少も肺高血圧を助長する．さらに，肺胞低酸素や慢性炎症が継続すると，筋性肺動脈の内膜の増殖と，血管平滑筋の肥大といった不可逆的な形態学的変化，いわゆる肺血管のリモデリングが起こり，肺動脈血流抵抗の上昇をきたす．そのほか呼吸性アシドーシスや低酸素に起因する二次性の多血症による血液粘性の増加も PH を増強させる(表 1)．

血管拡張作用のある一酸化窒素(nitric oxide：NO)や血管収縮作用のあるエンドセリン 1 も PH

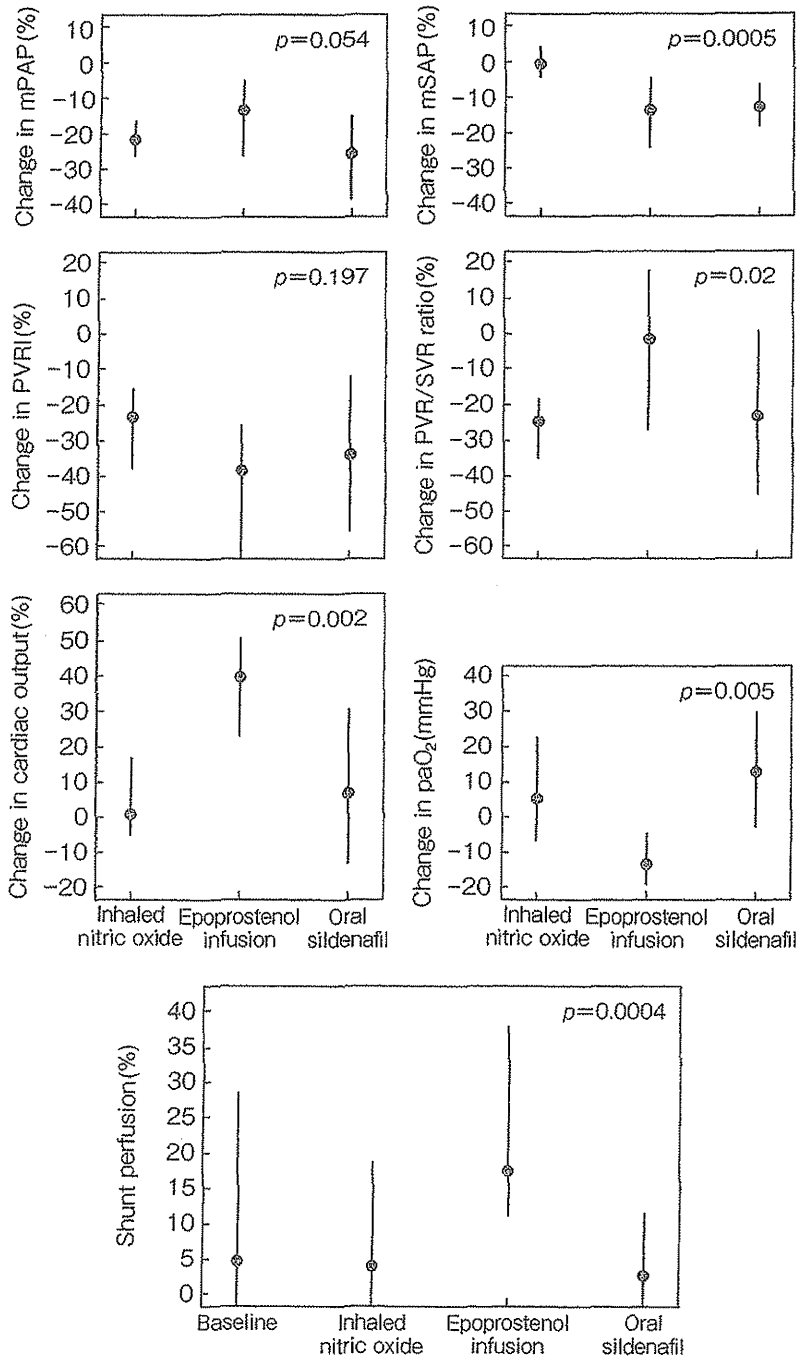

図 2　PH合併肺線維症に対するランダム化比較試験[13]

