not associated with prolonged survival. Previous studies have shown an approximately 3 times higher incidence of *EGFR* mutations in East Asians than in Caucasians.[7,9–12,16,17,19,21,28–30] FISH-positive results do not appear to contribute significantly to the response to gefitinib or to survival in populations with high percentages of *EGFR* mutations.

The incidence of L858R in our study seemed low compared with the incidence of exon 19 deletion. Previous studies have demonstrated that the incidence of deletion mutations in exon 19 is almost the same as the incidence of point mutations in exon 21.[7,9–12,16,17,19,21,28–30] Because the direct sequencing method usually was used to detect *EGFR* mutations, it is unlikely that the low frequency of the L858R mutation was caused by assay-related, false-negative findings. Our results of the incidence of L858R mutation and exon 19 deletion mutations may also produce some distortion with regard to the analysis of gene copy numbers because the number of patients with high gene copy numbers has been observed to be higher in those with deletion mutations in exon 19 than with point mutations in exon 21. Further analyses in much larger groups of patients will be necessary to clarify the frequency of the 2 most common mutations.

Takano et al. demonstrated an association between increased *EGFR* copy numbers measured by quantitative PCR (qPCR) and both higher a response rate and longer TTP.[15] Dziadziuszko et al. reported that EGFR messenger RNA (mRNA) expression in tumor samples measured by qPCR was a predictive biomarker for response to gefitinib and longer progression-free survival. Those investigators also demonstrated that *EGFR* mRNA expression measured by qPCR was correlated significantly with FISH-positive results.[31] It is possible that qPCR may enable us to make a more reliable distinction between specific and nonspecific amplification of the *EGFR* gene.[13] We plan to compare *EGFR* gene copy numbers in corresponding samples measured with qPCR to confirm our results. We classified all patients into a FISH-positive group and a FISH-negative group according to the scoring system published by Cappuzzo et al. *EGFR* gene copy numbers also may vary according to ethnicity, similar to the differences in *EGFR* mutation frequency. The definition of FISH-positive results may need to be modified to use it as a predictor of gefitinib efficacy in Japanese patients with NSCLC.

In conclusion, the results of the current study suggest that the presence of *EGFR* mutations detected in biopsy specimens is an independent and significant predictor of response to gefitinib and survival in Japanese patients with advanced NSCLC. However, the role of *EGFR* gene amplification was not identified as a predictor of gefitinib efficacy in Japanese patients. Precise measurements are needed, and the validity of the classification must be confirmed in a prospective study.

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Review Article

Current Trends and Controversies over Pre-operative Chemotherapy for Women with Operable Breast Cancer

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The multi-disciplinary approach, including surgery, chemotherapy, endocrine therapy and radiation therapy, has become the standard treatment for primary breast cancer patients. The indication of pre-operative chemotherapy has been extended to women with potentially operable breast cancer based on the results of large randomized studies and has become an attractive option that extends the chance of breast conservation. The clinical and pathological responses to pre-operative chemotherapy correlates with long-term outcome. The anthracycline-containing regimen is now considered the standard. Sequential administration of non-cross-resistant drugs, namely taxanes, improves local tumor response but its long-term benefit has been controversial. Prediction of response to pre-operative chemotherapy still remains a challenge. Identification of useful predictive markers and development of molecular-targeted drugs is the key to individualized therapy in the future.

Key words: pre-operative chemotherapy – breast cancer – advantage – response – long-term outcome – prediction

INTRODUCTION

The multi-disciplinary approach, including surgery, chemotherapy, endocrine therapy and radiation therapy, has become the standard treatment for primary breast cancer patients with a high risk of recurrence. Although mortality from breast cancer is decreasing in western countries thanks mainly to early detection of the disease by mammography screening and wide usage of post-operative adjuvant systemic therapy (1), its incidence and mortality are steadily increasing in the rest of the world, including Japan (2).

When it first emerged in late 1970s, the use of pre-operative (primary) chemotherapy had been primarily limited to women with inoperable locally advanced breast cancer to enable optimal local therapy (3–5). Later on, large randomized trials proved that pre-operative chemotherapy has at least the same survival benefit as the post-operative chemotherapy (6), and its indication has been extended to women with potentially operable breast cancer.

However, with long-term survivors increasing by systemic therapy in early breast cancer, the 'survivorship' or importance of quality of life after primary therapy has recently come into the limelight. Whether an attempt at breast conservation can be made at the time of definitive surgery is one of the important issues discussed among patients and physicians. Pre-operative chemotherapy is an attractive option for those who have large tumors but a strong interest in breast conserving surgery.

In this review, we describe available evidence and discuss current controversies and future prospects of pre-operative chemotherapy, taking account of its two major clinical roles; eradication of micrometastatis and increased chance of breast conservation.

RATIONALE OF PRE-OPERATIVE CHEMOTHERAPY

Biologic rationale for pre-operative adjuvant chemotherapy was derived from the pre-clinical studies in animal models. It had been known that growth kinetics of metastatic tumors change after surgical removal of the primary lesion (7). The greatest effect of chemotherapy was observed when it was administered prior to operation (8, 9). These observations led to a hypothesis that early systemic chemotherapy prior to surgery might further reduce the risk of metastasis.

The landmark trial in a clinical setting was the National Surgical Adjuvant Breast and Bowel Project (NSABP)

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B-18 trial, which showed pre-operative chemotherapy for operable breast cancer by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) was at least as effective as post-operative adjuvant chemotherapy with the same regimen in terms of disease-free and overall survival (10). The results were consistent over a longer follow-up period (6) and the result of another large randomized trial conducted in Europe was also confirmatory (11). A recent meta-analysis of pre-operative and post-operative chemotherapy (partly including T4 disease) indicated that pre-operative chemotherapy was equivalent to post-operative therapy in terms of survival and disease progression (12).

Thus the available clinical data has not demonstrated a convincing difference in long-term outcome as hypothesized in pre-clinical studies. However, a higher proportion of women were able to undergo breast conservation surgery. In addition, because the extent of clinical and pathological responses to pre-operative chemotherapy correlates with survival (10), improved tumor response in this setting is expected to improve the overall outcome.

ADVANTAGE OF PRE-OPERATIVE CHEMOTHERAPY

The advantage of pre-operative therapy is that one can subjectively evaluate the response to systemic therapy *in vivo*. Both clinical and pathological responses have been associated with prolonged disease-free and overall survival (6, 8) and they are used as the primary endpoint in clinical trials. Unlike post-operative adjuvant chemotherapy, one can avoid or minimize the unnecessary toxicities from cytotoxic agents by changing treatment strategy when the tumor is not responding to a certain regimen.

Pre-operative chemotherapy is an attractive option for women who wish to reduce the extent of local surgery. Clinical trials provide evidences that 28–89% of women can undergo breast conserving surgery when they might not be otherwise qualified (12).

Because breasts are located on the body surface, one can easily obtain the tumor cells or tissue by either fine needle aspiration or core needle biopsy with minimal invasions. As one can also evaluate the response to systemic therapy in a subjective manner and because patients are usually chemotherapy naïve, a pre-operative setting can be an ideal *in vivo* laboratory for biomarker studies using tumor specimens.

DISADVANTAGE OF PRE-OPERATIVE CHEMOTHERAPY

The overall response rate of pre-operative chemotherapy is 75% on average (range 49–100%), whereas fewer than 5% of the patients with operable breast cancer progress during pre-operative chemotherapy and some more do not even show major responses (13). For such patients with progression, the delay of local treatment may be of disadvantage at least in terms of local control. Pre-operative chemotherapy is also associated with significantly increased risk of loco-regional disease recurrence (12).