一酸化窒素(NO)吸入 vs. エポプロステノール静注 vs. シルデナフィル経口.

mPAP：mean pulmonary arterial pressure(平均肺動脈圧), mSAP：mean systemic arterial pressure(平均全身血圧), PVRI：pulmonary vascular resistance index(肺血管抵抗係数), PVR/SVR ratio：ratio of pulmonary to systemic vascular resistance(肺血管抵抗/体血管抵抗比), paO_2：partial pressure of arterial oxygen(動脈血酸素分圧).

の病態に関与していると考えられており，PH合併COPD患者における呼気中のNO低下や，呼気濃縮液や末梢血中のエンドセリン1の上昇が報告されている[8].

診断

PHと呼吸器疾患の臨床症状や身体的徴候は共通する部分が多く，呼吸器疾患がある患者ではPHの存在を予測することは困難なことがある.

心エコーは非侵襲的であり，PHのスクリーニングとしては有効な手段であるが，正確さにおいては右心カテーテルに劣る．進行した肺疾患における右心カテーテルの適応としては，PHの疑いが強く，①外科的治療(移植，肺容積縮小術)を考慮する症例，②PAH特異的薬物療法の無作為化対照試験に組み入れられる可能性がある“不釣り合い(out of proportion)”なPHが疑われる症例，③頻繁な右心不全のエピソードがある症例，④心エコー法では結論が出なかった症例である．

対策(治療)

COPDや間質性肺疾患に伴うPHに対しては，長期酸素療法(long-term oxygen therapy：LTOT)が主体となる．酸素投与により低酸素肺血管攣縮(HPV)はある程度解除されると考えられるが，肺血管の構造的変化が回復することはなく，PAP値が正常にまで復することは期待できない．COPDでは長期酸素投与によってPHの進行をいくぶん抑え，QOL(quality of life)と予後を改善するが[9]，間質性肺疾患におけるPHについてはLTOTの効果を示すエビデンスは少ない．

右心不全に対しては安静，減塩・水分制限，利尿薬の投与が施行され，低血圧をきたしている場合には強心昇圧剤(ドパミン・ドブタミン)などが投与される．

肺動脈性肺高血圧症に対して使用される肺血管拡張薬は，呼吸器疾患に伴うPHにおいては換気/血流の不均等分布が顕著化することによる低酸素血症の増悪が危惧されるため，その有効性については慎重に検討する必要がある．

COPDにおいてはphosphodiesterase-5阻害薬であるシルデナフィル，およびエンドセリン受容体拮抗薬であるボセンタンの有効性は示されなかった[10,11]．

IPFにおいてはプロスタサイクリンの静注はmPAPを低下させたが，換気/血流の不均等分布を増悪させ低酸素血症を増悪させた．一方，NOの吸入やプロスタサイクリン誘導体であるイロプロストの吸入は換気/血流比は維持したままmPAPを低下させるため，有効性が期待されている[12]．また，シルデナフィルは経口投与にもかかわらず，吸入療法で期待しうるような換気/血流バランスの改善を伴うPHの治療効果や[13]，呼吸困難やQOLの改善にも寄与することが報告されている[14](図2)．シルデナフィルの肺の換気の良好な部位で効果をとくに発揮するという特徴が，換気/血流バランスの悪化なく肺血管抵抗低下やガス交換の改善に寄与すると考えられており，今後有効性が期待される薬剤である．また，エンドセリン受容体拮抗薬であるボセンタンは抗線維化作用を有しており，PHの有無に関係なくIPFに対する治験が行われており，BUILD-1研究では病状進行抑制やQOLの改善傾向がみられた[15]．しかしその後，3年以内に外科的肺生検でIPF/UIPと診断され，高分解能CTで蜂巣肺がめだたない，つまり早期IPF患者を対象としたBUILD-3研究が実施されたが，ボセンタンの病状進行抑制効果やQOL改善効果は証明されなかった[16]．

このように呼吸器疾患に伴うPHに対する肺血管拡張薬の使用についてはその是非についてさまざまな見解があり，今後，長期予後も含めた大規模臨床試験による十分な検討が必要である．

また，IPF合併PHにおいては肺動脈内微小血栓がPHの進行の一因となっている可能性がある．ワルファリン投与によってIPFの予後が改善したとの報告もあり[17]，抗凝固療法も治療のひとつの選択肢である．

最近のあらたな知見

——out of proportionなPH

COPDや肺線維症の患者の場合，多くはmPAP 20～35 mmHgとPHは軽症である[1]．しかし，一部の患者において肺の機能的障害が中等度にすぎないにもかかわらず，mPAP 35～50 mmHgと著明な上昇と顕著な呼吸困難を示す，いわゆる“不釣り合い”(out of proportion)なPH症例が存在することが明らかとなってきている[2]．Chaouatらの報告によると[3]，COPDを有し右心カテーテル検査を受けた患者998例中，重度のPH(mPAP >40 mmHg)を認めたものは27例(2.8%)であった．そのうちの16例(1.7%)では食欲抑制を目的とした食品の摂取，膠原病，門脈圧亢進，左心系の疾患，慢性肺血栓塞栓症，拘束性肺障害，閉塞

表 2　肺疾患によるPHに関する推奨事項[18]

推奨事項	推奨度	エビデンスレベル
肺疾患によるPHを評価するためのスクリーニング方法としては，心エコー法が推奨される	I	C
肺疾患によるPHの確定診断には右心カテーテルが推奨される	I	C
肺疾患によるPHの患者には慢性低酸素血症患者を対象とした長期酸素療法を含む，根底にある肺疾患の至適治療が推奨される	I	C
肺疾患による“不釣り合い(out of proportion)”PHの患者はPAH特異的薬物療法の無作為化対照試験に組み入れるべきである	IIa	C
肺疾患によるPHの患者にはPAH特異的薬物療法の適用は勧められない	III	C

性睡眠時無呼吸症候群といったPHをきたす要因が併存していた．一方，他の11例(1.1％)はCOPD以外にPHの要因となる併存疾患を見出せず，軽度～中等度の気道閉塞，重度の低酸素血症，低炭酸ガス血症，極端に低い一酸化炭素拡散能といった所見を有しており，病態的には特発性肺動脈性肺高血圧症(IPAH)の合併と考えられた．またこれらの症例では重度の呼吸困難や，生存の短縮を認めた(図1)．従来，呼吸器疾患に合併するPHは比較的軽度であることより酸素療法以外の特異的治療法は行われてこなかったが，このような症例にはPAHで使用される肺血管拡張剤の適応を前向きに検討すべきである．