Another potential disadvantage of pre-operative chemotherapy is the loss of initial histological information such as tumor size, nodal status and biologic markers. According to the current guidelines, application of post-operative chemotherapy is to be decided by weighing the baseline risk, endocrine responsiveness and estimated risk reduction and harm of the treatment (14). Risk of recurrence is estimated based on the clinical and pathological information obtained from surgical specimens. In a pre-operative setting the information on tumor size and nodal status will inevitably be imprecise and intra-tumor heterogeneity of histologic type, histologic grade and biomarker expression cannot be taken into account. It may potentially put patients into danger of over- or under-treatment. Currently, core-needle biopsy is mandatory prior to pre-operative chemotherapy to obtain as much pre-treatment histopathological information as possible.

TREATMENT REGIMENS

Using clinical or pathological responses as surrogate endpoints of overall survival, optimal systemic therapies have been investigated in pre-operative settings in patients with early breast cancer. The general consensus reached is that an anthracycline-containing doublet (doxorubicin or epirubicin with cyclophosphamide) or triplet (doxorubicin or epirubicin with cyclophosphamide and 5-fluorouracil) should be used as the initial chemotherapy strategy for pre-operative chemotherapy (15, 16).

The sequential use of non-cross-resistant agents is likely to augment the response of pre-operative chemotherapy (17, 18), among which taxanes are the most investigated drug. Overall, results of randomized trials indicate that the incorporation of taxane increases the rate of pathological complete response (pCR) by 6–16% compared to anthracycline/cyclophosphamide-based regimens (19, 20). Smith et al. randomized patients who achieved clinical response to the initial four cycles of cyclophosphamide/vincristin/doxorubicin/predonisone (CVAP) therapy to receive further four cycles of CVAP or four cycles of docetaxel (Aberdeen trial) (21). The sequential use of docetaxel resulted in enhanced clinical and pathological responses even in anthracycline-sensitive tumors. In NSABP-B27 trial, the addition of four cycles of docetaxel after pre-operative AC increased the clinical complete response rate (40% versus 63%), clinical overall response rate (86% versus 91%) and the pCR rate (14% versus 26%) compared with pre-operative AC therapy alone (20). However, the addition of taxane in pre-operative or post-operative setting after AC did not improve the long-term outcome in this trial (22).

Treatments incorporating molecular-targeting drugs are of interest. Trastuzumab is effective for patients with advanced

breast cancer over expressing HER2 (23). In adjuvant settings, at least one year of trastuzumab given sequentially or concomitantly with chemotherapy significantly improves disease-free and overall survival (24, 25). Moreover a short course (9 weeks) of trastuzumab administered concomitantly with docetaxel or vinorelbine seems to be effective in HER2-positive subset of patients in adjuvant settings (26).

For pre-operative settings, there are a limited number of phase II studies reporting the use of trastuzumab (25, 27, 28). The only randomized trial reported was by Buzdar et al., who compared neoadjuvant chemotherapy for HER2-positive, operable breast cancer with or without administration of trastuzumab (29). This study was closed by the recommendation of Data and Safety Monitoring Board of the institution according to early-stopping rule, because pCR rate, the primary endpoint, was strikingly superior in the chemotherapy plus trastuzumab arm (given simultaneously for 24 weeks) compared with the chemotherapy-alone arm (65% versus 26%, $p = 0.016$). We still need to confirm if this significant difference in pathological response will be translated into prolonged overall survival by long-term follow-up and also the cardiac safety of trastuzumab in combination with chemotherapy should be assessed.

CONTROVERSIES OVER PRE-OPERATIVE CHEMOTHERAPY

Evaluation of Residual Tumor for Optimal Surgery

Optimal imaging modality has not been established to definitely localize the remaining tumor. Usually, serial imaging studies are performed before and after pre-operative chemotherapy. Magnetic resonance imaging or computerized-tomography scanning may supplement conventional breast imaging studies by mammography and ultrasonography (30–33).

The use of functional imaging techniques such as fluorine-18 fluorodexyglucose positron emission tomography ([^{18}F]-FDG PET) is of interest for the evaluation of therapeutic response to systemic therapy in breast cancer. The change in [^{18}F]-FDG uptake reflects the alteration in cellular glycolysis. Some relatively small studies reported that [^{18}F]-FDG PET after a single pulse of chemotherapy predicted pCR or minimal residual disease with a sensitivity of 85–100% and a specificity of 74–85% (34–36). FDG-PET is promising for clinical application in future to detect non-responding tumor to avoid unnecessary toxicities from cytotoxic therapy.

Feasibility of Sentinel Lymph-Node Biopsy (SNB) in Patients Treated with Pre-operative Chemotherapy

Axillary staging by SNB may allow omission of axillary dissection in sentinel-node negative patients without compromising the long-term outcome (37). However the optimal timing and feasibility of SNB in the setting of pre-operative chemotherapy have not been established.

Identification rate of SNB following pre-operative chemotherapy are reported to be 84–93% and 78–93%, in single-institution series and multi-center studies (38), respectively. High false-negative rates up to 25–33% have been reported for several small single institution studies (39, 40), but in multi-institutional studies using radiocolloid with or without blue dye, false-negative rates range between 5 and 13% (38), which are similar to those observed when it was carried out before systemic chemotherapy.

There still remain concerns about the use of SNB following chemotherapy in patients with clinically positive axilla (41). SNB after chemotherapy possesses a potential to maximize the benefit of axillary downstaging by pre-operative systemic treatment, in other words, avoidance of complications related to axillary dissection and decision-making of adding further chemotherapy.

Alteration of Biological Markers

The changes in the expression of hormone receptors and HER2 protein during pre-operative chemotherapy may influence the clinical decision of adjuvant hormonal and trastuzumab therapy. In studies using immunohistochemistry, the administration of pre-operative chemotherapy did not alter the expression patterns of HER2 and hormone receptors (42–45).

However, a study was conducted to compare gene expression profile of pre-treatment biopsy specimens with those in tumors remaining after doxorubicin-containing pre-operative chemotherapy using DNA array. There were differences in the gene expression profile in tumors that showed a response, but not in tumors that did not respond to therapy (46). Biological and clinical implications of the change of gene expression profile in responding tumors need further elucidation.

Definition of Pathological Response

Primary systemic treatment is increasingly recognized as the best model for the quick development of new treatment strategies in early breast cancer. pCR after pre-operative chemotherapy has been chosen as the primary endpoint of clinical trials, because it is validated as the surrogate marker of improved outcome (47, 48). However, diverse definitions of pathological response are used by different investigators (10, 47, 49–53). Some of these grading systems allow inclusion of residual ductal caricinoma *in situ* (DCIS) without invasive component in the definition of pCR. However, there is no confirmatory data to justify the concept that there is no difference in prognosis between patients with no invasive or *in situ* disease and those with residual DCIS. Jones et al. investigated whether the prognosis for patients with residual DCIS is the same as that for patients with no residual tumor cells, but could not demonstrate significant

prognostic difference (54). However, this study was statistically underpowered to draw any conclusions.