2009年に報告されたPHの診断治療に関するガイドライン[18]に記載されている呼吸器疾患に合併するPHに関する推奨事項を表2に示す．

文献

1) Weitzenblum, E. et al.: *Thorax*, **36**：752-758, 1981.
2) Thabut, G. et al.: *Chest*, **127**：1531-1536, 2005.
3) Chaouat, A. et al.: *Am. J. Respir. Crit. Care Med.*, **172**：189-194, 2005.
4) Lettieri, C. J. et al.: *Chest*, **129**：746-752, 2006.
5) Cottin, V. et al.: *Eur. Respir. J.*, **26**：586-593, 2005.
6) Kessler, R. et al.: *Am. J. Respir. Crit. Care Med.*, **159**：158-164, 1999.
7) Mejia, M. et al.: *Chest*, **136**：10-15, 2009.
8) Carratu, P. et al.: *BMC Pulm. Med.*, **8**：20, 2008.
9) Report of the Medical Research Council Working Party：*Lancet*, **1**：681-686, 1981.
10) Rietema, H. et al.: *Eur. Respir. J.*, **31**：759-764, 2008.
11) Stolz, D. et al.: *Eur. Respir. J.*, **32**：619-628, 2008.
12) Olschewski, H. et al.: *Am. J. Respir. Crit. Care Med.*, **160**：600-607, 1999.
13) Ghofrani, H. A. et al.: *Lancet*, **360**：895-900, 2002.
14) Zisman, D. A. et al.: *N. Engl. J. Med.*, **363**：620-628, 2010.
15) King, T. E. et al.: *Am. J. Respir. Crit. Care Med.*, **177**：75-81, 2008.
16) King, T. E. et al.: *Am. J. Respir. Crit. Care Med.*, **184**：92-99, 2011.
17) Kubo, H. et al.: *Chest*, **128**：1475-1482, 2005.
18) Galie, N. et al.: *Eur. Respir. J.*, **34**：1219-1263, 2009.
19) Chaouat, A. et al.: *Eur. Respir. J.*, **32**：1371-1385, 2008.
20) 厚生省特定疾患びまん性肺疾患調査研究班：特発性間質性肺炎の臨床的診断基準(第三次改定案)，1991.
21) 丸山雄一朗・他：低線量薄層CTを用いたCOPD画像疫学調査に関する研究．厚生労働科学研究費補助金難治性疾患克服研究事業呼吸不全に関する調査研究，平成17年度研究報告書，2006，pp.102-105.
22) Niewoehner, D. E. et al.: *Science*, **217**：359-360, 1982.

*　　*　　*

1986

カラー版

内科学

総編集

門脇　孝　永井良三

編集委員

赤林　朗　大内尉義　黒川峰夫
小池和彦　辻　省次　長瀬隆英
藤田敏郎　森屋恭爾　山本一彦

西村書店

あげられる。

と薬理メカニズム(図 12-1-3)[4]

護管理：呼吸管理では酸素吸入療法あるいは挿管に工換気によって経皮的動脈血酸素飽和度(SpO_2)動脈血酸素分圧〈PaO_2〉60 Torr)以上に維持する。循では陽性変力作用を有するドブタミン，ドパミン，ドレナリンなどの強心薬の使用によって右心拍出量させる。

療法：治療の第一選択は未分画ヘパリンによる抗凝である。抗凝固療法は急性肺血栓塞栓症に対する急率の改善効果と再発低下効果が示されており，でき早期に施行する。5,000 単位を単回静脈投与し，確後は活性化部分トロンボプラスチン時間(APTT)がコールの 1.5～2.5 倍を保つように調節する。慢性期で未分画ヘパリンからワルファリン内服に変更して ワルファリンはプロトロンビン時間国際標準比R)が 1.5～2.5 になるように調節する。

解療法：血行動態が不安定な広範型以上の重症例に行う。血栓溶解療法は抗凝固薬であるヘパリン投与して迅速に血栓を溶解し血行動態を改善するが，死亡や再発率の低下といった予後改善効果は明らかでわが国ではウロキナーゼと遺伝子組換え組織型プノーゲン活性化因子(tissue-type plasminogen r：t-PA)を用いる。

テル治療：急性広範型肺血栓塞栓症において積極的治療にもかかわらず血行動態が不安定な症例に対し肺動脈に比べてはるかに大きな末梢血管床へ血栓飛ばすことによる圧負荷軽減をめざしたものであテーテルを用いて肺動脈血栓を破砕，吸引して血流させる。血栓吸引には冠血管形成術用のガイディンテルを使用し，血栓破砕はガイドワイヤーや回転テールカテーテルなどを用いる。

治療：循環不全やショックを呈した重症例，血栓溶を行ったにもかかわらず効果がみられない症例，血療法禁忌例では，人工心肺を用いた直視下肺動脈血術を考慮する。しかし手術死亡率が高く，施行するまぎられる。