Ideally, response to chemotherapy should be measured as a continuous variable. No system satisfies the need of accurate pathologic evaluation for the majority of patients who achieve partial or minor response to pre-operative chemotherapy. Rajan et al. proposed that the product of residual tumor size and cellularity might be a more clinically relevant indicator of tumor response than assessing tumor size alone (55). Though it is an interesting proposal, the method needs to be validated in correlation with long-term outcome.

Outcome after Pre-operative Chemotherapy and Surgery

Several studies have attempted to find more accurate predictors for survival after pre-operative chemotherapy than pCR in the primary tumor. This is because substantial risk of systemic recurrence still remains even if pCR is achieved, whereas substantial patients have excellent prognosis even if pCR is not achieved. If the long-term risk is high, they will be the candidates for clinical trials to determine whether additional aggressive therapy will be of benefit. If a good prognosis is expected even without good response to pre-operative therapy, aggressive chemotherapy might be over-treatment in pre-operative setting.

In the report of retrospective studies from Royal Marsden Hospital and M. D. Anderson Cancer Center, pathologically negative axillary lymph nodes after pre-operative chemotherapy, not pCR in the primary tumor, remained the independent prognostic factor for disease-free survival and overall survival in multivariate analysis adjusted for other prognostic factors (56–58).

It was revealed by a retrospective multivariate analysis of the clinicopathological factors of the 226 patients who had pCR after pre-operative chemotherapy that pre-operative clinical stage IIIB, IIIC, and inflammatory breast cancer, axillary lymph nodes more than 10, and pre-menopausal status were the independent prognostic factors of distant metastasis (59). In another study, only histological grading had an independent prognostic impact on disease-free and overall survival after adjustment for pCR to pre-operative chemotherapy containing doxorubicin (60). Carey et al. found that American Joint Committee on Cancer Tumor-Node-Metastasis staging after pre-operative chemotherapy was useful in prediction of distant disease-free survival and overall survival (61).

Rouzier et al. constructed nomograms combining clinical variables associated with pCR that might accurately predict pCR and distant disease-free survival (62). This was confirmed in an independent dataset within the study. The nomogram included size of residual tumor and the number of metastatic nodes at the time of surgery, histologic grade, estrogen receptor (ER) status and histologic type. On the other hand, biologic markers such as expression of HER2 (63), EGFR (64), p53 (65) or MDR1 gene (66) in tumor specimen before pre-operative chemotherapy, reduction of expression in topoisomerase II-α (70) or MLH1 (71) after pre-operative chemotherapy are suggested to predict long-term outcome. Although it is not known whether these markers would add to or replace the nomogram, development of more accurate and comprehensive tools for prediction of prognosis is awaited.

Prediction of Response to Pre-operative Chemotherapy

The pre-operative setting is ideal to explore molecular predictors of response to therapy. Various clinical and pathologic variables have been studied. Among them, ER status, histologic grade and smaller tumor size seem to be associated with the response to pre-operative chemotherapy (47, 69).

In previous retrospective studies, clinical and pathological responses to pre-operative chemotherapy appear to be lower in invasive lobular carcinoma (ILC) as compared to invasive ductal carcinoma (IDC), and patients with ILC were more likely to receive mastectomy after initial attempt for breast conservation (70–73). However, low pCR rates in ILC have not been translated into survival disadvantage (70–72). These data suggest that different approach should be taken in the clinical management of patients with ILC.

In a biomarker study, ER expression, absence of HER2 and a decrease in Ki67 correlated with good clinical responses subsequent to a pre-operative chemoendocrine therapy (74). Among other biomarkers, bcl-2 and p53 have been studied. bcl-2 has been shown to protect cells from apoptosis induced by chemotherapeutic drugs (75). Although high expression of bcl-2 has been hypothesized to play a role in resistance to chemotherapy, it is still controversial. In one study, higher bcl-2 expression at diagnosis was predictive of pCR in univariate analysis but it did not retain its impact in multivariate analysis (76), while other studies did not find any correlation between bcl-2 expression and the response (77, 78).

p53 is also a potential predictive marker. Active p53 promotes apoptosis in growth-arrested cells whereas loss of p53 function has been reported to enhance cellular resistance to various chemotherapeutics (79). In a clinical setting, in patients treated with single agent epirubicin, mutant p53 was a significant predictor for poor clinical response, but the association was weaker in patients treated with cyclophosphamide/methotrexate/5FU with or without tamoxifen (65). Another study demonstrated that a tumor expressing wild-type p53 was related to resistance to single agent doxorubicin therapy in multivariate analysis (80). *TP53* gene mutation and over expression of p53 were related to epirubicin-containing chemotherapy, but response to paclitaxel seemed to be related to p53-negative tumors (81).

Tumor response and toxicities are different among individual patients. Pharmacogenomic studies aim to elucidate the genetic bases for inter-individual differences and to enable individualization of care. DNA microarray is one of the modern high-throughput biotechnologies that allow

researchers to analyze expression of multiple genes in concert and relate the findings to clinical parameters. In breast cancer, several groups have reported preliminary results suggesting that the gene expression profile of the primary tumor may predict the tumor's response to pre-operative chemotherapy (82–86). One major limitation of microarray studies is overfitting of the prediction: the number of mRNA transcripts far exceed the number of samples (87, 88). The accuracy of the predictive model is low in independent data set (89). More rigorous and critical evidence is necessary before multi-gene predictors can be accepted as a useful and reliable tool in clinical practice.

Pre-operative Endocrine Therapy

The relative benefit of chemotherapy is less in endocrine-responsive disease as compared with endocrine non-responsive disease (1) and recent consensus of the clinical community lays emphasis on the endocrine responsiveness in decision-making of adjuvant systemic therapy (14). Pre-operative endocrine therapy is an attractive alternative for endocrine-responsive disease, because it is easy to perform and can also avoid acute and late side effects caused by cytotoxic chemotherapy, but pre-operative endocrine therapy has not been accepted as the standard therapy because of the slow rate of response (90). We need more accurate measures to select the patients who are most likely to respond to endocrine therapy without compromising the potential benefit of chemotherapy.

Application to Molecular-Targeted Therapy

Molecular-targeted drugs are anticipated to individualize the therapeutic strategy based on the biology of the tumor. To date, the presence of a target still does not satisfactorily guarantee a response to therapy, but efforts are being made to elucidate the key components of the molecular pathways targeted by a specific agent.

Moshin et al. reported a pre-operative study of trastuzumab as a single agent in HER2-positive locally advanced breast cancer (91). They administered trastuzumab as a single agent for the first 3 weeks, followed by a combination of trastuzumab and docetaxel. Of note, partial response was observed in eight among 35 patients after only 3 weeks of trastuzumab. The accompanying biomarker study suggested that the main mechanism of action of trastuzumab is inhibition of the PI3K/Akt pathway, which results in an increase of apoptosis (79). The clinical role of single-agent trastuzumab in HER2-positive tumors has not been determined, but it is attractive if we can select the responders to trastuzumab as this is usually less toxic than cytotoxic chemotherapy.

A report by Polychronis et al. is unique in respect of testing the efficacy of combination of targeted therapy based on biology-derived hypothesis (92). It was a double-blind placebo controlled phase II randomize trial of pre-operative gefitinib versus gefitinib versus anastrozole in post-menopausal patients with ER- and EGFR-positive primary breast cancer. The tumors of patients assigned to combination therapy had a greater reduction of Ki67 labeling index than those assigned to gefinitib alone. Although the number of patients in this study was so small that we do not yet know whether reduction in proliferation will be translated into clinical benefit, we foresee a future of individualized therapy.