フィルター：下大静脈フィルターは，下肢や骨盤内静脈血栓が遊離して肺動脈に達する前に下大静脈で的で用いられる。

・予後 肺血栓塞栓症は急性期の死亡率が約 10%死亡例の多くが発症直後の突然死である。治療がれば生命予後は良好であるが，症状消失後も再発のがあり，抗凝固療法を続ける必要がある。

【似内 郁雄・山内 広平】

文献

1. Dantzker DR, Brandt CG : Pulmonary physiology during pulmonary embolism. Chest 101(Suppl) : 163S-171S, 1992
2. Goldhaber SZ, Visani VF : Acute pulmonary embolism. N Engl J Med 358: 1037-1052, 2008
3. Konstantinides S : Clinical practice. Acute pulmonary embolism. N Engl J Med 359: 2804-2813, 2008
4. 山口悟三ほか：循環器病の診断と治療に関するガイドライン(2008 合同研究班報告)：肺血栓塞栓症および深部静脈血栓症の診断，治療，予防に関するガイドライン 2009 年改訂版

2 肺高血圧症

定義，概念 肺高血圧症(pulmonary hypertension：PH)とは安静時における平均肺動脈圧が 25 mmHg 以上のものと定義される。ただし，健常者においては安静時の平均肺動脈圧は 20 mmHg 以上にならないことより，慢性閉塞性肺疾患(COPD)や間質性肺炎などの呼吸器疾患においては，平均肺動脈圧が 20 mmHg 以上の場合に PH と診断する。病態生理学的には，平均肺動脈圧が 25 mmHg 以上で，肺動脈楔入圧が 15 mmHg 以下の場合は肺動脈性肺高血圧症(pulmonary arterial hypertension：PAH)(もしくは，前毛細血管性肺高血圧症)，肺動脈楔入圧が 15 mmHg 以上の場合は肺静脈性肺高血圧症(後毛細血管性肺高血圧症)という。一方，臨床分類(2008 年，Dana Point 分類)では，肺動脈性肺高血圧症(PAH)(第 1 群)，肺静脈閉塞性疾患/肺毛細血管腫症(第 1' 群)，左心疾患による肺高血圧症(第 2 群)，肺疾患/低酸素血症による肺高血圧症(第 3 群)，慢性血栓塞栓性肺高血圧症(chronic thromboembolic pulmonary hypertension：CTEPH)(第 4 群)，その他の原因不明/多因子性肺高血圧症(第 5 群)と分類される(表 12-2-1)。臨床分類の PAH は，前毛細血管性肺高血圧症につながる他の原因(第 2 群～第 5 群の原因)を認めないにもかかわらず，前毛細血管性肺高血圧症が発症することを特徴としており，臨床像，肺微小循環の異常，治療反応性が類似した病型が含まれる(図 12-2-1)。PAH のうち，膠原病，門脈圧亢進症，HIV 感染症，先天性心疾患などに伴う肺高血圧症は associated with PAH(APAH)と呼ぶ。

特発性肺動脈性肺高血圧症(idiopathic pulmonary arterial hypertension：IPAH)とは，PAH のうち，APAH，薬物に伴うもの，新生児遷延性のもの以外をさす。従来から，広く用いられてきた原発性肺高血圧症(primary pulmonary hypertension：PPH)とは IPAH と遺伝子異常を伴う遺伝性 PAH を包括したものである。PH はその臨床的分類により重症度が異なるため，ここでは PAH を中心に解説する。

疫学，経過・予後 PPH(IPAH)の全国平均有病率は，わが国の認定患者数の調査結果からは，人口 10 万人あたり 0.89 人と計算される(平成 20 年度)。本症の診断においては右心カテーテルを必須とするため，確定診断までいたらない症例も多数存在すると推測される。発症年齢は 0～70 歳代まで広い年齢層に分布するが，ピークは 20～40 歳までの若年者に多くみられる。小児では明らかな性差が認められないのに対して，成人においては女性に多くみられ，その男女比は約 1：2 とされている。

予後に関しては，従来は確定診断からの中間生存率は 2.5～3 年，5 年生存率は 40%前後ときわめて不良であった。しかし，近年，プロスタサイクリン持続療法やエンドセリン受容体拮抗薬，ホスホジエステラーゼ 5(PDE5)阻害薬などが導入されて以来，著しい改善がみられる。死因としては右心不全が約 50%に，突然死が約 25%にみられる。

病因・病態生理とメカニズム 肺循環系の血圧，血管抵抗は，体循環系と比較して約 1/5～1/6 であり低圧

表 12-2-1 肺高血圧症の臨床分類

1. 肺動脈性肺高血圧症(PAH)
- 特発性(IPAH)
- 遺伝性
- 薬物および毒物誘発性
- 各種疾患に伴う PAH(APAH)
  - ・結合組織病
  - ・門脈圧亢進症
  - ・HIV 感染症
  - ・先天性心疾患
  - ・住血吸虫症
  - ・慢性溶血性貧血
- 新生児遷延性肺高血圧症

1'. 肺静脈閉塞性疾患および/または肺毛細血管腫症

2. 左心疾患による肺高血圧症

3. 肺疾患および/または低酸素血症による肺高血圧症
- COPD
- 間質性肺疾患
- 拘束性および閉塞性の混合パターンをとる肺疾患
- 睡眠呼吸障害
- 肺胞低換気障害
- 高所の慢性曝露
- 成長障害

4. 慢性血栓塞栓性肺高血圧症(CTEPH)

5. 原因不明および/または多因子性肺高血圧症
- 血液疾患：骨髄増殖性疾患，脾摘出
- 全身性疾患：サルコイドーシス，肺 Langerhans 細胞組織球症，リンパ脈管筋腫症，神経線維腫症，血管炎
- 代謝疾患：糖原病，Gaucher 病，甲状腺疾患
- その他：腫瘍性閉塞，線維性縦隔炎，透析を要する慢性腎疾患

HIV：ヒト免疫不全ウイルス，COPD：慢性閉塞性肺疾患
(Dana Point 分類，2008)(文献 2 を引用)

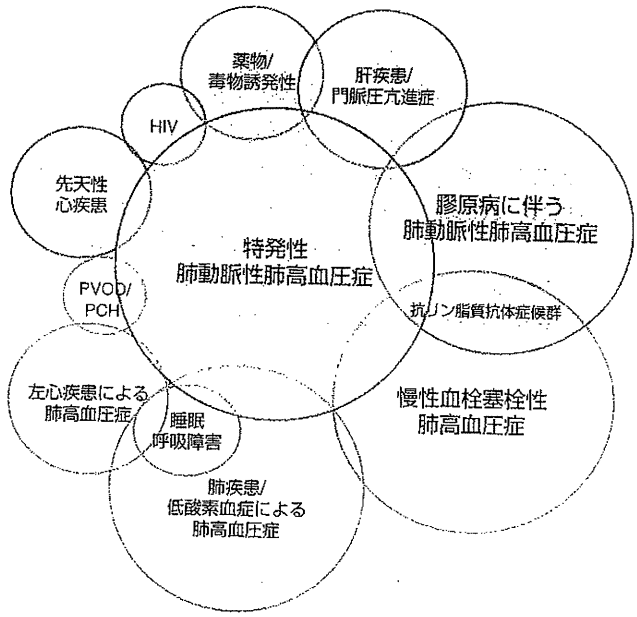

図 12-2-1 肺高血圧症の診断における相互関係
HIV：ヒト免疫不全ウイルス，PVOD：肺静脈閉塞症，PCH：肺毛細血管腫症
(木村弘，2011)