FUTURE DIRECTIONS

Pre-operative chemotherapy has become the standard of care in management of primary breast cancer. However, we should be aware that a substantial portion of patients may be over-treated by pre-operative chemotherapy because of inaccurate pre-treatment staging. In NSABP-B27 study, addition of docetaxel was beneficial in terms of disease-free survival not in complete responders or non-responders but only in partial responders in a subset analysis according to clinical response after AC. Who needs additional systemic therapy? Who can avoid systemic therapy?

Development of endocrine therapy and trastuzumab has opened the door to important therapeutic advance of 'molecular-targeted therapy'. Transcriptional profiling has revealed that expression levels of these targets, i.e. ER and HER2, are the major genetic determinants of the biology of the disease (93). Thus, we can foresee the future of systemic therapy individualized with endocrine responsiveness and involvement of HER2 signaling pathway. However, to date, the predictive value of screening test for molecular targets remains unsatisfactory.

Identification of clinically useful, prognostic and predictive molecular markers is highly anticipated to optimize therapeutic regimens. The current probability-based therapeutic strategy, 'empiric treatment' so to speak, might give way to biology-based, individualized strategy, 'marker-based treatment', when additional biologic markers are identified that make 'targeted therapy' more targeted and effective. Pharmacogenomic researches that accompany pre-operative therapy might help better understand the biology of breast cancer and thus promote the development of new therapeutic strategies.

Conflict of interest statement
None declared.

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Daytime Hypercapnia in Obstructive Sleep Apnea Syndrome

Naoko Kawata, Koichiro Tatsumi, Jiro Terada, Yuji Tada, Nobuhiro Tanabe, Yuichi Takiguchi and Takayuki Kuriyama

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SLEEP MEDICINE

Daytime Hypercapnia in Obstructive Sleep Apnea Syndrome*

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Background: **The pathogenesis of daytime hypercapnia ($Paco_2$ ≥ 45 mm Hg) may be directly linked to the existence of obstructive sleep apnea syndrome (OSAS) *per se*, although only some patients with OSAS exhibit daytime hypercapnia.**

Objective: **To investigate the prevalence of daytime hypercapnia in patients with OSAS; the association of daytime hypercapnia and obesity, obstructive airflow limitation, restrictive lung impairment, and severity of sleep apnea; and the response to continuous positive airway pressure (CPAP) therapy in a subset of subjects.**

Methods: **The study involved 1,227 patients with OSAS who visited a sleep clinic and were examined using polysomnography. As for the response to CPAP therapy, the patients were considered good responders if their daytime $Paco_2$ decreased ≥ 5 mm Hg and poor responders if it decreased < 5 mm Hg.**

Results: **Fourteen percent (168 of 1,227 patients) exhibited daytime hypercapnia. These patients had significantly higher body mass index (BMI) and apnea-hypopnea index (AHI) values compared with normocapnic patients, while percentage of predicted vital capacity (%VC) and FEV_1/FVC ratio did not differ between the two groups. Logistic regression analysis showed that only AHI was a predictor of daytime hypercapnia ($p < 0.0001$), while BMI ($p = 0.051$) and %VC ($p = 0.062$) were borderline predictors of daytime hypercapnia. Daytime hypercapnia was corrected in some patients (51%, 19 of 37 patients) with severe OSAS after 3 months of CPAP therapy.**

Conclusion: **The pathogenesis of daytime hypercapnia may be directly linked to sleep apnea in a subgroup of patients with OSAS.** ***(CHEST 2007; 132:1832–1838)***

Key words: continuous positive airway pressure; hypercapnia; hypoventilation; obesity; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; FEV_1% = FEV_1/FVC ratio; OSA = obstructive sleep apnea; OSAS = obstructive sleep apnea syndrome; OHS = obesity hypoventilation syndrome; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference; Sao_2 = arterial oxygen saturation; %VC = percentage of predicted vital capacity

Obstructive sleep apnea (OSA) is characterized by intermittent closure of the pharyngeal airway during sleep, resulting in episodic hypoxemia and sleep disruption. To date, no single pathophysiologic mechanism has been identified. It is possible that the cause of OSA is multifactorial. Some patients with OSA syndrome (OSAS) exhibit daytime hypercapnia. The prevalence of daytime hypercapnia in these patients varies from 11 to 43% according to previous reports.[1–5] Mechanical impairment of the respiratory system due to obesity[5,6] and COPD[3,4] are known causes of daytime hypercapnia in patients with OSAS. It is generally accepted that there is no direct association of OSAS with hypercapnia.[7] However, in these patients daytime $Paco_2$ may be an end product of complex factors including severity of sleep apnea; obesity; daytime Pao_2; chemosensitivity; respiratory mechanics, including chronic airflow limitation; respiratory muscle strength; metabolic rate; daytime symptoms of sleepiness; endocrine modulation; cardiac function; face, nose, and cranial bony structure (cephalometry); and others. Thus, daytime hypercapnia may exist without obesity and/or airflow limitation.

For editorial comment see page 1729

The hypothesis of the present study was that the levels of daytime $PaCO_2$ in patients with OSAS are partly influenced by the degree of OSAS, as expressed by the apnea-hypopnea index (AHI). Since continuous positive airway pressure (CPAP) therapy can reverse CO_2 retention in some patients with hypercapnic OSAS,[8] the pathogenesis of daytime hypercapnia may be directly linked to the existence of OSAS *per se*, although only some patients with OSAS exhibit daytime hypercapnia.

The prevalence of OSAS in Asian countries has recently been reported[9–11]; however, no such epidemiologic studies have been performed in Japan. Obesity appears to be a common and important risk factor for sleep-disordered breathing in previous studies done in Western countries. However, the evaluation of daytime hypercapnia in patients with OSAS has been limited in Asian countries.[12] Ethnic differences between Asian and Western populations might influence the pathogenesis of OSAS, which might limit the relevance of this study, but at the same time emphasize the heterogeneity of OSAS. Therefore, the aim of the present study was first to assess the prevalence of daytime hypercapnia in a large group of patients who visited a sleep clinic; then to evaluate a possible association between daytime hypercapnia and obesity, obstructive airflow limitation, restrictive lung impairment, and severity of sleep apnea; and finally to examine the response to CPAP therapy in a subgroup of patients.

Materials and Methods

Subjects

The subjects of this study were 1,407 consecutive patients with clinical symptoms of sleep apnea who sought treatment from January 2002 to December 2005 and were examined using polysomnography. The patients were recruited from the sleep clinic where they had been referred for further investigation regarding snoring or possible OSAS. Presenting symptoms were either snoring or daytime sleepiness or both. The subjects were all Japanese.

Patients who exhibited Cheyne-Stokes breathing with central sleep apnea (n = 4), those receiving cardiac drugs (digitalis and β-blockers) due to heart failure (n = 2), and patients with restrictive diseases such as kyphoscoliosis (n = 2) and diffuse interstitial fibrosis (n = 2) were excluded from this study. OSAS was established on the basis of clinical and polysomnographic criteria. AHI was calculated as the sum of sleep-disordered breathing events. In addition to clinical symptoms, an AHI > 5 events per hour was also used as a selection criterion of OSAS. The patients (n = 1,399) were distributed into two groups according to AHI (AHI ≥ 5/h, n = 1,227; AHI < 5/h, n = 172). Patients with hypercapnic OSAS who satisfied the criteria of obesity hypoventilation syndrome (OHS) were included in this study if their body mass index (BMI) was ≥ 30 kg/m^2, which indicated obesity.