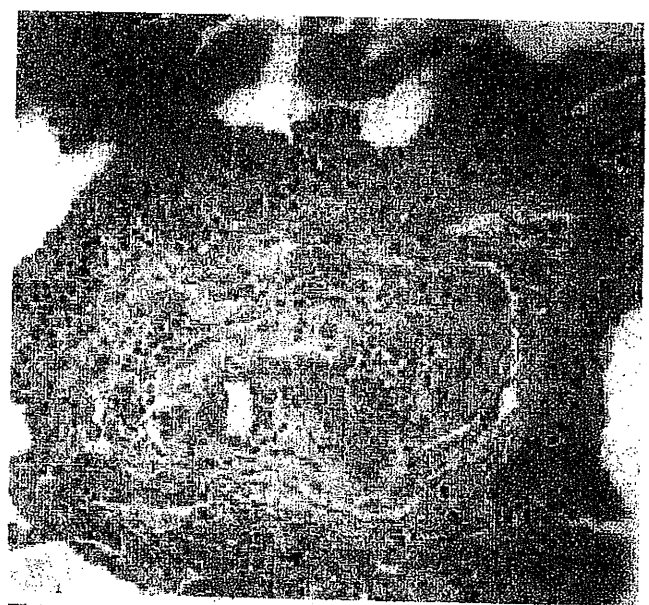

図 12-2-2 肺高血圧症患者における肺小動脈の叢状病変(plexiform lesion)[6]

低抵抗系である。しかし PAH では，なんらかの機序で肺循環系への傷害がもたらされ，末梢肺小動脈における内膜(血管内皮細胞)および中膜の増殖性変化，つまり肺血管のリモデリング(組織改築)が生じる(図 12-2-2)。そのために肺動脈圧および肺血管抵抗の上昇がもたらされる。初期の段階では，肺動脈圧上昇の機序としては機能的な肺血管攣縮も関与する。肺血管病変は肺毛細血管より上流に位置するため(前毛細血管性肺高血圧症)，肺動脈楔入圧の上昇は認めない。肺動脈圧の上昇，つまり右室に対する後負荷の増大により，右室の拡張，さらには右室肥大が生じるが，初期には右室拍出量は維持される。しかし，後負荷の増大が急激であったり，右室の限界を越える場合には右心不全が引き起こされる。右室拍出量の制限に，心室中隔の左室壁後方への偏位による左室拡張制限も加わり，心拍出量は低下するため体血圧は低下する。体動時に四肢筋への血流分布が増大すると，脳血流が低下し失神発作を引き起こすこともある。肺高血圧症では，動脈血酸素分圧(PaO_2)は，肺血栓塞栓症の関与を認めないかぎり，多くの場合は正常か軽度の低下にとどまる。PaO_2の低下は，心拍出量の低下に起因する組織低酸素(右心カテーテル時の混合静脈血酸素分圧〈$P\bar{v}O_2$〉の低下)，肺毛細血管レベルでの肺胞気との接触時間の短縮，左心不全の合併による肺内うっ血による換気血流のミスマッチなどに起因する。

PAH の発症における遺伝子異常に関しては，TGF-β(トランスフォーミング増殖因子β)スーパーファミリーに属する骨形成蛋白質の受容体タイプⅡ(bone morphogenic protein receptor type Ⅱ：BMPR Ⅱ)の異常が 2000 年になり報告された。*BMPR Ⅱ*遺伝子は肺血管の構成細胞における増殖および細胞死に関係する遺伝子である。この遺伝子異常は肺血管においてアポトーシス抵抗性細胞の増殖を招き，PH の病因に深くかかわると考えられているが，遺伝性 PAH で 50～100%，IPAH では約 25%で異常を認めるにとどまる。また，遺伝性出血性毛細血管拡張症に伴う PAH では，TGF-β スーパーファミリーに属する activin receptor-like kinase-1(ALK-1)の遺伝子異常が報告されている。

臨床症状・検査成績 PH の初期臨床症状としては，①労作時の息切れ，②易疲労感・全身倦怠感，③動悸，④めまい・立ちくらみ，⑤失神，⑥浮腫，⑦血痰，⑧胸痛などがあげられる。理学所見としては，PH の存在を示唆する心音Ⅱ音における肺動脈成分の亢進が重要である。また