Pulmonary function tests were performed to determine vital capacity, FEV_1, and FVC using a standard spirometer (Fudac-60; Fukuda Denshi; Tokyo, Japan). Arterial blood was drawn with the patient resting in the supine position between 9:00 AM and 10:00 AM the morning after the sleep study to measure Pao_2 and $PaCO_2$ during room air breathing in a blood gas analyzer (Model ABL555; Radiometer; Tokyo, Japan). The supine position was selected when arterial blood was obtained because polysomnography was started with the patient in that position. Hypercapnia was defined as $PaCO_2$ ≥ 45 mm Hg, and normocapnia was defined as $PaCO_2$ < 45 mm Hg. The ideal alveolar gas equation was used to calculate alveolar Po_2 so that the alveolar-arterial oxygen pressure difference ($P|A\text{-}a|O_2$) could be calculated. The study protocol was approved by the Research Ethics Committee of Chiba University School of Medicine, and all patients gave their informed consent prior to the study.

Polysomnography

Overnight polysomnography (P Series or E Series Polygrapher; Compumedics; Melbourne, Australia) was performed between 9:00 PM and 6:00 AM. Polysomnography consisted of continuous polygraphic recording from surface leads for EEG; electrooculography; electromyography; ECG; thermistors for nasal and oral airflow; thoracic and abdominal impedance belts for respiratory effort; pulse oximetry for oxyhemoglobin level; tracheal microphone for snoring; and sensor for the position during sleep. Respiratory events were basically scored according to American Academy of Sleep Medicine criteria: apnea was defined as complete cessation of airflow lasting ≥ 10 s; hypopnea was defined as a ≥ 50% reduction of airflow from baseline for 10 s that was associated with an oxygen desaturation > 3% or an arousal. Polysomnograms were staged manually according to standard criteria.[13,14] Severity of OSAS was determined based on the AHI, and lowest and average values of arterial oxygen saturation (Sao_2) during sleep.

CPAP Treatment

Arterial blood gas analysis was re-evaluated 3 months after the initiation of CPAP therapy (AutoSet; ResMed; Sydney, Australia). The subjects were consecutive hypercapnic OSAS patients (n = 55) examined using polysomnography from January to December 2005 with AHI values > 40/h. Thirty-seven patients could tolerate CPAP treatment and were successfully treated for 3 months with CPAP. CPAP tolerance was considered adequate when the system counter indicated that the patient was using the

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device for at least 4 h at night during at least 70% of the follow-up nights. Nonadherence to CPAP therapy was observed in 18 patients.

Statistical Analysis

The results are expressed as mean ± SE. All clinical parameters are summarized by descriptive statistics. The Mann-Whitney *U* test was used to compare age, BMI, pulmonary functions, and sleep parameters between two groups of patients. Proportions were compared using the χ^2 test. Linear regression analysis was performed to examine the association between two parameters. The patients were distributed into five groups according to BMI (18.5 to 25 kg/m^2, 25 to 30 kg/m^2, 30 to 35 kg/m^2, 35 to 40 kg/m^2, and ≥ 40 kg/m^2), percentage of predicted vital capacity (%VC) [70%, 70 to 80%, 80 to 90%, 90 to 100%, and ≥ 100%]; FEV_1/FVC ratio (FEV_1%) [≤ 60%, 60 to 70%, 70 to 80%, 80 to 90%, and ≥ 90%]; and AHI (5 to 15/h, 15 to 30/h, 30 to 45/h, 45 to 60/h, and ≥ 60/h). Groups 1 to 4 were defined according to AHI levels. Levels of BMI were classified according to World Health Organization criteria.[5] Analysis of variance was used to compare levels among the groups. This was followed by a *post hoc* Bonferroni multiple-comparison test. Logistic regression analysis was applied to predict daytime hypercapnia using the category classification of BMI, %VC, FEV_1%, and AHI as potential predictors. AHI was a parameter for the degree of sleep apnea, BMI for obesity, %VC for obesity-related impairment of lung function, and FEV_1% for obstructive impairment of lung function; p values < 0.05 were considered statistically significant.

Results

Patients With OSAS vs Without OSAS

The male to female ratio in patients with OSAS was approximately 8, while it was approximately 3 in non-OSAS patients ($p < 0.01$, χ^2 test). Mean age was higher in the OSAS group. FEV_1% and Pao_2 values were lower, while BMI and $P(A\text{-}a)O_2$ values were higher in the OSAS group. $PaCO_2$ values were not statistically different between two groups (Table 1).

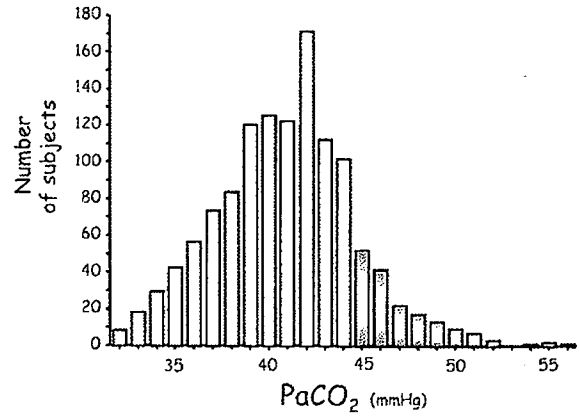

FIGURE 1. Distribution of patients according to $PaCO_2$. Open and closed bar show patients without and with hypercapnia, respectively.

Patients With Hypercapnia vs Normocapnia

Fourteen percent (168 of 1,227 patients) of those with OSAS showed daytime hypercapnia ($PaCO_2$ ≥ 45 mm Hg) [Fig 1]. Fourteen percent of men and 8% of women (no significant difference in gender) exhibited daytime hypercapnia. %VC was slightly lower in hypercapnic patients compared with normocapnic patients, while FEV_1% was similar between the two groups. Pao_2 was significantly lower in hypercapnic patients. $P(A\text{-}a)O_2$ values were similar between the two groups. BMI and AHI were significantly higher in hypercapnic patients (Table 2).

Predictive Factors for Daytime Hypercapnia

Age and gender distribution differed between the OSAS group and the non-OSAS group (Table 1). However, no gender difference in $PaCO_2$ levels was observed in either group. In addition, no significant

Table 1—*Characteristics of Patients With OSAS vs Without OSAS**

Variables	AHI ≥ 5/h (n = 1,227)	AHI < 5/h (n = 172)	p Value
Men/women, No.	1,091/136	130/42	< 0.01
Age, yr	49.9 ± 0.8	45.3 ± 1.1	< 0.01
%VC	100.7 ± 0.5	100.2 ± 1.5	NS
FEV_1%	82.3 ± 0.2	84.5 ± 0.5	< 0.01
Pao_2, mm Hg	80.8 ± 0.3	87.8 ± 0.7	< 0.01
$PaCO_2$, mm Hg	41.3 ± 0.1	40.8 ± 0.2	NS
$P(A\text{-}a)O_2$, mm Hg	11.1 ± 0.7	17.6 ± 0.3	< 0.01
AHI, events/h	42.0 ± 0.8	2.2 ± 0.1	< 0.01
Lowest Sao_2, %	74.5 ± 0.3	85.4 ± 0.4	< 0.01
Average Sao_2, %	90.9 ± 0.2	96.5 ± 0.1	< 0.01
BMI, kg/m^2	28.6 ± 0.2	25.0 ± 0.4	< 0.01

*Data are presented as mean ± SE unless otherwise indicated. NS = not significant.

Table 2—*Characteristics of Patients With Hypercapnia vs Normocapnia**

Variables	$PaCO_2$ < 45 mm Hg (n = 1,059)	$PaCO_2$ ≥ 45 mm Hg (n = 168)	p Value
Men/women, No.	935/124	156/12	NS
Age, yr	50.0 ± 0.4	49.3 ± 1.0	NS
%VC	100.8 ± 0.5	97.5 ± 1.5	< 0.05
FEV_1/FVC, %	82.9 ± 0.2	82.5 ± 0.5	NS
Pao_2, mm Hg	81.9 ± 0.3	73.9 ± 0.8	< 0.01
$PaCO_2$, mm Hg	40.4 ± 0.1	47.4 ± 0.2	< 0.01
$P(A\text{-}a)O_2$, mm Hg	17.7 ± 0.4	16.9 ± 0.7	NS
AHI, events/h	39.3 ± 0.8	58.8 ± 2.0	< 0.01
Lowest Sao_2, %	75.6 ± 0.3	67.5 ± 1.0	< 0.01
Average Sao_2, %	91.5 ± 0.2	86.9 ± 0.6	< 0.01
BMI, kg/m^2	28.2 ± 0.2	31.1 ± 0.6	< 0.01

*Data are presented as mean ± SE unless otherwise indicated. See Table 1 for expansion of abbreviation.

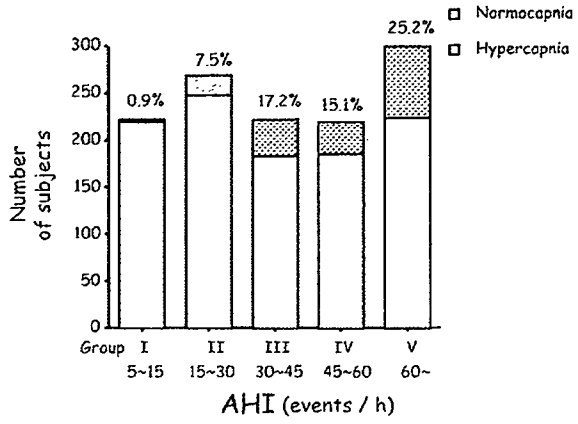

FIGURE 2. Prevalence of daytime hypercapnia in patients with OSAS distributed according to AHI.

correlation was observed between age and $Paco_2$ levels in patients with OSAS.

Hypoxemia (Pao_2) is a predictive factor for daytime hypercapnia when alveolar hypoventilation is the main cause of hypercapnia. In the present population, alveolar Po_2 was a definite predictive factor for hypercapnia because $P(A\text{-}a)O_2$ values were similar in the two groups. Therefore, the predictive values of BMI, $FEV_1\%$, %VC, and/or AHI for daytime hypercapnia were examined. Univariate analysis showed that $Paco_2$ significantly correlated with AHI, BMI, and %VC, while $Paco_2$ did not correlate with $FEV_1\%$. The prevalence of daytime hypercapnia differed according to BMI, %VC, and AHI (Fig 2) but not according to $FEV_1\%$. The logistic regression analysis for prediction of daytime hypercapnia showed that only AHI values were predictors for the presence of daytime hypercapnia, while BMI and %VC were borderline predictors and $FEV_1\%$ was not a predictor (Table 3).

Table 3—*Univariate Analysis of $Paco_2$ Values and Multivariate Analysis of Potential Predictors of Daytime Hypercapnia ($Paco_2 \geq 45$ mm Hg)**

	Univariate		Multivariate	
Variables	*r* Value	p Value	p Value	Relative Risk (95% CI)
AHI, events/h	0.21	< 0.0001	< 0.0001	
5 to 15				1.00
15 to 30				4.72 (1.59–14.01)
30 to 45				11.74 (4.08–33.77)
45 to 60				10.27 (3.53–29.86)
> 60				16.26 (5.69–46.4)
BMI	0.16	< 0.0001	0.051	
%VC	−0.06	0.03	0.062	
$FEV_1\%$	0.03	0.38	0.558	

*CI = confidence interval.

Because only AHI values were predictive for the presence of daytime hypercapnia, anthropometric, blood gas, and sleep study data were analyzed in patients with OSAS distributed according to AHI (Table 4). $Paco_2$ in group 5 was the highest ($p < 0.05$) among the five groups. $Paco_2$ in group 4 was significantly higher than that in group 1 (Fig 3). BMI in group 5 was the highest ($p < 0.05$) among the five groups. BMI in group 4 was significantly ($p < 0.05$) higher than that in groups 1 and 11, and BMI in group 3 was significantly ($p < 0.05$) higher than that in group 1 (Fig 4).

In the present study, we used logistic regression analysis to predict daytime hypercapnia. However, when we used multiple regression analysis, the results were similar to those obtained using AHI as the only statistically significant variable to predict hypercapnia.

Responses of $Paco_2$ to CPAP Therapy

Based on the response of $Paco_2$ to CPAP therapy, patients were distributed into good responders ($n = 19$) showing a decrease of $Paco_2$ by 5 mm Hg; poor responders ($n = 18$) showing a decrease of < 5 mm Hg after 3 months on CPAP therapy; and nonadherents ($n = 18$) [Table 5]. Sex distribution, age, pulmonary function (%VC, $FEV_1\%$), arterial blood gas analyses (Pao_2, $Paco_2$), and AHI did not differ significantly between good and poor responders. BMI was lower in good responders than in poor responders. The degree of sleep desaturation was more severe in poor responders than in good responders. BMI decreased significantly after 3 months of CPAP therapy in good and poor responders ($p < 0.05$). Nonadherents to CPAP therapy were older, not obese, and had milder degree of hypercapnia and sleep apnea (Table 5).

DISCUSSION

The present study showed that 13.7% (168 of 1,227 patients) of a relative large group of patients with OSAS examined using polysomnography had daytime hypercapnia. Patients with daytime hypercapnia had significantly higher BMI and AHI, and lower Pao_2 and %VC values compared with normocapnic patients, while $FEV_1\%$ did not differ between the two groups. Logistic regression analysis showed that only AHI was a predictor of daytime hypercapnia, although this index was not independent of BMI. Obesity partly contributed to the presence of daytime hypercapnia in our patients, suggesting that BMI acts as a modifier. In some patients with OSAS, daytime hypercapnia responded to CPAP therapy for 3 months. These data suggest that the pathogenesis of daytime hypercapnia might be directly linked to OSAS *per se* in a subset of patients with OSAS.

Table 4—*Anthropometric, Blood Gas, and Sleep Study Data of OSAS Patients Distributed According to AHI

Variables	Group 1, AHI ≥ 5 to < 15/h (n = 222)	Group 2, AHI ≥ 15 to < 30/h (n = 268)	Group 3, AHI ≥ 30 to < 45/h (n = 221)	Group 4, AHI ≥ 45 to < 60/h (n = 218)	Group 5, AHI ≥ 60/h (n = 298)
Men/women, No.	184/38	229/39	207/14	204/14	267/31
Age, yr	50.6 ± 0.9	50.8 ± 0.8	51.6 ± 0.8	50.9 ± 0.9	46.6 ± 0.7†
%VC, %	107.4 ± 1.1	106.6 ± 1.1	107.4 ± 1.2	106.0 ± 1.3	101.7 ± 1.0†
FEV_1%, %	83.5 ± 0.4	82.7 ± 0.4	81.9 ± 0.4	82.6 ± 0.4	83.1 ± 0.3
PaO_2, mm Hg	86.2 ± 0.6	82.5 ± 0.6†	81.8 ± 0.6†	80.1 ± 0.7†	74.8 ± 0.6†
$PaCO_2$, mm Hg	40.4 ± 0.2	40.7 ± 0.2	41.2 ± 0.3	41.4 ± 0.3†	42.6 ± 0.2†
$P(A\text{-}a)O_2$, mm Hg	13.3 ± 0.6	16.5 ± 0.6†	16.6 ± 0.6†	18.2 ± 0.7†	22.0 ± 0.6†
BMI, kg/m^2	25.5 ± 0.3	27.1 ± 0.3†	27.6 ± 0.3†	28.6 ± 0.4†	32.9 ± 0.4†

*Data are presented as mean ± SE unless otherwise indicated.
†$p < 0.05$ vs group 1.

The pathogenesis of OSAS and/or hypoventilation (daytime hypercapnia) may differ between Western and Asian populations including Japan because different genetic factors may contribute to the development of these disorders.[16] In the present study, mean AHI in the normocapnic and hypercapnic OSAS groups was 28.2/h and 31.1/h, respectively, which was lower than that found in previous reports[1–8] from Western countries. In addition, the level of hypercapnia was relatively mild (mean, 47.4 mm Hg) in our cohort, and the proportion of patients with a $PaCO_2 \geq 50$ mm Hg was only 13.7% (23 of 168 hypercapnic patients) [Fig 5]. Therefore, it is unclear whether the results of this study could be explored to white patients.

Daytime hypercapnia was corrected in approximately half of our patients treated with CPAP. A limitation of this result was that the patients who tolerated this therapy were not representative of the entire hypercapnic OSAS group because their AHI and BMI values were higher than those observed in the whole group of hypercapnic patients. Another limitation was that we did not measure the time course of $PaCO_2$ changes during the usage of auto-CPAP. However, our result was similar to that reported by Rapoport et al,[8] who found that four patients became eucapnic within 2 weeks of CPAP therapy, while four others remained hypercapnic, although the subjects were morbid obese. Rapoport et al[8] proposed that two separate mechanisms exist for hypercapnia in OSAS. The pathogenetic mechanisms of daytime hypercapnia in patients with OSAS who responded to CPAP therapy may be a balance between ventilation while awake and hypoventilation due to repetitive sleep apnea; thus, the effects of sleep apnea on daytime hypercapnia could be abolished by CPAP therapy. Han et al[17] reported that $PaCO_2$ had fallen to < 45 mm Hg and hypoxic and hypercapnic chemosensitivity had increased 4 to 6 weeks after CPAP therapy, without body weight

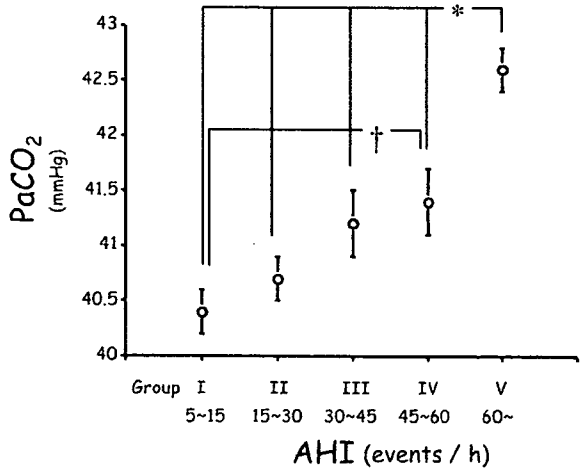

FIGURE 3. $PaCO_2$ values in patients with OSAS distributed according to AHI. *$p < 0.05$ vs every other group. †$p < 0.05$ vs group 1.

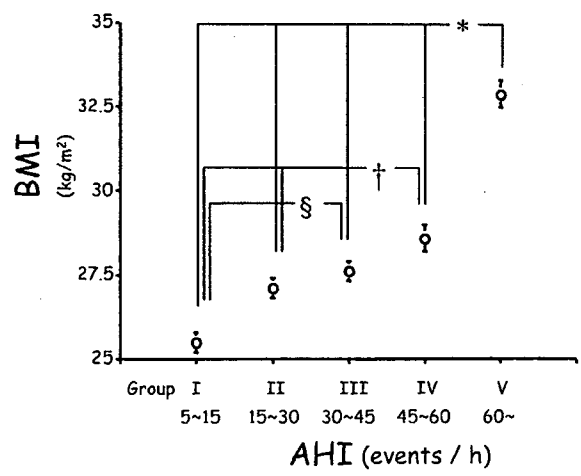

FIGURE 4. BMI in patients with OSAS distributed according to AHI. *$p < 0.05$ vs every other group. †$p < 0.05$ vs groups 1 and 2. §$p < 0.05$ vs group 1.

Table 5—*Good Responders, Poor Responders, and Nonadherents to CPAP Therapy

Variables	Good Responders (n = 19)	Poor Responders (n = 18)	Nonadherents (n = 18)
Men/women, No.	19/0	15/3	15/3
Age, yr	44.4 ± 2.4	48.1 ± 3.2	63.8 ± 2.3§
%VC	97.6 ± 4.8	90.9 ± 3.0	94.0 ± 6.1
FEV_1/FVC, %	84.3 ± 1.3	86.1 ± 1.4	79.4 ± 1.5§
PaO_2, mm Hg	71.0 ± 2.4	65.3 ± 2.7	76.8 ± 1.5§
$PaCO_2$, mm Hg	48.8 ± 0.6	49.2 ± 0.8	47.2 ± 0.5§
AHI, events/h	61.6 ± 6.5	63.2 ± 6.9	51.2 ± 1.7§
Lowest SaO_2, %	63.6 ± 3.0	53.9 ± 2.9	68.6 ± 2.1§
Average SaO_2, %	83.8 ± 1.8	79.1 ± 2.3	90.1 ± 0.7§
BMI before therapy, kg/m^2	32.5 ± 1.1	42.4 ± 2.7†	26.1 ± 1.0§
BMI after therapy, kg/m^2	31.9 ± 1.1†	42.0 ± 2.8†‡	26.0 ± 1.1§

*Data are presented as mean ± SE unless otherwise indicated.
†$p < 0.05$ compared with BMI before CPAP therapy.
‡$p < 0.05$ compared with good responders.
§$p < 0.05$ compared with poor responders.

changes, in hypercapnic patients with OSAS (n = 5), suggesting that depressed chemoresponsiveness plays a role independent of obesity in the development of CO_2 retention in some of these patients; and it may be a response to sleep-disordered breathing. In the present study, one possible pathomechanism of hypercapnia in good responders may be upper airway resistance because in this group BMI was slightly lower than in poor responders and upper airway resistance was easily ameliorated after CPAP therapy. However, daytime $PaCO_2$ levels in OSAS patients may be an end product of a complex conglomerate, influenced by factors such as severity of sleep apnea; obesity; daytime PaO_2; chemosensitivity; respiratory mechanics; respiratory muscle strength; metabolic rate; daytime symptoms of sleepiness; endocrine modulation; cardiac function; and face, nose, and cranial bony structure (cephalometry). Several undefined pathomechanisms of daytime hypercapnia may exist in patients with OSAS, whose $PaCO_2$ did not decrease after CPAP therapy.

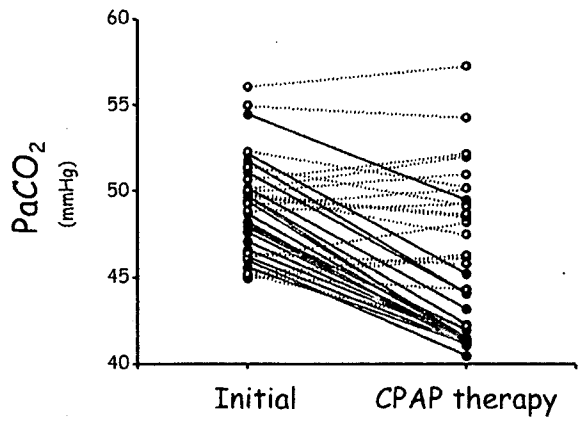

FIGURE 5. The responses of $PaCO_2$ to CPAP therapy. Closed circle with solid line represents good responder, while open circle with dashed line represents poor responder.

Our study did not focus on the causal relationship between OSAS and OHS. It has been reported that OHS can occur without significant OSAS[18] (*ie*, OHS patients could exhibit nocturnal hypoventilation unrelated to upper airway obstruction).[8] Forty-three percent (73 of 168 patients) of our hypercapnic patients with OSAS satisfied the criteria of OHS, when obesity was defined as BMI ≥ 30 kg/m^2. In other words, more than half of hypercapnic patients with OSAS were not obese based on Western criteria. In addition, nocturnal desaturation in our hypercapnic patients with OSAS was mostly due to upper airway obstruction, partly because the degrees of daytime hypercapnia and obesity were mild compared with those of previous reports from Western countries.[1–5] There may exist some ethnic differences regarding the characteristics of OHS between Japan and Western countries. In the present study, logistic regression analysis showed that BMI could be a predictor of daytime hypercapnia ($p = 0.051$), suggesting that obesity may have partly contributed to the presence of daytime hypercapnia in our patients. Therefore, the predictive value of AHI may not be independent of BMI; rather, BMI could be a modifier.

Our data showed that chronic airflow limitation was not a prerequisite for the presence of daytime hypercapnia.[6] We did not intend to exclude any patient suspected of COPD in our study, and no patients showed an $FEV_1\% < 60\%$. Only 3.5% of the patients with hypercapnia (6 of 168 patients) had mild obstructive airflow limitation ($FEV_1\% \geq 60\%$ to $< 70\%$). Overlap syndrome (the association of OSAS with COPD)[19] may be rare in the Japanese population. However, a relationship of obstructive impairment with hypercapnia in patients with OSAS cannot be ruled out because our study population was a convenient sample of patients attending a sleep clinic.

The poor responders to CPAP therapy showed a decrease of AHI after receiving auto-CPAP therapy, and their clinical conditions (the degree of daytime sleepiness decreased) improved, although the levels of daytime $PaCO_2$ did not decrease ≥ 5 mm Hg. Current therapeutic options available for hypoventilation syndrome include bilevel pressure support ventilation with or without supplemental oxygen.[20] A future challenge is to investigate whether poor responders to CPAP therapy would respond to bilevel pressure support ventilation.

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Decreased Lipoprotein Lipase in Obstructive Sleep Apnea Syndrome

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Background Lipoprotein lipase (LPL) might play a major role in lipid metabolism by hydrolyzing triglyceride-rich lipoproteins. Decreased LPL activity can trigger early inflammatory responses central to atherosclerosis. However, whether repeated apnea-related hypoxemia influences lipid metabolism in patients with obstructive sleep apnea syndrome (OSAS) remain undefined. This investigation determined whether circulating LPL was influenced by repeated apnea-related hypoxemia, and the effect of nasal continuous positive airway pressure (CPAP) therapy on LPL concentrations in OSAS patients.

Methods and Results The participants of the study were 155 men with OSAS and 39 men without OSAS. Circulating LPL concentrations decreased with the severity of OSAS. They correlated negatively with serum triglyceride, and the linear regression lines between LPL concentrations and triglyceride in OSAS patients were shifted downward compared with those in non-OSAS patients, suggesting that any pathophysiological factor might decrease LPL activity in OSAS patients. Some OSAS patients were subjected to CPAP therapy for 3 months. CPAP therapy increased LPL concentrations and decreased C-reactive protein (CRP) concentrations.

Conclusions The present study suggests that repeated apnea-related hypoxemia might affect lipid metabolism and augment inflammatory responses, and CPAP therapy could be effective to decrease inflammatory responses and ameliorate lipid metabolism in patients with OSAS. (*Circ J* 2007; **71**: 1293–1298)

Key Words: Atherosclerosis; Inflammation; Lipid metabolism; Sleep apnea

Increased concentrations of triglyceride (TG)-rich lipoproteins provoke lipid accumulation in the artery wall, triggering early inflammatory responses central to atherosclerosis.[1] Lipoprotein lipase (LPL) might play a major role in lipid metabolism by hydrolyzing TG-rich lipoproteins and releasing fatty acids.[2] Peroxisome proliferators-activated receptor (PPAR)-α might be activated by fatty acids to induce the transcription of genes involved in the oxidation of fatty acids. Then, LPL could act on circulating lipoproteins to generate PPAR-α ligands. PPAR-α activation might exert cardiovascular protective effects in hypertension or other forms of cardiovascular disease.[3]

There is a continuous dissociation of LPL from the endothelium to blood.[4] Therefore, blood levels of LPL might be associated with the pathogenesis of cardiovascular diseases,[5] including the complications of obstructive sleep apnea syndrome (OSAS). However, the roles of LPL in inflammatory responses, atherosclerosis and cardiovascular complications in patients with OSAS remain undefined. Assuming that the pathophysiology of OSAS manifests a systemic inflammatory response, repeated hypoxemia and recovery to normoxemia could affect LPL activity.

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Serum levels of TG and body mass index (BMI) have been reported to correlate negatively with the blood concentrations of LPL.[5–7] We hypothesized that the pathophysiological conditions, related to the severity of OSAS, might affect the blood concentrations of LPL.[3–5] The purpose of the present study was to examine whether the blood concentrations of LPL are influenced by repeated apnea-related hypoxemia in patients with OSAS and to determine whether nasal continuous positive airway pressure (CPAP) therapy ameliorate the levels of LPL.

Methods

Subjects

A consecutive male population with clinical symptoms of sleep apnea (n=260), who were examined by polysomnography (PSG) from August 2003 to October 2004, was first divided into 2 groups according to their apnea-hypopnea index (AHI) (AHI ≥5: n=214, AHI <5: n=46). The patients were recruited from the sleep clinic where they had been referred for further investigation regarding snoring or possible OSAS. Presenting symptoms were either snoring or daytime sleepiness or both. The subjects were all Japanese, and no other ethnic group was included to avoid the effects of ethnic difference.

Patients with heart failure, or other respiratory problems, including chronic obstructive pulmonary disease were excluded from the study. Subjects with kidney disease and hormonal disease were also excluded. Subjects on medication known to affect insulin action, including the treatments for diabetes mellitus, or plasma lipoprotein concentrations,